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Ruthenium-Catalyzed Asymmetric *N*-Demethylative Rearrangement of Isoxazolidines and Its Application in the Asymmetric Total Syntheses of (−)-(1*R*,3*S*)-HPA-12 and (+)-(1*S*,3*R*)-HPA-12

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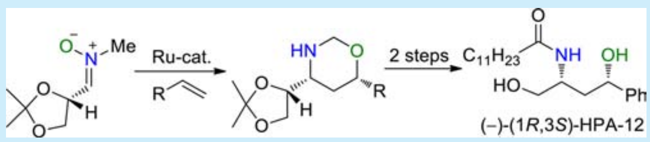
Supporting Information

ABSTRACT: An asymmetric *N*-demethylative rearrangement of 1,2-isoxazolidines catalyzed by ruthenium is described. Enantioenriched *syn*-1,3-aminoalcohols as well as *cis*-1,3-oxazinanes, which are useful building blocks, can be efficiently prepared stereospecifically by this reaction in good yields, via the isoxazolidine intermediates *in situ* generated from a nitrone bearing a chiral auxiliary and styrenes. This asymmetric reaction was also applied in the asymmetric total syntheses of both (−)-(1*R*,3*S*)-HPA-12 and (+)-(1*S*,3*R*)-HPA-12.



1,3-Oxazinanes,[1] especially chiral 1,3-oxazinanes,[2] are important subunits in natural products[3] and useful building blocks among which some can be easily hydrolyzed to 1,3-aminoalcohols.[4,5] However, efficient and stereospecific routes to *N*—H *cis*-1,3-oxazinane are rare.[2] Enantioenriched *syn*-1,3-aminoalcohols are useful synthetic intermediates or targets for bioactive compounds; thus, it is important to develop divergent methods to afford different *syn*-1,3-aminoalcohols. Although types of enantioselective reduction of *β*-hydroxyl imines[6] or *β*-amino ketones[7] and intramolecular allylic functionalization or substitutions[8] have been well established to prepare enantioenriched *syn*-1,3-aminolalcohols, normally it is difficult to furnish *syn* specific 1,3-aminoalcohols in the reduction. Among different derivatives of 1,3-aminolalcohol, HPA-12 is a novel inhibitor of ceramide trafficking from the endoplasmic reticulum to the site of sphingomyelin synthesis.[9] HPA-12 was first synthesized in 2002 and assigned as 1,3-*anti* by Kobayashi et al.[9a] In 2011, the stereoconfiguration of HPA-12 was revised as *syn* by Berkeš et al.[10] Then Kobayashi et al. confirmed the stereochemistry.[11] The problem emerging in the assignment of stereoconfiguration was partially due to the original synthetic procedure. Thus, a reliable, highly efficient, and stereoselective method for the asymmetric *cis*-specific synthesis of HPA-12 is still valuable. In this work, we wish to report a highly efficient stereospecific synthesis of enantioenriched *syn*-1,3-aminoalcohols and *cis*-1,3-oxazinanes via a ruthenium-catalyzed asymmetric *N*-demethylative rearrangement of 1,2-isoxazolidines.

Chiral nitrone *ent*-**1** bearing a chiral auxiliary was subjected to the ruthenium-catalyzed *N*-demethylative rearrangement of the *in situ* generated isoxazolidine intermediate, affording the chiral *cis*-1,3-oxazinane *ent*-**3a** in 84% yield as a single diastereomer (Table 1). Other products bearing substituents such as 4-fluruophenyl, 4-methylphenyl, and 1-naphthyl were all obtained in good yields. The phenyl with a strong electron-donating group such as a methoxyl group afforded a relatively lower yield of *ent*-**3e**. For the aliphatic substituents, several alkenes such as 1-octene and allylbenzyl ether were also tested (not shown in the table). The reaction afforded an inseparable mixture of the diastereomers. Thus, only aryl alkenes are so far reported here. Generally, all the aromatic alkenes investigated gave corresponding enantioenriched oxazinane products in good yields.

