Chiral phosphine-catalyzed tunable cycloaddition reactions of allenoates with benzofuranone-derived olefins for a highly regio-, diastereo- and enantioselective synthesis of spiro-benzofuranones†

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Phosphine-catalyzed [3 + 2] cycloaddition of electron-deficient olefins with allenoates, which provides alternative access to a variety of useful carbocycles, was first reported by Zhang and Lu in 1995. Pioneering work on the catalytic asymmetric Lu’s [3 + 2] cycloaddition of allenoates with olefins was disclosed by Zhang in 1997. No further progress was made on the development of this enantioselective [3 + 2] cyclization for about a decade after Zhang’s promising results, until Fu and co-workers recently developed a series of axially chiral binaphthyl frameworks containing phosphines that catalyzed the asymmetric cycloaddition of allenoates with electron-deficient olefins, affording the corresponding cycloadducts in good yields with excellent diastereo- and enantioselectivities. 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. A variety of multifunctional chiral phosphines derived from natural amino acids have also emerged as powerful catalysts to promote the [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. For example, Miller and co-workers achieved the enantioselective cyclization of allenoates and enones using phosphines containing α-amino acids. Jacobsen and co-workers utilized phosphine–thiourea catalysts for enantioselective annihilations of allenes and imines. Zhao and Lu 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. Recently, Kwon’s group developed a new class of rigid chiral bicyclic phosphines and applied them to the asymmetric synthesis of multi-substituted pyrrolines. In addition, some commercially available bidentate chiral phosphine-promoted [3 + 2] cycloadditions have also been reported. The phosphine-catalyzed [3 + 2] cycloaddition of electron-deficient olefins with allenoates was commonly considered to start from the formation of the corresponding zwitierionic intermediate I between PR3 and the allenoate. The nature of this zwitierionic 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 the 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 have made efforts to obtain both the α-addition and γ-addition isomers in a controllable way with high regio-, diastereo- and enantioselective values, not to mention the mechanistic study of the regioselectivity.
Benzofuranones as one of the important building blocks exist in a variety of natural products and potential medicines. The enantioselective synthesis of chiral benzofuranones remains a considerable challenge, especially in the field of construction of a chiral spiro-quaternary center at the C3 position of benzofuranones. As part of our ongoing investigation on phosphine-catalyzed asymmetric cycloaddition, we wish to report a spiro phosphine (R)-SITCP catalyzed asymmetric [3 + 2] cycloaddition of allenic esters with benzofuranones, furnishing the spiro cycloadducts in good yields with excellent regio-, diastereo- and enantioselectivities, by adjusting the substituents of the allenic esters to obtain both the α-addition and γ-addition products, and using rational DFT calculations to reveal the reason for the regioselectivity. This asymmetric [3 + 2] cycloaddition catalyzed by a chiral phosphine features the simultaneous formation of spiro-quaternary and tertiary sterocenters (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 have promising applications.

We initially screened a variety of chiral phosphines 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 the γ-addition product 3a as the main product and the α-addition product 3a’ as the minor product, which were obtained in 26–92% total yields, with the regioselectivity ratios (r.r.) of 3a : 3a’ from 86 : 14 to 95 : 5, and excellent diastereoselectivities (the minor diastereom almost could not be detected by 1H NMR); the ee value of the main product 3a is obtained from 8% to 99% ee values and 88 : 12 to 99% ee value in toluene, however, the reaction proceeded in DCM, diminishing the yield, r.r. and ee value significantly (Scheme 3, eqn (1)). Using γ-phenyl allenote 4a as the Michael acceptor, the reaction proceeded smoothly to give the α-addition product as the major product in 96% yield, with >19 : 1 r.r. and >99% ee value in tolune, the reactions proceeded in DCM, diminishing the yield, r.r. and ee value significantly (Scheme 3, eqn (2)).

