

A Catalytic Asymmetric 1,3-Dipolar Cycloaddition of Nitrones to Allyl Alcohol

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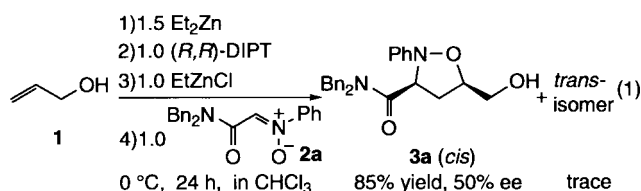
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A highly diastereo- and enantioselective 1,3-dipolar cycloaddition of nitrones bearing an amide moiety to allyl alcohol has been realized by using a catalytic amount of diisopropyl (*R,R*)-tartrate as a chiral auxiliary. Addition of amine *N*-oxide such as pyridine *N*-oxide, was crucial to realize a reproducible excellent enantioselectivity up to 98% ee.

A 1,3-dipolar cycloaddition is one of the most important reactions for the construction of 5-membered heterocyclic compounds. Among the 1,3-dipolar cycloadditions, the asymmetric one of nitrones to olefins seems to be a useful reaction to prepare isoxazolidines which are key synthetic intermediates for the synthesis of optically active nitrogen-containing chemicals such as γ -amino alcohols. Recently, the development of this type of reaction has entered a new stage to control the enantioselectivity in the addition step.¹ For example, several stereocontrolled 1,3-dipolar cycloadditions to olefins with oxazolidone moiety utilizing chiral Lewis acids were reported.^{2,3} As a part of our research on asymmetric 1,3-dipolar cycloadditions,⁴ we have reported the enantioselective 1,3-dipolar cycloaddition of nitrones possessing a *t*-butoxycarbonyl or cyano group to allyl alcohol by the use of a stoichiometric amount of diisopropyl (*R,R*)-tartrate [(*R,R*)-DIPT] as a chiral auxiliary to afford the optically active *trans*-isoxazolidines.⁵ Herein, we wish to describe a catalytic enantioselective 1,3-dipolar cycloaddition of nitrones bearing an amide group to afford the corresponding *cis*-isoxazolidines, in contrast to the previous *trans*-adducts, with high regio-, diastereo- and enantioselectivities.

Firstly, a 1,3-dipolar cycloaddition of a nitrone **2a**⁶ bearing dibenzylamide moiety to allyl alcohol (**1**) was investigated using a stoichiometric amount of (*R,R*)-DIPT (eq 1). To our surprise, the corresponding optically active *cis*-isoxazolidine **3a** was obtained in 85% yield with 50% ee along with a trace amount of its *trans*-isomer.



The modest enantioselectivity obtained above prompted us to optimize the conditions toward the catalytic reaction using a 0.2 molar amount of (*R,R*)-DIPT. In order to obtain the reproducible results, it was required to generate zinc halide species *in situ*⁷ from ethylzinc species and iodine to avoid moisture (eq 2). Furthermore, the addition of an additive was found to be markedly effective to realize reproducible high enantioselectivity by dis-

solving the precipitate which appeared in the catalytic reaction, probably as highly aggregated complex of zinc salts containing (*R,R*)-DIPT moiety. Since the additive was crucial to realize high stereoselectivity, a series of reactions of nitrone **2a** were carried out in the presence of various kinds of amine *N*-oxides, or some other additives.⁸ As shown in Table 1, the addition of pyridine *N*-oxide was found to be most effective to produce *cis*-isoxazolidine with good enantioselectivity of 64% ee (Entry 4).

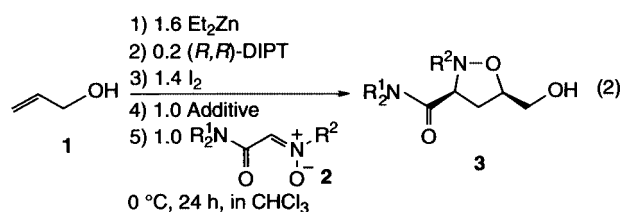


Table 1. The effect of additives in the catalytic 1,3-dipolar cycloaddition of nitrone **2a** (R¹ = Bn, R² = Ph)

Entry	Additive	Yield/%	ee/% ^a	Entry	Additive	Yield/%	ee/% ^a
1	---	78	34	6		77	55
2	Me ₃ N ⁺ -O ⁻	28	52	7	Me ₂ S ⁺ -O ⁻	78	43
3		71	58	8	Ph ₃ P ⁺ -O ⁻	77	44
4		70	64	9	ⁿ Bu ₃ P ⁺ -O ⁻	60	45
5		70	49				

^aOptical yields were determined by HPLC analysis (Daicel Chiralcel OD-H).

