Catalytic Asymmetric 1,3-Dipolar Cycloaddition of Nitrile Oxides to an Achiral Allyl Alcohol Utilizing Diisopropyl Tartrate as a Chiral Auxiliary

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(Received March 5, 1996)

The catalytic asymmetric 1,3-dipolar cycloaddition of nitrile oxides to an achiral allyl alcohol was achieved by the use of a catalytic amount of diisopropyl (*R*,*R*)-tartrate as a chiral auxiliary to afford the corresponding (*R*)-2-isoxazolines with high enantioselectivity. In order to realize reproducible higher stereoselection, the addition of a small amount of ethereal compound such as 1,4-dioxane was crucial.

Cycloaddition reaction has been the focus of great attention in synthetic organic chemistry.[1] For the synthesis of optically active six-membered compounds, catalytic asymmetric Diels-Alder reaction using chiral Lewis acids stands as a landmark achievement.[2] By contrast, the catalytic asymmetric 1,3-dipolar cycloaddition has yet to meet with success.[3] Recently, we reported an efficient enantioselective 1,3-dipolar cycloaddition of nitrile oxide to an achiral allyl alcohol using a stoichiometric amount of diisopropyl (*R*,*R*)-tartrate [(*R*,*R*)-DIPT] to give the corresponding optically active 2-isoxazolines.[4] In the course of developing this method, we made efforts toward achieving the catalytic reaction. Herein, we describe the first enantioselective 1,3-dipolar cycloaddition of nitrile oxide using a catalytic amount of (*R*,*R*)-DIPT as a chiral auxiliary.[5,6]

First the 1,3-dipolar cycloaddition reaction using a catalytic amount (0.2 molar amounts) of (*R*,*R*)-DIPT was examined paying attention to especially the order of the addition and the molar amounts of the reagents, and the optically active 2-isoxazoline was found to be obtained. That is, when allyl alcohol (**1**) was treated with 1.7 molar amounts of Et_2Zn, 0.2 molar amounts of (*R*,*R*)-DIPT, and 1.5 molar amounts of hydroximoyl chloride **2a** successively in $CHCl_3$ at 0 °C, 2-isoxazoline **3a** was obtained in 88% yield with the selectivity of 90% ee. Unfortunately the enantioselectivity was not reproducible. For example, **3a** was obtained in 82% yield with the poor selectivity of 36% ee in the case where the white precipitate, which appeared at the addition of hydroximoyl chloride, remained during the reaction. These unexpected results might be explained as follows: The precipitate might be the highly aggregated complex of the zinc salts containing (*R*,*R*)-DIPT moiety which would prevent the favorable catalytic cycle. In order to dissociate the aggregation and to realize the reproducible enantioselectivities, the addition of a small amount of ethereal compound was effective as shown in the Table 1.[7] In the case of Et_2O, the precipitate still appeared and gave **3a** in poor optical yield (Entry 1), whereas the addition of THF achieved high selectivity (Entry 2). Among the ethereal compounds examined, 1,4-dioxane and DME were more effective (Entries 1-5, 7). Even the use of reduced amounts of Et_2Zn (1.2 molar amounts) and hydroximoyl chloride **2a** (1.0 molar amount) also afforded the 2-isoxazoline **3a** in high yield with high enantioselectivity (Entry 6).

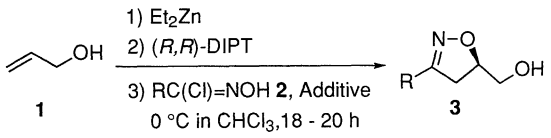

Table 1. The catalytic asymmetric 1,3-dipolar cycloaddition of nitrile oxides to allyl alcohol (**1**) using (*R*,*R*)-DIPT

Entry	R		Additive	Yield/%	ee/%
1[a]	*p*-$MeOC_6H_4$	**a**	Et_2O	83	38[b]
2[a]			THF	86	85[b]
3[a]			tetrahydropyran	98	89[b]
4[a]			DME	95	92[b]
5[a]			1,4-dioxane	95	92[b]
6[c]			1,4-dioxane	98	90[b]
7[a]			1,3,5-trioxane	96	88[b]
8[c]	*p*-ClC_6H_4	**b**	1,4-dioxane	91	90[b]
9[c]	C_6H_5	**c**	1,4-dioxane	87	84[b]
10[c]	$(CH_3)_3C$	**d**	1,4-dioxane	91	93[d]
11[c]	$CH_3(CH_2)_6$	**e**	1,4-dioxane	62	92[d]

[a]The molar amounts of Et_2Zn, (*R*,*R*)-DIPT, additive, and hydroximoyl chloride **2** were 1.7, 0.2, 2.5 and 1.5, respectively. [b]Optical yields were determined by direct HPLC analysis (Daicel Chiralcel OB-H). [c]The molar amounts of Et_2Zn, (*R*,*R*)-DIPT, additive, and hydroximoyl chloride **2** were 1.2, 0.2, 1.5 and 1.0, respectively. [d]Optical yields were determined by HPLC analysis (Daicel Chiralcel OD-H) of the (*R*)-MTPA ester derivatives.

