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Enantioselective [3 + 2] Cycloaddition of Allenes to Acrylates Catalyzed by Dipeptide-Derived Phosphines: Facile Creation of Functionalized Cyclopentenes Containing Quaternary Stereogenic Centers

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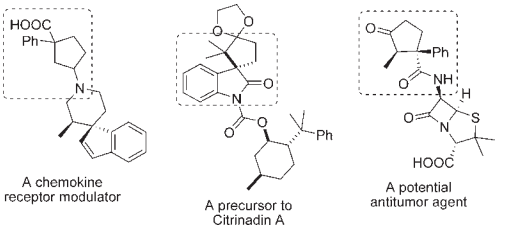
Supporting Information

ABSTRACT: A new family of dipeptide-based chiral phosphines was designed and prepared. D-Thr-L-*tert*-Leu-derived catalyst **4c** promoted [3 + 2] cycloaddition of allenoates to α-substituted acrylates in a regiospecific and stereoselective manner, furnishing functionalized cyclopentenes with quaternary stereogenic centers in high yields and with excellent enantioselectivities.

Functionalized five-membered carbocycles are structural motifs often found in natural products and medicinally important agents.[1] Among the known synthetic methods, phosphine-catalyzed [3 + 2] cycloaddition, developed by Lu in 1995,[2] is considered to be one of the most efficient synthetic approaches. By employing electron-deficient olefins and imines, cyclopentenes and pyrrolidines can be prepared via phosphine-catalyzed cycloadditions, respectively.[3] The first asymmetric [3 + 2] cycloaddition between allenoates and acrylates catalyzed by a bicyclic chiral phosphine was reported by Zhang in 1997.[4] Recently, enantioselective cyclizations of allenoates and enones were achieved by Fu[5] and Miller,[6] utilizing a binaphthyl-based *C*2-symmetric chiral phosphine and a multifunctional phosphine-containing α-amino acid, respectively. Jacobsen designed a series of bifunctional phosphine−thiourea catalysts and applied them to the enantioselective imine−allene annulations.[7] Planar chiral 2-phospha[3]-ferrocenophanes, introduced by Marinetti, were shown to promote enantioselective [3 + 2] additions of allenic esters and phosphonates with enones.[8] Very recently, Loh discovered that commercially available chiral phosphines could promote the cycloaddition of 3-butynoates to enones.[9] Zhao reported bifunctional *N*-acyl amino phosphines were effective catalysts for the asymmetric [3 + 2] cycloadditions of allenoates and activated olefins.[10] Despite the above impressive achievements, comparing to the widespread applications of phosphine-mediated processes, the design and development of chiral phosphine catalysts are still under-explored. When the phosphine-catalyzed [3 + 2] cyclizations are concerned, acrylates remain as elusive substrates;[11] thus, an enantioselective [3 + 2] cycloaddition applicable to substituted acrylates is highly desirable.

Scheme 1. Cyclopentane Structures with a Quaternary Carbon



Creation of quaternary stereocenters is a challenging task in organic synthesis,[12] and we recently became interested in devising organocatalytic methods to access molecules with chiral quaternary centers.[13] Five-membered carbocycles with a quaternary stereogenic center are interesting substructures often found in many natural products and bioactive molecules (Scheme 1);[14] we envisioned that phosphine-catalyzed [3 + 2] annulations between α-substituted acrylates and allenes may be utilized to construct such five-membered ring systems. Our group has been actively investigating asymmetric organic transformations that can be promoted by organocatalysts derived from primary amino acids in the past few years,[13a−13d,15] and thus, we have keen interest in deriving versatile amino acid-based novel phosphines. To ensure effective chiral communications with the substrates and to make the catalysts readily accessible, we chose dipeptide[16] as the basic chiral backbone for our catalyst development (Scheme 2). The carboxylic acid group can be easily converted to a phosphine, which is expected to be highly nucleophilic as the phosphorus atom is connected to a primary carbon. The substrate-interacting chiral pocket derived from the dipeptide is highly tunable by simply varying the amino acid side chains. Herein, we describe the first enantioselective [3 + 2] cycloaddition between α-substituted acrylates and allenoates mediated by dipeptide-based novel phosphine catalysts, creating chiral cyclopentenes containing a quaternary stereogenic center.