After establishing the method, it was applied in a gram-scale asymmetric total synthesis of each enantiomer of HPA-12 (Scheme 1). First, *N*—H *cis*-oxazinane **3h** was prepared from **1** and styrene in 55% yield. After acylation with lauroyl chloride, the intermediate was subjected to the hydrolysis—oxidation—reduction procedure[12] to produce the alcohol intermediate **4**. Final target (−)-(1*R*,3*S*)-HPA-12 **5** (1.2 g) was obtained in overall 18.2% yield via a mild hydrolysis of **4** with $NH_2OH{\cdot}HCl$ in wet acidic methanol.[13] The enantiomeric excess value of the product (−)-**5** was determined to be 99.6% by HPLC on a chiral AD-H column. The $[\alpha]_D^{20}$ value was −38.9 (*c* 0.36, $CHCl_3$), which matched the literature report (−34.4).[10] To further confirm the stereoconfiguration of **5**, its enantiomer (+)-(1*S*,3*R*)-HPA-12 (*ent*-**5**) was also synthesized from *ent*-**1** using the same procedure and obtained in 19.5% yield (1.27 g, 99.4% ee). The $[\alpha]_D^{20}$ value of *ent*-**5** was determined to be +36.1, which was comparable to that of **5**.

The stereochemistry of this reaction could probably be understood using the model demonstrated in Scheme 2. The chiral auxiliary on nitrone **1** effects the steric hindrance in the transition state, where **1** could be attacked by styrene from both sides. Whereas the left side (a) has a larger steric hindrance, which gives rise to a disfavored transition state, the right side (b) attack is favored, which gives the (3*R*,5*S*)-diastereomer as the major isoxazolidine intermediate. The *cis*-selectivity for the isoxazolidine intermediate arises from the intrinsic *exo*-selective nature of 1,3-dipolar cycloaddition of an *N*-Me nitrone and

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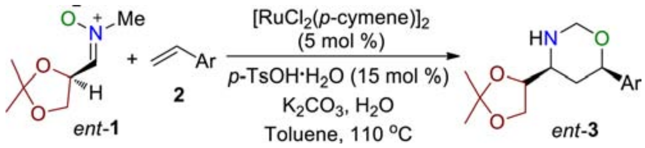
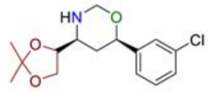
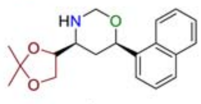
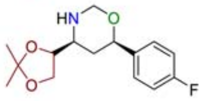
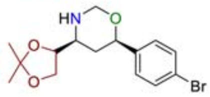
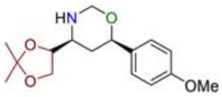
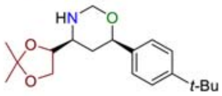
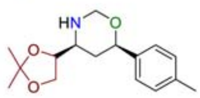
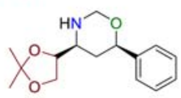
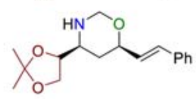
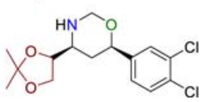
Table 1. Ruthenium-Catalyzed Asymmetric Synthesis of *N*-H 1,3-Oxazinanes via the *N*-Demethylative Rearrangement of Isoxazolidines[a]



