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Asymmetric 1,3-Dipolar Cycloadditions of *N*-Benzyl and *N*-Diphenylmethyl Nitrones and α,β-Unsaturated Aldehydes Catalyzed by Bis-Titanium Chiral Lewis Acids

Takuya Hashimoto, Masato Omote, Yoshio Hato, Taichi Kano, and Keiji Maruoka*[a]

Dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday

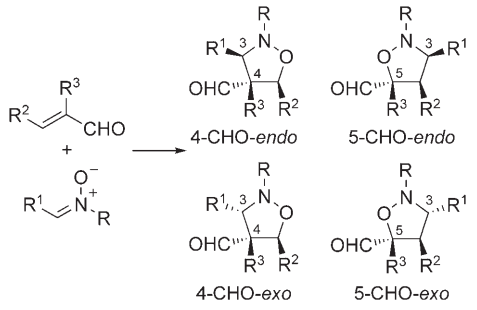
Abstract: Bis-titanium chiral Lewis acids that contain two oxygen-bridged titanium centers were successfully applied to the asymmetric 1,3-dipolar cycloaddition of nitrones and α,β-unsaturated aldehydes. The introduction of the diphenylmethyl group as the N substituent on the nitrones, with the aim of destabilizing the nitrone–Lewis acid complex, led to the drastic enhancement of not only the reactivity but also the enantioselectivity. By employing this approach, 1,3-dipolar cycloadditions of nitrones and the rather unreactive methacrolein were facilitated to give cycloadducts that bear one all-carbon quaternary center with unique regioselectivity and excellent stereoselectivity.

Keywords: aldehydes · asymmetric catalysis · cycloaddition · nitrones · titanium

Introduction

1,3-Dipolar cycloadditions of nitrones and alkenes have been widely recognized as a powerful synthetic tool to build up complex heterocycles with up to three contiguous stereogenic centers starting from simple substrates.[1] Because of the practical aspects of the produced isoxazolidines, which can be further converted into a variety of chiral building blocks such as β-amino alcohols, β-amino acids, and β-lactams, the methods for the preparation of optically enriched isoxazolidines by the use of chiral auxiliary or asymmetric catalysis have been investigated intensively. In particular, metal-catalyzed asymmetric processes that utilize the LUMO (lowest unoccupied molecular orbital) lowering of α,β-unsaturated carbonyl compounds by the coordination of a Lewis acid, designated as normal-electron-demand 1,3-dipolar cycloadditions, have been developed in the past decade as an attractive method.[2] However, the strong coordinative character of nitrones to Lewis acids, which results in the deactivation of the catalyst, hampered the quest for the use of simple α,β-unsaturated aldehydes as dipolarophiles due to their lower affinity to Lewis acids relative to nitrones. Furthermore, the difficulty in controlling the regio-, stereo-, and enantioselectivity simultaneously remains a challenging task, along with insufficient substrate generality (Scheme 1).

The pioneering finding of Kanemasa et al. that stoichiometric amounts of achiral Lewis acids accelerate the reaction of nitrones and α,β-unsaturated ketones[3] gave an impetus to the development of metal-catalyzed asymmetric 1,3-dipolar cycloadditions of nitrones. The first reports of the catalytic asymmetric normal-electron-demand 1,3-dipo-



Scheme 1. Four possible regio- and *endo*/*exo* isomers obtained in the 1,3-dipolar cycloaddition of nitrones and α,β-unsaturated aldehydes.

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lar cycloaddition of nitrones appeared in 1994, in which Gothelf and Jørgensen described the reaction with 3-(2-alkenoyl)-2-oxazolidinones in the presence of a catalytic amount of titanium TADDOLate (TADDOL = 2,2-dimethyl-α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol).[2a] Use of the oxazolidinone template was required to facilitate the preferential coordination of the dipolarophile to the Lewis acid in a bidentate fashion. Since then, the employment of 3-(2-alkenoyl)-2-oxazolidinone became the reaction system of choice to evaluate newly designed chiral Lewis acid catalysts, and several novel catalysts appeared to provide isoxazolidines in a highly stereoselective manner.

