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# Design, synthesis and application of a new type of bifunctional Le-Phos in highly enantioselective $\gamma$ -addition reactions of N-centered nucleophiles to allenates†

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A novel class of cyclic phosphine derived bifunctional catalysts (**Le-Phos**) is reported, which can be readily prepared from inexpensive and commercially available starting materials and exhibit good performances in enantioselective  $\gamma$ -addition reactions of N-centered nucleophiles and allenates under mild conditions. The salient features of this reaction include high product yields, good enantioselectivity, mild reaction conditions, and broad substrate scope and gram-scale scalability.

## Introduction

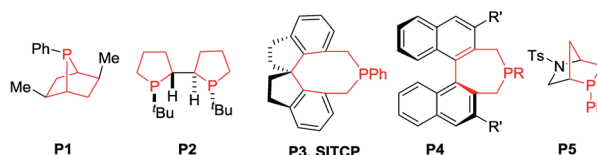
Over the past few years, asymmetric phosphine-catalyzed reactions have emerged as powerful and versatile tools for the construction of C–C and C–X bonds,<sup>1</sup> which relies very much on the evolution of various new chiral phosphine catalysts.<sup>2</sup> There are mainly two types of chiral phosphine catalysts developed: highly nucleophilic monofunctional phosphine catalysts such as cyclic phosphines **P1–P5** (Fig. 1, Type 1) and diphenylphosphine-derived bifunctional catalysts bearing a hydrogen donor such as **P6–P9** (Fig. 1, Type 2). Both displayed good catalytic activities and were effective in enantiomeric control in asymmetric phosphine catalysis.<sup>1a,g,3</sup> Recently, we developed several novel diphenylphosphine-derived bifunctional phosphines from commercially available chiral sulfonamide.<sup>4</sup> To further advance a new catalyst design, we aimed to combine the advantages of the aforementioned two types of phosphine catalysts, thus developing a novel bifunctional cyclic phosphine catalyst. We report herein the design and synthesis of **Le-Phos**, and its application in highly enantioselective phosphine catalyzed  $\gamma$ -addition of N-centered nucleophiles to allenates.

## Results and discussion

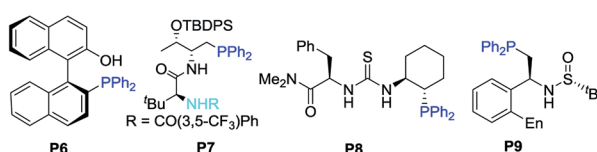
Fortunately, we found that **Le-Phos** could be easily prepared from commercially available inexpensive *tert*-butylsulfonamide,

### Previous work

#### Type 1: Cyclic phosphine as monofunctional catalysts



#### Type 2: Diphenyl phosphine derived bifunctional catalysts



#### Type 3: Bifunctional cyclic phosphine catalysts (This work)

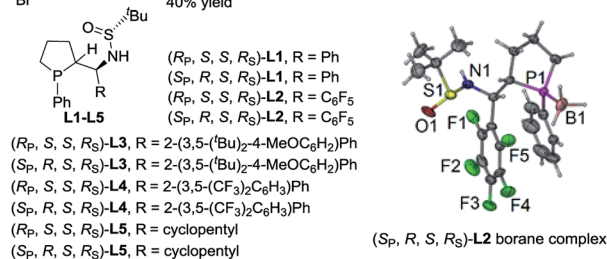
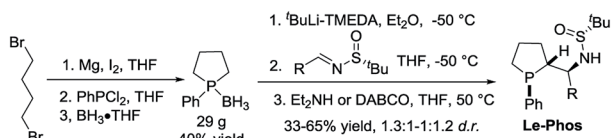
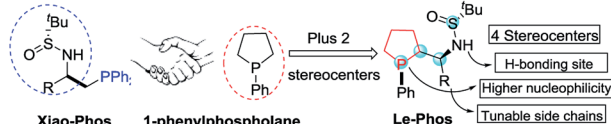


Fig. 1 Different types of chiral phosphine catalysts.

