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Rhodium(I)-Catalyzed Allenic Carbocyclization Reaction Affording δ - and ϵ -Lactams

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Abstract

This communication extends the scope of the rhodium(I)-catalyzed allenic Alder-ene carbocyclization reaction to the preparation of δ - and ϵ -lactams from amides. A variety of allenic propiolamides were cycloisomerized to give a number of unsaturated δ -lactams. In addition, allenic propargylamides give good yields of the corresponding ϵ -lactams. Formation of lactams possessing these ring sizes has rarely been accomplished via transition-metal catalyzed carbon-carbon bond forming strategies. Thus, this approach provides an alternative strategy for synthesizing these substructures.

Discovery of new and biologically significant compounds from nature provides a remarkable collection of structurally complex targets. Thus, there is a continual need for the development of new, more robust strategies for stitching atoms together. Expanding the synthetic toolbox to include under-utilized functional groups can serve as a springboard for these investigations. Our group is involved in examining transition metal catalyzed reactions of allenes, and these investigations have led to useful arrays of functionality via novel cyclocarbonylation and carbocyclization reactions. For example, we have previously demonstrated that the Rh(I)-catalyzed Alder-ene carbocyclization process affords cross-conjugated trienes in high yields and is tolerant of a wide array of functionality.¹ Moreover, the resulting trienes can be used in a variety of ways, including tandem transition metal catalyzed carbon-carbon bond forming reactions² and DOS strategies.³ It was upon consideration of these triene products that inspired us to explore the formal Alder-ene reaction of alkynyl allenes possessing amide tethers as a method for preparing highly unsaturated lactams.⁴ Lactams are most commonly obtained via cyclodehydration reactions of amino acids, from ketones using either the Schmidt or Beckmann rearrangement reactions or cyclization of the amide nitrogen onto an alkene, alkyne or allene.⁵ It is much less common to access amides via carbon-carbon bond forming reactions.⁶ There are a handful of reports demonstrating the feasibility of an amide tether in carbocyclization reactions but these protocols have been limited to the preparation of γ -lactams.⁷ Moreover, the reaction conditions are not generally tolerant of an unprotected amide, which is typically attributed to a disfavored rotamer population of the amide bond.⁸ We would now like to report on our

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Supporting Information Available. Characterization data and full experimental procedures are provided for all compounds in Tables 1 and 2 and Schemes 1, 2 and 3. This material is available free of charge via the internet at <http://pubs.acs.org>.

progress towards extending the scope of the allenic Alder-ene carbocyclization reaction to amides for the formation of δ - and ϵ -lactams.⁹

Allenic amino ester **1a** was prepared as a single diastereomer using a Claisen rearrangement protocol developed in the Kizmaier laboratories.¹⁰ Allenic amino esters **1b** and **1c** were obtained using a Claisen rearrangement procedure developed by Krantz,¹¹ that proceeds thorough an oxazolidinone intermediate and affords a mixture of diastereomers (typically 1 : 1, Scheme 1). Allenic amino esters **1a–c** were prepared in yields ranging from 60–95% and both protocols afford racemic products. The amine protecting groups are removed from **1a–c** affording **2a–c** and the resulting amine is coupled to the corresponding alkynoic acids **3a–d** to give amides **4a–l** (55–95% yield). Next, subjecting amides **4a–l** to 10 mol% rhodium biscarbonylchloride dimer $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ gives the δ -lactams **5a–l** in high yields (Table 1). In most cases the Alder-ene reactions proceed at 90 °C in less than 15 min. The high temperature required to affect this carbocyclization process is attributed to the secondary amide, because protection of the amide nitrogen as a benzamide affords the carbocyclization product in less than an hour at room temperature (entry **5l**, Table 1). In all cases (except when $\text{R}^2 = \text{H}$), the *Z*-alkylidene geometry is obtained exclusively. This is a direct result of the mechanism of this reaction and has no bearing on the diastereomeric purity of the allenyl precursors.¹

Furthermore, it is important to note that the reaction concentrations are somewhat low (0.01–0.05 M) but this proved crucial to the success of the reaction; higher concentrations give an insoluble precipitate and resulted in lower yielding reactions. Efforts expended in trying to characterize this precipitate have not been successful. Most of these reactions were run on small scale for convenience (~0.1 mmol), but conversion of **4b** to **5b** was done on nearly a gram of material and the product was obtained in 92% yield. Finally, attempts were made to decrease the catalyst loading from 10 to 5 mol %; however, the reactions did not go to completion.

