Development of Titanium-BINOLates Catalyzed Asymmetric 1,3-Dipolar Cycloaddition Reactions with α,β-Unsaturated Aldehydes

Takuya Hashimoto

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Chapter 1

Introduction

1.1 Historical Perspective of 1,3-Dipolar Cycloaddition Reactions

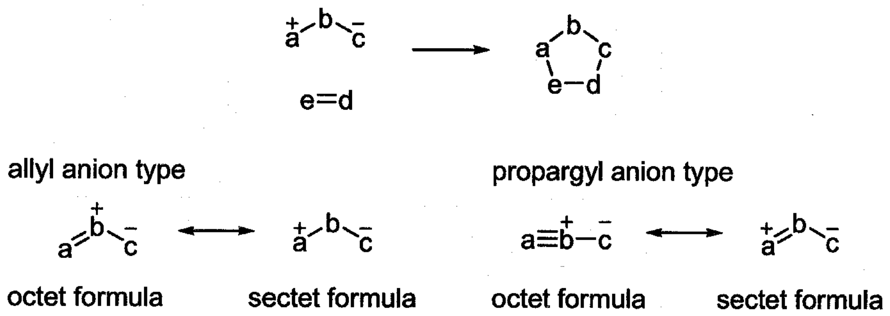
The discovery of 1,3-dipolar cycloaddition dates back to 19th century,[1] when E. Buchner carried out the reaction of methyl diazoacetate and methyl acrylate to obtain Δ^2-pyrazoline in 1888 (Scheme 1.1).

Scheme 1.1

The importance of cycloaddition reactions became crucial after the landmark discovery made by Otto Diels and Kurt Alder in 1928.[2] Since then, cycloaddition reactions have long been considered as the most powerful and promising synthetic tools to construct complex natural products and biologically active materials.[3] In the field of 1,3-dipolar cycloaddition reactions, Rolf Huisgen and co-workers established the definition of 1,3-dipolar cycloaddition reactions by their long term seminal works.[4] Huisgen delineated the definition of 1,3-dipolar cycloaddition reaction in his review article as follows.

"1,3-Dipole, *a-b-c*, must be difined, such that atom *a* posseses an electron sextet, *i.e.* an incomplete valence shell combined with a positive formal charge, and that atom *c*, the negatively charged center, has an unshared electron pair. Combination of such a 1,3-dipole with a multiple bond system *d-e*, termed the dipolarophile, is referred to as a 1,3-dipolar cycloaddition."

Huisgen classified 1,3-dipoles into two different types: allyl anion type, e.g., nitrones, diazo comopounds and azomethine ylides; and propargyl anion type, e.g., nitrile oxides and nitrile imines (Scheme 1.2). Their systematic studies certainly opened the door to intensive researches on 1,3-dipolar cycloaddition reactions.



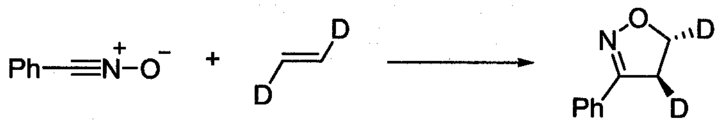
Scheme 1.2

Since then, a myriad of methods to prepare complex molecules in a stereoselective manner utilizing 1,3-dipolar cycloaddition reactions have been disclosed due to their unique properties to form heterocycles with up to 4 stereogenic centers in a single step. Nevertheless, the development of catalytic asymmetric 1,3-dipolar cycloadditions are far less matured compared to the well-explored catalytic asymmetric [4+2] cycloaddition reactions and many researchers still devote their passions to the development of these challenging areas.

1.2 Theoretical Basis

1.2.1 Frontier Molecular Orbital Interactions

The reaction mechanism of 1,3-dipolar cycloaddition reactions had been a dispute in 1960s, where a concerted mechanism and a radical mechanism were suggested, the former by Huisgen and the latter by Firestone.^{5} The concerted mechanism was finally supported by the experimental fact that benzonitrile oxide reacted with *trans*-dideuterated ethylene to give the *trans*-dideuterated isoxazoline stereospecifically (Scheme 1.3).^{6} If the reaction took place via the radical intermediate, the product should be a mixture of *cis*- and *trans*-isoxazolines.



Scheme 1.3

In 1973, Houk et al. established a now well-accepted theory of concerted mechanism of 1,3-dipolar cycloaddition reactions based on Woodward-Hoffman rules.^{7} Sustman et al. classified 1,3-dipolar cycloaddition reactions in 3 types as shown in Figure 1.1.^{8} In the case of type I, $\text{HOMO}_{\text{dipole}}$ and $\text{LUMO}_{\text{dipolarophile}}$ interact dominantly. Type III reactions take place by the interaction between $\mathrm{HOMO_{dipolarophile}}$ and $\mathrm{LUMO_{dipole}}$. As for the type II, both $\mathrm{HOMO_{dipole}}$-$\mathrm{LUMO_{dipolarophile}}$ interaction and $\mathrm{HOMO_{dipolarophile}}$-$\mathrm{LUMO_{dipole}}$ interaction can be a dominant transition model depending on the reaction conditions.

It should be also noted that Huisgen et al. later found the 1,3-dipolar cycloaddition reaction which proceeded via a stepwise mechanism in the case of thiocarbonyl ylide used as a 1,3-dipole.[9]

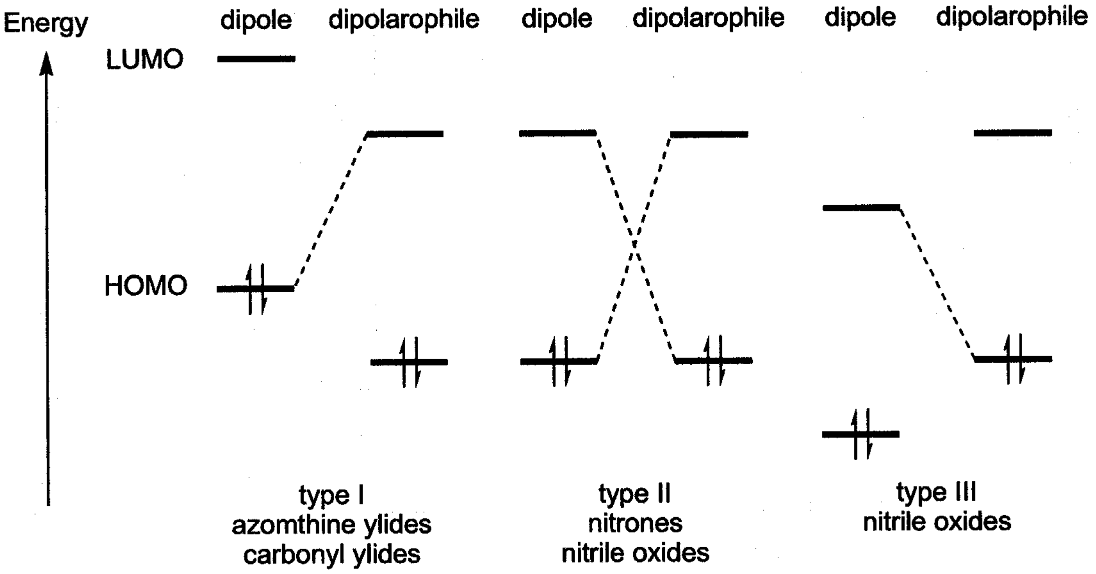
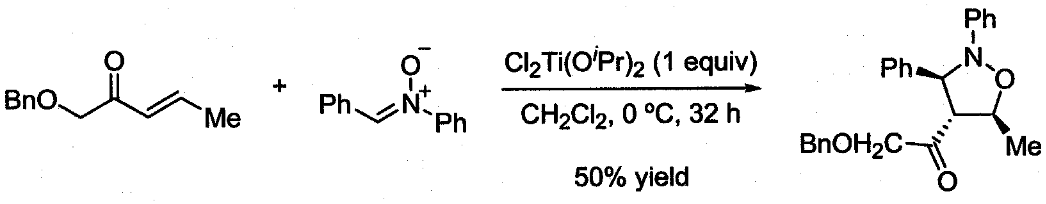


Figure 1.1

1.2.2 FMO Interactions of Lewis Acid (L.A.) Catalyzed 1,3-Dipolar Cycloadditions

The acceleration of 1,3-dipolar cycloaddition reactions in the presence of a catalytic amount of an "activator" is a key issue to realize catalytic asymmetric 1,3-dipolar cycloaddition reactions. Lewis acid is actually a leading candidate of an "activator" and Kanemasa et al. realized the first Lewis acid catalyzed 1,3-dipolar cycloaddition reaction between nitrones and α,β-unsaturated ketones containing a chelating alkoxy group (Scheme 1.4).[10]



Scheme 1.4

Theoretical basis of Lewis acid catalyzed 1,3-dipolar cycloaddition reaction is explained by the FMO interactions as shown below (Figure 1.2). The activation mechanism of the reaction is divided into two ways: (a) lowering $\mathrm{LUMO_{dipolarophile}}$ by the coordination of a Lewis acid to the electron deficient olefin to activate $\mathrm{HOMO_{dipole}}$-$\mathrm{LUMO_{dipolarophile}}$ interaction (normal electron demand 1,3-dipolar cycloaddition reaction); this is the case of Kanemasa's report, (b) lowering $\mathrm{LUMO_{dipole}}$ by the coordination of a Lewis acid to a nitrone to activate $\mathrm{HOMO_{dipolarophile}}$-$\mathrm{LUMO_{dipole}}$ interaction (inverse electron demand 1,3-dipolar cycloaddition reaction).