Recently, certain chiral Lewis acid catalysts[4,5] were found to be capable of achieving 1,3-dipolar cycloadditions between nitrones and monodentate dipolarophiles, especially α,β-unsaturated aldehydes, by exploiting their low affinity to nitrones. Kündig and co-workers demonstrated the remarkable potential of chiral iron and ruthenium Lewis acids in facilitating the reaction of some cyclic nitrones and methacrolein with excellent enantioselectivities.[4a] Carmona et al. described the rhodium and iridium chiral Lewis acid catalyzed 1,3-dipolar cycloaddition of several nitrones and aldehydes based on the extensive investigation of X-ray crystallographic analyses of Lewis acid catalysts coordinated by α,β-unsaturated aldehydes.[4f–i] In a different way, Kanemasa and co-workers applied their DBFOX/Ph (4,6-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline)) ligand to the 1,3-dipolar cycloaddition of acyclic *N*-phenyl nitrones and various α,β-unsaturated aldehydes by the judicious choice of the central metals.[4e] Yamada and co-workers showed the ability of the chiral β-ketoiminato cobalt complexes, especially in the reaction of acyclic *C*-aryl-*N*-phenyl nitrones and 1-cyclopentene-1-carbaldehyde.[4b–d] At present, however, acyclic nitrones containing a functionally inert phenyl group on the nitrogen atom are utilized in most cases, and synthetic applications of these cycloadducts to valuable chiral building blocks are rarely described.

In our recent study on asymmetric 1,3-dipolar cycloadditions, a bis-titanium chiral Lewis acid was found to catalyze successfully the reaction of *N*-benzyl nitrones and acrolein.[6a] The use of *N*-benzyl nitrones enabled the further transformation of the cycloadduct, and we indeed demonstrated the conversion of *N*-benzylisoxazolidine into the optically enriched 1,3-amino alcohol. Furthermore, the substrate limitations encountered in this investigation could be overcome by employing two distinctive approaches: further catalyst design and modification of the N substituent on the nitrones.[6b] In this article, we describe the full detail of our designer bis-titanium chiral Lewis acid catalyzed asymmetric 1,3-dipolar cycloaddtions of nitrones and α,β-unsaturated aldehydes.

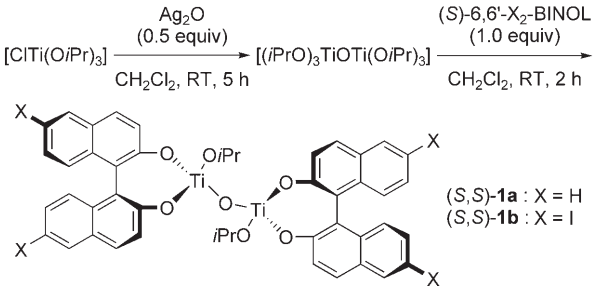
Abstract in Japanese:

ルイス酸間に酸素架橋構造を有する光学活性ビスチタンルイス酸触媒を利用することにより、ニトロンと α,β-不飽和アルデヒドとの不斉 1,3-双極子付加環化反応が高位置および立体選択的に進行することを見出した。ニトロンの窒素上置換基として嵩高いジフェニルメチル基を導入しニトロン-ルイス酸錯体の形成を阻害することにより、反応性およびエナンチオ選択性が飛躍的に向上することを明らかとした。その結果、反応性の乏しいメタクロレインを基質として用いた環化反応においても、位置特異的かつ優れた立体選択性で 4 級炭素部位を有する環化付加体を生成することに成功した。

Results and Discussion

Asymmetric 1,3-Dipolar Cycloaddition of *N*-Benzyl Nitrones and Acrolein Catalyzed by a Bis-Titanium Chiral Lewis Acid

The requisite bis-titanium chiral Lewis acid was easily prepared by just mixing the readily available materials in the order shown in Scheme 2, according to the procedure established during the related study on the catalytic asymmetric allylation of aldehydes.[7,8]



Scheme 2. Preparation of bis-titanium chiral Lewis acid catalysts. BINOL = 1,1′-bi-2,2′-naphthol.