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aldehyde and 1-phenylphospholane borane complexes in simple steps. Treatment of 1-phenylphospholane borane complexes<sup>5</sup> with <sup>t</sup>BuLi in the presence of TMEDA at  $-50\text{ }^{\circ}\text{C}$  for 4 h gave the lithium intermediate, which added to chiral (*R*<sub>S</sub>)-sulfinimines, furnishing a pair of major diastereomers of **Le-Phos** **L1–L5** in 33–65% total yields after removal of borane.<sup>6</sup> To our delight, these two major diastereoisomers could be separated by flash column chromatography on silica gel. The absolute configurations of (*R*<sub>P</sub>,*S*,*S*,*R*<sub>S</sub>)-**L2** and (*S*<sub>P</sub>,*R*,*S*,*R*<sub>S</sub>)-**L2** were established by single crystal X-ray diffraction analysis.<sup>7</sup>

Asymmetric phosphine-catalyzed  $\gamma$ -addition reactions of various nucleophiles to allenates have attracted much attention in the past few years.<sup>8–10</sup> In 1998, Zhang and co-workers reported the catalyzed asymmetric  $\gamma$ -addition of 1,3-dicarbonyl compounds to terminal allenates using bicyclic phosphine **P2** for the first time.<sup>9</sup> Furthermore, Fu, Jacobsen, Lu and our groups have successfully expanded the scope of nucleophiles such as alcohols, thiols, carbon, amides and ketimines by the employment of different types of phosphine catalysts.<sup>10</sup> The asymmetric  $\gamma$ -addition<sup>8–11</sup> of N-centered nucleophiles with *pK*<sub>a</sub> values between 8 and 10 (in H<sub>2</sub>O) to  $\gamma$ -substituted allenates has been only partially realized by the group of Jacobsen, in which **P8** was used as the catalyst.<sup>10m</sup> Very recently, Guo and coworkers successfully extended N-centered nucleophiles to pyrazoles and imidazoles with the use of (*S*)-SITCP and (*S*)-BINOL as cocatalysts.<sup>13</sup> However, there still lacks a robust catalyst system for the asymmetric  $\gamma$ -addition of various N-centered nucleophiles to allenates. For example, (*S*)-SITCP, **P8** and our developed Xiao-Phos **P9** could not yield satisfactory results for the asymmetric  $\gamma$ -addition of 2-oxazolidone **1a** to allenate **2a** (Table 1, entries 1–3). Interestingly, (*S*<sub>P</sub>,*R*,*S*,*R*<sub>S</sub>)-**L1–L4** showed much higher catalytic activity and much better enantioselectivity than their diastereoisomers (*R*<sub>P</sub>,*S*,*S*,*R*<sub>S</sub>)-**L1–L4** (Table 1, entries 4–11). To our delight, 54% yield of **3aa** with 97% ee and *E/Z* > 20 : 1 could be achieved with the use of (*S*<sub>P</sub>,*R*,*S*,*R*<sub>S</sub>)-**L4** (Table 1, entry 11). Due to the competitive isomerization and partial kinetic resolution,<sup>10f</sup> increasing allenate **2a** to two equivalents could improve the 68% yield (Table 1, entry 13). Changing the solvent from toluene to PhCF<sub>3</sub>, DCM and DCE led to around 90% yield with 96–97% ees (Table 1, entries 14–17).

Having identified the optimal reaction conditions, the substrate scope was then examined and it proved to be quite general (Scheme 1). Linear alkyl (**3ab–3ad**), branched alkyl (**3ae**), and various alkyl groups bearing functional groups such as phenyl (**3af**), esters (**3ag** and **3ak**), terminal alkenes and alkynyl (**3ah–3ai**), and halogen (**3aj**) were well tolerated and provided high levels of yields and enantioselectivities (94–98% ees). Cyclic alkyl groups such as cyclopentyl (**3al**), cyclohexyl (**3am**), and NPhth groups (**3an**) could also be well compatible, delivering the corresponding adducts in high yields with 95–96% ees. It seems that the ester moiety did not affect the reaction much, furnishing **3ao–3aq** in high yields with 93–97% ees and *E/Z* > 20 : 1.

