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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

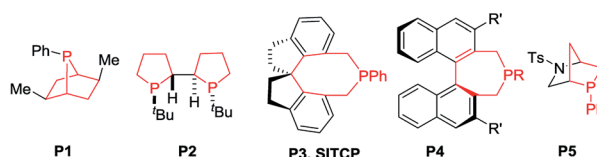
Over the past few years, asymmetric phosphine-catalyzed reactions have emerged as powerful and versatile tools for the construction of C–C and C–X bonds,<sup>1</sup> which relies very much on the evolution of various new chiral phosphine catalysts.<sup>2</sup> There are mainly two types of chiral phosphine 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

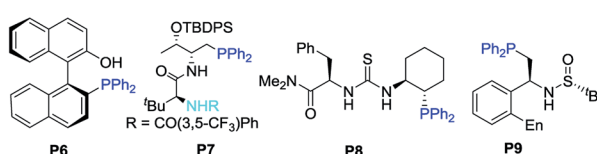
Fortunately, we found that **Le-Phos** could be easily prepared from commercially available inexpensive *tert*-butylsulfonamide,

### Previous work

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



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



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

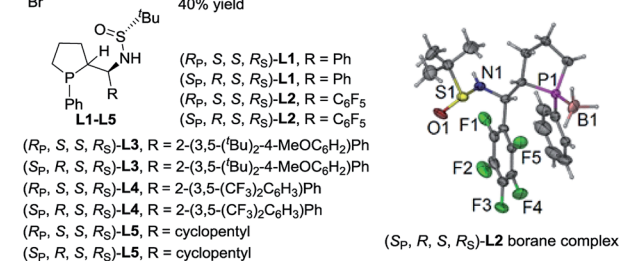
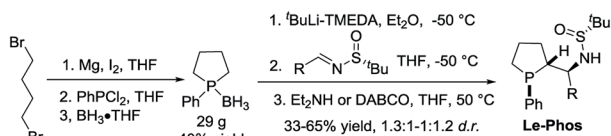
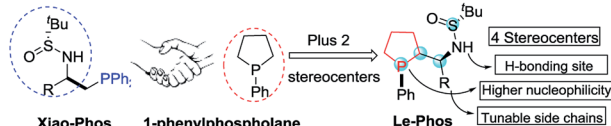


Fig. 1 Different types of chiral phosphine catalysts.

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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 °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<sub>S</sub>*,*R<sub>S</sub>*)-**L2** and (*S<sub>P</sub>*,*R<sub>S</sub>*,*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<sub>S</sub>*,*R<sub>S</sub>*)-**L1–L4** showed much higher catalytic activity and much better enantioselectivity than their diastereoisomers (*R<sub>P</sub>*,*S<sub>S</sub>*,*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<sub>S</sub>*,*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.

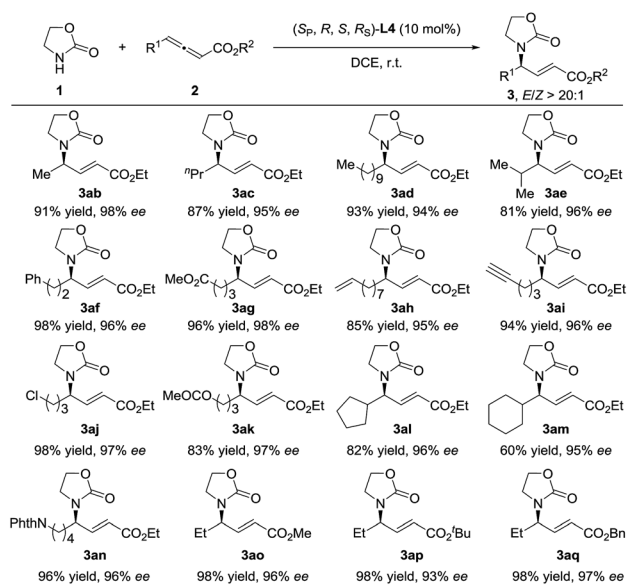
The reactions of chiral 2-oxazolidones also proceeded well, delivering **3ca–3ea** in satisfactory yields with high *des* and *E/Z* > 20 : 1 (Scheme 2). The addition of racemic 2-oxazolidone **1f** did

