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Asymmetric 1,3-Dipolar Cycloaddition Utilizing Tartaric Acid Ester as a Chiral Auxiliary

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In order to develop a practical method for the construction of chiral molecules, we have designed a novel chiral system possessing two metal centers utilizing tartaric acid esters. Based on this concept, catalytic asymmetric 1,3-dipolar cycloaddition of nitrile oxides and nitrones could be achieved with an high level of stereocontrol.

INTRODUCTION

The development of a practical and efficient method for the construction of chiral molecules is essential to explore new medicines and agricultural chemicals. It is obvious that the design of a specific chiral environment utilizing chiral auxiliaries, both enantiomers of which are easily available, provides a useful

way to prepare optically active substances. Among such chiral auxiliaries, tartaric acid esters are one of the most promising and readily available candidates.

We have designed a novel chiral system possessing two metal centers utilizing tartaric acid esters. If two reactants were bound to two different metal centers of the dialkoxide derived from tartaric acid ester, which might form a rigid 5/5-fused bicyclic dinucleating structure, they might be ideally oriented and/or activated by the metals, and the subsequent reaction might proceed in an enantioselective manner to afford the corresponding optically active products (Fig. 1). According to this hypothesis, we already developed an asymmetric Simmons-Smith reaction.[1)] In this article, we wish to describe asymmetric 1,3-dipolar cycloadditions of nitrile oxides and nitrones.

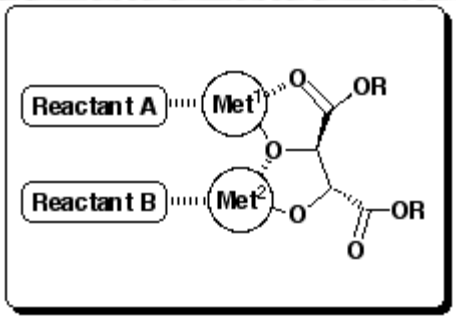
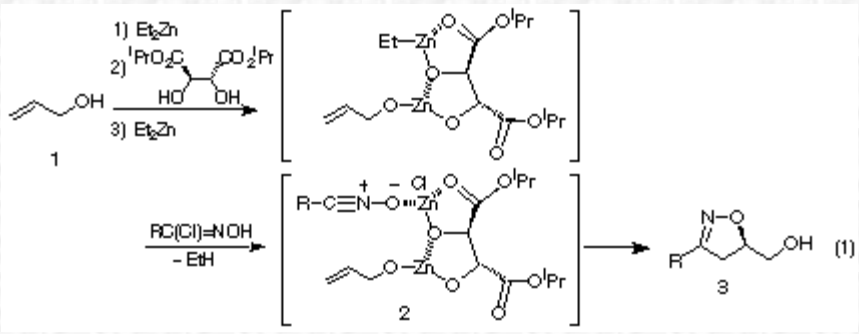


Fig. 1. A novel chiral dinucleating system derived from tartaric acid esters

1. Stoichiometric Asymmetric 1,3-Dipolar Cycloaddition of Nitrile Oxides

Our new idea was as follows: when allyl alcohol (1) was successively treated with diethylzinc, (*R,R*)-tartaric acid ester, a second diethylzinc, and hydroximoyl chloride, the dinucleating intermediate 2 might be formed by action of ethylzinc as a base toward hydroximoyl chloride to generate the nitrile oxide *in situ*, and the subsequent 1,3-dipolar cycloaddition was anticipated to proceed in a stereoselective manner to give the corresponding 2-isoxazoline 3 in an optically active form (Eq. (1)).



In accordance with this hypothesis, the asymmetric 1,3-dipolar cycloaddition was performed (Eq. (2)). After optimizing the molar amounts of diethylzinc and hydroximoyl chloride, the corresponding 2-isoxazolines 3 could be obtained in excellent optical yields up to 98% ee, not only for aromatic nitrile oxides but also for aliphatic ones.[2] Optimal molar amounts might be related to the reactivity of nitrile oxides toward dimerization and/or the ethylzinc reagent as well as toward allyl alcohol (1) through 2.