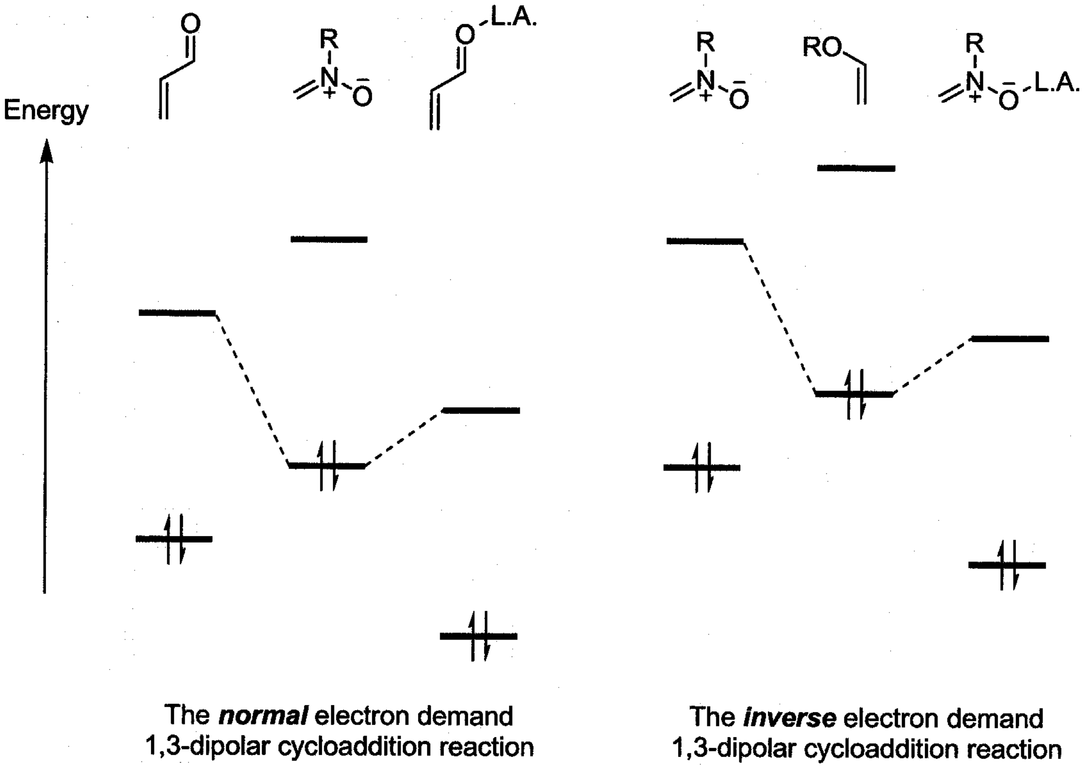


Figure 1.2

1.2.3 Regioselectivity of 1,3-Dipolar Cycloaddition Reaction

The regioselectivity of 1,3-dipolar cycloaddition reaction is usually affected by both electronic and steric factors. In this section, the regiochemistry of 1,3-dipolar cycloaddition reaction of nitrones and terminal alkenes is chosen as a representative example and illustrated. According to the steric factor, the reaction proceeds avoiding the repulsion between a *C*-substituent on the nitrone and a more hindered site of the alkene. Consequently, the 3,5-disubstituted isoxazolidine was formed predominantly (Figure 1.3).

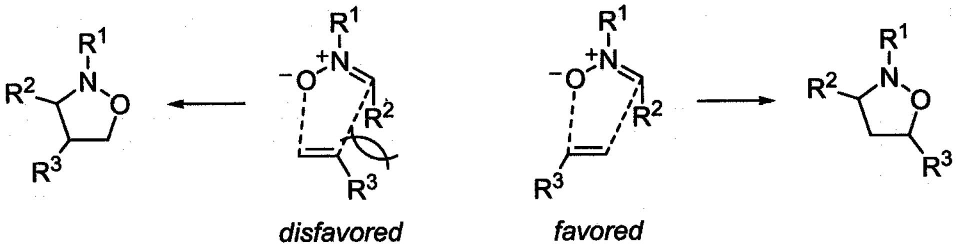


Figure 1.3

However, in some cases, steric effects may be overruled by electronic contributions. The reaction between a nitrone and electron-deficient alkene such as an α,β-unsaturated carbonyl compound (normal electron demand reaction) is primarily controlled by the HOMO$_{dipole}$-LUMO$_{dipolarophile}$ interaction (Figure 1.4). The HOMO$_{dipole}$ has the largest coefficient at the oxygen atom, whereas the LUMO$_{dipolarophile}$ has the largest coefficient at the terminal carbon atom. As a result, formation of the 3,4-substituted isoxazolidine became favorable despite the steric preference to give the 3,5-substituted isoxazolidine. In the case of the inverse electron demand reaction, the steric effect is further strengthened by the electronic factor to give the 3,5-substituted isoxazolidine.

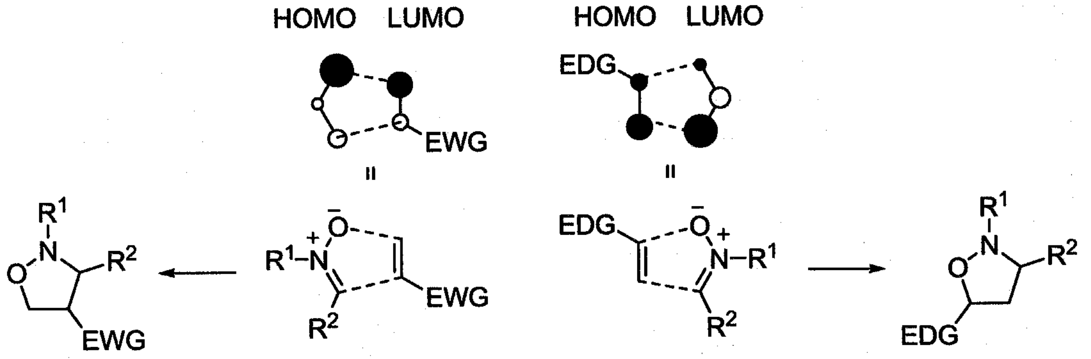


Figure 1.4

1.2.4 Stereoselectivity of 1,3-Dipolar Cycloaddition Reaction

1,3-Dipolar cycloaddition reactions of some dipoles, such as nitrones, normally afford two diastereoisomers designated as endo and exo isomers. The endo isomer arises from the transition model, in which nitrogen atom of the nitrone points in the same direction as the substituent of the alkene. On the other hand, the exo isomer is formed via the interaction of the alkene and nitrone pointing the opposite directions each other (Figure 1.5). However, unlike the Diels-Alder reaction, the orbital interaction is rather small and the steric interaction of substrates and catalysts has a predominant influence. Additionally, the *E*/*Z* isomerization of the 1,3-dipole must be taken into consideration, since the isomerization may result in the formation of the opposite diastereomer. For this reason, the cis/trans nomenclature is preferred in the case of easily isomerizable 1,3-dipoles.

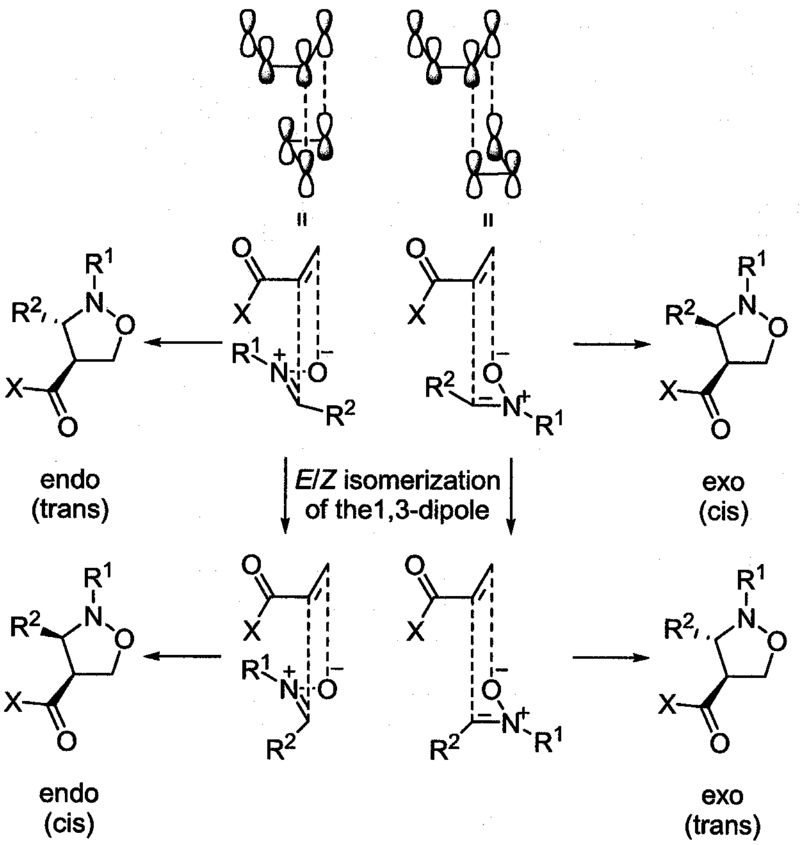
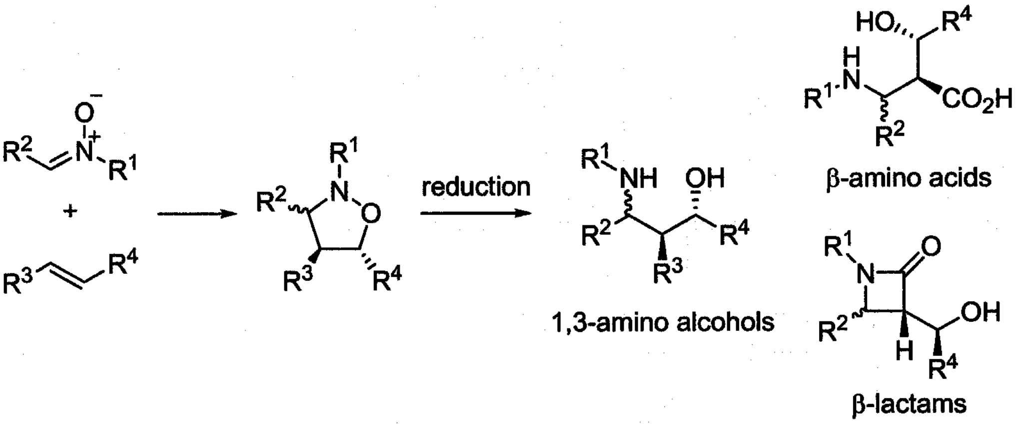


