

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.

 $F_{\rm often}$ 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 Fu⁵ and Miller,⁶ utilizing a binaphthyl-based C2-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 dipeptide¹⁶ 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 AcrylatesCatalyzed by Different Amino Acid-Based Phosphines^a



^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 ¹H 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 moiety¹⁸ 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



^{*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 ¹H 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*} CH₂Cl₂ 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 tertbutyl 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 solvents¹⁹ 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

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



entry	product (R^1)	time	yield $(\%)^b$	ee (%) ^c
1	7 b (Ph)	30 min	95	91
2	$7c(4-ClC_6H_4)$	10 min	96	94
3	7d (4-BrC ₆ H ₄)	10 min	97	93
4	$7e(4-MeC_6H_4)$	3 h	81	90
5	7f (4-OMeC ₆ H ₄)	24 h	61	87
6	$7 g (4 - t Bu C_6 H_4)$	3 h	87	90
7	$7h(4-CNC_6H_4)$	10 min	97	94
8	7i (3-MeC ₆ H ₄)	3 h	96	88
9	7j (2-NO ₂ C ₆ H ₄)	10 min	96	90
10	7k (3,4-ClC ₆ H ₄)	10 min	94	92
11	7l (1-naphthyl)	30 min	96	80
12	7m (2-naphthyl)	30 min	92	91
13	7 n (CH ₂ Ph)	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 enantioselectivity²⁰ (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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(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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