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Asymmetric [3+2] annulation of allenes with maleimides catalyzed by dipeptide-derived phosphines: facile creation of functionalized bicyclic cyclopentenes containing two tertiary stereogenic centers[†]

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D-Threonine-L-*tert*-leucine-derived bifunctional phosphine, Cat. 11, catalyzed highly enantioselective [3+2] annulation of maleimides with allenes has been disclosed, allowing the synthesis of optically active functionalized bicyclic cyclopentenes containing two tertiary stereogenic centers in good to high yields along with good to high enantioselectivities.

It has been well known that phosphine-mediated [3+2]cycloaddition between electron-deficient alkenes and allenes or alkynes is a powerful approach for the construction of functionalized cyclopentenes,¹ which are important structural motifs presented in a huge number of pharmaceutically interesting substances and biologically active natural products.² The pioneering work of phosphine-catalyzed [3+2] cycloaddition was developed by Lu in 1995,³ while the first asymmetric [3+2]annulation of allenoates with acrylates catalyzed by a bicyclic chiral phosphine was achieved by Zhang in 1997.⁴ Later on, significant progress on the asymmetric phosphine-mediated [3+2]cycloaddition between electron-deficient alkenes and allenes or alkynes had been made by Fu,⁵ Miller,⁶ Jacobsen⁷ and other researchers.^{8–10} Very recently, Lu's group developed a new family of dipeptide-based¹¹ chiral phosphines which could smoothly promote the [3+2] cycloaddition of allenoates and α -substituted acrylates, furnishing the corresponding functionalized cyclopentenes with quaternary stereogenic centers in high yields with excellent enantioselectivities.¹² Moreover, they disclosed the first direct application of acrylamides in the phosphine-catalyzed asymmetric [3+2] cycloaddition with allenes using such dipeptidebased chiral phosphines, but only giving the desired products in moderate enantioselectivities (36-66% ee's).13

Recently, a PPh₃-catalyzed [3+2] annulation reaction of cyanoallenes with maleimides to give the functionalized bicyclic cyclopentene derivatives has been reported by Kinderman.¹⁴ Lu and his coworkers also reported a PPh₃-catalyzed [3+2] reaction of 2-(bromomethyl)acrylates with maleimides to give the similar compounds.^{15,16} Herein, we wish to describe a highly enantioselective maleimide–allene [3+2] cycloaddition catalyzed by dipeptide derived bifunctional phosphines, affording the corresponding functionalized bicyclic cyclopentenes containing two tertiary stereogenic centers in good to high yields along with good to high enantioselectivities.

We initiated our investigations by seeking the optimal reaction conditions for the [3 + 2] cycloaddition of maleimide **1a** with ethyl allenoate **2a**. After screening of the catalyst and the investigation of solvent effects, reaction time and temperature on the reaction outcomes, we identified that the optimal reaction conditions are to carry out the reaction in toluene at room temperature for 9 h using triphenylphosphine (PPh₃) (5 mol%) as the catalyst (see Table S1 in the ESI† for details). Under the optimal reaction conditions, we next set out to examine the scope and limitations of this reaction using various maleimides **1** and electron-deficient allenes **2** and we found that all of these *N*-alkyl, *N*-aryl, and *N*-benzyl substituted maleimides **1** could react with **2** smoothly to give the corresponding [3 + 2] cycloaddition products **3** in excellent yields (90–99%) under the standard conditions (Scheme 1) (see Table S2 in the ESI† for details).

In view of our results on the [3+2] cycloaddition of maleimides 1 with allenes 2 catalyzed by PPh₃ effectively, the next logical step was to investigate the asymmetric version of this reaction by using phosphine containing chiral organocatalysts under the above standard conditions. Screening of chiral phosphine catalysts revealed that D-threonine-L-*tert*-leucine-derived bifunctional phosphine, **Cat. 11**, developed by Lu's group¹² was the most effective catalyst in this reaction,



Scheme 1 PPh₃-catalyzed [3+2] cycloaddition of maleimides 1 with allenes 2.

