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Stereoselective Synthesis of Functionalized Cyclic Amino Acid Derivatives via a [2,3]-Stevens Rearrangement and Ring-Closing Metathesis

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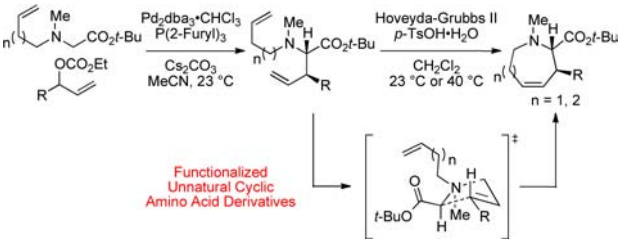
ABSTRACT



Unnatural cyclic amino acids are valuable tools in biomedical research and drug discovery. A two-step stereoselective strategy for converting simple glycine-derived aminoesters into unnatural cyclic amino acid derivatives has been developed. The process includes a palladium-catalyzed tandem allylic amination/[2,3]-Stevens rearrangement followed by a ruthenium-catalyzed ring-closing metathesis. The [2,3]-rearrangement proceeds with high diastereoselectivity through an *exo* transition state. Oppolzer's chiral auxiliary was utilized to access an enantiopure cyclic amino acid by this approach, which will enable future biological applications.

Cyclic amino acids are an important class of compounds for drug discovery and biomedical research, because they adopt unique amide bond conformations that influence the three-dimensional structure of peptides and proteins.[1] For example, while acyclic amino acids preferentially form amide bonds in the *trans* conformation, this preference is less pronounced for cyclic amino acids such as proline (**1**, Figure 1).[2] The subtle changes in relative equilibria of *cis* and *trans* amide bonds for acyclic and cyclic amino acids can have profound effects on the structure and function of

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peptides and proteins. As a result, polypeptide chains with unnatural cyclic amino acids have served as leads in medicinal chemistry programs[3] and are useful chemical tools for elucidating novel biochemical pathways.[4] Although unnatural cyclic amino acids exhibit the potential for important biological applications, their stereoselective synthesis with functionally diverse side chains and multiple stereocenters remains a challenging problem.[5]

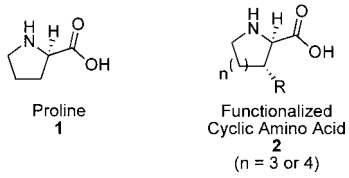
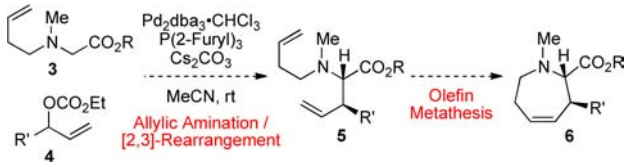


Figure 1. Natural and unnatural cyclic amino acids.

We became interested in developing a stereoselective strategy to construct functionalized cyclic amino acid derivatives with medium-sized rings and multiple stereocenters (**2**, Figure 1). We reasoned that amino acid derivatives with seven- and eight-membered rings would provide a unique opportunity for generating structures with multiple stereocenters and diverse functional groups. Moreover, these larger rings would maintain the conformational benefits of proline and other cyclic amino acids.[6] Herein, we describe a two-step diastereoselective protocol for synthesizing cyclic amino acid derivatives with multiple stereocenters that meets these criteria. The mild conditions of this strategy are compatible with a wide range of chemical functionality and are utilized to generate an enantioenriched cyclic amino acid.

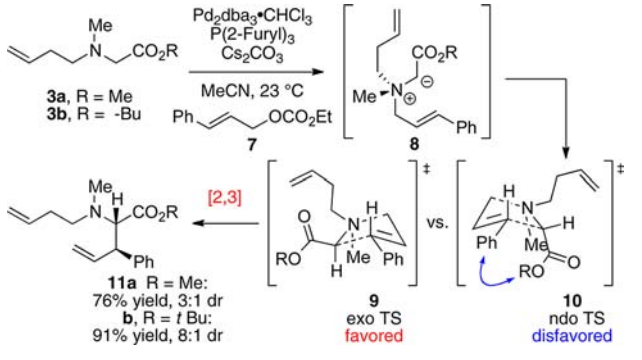
Our approach for synthesizing functionalized cyclic amino acid derivatives was based on a tandem palladium-catalyzed allylic amination/[2,3]-Stevens rearrangement previously developed by our group.[7] This work represented the first example of using tertiary amines as intermolecular nucleophiles in metal-catalyzed allylic substitution chemistry.[8] By utilizing homoallylic aminoesters **3** and allylic carbonates **4** in this approach, we expected to directly access polyunsaturated amino acid derivatives **5** through a diastereoselective [2,3]-rearrangement (Scheme 1).[9] These rearrangement products could be subjected to a subsequent ring-closing metathesis to obtain novel cyclic amino acid derivatives **6** with multiple stereocenters.[10]