Having identified the 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 is an electrondonor 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 to >99 : 1 r.r. (Table 2, entries 1–9). In the case of 4-CF3C6H4 benzofuranone 1e, the regioselectivity ratio decreased to 88 : 12 room temperature for 12 h in 78% yield with >19 : 1 r.r. and 99% ee value, which served as the best reaction conditions for this reaction (Scheme 3, eqn(1)). Using γ-phenyl allenote 4a as the Michael acceptor, the reaction proceeded smoothly to give the α-addition product as the major product in 96% yield, with >19 : 1 r.r. and 99% ee value in toluene, however, the reaction proceeded in DCM, diminishing the yield, r.r. and ee value significantly (Scheme 3, eqn (2)).

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.ᵃ</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Yieldb (%)</th>
<th>r.r.c (3a : 3a’)</th>
<th>ee (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>CP1</td>
<td>Toluene</td>
<td>25</td>
<td>37</td>
<td>90 : 10</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>CP2</td>
<td>Toluene</td>
<td>25</td>
<td>32</td>
<td>88 : 12</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>CP3</td>
<td>Toluene</td>
<td>25</td>
<td>26</td>
<td>86 : 14</td>
<td>14</td>
</tr>
<tr>
<td>4ᵇ</td>
<td>CP4</td>
<td>Toluene</td>
<td>25</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>CP5</td>
<td>Toluene</td>
<td>25</td>
<td>92</td>
<td>96 : 4</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>CP6</td>
<td>Toluene</td>
<td>25</td>
<td>72</td>
<td>95 : 5</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>CP7</td>
<td>Toluene</td>
<td>25</td>
<td>74</td>
<td>94 : 6</td>
<td>88</td>
</tr>
<tr>
<td>8</td>
<td>CP8</td>
<td>Toluene</td>
<td>25</td>
<td>Trace</td>
<td>92 : 8</td>
<td>13</td>
</tr>
<tr>
<td>9</td>
<td>CP5</td>
<td>DCM</td>
<td>25</td>
<td>58</td>
<td>&gt;19 : 1</td>
<td>&gt;99</td>
</tr>
<tr>
<td>10</td>
<td>CP5</td>
<td>THF</td>
<td>25</td>
<td>47</td>
<td>94 : 6</td>
<td>93</td>
</tr>
<tr>
<td>11</td>
<td>CP5</td>
<td>CH₂CN</td>
<td>25</td>
<td>22</td>
<td>72 : 28</td>
<td>94</td>
</tr>
<tr>
<td>12</td>
<td>CP5</td>
<td>Toluene/DCM</td>
<td>25</td>
<td>85</td>
<td>&gt;19 : 1</td>
<td>91</td>
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<tr>
<td>13</td>
<td>CP5</td>
<td>Toluene/DCM</td>
<td>25</td>
<td>64</td>
<td>&gt;19 : 1</td>
<td>98</td>
</tr>
<tr>
<td>14</td>
<td>CP5</td>
<td>Toluene/DCM</td>
<td>25</td>
<td>78</td>
<td>&gt;19 : 1</td>
<td>99</td>
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<tr>
<td>15</td>
<td>CP5</td>
<td>Toluene/DCM</td>
<td>0</td>
<td>53</td>
<td>&gt;19 : 1</td>
<td>99</td>
</tr>
</tbody>
</table>

ᵃ All reactions were carried out with 1a (0.1 mmol), 2a (0.15 mmol), and catalyst (10 mol%) in solvent (1.0 mL). b Isolated yield. c Determined using 1H NMR of the crude product; determined using HPLC. d Disordered. e Toluene/DCM = 4 : 1. f Toluene/DCM = 1 : 1. g Toluene/DCM = 1 : 1, 4 Å MS (30 mg) was added as the additive.
regioselectivity ratio (Table 2, entry 13). Other electron deficient allenes such as ethyl-2,3-butanedioate and penta-3,4-dien-2-one 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 using X-ray diffraction as 1S, 5R. The ORTEP drawing and the CIF data are summarized in the ESI.†