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<sub>P</sub></i> , <i>S<sub>S</sub></i> , <i>R<sub>S</sub></i> )- <b>L1</b> | Toluene           | 3 : 1                   | 7                      | 19                  |
| 5               | ( <i>R<sub>P</sub></i> , <i>S<sub>S</sub></i> , <i>R<sub>S</sub></i> )- <b>L2</b> | Toluene           | —                       | NR                     | —                   |
| 6               | ( <i>R<sub>P</sub></i> , <i>S<sub>S</sub></i> , <i>R<sub>S</sub></i> )- <b>L3</b> | Toluene           | 2 : 1                   | 5                      | 46                  |
| 7               | ( <i>R<sub>P</sub></i> , <i>S<sub>S</sub></i> , <i>R<sub>S</sub></i> )- <b>L4</b> | Toluene           | 2 : 1                   | 9                      | 11                  |
| 8               | ( <i>S<sub>P</sub></i> , <i>R<sub>S</sub></i> , <i>R<sub>S</sub></i> )- <b>L1</b> | Toluene           | >20 : 1                 | 40                     | 86                  |
| 9               | ( <i>S<sub>P</sub></i> , <i>R<sub>S</sub></i> , <i>R<sub>S</sub></i> )- <b>L2</b> | Toluene           | >20 : 1                 | 10                     | 69                  |
| 10              | ( <i>S<sub>P</sub></i> , <i>R<sub>S</sub></i> , <i>R<sub>S</sub></i> )- <b>L3</b> | Toluene           | >20 : 1                 | 46                     | 97                  |
| 11              | ( <i>S<sub>P</sub></i> , <i>R<sub>S</sub></i> , <i>R<sub>S</sub></i> )- <b>L4</b> | Toluene           | >20 : 1                 | 54                     | 97                  |
| 12 <sup>d</sup> | ( <i>S<sub>P</sub></i> , <i>R<sub>S</sub></i> , <i>R<sub>S</sub></i> )- <b>L4</b> | Toluene           | >20 : 1                 | 60                     | 97                  |
| 13 <sup>e</sup> | ( <i>S<sub>P</sub></i> , <i>R<sub>S</sub></i> , <i>R<sub>S</sub></i> )- <b>L4</b> | Toluene           | >20 : 1                 | 68                     | 97                  |
| 14 <sup>e</sup> | ( <i>S<sub>P</sub></i> , <i>R<sub>S</sub></i> , <i>R<sub>S</sub></i> )- <b>L4</b> | Et <sub>2</sub> O | >20 : 1                 | 60                     | 97                  |
| 15 <sup>e</sup> | ( <i>S<sub>P</sub></i> , <i>R<sub>S</sub></i> , <i>R<sub>S</sub></i> )- <b>L4</b> | PhCF <sub>3</sub> | >20 : 1                 | 90                     | 97                  |
| 16 <sup>e</sup> | ( <i>S<sub>P</sub></i> , <i>R<sub>S</sub></i> , <i>R<sub>S</sub></i> )- <b>L4</b> | DCM               | >20 : 1                 | 89                     | 96                  |
| 17 <sup>e</sup> | ( <i>S<sub>P</sub></i> , <i>R<sub>S</sub></i> , <i>R<sub>S</sub></i> )- <b>L4</b> | DCE               | >20 : 1                 | 90                     | 97                  |