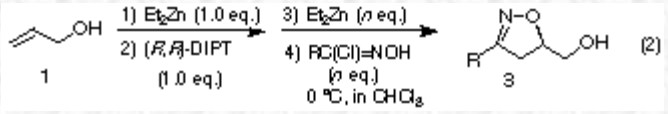


Table I. Asymmetric 1,3-dipolar cycloaddition of nitrile oxides to 1

Entry	R	*n*	3	Yield/%	ee/%
1	C_6H_5	2.0	a	78	96
2	4-$CH_3OC_6H_4$	1.1	b	83	98
3	4-ClC_6H_4	1.1	c	74	93
4	$(CH_3)_3C$	1.5	d	92	96
5	$CH_3(CH_2)_5CH_2$	1.5	e	64	95

2. Catalytic Asymmetric 1,3-Dipolar Cycloaddition of Nitrile Oxides

Among [4p+2p] cycloadditions, many catalytic asymmetric Diels-Alder reactions using chiral Lewis acids have been reported. By contrast, the catalytic asymmetric 1,3-dipolar cycloaddition has not yet met with success. The achievement of a catalytic 1,3-dipolar cycloaddition of a nitrile oxide was rather difficult because the reagent is usually too unstable to be isolated and must be generated *in situ*.

The 1,3-dipolar cycloaddition of nitrile oxide using a catalytic amount (0.2 molar amount) of (*R,R*)-DIPT was examined with special attention directed to the order of addition and the molar ratio of the reagents. In the attempts to realize reproducibly high enantioselectivity, the addition of a small amount of an ethereal compound such as 1,4-dioxane was found to be markedly effective. As shown in Table II, the corresponding 2-isoxazolines 3 could be reproducibly obtained with high enantioselectivity not only

for aromatic nitrile oxides but also for aliphatic ones.[3)]

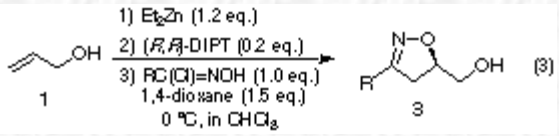
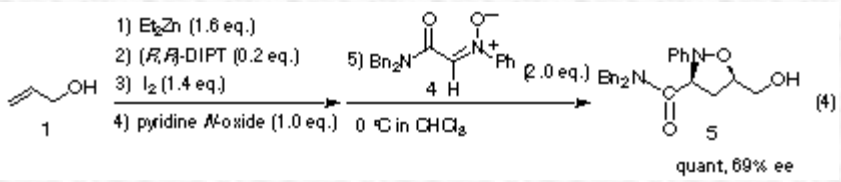


Table II. Catalytic asymmetric 1,3-dipolar cycloaddition of nitrile oxides

Entry	R	3	Yield/%	ee/%
1	C_6H_5	a	87	84
2	4-$CH_3OC_6H_4$	b	98	90
3	4-ClC_6H_4	c	91	90
4	$(CH_3)_3C$	d	91	93
5	$CH_3(CH_2)_5CH_2$	e	62	92

3. Catalytic Asymmetric 1,3-Dipolar Cycloaddition of Nitrone

The catalytic asymmetric 1,3-dipolar cycloaddition of nitrone 4 to an achiral allyl alcohol (1) also proceeded enantioselectively when a catalytic amount of (*R,R*)-DIPT was used as a chiral auxiliary to afford *cis*-isoxazolidine 5 in good optical yield. The addition of an amine oxide such as pyridine *N*-oxide was essential to realize reproducible stereoselection.[4)]