Figure 1.5

1.3 Asymmetric 1,3-Dipolar Cycloaddition Reaction of Nitrones

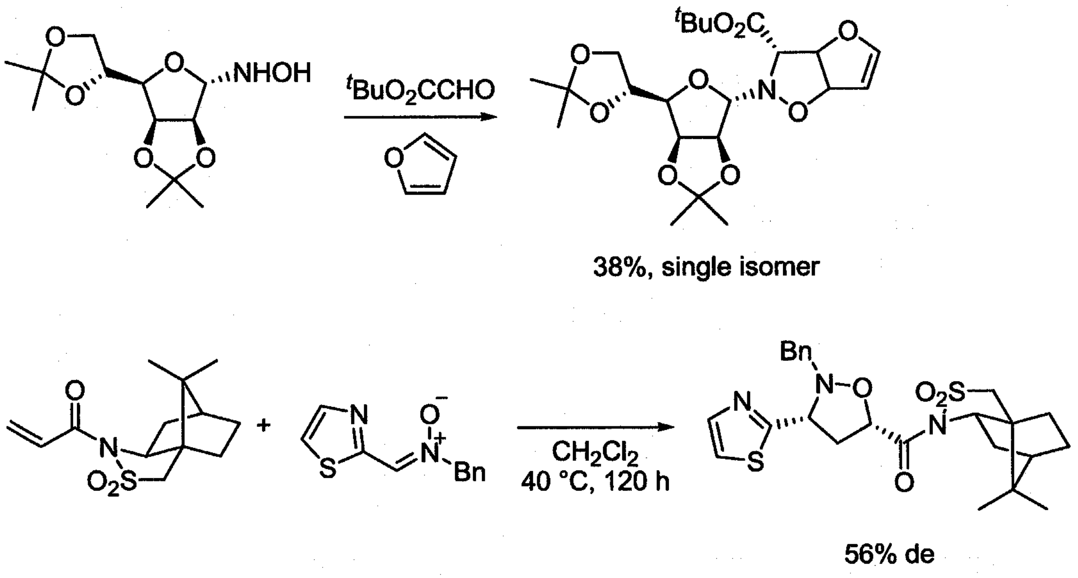
Nitrones were first discovered by Beckmann et al. in 1890[11] and have been utilized in various fields of organic chemistry. Because of their intrinsic character as a stable and isolable 1,3-dipole in contrast to the labile nature of other dipoles, which are commonly evolved in situ, 1,3-dipolar cycloaddition reaction of nitrones became the most studied area of 1,3-dipolar cycloaddition chemistry. The 1,3-dipolar cycloaddition reaction of nitrones with alkenes offers an opportunity to construct up to three contiguous stereogenic centers with nitrogen and oxygen functionalities. Importantly, isoxazolidines thus formed can be easily converted to 1,3-amino alcohols, β-amino acids and β-lactams, which are useful chiral building blocks for the synthesis of biologically active compounds (Scheme 1.5).



Scheme 1.5

1.3.1 Asymmetric 1,3-Dipolar Cycloaddtion Reaction of Nitrones Utilizing Chiral Auxiliaries

There has been a numerous number of reports concerning about the diastereoselective preparations of chiral isoxazolidines. Herein, selected two intermolecular reactions are illustrated, one of which proceeds by the inverse electron demand reaction pathway and the other by the normal electron demand reaction pathway (Scheme 1.6).[12,13]

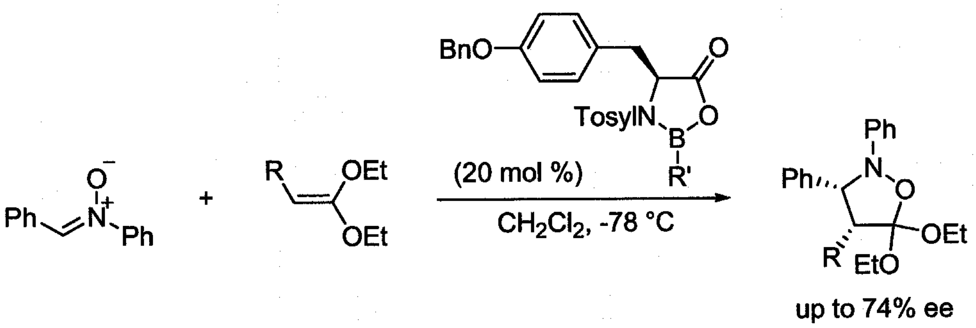


Scheme 1.6

1.3.2 Catalytic Asymmetric Inverse Electron Demand 1,3-Dipolar Cycloaddition Reaction of Nitrones

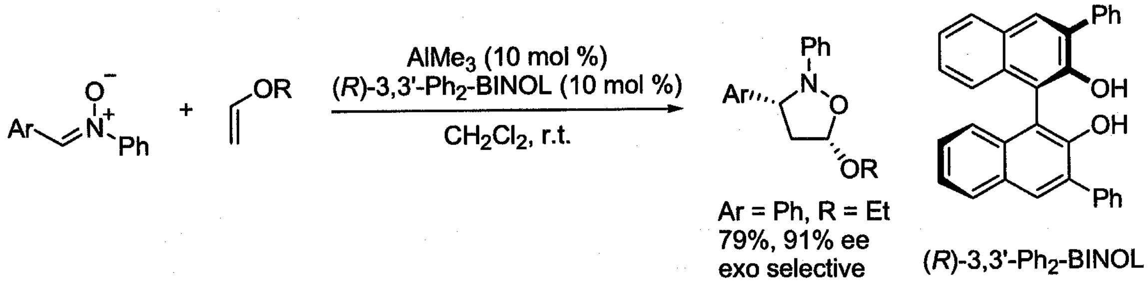
The first catalytic asymmetric 1,3-dipolar cycloaddition was reported in 1994 by

Sheeren and co-workers,[14] where *N*-benzylideneaniline *N*-oxide and ketene acetals were annulated in the presence of the amino acid derived oxazaborolidine as a chiral Lewis acid catalyst (Scheme 1.7). The mode of reaction was designated as inverse electron demand 1,3-dipolar cycloaddition reaction according to the classification illustrated in Chapter 1.2.2.



Scheme 1.7

In 1999, Jørgensen et al. used the combination of $AlMe_3$ and the axially chiral 3,3'-disubstituted BINOL to facilitate this type of 1,3-dipolar cycloaddition reaction of nitrones, and consequently, various 5-alkoxy-2-aryl-isoxazolidines were obtained in good yields and enantioselectivities (Scheme 1.8).[15]

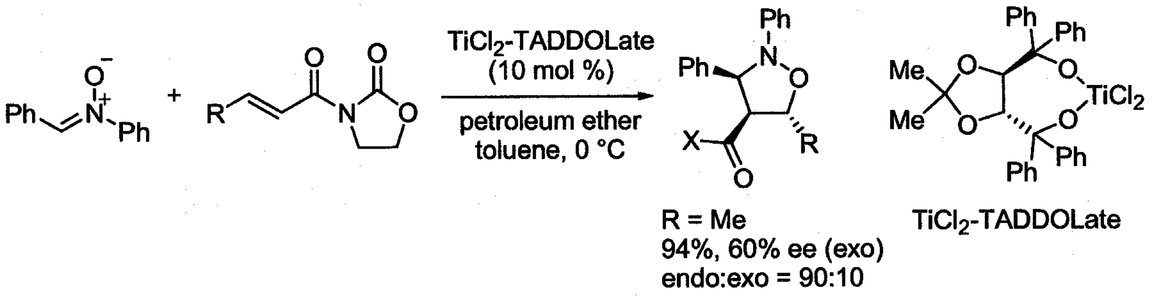


Scheme 1.8

In other reports, use of titanium and copper complexes as Lewis acid catalysts were disclosed to facilitate the reaction. However, the number of reports concerning about the inverse electron demand reaction is rather limited compared to that of the normal electron demand reactions.

