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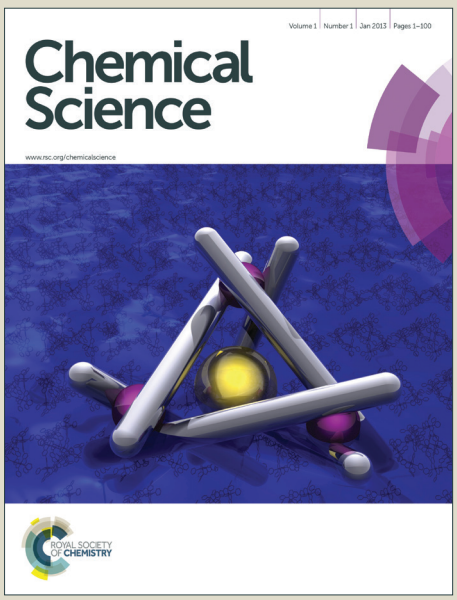

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ARTICLE TYPE

Chiral Phosphine-Catalyzed Tunable Cycloaddition Reactions of Allenoates with Benzofuranone Derived Olefins for Highly Regio-, Diastereo- and Enantioselective Synthesis of Spiro-Benzofuranones

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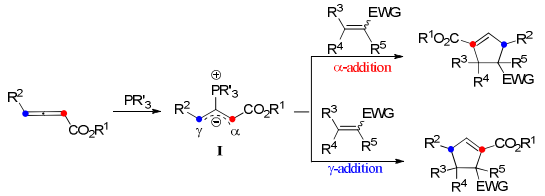
The first regioselectively catalytic asymmetric [3+2] cycloadditions of benzofuranone derived olefins with allenoate and substituted allenoates have been developed in the presence of (R)-SITCP, affording different functionalized 3-spirocyclopentene benzofuran-2-ones in good yields with high enantioselectivities under mild condition. The substrate scope has been also examined. The regioselective outcomes for this phosphine-catalyzed [3+2] cycloaddition reaction can be rationalized by DFT calculations.

Phosphine-catalyzed [3+2] cycloaddition of electron-deficient olefins with allenoates, which provides an alternative access to a variety of useful carbocycles, was first reported by Zhang and Lu in 1995.[1,2] Pioneering work of catalytic asymmetric Lu's [3+2] cycloaddition of allenoates with olefins was disclosed by Zhang in 1997.[3] No further progress has been made on the development of this enantioselective [3+2] cyclization for about a decade after Zhang's promising results, until Fu and co-workers have recently developed a series of axially chiral binaphthyl framework containing phosphines catalyzed asymmetric cycloaddition of allenoates with electron-deficient olefins, affording the corresponding cycloadducts in good yields with excellent diastereo- and enantioselectivities.[4] Moreover, Marinetti and co-workers have also discovered that chiral phosphines based on a planar chiral 2-phospha[3]ferrocenophane scaffold were efficient catalysts for this type of asymmetric reaction as well.[5] A variety of multifunctional chiral phosphines derived from natural amino acids have also emerged as powerful catalysts to promote [3+2] cycloaddition of allenoates with electron-deficient olefins or imines, affording a variety of cyclopentene or pyrrolidine derivatives in good yields with high diastereo- and enantioselectivities under mild conditions.[6] For example, Miller and co-workers achieved enantioselective cyclization of allenoates and enones by using phosphines containing α-amino acids.[6a] Jacobsen and co-workers utilized phosphine-thiourea catalysts for enantioselective annulations of allene and imine.[6b] Zhao[6c] and Lu[6d-s] developed a series of multifunctional phosphine catalysts based on different types of amino acids, and applied these functional phosphine containing catalysts to different types of cycloadditions, respectively. Recently, Kwon's group developed a new class of rigid chiral bicyclicphosphines and applied them to asymmetric synthesis of multi-substituted pyrrolines.[6t] In addition, some commercially available bidentate chiral phosphine-promoted [3+2] cycloadditions have also been reported.[7]