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Scheme 2 Optimization of the asymmetric [3+2] cycloaddition reaction conditions.

giving **3aa** in 97% yield and 86% ee within 24 h (see Fig. S1 in the ESI† for details). Further screening of the solvent effects and reaction temperature on the reaction outcome revealed that using 10 mol% of **Cat. 11** as the catalyst and carrying out the reaction in toluene/CHCl₃ = 1:1 (v/v) at 0 °C for 72 h were the optimal reaction conditions, giving **3aa** in 92% yield and 92% ee within 72 h (Scheme 2) (see Table S3 in the ESI† for details). The mixed solvent can improve the enantioselectivities of the reaction products, but decelerate the reaction rates according to the investigation of the reaction conditions shown in Table S3 in the ESI.† It is necessary to prolong the reaction time to achieve both good yields and high enantioselectivities.

With these optimal reaction conditions in hand, we subsequently turned our attention to examine the substrate scope of this interesting asymmetric [3+2] cycloaddition with respect to a variety of maleimides and electron deficient allenes. The results are summarized in Table 1. As can be seen from Table 1. N-benzyl maleimide **1a** and a variety of N-benzyl maleimide derivatives 1b-1g having electron-rich or electronpoor aromatic groups on their \mathbf{R}^1 groups or N-2-thienylmethyl maleimide **1h** bearing a heteroaromatic group on its \mathbf{R}^1 group could react with electron deficient allene 2a smoothly to give the corresponding [3+2] cycloaddition products **3aa–3ha** in good to high yields along with 85-92% enantiomeric excesses (Table 1, entries 1-8). When R^1 is cyclohexylmethyl, the highest enantiomeric excess (up to 95%) was obtained along with 89% yield for the cycloaddition of maleimide 1i with allenoate 2a (Table 1, entry 9). Employing allenoates 2b-2d with more sterically bulky substitutents or allenic ketone 2e led to relatively lower yields and enantiomeric excesses (Table 1, entries 10-13). Maleimide 1j bearing an N-Me group gave the corresponding cycloaddition product 3ja in 85% yield with 80% ee, however, maleimide 1k bearing an N-H group led to almost no product (Table 1, entries 14 and 15). In the case of maleimides **11–10** in which R¹ are aromatic groups, the reactions also proceeded smoothly to give the corresponding cycloaddition products 3la-3oa in 76-87% yields with 38-68% enantiomeric excesses (Table 1, entries 16-19). The relatively lower enantiomeric excesses of 3ic-3oa (Table 1, entries 11-19) were presumably due to the electronic and steric effects of N-aryl or N-alkyl maleimides 1i-1o and allenes 2c-2e. The absolute configuration of products 3 was unambiguously assigned as S,S-configuration on the basis of the X-ray crystallographic analysis of product 3fa which has a bromine atom on the benzene ring (Fig. S3, ESI⁺).

To illustrate the synthetic utility of these obtained optically active [3+2] cycloaddition products **3**, further transformation of **3id** was performed in the presence of Pd/C and H₂ under mild conditions (Scheme 3). Upon hydrogenation of **3id** with Pd/C in THF for 7 h, the corresponding product **4** was

Table 1 Substrate scope of the asymmetric [3+2] cycloaddition ofmaleimides 1 with electron deficient allenes 2 catalyzed by Cat. 11^a