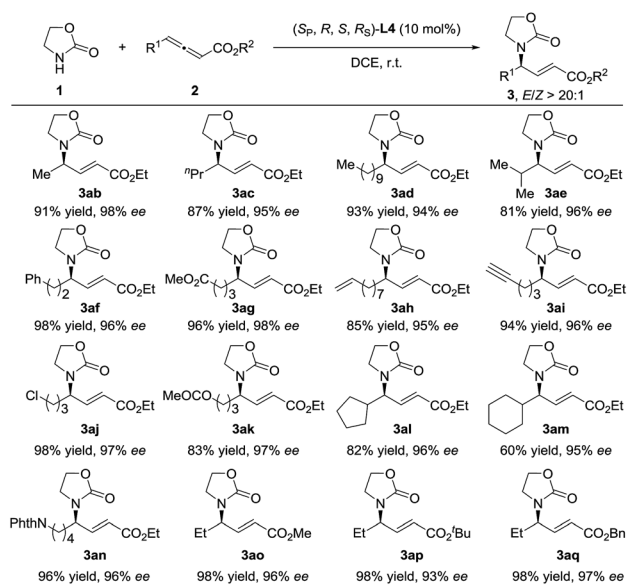
The reactions of chiral 2-oxazolidones also proceeded well, delivering **3ca–3ea** in satisfactory yields with high *des* and *E/Z* > 20 : 1 (Scheme 2). The addition of racemic 2-oxazolidone **1f** did

Table 1 Screening reaction conditions<sup>a</sup>

Entry	Catalyst	Solvent	<i>E/Z</i> <sup>b</sup>	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	( <i>S</i> )-SITCP	Toluene	5 : 1	39	87
2	<b>P8</b>	Toluene	4 : 1	11	72
3	<b>P9</b>	Toluene	2 : 1	21	57
4	( <i>R</i> <sub>P</sub> , <i>S</i> , <i>S</i> , <i>R</i> <sub>S</sub> )- <b>L1</b>	Toluene	3 : 1	7	19
5	( <i>R</i> <sub>P</sub> , <i>S</i> , <i>S</i> , <i>R</i> <sub>S</sub> )- <b>L2</b>	Toluene	—	NR	—
6	( <i>R</i> <sub>P</sub> , <i>S</i> , <i>S</i> , <i>R</i> <sub>S</sub> )- <b>L3</b>	Toluene	2 : 1	5	46
7	( <i>R</i> <sub>P</sub> , <i>S</i> , <i>S</i> , <i>R</i> <sub>S</sub> )- <b>L4</b>	Toluene	2 : 1	9	11
8	( <i>S</i> <sub>P</sub> , <i>R</i> , <i>S</i> , <i>R</i> <sub>S</sub> )- <b>L1</b>	Toluene	>20 : 1	40	86
9	( <i>S</i> <sub>P</sub> , <i>R</i> , <i>S</i> , <i>R</i> <sub>S</sub> )- <b>L2</b>	Toluene	>20 : 1	10	69
10	( <i>S</i> <sub>P</sub> , <i>R</i> , <i>S</i> , <i>R</i> <sub>S</sub> )- <b>L3</b>	Toluene	>20 : 1	46	97
11	( <i>S</i> <sub>P</sub> , <i>R</i> , <i>S</i> , <i>R</i> <sub>S</sub> )- <b>L4</b>	Toluene	>20 : 1	54	97
12 <sup>d</sup>	( <i>S</i> <sub>P</sub> , <i>R</i> , <i>S</i> , <i>R</i> <sub>S</sub> )- <b>L4</b>	Toluene	>20 : 1	60	97
13 <sup>e</sup>	( <i>S</i> <sub>P</sub> , <i>R</i> , <i>S</i> , <i>R</i> <sub>S</sub> )- <b>L4</b>	Toluene	>20 : 1	68	97
14 <sup>e</sup>	( <i>S</i> <sub>P</sub> , <i>R</i> , <i>S</i> , <i>R</i> <sub>S</sub> )- <b>L4</b>	Et <sub>2</sub> O	>20 : 1	60	97
15 <sup>e</sup>	( <i>S</i> <sub>P</sub> , <i>R</i> , <i>S</i> , <i>R</i> <sub>S</sub> )- <b>L4</b>	PhCF <sub>3</sub>	>20 : 1	90	97
16 <sup>e</sup>	( <i>S</i> <sub>P</sub> , <i>R</i> , <i>S</i> , <i>R</i> <sub>S</sub> )- <b>L4</b>	DCM	>20 : 1	89	96
17 <sup>e</sup>	( <i>S</i> <sub>P</sub> , <i>R</i> , <i>S</i> , <i>R</i> <sub>S</sub> )- <b>L4</b>	DCE	>20 : 1	90	97