The phosphine-catalyzed [3+2] cycloaddition of electron-deficient olefins with allenoates was commonly considered as starting from the formation of the corresponding zwitterionic intermediate **I** between PR_3 and allenoate. The nature of this zwitterion shown in Scheme 1 may be depicted in two ways, which include anion localization at the α-carbon or γ-carbon, thus two regioisomers derived from α-addition and γ-addition could be produced at the same time (Scheme 1). Therefore, the selective synthesis of highly regio-, diastereo- and enantioselective products becomes a big challenge. Previous reports mainly focus on how to obtain a single highly regioselective product; however, few people make efforts to obtain both α-addition and γ-addition isomers in a controllable way with highly regio-, diastereo- and enantioselective values, not to mention the mechanistic study of regioselectivity.[8]



Scheme 1. Model of Phosphine Catalyzed [3+2] Cycloaddition

Benzofuranones as one of important building blocks exist in a variety of natural product[9] and potential medicines.[10] Enantioselective synthesis of chiral benzofuranones remains a considerable challenge,[11] especially in the field on construction of chiral spiro-quaternary center at C3 position of benzofuranones.[12] As our ongoing investigation on phosphine catalyzed asymmetric cycloaddition,[13] we wish to report a spiro phosphine (*R*)-SITCP[14] catalyzed asymmetric [3+2] cycloaddition of allenic esters with benzofuranones, furnishing the spiro cycloadducts in good yields with excellent regio-,

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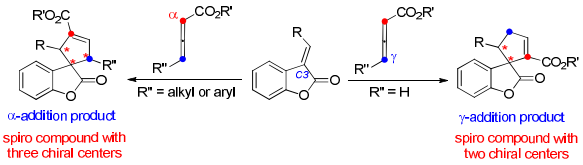
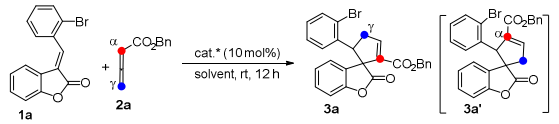
diastereo- and enantioselectivities, by adjusting of the substituents of allenic esters to obtain both α-addition and γ-addition products, and by using rational DFT calculations to reveal the reason of regioselectivity. This asymmetric [3+2] cycloaddition catalyzed by chiral phosphine features the simultaneous formation of spiro-quaternary and tertiary stereocenters (two or three chiral centers) in a single step (Scheme 2). In addition, this type of reaction is also suitable for substrates such as arylideneoxindole and alkylidene azlactone, which makes this type of reaction having a promising application.



Scheme 2. Asymmetric Approaches of α- and γ-Addition Product

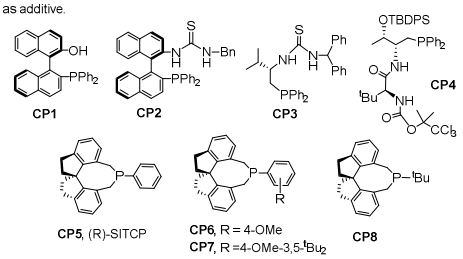
We initially screened a variety of chiral phosphines **CP1-CP8** by using (*E*)-3-(2-bromobenzylidene)benzofuran-2(3H)-one **1a** and benzyl 2,3-butadienoate **2a** as the model substrates in toluene. The results are summarized in Table 1. We found that γ-addition product **3a** as main product and α-addition product **3a'** as minor product were obtained in 26-92% total yields, with the regioselective ratios (r.r.) of **3a**:**3a'** from 86:14 to 95:5, and excellent diastereoselectivities (the minor diastereomer almost could not be detected by ^{1}H NMR); the ee value of main product **3a** is obtained from 8% to 88% (Table 1, entries 1-8). Catalyst **CP5** gave the highest yield, regio- and enantioselectivity compared to other catalysts (Table 1, entry 5). Having identified the best catalyst in this reaction, we next attempted to further optimization of reaction conditions by screening of the solvent and reaction temperature (Table 1, entries 8-14). The reaction outcomes revealed that using 10 mol% **CP5** as the catalyst and carrying out the reaction in dichloromethane (DCM) and toluene as mixing solvent (1:1) with 4Å MS (30 mg) as the additive afford **3a** at room temperature in 78% yield for 12 h with >19:1 r.r. and 99% ee value, which served as the best reaction conditions in this reaction (Scheme 3, eq.1). Using γ-phenyl allenoate **4a** as the Michael acceptor, the reaction proceeded smoothly to give α-addition product as the major product in 96% yield, with >19:1 r.r. and 95% ee value in toluene; however, the reaction proceeded in DCM, diminishing yield, r.r. and ee value significantly (Scheme 3, eq.2).

