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Enantioselective Synthesis of 2-Isoxazolines *via* Asymmetric 1,3-Dipolar Cycloaddition of Nitrile Oxide to Achiral Allyl Alcohol

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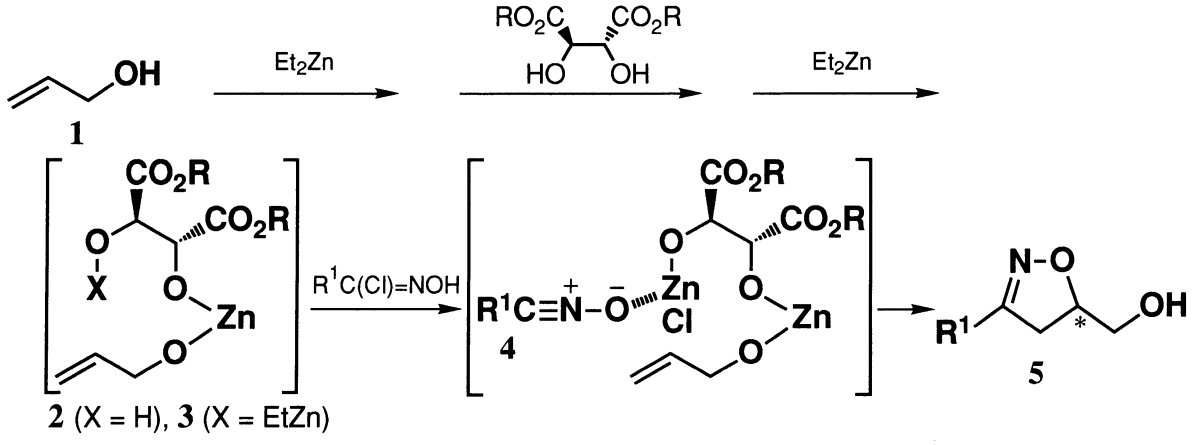
The asymmetric1,3-dipolar cycloaddition of a nitrile oxide to an achiral allyl alcohol was achieved by the use of (*R*,*R*)-diisopropyl tartrate as a chiral auxiliary. Treatment of the allyl alcohol with diethylzinc and the tartrate, followed by the addition of diethylzinc and a hydroximoyl chloride, afforded the corresponding (*R*)-2-isoxazolines with excellent enantioselectivity.

2-Isoxazolines are versatile intermediates in organic synthesis.[1] Reductive cleavage of the N-O bond provides β-hydroxy ketones or β-amino alcohols. 1,3-Dipolar cycloaddition of nitrile oxide to olefins is the most useful method for the preparation of 2-isoxazolines, and several methods have been reported for the synthesis of optically active 2-isoxazolines *via* cycloaddition of nitrile oxide to acrylic acid derivatives possessing chiral auxiliaries.[2] However, those methods still required introduction and removal of chiral auxiliaries on the olefinic acceptor. In this paper, we wish to describe the first example of the direct enantioselective construction of 2-isoxazolines by the asymmetric 1,3-dipolar cycloaddition of a nitrile oxide to an achiral allyl alcohol.

Recently, we reported an asymmetric Simmons-Smith reaction of allylic alcohols by the use of diethylzinc, diiodomethane, and tartaric acid ester as a chiral auxiliary to give optically active cyclopropylmethyl alcohols.[3] We expected that this kind of the enantioselective cycloaddition would be extended to other cycloaddition to allylic alcohols. For instance, when allyl alcohol (**1**) was treated with equimolar amounts of diethylzinc and a (*R*,*R*)-tartaric acid ester, the zinc-bridging intermediate **2** was presumably formed as described in the asymmetric Simmons-Smith reaction we have reported. To the



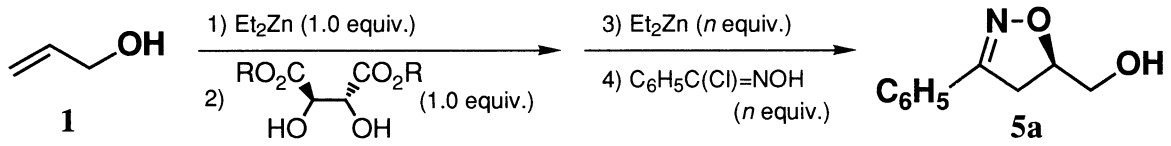


Table 1. The 1,3-dipolar cycloaddition of benzonitrile oxide to allyl alcohol (**1**) using (*R*,*R*)-tartaric acid esters