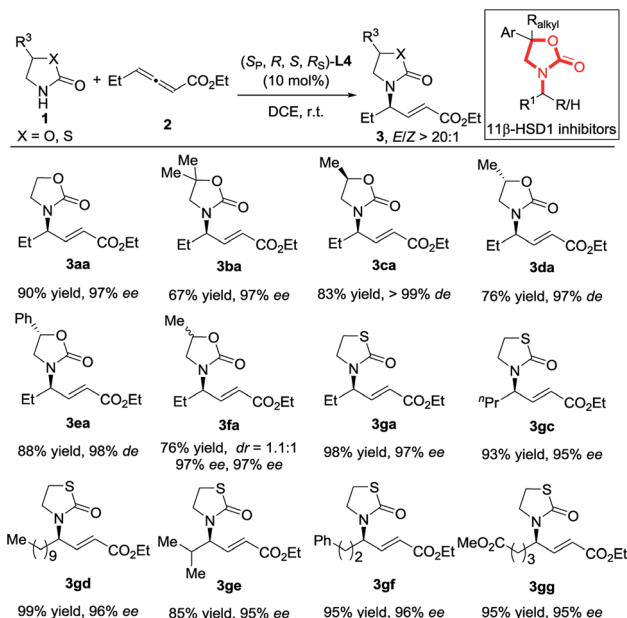
<sup>a</sup> Reaction conditions: **1a** (0.10 mmol), **2a** (0.12 mmol), and the catalyst (0.01 mmol) in toluene (1.5 mL) at room temperature. <sup>b</sup> NMR yield with the use of CH<sub>2</sub>Br<sub>2</sub> as the internal standard. <sup>c</sup> Determined by HPLC analysis on a chiral stationary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

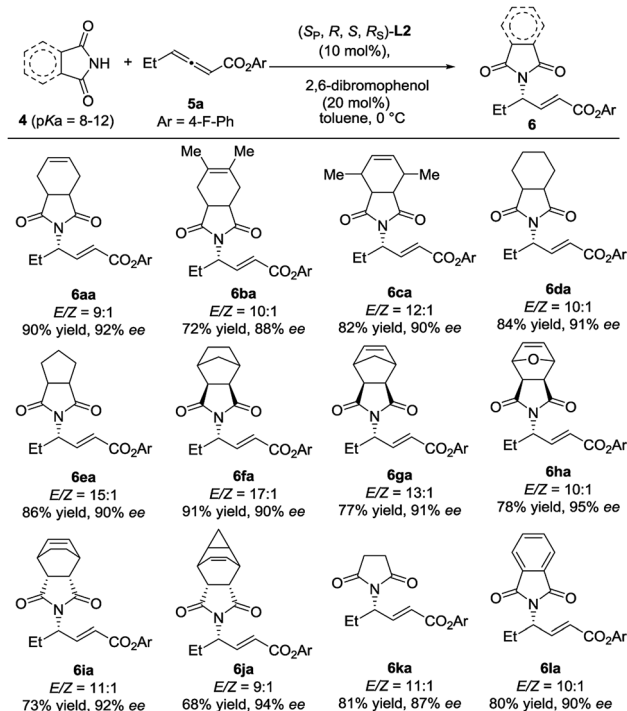




Scheme 2 Investigation of the scope by variation of 2-oxazolidone.

96% ees. It should be pointed out that these products share the same skeleton with patented 11β-HSD1 inhibitors (11β-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>S</sub>*)-L2 was found to be the most efficient catalyst, indicating that the reaction is quite sensitive to the

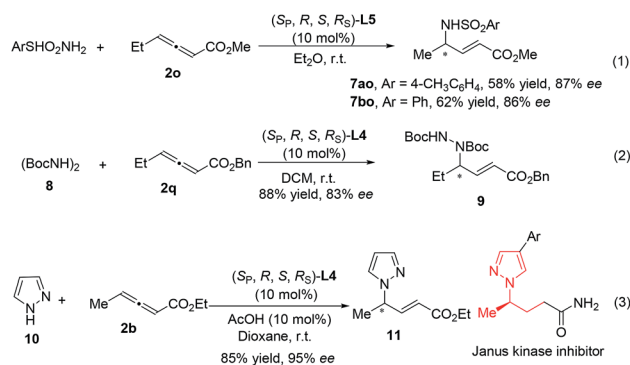


Scheme 3 Investigation of the scope of pyrrolidine-2,5-diones.

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 γ-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.

