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Synthesis of *syn*-1,3-Aminoalcohols via a Ru-Catalyzed *N*-Demethylative Rearrangement of Isoxazolidines and Its Application in a Three-Step Total Synthesis of HPA-12

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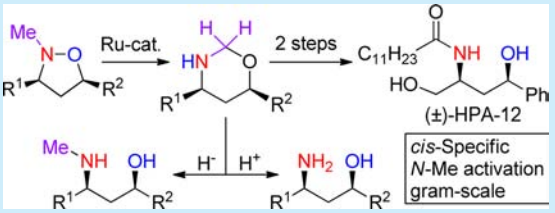
Supporting Information

ABSTRACT: A highly efficient ruthenium-catalyzed stereospecific *N*-demethylative rearrangement of isoxazolidines to synthetically useful *N*−H-1,3-oxazinanes is described. 1,3-Oxazinanes are useful building blocks, which can be further converted to *N*−H-1,3-aminoalcohols in one step. This new method was used in a three-step gram-scale total synthesis of HPA-12 in an overall 24% yield.

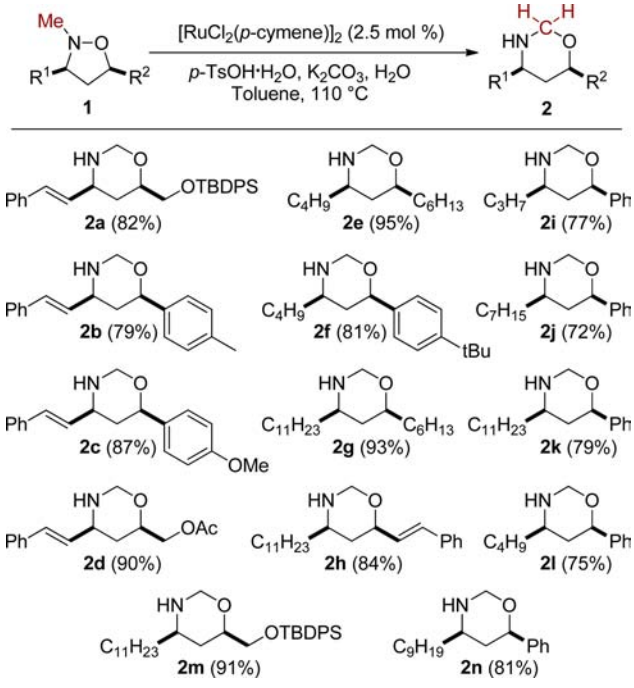


1,3-Oxazinanes are useful bioactive compounds and synthetic intermediates,[1] which can be hydrolyzed to prepare *N*−H 1,3-aminoalcohols. 1,3-Aminoalcohols[2] are also useful synthetic intermediates or targets for many natural products or bioactive compounds such as HPA-12. A Mannich or aldol reaction followed by reduction is usually used to prepare 1,3-aminoalcohols.[3] HPA-12 is a novel inhibitor of ceramide trafficking from the endoplasmic reticulum to the site of sphingomyelin synthesis.[4] It was first discovered in 2001 and originally assigned as 1,3-*anti*.[4a] In 2011, Berkeš et al. reported a synthesis of HPA-12, and its stereoconfiguration was revised as *syn*.[5] In 2013, Kobayashi et al. confirmed this stereochemistry.[6] In this work, we wish to report our recent progress on the stereospecific synthesis of *syn*-*N*−H-1,3-aminoalcohols via a ruthenium-catalyzed *N*-demethylative isomerization of isozaolidines and its application in the short total synthesis of HPA-12.

First, *cis*-isoxazolidines **1a**−**1n** were subjected to the catalytic conditions to afford the *N*−H 1,3-oxazinanes **2** in generally high yields (Scheme 1). The *N*-methyl group was activated to gain insertion into the N−O bonds, forming the ring expanded products **2a**−**2n**. The N−O bond cleavage does not need an extra hydride; thus, a self-hydride transferring strategy was involved. Since **2** could be hydrolyzed to remove the methylene group, here the methyl group formally worked as a protecting group. Various aliphatic as well as aromatic substituents were investigated. In all cases only *cis*-products were obtained. With respect to the *N*−H 1,3-oxazinane with a fused ring skeleton, **2o** was obtained from corresponding starting material **1o** in 71% yield (Scheme 2).

A proposed reaction mechanism is shown in Scheme 3. The reaction might pass through an N−O oxidative insertion pathway (a) or a single-electron-transfer (SET) pathway (b), all via the key intermediate **C**. The Ru-catalyst is regenerated after the proton transfer. Both pathways seem possible. So far, we still cannot be able to determine which one could be more rational.