Next, the catalytic asymmetric cycloaddition of other several nitrile oxides to allyl alcohol (**1**) was performed (Entries 8-11). It was found that the corresponding 2-isoxazolines **3** could be obtained with high enantioselectivity in the cases of not only aromatic nitrile oxides but also aliphatic ones.

Nonlinear effect is one of the most interesting phenomena in asymmetric synthesis.[6a,8] In our present asymmetric 1,3-dipolar cycloaddition of nitrile oxide, the positive nonlinear effect was observed (Figure 1). This phenomenon suggested that the highly aggregated zinc complex disfavored the asymmetric catalytic reaction cycle.[8]

Although the precise mechanism is still an open question, the catalytic system of the present reaction could be proposed as shown in Figure 2. The asymmetric 1,3-dipolar cycloaddition of nitrile oxide coordinated to two metal ions of zinc alkoxide of tartrate with a bridging skeleton **4** might be much more accelerated than the cycloaddition of nitrile oxide coordinated to zinc allyloxide **6**.[9] Furthermore, the oxygen of 2-isoxazoline ring in **5** is less Lewis-basic than the oxygen of nitrile oxide in

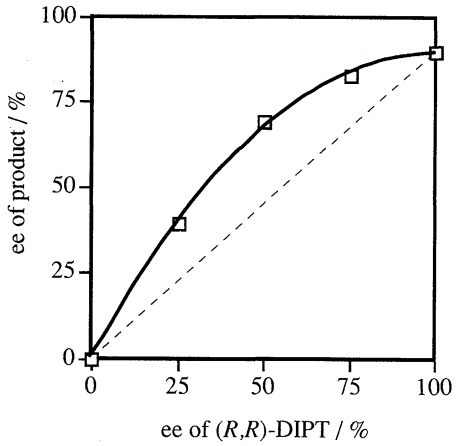

Figure 1. Nonlinear effect observed in the reaction of allyl alcohol and *p*-methoxybenzonitrile oxide under the conditions of Entry 6 in the Table 1.

6, which would enable the formed 2-isoxazoline in **5** to be replaced by the unreacted nitrile oxide to produce **4** and **7**.

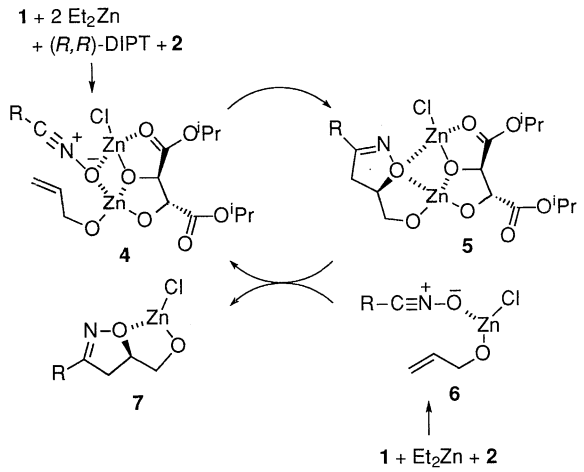

Figure 2.

A typical procedure is described as follows: To a $CHCl_3$ (3 ml) solution of allyl alcohol (**1**) (29 mg, 0.50 mmol) was added Et_2Zn (0.60 mmol, 0.60 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 $CHCl_3$ (3 ml) solution of (*R,R*)-DIPT (24 mg, 0.10 mmol) was added and the mixture was stirred for 1 h. A $CHCl_3$ (3 ml) solution of *p*-methoxybenzohydroximoyl chloride (**2a**) (93 mg, 0.50 mmol) and 1,4-dioxane (66 mg, 0.75 mmol) was added, and the resulting solution was stirred for 19 h at 0 °C. The reaction was quenched by addition of saturated aq NH_4Cl. Purification by TLC on silica gel afforded the 2-isoxazoline **3a** (101 mg, 98%) with the selectivity of 90% ee.

In summary, the enantioselective synthetic method for 2-isoxazolines was achieved starting from an achiral allyl alcohol using catalytic amount of DIPT. Because of easy availability of (*R,R*)- and (*S,S*)-DIPT, this method provides the useful way to prepare both enantiomers of 2-isoxazolines,[10,11] which are versatile intermediates in organic synthesis for such as β-hydroxy ketones and γ-amino alcohols by reductive cleavage of the nitrogen-oxygen bond.[1]

The present work was partially supported by Tanabe Seiyaku Co., Ltd. Award in Synthetic Organic Chemistry, Japan and Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture.

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