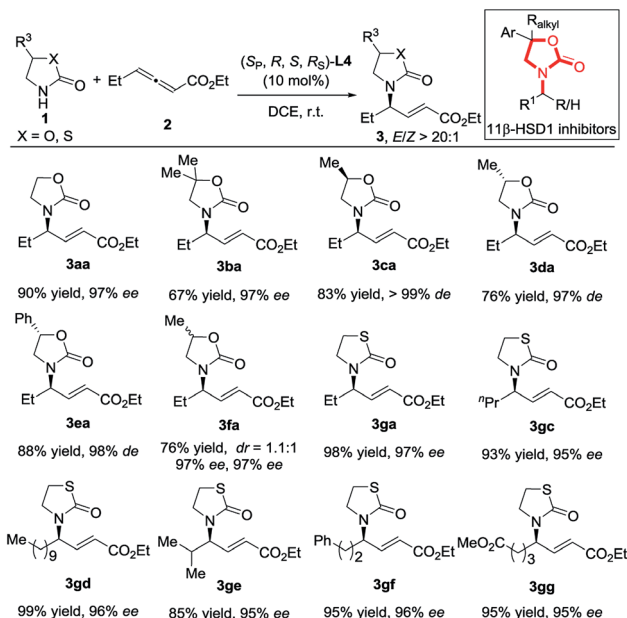
<sup>a</sup> Reaction conditions: **1a** (0.10 mmol), **2a** (0.12 mmol), and the catalyst (0.01 mmol) in toluene (1.5 mL) at room temperature. <sup>b</sup> NMR yield with the use of CH<sub>2</sub>Br<sub>2</sub> as the internal standard. <sup>c</sup> Determined by HPLC analysis on a chiral stationary phase. <sup>d</sup> Performed with **2a** (0.15 mmol). <sup>e</sup> Performed with **2a** (0.20 mmol). DCM = dichloromethane, DCE = 1,2-dichloroethane.

not show good diastereoselectivity but still delivered high enantioselectivity. Then, the reactions of thiazolidin-2-one (*pK*<sub>a</sub> ~ 12.8) with various allenates also proceeded smoothly, furnishing products **3ga** and **3gc–3gg** in 85–99% yields with 95–



Scheme 1 Investigation of the scope by variation of the allenate component.