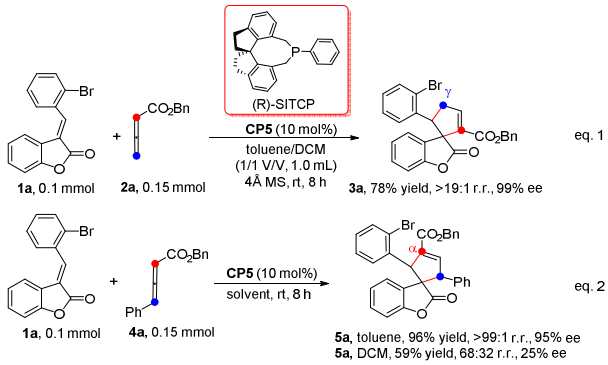
Table 1. Optimization of the reaction conditions of α-addition



entry[a]	cat.*	solvent	T (°C)	yield[b] (%)	r.r.[c] (**3a**:**3a'**)	ee[c] (%)
1	**CP1**	toluene	25	37	90:10	8
2	**CP2**	toluene	25	32	88:12	20
3	**CP3**	toluene	25	26	86:14	14
4[d]	**CP4**	toluene	25	-	-	-
5	**CP5**	toluene	25	92	96:4	88
6	**CP6**	toluene	25	72	95:5	83
7	**CP7**	toluene	25	74	94:6	88
8	**CP8**	toluene	25	trace	92:8	13
9	**CP5**	DCM	25	58	>19:1	>99
10	**CP5**	THF	25	47	94:6	93
11	**CP5**	CH_3CN	25	22	72:28	94
12	**CP5**	toluene/DCM[e]	25	85	>19:1	91
13	**CP5**	toluene/DCM[f]	25	64	>19:1	98
14	***CP5***	*toluene/DCM[g]*	*25*	*78*	*>19:1*	*99*
15	**CP5**	toluene/DCM[g]	0	53	>19:1	99

[a] All reactions were carried out with **1a** (0.1 mmol), **2a** (0.15 mmol), catalyst (10 mol%) in solvent (1.0 mL); [b] Isolated yield; [c] Determined by ^{1}H NMR of crude product; Determined by HPLC; [d] disordered; [e] toluene/DCM = 4:1; [f] toluene/DCM = 1:1; [g] toluene/DCM = 1:1, 4Å MS (30 mg) was added as additive.



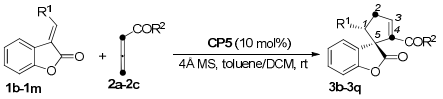


Scheme 3. Optimal Conditions of α- and γ-Addition.