We next attempted to examine the asymmetric α-addition [3 + 2] cycloaddition reactions of the benzofuranones 1 and the γ-substituted allenones 4 (Table 3). As for substrate 1b, product 5b was obtained in 91% yield, along with 84 : 16 r.r. and an 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 regioselectivity ratios (Table 3, entries 5–12). The aliphatic group is also suitable for this reaction (Table 3, entry 13). Some other alkenyl esters such as ethyl-, tert-butyl-4-phenylbuto-2,3-dienoates or benzyl penta-

\[
\begin{array}{ccccccc}
\text{Entry} & 1 (R^1) & 2 (R^2) & \text{Yield}^b (\%) & \text{r.r.}^c & \text{ee} (\%)^d \\
1 & 1b & (4-BrC_6H_4) & 2a (OBn) & 3b: 92 & >99 : 1 & 95 \\
2 & 1c & (4-CH_3C_6H_4) & 2a (OBn) & 3c: 76 & 92 : 8 & 91 \\
3 & 1d & (4-CH_3OC_6H_4) & 2a (OBn) & 3d: 72 & 98 : 2 & 96 \\
4 & 1e & (4-CF_3C_6H_4) & 2a (OBn) & 3e: 87 & 88 : 12 & 91 \\
5 & 1f & (4-FC_6H_4) & 2a (OBn) & 3f: 67 & 98 : 2 & 94 \\
6 & 1g & (4-CNCC_6H_4) & 2a (OBn) & 3g: 57 & 92 : 8 & 88 \\
7 & 1h & (3,4-Cl_2C_6H_3) & 2a (OBn) & 3h: 82 & 92 : 8 & 90 \\
8 & 1i & (C_6H_5) & 2a (OBn) & 3i: 79 & 98 : 2 & 94 \\
9 & 1j & (4-PhC_6H_4) & 2a (OBn) & 3j: 76 & >99 : 1 & 96 \\
10 & 1k & (2-furyl) & 2a (OBn) & 3k: 48 & 95 : 5 & 96 \\
11 & 1l & (2-thienyl) & 2a (OBn) & 3l: 67 & 90 : 10 & 93 \\
12 & 1m & (1-naphthyl) & 2a (OBn) & 3m: 99 & 97 : 3 & 99 \\
13 & 1n & (cyclohexyl) & 2a (OBn) & 3n: 68 & 98 : 2 & 95 \\
14 & 1a & (2-BrC_6H_4) & 2b (OEt) & 3o: 94 & >99 : 1 & 99 \\
15 & 1a & (2-BrC_6H_4) & 2c (Me) & 3p: 83 & >99 : 1 & 96 \\
\end{array}
\]

\(a\) The reactions were carried out with 1 (0.1 mmol), 2a (0.15 mmol), CP5 (0.01 mmol) and 4 Å MS (30 mg) in DCM (0.5 mL) and toluene (0.5 mL) at rt for 12 h. Unless otherwise mentioned, the compounds were 1-E-isomers. Isolated yield using column chromatography. Regioselectivity ratios determined using crude \(^1\)H NMR spectroscopy; r.r. = regioselectivity ratio. Determined using chiral HPLC analysis. The absolute configuration of 3m has been determined using X-ray diffraction as (1S, 5R). Compound 1n was the mixture of Z and E isomers, Z/E = 1/1 based on \(^1\)H NMR analysis.

