

trifluoroacetic acid (0.012 mL). After stirring for 3 h, NEt₃ (three drops) and AcOEt (20 mL) were added. The solution was poured into saturated aqueous NaHCO₃, the phases were separated, and the organic phase was washed (sat. aq. NaCl), dried (Na₂SO₄), and concentrated. Yield: 50 mg (85 %). ¹H NMR (360 MHz, CDCl₃): δ = 3.67 ppm (dd, J (H,H) = 6.2 and 5.65 Hz (coupling with 1 H of CH₂ and with CH), 1 H; CH–O). Characteristic data of **17**: ¹H NMR (360 MHz, CDCl₃): δ = 4.29 ppm (dd, J (H,H) = 9.5 and 4 Hz (coupling with CH₂), 1 H; CH–O).

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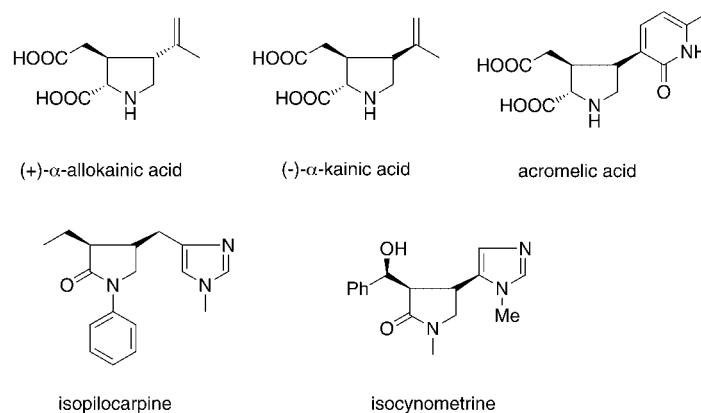
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Highly Enantioselective Cycloisomerization of Enynes Catalyzed by Rhodium for the Preparation of Functionalized Lactams**

Aiwen Lei, Jason P. Waldkirch, Minsheng He, and Xumu Zhang*

The rising demand for chiral raw materials, intermediates, and active ingredients in pharmaceuticals, agrochemicals, food additives, and fragrances provides the impetus for rapid developments in chiral technology.^[1] It remains a huge challenge for organic chemists to develop highly enantiose-

lective reactions for the preparation of enantiomerically pure compounds in a cost-effective manner. Lactams are a versatile motif in organic chemistry and when functionalized, lactams often either show biological activity themselves, or are important building blocks for biologically active molecules such as (+)- α -allokainic acid, (+)- α -kainic acid,^[2] acromelic



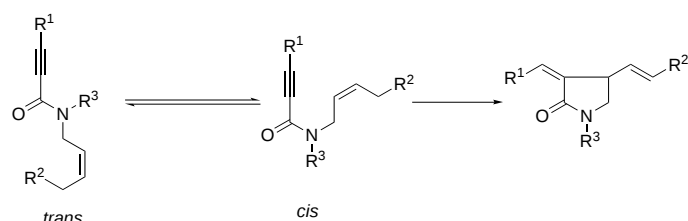
acid,^[3] isopilcarpine,^[4] and isocynometriner.^[5] Generally, lactams are synthesized by intramolecular C–N bond formation. However, this method for the synthesis of enantiomerically pure and functionalized lactams requires that the chiral centers and functional groups must be assembled in advance. Therefore, methodology that allows enantioselective carbon–carbon bond formation for the generation of functionalized lactams without presetting the chiral centers will be a significant advance in synthetic organic chemistry.

The transition-metal-catalyzed intramolecular Alder-ene-type reactions of enynes are well-developed^[6] and provide efficient entries to a variety of useful functionalized carbocyclic^[7] and heterocyclic compounds.^[8] However, the number of lactam preparations reported involving the transition-metal-catalyzed cycloisomerization of enynes is limited. In fact, the literature contains only a single example describing a palladium-catalyzed cycloisomerization of alkynyl *N*-acyl enamines.^[9] Very recently, a mechanistically different palladium(II)-catalyzed synthesis of α -alkylidene- γ -butyrolactams was reported.^[10] Previously, we have discovered a Rh-catalyzed cycloisomerization of enynes and developed its asymmetric version.^[11] Although this was a substrate- and ligand-dependent reaction, up to 96 % *ee* was achieved.^[11b] This led us to consider strategies for expanding the scope of the reaction as well as improving the enantioselectivity. We report herein the results of this effort: in an efficient, mild, and general route to synthesize a variety of lactams in high enantioselectivity using a catalyst derived from a commercially available metal precursor [$\text{Rh}(\text{cod})\text{Cl}$]₂ and the ligand binap.^[12]