Having identified optimal reaction conditions, the generality of this (*R*)-SITCP (**CP5**) catalyzed asymmetric γ-addition [3+2] cycloaddition was examined using a variety of aryl or alkyl-substituted benzofuranones **1** and allenic esters **2**. The results are summarized in Table 2. Whether R^1 is an electron-rich or -deficient aromatic ring, the reactions proceeded smoothly to give the corresponding spiro-cycloadducts **3b-3j** in moderate to good yields with 87-96% ee values and 88:12->99:1 r.r. (Table 2, entries 1-9). In the case of 4-$CF_3C_6H_4$ benzofuranon **1e**, the regioselective ratio decreased to 88:12 (Table 2, entry 4). Using 4-CNC_6H_4 benzofuranone **1g** as the substrate, the corresponding adduct was obtained in 57% yield along with relatively lower ee value (87% ee) (Table 2, entry 6). When R^1 is a heteroaromatic group (R^1 = 2-furyl, 2-thienyl) or a sterically hindered 1-naphthyl moiety, the reactions also proceeded efficiently to afford the corresponding products **3k**-**3m** in 48-99% yields with 93-99% ee values and good regioselectivities (Table 2, entries 10-12). Changing R^1 from the aromatic group to aliphatic group provided the corresponding product **3n** in 68% yield with 95% ee and 98:2 regioselective ratio (Table 2, entry 13). Other electron-deficient allenes such as ethyl-2,3-butadienoate and penta 3,4-dien-2one are also suitable for this asymmetric [3+2] cycloaddition, giving

the corresponding products in 94% and 83% yields with 99% and 96% ee values as well as excellent regioselectivities, respectively (Table 2, entries 14 and 15). The absolute configuration of **3m** has been assigned by X-ray diffraction as 1*S*, 5*R*. The ORTEP drawing and the CIF data are summarized in the Supporting Information.[19]

Table 2. Scope of the asymmetric [3+2] cycloaddition to afford cycloadducts **3b-3q**

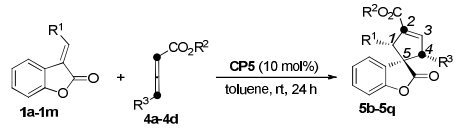


entry[a]	1 (R^1)	2 (R^2)	yield[b] (%)	r.r.[c]	ee (%)[d]
1	**1b** (4-BrC_6H_4)	**2a** (OBn)	**3b**: 92	>99:1	95
2	**1c** (4-$CH_3C_6H_4$)	**2a** (OBn)	**3c**: 76	92:8	91
3	**1d** (4-$CH_3OC_6H_4$)	**2a** (OBn)	**3d**: 72	98:2	96
4	**1e** (4-$CF_3C_6H_4$)	**2a** (OBn)	**3e**: 87	88:12	91
5	**1f** (4-FC_6H_4)	**2a** (OBn)	**3f**: 67	98:2	94
6	**1g** (4-CNC_6H_4)	**2a** (OBn)	**3g**: 57	92:8	87
7	**1h** (3,4-$Cl_2C_6H_3$)	**2a** (OBn)	**3h**: 82	92:8	90
8	**1i** (C_6H_5)	**2a** (OBn)	**3i**: 79	98:2	94
9	**1j** (4-PhC_6H_4)	**2a** (OBn)	**3j**: 76	>99:1	96
10	**1k** (2-furyl)	**2a** (OBn)	**3k**: 48	95:5	96
11	**1l** (2-thienyl)	**2a** (OBn)	**3l**: 67	90:10	93
12[e]	**1m** (1-naphthyl)	**2a** (OBn)	**3m**: 99	97:3	99
13	**1n** (cyclohexyl)[f]	**2a** (OBn)	**3n**: 68	98:2	95
14	**1a** (2-BrC_6H_4)	**2b** (OEt)	**3o**: 94	>99:1	99
15	**1a** (2-BrC_6H_4)	**2c** (Me)	**3p**: 83	>99:1	96

[a] The reactions were carried out with **1** (0.1 mmol), **2a** (0.15 mmol), **CP5** (0.01 mmol) and 4Å MS (30 mg) in DCM (0.5 mL) and toluene (0.5 mL) at rt for 12 h. Unless otherwise mentioned, the compounds **1** were *E*-isomer. b Isolated yield by column chromatography. c Regioselective ratios determined by crude ^{1}H NMR spectroscopy; r.r. = regioselective ratios. d Determined by chiral HPLC analysis. e The absolute configuration of **3m** has been determined by X-ray diffraction as (1*S*, 5*R*). f Compound **1n** was the mixtrue of *Z* and *E* isomers, *Z*/*E* = 1/1 based on ^{1}H NMR analysis.