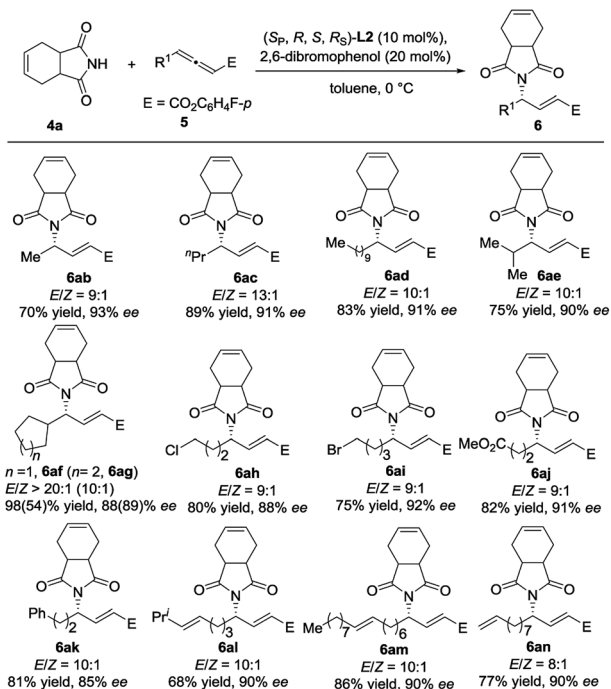
We next examined the reaction scope with respect to the allenolate component (Scheme 4). A variety of γ-substituted allenolates (*R*<sup>1</sup>) were applicable to this asymmetric γ-addition. In general, both linear and branched cycloalkyl groups at the γ-position were well tolerated. For example, allenolates **5b–5g** with various acyclic and cyclic alkyl groups at the γ-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)).

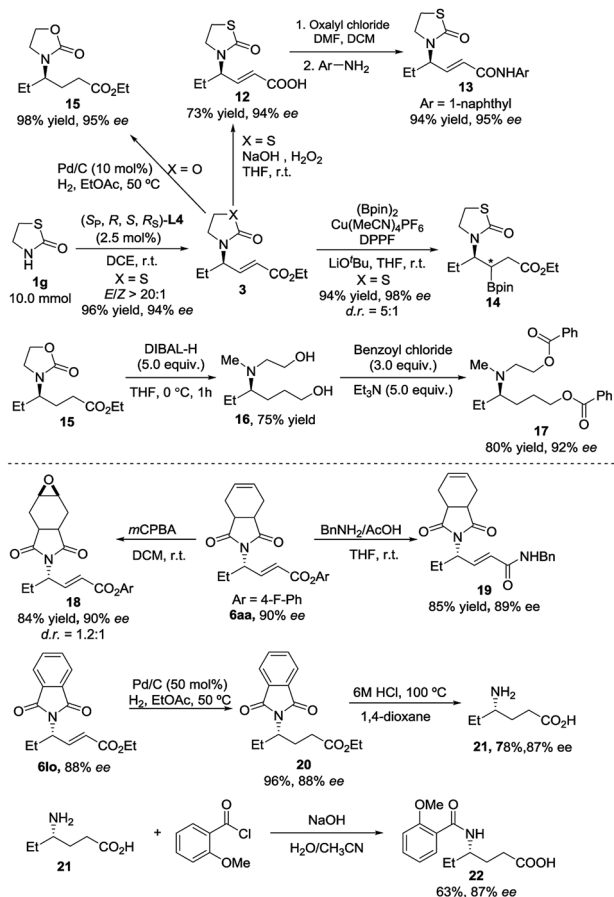


We were pleased to find that the desired product **3ga** could be obtained in 96% yield, 94% ee and *E/Z* > 20 : 1 with only 2.5 mol% catalyst loading on a 10 mmol scale (Scheme 5). The synthetic utilities of the representative product **3ga** were then showcased. The hydrolysis of the ester moiety was 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,

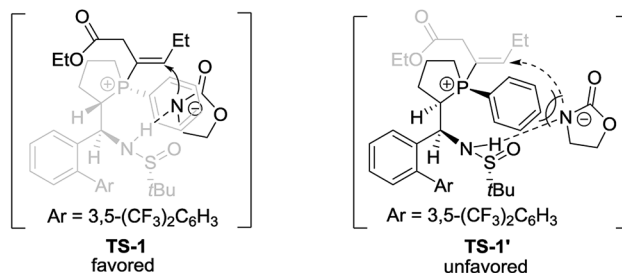




Scheme 4 Investigation of the scope by variation of the allenolate component.