The reaction of *C*-phenyl *N*-benzyl nitrone **2** and acrolein (1.5 equiv) under the influence of 10 mol% bis-titanium chiral Lewis acid (*S*,*S*)-**1a** in CH_2Cl_2 at 0 °C for 2 h afforded (3*S*,4*S*)-2-benzyl-4-hydroxymethyl-3-phenylisoxazolidine in 78% yield with 89% *ee* as a single regio- and *endo* isomer (Table 1, entry 1). The aldehyde moiety was reduced in situ by treatment with $NaBH_4$, with the possibility of epimerization at the α-carbon atom of the aldehyde taken into account. Control experiments were also performed with other titanium BINOLates, such as (*S*)-BINOL/[Ti(O*i*Pr)$_4$] (1:1 molar ratio) complex and (*S*)-BINOL/[ClTi(O*i*Pr)$_3$] (1:1 molar ratio) complex, under similar reaction conditions (Table 1, entries 2–4). In all cases, erosion of enantioselectivities was observed. The enantioselectivity of the (*S*,*S*)-**1a**-catalyzed reaction was increased by lowering the reaction temperature, and the cycloadduct was finally obtained in 94% yield with 93% *ee* by performing the reaction at −40 °C (Table 1, entry 6).

The scope and limitation of the 1,3-dipolar cycloaddition of various nitrones and acrolein was investigated under the optimized reaction conditions summarized in Table 2. Nitrones bearing an *o*-, *m*-, or *p*-substituted aryl group were tolerated (Table 2, entries 2–4). Reactions with electronically different *C*-aryl nitrones gave the corresponding isoxazolidines

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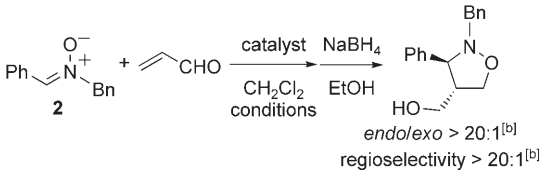
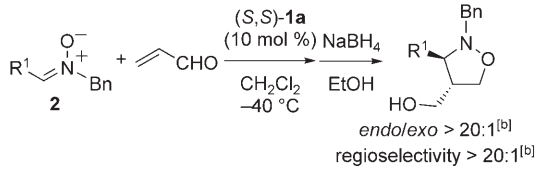
Table 1. Asymmetric 1,3-dipolar cycloaddition of *C*-phenyl *N*-benzyl nitrone **2** and acrolein.[a]



Entry	Catalyst	[mol%]	T [°C], t [h]	Yield[c] [%]	*ee*[d] [%]
1	(*S*,*S*)-**1a**	10	0, 2	78	89
2	[Ti(O*i*Pr)$_4$]/(*S*)-BINOL	20	0, 2	40	60
3	[ClTi(O*i*Pr)$_3$]/(*S*)-BINOL	20	0, 2	36	60
4	[Ti(O*i*Pr)$_4$]/2 (*S*)-BINOL	20	0, 2	90	80
5	(*S*,*S*)-**1a**	10	−20, 17	90	91
6	(*S*,*S*)-**1a**	10	−40, 24	94	93

[a] The reaction of nitrone **2** and acrolein (1.5 equiv) was carried out in the presence of 10 mol% (*S*,*S*)-**1a** or 20 mol% chiral monotitanium catalyst in CH_2Cl_2. [b] Determined by ^{1}H NMR spectroscopy. [c] Yield of isolated product. [d] Determined by HPLC analysis with chiral columns. Bn = benzyl.