We began our investigation by selecting [3 + 2] cycloaddition between 2-phenyl-substituted acrylate **5a** and benzyl allenoate **6a** as a model reaction (Table 1). It should be noted that employment of

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Scheme 2. Phosphine Catalysts Based on Dipeptides

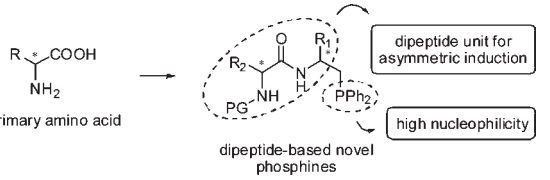
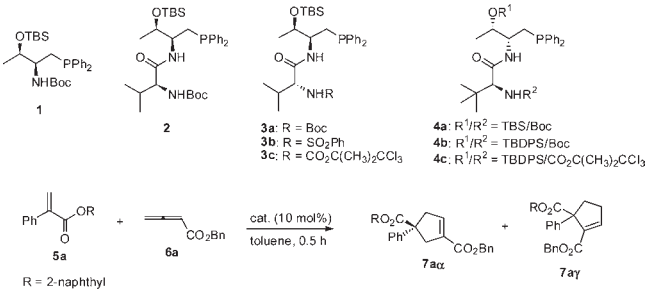


Table 1. [3 + 2] Cycloaddition of Allenoates with Acrylates Catalyzed by Different Amino Acid-Based Phosphines[a]

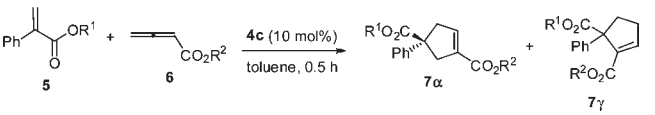


entry	cat.	7aα:7aγ[b]	yield (%)[c]	ee (%)[d]
1	**1**	83:17	88	−36
2	**2**	84:16	90	−52
3	**3a**	89:11	96	−60
4	**3b**	74:26	90	−57
5	**3c**	92:8	93	−61
6	**4a**	93:7	93	63
7	**4b**	94:6	95	74
8	**4c**	95:5	96	78

[a] Reactions were performed with **5a** (0.05 mmol), **6a** (0.075 mmol) and the catalyst (10 mol %) in toluene (0.5 mL) at room temperature. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Isolated yield. [d] The ee value of the major stereroisomer, determined by HPLC analysis on a chiral stationary phase.

α-substituted acrylates in asymmetric [3 + 2] cycloadditions is virtually unexplored.[17] For the design of effective catalysts, given our success in threonine-based catalytic systems,[15b−15e] we chose threonine as the first amino acid residue, and a number of dipeptide-derived phosphines **2**−**4** were prepared. We hypothesize judicious selection of the side chains may facilitate the dipeptide catalyst to adopt a relatively rigid conformation, favoring its interactions with substrates. L-Threonine-derived phosphine **1** led to the formation of α-selective product with low ee (entry 1). On the other hand, dipeptide-based phosphines turned out to be more effective. L-Thr-L-Val-derived **2** led to substantially improved results; moderate ee was attainable (entry 2). Combining L-Thr and D-Val yielded a better catalytic system, and the ee value was further improved to 60% (entry 3). Employment of sulfonamide as Brønsted acid moiety[18] in the catalyst did not offer better results (entry 4), and higher α-selectivity was achieved by utilizing an even more sterically hindered carbamate (entry 5). The catalyst structures were further tuned by engaging *tert*-leucine as the second amino acid residue and varying the siloxy groups on the OH of threonine. To make the catalyst more economical, D-Thr-L-*tert*-Leu dipeptidic backbone was selected for structural elaborations.