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-amino acid **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 (Sp,R,S,Rs)-L4 and possible transition state (TS-1') for (Rp,S,S,Rs)-L4 to control stereoselectivity are proposed in Scheme 6. For the reaction using (Sp,R,S,Rs)-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 (Rp,S,S,Rs)-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. (Sp,R,S,Rs)-**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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## Notes and references

- For reviews containing the construction of C–C and C–X bonds by phosphines, see: (a) Y. Xiao, Z. Sun, H. Guo and O. Kwon, *Beilstein J. Org. Chem.*, 2014, **10**, 2089; (b) W. Li and J. Zhang, *Chem. Soc. Rev.*, 2016, **45**, 1657; (c) T. Wang, X. Han, F. Zhong, W. Yao and Y. Lu, *Acc. Chem. Res.*, 2016, **49**, 1369; (d) H. Li and Y. Lu, *Asian J. Org. Chem.*, 2017, **6**, 1130; (e) Y. Wei and M. Shi, *Org. Chem. Front.*, 2017, **4**, 1876; (f) H. Guo, Y. Fan, Z. Sun, Y. Wu and O. Kwon, *Chem. Rev.*, 2018, **118**, 10049; (g) H. Ni, W.-L. Chan and Y. Lu, *Chem. Rev.*, 2018, **118**, 9344; for some selected examples on phosphine-catalyzed reactions, see: (h) S. Takizawa, T. M.-N. Nguyen, A. Grossmann, D. Enders and H. Sasai, *Angew. Chem., Int. Ed.*, 2012, **51**, 5423; *Angew. Chem.*, 2012, **124**, 5519; (i) X. Han, W.-L. Chan, W. Yao, Y. Wang and Y. Lu, *Angew. Chem., Int. Ed.*, 2016, **55**, 6492; *Angew. Chem.*, 2016, **128**, 6602; (j) J.-J. Xing, Y.-N. Gao and M. Shi, *Adv. Synth. Catal.*, 2018, **360**, 2552; (k) Y. Gu, P. Hu, C. Ni and X. Tong, *J. Am. Chem. Soc.*, 2015, **137**, 6400; (l) D. Wang, W. Liu, Y. Hong and X. Tong, *Org. Lett.*, 2018, **20**, 5002; (m) E. Li, H. Jin, P. Jia, X. Dong and Y. Huang, *Angew. Chem., Int. Ed.*, 2016, **55**, 11591; *Angew. Chem.*, 2016, **128**, 11763; (n) J. Chen and Y. Huang, *Org. Lett.*, 2017, **19**, 5609; (o) B. Mao, W. Shi, J. Liao, H. Liu, C. Zhang and H. Guo, *Org. Lett.*, 2017, **19**, 6340; (p) C. Qin, Y. Liu, Y. Yu, Y. Fu, H. Li and W. Wang, *Org. Lett.*, 2018, **20**, 1304; (q) M. Shi, L.-H. Chen and C.-Q. Li, *J. Am. Chem. Soc.*, 2005, **127**, 3790; (r) Y.-Q. Jiang, Y.-L. Shi and M. Shi, *J. Am. Chem. Soc.*, 2008, **130**, 7202.
- (a) E. Vedejs, O. Daugulis and S. T. Diver, *J. Org. Chem.*, 1996, **61**, 430; (b) E. Vedejs and O. Daugulis, *J. Am. Chem. Soc.*, 1999, **121**, 5813.
- For some selected examples based on application of two types of chiral phosphines, see: (a) Q.-G. Wang, S.-F. Zhu, L.-W. Ye, C.-Y. Zhou, X.-L. Sun, Y. Tang and Q.-L. Zhou, *Adv. Synth. Catal.*, 2010, **352**, 1914; (b) F. Zhong, X. Han, Y. Wang and Y. Lu, *Angew. Chem., Int. Ed.*, 2011, **50**, 7837; *Angew. Chem.*, 2011, **123**, 7983; (c) B. Tan, N. R. Candeias and C. F. Barbas III, *J. Am. Chem. Soc.*, 2011, **133**, 4672; (d) Y. Fujiwara and G. C. Fu, *J. Am. Chem. Soc.*, 2011, **133**, 12293; (e) N. Pinto, P. Retailleau, A. Voituriez and A. Marinetti, *Chem. Commun.*, 2011, **47**, 1015; (f) I. P. Andrews and O. Kwon, *Chem. Sci.*, 2012, **3**, 2510; (g) Z. Shi, P. Yu, T.-P. Loh and G. Zhong, *Angew. Chem., Int. Ed.*, 2012, **51**, 7825; *Angew. Chem.*, 2012, **124**, 7945; (h) Z. Jin, R. Yang, Y. Du, B. Tiwari, R. Ganguly and Y. R. Chi, *Org. Lett.*, 2012, **14**, 3226; (i) F. Zhong, X. Dou, X. Han, W. Yao, Q. Zhu, Y. Meng and Y. Lu, *Angew. Chem., Int. Ed.*, 2013, **52**, 943; *Angew. Chem.*, 2013, **125**, 977; (j) C. E. Henry, Q. Xu, Y. C. Fan, T. J. Martin, L. Belding, T. Dudding and O. Kwon, *J. Am. Chem. Soc.*, 2014, **136**, 11890; (k) L. Cai, K. Zhang and O. Kwon, *J. Am. Chem. Soc.*, 2016, **138**, 3298.