Initially, the reaction was studied with unprotected enyne amides (Scheme 1, R³ = H) as the cycloisomerization substrates. However, none of the desired cyclization products were detected and the starting materials were recovered. The negative results may be because the *trans*-isomer of this type of unprotected enyne amide is dominant, which would be unfavorable for the cycloisomerization (Scheme 1).^[13] There-

[*] Prof. Dr. X. Zhang, Dr. A. Lei, J. P. Waldkirch, M. He
 Department of Chemistry
 The Pennsylvania State University
 University Park, PA 16802 (USA)
 Fax: (+1) 814-863-8403
 E-mail: xumu@chem.psu.edu

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Scheme 1. Effect of *trans/cis*-isomers in the Rh-catalyzed Alder-ene reaction.

fore, we turned our efforts to making the protected enyne amides (Scheme 1, $R^3 \neq H$). The reaction of **1a** in the presence of $[(Rh(cod)Cl)_2]$, (*rac*)-binap, and $AgSbF_6$ provided the desired γ -lactam **2a** in 95 % yield at RT. Further experimentation indicated that high enantioselectivity (> 99 % *ee*) was obtained using (*S*)-binap while the other enantiomer was obtained in high enantioselectivity using (*R*)-binap as the ligand (Table 1, entries 1 and 2).

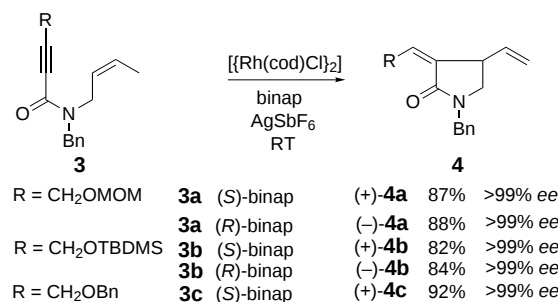
Table 1. Rh^I -catalyzed intramolecular Alder-ene reaction.^[a]

Entry	1	R ¹	Substrate R ²	R ³	binap	2	Product Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	1a	Ph	Et	Bn	(<i>S</i>)	(+)- 2a	95	> 99
2	1a	Ph	Et	Bn	(<i>R</i>)	(-)- 2a	96	> 99
3	1b	Ph	H	Bn	(<i>S</i>)	(+)- 2b	90	> 99
4	1c	Ph	Me	Bn	(<i>S</i>)	(+)- 2c	91	> 99
5	1d	Me	H	Bn	(<i>R</i>)	(-)- 2d	91	> 99
6	1d	Me	H	Bn	(<i>S</i>)	(+)- 2d	92	> 99
7	1e	Me	H	Me	(<i>S</i>)	(+)- 2e	91	> 99
8	1f	Me	Me	Bn	(<i>S</i>)	(+)- 2f	96	> 99
9	1g	<i>n</i> -C ₅ H ₁₁	H	Bn	(<i>S</i>)	(+)- 2g	93	> 99
10	1h	<i>n</i> -C ₅ H ₁₁	Me	Bn	(<i>S</i>)	(+)- 2h	91	> 99
11	1i	<i>n</i> -C ₅ H ₁₁	Et	Bn	(<i>S</i>)	(+)- 2i	92	> 99
12	1j	<i>n</i> -C ₅ H ₁₁	Et	Bn	(<i>S</i>)	(+)- 2j	90	> 99

[a] All the reactions were carried out in 1 mL $ClCH_2CH_2Cl$ on a 0.1 mmol scale. The ratio of substrate/ $[(Rh(cod)Cl)_2]$ /binap/ $AgSbF_6$ was 1:0.05:0.12:0.20. [b] Yield of product isolated. [c] The *ee* value was measured by HPLC.