Table 2. Optimization of Reaction Conditions[a]



entry	R^1/R^2	α:γ[b]	yield (%)[c]	ee (%)[d]
1	2-naphthyl/Et	94:6	91	74
2	2-naphthyl/*t*-Bu	96:4	94	84
3	2-naphthyl/Ph	89:11	95	84
4	*i*-Pr/*t*-Bu	97:3	72	24
5	Ph/*t*-Bu	97:3	92	76
6	1-napthyl/*t*-Bu	98:2	93	81
7	9-phenanthryl/*t*-Bu	>99:1	95	91
8	9-anthryl/*t*-Bu	>99:1	95	80
9[e]	9-phenanthryl/*t*-Bu	>99:1	92	70
10[f]	9-phenanthryl/*t*-Bu	>99:1	93	67
11[g]	9-phenanthryl/*t*-Bu	>99:1	84	88
12[h]	9-phenanthryl/*t*-Bu	>99:1	95	91
13[i]	9-phenanthryl/*t*-Bu	>99:1	93	90

[a] Unless otherwise specified, reactions were performed with **5** (0.05 mmol), **6** (0.075 mmol), and **4c** (10 mol %) in toluene (0.5 mL) at room temperature. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Isolated yield. [d] The ee value of the major stereoisomer, determined by HPLC analysis on a chiral stationary phase. [e] CH_2Cl_2 was used as the solvent. [f] THF was used as the solvent. [g] The reaction was performed at −20 °C for 5 h. [h] The catalyst loading was 5 mol %. [i] The catalyst loading was 2 mol %.

Finally, *O*-TBDPS-D-Thr-L-*tert*-Leu-derived **4c** was found to be the best catalyst, affording the desired adduct **7a** in 96% yield, with an α to γ ratio of 95:5 and 78% ee (entry 8).

Having identified the best catalyst **4c**, we then focused on tuning the ester moieties in acrylates and allenoates (Table 2). The *tert*-butyl ester proved to be superior to other esters in the allenoate structures, the ratio of α- to γ-isomer could be improved to 96:4, and ee of the major isomer reached 84% (entries 1−3). Among the different acrylate esters, 9-phenanthryl acrylate was found to be the best, and its cycloaddition with *tert*-butyl allenoate led to the formation of only α-isomer in 95% yield and 91% ee (entry 7). Performing reactions in different solvents[19] and lowering the reaction temperature did not result in further improvement (entries 9−11). To make the methodology more practical, catalyst loading was further decreased. With 5 mol % **4c**, the [3 + 2] cycloaddition could be completed within half an hour, furnishing α-isomer in 95% yield and with 91% ee (entry 12). It should be noted that the catalyst loading could go as low as 2 mol %, with marginally reduced yield and enantioselectivity (entry 13).

With the optimized reaction conditions in hand, the substrate scope of **4c**-catalyzed enantioselective [3 + 2] cycloaddition between allenes and acrylates was examined (Table 3). Different α-aryl-substituted acrylates could be employed, α-isomers were regiospecifically formed, and enantioselectivities were excellent in all the examples examined. Reactions of acrylates bearing electron-withdrawing aryl substituents proceeded very fast, typically completing in 10 min, while longer reaction time was required for the cyclization of the acrylate with electron-rich phenyl group at its α-position (entry 5). The acrylate with 1- or 2-naphthyl substitution, or disubstituted phenyl was well-tolerated for the reaction (entries

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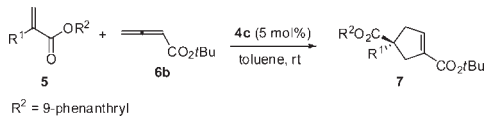
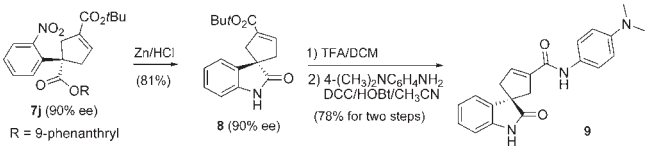
Table 3. Enantioselective Allene−Acrylates [3 + 2] Cycloadditions Catalyzed by 4c[a]



entry	product (R^1)	time	yield (%)[b]	ee (%)[c]
1	**7b** (Ph)	30 min	95	91
2	**7c** (4-ClC_6H_4)	10 min	96	94
3	**7d** (4-BrC_6H_4)	10 min	97	93
4	**7e** (4-MeC_6H_4)	3 h	81	90
5	**7f** (4-$OMeC_6H_4$)	24 h	61	87
6	**7g** (4-$tBuC_6H_4$)	3 h	87	90
7	**7h** (4-CNC_6H_4)	10 min	97	94
8	**7i** (3-MeC_6H_4)	3 h	96	88
9	**7j** (2-$NO_2C_6H_4$)	10 min	96	90
10	**7k** (3,4-ClC_6H_4)	10 min	94	92
11	**7l** (1-naphthyl)	30 min	96	80
12	**7m** (2-naphthyl)	30 min	92	91
13	**7n** (CH_2Ph)	5 h	91	68

[a] Reactions were performed with **5** (0.05 mmol), **6b** (0.075 mmol), and **4c** (5 mol %) in toluene (0.5 mL) at room temperature. [b] Isolated yield. [c] The ee value was determined by HPLC analysis on a chiral stationary phase.