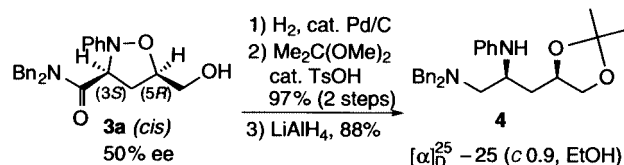
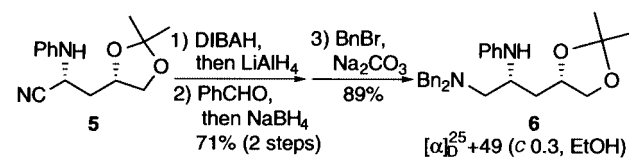
Next, the influence of the substituents on the amide nitrogen of nitrone **2** was examined as shown in Table 2. That is, allyl alcohol (**1**) was successively treated with 1.6 molar amounts of diethylzinc (in hexane), a 0.2 molar amount of (*R,R*)-DIPT, 1.4 molar amounts of iodine (dissolved in THF), a 1.0 molar amount of pyridine *N*-oxide in CHCl₃, followed by addition of nitrone **2**, and the resulting solution was stirred for 24 h at 0 °C. Almost the same asymmetric inductions were observed for benzyl, ethyl, or phenyl group on the amide nitrogen of nitrones **2** (Entries 1–3), whereas a remarkably high enantioselectivity was achieved by employing a bulky dialkylamide group bearing secondary alkyl substituents (Entries 4 and 6). Particularly, the reaction of a nitrone **2d**⁶ possessing diisopropylamide moiety furnished the corresponding *cis*-cycloadduct **3d** in an excellent enantioselectivity of 98% ee (Entry 4). The reaction of an *N*-benzyl nitrone **2e** gave the *cis*-cycloadduct **3e** diastereoselectively in lower chemical yield, but still with good enantioselectivity (Entry 5).

Table 2. The catalytic asymmetric 1,3-dipolar cycloaddition of nitrones **2** to allyl alcohol (**1**)

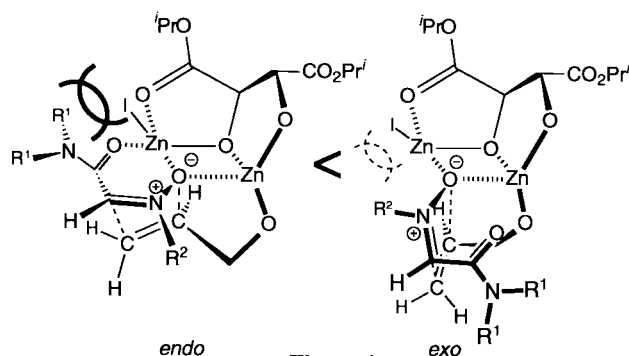
Entry	2	R ¹	R ²	Yield of 3 /%	ee/%	[α] _D ²⁵ (c, EtOH)
1	a	Bn	Ph	70	64 ^a	-74 (1.40)
2	b	Et	Ph	35	57 ^b	-93 (0.27)
3	c	Ph	Ph	37	60 ^a	-180 (0.64)
4	d	<i>i</i> Pr	Ph	69	98 ^a	-135 (1.04)
5	e	<i>i</i> Pr	Bn	20 ^c	78 ^a	-22 (0.20) ^d
6	f	Et ₂ CH	Ph	41	93 ^a	-113 (0.55)

^aOptical yields were determined by HPLC analysis (Daicel Chiralcel OD-H).^bOptical yield was determined by HPLC analysis (Daicel Chiralcel OJ).^cThe product was isolated as the corresponding acetate. ^dThe specific rotation of the corresponding acetate of **3e** was measured.

The relative stereochemistry of the cycloadducts **3a,d** was determined by NOE analysis.⁹ Furthermore, the absolute configuration of the *cis*-isoxazolidine **3a** was confirmed to be 3*S*,5*R* by the chemical correlation between its derivative and the stereochemically unambiguous authentic sample. The obtained *cis*-cycloadduct **3a** (50% ee) was transformed to the compound **4** (Scheme 1), whose specific optical rotation was opposite to that of the authentic sample **6** derived from **5** which was prepared from (*S*)-malic acid⁵ (Scheme 2). The absolute configurations of the products **3b-f** were tentatively determined to be also 3*S*,5*R*.

**Scheme 1.****Scheme 2.**

Although the precise mechanism of the asymmetric 1,3-dipolar cycloaddition reaction is not yet clear, it is possible to postulate that there is significant steric repulsion between the amide group of nitrone and the ester moiety in DIPT for the *endo*-approach as depicted in Figure 1. This repulsive interaction might disfavor the *endo*-transition state leading to the *trans*-adduct. There is less significant steric interaction in *exo*-

**Figure 1.**

approach of the nitrone. As a result, the corresponding *cis*-isoxazolidine was selectively obtained via the *exo*-transition state.

In conclusion, we could establish an efficient asymmetric route to the optically active isoxazolidines by the catalytic asymmetric 1,3-dipolar cycloaddition of nitrones to allyl alcohol. A complete *cis*-selectivity was observed for the present reaction, in striking contrast to the results of the cycloaddition of the nitrone possessing a *t*-butoxycarbonyl or cyano group previously reported.⁵ The ready availability of (*R,R*)- and (*S,S*)-DIPT indicates that this method provides a rich opportunity for preparation of both enantiomers of isoxazolidines which are versatile synthetic intermediates for nitrogen-containing chemicals.

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References and Notes

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- 5 Y. Ukaji, K. Taniguchi, K. Sada, and K. Inomata, *Chem. Lett.*, **1997**, 547.
- 6 The stereochemistry of the nitrones **2a,d** was determined by NOE analysis to be *Z*.
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- 8 Etheral compounds used for the catalytic 1,3-dipolar cycloaddition of nitrile oxides^{4b} were not so effective. Amine *N*-oxides might be able to coordinate more effectively to zinc metal like nitrones to avoid the unfavorable aggregation.
- 9 NOE established the *cis* relationship of cycloadducts **3a,d** as shown below.