We next attempted to examine the asymmetric α-addition [3+2] cycloaddition reactions of benzofuranone **1** and γ-substituted allenoates **4** (Table 3). As for substrate **1b**, product **5b** was obtained in 91% yield, along with 84:16 r.r. and 85% ee value (Table 3, entry 2). For these substrates with electron-rich substituents on their aromatic rings, spiro-cycloadducts **5c-5d** were obtained in relatively moderate yields but with high ee values and regioselectivities (Table 3, entries 3-4). The substrates **1e-1m** with various electron-poor substituents on their aromatic rings were more suitable for this reaction, affording the corresponding cycloadducts in good yields with 91%-99% ee values and 92:8 to >99:1 regioselective ratios (Table 3, entries 5-12). Aliphatic group is also suitable for this reaction (Table 3, entry 13). Some other allenic esters such as ethyl-, *tert*-butyl 4-phenylbuta-2,3-dienoates or benzyl penta-2,3-dienoate are also suitable for this asymmetric [3+2] cycloaddition, giving the corresponding products in 67-83% yields with 90-97% ee values and 95:5->99:1 regioselectivities (Table 3, entries 14-16). The absolute configuration of **5j** has been assigned by X-ray diffraction as 1*R*, 4*R*, 5*R*. The ORTEP drawing and the CIF data are summarized in the Supporting Information.[19]

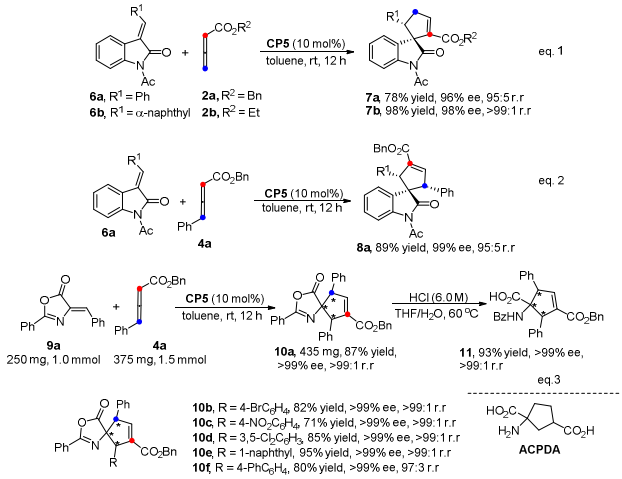
Table 3. Scope of the asymmetric [3+2] cycloaddition to afford cycloadducts **5b-5q**



entry[a]	1 (R^1)	4 (R^2/R^3)	yield[b] (%)	r.r.[c]	ee (%)[d]
1	**1a** (2-BrC_6H_4)	**4a** (Bn/Ph)	**5a**: 96	>99:1	95
2	**1b** (4-BrC_6H_4)	**4a** (Bn/Ph)	**5b**: 91	84:16	85
3	**1c** (4-$CH_3C_6H_4$)	**4a** (Bn/Ph)	**5c**: 72	92:8	99
4	**1d** (4-$CH_3OC_6H_4$)	**4a** (Bn/Ph)	**5d**: 68	98:2	96
5	**1e** (4-$CF_3C_6H_4$)	**4a** (Bn/Ph)	**5e**: 92	99:1	92
6	**1f** (4-FC_6H_4)	**4a** (Bn/Ph)	**5f**: 78	95:5	99
7	**1g** (4-CNC_6H_4)	**4a** (Bn/Ph)	**5g**: 75	>99:1	99
8	**1h** (3,4-$Cl_2C_6H_3$)	**4a** (Bn/Ph)	**5h**: 82	92:8	99
9	**1i** (C_6H_5)	**4a** (Bn/Ph)	**5i**: 86	>99:1	99
10[e]	**1j** (4-PhC_6H_4)	**4a** (Bn/Ph)	**5j**: 83	>99:1	99
11	**1k** (2-furyl)	**4a** (Bn/Ph)	**5k**: 77	>99:1	99
12	**1m** (1-naphthyl)	**4a** (Bn/Ph)	**5l**: 73	>99:1	90
13	**1n** (cyclohexyl)[f]	**4a** (Bn/Ph)	**5m**: 92	>99:1	99
14	**1c** (4-$CH_3C_6H_4$)	**4b** (Et/Ph)	**5n**: 67	95:5	90
15	**1c** (4-$CH_3C_6H_4$)	**4c** (^{t}Bu/Ph)	**5o**: 83	>99:1	97
16	**1c** (4-$CH_3C_6H_4$)	**4d** (Bn/Me)	**5p**: 62	95:5	94