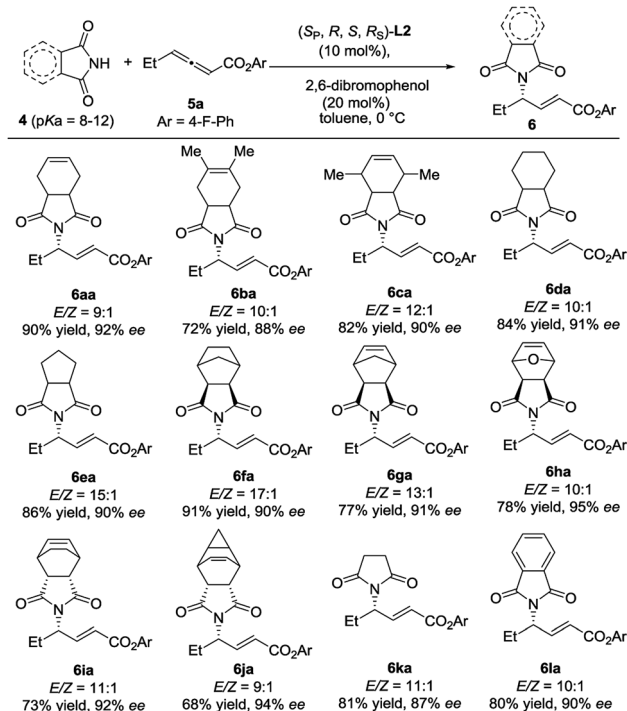




Scheme 2 Investigation of the scope by variation of 2-oxazolidone.

96% ees. It should be pointed out that these products share the same skeleton with patented 11 $\beta$ -HSD1 inhibitors (11 $\beta$ -hydroxysteroid dehydrogenase type 1 inhibitors).<sup>12</sup>

The scope of N-centered nucleophiles was then extended to much weak nucleophilic pyrrolidine-2,5-diones (Scheme 3). In this case, (*S*<sub>P</sub>,*R*,*S*,*R*<sub>5</sub>)-L2 was found to be the most efficient catalyst, indicating that the reaction is quite sensitive to the

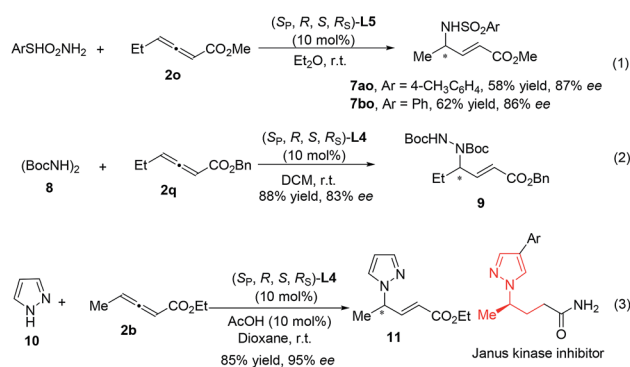


Scheme 3 Investigation of the scope of pyrrolidine-2,5-diones.

structure of N-centered nucleophiles, which further supports that the development of new catalysts with structural diversity is quite important. The reactions of various substituted pyrrolidine-2,5-diones with **5a** delivered the desired  $\gamma$ -addition adducts in 68–91% yields with 87–94% ees. The absolute configuration of **6ba** was established by single crystal X-ray diffraction analysis.<sup>7</sup> It is interesting to find that the absolute configuration of **6ba** is different from that of compound **3**; despite this, the catalysts have the same absolute configuration.