Table 2. Asymmetric 1,3-dipolar cycloaddition of *N*-benzyl nitrones and acrolein.[a]

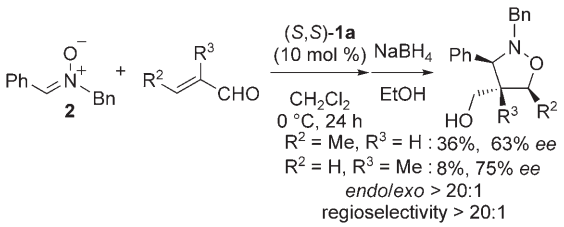


Entry	R^1	t [h]	Yield[c] [%]	*ee*[d] [%]
1	Ph	24	94	93
2	4-tolyl	24	81	94
3	3-tolyl	24	89	89
4	2-tolyl	28	59	95
5	4-MeOC_6H_4	40	76	88
6	4-ClC_6H_4	39	85	88
7	2-Np	24	92	93
8	*t*Bu	14	90	97
9		24	86	97
10	Cy	24	62	70
11	*i*Pr	26	43	54

[a] The reaction of nitrone and acrolein (1.5 equiv) was carried out in the presence of 10 mol% (*S*,*S*)-**1a** in CH_2Cl_2. [b] Determined by ^{1}H NMR spectroscopy. [c] Yield of isolated product. [d] Determined by HPLC analysis with chiral columns. Cy = cyclohexyl, Np = naphthyl.

in high to excellent yields with rigorous stereoselectivities (Table 2, entries 5–7). Subsequently, we examined the reaction of *C*-alkyl-substituted nitrones. It turned out that nitrones containing bulky *C* substituents were suitable substrates that provided the cycloadducts in excellent yields and selectivities (Table 2, entries 8 and 9). *C*-Isopropyl and cyclohexyl nitrones were converted into the corresponding isoxazolidines in only moderate yields and enantioselectivities, although the high regio- and *endo* selectivities were maintained.

This protocol was then applied to other α,β-unsaturated aldehydes, methacrolein and crotonaldehyde being two representatives. In a preliminary experiment, the reaction of *C*-phenyl *N*-benzyl nitrone **2** and the respective aldehydes was conducted in the presence of 10 mol% bis-titanium chiral Lewis acid (*S*,*S*)-**1a** in CH_2Cl_2 at 0 °C for 24 h. The reaction of each aldehyde gave the corresponding isoxazolidines in only poor yields with moderate levels of enantiofacial discrimination, whereas the regio- and *endo*/*exo* selectivities were exclusively controlled (Scheme 3).



Scheme 3. Asymmetric 1,3-dipolar cycloaddition of *C*-phenyl *N*-benzyl nitrone **2** and substituted acroleins.

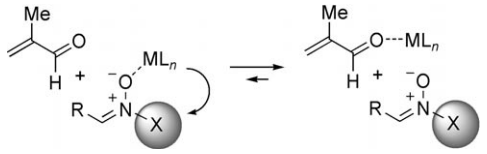
The substrate limitation in our methodology now became clear: 1) use of nitrones bearing small *C* substituents led to unsatisfactory yields and enantioselectivities, and 2) the reaction with α- or β-substituted acroleins was not feasible. In this regard, we commenced our studies in depth to find a general method applicable to various combinations of nitrones and α,β-unsaturated aldehydes.

Investigation of the Steric Effect of the *N* Substituent on Nitrones: Asymmetric 1,3-Dipolar Cycloaddition of *N*-Diphenylmethyl Nitrones and Methacrolein

The asymmetric 1,3-dipolar cycloadditions of nitrones and methacrolein reported to date have been limited to the preferential formation of the 5-CHO-*endo* isomer[4a,c,d,e] or the generation of both 5-CHO-*endo* and 4-CHO-*endo* isomers in the moderate preference to the 4-CHO-*endo* isomer (Scheme 1).[4f–h] Contrary to these results, our research revealed that the regiochemical outcome of the bis-titanium chiral Lewis acid catalyzed reaction of *N*-benzyl nitrone and methacrolein was found to be exclusively 4-CHO-*endo*-selective, albeit in quite low yield.[9] This intriguing observation prompted us to focus especially on this reaction system. A further attraction of this reaction can be seen in the unique structure of the cycloadduct, which includes one all-carbon quaternary stereocenter and one secondary amine moiety vicinally positioned.[10]

