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A Switch of Enantiofacial Selectivity in Chiral Ytterbium-Catalyzed 1,3-Dipolar Cycloaddition Reactions

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Abstract: *Synthesis of both enantiomers of the 1,3-dipolar cycloaddition adducts between nitrones and alkenes has been achieved using the same chiral ytterbium catalyst choosing achiral additives, nitrone and MS 4A.* © 1999 Elsevier Science Ltd. All rights reserved.

Synthesis of both enantiomers is an important task in organic chemistry as well as in medicinal and bioorganic chemistry.[1] In chemical transformations, syntheses of both enantiomers are generally carried out using both enantiomers of chiral sources. However, it is sometimes difficult to obtain both enantiomers of a chiral source such as amino acids, monosaccharides, alkaloids, etc. It is desirable from a synthetic point of view that both enantiomers are prepared by using the same chiral source.[2] In this paper, we demonstrate such examples in the asymmetric 1,3-dipolar cycloaddition reactions of nitrones.

The asymmetric 1,3-dipolar cycloaddition reactions of nitrones with alkenes provide a useful method for synthesis of optically active isoxazolidine derivatives, which can be readily converted to γ-amino alcohols.[3] In these reactions, use of chiral metal complexes as catalysts has been extensively studied.[4] Recently, we reported that a heterochiral ytterbium complex, which was prepared from $Yb(OTf)_3$, (*S*)-1,1'-binaphthol ((*S*)-BINOL), and *N*-methyl-bis[(*R*)-1-(1-naphthyl)ethyl]amine ((*R*)-MNEA), was quite effective in catalytic enantioselective 1,3-dipolar cycloaddition of nitrones.[5] In this reaction, molecular sieves 4A (MS 4A) were essential to provide high enantioselectivity. While MS 4A was first used as a dehydration agent to remove a small amount of water existing in a solvent, etc., it was found that reverse enantiofacial selectivity was obtained in the absence of MS 4A.[6] That is, in the presence of MS 4A the absolute configuration of the major product of the cycloaddition of nitrone **1** to *N*-crotonoyl-1,3-oxazolidin-2-one (**2**) was *3R, 4S, 5R,* while an adduct

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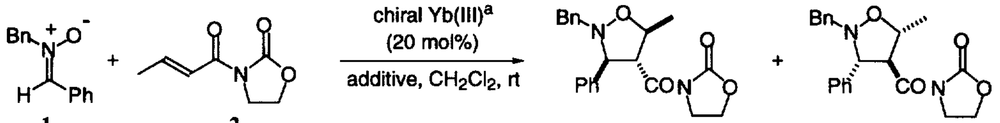
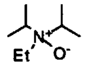
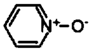
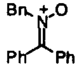
with the absolute configuration of *3S, 4R, 5S* was obtained in moderate selectivity in the absence of MS 4A. We already reported that a similar ytterbium catalyst was effective for asymmetric Diels-Alder reactions.[2a,b] However, in the Diels-Alder reaction of cyclopentadiene with **2**, the same enantiofacial selectivities were obtained using the same chiral Yb(III) catalyst in the presence and absence of MS 4A. These results suggested that the nitrone would affect the enantiofacial selectivity in the 1,3-dipolar cycloaddition. On the other hand, it was found that the *3S, 4R, 5S* selectivity was increased when one equivalent of the nitrone was added to the chiral Yb(III) catalyst as an additive before adding the substrates, **1** and **2**. Namely, when an equimolar amount of $Yb(OTf)_3$, (*S*)-BINOL, (*R*)-MNEA, and **1** were combined and then **1** and **2** were added, the desired *endo* adduct was obtained in 90% yield with 83% ee (*endo*/*exo* = 99/1). Several additives other than **1** were then examined, and the results are summarized in Table 1. It is noted that amine *N*-oxides such as *N*-methylmorpholine oxide (NMO) were also effective for obtaining the cycloaddition adduct with *3R, 4S, 5R* configuration in high selectivity. The best selectivity was obtained by using one equivalent of **1** as an additive, while the selectivity decreased when two equivalents of **1** were used.



