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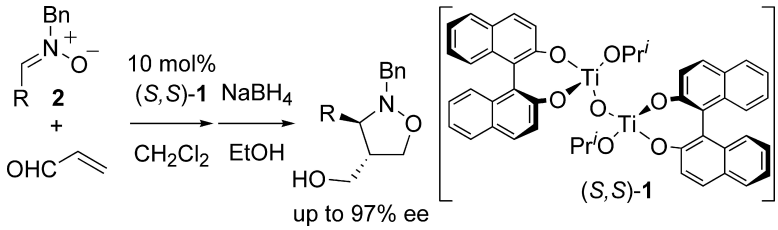

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Asymmetric 1,3-Dipolar Cycloaddition Reaction of Nitrones and Acrolein with a Bis-Titanium Catalyst as Chiral Lewis Acid

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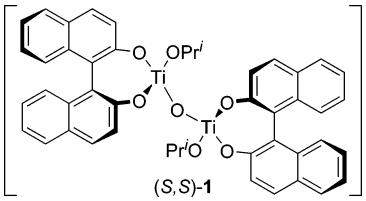
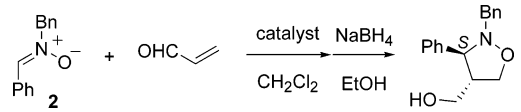
The asymmetric 1,3-dipolar cycloaddition reaction between nitrones and alkenes is still of great interest in organic synthesis since the resulting optically active isoxazolidines can easily be converted into biologically active β-amino acids and β-lactams, as well as important chiral building blocks, such as γ-amino alcohols.[1] In this area, Lewis acid-catalyzed asymmetric 1,3-dipolar cycloaddition reactions between nitrones and electron-deficient alkenes (normal electron demand reaction) have been investigated intensely.[2−4] In most cases, bidentate dipolarophiles, such as 3-(2-alkenoyl)-2-oxazolidinones, can be utilized to facilitate the effective coordination to Lewis acid catalysts in the presence of nitrones having strong coordination ability.[2,4d] In addition, *N*-benzylideneaniline-*N*-oxide is employed as a typical acyclic nitrone to achieve high levels of enantioselectivity; however, such cycloaddition products are not suitable for further transformations due to the functionally stable phenyl group on the nitrogen atom.[3] Although there have been several examples of the catalytic asymmetric 1,3-dipolar cycloaddition with α,β-unsaturated aldehydes as monodentate dipolarophiles, the scope and generality of the nitrones remain insufficient.[4,5] In this context, we are interested in the possibility of using chiral bis-metal Lewis acids[6−9] that often exhibit unique reactivity and selectivity in several asymmetric reactions. Here, we wish to report that bis-Ti(IV) catalyst of type **1** can be successfully utilized to realize the asymmetric 1,3-dipolar cycloaddition reactions between various nitrones and acrolein.



The requisite μ-oxo-type bis-Ti(IV) oxide (*S*,*S*)-**1** was prepared as described previously by treatment of triisopropoxytitanium chloride (2 equiv) with Ag_2O and subsequent addition of (*S*)-BINOL (2 equiv).[6] We first investigated the asymmetric 1,3-dipolar cycloaddition between acrolein and nitrone **2** bearing an easily removable *N*-benzyl group, as shown in Table 1. Thus, in the presence of 10 mol % of bis-Ti(IV) oxide (*S*,*S*)-**1**, nitrone **2** was treated with acrolein (1.5 equiv) at 0 °C for 2 h to afford the desired *endo*-isoxazolidine in 78% yield and 89% ee (entry 1). In contrast, the reaction catalyzed by 20 mol % of (*S*)-BINOL/Ti(IV) complexes prepared from (*S*)-BINOL/Ti(O*i*-Pr)$_4$ or (*S*)-BINOL/ClTi(O*i*-Pr)$_3$ (1:1 molar ratio) gave the cycloadduct in low yields with moderate enantioselectivities under the same conditions (entries 2 and 3). Upon further investigation, it was found that by using the lower temperature (−20 and −40 °C), the isoxazolidine was obtained in good yields with high enantioselectivities at the expense of the reaction rate (entries 4 and 5).

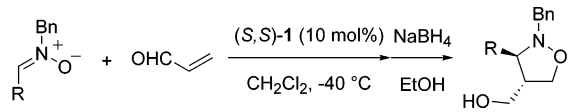
Table 1. Asymmetric 1,3-Dipolar Cycloaddition between Nitrone **2** and Acrolein[a]



entry	catalyst	(mol %)	conditions (°C, h)	yield (%)[b,c]	ee (%)[d] [config][e]
1	(*S*,*S*)-**1**	10	0, 2	78	89 [*S*]
2	Ti(O*i*-Pr)$_4$ (*S*)-BINOL	20	0, 2	40	60 [*S*]
3	ClTi(O*i*-Pr)$_3$ (*S*)-BINOL	20	0, 2	36	60 [*S*]
4	(*S*,*S*)-**1**	10	−20, 17	90	91 [*S*]
5	(*S*,*S*)-**1**	10	−40, 24	94	93 [*S*]