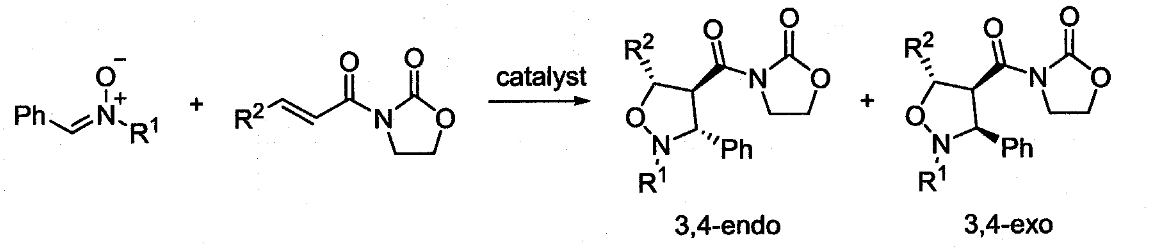
1.3.3 Catalytic Asymmetric Normal Electron Demand 1,3-Dipolar Cycloaddition Reaction of Nitrones

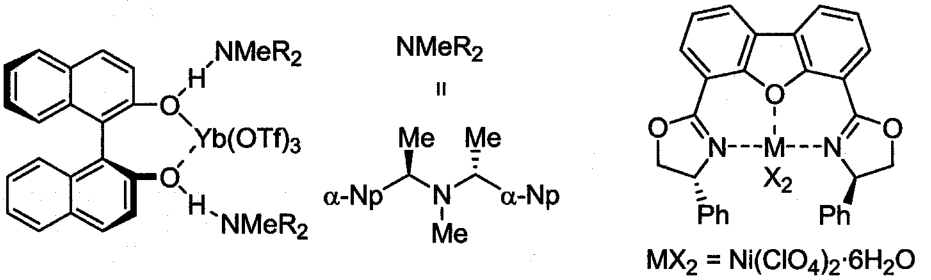
Jørgensen et al. played a leading role in the development of 1,3-dipolar cycloaddition reactions of nitrones and reported the first catalytic asymmetric normal electron demand 1,3-dipolar cycloaddition of nitrones, in which 3-(2-alkenoyl)-2-oxazolidinones were utilized as dipolarophiles under the influence of a titanium-TADDOLate (Scheme 1.9).[16] Employment of dipolarophiles which can coordinate to the Lewis acid in a bidentate fashion is crucial in their reaction system, since coordination of the oxygen atom of nitrones to the Lewis acid is generally stronger rather than that of poorly basic simple carbonyls, resulting in the deactivation of the reaction. Since their publication, the combination of *C,N*-diphenylnitrone and 3-(2-alkenoyl)-2-oxazolidinones became a model system of choice to evaluate newly designed chiral Lewis acids, and some highly effective catalysts, which could efficiently provide the cycloadducts in high regio-, diastereo- and enantioselectivities, were developed.



Scheme 1.9

Among contributions in this area,[17] Kobayashi et al. succeeded in obtaining isoxazolidines in excellent yields with almost complete stereoselectivities by using the catalyst consisted of a 1:1:2 mixture of $Yb(OTf)_3$, BINOL and a chiral tertiary amine. (Scheme 1.10).[18] Another notable aspect of their report is the elegant derivatization of isoxazolidine thus obtained to the β-lactam (Scheme 1.11). It could only be realized when a nitrone bearing a cleavable *N*-benzyl substituent was employed in the reaction, whereas many methods developed to date utilized inert *N*-phenyl substituted nitrones. At the same time, Kanemasa et al. described the highly stereoselective 1,3-dipolar cycloaddition reaction utilizing DBFOX-$Ni(ClO_4)_2$ as a chiral Lewis acid (Scheme 1.10).[19]

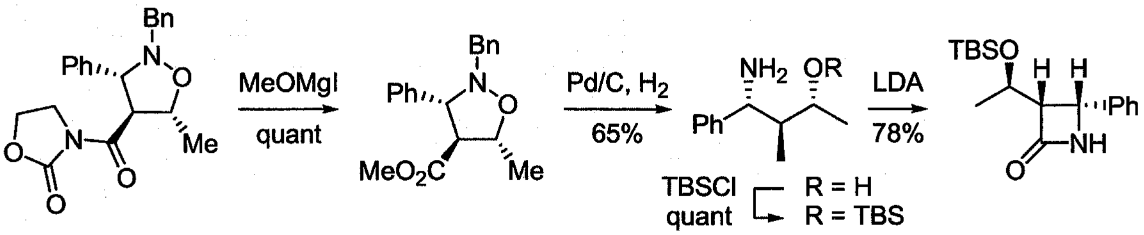




Kobayashi et al.
R^1 = Bn; R^2 = H or alkyl
up to 98% ee (endo)
endo/exo = >95:5

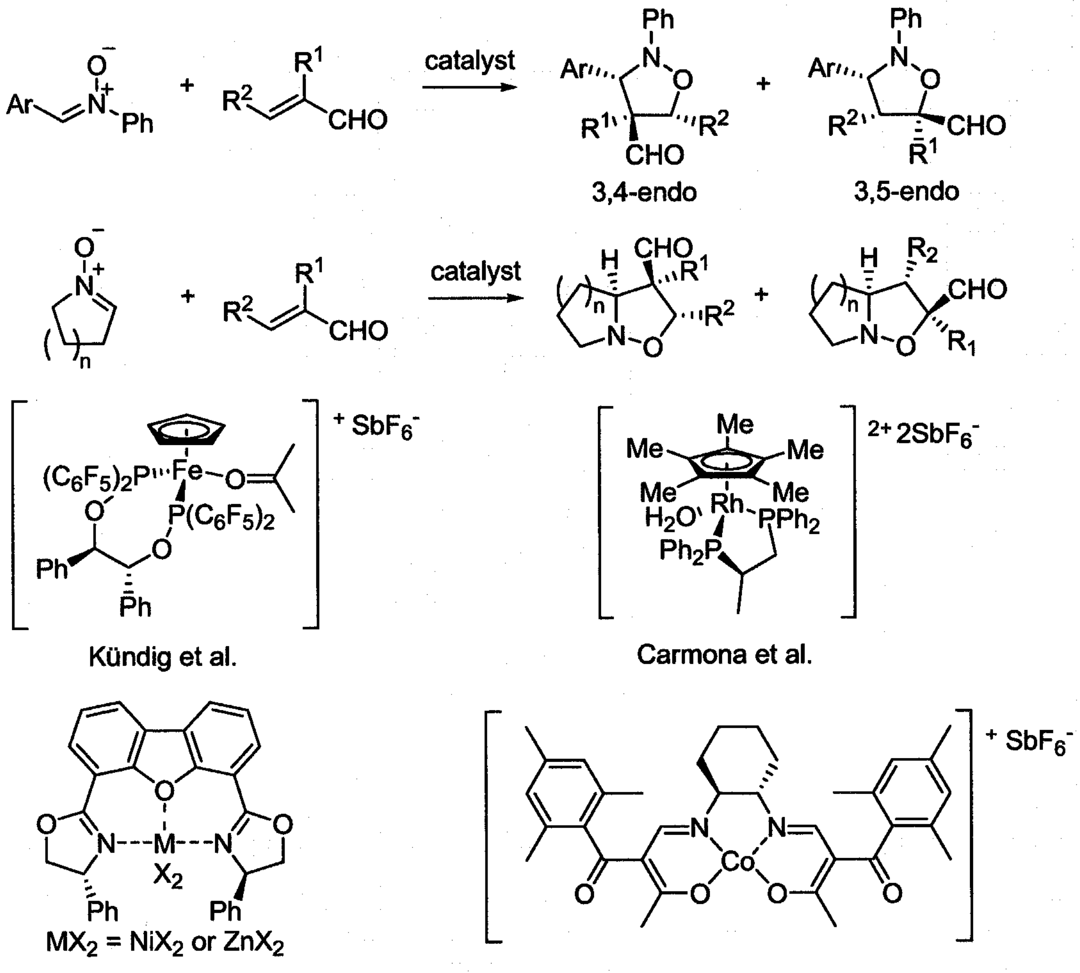
Kanemasa et al.
R^1 = Ph, Bn or Me; R^2 = Me
up to >99% ee (endo)
endo/exo = >95:5

Scheme 1.10



Scheme 1.11

The activation of poorly coordinative α,β-unsaturated aldehydes by a Lewis acid catalyst was realized only recently (Scheme 1.12). Kündig and co-workers demonstrated the remarkable potential of chiral iron and ruthenium Lewis acids, which facilitated the reaction of some cyclic nitrones and α,β-unsaturated aldehydes, such as methacrolein and crotonaldehyde to give the cycloadducts in the enantioselectivities of over 94% ee.[20] Carmona et al. also described the rhodium and iridium chiral Lewis acid catalysts were suitable for providing isoxazolidines derived from cyclic nitrones and methacrolein.[21] However, in both cases, the reaction of acyclic *C,N*-diphenyl nitrone afforded the 3,4-endo isoxazolidine and 3,5-endo isoxazolidine in poor selectivity. In other ways, Yamada et al. showed the ability of the chiral β-ketoiminato cobalt complex in the 1,3-dipolar cycloaddition reaction of acyclic *N*-phenyl nitrones and α,β-unsaturated aldehydes.[22] They observed high levels of stereoinduction in the reaction of acyclic *C*-(2-halophenyl)-*N*-phenyl nitrone and 1-cyclopentene-1-carbaldehyde. Kanemasa and co-workers applied their DBFOX/Ph-metal complexes to the reaction of *C,N*-diphenyl nitrone and succeeded to obtain the cycloadducts in moderate to high regio-, diastereo- and enantioselectivities by tuning the central metal depending on the substitution patterns of α,β-unsaturated aldehydes.[23]



Kündig et al.