Scheme 1. Two-Step Strategy for Synthesizing Cyclic Amino Acid Derivatives



Our investigation began by an examination of the reactivity and stereoselectivity of homoallylic glycine derivatives **3a** and **3b** in the tandem palladium-catalyzed allylic amination/[2,3]-Stevens rearrangement (Scheme 2). Treatment of aminoesters **3a** and **3b** with cinnamyl ethyl carbonate **7**, 1 mol % $Pd_2dba_3 \cdot CHCl_3$, 3 mol % P(2-Furyl)$_3$, and Cs_2CO_3 as an exogenous base resulted in the formation of rearrangement products **11a** and **11b**. To our delight, polyunsaturated aminoesters **11a** and **11b** were both generated in acceptable yields. However, the less sterically encumbered methyl ester derivative was generated in a 3:1 diastereomeric ratio, while the *tert*-butyl ester derivative was isolated as a more desirable 8:1 mixture of diastereomers. The major diastereomer was presumably formed through the *exo* transition state **9** of the [2,3]-rearrangement, with the large *tert*-butyl ester and the phenyl ring oriented in an *anti* configuration.[7,9]

Scheme 2. Diastereoselective Palladium-Catalyzed Tandem Allylic Amination/[2,3]-Stevens Rearrangement



Once we identified an efficient approach to polyunsaturated amino acid derivative **11b**, we optimized the ring-closing metathesis step of our approach to cyclic amino

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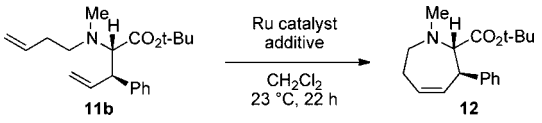
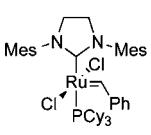
Table 1. Optimization of Ring-Closing Metathesis Step

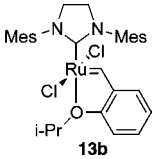


entry	catalyst (mol %)	additive (1.5 equiv)	yield (%)[a]
1[b]	**13a** (5)	–	<5
2[b]	**13b** (5)	–	<5
3[b]	**13a** (5)	$Ti(Oi\text{-}Pr)_4$	<5
4[b]	**13b** (5)	$Ti(Oi\text{-}Pr)_4$	<5
5	**13a** (5)	$p\text{-TsOH}\cdot H_2O$	<5
6	**13b** (5)	$p\text{-TsOH}\cdot H_2O$	50
7	**13b** (5)	$p\text{-TsOH}\cdot H_2O$[c]	65
8	**13b** (10)	$p\text{-TsOH}\cdot H_2O$	58
9	**13b** (10)[d]	$p\text{-TsOH}\cdot H_2O$	85

[a] Isolated yield. [b] Reaction also resulted in no product in refluxing CH_2Cl_2. [c] 3 equiv of $p\text{-TsOH}\cdot H_2O$. [d] Catalyst was added as two separate amounts of 5 mol % at the beginning and 6 h into the reaction.