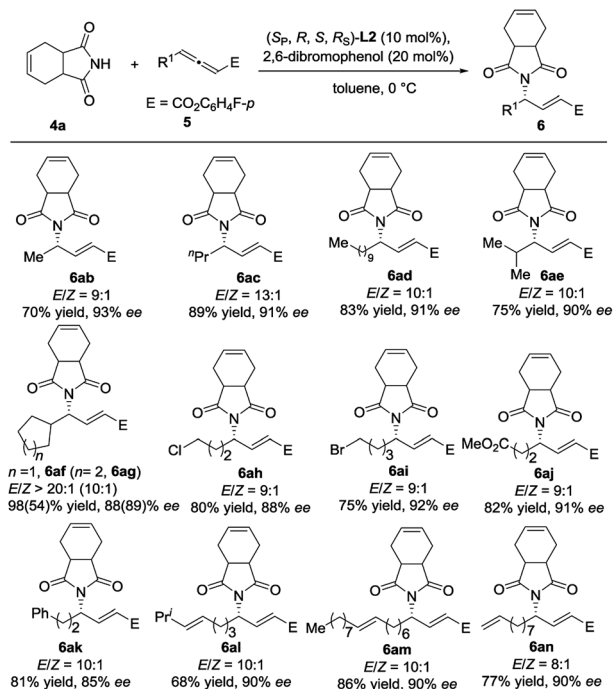
We next examined the reaction scope with respect to the allenolate component (Scheme 4). A variety of  $\gamma$ -substituted allenolates (**R**<sup>1</sup>) were applicable to this asymmetric  $\gamma$ -addition. In general, both linear and branched cycloalkyl groups at the  $\gamma$ -position were well tolerated. For example, allenolates **5b–5g** with various acyclic and cyclic alkyl groups at the  $\gamma$ -position could be well compatible, and the desired adducts were obtained in high yields with up to 93% ee. Satisfactorily, various functional groups such as halogens (**5h** and **5i**), ester (**5j**), phenyl (**5k**), and terminal and internal alkenes (**5l–5n**) were well tolerated and the desired adducts were obtained in moderate to good yields with up to 92% ee and >20 : 1 *E/Z* selectivity.

Additionally, the additions of TsNH<sub>2</sub> (*pK*<sub>a</sub> ~ 10.2), PhSO<sub>2</sub>NH<sub>2</sub> (*pK*<sub>a</sub> ~ 10.1), (BocNH)<sub>2</sub> (*pK*<sub>a</sub> ~ 8.7) and pyrazole (*pK*<sub>a</sub> ~ 2.5)<sup>13</sup> also proceeded smoothly under the catalysis of **Le-Phos** with different *R* groups (eqn (1)–(3)).