[a] The reaction of nitrone **2** and acrolein (1.5 equiv) was carried out in the presence of chiral bis-Ti(IV) oxide (*S*,*S*)-**1** or chiral mono-Ti(IV) in CH_2Cl_2. [b] Isolated yield. [c] Only the endo isomer was detected by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis using chiral column (Chiralpak OD-H, Daicel Chemical Industries, Ltd.). [e] Determined by comparison of the sign of optical rotation with the reported value.[5a]

Table 2. Asymmetric 1,3-Dipolar Cycloadditions between Nitrones and Acrolein[a]



entry	R	time (h)	yield (%)[b,c]	ee (%)[d]
1	Ph	24	94	93
2	4-MePh	24	81	94
3	4-MeOPh	40	76	88
4	4-ClPh	39	85	88
5	2-naphthyl	24	92	93
6	*t*-Bu	14	90	97
7	cyclohexyl	24	62	70
8		24	86	97

[a] The reaction of nitrones and acrolein (1.5 equiv) was carried out in the presence of chiral bis-Ti(IV) oxide (*S*,*S*)-**1** in CH_2Cl_2 at −40 °C. [b] Isolated yield. [c] Only the endo isomer was detected by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis using chiral column (Chiralpak OD-H, Daicel Chemical Industries, Ltd.).

We next examined the scope of asymmetric 1,3-dipolar cycloaddition between various nitrones and acrolein catalyzed by bis-Ti(IV) oxide (*S*,*S*)-**1** under the optimized conditions (Table 2). The reactions with various aryl-substituted nitrones provided the corresponding isoxazolidines with rigorous endoselectivity in high to

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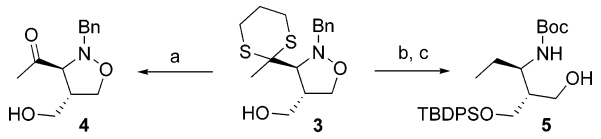
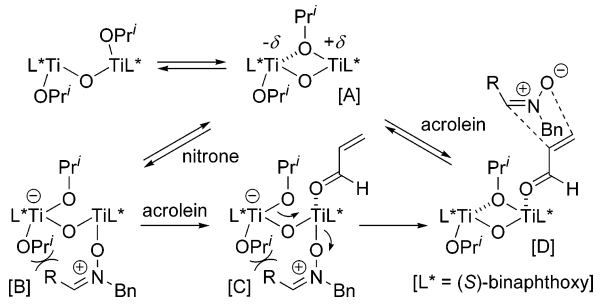
Scheme 1



(a) HgO, $HgCl_2$, CH_3CN, 75%; (b) TBDPSCl, Et_3N, DMAP, CH_2Cl_2; (c) Raney Ni, $(Boc)_2O$, *i*-PrOH, H_2, 46% (2 steps).

excellent enantiomeric excesses (88−94% ee) (entries 1−5). The sterically hindered *tert*-butyl-substituted nitrone also showed excellent enantioselectivity (entry 6), while the use of the cyclohexyl analogue lowered the enantioselectivity (entry 7). Furthermore, the synthetically useful nitrone with a 1,3-dithianyl group[10] could be successfully utilized in the 1,3-dipolar cycloaddition (entry 8). Indeed, hydrolysis of the resulting isoxazolidine **3** with mercuric salts produced the corresponding acetyl isoxazolidine **4** in good yield (Scheme 1). Meanwhile, TBDPS protection of **3**, followed by reductive desulfurization with Raney-nickel, provided amino alcohol **5** in moderate yield. In both cases, the transformations proceeded without any loss of enantiomeric purity.

Plausible reaction pathways have been proposed to account for the higher reactivity and selectivity of bis-Ti(IV) oxide (*S*,*S*)-**1** compared to that of other mono-Ti(IV)/BINOL complexes. First, the Lewis acidity of one titanium center may be enhanced by the intramolecular coordination of one isopropoxy oxygen to the other titanium, as shown in [A].[6,11] With the coordination of nitrone to the more acidic titanium center in [A], this isopropoxy group shifts to the other titanium, as shown in [B], thereby inducing the coordination of acrolein to furnish [C]. Here, the steric repulsion between the nitrone and the ligand in (*S*,*S*)-**1** would contribute to the decomplexation of the nitrone.[12,13] Then, the activated acrolein may react with the free nitrone, as indicated in [D], to give the corresponding cycloadduct. The direct attack of acrolein to [A] is also conceivable.



In summary, we have developed an asymmetric 1,3-dipolar cycloaddition reaction between various nitrones and acrolein catalyzed by the μ-oxo-type chiral bis-Ti(IV) oxide (*S*,*S*)-**1**, which gave rise to the corresponding isoxazolidines with high to excellent enantioselectivities. Further study is underway to expand the scope of this methodology, as well as to ascertain mechanistic details of the bis-Ti(IV)-catalyzed asymmetric process.

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Supporting Information Available: Experimental details and characterization data for new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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