3a



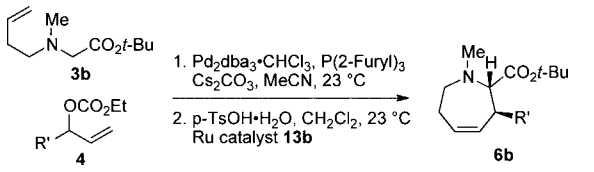
13b

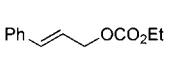
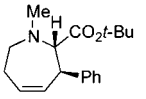
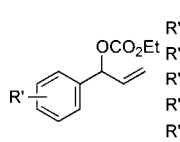
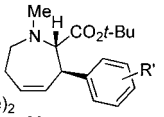
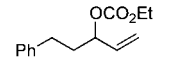
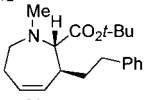
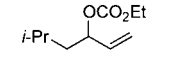
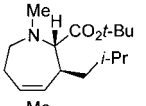
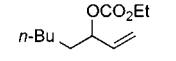
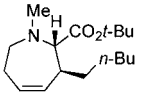
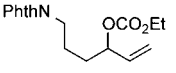
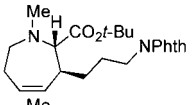
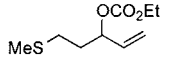
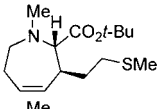
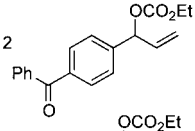
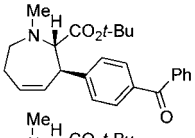
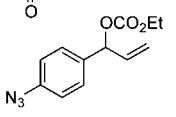
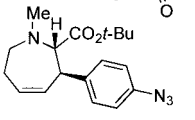
acid derivatives with commercially available ruthenium catalysts (Table 1).[11] The Grubbs second generation catalyst **13a** and the Hoveyda–Grubbs second generation catalyst **13b** were both ineffective in facilitating the desired ring-closing event (entries 1 and 2), presumably because of catalyst inhibition by the Lewis basic amine starting material.[12]

Pretreatment of basic amine substrates with Lewis acid additives, such as $Ti(Oi\text{-}Pr)_4$, is a well-known strategy for engaging unsaturated amines in ring-closing metatheses.[13] Unfortunately, this approach proved unsuccessful for aminoester **11b** (entries 3 and 4).

We also examined the formation of the ammonium salt of aminoester **11b** in the presence of Brønsted acids to mitigate the basicity of the nitrogen in the substrate (entries 5–9).[14] While the ring-closing metathesis of aminoester **11b** was unsuccessful with 5 mol % Grubbs second generation catalyst **13a** and *p*-toluenesulfonic acid monohydrate (entry 5), we were delighted to obtain a 50% isolated yield for cyclic aminoester **12** in the presence of 5 mol % Hoveyda–Grubbs second generation catalyst **13b** and *p*-toluenesulfonic acid monohydrate (entry 6). We suspected that the reaction was not proceeding to complete conversion because of slow inhibition or decomposition of the 5 mol % loading of catalyst **13b**. To alleviate this problem, we increased the amount of Brønsted acid (entry 7) and catalyst

Table 2. Substrate Scope of Allylic Carbonate[a]



entry	carbonate	cyclic product	yield (%)[b]	dr[c]
1			85	8:1
2	 R' = 3-Me		80	10:1
3	R' = 4-Cl		72	6:1
4	R' = 4-F		84	6:1
5	R' = 3-Br		86	7:1
6	R' = 3,5-(OMe)2		72	8:1
7			78	>20:1
8			72	>20:1
9			69	>20:1
10			43	>20:1
11[d]			41	>20:1
12			78	5:1
13			60	16:1

[a] *Step 1:* 1.25 equiv of aminoester **3b**, 1 equiv of allylcarbonate **4**, 1 mol % $Pd_2dba_3\cdot CHCl_3$, 4 mol % P(2-Furyl)$_3$, 3 equiv of Cs_2CO_3, 0.2 M in MeCN. *Step 2:* 1.5 equiv of $p\text{-TsOH}\cdot H_2O$, 0.01 M CH_2Cl_2; 10 mol % catalyst **13b** (added in two batches). [b] Isolated yield for 2 steps. [c] Diastereomeric ratios as determined by NMR analysis. [d] Ru catalyst **13a** was used.

13b (entry 8), which only increased the yield to 65% and 58%, respectively. Gratifyingly, when we added a second 5 mol % loading of catalyst **13b** after 6 h, we obtained desired product **12** in 85% yield (entry 9).

With optimized conditions in hand for the two-step conversion of homoallylic glycine derivative **3b** to cyclic aminoesters, we surveyed the scope of functionalized allylic carbonates **4** that were compatible with this process (Table 2). To streamline the procedure, we performed both steps in a telescoped sequence by simply filtering and concentrating the reaction mixture after completion of the first step. We then redissolved the rearrangement product in CH_2Cl_2 and subjected it to ring-closing metathesis conditions.