Entry	R	*n*	Solvent	Temp/ °C	Time/h	Yield/%	Optical yield/% ee[a)]
1	CH_3CH_2	2.0	THF	0	24	35	51
2		2.0	$(CH_3CH_2)_2O$	0	20	55	58
3		2.0	$C_6H_5CH_3$	0	12	60	77
4		1.0	CH_2Cl_2	0	16	50	65
5		1.5	CH_2Cl_2	0	9	60	84
6		2.0	CH_2Cl_2	0	19	63	89
7		2.5	CH_2Cl_2	0	14	67	65
8		2.0	$ClCH_2CH_2Cl$	0	17	65	88
9		2.0	$CHCl_3$	0	11	69	95
10		2.0	CCl_4	0	12	71	85
11	CH_3	2.0	$CHCl_3$	0	11	69	92
12	$(CH_3)_2CH$	2.0	$CHCl_3$	0	12	78	96
13		2.0	$CHCl_3$	-20	5	83	89
14	$CH_3(CH_2)_3$	2.0	$CHCl_3$	0	11	58	94

a) Optical yields were determined by HPLC analysis (Daicel Chiralcel OD-H) of the (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) ester derivatives.

intermediate was added another equivalent of diethylzinc to afford zinc alkoxide **3**. Subsequently, a hydroximoyl chloride was added to generate the nitrile oxide **4**, which would coordinated to zinc metal,[4)] and the 1,3-dipolar cycloaddition would be anticipated to proceed in a stereoselective manner to give the corresponding 2-isoxazoline **5** in optically active form. According to this hypothesis, the asymmetric 1,3-dipolar cycloaddition was investigated for various tartaric acid esters as chiral auxiliaries.

First, the reaction between benzonitrile oxide (**4a**) and allyl alcohol (**1**) was examined in several solvents at 0 °C and the results were summarized in Table 1. When (*R*,*R*)-diethyl tartrate was used as a chiral auxiliary, CH_2Cl_2 was more effective than THF, $(CH_3CH_2)_2O$, and $C_6H_5CH_3$ (Entries 1-3, 6). After the detailed examination using halogenated solvents, it was found that $CHCl_3$ was the solvent of choice for the asymmetric 1,3-dipolar cycloaddition to produce the corresponding 2-isoxazoline **5a** in 95% ee (Entries 6, 8-10). In this 1,3-dipolar cycloaddition, propiophenone oxime and dimer of benzonitrile oxide were obtained as by-products. Further, the molar quantities of the latter diethylzinc and hydroximoyl chloride were found to influence the optical yield. In the reaction of benzonitrile oxide, the use of 2.0 equivalents of diethylzinc and hydroximoyl chloride was favorable (Entries 4-7). Although little difference appeared in the stereoselectivities among the used esters of tartaric acids such as methyl, ethyl, isopropyl, and butyl esters, higher yield was achieved utilizing diisopropyl tartrate (DIPT) with the selectivity of 96% ee (Entries 9, 11, 12, and 14). The reaction using DIPT at -20 °C could not be improved for the stereoselectivity (Entry 13).

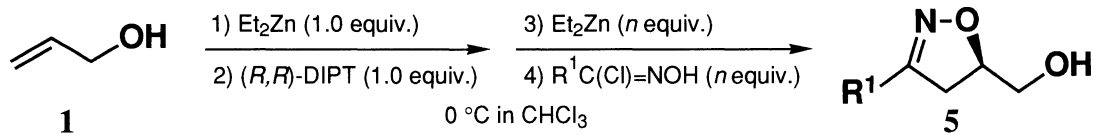


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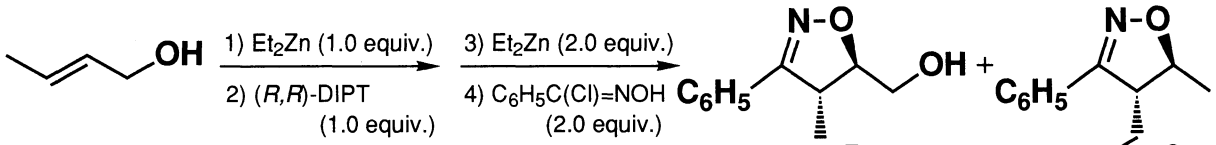
Table 2. The asymmetric 1,3-dipolar cycloaddition of nitrile oxides to allyl alcohol (**1**) using (*R,R*)-DIPT[a)]

Entry	R^1		*n*	Time/h	Yield/%	Optical yield/% ee	$[\alpha]_D^{25}$
1	C_6H_5	**a**	2.0	12	78	96[b)]	-164° (c 0.7, $CHCl_3$)
2	*p*-ClC_6H_4	**b**	1.1	16	74	93[c)]	-129° (c 0.7, MeOH)
3	*p*-$CH_3OC_6H_4$	**c**	1.1	16	83 (65)[d)]	98[c)]	-120° (c 0.4, MeOH)
4	$(CH_3)_3C$	**d**	1.5	17	92	96[b)]	-116° (c 0.4, $CHCl_3$)
5	$CH_3(CH_2)_6$[e)]	**e**	1.5	20	64	95[b)]	-91° (c 0.7, MeOH)

a) Reactions were performed on 0.5 mmol scale. b) Optical yields were determined by HPLC analysis (Daicel Chiralcel OD-H) of the (*R*)-MTPA ester derivatives. c) Optical yields were determined by direct HPLC analysis (Daicel Chiralcel OD-H). d) Yield of the reaction on 7.5 mmol scale as described in the text. e) Crude hydroximoyl chloride, prepared from the corresponding oxime,[5)] was used without further purification.