	$\int_{1}^{0} N-R^{1} + \sum_{COR^{2} \text{ toluer (v/v)}} \frac{Cat.}{toluer (v/v)}$	11 (10 mol%) ne/CHCl ₃ = 1:1 i), 0 °C, 72 h	$\begin{array}{c} H \\ R^{2}OC \\ 3 \end{array}$	R ¹
Entry	\mathbf{R}^1	\mathbb{R}^2	$\operatorname{Yield}^{b}(\%)$	ee^{c} (%)
1	1a, Bn	2a, OEt	3aa , 92	92
2	1b , 1-naphthalenemethyl	2a, OEt	3ba , 84	85
3	1c, 4-MeOC ₆ H ₄ CH ₂	2a, OEt	3ca , 80	91
4	1d, 3 -MeOC ₆ H ₄ CH ₂	2a, OEt	3da , 79	92
5	1e, 3, 4-(MeO) $_2C_6H_3CH_2$	2a, OEt	3ea , 78	92
6	1f, 4 -BrC ₆ H ₄ CH ₂	2a, OEt	3fa, 81	91
7	$1g, 4-FC_6H_4CH_2$	2a, OEt	3ga , 86	90
8	1h , 2-thienylmethyl	2a, OEt	3ha , 82	90
9	1i, cyclohexylmethyl	2a, OEt	3ia , 89	95
10	1i, cyclohexylmethyl	2b , O ⁱ Pr	3ib , 80	91
11	1i, cyclohexylmethyl	$2c, O^{t}Bu$	3ic , 82	77
12	1i, cyclohexylmethyl	2d, OBn	3id , 98	87
13	1i, cyclohexylmethyl	2e , Me	3ie , 94	70
14	1j,Me	2a, OEt	3ja , 85	80
15	1k, H	2a, OEt	3ka, trace	
16	11 , Ph	2a, OEt	3la , 76	68
17	1m, 4 -MeOC ₆ H ₄	2a, OEt	3ma , 87	64
18	1n, 3, 5-(MeO) $_{2}C_{6}H_{3}$	2a, OEt	3na , 83	61
19	10 , 2,4,6-Br ₃ C ₆ H ₂	2a, OEt	3oa , 79	38
			<i>,</i>	

^{*a*} The reaction was carried out on a 0.15 mmol scale with 10 mol% catalyst under Ar in toluene/CHCl₃ = 1:1 (v/v) (1.0 mL) at 0 °C for 72 h, and the ratio of 1/2 was 1.0/2.0. ^{*b*} Isolated yield. ^{*c*} Determined by chiral HPLC analysis, and the absolute configuration was determined by X-ray diffraction of **3fa**.

produced in over 99% yield and excellent diastereoselectivity (dr > 99:1), which could be further transformed to amide 5 in 76% yield with the ee value retained by the reaction with *m*-bromoaniline (2.0 equiv.) in the presence of N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (3.0 equiv.) and 1-hydroxy N-hydroxybenzotriazole (HOBt) (4.0 equiv.) in N,N-dimethylformamide (DMF). As for product 4, the newly generated stereogenic center at the C3 position was assigned as 3R on the basis of the X-ray crystallographic analysis of racemic product rac-5 (see Fig. S4 in the ESI[†] for details) and the S,S-configuration of 3id could be determined by the X-ray crystallographic analysis of [3+2] annulation product 3fa. Furthermore, imide 4 could also be transformed to the corresponding amino alcohol 6 in 99% yield with 87% ee by the standard reduction of carbonyl groups with lithium aluminium hydride (LiAlH₄),¹⁷ which contains a core unit



Scheme 3 Further transformation of the obtained [3+2] annulation product 3id.

Fig. 1 Plausible transition-state model.

of known hepatitis C virus protease inhibitor telaprevir (compound 7, see Fig. S2 in the ESI† for details; Vertex Pharmaceuticals).¹⁸

Based on previous mechanistic studies by Lu and co-workers,¹² a plausible transition-state model is proposed as shown in Fig. 1. The phosphonium enolate intermediate, adopting a conformation favoring its hydrogen-bonding and steric interactions with the maleimide substrate and generated from the nucleophilic attack of the phosphine catalyst **Cat. 11** at the allene, approaches the *Re* face of C3 in the maleimide, and simultaneously, the *Si* face of C4 in the maleimide approaches the phosphonium enolate intermediate to provide the [3+2] annulation (*S*,*S*)-stereoisomer predominantly.

In summary, we have developed a highly enantioselective [3+2] annulation of maleimides with allenes, affording the corresponding functionalized bicyclic cyclopentenes containing two tertiary stereogenic centers in good to high yields along with good to high enantioselectivities catalyzed by D-threonine-L-*tert*-leucine-derived bifunctional phosphine **Cat. 11** (5 mol%) in toluene/CHCl₃ = 1:1 (v/v) at 0 °C. A plausible transition-state model has also been proposed on the basis of previous literature.

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