Encouraged by the above results, a range of substrates were examined and the results are summarized in Table 1. A variety of γ -lactams were formed in high yields (90–96 %) by the Rh-catalyzed cycloisomerization of a broad range of the enyne amides **1**. Significantly, all substrates listed in Table 1 gave the corresponding lactams with high enantioselectivity (> 99 % *ee*) using binap as the ligand.^[14] These results demonstrate the great potential of this reaction in organic synthesis.

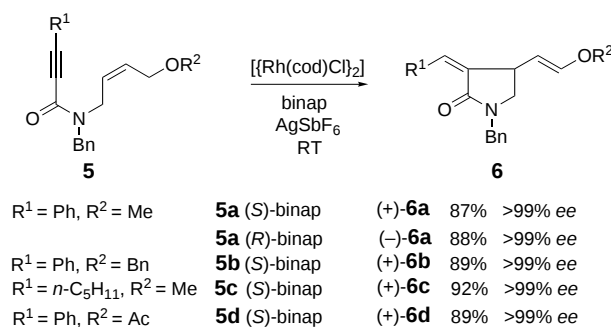
To examine the functional-group tolerance of this Rh-catalyzed cycloisomerization, the reactions of the enyne substrates **3a–c** functionalized at the alkynyl terminus were investigated under the above-described conditions. The results listed in Scheme 2 showed that a number of functionalized γ -lactams were isolated in high yields (82–92 %) and excellent enantioselectivities (> 99 % *ee*).



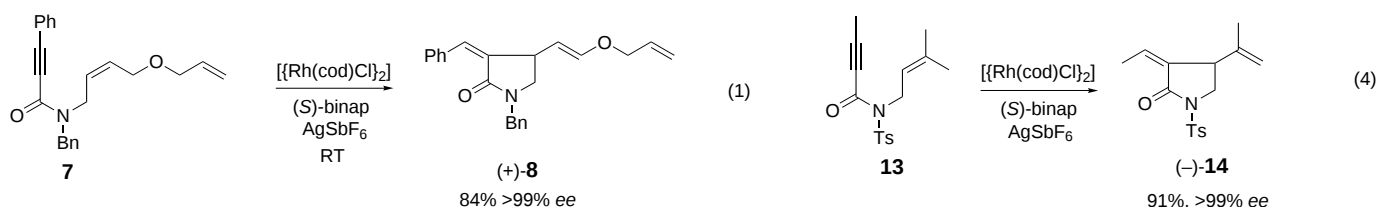
Scheme 2. High functional tolerance of the Rh-catalyzed Alder-ene reaction. MOM = methoxymethyl, TBDMS = *tert*-butyldimethylsilyl, Bn = benzyl.

Vinyl ethers and vinyl acetates are versatile building blocks.^[15] Developing efficient routes toward these types of compounds would be valuable. On the basis of the mechanism of the Rh-catalyzed cycloisomerization reaction, we envisioned that functional vinyl derivatives would form by regioselective β -H elimination. Therefore, we investigated the behavior of the enynes **5** as potential substrates in the cycloisomerization process. This path would provide efficient entries to a variety of useful vinyl ethers and vinyl esters from readily available allylic ether or allylic acetate compounds. The vinyl methyl ether, vinyl benzyl ether, and vinyl acetate containing lactams were synthesized in high yields and over 99 % *ee* (Scheme 3). Further experiments revealed that this reaction can tolerate terminal olefins. The vinyl allylic ether^[16] substituted lactam **8**, which is an excellent substrate for the Claisen rearrangement, was obtained in 84 % yield and over 99 % *ee* [Eq. (1)].

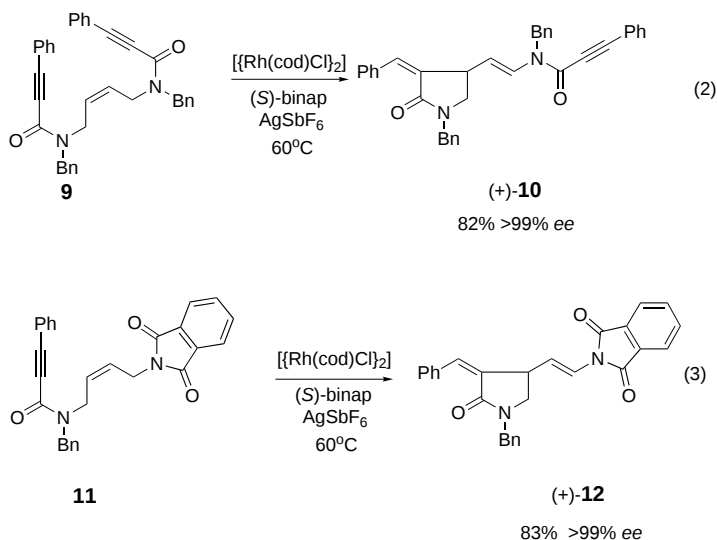
To expand the scope of the functionalized vinyl derivatives, we investigated the method for the preparation of versatile enamides,^[17] which are important organic synthetic intermediates. Although the reactions list-