- (a) X. Su, W. Zhou, Y. Li and J. Zhang, *Angew. Chem., Int. Ed.*, 2015, **54**, 6874; *Angew. Chem.*, 2015, **127**, 6978; (b) W. Zhou, X. Su, M. Tao, C. Zhu, Q. Zhao and J. Zhang, *Angew. Chem., Int. Ed.*, 2015, **54**, 14853; *Angew. Chem.*, 2015, **127**, 15066; (c) W. Zhou, P. Chen, M. Tao, X. Su, Q. Zhao and J. Zhang, *Chem. Commun.*, 2016, **52**, 7612.
- X.-M. Sun, K. Manabe, W. W.-L. Lam, N. Shiraishi, J. Kobayashi, M. Shiro, H. Utsumi and S. Kobayashi, *Chem.-Eur. J.*, 2005, **11**, 361.
- Other tiny diastereomers exist as a mixture and it is difficult to get clean NMR.
- CCDC 1819863 ((*R<sub>p</sub>*,*S<sub>s</sub>*,*R<sub>s</sub>*)-**L2** with borane), 1819864 ((*S<sub>p</sub>*,*R<sub>s</sub>*,*R<sub>s</sub>*)-**L2** with borane), 181986 (**6ba**), and 1860469 (**13**) contain the supplementary crystallographic data for this paper.†
- (a) B. M. Trost and C.-J. Li, *J. Am. Chem. Soc.*, 1994, **116**, 3167; (b) B. M. Trost and C.-J. Li, *J. Am. Chem. Soc.*, 1994, **116**, 10819; (c) B. M. Trost and G. R. Drake, *J. Org. Chem.*, 1997, **62**, 5670; (d) C. Alvarez-Ibarra, A. G. Csáký and C. Gómez de la Oliva, *Tetrahedron Lett.*, 1999, **40**, 8465; (e) C. Alvarez-Ibarra, A. G. Csáký and C. Gómez de la Oliva, *J. Org. Chem.*, 2000, **65**, 3544; (f) D. Virieux, A.-F. Guillouze and H.-J. Cristau, *Tetrahedron*, 2006, **62**, 3710; (g) Q.-F. Zhou, K. Zhang and O. Kwon, *Tetrahedron*, 2015, **56**, 3273; (h) Z. Huang, X. Yang, F. Yang, T. Lu and Q. Zhou, *Org. Lett.*, 2017, **19**, 3524.
- Z. Chen, G. Zhu, Q. Jiang, D. Xiao, P. Cao and X. Zhang, *J. Org. Chem.*, 1998, **63**, 5631.
- (a) T. Wang, W. Yao, F. Zhong, G.-H. Pang and Y. Lu, *Angew. Chem., Int. Ed.*, 2014, **53**, 2964; (b) T. Wang, D. L. Hoon and Y. Lu, *Chem. Commun.*, 2015, **51**, 10186; (c) T. Wang, Z. Yu, D. L. Hoon, K.-W. Huang, Y. Lan and Y. Lu, *Chem. Sci.*, 2015, **6**, 4912; (d) T. Wang, Z. Yu, D. L. Hoon, C. Phee, Y. Lan and Y. Lu, *J. Am. Chem. Soc.*, 2016, **138**, 265; (e) P. Chen and J. Zhang, *Org. Lett.*, 2017, **19**, 6550; (f) Y. K. Chung and G. C. Fu, *Angew. Chem., Int. Ed.*, 2009, **48**, 2225; *Angew. Chem.*, 2009, **121**, 2259; (g) S. W. Smith and G. C. Fu, *J. Am. Chem. Soc.*, 2009, **131**, 14231; (h) R. Sinisi, J. Sun and G. C. Fu, *Proc. Natl. Acad. Sci. U. S. A.*, 2010, **107**, 20652; (i) J. Sun and G. C. Fu, *J. Am. Chem. Soc.*, 2010, **132**, 4568; (j) Y. Fujiwara, J. Sun and G. C. Fu, *Chem. Sci.*, 2011, **2**, 2196; (k) R. J. Lundgren, A. Wilsily, N. Marion, C. Ma, Y. K. Chung and G. C. Fu, *Angew. Chem., Int. Ed.*, 2013, **52**, 2525; *Angew. Chem.*, 2013, **125**, 2585; (l) M. Kalek and G. C. Fu, *J. Am. Chem. Soc.*, 2015, **137**, 9438; (m) D. T. Ziegler and G. C. Fu, *J. Am. Chem. Soc.*, 2016, **138**, 12069; (n) Y.-Q. Fang, P. M. Tadross and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2014, **136**, 17966.
- For metal-catalyzed symmetric  $\gamma$ -addition: (a) R. E. Kinder, Z. Zhang and R. A. Widenhofer, *Org. Lett.*, 2008, **10**, 3157; (b) C. Michon, F. Medina, M.-A. Abadie and F. Agbossou-Niedercorn, *Organometallics*, 2013, **32**, 5589; (c) B. Alcaide, P. Almendros, I. Fernández, R. Martín-Montero, F. Martínez-Peña, M. P. Ruiz and M. R. Torres, *ACS Catal.*,