\[
\begin{array}{ccccccc}
\text{Entry} & 1 (R^1) & 4 (R^2) & \text{Yield}^b (\%) & \text{r.r.}^c & \text{ee} (\%)^d \\
1 & 1a & (2-BrC_6H_4) & 4a (Bn/Ph) & 5a: 96 & >99 : 1 & 95 \\
2 & 1b & (4-BrC_6H_4) & 4a (Bn/Ph) & 5b: 91 & 84 : 16 & 85 \\
3 & 1c & (4-CH_3C_6H_4) & 4a (Bn/Ph) & 5c: 72 & 92 : 8 & 99 \\
4 & 1d & (4-CH_3OC_6H_4) & 4a (Bn/Ph) & 5d: 60 & 98 : 2 & 96 \\
5 & 1e & (4-F_2C_6H_4) & 4a (Bn/Ph) & 5e: 92 & 99 : 1 & 92 \\
6 & 1f & (4-FC_6H_4) & 4a (Bn/Ph) & 5f: 78 & 95 : 5 & 99 \\
7 & 1g & (4-CNCC_6H_4) & 4a (Bn/Ph) & 5g: 75 & >99 : 1 & 91 \\
8 & 1h & (3,4-Cl_2C_6H_3) & 4a (Bn/Ph) & 5h: 82 & >92 : 8 & 99 \\
9 & 1i & (C_6H_5) & 4a (Bn/Ph) & 5i: 86 & >99 : 1 & 99 \\
10 & 1j & (4-PhC_6H_4) & 4a (Bn/Ph) & 5j: 83 & >99 : 1 & 99 \\
11 & 1k & (2-furyl) & 4a (Bn/Ph) & 5k: 77 & >99 : 1 & 99 \\
12 & 1m & (1-naphthyl) & 4a (Bn/Ph) & 5l: 73 & >99 : 1 & 90 \\
13 & 1n & (cyclohexyl) & 4a (Bn/Ph) & 5m: 92 & >99 : 1 & 99 \\
14 & 1c & (4-CH_3C_6H_4) & 4b (Et/Ph) & 5n: 67 & 95 : 5 & 90 \\
15 & 1c & (4-CH_3C_6H_4) & 4c (Bu/Ph) & 5o: 83 & >99 : 1 & 97 \\
16 & 1c & (4-CH_3C_6H_4) & 4d (Bn/Me) & 5p: 62 & 95 : 5 & 94 \\
\end{array}
\]

\(a\) The reactions were carried out with 1a (0.1 mmol), 2a (0.12 mmol), and CP5 (0.01 mmol) in toluene (1.0 mL) at rt for 24 h. Unless otherwise mentioned, the compounds were 1-E-isomers. Isolated yield using column chromatography. Regioselectivity ratios determined using crude \(^1\)H NMR spectroscopy; r.r. = regioselectivity ratios. Determined using chiral HPLC analysis. The absolute configuration of 5j has been determined using X-ray diffraction as (1R, 4R, 5R). Compound 1n was a mixture of Z and E isomers, Z/E = 1/1 based on \(^1\)H NMR analysis.
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 to >99 : 1 regioselectivities (Table 3, entries 14–16). The absolute configuration of 5j has been assigned using X-ray diffraction as 1R, 4R, 5R. The ORTEP drawing and the CIF data are summarized in the ESI.

It is noteworthy that this catalytic system can also be applied in the regioselective construction of spiroindolines\(^5\text{h},6\text{a},15\) in good yields, with high ee values and high regioselectivities (Scheme 4, eqn [1] and eqn [2]). The \(\gamma\)-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 \(\alpha\)-addition [3 + 2] cycloadduct 8a was formed in 89% yield, 99% ee value and 95 : 5 r.r. The enantiomeric approach for the construction of spirocyclic oxindolic cyclopentanes based on a phosphate-mediated \(\gamma\)-addition has been reported by Marini- tti’s group.\(^5\text{h}\) Furthermore, the preparations of carbocyclic amino acids have received great attention in medicinal chemistry recently due to their unique biological activities.\(^3\text{e},16\) As illustrated in Scheme 4 (eqn [3]), the spiro-cycloadduct 10a was obtained in 87% yield with a >99% ee value and a high regioselectivity using alkyldiene azlactone 9a (1.0 mmol) and the substituted allenolate 4a (1.5 mmol) as the 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 \(\alpha\)-amino acid product 11 was easily obtained via treatment with 6 M HCl in high yield without the ee value diminishing (Scheme 4, eqn [3]).