Scheme 3. Functionalized lactams prepared from the highly regioselective Alder-ene reaction.



ed in Equation (2) and Equation (3) are very slow at RT, at 60°C the cycloisomerization proceeded smoothly and yielded the desired enamides in high yields and over 99% ee.



The use of an enyne substrate containing a trisubstituted olefin was investigated in the Rh-catalyzed cycloisomerization reaction. The cyclization of the *N*-tosylate-protected amide **13** produced the desired lactam in high yield and high enantioselectivity within 24 h at RT [Equation (4)]. The presence of the tosylate group was important to the success of this cyclization.^[18]

A catalytic cycle has been proposed for the Rh-catalyzed intramolecular Alder-ene reaction (Scheme 4).^[6c,7a,19] We believe that the reaction, by the coordination of enynes with a Rh^{I} species, forms the coordinated intermediate **II**. Oxidative cyclization of enynes affords the metallacyclopentane **III**. Subsequently, β -H elimination of the metallacyclopentane **III-A** yields the Rh-H species **IV**. Finally, the reductive elimination of this Rh-H species **IV** produces the desired product.

The high regioselectivity of the formation of 1,4-diene products can be explained by the *cis*-relationship between the C–Rh and C–H bonds for the β -H elimination in Scheme 4.^[6a] Based on the proposed mechanistic rationale, the *E* geometry of the double bond formed by the β -H elimination can be expected because of the less sterically hindered metallacyclopenta-

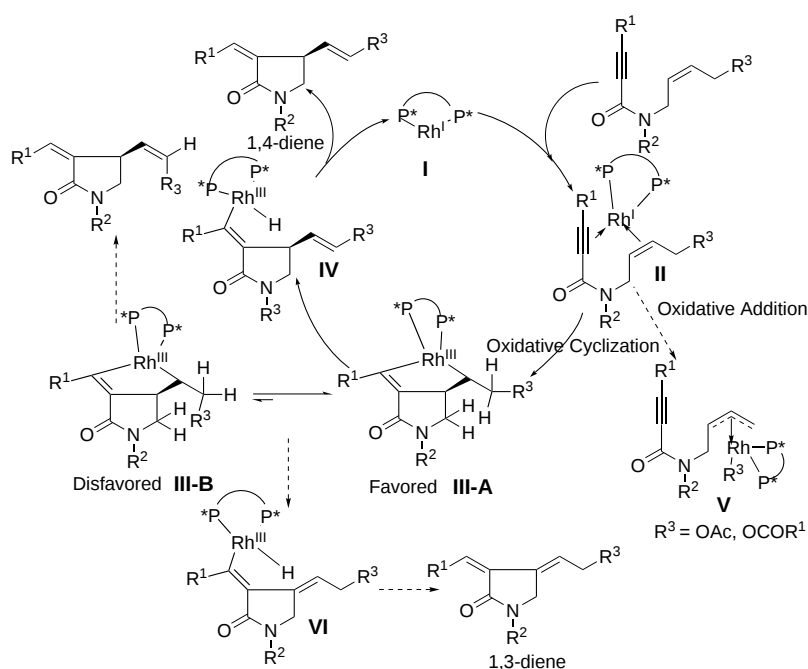
nes **III-A**, and the *Z* geometry of the exocyclic double bond should form from the reductive elimination of the Rh-H intermediate **IV**. The NOE investigation of **6a** does confirm the expected geometry of the double bonds.

The information gained from the reaction of **5d** was important. It showed that the cycloisomerization can tolerate the allylic acetate group, which has high reactivity towards low-valent transition metals, such as Pd^0 , Ni^0 , etc. in oxidative addition. The clean and high-yielding reaction reveals that, at least in this system, oxidative cyclization is strongly favored over any other competitive reaction pathways.