On the basis of the fact that the poor reactivity of Lewis acid catalyzed normal-electron-demand 1,3-dipolar cycloadditions is mainly due to the undesired and rather strong complexation of nitrone and Lewis acid, which hampers the formation of the reactive dipolarophile–Lewis acid complex, it can be expected that the destabilization of this complexation by lowering the coordination ability of nitrone to Lewis acid would lead to enhancement of the reactivity.[11] In this regard, we envisioned that the kinetic destabilization of the

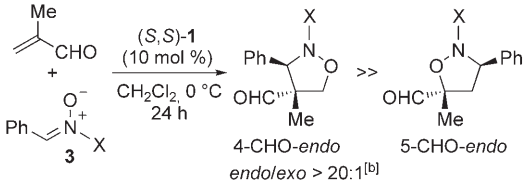
Lewis acid–nitrone complex might be possible by the introduction of a bulky *N* substituent on nitrones, which would cause severe steric repulsion with the ligand of the Lewis acid catalyst (Scheme 4).



Scheme 4. Kinetic destabilization of the Lewis acid–nitrone complex by steric repulsion.

As a proof of principle, the *N*-benzyl nitrone was replaced by the more sterically demanding *N*-diphenylmethyl nitrone **3** (R = Ph_2CH),[12] and the reaction catalyzed by 10 mol% (*S*,*S*)-**1a** was implemented (Table 3). To our delight, a pronounced effect of the N substituent was actually observed, and the cycloadduct was obtained in 58% yield after 24 h of

Table 3. Comparison of the reactivity and selectivity of N-substituted nitrones.[a]



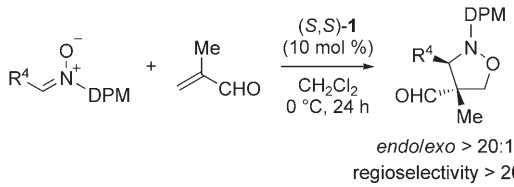
Entry	X	Catalyst	Yield[c] [%]	*ee*[d] [%]
1	$PhCH_2$	(*S*,*S*)-**1a**	8	75
2	Ph_2CH	(*S*,*S*)-**1a**	58	90
3	Ph_2CH	(*S*,*S*)-**1b**	80	93
4	1-$NpCH_2$	(*S*,*S*)-**1b**	24	78
5	$(2\text{-tolyl})_2CH$	(*S*,*S*)-**1b**	trace	–

[a] Reaction of nitrone and methacrolein (3 equiv) was performed in the presence of 10 mol% (*S*,*S*)-**1** in CH_2Cl_2. [b] Determined by ^1H NMR spectroscopy. [c] Yield of isolated product. [d] Determined by HPLC analysis with chiral columns after reduction of the aldehyde moiety.

stirring at 0°C without affecting the unique high 4-CHO-*endo* selectivity (Table 3, entries 1 and 2). Furthermore, a drastic increase in enantioselectivity was observed. Further improvement of the reaction efficiency was then attempted by tuning the ligand of the catalyst, and we found the introduction of 6,6′-I_2-BINOL as a chiral ligand to be effective (Table 3, entry 3). The examination of *N* substituents on nitrone with the optimal catalyst (*S*,*S*)-**1b** ascertained the superiority of the diphenylmethyl group (Table 3, entries 4 and 5).

With this promising protocol in hand, the scope and limitations of the reaction of various *N*-diphenylmethyl nitrones and methacrolein in the presence of (*S*,*S*)-**1b** were investigated (Table 4). The reactions with the nitrones bearing an

Table 4. Asymmetric 1,3-dipolar cycloaddition of *N*-diphenylmethyl nitrones and methacrolein.[a]