- 2015, **5**, 4842; (d) R. J. Harris, R. G. Carden, A. N. Duncan and R. A. Widenhoefer, *ACS Catal.*, 2018, **8**, 8941.
- 12 (a) D. A. Claremon, L. Zhuang, Y. Ye, S. B. Singh, C. M. Tice and G. Mcgeehan, Inhibitors of 11 $\beta$ -Hydroxysteroid Dehydrogenase Type 1, WO/2009/117109, Sep 24, 2009; (b) L. Sun, J.-H. Ye, W.-J. Zhou, X. Zeng and D.-G. Yu, *Org. Lett.*, 2018, **20**, 3049.
- 13 H. Wang and C. Guo, *Angew. Chem., Int. Ed.*, 2019, **58**, 2854; *Angew. Chem.*, 2019, **131**, 2880.
- 14 S. L. Wiskur and G. C. Fu, *J. Am. Chem. Soc.*, 2005, **127**, 6176.
- 15 (a) H. E. Burks, S. Liu and J. P. Morken, *J. Am. Chem. Soc.*, 2007, **129**, 8766; (b) Z. Liu, H.-Q. Ni, T. Zeng and K. M. Engle, *J. Am. Chem. Soc.*, 2018, **140**, 3223.
- 16 K. N. Houk, Y. Lin and F. K. Brown, *J. Am. Chem. Soc.*, 1986, **108**, 554.
- 17 J. Li, W. Chang, W. Ren, J. Dai and Y. Shi, *Org. Lett.*, 2016, **18**, 5456.
- 18 M. Nasopoulou, D. Georgiadis, M. Matziari, V. Dive and A. Yiotakis, *J. Org. Chem.*, 2007, **72**, 7222.
- 19 B. M. Trost and C. Lee, *J. Am. Chem. Soc.*, 2001, **123**, 12191.