In summary, we successfully explored a highly enantioselective cycloisomerization of enynes for the preparation of functionalized lactams. The high ee value (>99%) obtained in these reactions was especially remarkable. The potential of this new reaction lies not only its broad functional tolerance, but in the functionalized vinyl derivatives such as vinyl ether, vinyl acetate, vinyl allylic ether, and enamides containing lactams that were formed. Further efforts towards the syntheses of biologically active compounds are in process and will be reported in due course.

Experimental Section

Procedure for the rhodium-catalyzed reaction of **3a** to form **(+)-4a**: In a flame-dried Schlenk tube, the $[\{\text{Rh}(\text{cod})\text{Cl}\}_2]$ (2.5 mg, 0.005 mmol) and (S)-binap (6.9 mg, 0.012 mmol) were dissolved in freshly distilled 1,2-dichloroethane (1 mL), then freshly prepared **3a** (28.7 mg, 0.1 mmol) was added to



Scheme 4. The proposed mechanism and competitive routes.

the solution at RT under nitrogen. After stirring for 1 min, AgSbF₆ (0.02 mmol in ClCH₂CH₂Cl) was added to the mixture. The reaction was completed within 5 min. The reaction mixture was directly subjected to column chromatography, from which (+)-**4a** (24.9 mg, 87%, over 99% ee^[20]) was obtained. The ee value was determined by HPLC with an OJ-H column (hexane:isopropanol = 95:5, 1 mL min⁻¹, 254 nm). [α]_D²⁵ = +3.52 (c = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ = 7.28–7.16 (m, 5 H), 5.85 (dt, *J* = 2.2, 5.9 Hz, 1 H), 5.58–5.53 (m, 1 H), 5.08–5.02 (m, 2 H), 4.80–4.77 (m, 2 H), 4.61 (s, 2 H), 4.48 (d, *J* = 14.6 Hz, 1 H), 4.35 (d, *J* = 14.6 Hz, 1 H), 3.32 ppm (s, 3 H); ¹³C NMR (90 MHz, CDCl₃) δ = 167.72, 137.76, 136.57, 134.50, 129.13, 128.65, 128.07, 118.00, 96.84, 95.57, 64.04, 54.54, 50.22, 47.15, 42.17 ppm; MS *m/z*: 288.1 [*M*⁺+1]; HRMS (APCI) calcd for C₁₇H₂₂NO₃ [*M*⁺+1]: 288.1600; found: 288.1603.

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Mechanistic Studies of HPP Epoxidase: Configuration of the Substrate Governs Its Enzymatic Fate**

Zongbao Zhao, Pinghua Liu, Kazuo Murakami, Tomohisa Kuzuyama, Haruo Seto, and Hungwen Liu*

Non-heme iron-dependent enzymes are an important class of catalysts involved in many biological transformations of medical, pharmaceutical, and environmental significance. Although considerable progress has been made in our understanding of their catalyses, characterization of the metal centers and the modes of dioxygen activation remain a challenge because of the great structural and mechanistic diversity found among these enzymes.^[1] Recently, HPP epoxidase,^[2] an enzyme in the biosynthetic pathway of the antibiotic fosfomycin, was recognized as a new member of this enzyme family.^[3] This epoxidase performs the final transformation in the fosfomycin biosynthesis by converting (*S*)-2-hydroxypropylphosphonic acid (HPP, (*S*)-**1**) to (1*R*,2*S*)-epoxypropylphosphonic acid (**2**), also known as fosfomycin

- [*] Prof. Dr. H.-w. Liu, Dr. Z. Zhao,⁺ Dr. P. Liu,⁺ Dr. K. Murakami
Division of Medicinal Chemistry
College of Pharmacy and
Department of Chemistry and Biochemistry
University of Texas
Austin, TX 78712 (USA)
Fax: (+1) 512-471-2746
E-mail: h.w.liu@mail.utexas.edu
Prof. Dr. T. Kuzuyama
Institute of Molecular and Cellular Biosciences
University of Tokyo
Bunkyo-ku, Tokyo 113-0032 (Japan)
Prof. Dr. H. Seto
Faculty of Applied Bio-Science
Tokyo University of Agriculture
Setagaya-ku, Tokyo 156-8502 (Japan)

[⁺] Contributed equally to the work.

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