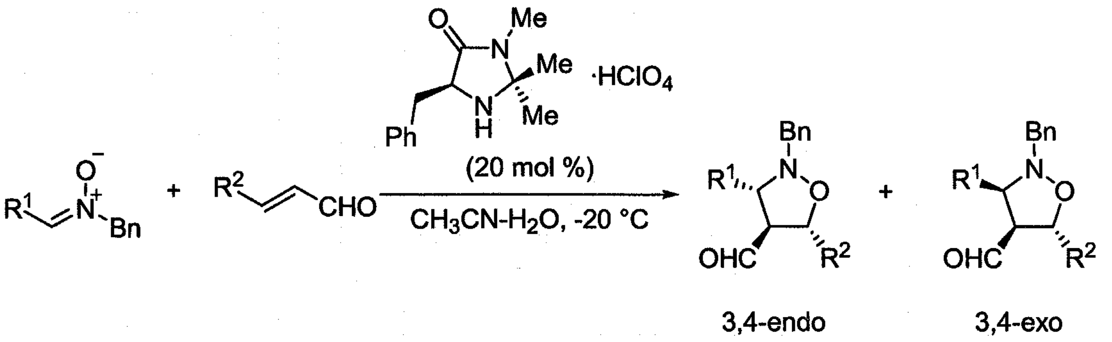
Carmona et al.

Kanemasa et al.

Yamada et al.

Scheme 1.12

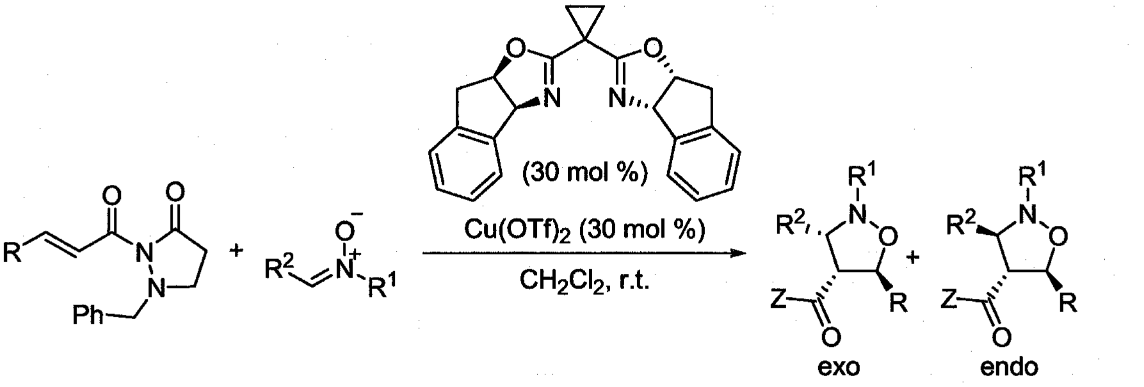
In a distinctive approach, MacMillan et al. reported the organocatalytic 1,3-dipolar cycloaddition reaction of nitrones, taking advantage of little affinity between nitrones and secondary ammonium salts (Scheme 1.13).[24] In their report, *N*-benzyl substituted nitrones were used to give the isoxazolidines with benzyl group on nitrogen atom as a cleavable protecting group.



R^1 = Ph, R^2 = CH$_3$
98%, 94% ee (endo), endo:exo = 94:6

Scheme 1.13

Most of catalytic asymmetric 1,3-dipolar cycloaddition reactions of nitrones developed to date are endo selective and the example of highly exo- and enantioselective reaction is rare. In this regard, Sibi et al. described the use of novel pyrazolidinone templates developed in their laboratory as a solution to this problem (Scheme 1.14).[25]



R = CH$_3$, R^1 = CH$_3$, R^2 = Ph
94%, 98% ee (exo), endo:exo = 4:96

Scheme 1.14

1.4 Asymmetric 1,3-Dipolar Cycloaddition of Diazo Compounds

The history of 1,3-dipolar cycloaddition reaction of diazoalkane started from the discovery made by Buchner (Chapter 1.1). The illustrative synthetic utility of this reaction is shown in Figure 1.6. The Δ^1-pyrazolines produced in the reaction are known as labile compounds, which form cyclopropanes by extrusion of nitrogen or Δ^2-pyrazolines by 1,3-hydrogen shift. Δ^2-Pyrazolines are usually further converted to pharmaceutically attractive compounds, such as pyrazoles by oxidation or 1,3-diamines by reduction.

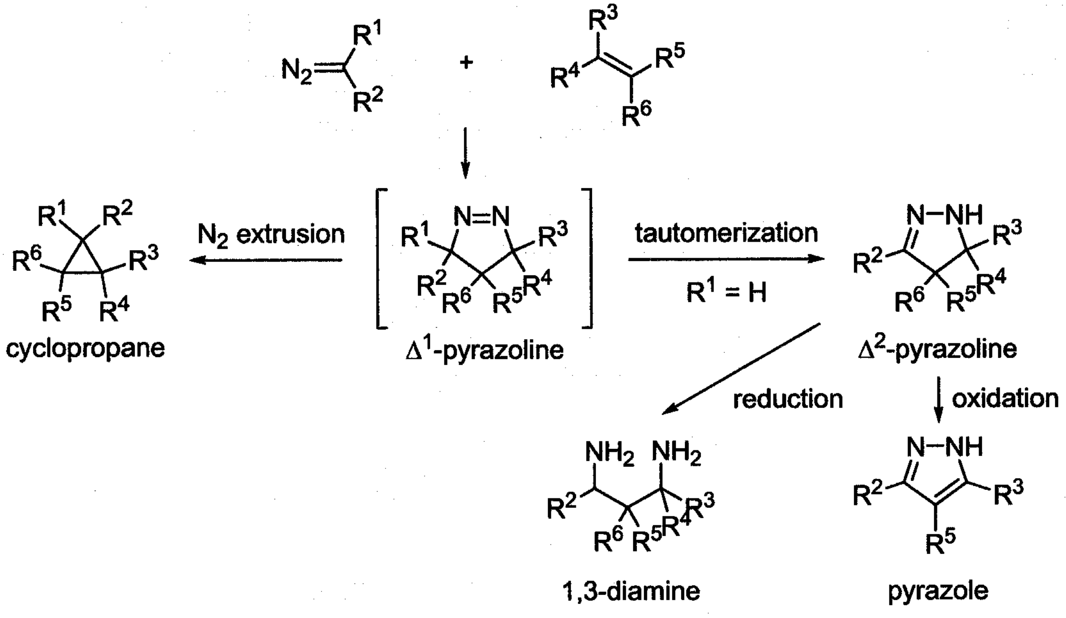


Figure 1.6

1.4.1 Asymmetric 1,3-Dipolar Cycloaddtion Reaction of Diazo Compounds Utilizing Chiral Auxiliaries

There have been a variety of reports concerning the diastereoselective 1,3-dipolar cycloaddition reaction of diazo compounds, though the number of the reports is far less than that of nitrones. In most cases, chiral auxiliaries are incorporated into the side of dipolarophiles, not into 1,3-dipoles, because of the difficulty to introduce effective chiral groups to diazo compounds. Some representative chiral dipolarophiles are showcased in Figure 1.7. [3a]