Next, the asymmetric cycloaddition of several nitrile oxides to allyl alcohol (**1**) was performed. After brief optimization of the molar quantities of diethylzinc and hydroximoyl chloride,[6)] the corresponding 2-isoxazolines **5** could be obtained in excellent optical yields (Table 2). Among the nitrile oxides, not only aromatic nitrile oxides **4a-c** but also aliphatic ones **4d**, **e** were found to react with excellent stereoselectivity.

Furthermore, the asymmetric 1,3-dipolar cycloaddition of benzonitrile oxide (**4a**) to (*E*)-2-buten-1-ol (**6**) was performed to give the corresponding (4*R*,5*R*)-2-isoxazoline **7** (28%, 64% ee) and the regioisomer **8** (8%, 2% ee[7)]). The enantioselectivity of **7** was not so high as the case of allyl alcohol (**1**).



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The absolute configurations of the 2-isoxazolines **5a** and **5d** were determined to be *R* by the comparison of their specific rotations with the reported data,[2a,e,f)] respectively. The stereochemical course of the 1,3-dipolar cycloaddition was found to be similar to the asymmetric Simmons-Smith reaction,[3)] that is, the nitrile oxides were added from the front side of the allyl alcohol when it was depicted like **1**. Although the precise mechanism is still an open question, the stereochemical course could be explained by a bimetallic transition state model (Fig. 1), in which the rigid 5/5-fused bicyclic structure is formed by zinc-bridging.

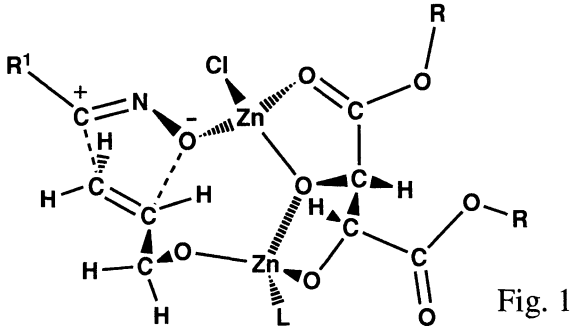

Fig. 1

The representative procedure for the enantioselective 1,3-dipolar cycloaddition reaction is as follows: To a $CHCl_3$ (15 ml) solution of an allyl alcohol (**1**) (0.436 g, 7.5 mmol) was added diethylzinc (7.6 mmol, 7.6 ml of 1.0 M solution in hexane) at 0 °C under an argon atmosphere, and the mixture was stirred for 10 min. To the solution, a $CHCl_3$ (15 ml) solution of (*R,R*)-DIPT (1.78 g, 7.6 mmol) was added and the mixture was stirred for 1 h. Diethylzinc (8.2 mmol) and a $CHCl_3$ (15 ml) solution of *p*-methoxybenzohydroximoyl chloride (1.52 g, 8.2 mmol) were added in successively, and the resulting solution was stirred for 16 h at 0 °C. The reaction was quenched by addition of saturated aq NH_4Cl. Purification by column chromatography on silica gel afforded (*R*)-5-(hydroxymethyl)-3-(*p*-methoxyphenyl)-2-isoxazoline (**5c**) (1.01 g, 65%) in 98% ee.

In summary, the enantioselective construction of 2-isoxazolines was developed starting from an achiral allyl alcohol. This method has merits to be noted; introduction of the chiral auxiliary to the substrate and its removal are not necessary; both enantiomers of 2-isoxazolines could be synthesized because of the availability of (*R,R*)- and (*S,S*)-tartaric acid esters. Thus, this method provides the useful way to prepare optically active 2-isoxazolines.

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4) It was reported that nitrile oxide was generated through *O*-metalation of hydroximoyl chloride. The subsequent cycloaddition to allylic alcohol proceeded diastereo- and regioselectively especially when the generated nitrile oxide coordinated to magnesium metal: S. Kanemasa, S. Kobayashi, M. Nishiuchi, H. Yamamoto, and E. Wada, *Tetrahedron Lett.*, **32**, 6367 (1991); S. Kanemasa, M. Nishiuchi, and E. Wada, *ibid.*, **33**, 1357 (1992).

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6) Optimal molar quantities might be related to the reactivity of nitrile oxides for dimerization and the reactivity of ethylzinc reagent to the nitrile oxides.

7) The absolute configuration of **8** was not determined.

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