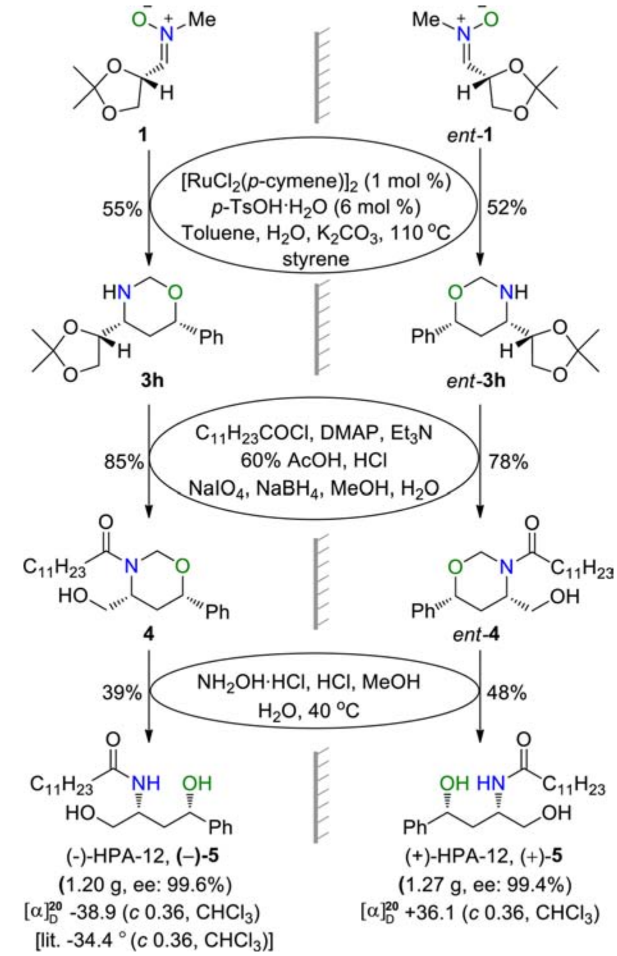
entry	*N*–H 1,3-oxazinane	*ent*-3	yield(%)[b]
1		*ent*-**3a**	84
2		*ent*-**3b**	78
3[c]		*ent*-**3c**	84
4		*ent*-**3d**	71
5		*ent*-**3e**	64
6		*ent*-**3f**	70
7		*ent*-**3g**	79
8		*ent*-**3h**	70
9		*ent*-**3i**	71
10		*ent*-**3j**	69

[a]Reaction conditions: *ent*-**1** (0.5 mmol), **2** (2 mmol), H_2O (1.0 mmol), K_2CO_3 (0.5 mmol), toluene (2 mL), 110 °C; then $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), *p*-TsOH·H_2O (15 mol %), 110 °C. See Supporting Information for details. [b]Isolated yields.

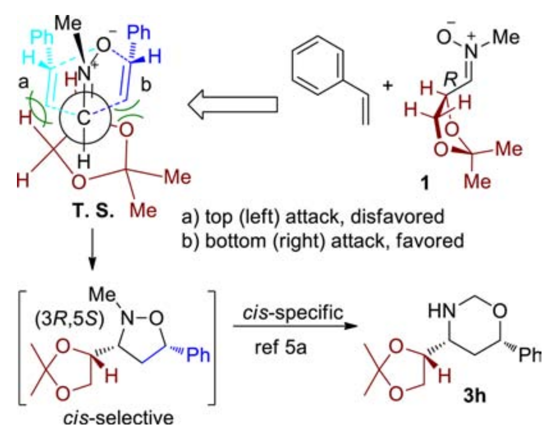
styrene, whose transition state needs to avoid the steric hindrance between the *N*-Me and the phenyl on the styrene. The *cis*-specific rearrangement of the *N*-Me isoxazolidine intermediate probably arises from the difference in steric hindrance between the Ru-catalyst and *cis*- or *trans*-isoxazolidine.[5a]

In conclusion, a highly efficient ruthenium-catalyzed asymmetric *N*-demethylative rearrangement of isoxazolidines has been developed. This reaction has been used as a powerful scaffold for the synthesis of optically active *syn*-1,3-amino-alcohols as well as *syn*-1,3-oxazinanes. This asymmetric reaction was also applied in the asymmetric total syntheses of (−)-(1*R*,3*S*)-HPA-12 and (+)-(1*S*,3*R*)-HPA-12. Easily available chiral substrates, highly *cis*-specific reactivity, and synthetic usefulness are all highlights of this reaction.

Scheme 1. Asymmetric Synthesis of HPA-12 via the *N*-Demethylative Rearrangement of Isoxazolidines



Scheme 2. Possible Model for the Stereochemistry



■ 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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