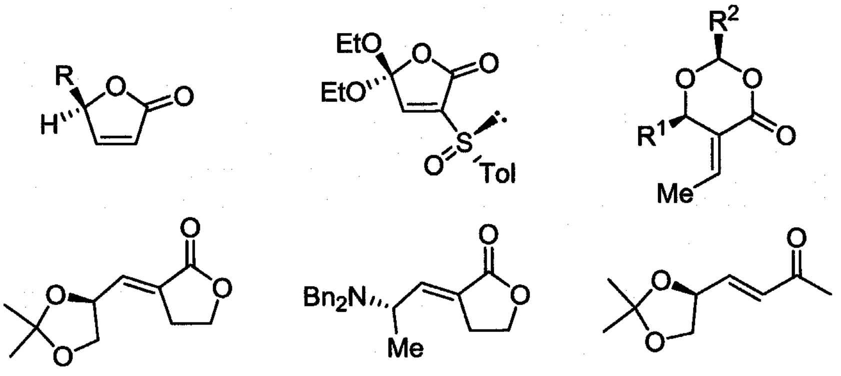
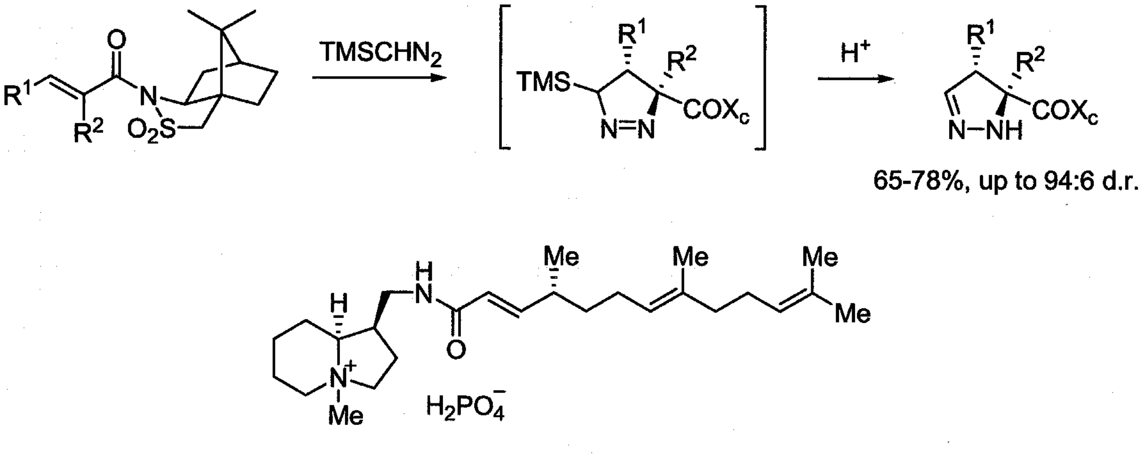


Figure 1.7

Among these diastereoselective approaches, Carreira and co-workers elegantly delineated the synthetic utility of camphor sultam-derived dipolarophiles in the reaction with $TMSCHN_2$ as a 1,3-dipole to obtain the optically enriched Δ^2-pyrazolines in excellent yields and high diastereoselectivities (Scheme 1.15).[26] They successfully applied their methodology to the total synthesis of *ent*-stellettamine A. It is also noteworthy that they observed the acceleration of the reaction in the presence of a catalytic amount of a Lewis acid catalyst.

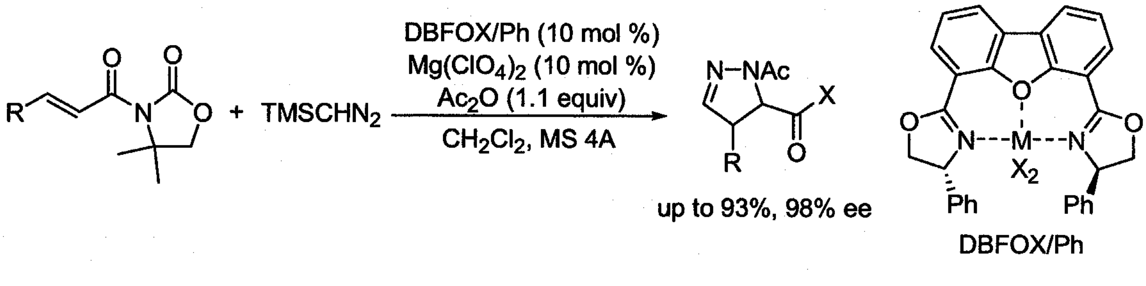


ent-stellettamide A

Scheme 1.15

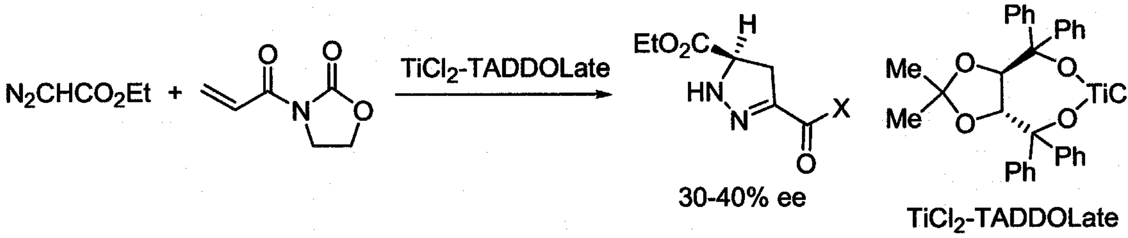
1.4.2 Lewis Acid Catalyzed Asymmetric Reactions

The first example of catalytic asymmetric 1,3-dipolar cycloaddition reaction of diazo compounds was realized by Kanemasa and co-workers in 2000.[27] They demonstrated the potential of their DBFOX-Mg complex in the reaction system closely related to Carreira's to provide Δ^2-pyrazolines in high yields and excellent enantioselectivities (Scheme 1.16).



Scheme 1.16

So far, the publication from Kanemasa's group is the only successful example of catalytic asymmetric 1,3-dipolar cycloaddition reaction of diazo compound. As a unpublished result, Jørgensen et al. described that the cycloaddition of 3-(2-acryloyl)-2-oxazolidinone and ethyl diazoacetate was facilitated in the presence of a catalytic amount of titanium TADDOLate to give the Δ^2-pyrazoline in moderate enantioselectivity (Scheme 1.17).[3b,3d]



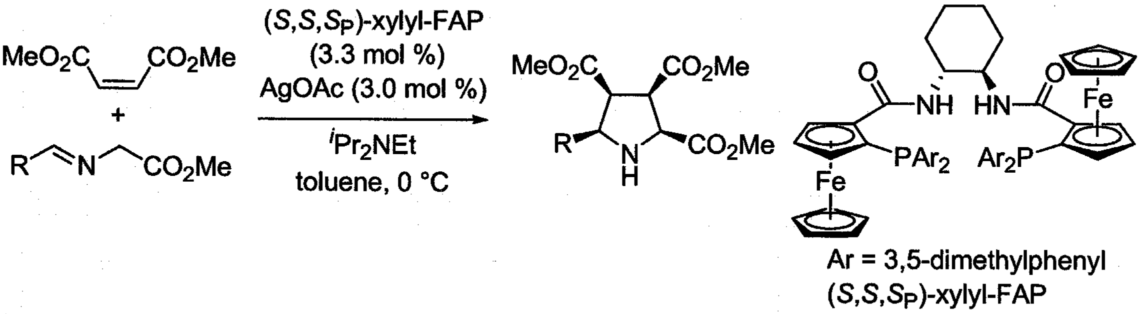
Scheme 1.17

1.5 Other 1,3-Dipoles for Catalytic Asymmetric 1,3-Dipolar Cycloaddition Reacitons

In contrast to the stable nature of nitrones and diazo compounds, it is normally a difficult task to provide other 1,3-dipoles as isolable compounds. Recently, several methods have been developed to carry out 1,3-dipolar cycloaddition reactions of such unstable 1,3-dipoles, which are generated in situ, with α,β-unsaturated carbonyl compounds. The two representative metal-catalyzed reactions of these dipoles are presented.

1.5.1 Catalytic Asymmetric 1,3-Dipolar Cycloaddition Reaction of Azomethine Ylides and Alkenes

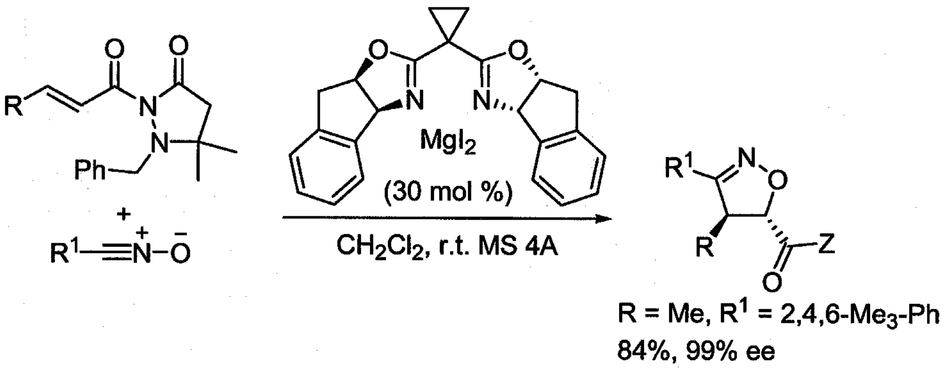
The 1,3-dipolar cycloaddition reaction of azomethine ylides allows the stereoselective synthesis of pyrrolidine derivatives with up to four stereogenic centers. Azomethine ylides are commonly generated in situ by the metalation of the corresponding imino esters.[28] In 2002, Zhang et al. disclosed the first successful catalytic asymmetric 1,3-dipolar cycloaddition reaction of azomethine ylides by the extensive screening of chiral phosphine ligand (Scheme 1.18).[29] They found out that bis-ferrocenyl amide phosphine ligands (FAP) developed in their laboratory provided excellent results.