Scheme 3. Preparation of a Spiral Oxindole Derivative

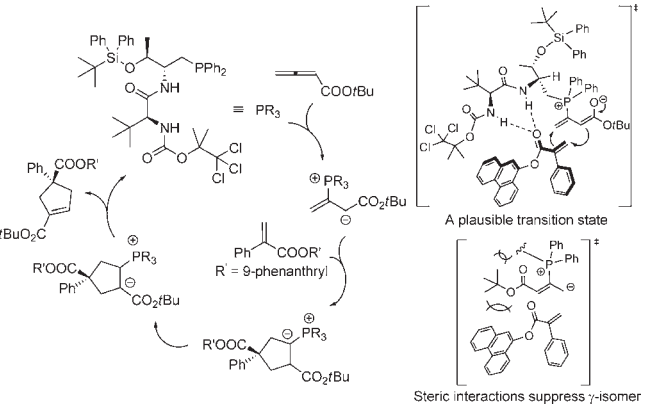


10−12). However, the use of α-alkyl-substituted acrylate resulted in the formation of the desired product in high yield, but only with moderate enantioselectivity[20] (entry 13). The absolute configurations of the cycloaddition products were determined on the basis of the X-ray crystal structure of **7k** (see the Supporting Information for details).

The optically enriched functionalized cyclopentenes **7** are valuable molecules, due to the importance of five-membered ring structures in natural products and medicinal chemistry.[1,14] With the established synthetic protocols,[5,21] such structures are also attractive synthetic intermediates. As oxindoles are important structural scaffolds in pharmaceutical industry,[22] synthetic value of the cycloaddition products was further demonstrated by converting **7j** into a spiral oxindole. As illustrated in Scheme 3, reduction of the nitro group resulted in a spontaneous lactam formation and yielded spiral oxindole core **8**, which was readily transformed to **9**, an agent displaying interesting cytotoxic activities.[23]

Mechanism of this reaction has not been rigorously investigated at this stage, based on Lu's initial proposal[2a] and recent excellent mechanistic studies;[24] a plausible mechanism and transition state model are presented in Scheme 4. We propose that the dipeptidic backbone of the catalyst adopts a conformation favoring its

Scheme 4. Proposed Mechanism and Transition State Model



hydrogen-bonding interactions with the acrylate substrate. The phosphonium enolate intermediate, generated from the nucleophilic attack of the phosphine catalyst at the allene, approaches the acrylate from its *Re* face to yield the major stereoisomer. The formation of the γ-regioisomer is suppressed by the unfavorable steric interactions of the bulky *tert*-butyl group with the acrylate substrate and the sterically hindered carbamate moiety in the catalyst, which is analogous to Lu's utilization of *tert*-butyl allenoate in an α-selective cycloaddition.[2e]

In summary, we have developed a new family of dipeptide-based chiral phosphines; such phosphine catalysts are highly reactive, and their structures are easily tunable. We have also employed α-substituted acrylates in the enantioselective cycloaddition reactions for the first time. D-Thr-L-*tert*-Leu-based phosphine **4c** catalyzed the allene−acrylate [3 + 2] cyclizations efficiently, affording functionalized cyclopentenes containing quaternary stereocenters in a regiospecific and enantioselective manner. Detailed mechanistic investigations and applications of this class of novel catalysts to other organic transformations are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information. Optimization of reaction conditions, preparation of catalysts and substrates, representative experimental procedures, X-ray crystallographic data of **7k**, HPLC chromatogram, and NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) For a complete survey of influences of different solvents on the reaction, see the Supporting Information.

(20) The acrylate with a benzyl substitution has a rather flexible conformation compared to that of other α-aryl-substituted acrylates, which may introduce unfavorable steric interactions with the phosphonium enolate, resulting in a less-defined transition state and decreased enantioselectivity.

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