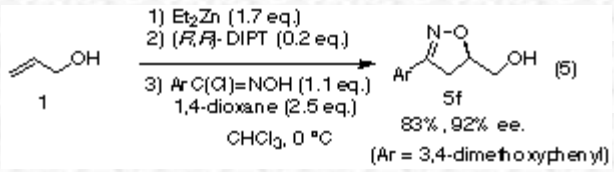


4. Enantioselective Synthesis of (-)-Lasubine II

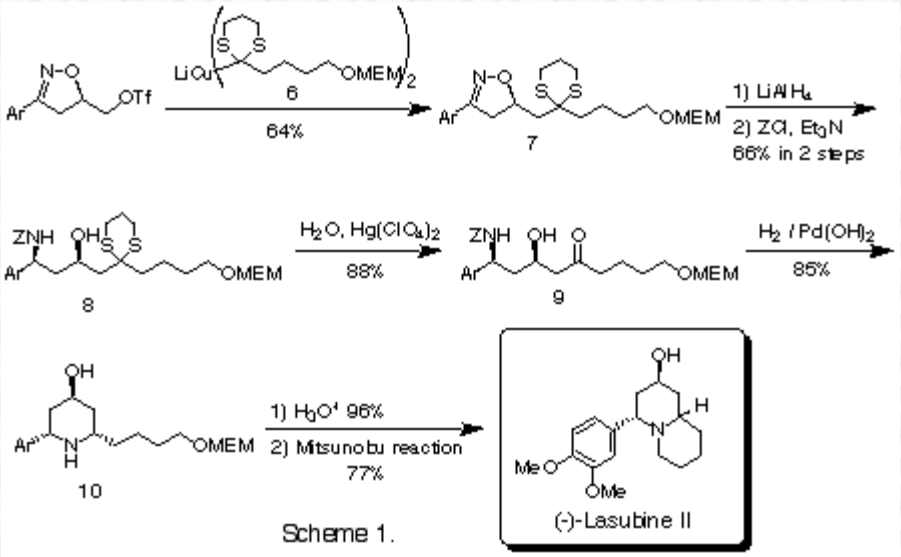
The utility of this asymmetric 1,3-dipolar cycloaddition in the challenging arena of total synthesis of natural products was next explored. The lythraceae alkaloid lasubine II was isolated from the leaves of *Lagerstroemia subcostata* Koehne. In our synthetic strategy for this target molecule, optically active 2-isoxazoline was firstly prepared and then transformed to bicyclic lasubine II stereoselectively by

sequential reduction and cyclization.

The catalytic asymmetric 1,3-dipolar cycloaddition of 3,4-dimethoxybenzonitrile oxide to allyl alcohol (1) gave the corresponding 2-isoxazoline 5f with excellent enantioselectivity (Eq. (5)).



The optically pure 2-isoxazoline 5f obtained by recrystallization was converted to its triflate and coupled with cuprate 6 to give 7. At this stage, the whole carbon skeleton required for the synthesis of lasubine II was arranged. The reduction of isoxazoline 7 followed by the protection of the resulting amino group gave mainly the *N*-protected *syn*-amino alcohol 8 along with its *anti*-isomer. After the hydrolysis of the dithioacetal group, the reductive deprotection of the amino group in b-hydroxy ketone 9 afforded the *cis*-2,6-disubstituted piperidin-4-ol 10 stereoselectively *via* spontaneous formation of cyclic imine and subsequent reduction. The amino alcohol derived from 10 by the hydrolysis of the MEM group was cyclized by applying the Mitsunobu reaction to afford optically active (-)-lasubine II.[5)]



Scheme 1.

CONCLUSIONS

We have designed a novel chiral system possessing two metal centers utilizing tartaric acid esters, and asymmetric cycloadditions have been developed. Although the evidence of a dinucleating species from X-ray analysisis was not yet shown directly, this concept can be extended to other asymmetric reactions

such as asymmetric nucleophilic addition,[6] since numerous combinations of metals are possible. Furthermore, the ready availability of (*R,R*)- and (*S,S*)-tartaric acid esters has made possible the preparation of both enantiomers of the required substances by simple procedures.

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