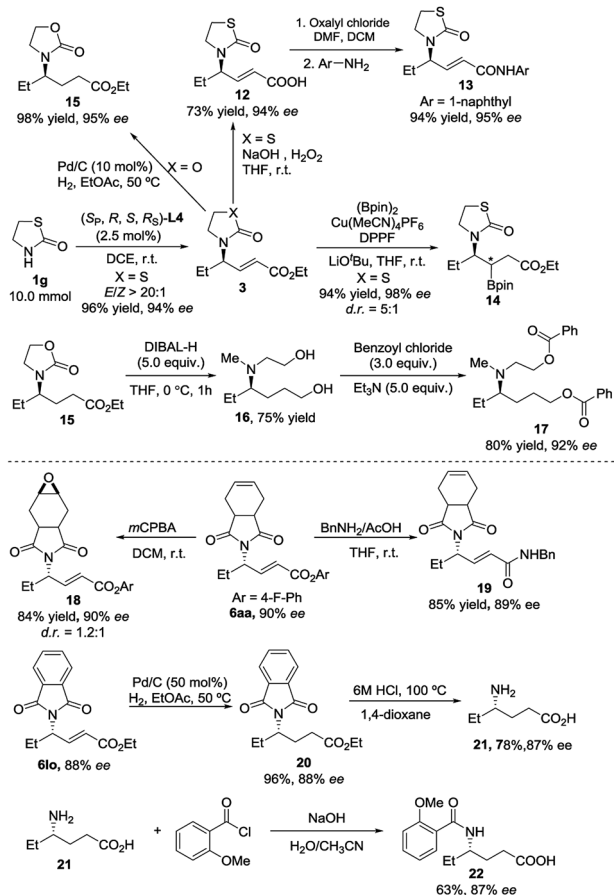


We were pleased to find that the desired product **3ga** could be obtained in 96% yield, 94% ee and *E/Z* > 20 : 1 with only 2.5 mol% catalyst loading on a 10 mmol scale (Scheme 5). The synthetic utilities of the representative product **3ga** were then showcased. The hydrolysis of the ester moiety was realized with NaOH/H<sub>2</sub>O<sub>2</sub><sup>14</sup> to give acid **12** in 73% yield without loss of enantioselectivity. The corresponding amide **13**<sup>7</sup> could be further delivered in 94% yield with 95% ee. The copper-catalyzed conjugate borylation of **3ga** proceeded smoothly at room temperature, furnishing the desired product **14** in 94% yield with 98% ee and 5 : 1 d.r.<sup>15</sup> Reduction of the double bond furnished the product **15** in 98% yield with 95% ee. Moreover, we could obtain an amino alcohol derivative **16** through reductive ring-opening of **15**, which afforded the diester **17** after further esterification. Furthermore, with the use of *m*CPBA,<sup>16</sup> the C–C double bond of **6aa** would undergo epoxidation to deliver the corresponding product **18** in good yield without loss of the enantioselectivity. The amidation reaction of **6aa** with BnNH<sub>2</sub>/AcOH<sup>17</sup> proceeded smoothly at room temperature,

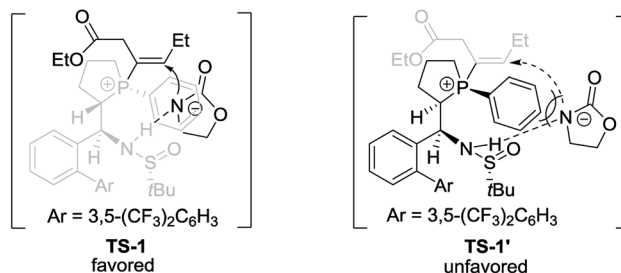




Scheme 4 Investigation of the scope by variation of the allenolate component.



Scheme 5 Elaboration of γ-addition adducts.



Scheme 6 Comparison of two transition states.

delivering the corresponding amide **19** in 85% yield with 89% ee. The reduction of the double bond of **6lo** was achieved *via* the Pd/C-catalyzed hydrogenation, furnishing product **20** in 96% yield without loss of the ee. The corresponding γ-aminoacid **21** was obtained in 78% yield by acidic deprotection.<sup>18</sup> Then, **21** was reacted with benzoyl chloride to deliver an amino acid derivative **22** in 63% yield with 87% ee.<sup>19</sup>

Based on the above experimental results and previous relevant studies, a possible transition state (**TS-1**) for  $(S_P, R, S, R_S)\text{-L4}$  and possible transition state (**TS-1'**) for  $(R_P, S, S, R_S)\text{-L4}$  to control stereoselectivity are proposed in Scheme 6. For the reaction using  $(S_P, R, S, R_S)\text{-L4}$  as the catalyst, the nucleophile and the double bond are located on the same side (transition state **TS-1**) *via* the hydrogen-bonding between nucleophiles and the NH moiety, which favors the formation of the *R*-enantiomer of **3**. In contrast, when  $(R_P, S, S, R_S)\text{-L4}$  was used as the catalyst, another transition state **TS-1'** was proposed, in which there may exist a steric repulsion between the phenyl linked to P and the nucleophile. Additionally, the nucleophile is located on different sides of the double bond and thus hindered the addition reaction to give the product in low yield and ee.

## Conclusions

In summary, we have developed a novel type of bifunctional chiral sulfinamide cyclic phosphine catalyst **Le-Phos**, which can be easily prepared on a gram scale from inexpensive commercially available starting materials in short steps.  $(S_P, R, S, R_S)\text{-Le-Phos}$  has shown excellent performance in the enantioselective γ-addition reactions of various N-centered nucleophiles to γ-substituted allenates, acquiring a series of γ-addition adducts in high yields with up to 98% ees and excellent regioselectivity and diastereoselectivity under mild conditions. Its prominent characteristics are general substrate scope, mild reaction conditions, good yields, high enantioselectivities, ease of scale-up to gram scale, and further synthetic transformations of products. Further explorations of **Le-Phos** as the organocatalyst and chiral ligand of transition metals in asymmetric catalysis are currently underway in our group and will be reported in due course.

## Conflicts of interest

There are no conflicts to declare.





## Acknowledgements

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- Other tiny diastereomers exist as a mixture and it is difficult to get clean NMR.
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