Next, we investigated the formation of ϵ -lactams. Allenyl ester **6a**¹² was alkylated using LDA and iodomethane in 70% yield and the resulting dimethyl allenyl ester **6b** was saponified using 2 M KOH in methanol to afford known allenyl acid **6c** in 90% yield (Scheme 2).¹³ Allenic acid **6c** was then converted to functionalized amides **8a–f** by reaction of the acid chloride with amines **7a–f**.¹⁴ The dialkyl substituent between the allene and carbonyl is essential to prevent isomerization of the 1,2-diene to a 1,3-diene, a reaction that is favored by the carbonyl proximity. To our satisfaction, substrates **8a–e** afforded the desired ϵ -lactams **9a–e** under the standard Rhodium(I)-catalyzed conditions in 49–65% yield (Table 2). Lactams **9d** and **9e** are obtained as single isomers possessing the *Z*-alkylidene geometry depicted in Scheme 2. Unfortunately, attempts to effect the carbocyclization reaction on a secondary amide **8f** gave 48% recovery of the starting material.

Next, with analogs of the natural product cephalotaxine as our target, the Alder-ene carbocyclization of model system **10** was investigated. Indeed, the trienyl bicyclic lactam **11** was achieved in 62% yield (Scheme 3). Cephalotaxane (**12**) is comprised of a unique benzazepine pentacyclic ring system that has been a proving ground for a number of new synthetic methods. To date, all syntheses of this class of compounds begin with the 2-(benzo[1,3]diox-6-yl)ethanamine component intact.¹⁶ The unique strategy proposed within arrives at this moiety via a Diels-Alder reaction opening potentially new avenues for analog synthesis.

In conclusion, we have shown that δ - and ϵ -lactams are obtained via a Rh(I)-catalyzed allenic-Alder-ene reaction, further demonstrating the scope and utility of this reaction by its ability to operate on different substrate classes. To date, the successful formation of lactams

possessing these ring sizes has rarely been accomplished via transition-metal catalyzed carbon-carbon bond forming strategies. Thus, this approach provides a potentially useful alternative for synthesizing these substructures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.
Allenic Alder-ene Approach to δ -Lactams

Scheme 2.
 ε-Lactams Using an Allenic Alder-ene Reaction

Scheme 3.
Allenic Alder-ene Approach to Cephalotaxane

Table 1 δ -Lactams Using an Allenic Alder-ene Reaction

entry ^a	R ¹	R ²	R ³	yield
5a	Bn	H	H	45% ^b
5b	Bn	Me	H	92%
5c	Bn	TMS	H	77%
5d	Bn	Ph	H	66%
5e	Me	H	H	70%
5f	Me	Me	H	84%
5g	Me	TMS	H	74%
5h	Me	Ph	H	72%
5i	<i>i</i> -Bu	Me	H	84%
5j	<i>i</i> -Bu	TMS	H	83%
5k	<i>i</i> -Bu	Ph	H	74%
5l	Bn	Me	Bz	75% ^c

Entries **5a–5d** run at 0.03 M; Entries **5e–5m** run at 0.01 M; For entries 5b–5k, reactions were complete in less than 15 min;

^b Reaction time, 2 h and the product **5a** decomposes upon concentration;

^c reaction takes place at room temperature in 1 h.

Table 2Allenic Alder-ene Approach to ϵ -Lactams¹⁵

entry	R ²	R ³	yield
9a	Bn	H	65
9b	(CH ₂) ₂ OTBS	H	67
9c	furfuryl	H	63
9d	Bn	Me	50
9e	Bn	C ₄ H ₄ - <i>p</i> -OMe	65
9f	H	H	8f , 48