[a] The reactions were carried out with **1a** (0.1 mmol), **2a** (0.12 mmol), **CP5** (0.01 mmol) in toluene (1.0 mL) at rt for 24 h. Unless otherwise mentioned, the compounds **1** were *E*-isomer. [b] Isolated yield by column chromatography. [c] Regioselectivity ratios determined by crude ^{1}H NMR spectroscopy; r.r. = regioselective ratios. [d] Determined by chiral HPLC analysis. [e] The absolute configuration of **5j** has been determined by X-ray diffraction as (1*R*, 4*R*, 5*R*). [f] Compound **1n** was the mixture of *Z* and E isomers, *Z*/*E* = 1/1 based on ^{1}H NMR analysis.

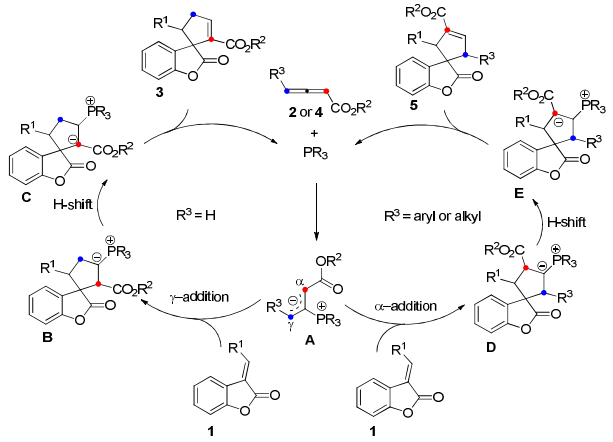
It is noteworthy that this catalytic system can be also applied in the regioselective construction of spiroindolines[5h, 8a, 15] in good yields, with high ee values and high regioselectivities (Scheme 4, eq. 1 and eq. 2). The γ-addition [3+2] cycloadducts **7a** and **7b** were obtained in 78% and 98% yields, 96% and 98% ee values and 95:5 and >99:1 r.r., respectively. The α-addition [3+2] cycloadduct **8a** was formed in 89% yield, 99% ee value and 95:5 r.r. The enantioselective approach for the construction of spirocyclic oxindolic cyclopentanes based on a phosphine-mediated γ-addition has been reported by Marinetti's group. Furthermore, the preparations of carbocyclic amino acids have received great attention in medicinal chemistry recently due to their unique biological activities.[13e, 16] As illustrated in Scheme 4 (eq. 3), the spiro-cycloadduct **10a** was obtained in 87% yield with >99% ee value and high regioselectivity by using alkylidene azlactone **9a** (1.0 mmol) and substituted allenoate **4a** (1.5 mmol) as substrates. The reactions of other substrates with different aromatic rings also proceeded smoothly, affording the corresponding cycloadducts **10b-10f** in good yields with high ee values (>99% ee) and excellent regioselectivities. The ring-opened product α-amino acid **11** was easily obtained by treatment with 6 M HCl in high yield without ee value diminishing (Scheme 4, eq.3).