Scheme 1.18

1.5.2 Catalytic Asymmetric 1,3-Dipolar Cycloaddition Reaction of Nitrile Oxides and Alkenes

Diastereoselective 1,3-dipolar cycloaddition reactions of nitrile oxides have been extensively studied, since the transformation of reaction products, isoxazolines, leads to α-hydroxyl carbonyl compounds or 1,3-amino alcohols as wishes. Nitrile oxides are known to dimerize easily and most of the reactions developed to date rely on the in situ generation of these nitrile oxides. The difficulty in handling the nitrile oxides and their coordinative character to the Lewis acid hampered the exploration of asymmetric catalysis. In this context, Sibi and co-workers recently developed highly regio- and enantioselective nitrile oxide cycloadditions to α,β-unsaturated carbonyls using substoichiometric amounts of a chiral Lewis acid (Scheme 1.19).[30]



Scheme 1.19

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Chapter 2

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

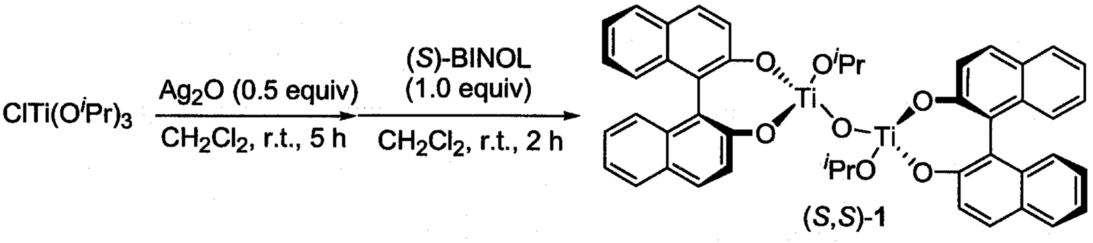
Introduction

The 1,3-dipolar cycloaddition reaction of nitrones and alkenes has 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] Since the produced isoxazolidines can be further converted to a variety of synthetically useful chiral building blocks, such as β-amino alcohols, β-amino acids and β-lactams, the preparation of enantiomerically enriched isoxazolidines by use of chiral auxiliary or asymmetric catalysis have been investigated intensively. Especially, metal-catalyzed asymmetric processes utilizing the lowered LUMO orbital energy of α,β-unsaturated carbonyls by coordination of the Lewis acid, designated as normal electron demand 1,3-dipolar cycloaddition reactions, have been developed in the past decade as an attractive method to construct such isoxazolidines efficiently.[2] Due to the strong coordinative character of nitrones to Lewis acids, bidentate dipolarophiles, such as 3-(2-alkenoyl)-2-oxazolidinones, are commonly utilized to facilitate the effective coordination of dipolarophiles to Lewis acid catalysts. In addition, *N*-benzylideneaniline *N*-oxide is employed as a typical acyclic nitrone to achieve high levels of enantioselectivity. Recently, certain chiral Lewis acid catalysts[3] and organocatalysts[4] have been found to be capable of achieving 1,3-dipolar cycloaddition reaction between nitrones and monodentate α,β-unsaturated aldehydes, exploiting the low affinity of these catalysts to nitrones. At present, however, nitrones containing functionally inert phenyl group on the nitrogen atom were utilized in most cases and synthetic applications of these cycloadducts to valuable chiral building blocks are rarely described.[4] Rigorous control of the regio- and stereochemistry simultaneously also remains as a challenging task, along with insufficient substrates generality.

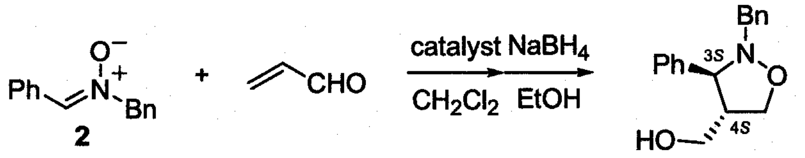
Herein, the author describes his works on such an asymmetric 1,3-dipolar cycloaddition reaction. A bis-titanium chiral Lewis acid[5-8] has been found to successfully catalyze the reaction of *N*-benzyl nitrones and monodentate acrolein, and the use of *N*-benzyl nitrones enabled the further transformation of the cycloadduct. Indeed, the author has demonstrated the conversion of the produced *N*-benzyl-isoxazolidine to the optically enriched 1,3-amino alcohol. The author also investigated the scope and generality of the reaction catalyzed by the designer bis-titanium chiral Lewis acid catalyst. Furhtermore, the substrate limitations in the reaction of *N*-benzyl nitrones were found to be overcome by using a unique approach, modification of *N*-substituent on nitrones.

Results and Discussion

The requisite μ-oxo-type bis-titanium chiral Lewis acid (*S*,*S*)-**1** was prepared by treatment of ClTi(O^{i}Pr)$_3$ (2 equiv) with Ag$_2$O and subsequent addition of (*S*)-BINOL (2 equiv), following the procedure established during his related studies on the catalytic asymmetric allylation (Scheme 2.1).[6] The author first investigated the asymmetric 1,3-dipolar cycloaddition between acrolein and nitrone **2** bearing easily removable *N*-benzyl group as shown in Table 2.1. Thus, in the presence of 10 mol % bis-titanium chiral Lewis acid (*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). The 2:1 complex of (*S*)-BINOL/Ti(O^{i}Pr)$_4$ facilitated the reaction smoothly, though the enantioselectivity was not satisfactory (entry 4). Upon further investigation, it was found that by lowering the temperature (–20 and –40 °C) the isoxazolidine was obtained in high yield with excellent enantioselectivity at the expense of the reaction rate (entries 5 and 6). The absolute configuration was determined to be (3*S*,4*S*) by the comparison with the data in the literature.[4a]



Scheme 2.1



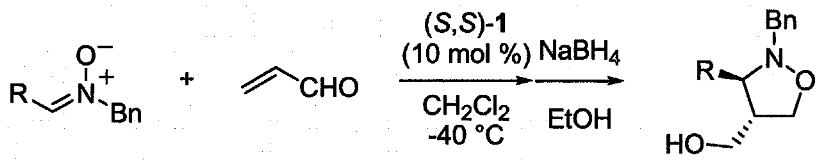
entry	catalyst (mol %)		conditions [°C, h]	yield (%)[b]	endo/exo[c]	ee (%)[d]
1	(*S*,*S*)-**1**	10	0, 2	78	>20/1	89
2	Ti(O^{i}Pr)$_4$ (*S*)-BINOL	20	0, 2	40	>20/1	60
3	ClTi(O^{i}Pr)$_3$ (*S*)-BINOL	20	0, 2	36	>20/1	60
4	Ti(O^{i}Pr)$_4$ 2(*S*)-BINOL	10	0, 2	90	>20/1	80
5	(*S*,*S*)-**1**	10	-20, 17	90	>20/1	91
6	(*S*,*S*)-**1**	10	-40, 24	94	>20/1	93

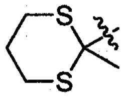
[a] Unless otherwise noted, the reaction of nitrone **2** and acrolein (1.5 equiv) was carried out in the presence of a chiral bis-Ti(IV) oxide (*S*,*S*)-**1** or chiral mono-Ti(IV) catalysts in CH_2Cl_2. [b] Isolated yield. [c] Determined by ^{1}H-NMR spectroscopy. [d] Determined by HPLC analysis using chiral column.

Table 2.1

The scope and limitation of 1,3-dipolar cycloaddition reaction of various nitrones and acrolein were investigated under the optimized reaction conditions (Table 2.2). Reactions with various electronically different *C*-aryl substituted nitrones gave the corresponding isoxazolidines in high to excellent enantioselectivities concomitant with rigorous regio- and diastereoselectivities. Substitution patterns on aryl groups, such as *ortho*-, *meta*-, or *para*-substitutions, were all tolerated under the standard conditions providing the cycloadducts in high selectivities (entries 2-4). Subsequently, the author examined the reaction of *C*-alkyl and alkenyl substituted nitrones. It turned out that the sterically hindered *tert*-butyl-substituted nitrone was a suitable substrate to afford the cycloadduct in the yield of 90% and excellent enantiomeric excess of 97% ee with exclusive endo selectivity. However, the reaction of nitrones bearing a secondary alkyl substituent afforded the cycloadducts in diminished yields and selectivities (entries 10 and 11). In the case of a nitrone bearing ethyl group (R = Et), the reaction led to the complete loss of stereoselectivity and poor reactivity (data not shown).

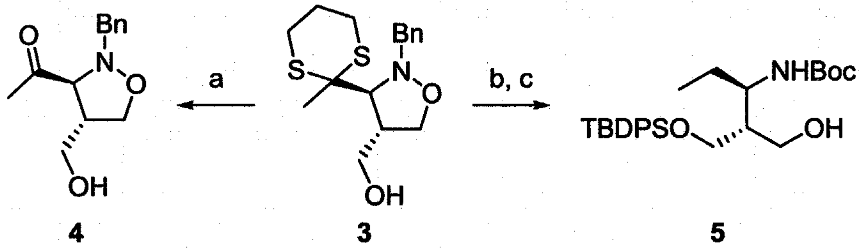
The synthetically useful nitrone with 1,3-dithianyl group[9] could be successfully utilized in the 1,3-dipolar cycloaddition reaction (entry 9). Indeed, hydrolysis of the resulting isoxazolidine **3** with mercuric salts produced the corresponding acetyl isoxazolidine **4** in good yield (Scheme 2.2). 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.



entry	R	time (h)	yield (%)[b]	endo/exo[c]	ee (%)[d]
1	Ph	24	94	>20/1	93
2	4-MePh	24	81	>20/1	94
3	3-MePh	24	89	>20/1	89
4	2-MePh	28	59	>20/1	95
5	4-MeOPh	40	76	>20/1	88
6	4-ClPh	39	85	>20/1	88
7	2-naphthyl	24	92	>20/1	93
8	*t*-Bu	14	90	>20/1	97
9		24	86	>20/1	97
10	cyclohexyl	24	62	>20/1	70
11	isopropyl	26	43	>20/1	54

[a] Unless otherwise noted, 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. [b] Isolated yield. [c] Determined by ^{1}H-NMR spectroscopy. [d] Determined by HPLC analysis using chiral columns.