1 2 (*3S, 4R, 5S*) (*3R, 4S, 5R*)

Table 1. Effect of Additives

Additive	(mol%)	Yield (%)	*endo*/*exo*	ee (%)	Config.
MS 4A		92	99/1	96	*3R, 4S, 5R*
none		83	98/2	50	*3S, 4R, 5S*
H_2O	(20)	81	95/5	8	*3S, 4R, 5S*
NMO	(20)	68	98/2	81	*3S, 4R, 5S*
$Me_3N^+–O^-$	(20)	79	>99/1	74	*3S, 4R, 5S*
	(20)	72	>99/1	72	*3S, 4R, 5S*
	(20)	78	99/1	65	*3S, 4R, 5S*
1	(20)	90	99/1	83	*3S, 4R, 5S*
1	(40)	83	>99/1	65	*3S, 4R, 5S*
	(20)	69	>99/1	41	*3S, 4R, 5S*

[a]Chiral Yb(III) = $Yb(OTf)_3$ + (*S*)-BINOL + (*R*)-MNEA. [b]Ee of the *endo* adducts.

Several examples of the 1,3-dipolar cycloaddition of nitrones using the heterochiral Yb(III) catalyst in the absence of MS 4A are shown in Table 2. The reactions were performed by adding one equivalent of the corresponding nitrone to the Yb(III) catalyst and then, successively, the same nitrone and a dipolarophile. A typical experimental procedure is described for the 1,3-dipolar cycloaddition of **1** to **2**. To a mixture of $Yb(OTf)_3$ (0.08 mmol), (*S*)-BINOL (0.08 mmol), and nitrone **1** (0.08 mmol) was added (*R*)-MNEA (0.16 mmol) in dichloromethane (1 mL) at 0 °C, and the mixture was stirred for 30 min at the same temperature. Nitrone **1** (0.4 mmol) in dichloromethane (0.3 mL) and dipolarophile **2** (0.4 mmol) in dichloromethane (0.3 mL) were successively added, and the mixture was stirred for 20 h at room temperature. Sat. Na_2CO_3 aq. was then added to quench the reaction. After the usual work-up, the crude product was purified by thin-layer chromatography on silica gel to afford the desired isoxazolidine derivative (90% yield, *endo/exo* = 99/1). The enantiomeric excess of the *endo* adduct was determined to be 83% ee by HPLC analysis (Daicel Chiralpak OD).[5] In all cases, reverse enantiofacial selectivities compared with those obtained in the presence of MS 4A were observed. When *N*-acryloyl-1,3-oxazolidin-2-one was used as a dipolarophile, the desired isoxazolidine derivative was obtained in 88% ee. Other substrates also gave high diastereo- and enantioselectivities in most cases. In the reaction of an aliphatic nitrone, low diastereoselectivity was observed, albeit the *endo* adduct was obtained in good yield and ee.

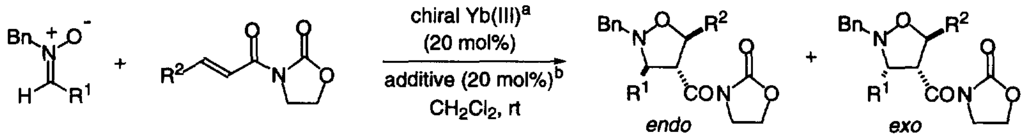


Table 2. Catalytic Enantioselective 1,3-Dipolar Cycloadditions

R^1	R^2	Yield (%)	*endo/exo*	ee (%)[c]	with MS 4A[d] Yield (%)	with MS 4A[d] *endo/exo*	with MS 4A[d] ee (%)
Ph	CH_3	90	99/1	83	92	99/1	-96
Ph	H	72	>99/1	88	91	>99/1	-79
Ph	C_3H_7	82	>99/1	83	89	98/2	-93
2-furyl	CH_3	75	99/1	76	89	95/5	-89
1-naphthyl	CH_3	83	97/3	81	88	98/2	-85
C_2H_5	CH_3	79	53/47	79	88	53/47	-96

[a] Chiral Yb(III) = $Yb(OTf)_3$ + (*S*)-BINOL + (*R*)-MNEA. [b] The corresponding nitrone was added as an additive (see text). [c] Ee of the *endo* adducts. [d] Ref. 5. Reverse enantioselectivities were observed.

In summary, synthesis of both enantiomers of 1,3-dipolar cycloaddition adducts has been achieved using the same chiral catalyst by choosing the achiral additives, nitrone and MS 4A. These results suggest a unique property of the ytterbium catalyst as well as a novel role of MS 4A besides that as a dehydration agent in organic synthesis. Further studies to find an alternative to MS 4A as well as to clarify the role of MS 4A from a mechanistic point of view are now in progress.

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