Scheme 4. Further Applications and Transformations

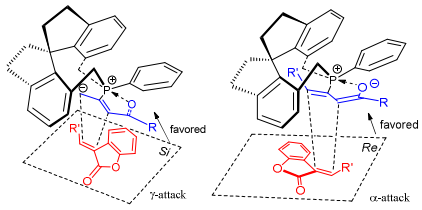
The plausible mechanisms for this phosphine-catalyzed [3+2]

cycloaddition have been proposed in Scheme 5 on the basis of our experiments and previous literatures.[1, 2] The reaction starts from the formation of a zwitterionic intermediate **A** between allenoate (**2** or **4**) and phosphine. Intermediate **A** acts as a 1,3-dipole and undergoes a [3+2] cycloaddition with benzofuranone **1** to give a phosphrous ylide **B** via γ-addition or **D** via α-addition. For allenoate **2** (R^3 = H), γ-addition is the main pathway. In contrast, allenoate **4** (R^3 = aryl or alkyl group) mainly undergoes α-addition. Then an intramolecular [1,2] proton transfer is speculated to convert the phosphorus ylide **B** or **D** to another zwitterionic intermediate **C** or **E**, which, upon elimination of the phosphine catalyst, gives rise to the final cycloadduct **3** or **5**.



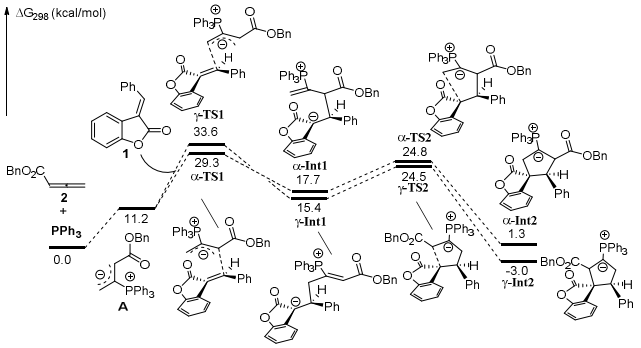
Scheme 5. Plausible Mechanism for Phosphine-catalyzed [3+2] Cycloaddition.

The possible transition state of this asymmetric [3+2] cycloaddition is illustrated in Scheme 6 which may account for the stereochemical outcomes. The zwitterionic intermediate[2s, 17] derived from chiral phosphine and allenoate could approach to benzofuranone **1** through either *Re* face or *Si* face. Presumably, due to the steric reasons, the zwitterionic intermediate (R^3 = H) is more favored to attack benzofuranone **1** from *Si* face to give the corresponding product (Scheme 6, left); however, the zwitterionic intermediate (R^3 = Ph or Me) is more favored to attack benzofuranone **1** from *Re* face to afford the corresponding product (Scheme 6, right).