The plausible mechanisms for this phosphine-catalyzed [3 + 2] cycloaddition have been proposed in Scheme 5 on the basis of our experiments and previous literature.\(^1,2\) The reaction starts from the formation of a zwitterionic intermediate A between the allenolate (2 or 4) and phosphate. Intermediate A acts as a 1,3-dipole and undergoes a [3 + 2] cycloaddition with benzofuranone 1 to give a phosphorus ylide B via \(\gamma\)-addition or D via \(\alpha\)-addition. For allenolate 2 (R^3 = H), \(\gamma\)-addition is the main pathway. In contrast, allenolate 4 (R^3 = aryl or alkyl group) mainly undergoes \(\alpha\)-addition. Then, an intramolecular\(^{12}\) proton transfer is speculated to convert the phosphorus ylide B or D to another zwitterionic intermediate C or E, which, upon elimination of the phosphate catalyst, gives rise to the final cycloadduct 3 or 5.

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

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 the mPW1K/6-31G(d) level with the Gaussian 09 program (see the ESI†). The calculation results indicated that the cycloaddition process is stepwise, which agrees with the previous theoretical studies by Yu’s group.\(^17\) For allenolate 2 (R^3 = H), two intermediates, \(\gamma\)-INT1 and \(\gamma\)-INT2, in the \(\gamma\)-addition mode are thermodynamically more favorable than those intermediates in the \(\alpha\)-addition mode, which may account for why the \(\gamma\)-addition adducts were experimentally obtained as the major products. In

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**Scheme 4** Further applications and transformations.

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**Scheme 5** Plausible mechanism for the phosphine-catalyzed [3 + 2] cycloaddition.

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**Scheme 6** Plausible transition states of the \(\gamma\)-addition and \(\alpha\)-addition.
contrast, using allenoate 4 ($R^1 = \text{Ph}$) as a substrate, the energies of the intermediates $\gamma$-INT1 and $\gamma$-INT2 in the $\gamma$-addition mode are higher than those of $\alpha$-INT1 and $\alpha$-INT2 in the $\alpha$-addition mode, probably due to the steric hindrance between the $R^1$ substituents and benzofuranone in the intermediates $\gamma$-INT1 and $\gamma$-INT2. Thus, the $\alpha$-addition mode is more favorable in this case (see Schemes 7 and 8). All of these DFT calculations have been summarized in the ESI.†

In summary, we have reported the first example of the successful asymmetric and regioselective construction of 3,3'-spirocyclopentenebenzofuranones catalyzed by a chiral phosphine (K-SITCP) by employing benzofuranone and two types of allenic esters. Under the present catalytic system, $\gamma$-addition products and $\alpha$-addition products can be obtained in 48–99% yields with 87–99% ee values and 88 : 12 to $>19$ : 1 regioselectivity ratios and in 62–96% yields with 85–99% ee values and 84 : 16 to $>19$ : 1 regioselectivity 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 spiroazlactone 10 which can be easily transformed to aspartic acid analogues. The DFT studies disclosed the origins of the regioselective outcomes for this phosphine-catalyzed [3 + 2] reaction. Further application of this type of reaction for the synthesis of more natural and natural-like spiro-compounds is ongoing.

Acknowledgements

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Notes and references


16 For selected examples see: (a) B. M. Trost and P. J. Morris, *Angew. Chem., Int. Ed.*, 2011, 50, 6167; (b) D. Uraguchi, K. Yoshika, Y. Ueki and T. Ooi, *J. Am. Chem. Soc.*, 2012, 134, 19370; for alkylidene azlactone, the \( \gamma \)-attack that initiated the asymmetric [3 + 2] cycloaddition with CP5 has been reported before (see ref. 13e).


19 ESI†