Entry	R^4	Catalyst	Yield[c] [%]	*ee*[d] [%]
1	Ph	(*S*,*S*)-**1b**	80	93
2	2-tolyl	(*S*,*S*)-**1b**	67	99
3	3-tolyl	(*S*,*S*)-**1b**	74	96
4	4-tolyl	(*S*,*S*)-**1a**	63	88
5	4-tolyl	(*S*,*S*)-**1b**	75	88
6	2-naphthyl	(*S*,*S*)-**1b**	51	95
7[e]	4-ClC_6H_4	(*S*,*S*)-**1b**	46	88
8	4-$MeOC_6H_4$	(*S*,*S*)-**1a**	47	89
9	4-$MeOC_6H_4$	(*S*,*S*)-**1b**	49	94
10[e]		(*S*,*S*)-**1b**	48	88
11		(*S*,*S*)-**1b**	65	91
12		(*S*,*S*)-**1b**	77	70

[a] Unless otherwise noted, the reaction of nitrones and methacrolein (3 equiv) was performed in the presence of 10 mol% (*S*,*S*)-**1** in CH_2Cl_2. [b] Determined by ^1H NMR spectroscopy. [c] Yield of isolated product. [d] Determined by HPLC analysis with chiral columns after reduction of the aldehyde moiety. [e] Performed with 20 mol% (*S*,*S*)-**1b**. DPM = diphenylmethyl.

o, *m*, or *p* substituent furnished the cycloadduct in high yields with remarkably high regio- and enantioselectivities (Table 4, entries 2–5). Introduction of electron-withdrawing or electron-donating groups on the nitrone was also tolerated, thus providing the cycloadducts in moderate yields (Table 4, entries 7–9). Olefins could also be incorporated into the cycloadduct with the enantiomeric excesses ranging from 70 to 91% (Table 4, entries 10–12). The limitation of this reaction was revealed in the reaction of *C*-alkyl nitrones, which led to poor conversion probably due to the severe steric hindrance between the alkyl group on the nitrone and the methyl group on the aldehyde (data not shown).

The focus was then moved to the reaction with crotonaldehyde as dipolarophile (Table 5). As in the case of the reaction of methacrolein, use of *N*-diphenylmethyl nitrone was apparently advantageous, and the reaction of *C*-phenyl *N*-diphenylmethyl nitrone and crotonaldehyde (1.5 equiv) catalyzed by 10 mol% (*S*,*S*)-**1a** provided the single isomer of the cycloadduct in 82% yield with 87% *ee* (Table 5, entry 1). A slight increase in enantioselectivity was observed by using (*S*,*S*)-**1b** as catalyst, although this tendency was not clear in the reaction with other nitrones (Table 5, entries 4 and 8). The reaction was also applicable to *C*-alkyl nitrones, thus providing the corresponding cycloadducts with high stereoselectivities (Table 5, entries 6 and 7).

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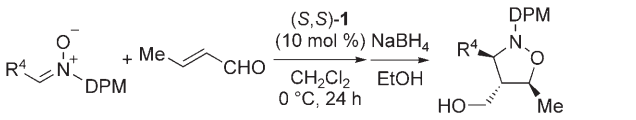
Table 5. Asymmetric 1,3-dipolar cycloaddition of *N*-diphenylmethyl nitrones and crotonaldehyde.[a]



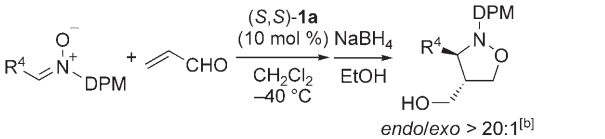
Entry	R^4	Catalyst	Yield[c] [%]	*ee*[d] [%]
1	Ph	(*S*,*S*)-**1a**	82	87
2	Ph	(*S*,*S*)-**1b**	94	89
3	4-tolyl	(*S*,*S*)-**1a**	93	89
4	4-tolyl	(*S*,*S*)-**1b**	89	81
5	4-$MeOC_6H_4$	(*S*,*S*)-**1a**	83	88
6	*t*Bu	(*S*,*S*)-**1a**	50	89
7	*i*Pr	(*S*,*S*)-**1a**	83	92
8	*i*Pr	(*S*,*S*)-**1b**	82	76

[a] The reaction of nitrone and crotonaldehyde (1.5 equiv) was performed in the presence of 10 mol% (*S*,*S*)-**1** in CH_2Cl_2. [b] Determined by ^1H NMR spectroscopy. [c] Yield of isolated product. [d] Determined by HPLC analysis with chiral columns.