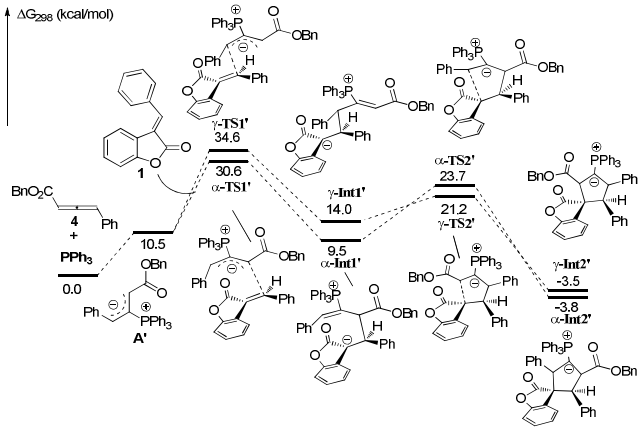


Scheme 6. Plausible Transition States of γ-Addition and α-Addition

In order to understand the regiochemical outcome of this reaction, we have done theoretical investigations on this [3+2] cycloaddition. All calculations have been performed at mPW1K/6-31G(d) level with Gaussian 09 program (see the Supporting Information). The calculation results indicated that the cycloaddition process is stepwise, which agrees with previous theoretical studies by Yu group.[17] *For allenoate **2** (R^3 = H), two intermediates γ-**INT1** and γ-**INT2** in the γ-addition mode are thermodynamically more favorable than those intermediates in the α-addition mode, which may account for why γ-addition adducts were experimentally obtained as the major products. In contrast, using allenoate **4** (R^3 = Ph) as a substrate, the energies of intermediates γ-**INT1'** and γ-**INT2'** in the γ-addition mode are higher than those of α-**INT1'** and α-**INT2'** in the α-addition mode, probably due to the steric hindrance between the R^3 substituents and benzofuranone in intermediates γ-**INT1'** and γ-**INT2'**. Thus, the α-addition mode is more favorable in this case (see Scheme 7 and Scheme 8). All of these DFT calculations have been summarized in the Supporting Information.*



Scheme 7. Theoretical Investigations on Phosphine-catalyzed [3+2] Cycloaddition of **1** and **2**.



Scheme 8. Theoretical Investigations on Phosphine-catalyzed [3+2] Cycloaddition of **1** and **4**.

In summary, we reported the first example on the successful asymmetric and regioselective construction of 3,3'-spirocyclopentenebenzofunanones catalyzed by chiral phosphine (*R*-SITCP) by employing benzofunanone and two types of allenic esters. Under the present catalytic system, γ-addition products and α-addition products can be obtained in 48-99% yields with 87-99% ee values, 88:12->19:1 regioselective ratios and in 62-96% yields with 85-99% ee values, 84:16->19:1 regioselective ratios, respectively. Moreover, this catalytic asymmetric [3+2] system can be also applied in the regioselective construction of spiro-oxindoles **7** and **8** as well as spiro-azlactone **10** which can be easily transformed to aspartic acid analogues.[18] The DFT studies disclosed the origins of regioselective outcomes for this phosphine-catalyzed [3+2] reaction. Further application of this type of reaction for synthesis of more natural and natural-like spiro-compounds is ongoing.

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21421091, 21372250, 21121062, 21302203, 20732008, and 21572052).

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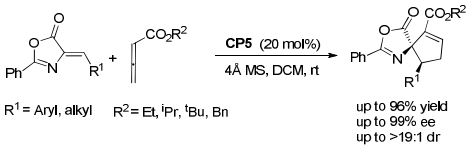
As for alkylidene azlactone, γ-attack initiated asymmetric [3+2] cycloaddition with **CP5** has been reported before (see Ref. 13e).



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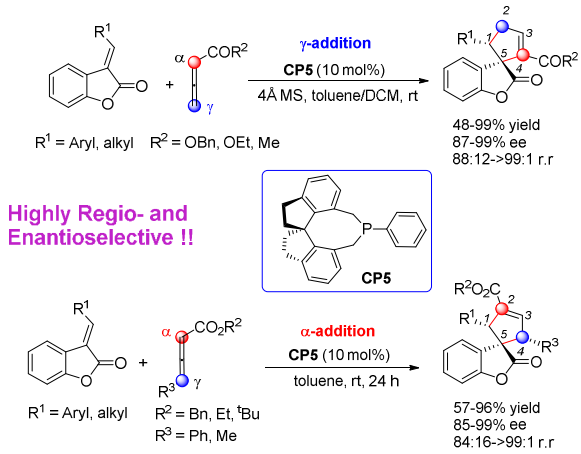
[19] CCDC 961159; CCDC 967550; CCDC 1010550; **3m**, **5j**, **7b** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Chiral Phosphine-Catalyzed Tunable Cycloaddition Reactions of Allenoates with Benzofuranon Derived Olefins for Highly Regio-, Diastereo- and Enantioselective Synthesis of Spiro-Benzofuranones



The first regioselectively catalytic asymmetric [3+2] cycloadditions of benzofuranone derived olefins with allenoate and substituted allenoates have been developed in the presence of (*R*)-SITCP, affording different functionalized 3-spirocyclopentene benzofuran-2-ones in good yields with high enantioselectivities.

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