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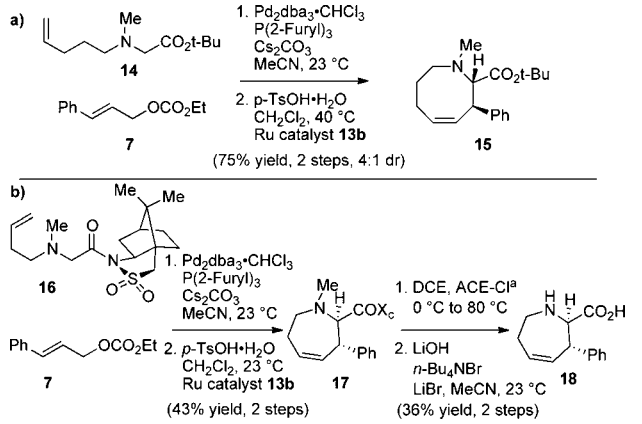
Scheme 3. Synthesis of Eight-Membered Ring and Enantiopure Amino Acid



[a] ACE-Cl = 2-chloroethyl chloroformate.

The product of the ring-closing metathesis was purified by flash chromatography to obtain a two-step isolated yield of cyclic aminoesters.

The method was tolerant of both linear and branched allylic carbonates (entries 1 and 2−13, respectively). Aryl rings with diverse substitution patterns could be incorporated, including electron-donating and -withdrawing groups (entries 2−6). Aliphatic allylic carbonates with hydrocarbon substituents, such as isopropyl, pentyl, and benzyl, furnished the desired cyclic aminoester products as predominantly single diastereomers (entries 7−9). Cyclic aminoester products with heteroatomic functional groups were also generated, including a phthalimide (entry 10) and a thioether (entry 11). We were interested in these heteroatom-bearing products because of their potential to be transformed into unnatural cyclic amino acids with nucleophilic side chains. Interestingly, ring-closing metathesis with the sulfur-containing substrate was only successful in the presence of the Grubbs second generation catalyst **13a**. Finally, cyclic aminoesters with benzophenone and azide substituents were generated in 63% and 60% yields over two steps, respectively (entries 12−13). We anticipate that the benzophenone product can be converted into a photo-cross-linking probe (entry 12), and the azide product can be useful for click chemistry applications (entry 13).

We explored the scope of this method further by examining aminoester **14** (Scheme 3a). This bis-homoallylic substrate underwent the palladium-catalyzed tandem allylic amination/[2,3]-Stevens rearrangement followed by a ruthenium-catalyzed ring-closing metathesis at 40 °C to furnish the eight-membered ring cyclic aminoester **15** in 75% yield and 4:1 dr. The relative stereochemistry of the major diastereomer was confirmed by X-ray crystallography.

Access to enantiopure unnatural cyclic amino acids is imperative for the integration of our method into biological applications. In this context, we subjected aminoester **16**, which was functionalized with Oppolzer's chiral auxiliary,[15,9f] to our two-step protocol (Scheme 3b). Gratifyingly, we isolated cyclic aminoester **17** as a single stereoisomer.[16] The absolute and relative stereochemistry of this ring-closing metathesis product was confirmed by X-ray crystallography. Moreover, aminoester **17** was converted in two steps to enantiopure cyclic amino acid **18**. Access to this unnatural cyclic amino acid will provide new opportunities for controlling the conformation of synthetic peptides.

In conclusion, we have developed a mild and stereoselective method to access unnatural cyclic amino acid derivatives via a palladium-catalyzed tandem allylic amination/[2,3]-Stevens rearrangement followed by a ring-closing metathesis. This method allows for the incorporation of multiple functionalized side chains, including substituted aromatic rings, nucleophilic groups, a benzophenone, and an azide. Utilization of Oppolzer's chiral auxiliary provides access to enantioenriched cyclic amino acids. We are exploring the incorporation of these cyclic amino acids into peptide chains via automated peptide synthesis for specific biological applications.

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Supporting Information Available. Full experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969.

(16) NMR analysis of the unpurified product from the allylic amination/[2,3]-rearrangement indicated an 8:2:1:0 dr.

The authors declare no competing financial interest.