Scheme 1. *N*-Demethylative Rearrangement of Isoxazolidines to *N*−H-1,3-Oxazinanes[a]



[a]Isolated yields. TBDPS = *tert*-butyldiphenylsilyl. See Supporting Information for details.

cis-1,3-Oxazinanes were further converted to *syn*-1,3-aminoalcohols via one simple step. Products **2** were treated with $NH_2OH{\cdot}HCl$ in wet methanol[7] to afford *syn*-*N*−H-1,3-aminoalcohols **3** (Scheme 4). If oxazinanes **2** were treated

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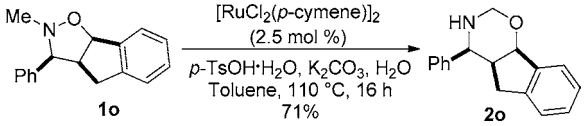
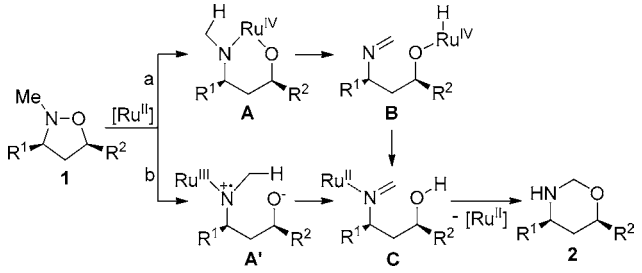
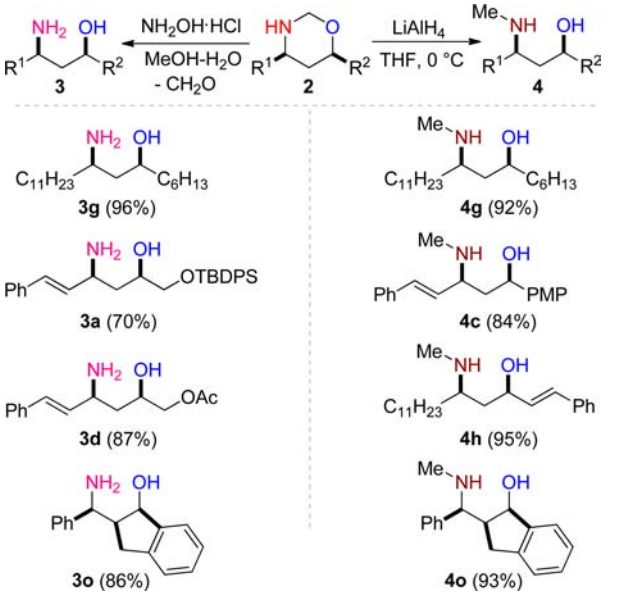
Scheme 2



Scheme 3. Possible Mechanism



Scheme 4. Synthesis of 1,3-Aminoalcohols from 2

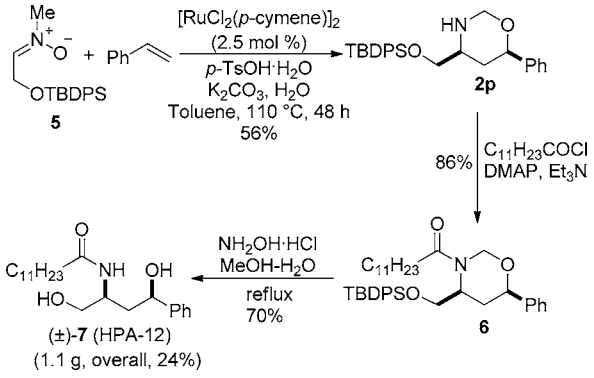


with $LiAlH_4$, the corresponding *syn*-*N*-methyl-1,3-aminoalcohols **4** were afforded in high yields.[8] Thus, from the same starting material **2**, both *N*−H and *N*-methyl 1,3-aminoalcohols could be prepared in high yields.

This method was used in the synthesis of HPA-12 (Scheme 5). Luckily, HPA-12 bears a *syn*-1,3-aminoalcohol moiety. The key *cis*-intermediate **2p** was obtained via the one-flask cycloaddition of nitrone **5** with styrene, followed by the ruthenium-catalyzed *N*-demethylative rearrangement of the isoxazolidine intermediate in 56% yield. The subsequent acylation with lauroyl chloride afforded **6** in 86% yield. At last, **6** was treated with $NH_2OH·HCl$ to furnish the final target **7** in 70% yield. In this three-step gram-scale total synthesis, 1.1 g of HPA-12 was obtained in an overall 24% yield.

In conclusion, we have developed a highly efficient ruthenium-catalyzed stereospecific *N*-demethylative rearrangement of isoxazolidines. By this method, synthetically useful *N*−H-1,3-oxazinanes were afforded in high yields. The oxazinanes were further converted to either *N*−H- or *N*-methyl-1,3-aminoalcohols in one step. This method was applied in a gram-scale three-step total synthesis of HPA-12 in an overall 24% yield.

Scheme 5. Three-Step Synthesis of (±)-HPA-12



■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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