Reexamination of Asymmetric 1,3-Dipolar Cycloaddition of *N*-Diphenylmethyl Nitrones and Acrolein

The results above clearly indicate the usefulness of *N*-diphenylmethyl nitrones in our bis-titanium chiral Lewis acid catalyzed 1,3-dipolar cycloadditions. In this context, we re-evaluated the reaction of *N*-benzyl nitrones and acrolein by replacing the *N*-benzyl group with the *N*-diphenyl group (Table 6). As expected, enhancement of both reactivity and enantioselectivity was observed. Especially notable is the fact that the cycloaddition was facilitated with C-secondary alkyl nitrones, thus providing the adduct in high yields with 97% *ee* (Table 6, entries 4 and 5; compare with Table 2, entries 10 and 11). The enhanced reactivity prompted us to lower the catalyst loading to 5 mol%. As a result, the reaction proceeded smoothly to give the cycloadduct in satisfactory yield with a slightly diminished *ee* of 95% (Table 6, entry 6).

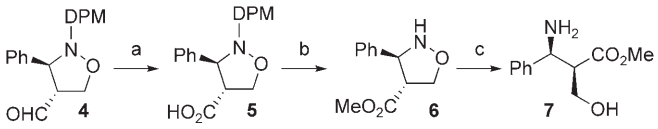
Table 6. Asymmetric 1,3-dipolar cycloaddition of *N*-diphenylmethyl nitrones and acrolein.[a]



Entry	R^4	*t* [h]	Yield[c] [%]	*ee*[d] [%]
1	Ph	13	91	97
2	4-tolyl	12	93	98
3	4-$MeOC_6H_4$	15	99	98
4	Cy	20	96	97
5	*i*Pr	5	83	97
6[e]	Ph	20	96	95

[a] Unless otherwise noted, the reaction of nitrone and acrolein (1.5 equiv) was performed in the presence of 10 mol% (*S*,*S*)-**1a** in CH_2Cl_2. [b] Determined by ^1H NMR spectroscopy. [c] Yield of isolated product. [d] Determined by HPLC analysis with chiral columns. [e] Performed with 5 mol% (*S*,*S*)-**1a**.

To highlight the synthetic utility of the cycloadduct thus obtained, the transformation of the adduct into the β-amino acid ester was then examined. Thus, 4-formyl isoxazolidine **4**, which was isolated from the reaction mixture without reduction of the aldehyde (Table 6, entry 1), was oxidized to afford the carboxylic acid **5** (Scheme 5). The diphenylmethyl group was then cleaved under strongly acidic conditions to provide isoxazolidine carboxylic acid methyl ester **6**. With the *N*-unsubstituted isoxazolidine in hand, reduction of the N–O bond by treatment with Raney nickel under hydrogen atmosphere was conducted to give the β-amino acid methyl ester **7** in 46% overall yield. Notably, the selective reduction of the N–O bond in the presence of the diphenylmethyl group on the nitrogen atom of the isoxazolidine was unexpectedly difficult.[13]



Scheme 5. Reagents and conditions: a) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH, H_2O, 91%; b) conc. HCl, MeOH, 50%; c) Raney Ni, H_2 (balloon), MeOH, quant.

Conclusions

In summary, we have developed asymmetric 1,3-dipolar cycloadditions of nitrones and α,β-unsaturated aldehydes catalyzed by designer bis-titanium chiral Lewis acids. High levels of regio- and stereoselectivities were attained for a wide scope of both nitrones and aldehydes by the use of the diphenylmethyl group as the N substituent on the nitrones. The synthetic application of this methodology was illustrated by the facile transformation of the cycloadduct into the β-amino acid ester by employing the acid-catalyzed removal of the diphenylmethyl group. This strategy offers a new practical benchmark reaction for the chiral Lewis acid catalyzed asymmetric 1,3-dipolar cycloadditions of nitrones.

Experimental Section

General

Infrared (IR) spectra were recorded on a Shimadzu IRPrestige-21 spectrometer. ^1H NMR spectra were recorded on a JEOL JNM-FX400 (400 MHz) spectrometer. ^{13}C NMR spectra were recorded on a JEOL JNM-FX400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm relative to the residual solvent as an internal standard. High-performance liquid chromatography (HPLC) was performed on Shimadzu 10A instruments at 220 nm with 4.6 nm × 25 cm Daicel Chiralcel OD-H and Chiralpak AD-H columns. High-resolution mass spectrometry (HRMS) was performed on an Applied Biosystems Brucker microTOF or a Mariner 8295 API-TOF workstation. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. For

thin-layer chromatography (TLC) used throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. The products were purified by flash column chromatography on silica gel 60 (Merck, 230–400 mesh). CH_2Cl_2 was purchased from Kanto Chemical Co., Inc. as "dehydrated" and was further purified by passing through neutral alumina under nitrogen atmosphere.

Syntheses

Representative procedure for the asymmetric 1,3-dipolar cycloaddition of nitrones and α,β-unsaturated aldehydes (Table 5, entry 1): A solution of $[ClTi(OiPr)_3]$ (1.0 M, 0.20 mmol, 200 μL) in hexanes was added to a stirred mixture of Ag_2O (0.10 mmol, 23.2 mg) in CH_2Cl_2 (1.0 mL) at room temperature under Ar. After the mixture was stirred for 5 h at room temperature, a solution of (*S*)-BINOL (0.20 mmol, 57.2 mg) in CH_2Cl_2 (2.0 mL) was added, and the resulting mixture was then stirred for 2 h at room temperature to afford a dark-colored solution of (*S*,*S*)-**1a**. Freshly distilled acrolein (1.5 mmol, 100 μL) and a solution of *C*-phenyl *N*-diphenylmethyl nitrone (1.0 mmol, 287 mg) in CH_2Cl_2 (1.0 mL) were added dropwise to the solution of catalyst prepared above at −40 °C. The reaction mixture was stirred at the same temperature for 13 h. The mixture was then treated with an ethanolic solution of $NaBH_4$ (2.0 mmol) and allowed to warm to 0 °C. After the mixture was stirred for 30 min at 0 °C, the reaction was quenched with aqueous NH_4Cl, and the mixture was filtered to remove insoluble materials and extracted with CH_2Cl_2. The combined organic layers were washed with 1 N NaOH to remove (*S*)-BINOL, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 3:1) to give the cycloadduct as a white powder (314 mg, 91 % yield, regioselectivity > 20:1, *endo*/*exo* > 20:1, *endo* 97 % *ee*). Enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 20:1, flow rate = 0.5 mL min^{-1}, t_R = 33.1 min (minor), 37.7 min (major)). $[\alpha]_D^{27} = -53.8$ (c = 1.0, $CHCl_3$; 97 % *ee*); IR (neat): $\tilde{\nu}$ = 3402, 3061, 3026, 2943, 2870, 1738, 1493, 1452, 1366, 1229, 1217, 1074, 1030, 999 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.03 (m, 15 H), 4.93 (s, 1 H), 4.22 (app t, J = 8.1 Hz, 1 H), 3.90 (dd, J = 8.6, 5.4 Hz, 1 H), 3.65 (m, 3 H), 2.73 ppm (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.3, 141.0, 140.5, 128.6, 128.1, 128.1, 128.0, 127.8, 127.5, 127.0, 126.9, 126.8, 72.5, 69.7, 68.7, 63.1, 55.8 ppm; HRMS (ESI): *m*/*z* calcd for $C_{23}H_{23}NO_2$: 368.1621 $[M+Na]^+$; found: 368.1625.

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[13] Oxidative cleavage of the diphenylmethyl group of the cycloadduct has been achieved in our preceding report; see reference [6b].

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