Table 2.2

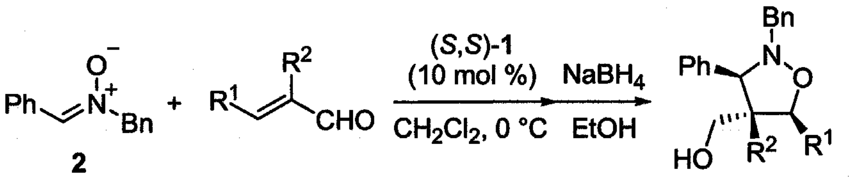


(a) HgO, $HgCl_2$, CH_3CN, H_2O, 75 %; (b) TBDPSCl, TEA, DMAP, CH_2Cl_2;
(c) Raney-Ni, H_2, Boc_2O, ${}^{i}PrOH$, 46% (2 steps).

Scheme 2.2

The Substrate Limitation of α,β-Unsaturated Aldehydes in Asymmetric 1,3-Dipolar Cycloaddition Reaction of Nitrones Catalyzed by a Bis-Titanium Chiral Lewis Acid

The author then applied this method to other α,β-unsaturated aldehydes, such as 2-substituted acroleins and 3-substituted acroleins. The author conducted the reaction of the nitrone **2** and monosubstituted α,β-unsaturated aldehydes, methacrolein and crotonaldehyde, in the presence of 10 mol % bis-titanium chiral Lewis acid (*S*,*S*)-**1** in CH_2Cl_2 at 0 °C for 24 h (Scheme 2.3). Both aldehydes gave the corresponding isoxazolidines in poor yields with moderate levels of enantiofacial discriminations, whereas the regio- and diastereochemistries were exclusively controlled.



R^1 = Me, R^2 = H
36%, 63% ee
R^1 = H, R^2 = Me
8%, 75% ee

Scheme 2.3

The substrate limitation in this methodology became now obvious: 1) small *C*-substituents, such as primary and secondary alkyl groups, on nitrones lead to poor yields and selectivities, 2) the reactions with α- or β-substituted acroleins are not feasible under the standard conditions. In this regard, the author commenced studies in depth to find a general method applicable to various combinations of nitrones and α,β-unsaturated aldehydes.

Steric Effects of Nitrones on the Reactivity in a Bis-Titanium Chiral Lewis Acid Catalyzed 1,3-Dipolar Cycloaddition Reaction

In the course of researches on 1,3-dipolar cycloaddition reaction of nitrones and acrolein, the author took notice of the intriguing observation that the reaction rate was proportional to the increase in the steric bulkiness of *C*-substituent on nitrones (R^2, Figure 2.1); e.g., *N-tert*-butylmethylidenebenzylamine *N*-oxide (R^1 = Bn, R^2 = ^{t}Bu) reacted faster than *N*-cyclohexylmethylidenebenzylamine *N*-oxide (R^1 = Bn, R^2 = Cy) with acrolein under the influence of the bis-titanium chiral Lewis acid (*S*,*S*)-**1**. The author speculated that this observation might be the result of lowered coordination ability of a sterically demanding nitrone to the Lewis acid due to a severe steric repulsion between them. In this regard, the author envisioned that introduction of a bulky *N*-substituent on nitrones also lead to the enhanced reactivity, and it would offer an alternative approach to facilitate the normal electron demand 1,3-dipolar cycloaddition reaction of nitrones (Figure 2.1).

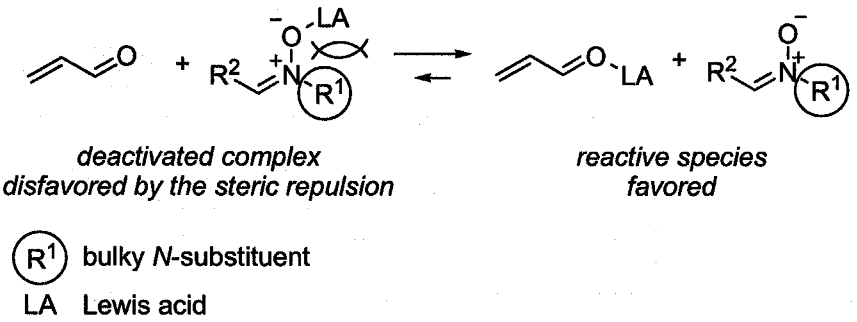
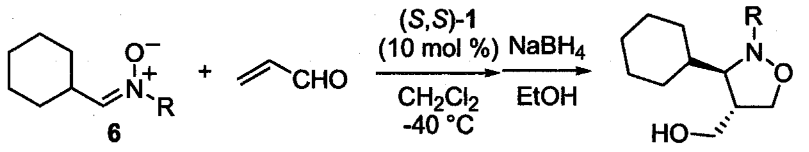


Figure 2.1

To investigate this possibility, the author selected *C*-cyclohexyl nitrones **6** as model substrates and systematically examined the relationship between the steric bulk of *N*-substituent on nitrones and the reaction rate (Table 2.3). Nitrones needed in this study were easily prepared by simply mixing cyclohexanecarboxaldehyde and the corresponding *N*-substituted hydroxylamines in CH_2Cl_2 at room temperature. Asymmetric 1,3-dipolar cycloaddition reactions of these nitrones were performed with 1.5 equiv of acrolein in the presence of the bis-titanium chiral Lewis acid (*S*,*S*)-**1** (10 mol %) in CH_2Cl_2 at –40 °C. Thus, *N*-2,4-dimethylbenzyl nitrone was subjected to the reaction anticipating the steric influence of dimethyl groups and, indeed, a smooth reaction took place to give the corresponding isoxazolidine in 88% yield, albeit with lower diastereo- and enantioselectivity (compare entries 1 and 2).

N-2-Naphthylmethyl nitrone exhibited similar reactivity with *N*-benzyl nitrone (entry 3). On the other hand, *N*-1-naphthylmethyl nitrone, which was expected to be sterically more demanding than 2-naphthylmethyl nitrone around the coordinative oxygen atom of the nitrone, actually reacted faster to provide the isoxazolidine in 94% yield, though in moderate enantioselectivity and endo selectivity (entry 4). Much to his delight, the reaction of *N*-diphenylmethyl nitrone[11] proceeded fairly well to give the endo cycloadduct exclusively in 96% yield with excellent enantioselectivity of 93% (entry 5). As expected, *N*-methyl nitrone completely inhibited the cycloaddition reaction (entry 6).

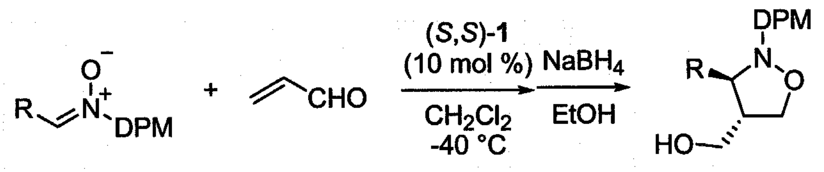


entry	R	time (h)	yield (%)^b	endo/exo^c	ee (%)^d
1	benzyl	24	62	>20/1	70
2	2,4-dimethylbenzyl	24	88	9/1	65
3	1-naphthylmethyl	25	94	9/1	66
4	2-naphthylmethyl	25	52	5/1	46
5	diphenylmethyl (DPM)	20	96	>20/1	97
6	methyl	24	0	-	-

[a] Unless otherwise noted, the reaction of nitrone **6** and acrolein (1.5 equiv) was carried out in the presence of chiral bis-Ti(IV) oxide (*S*,*S*)-**1** in CH_2Cl_2. [b] Isolated yield. [c] Determined by ^{1}H-NMR spectroscopy. [d] Determined by HPLC analysis using chiral columns.

Table 2.3

With this promising approach in hand, the author investigated the scope and limitation of the reaction with a number of *N*-diphenylmethyl nitrones in the presence of a catalytic amount of a bis-titanium chiral Lewis acid (*S*,*S*)-**1** (Table 2.4). The reaction with various *C*-aryl *N*-diphenylmethylnitrones actually led to the higher reactivity and enantioselectivity compared to the reaction of *N*-benzyl nitrones (entries 1-4). Nitrones bearing electron donating or withdrawing groups at *C*-aryl also showed high reactivities comparable to the *C*-phenyl nitrone, though in a slightly diminished diastereoselectivity (entries 3 and 4). Nitrones containing other *C*-alkyl groups were then examined and, indeed, secondary and tertiary alkyl substituted nitrones provided the corresponding isoxazolidines in excellent yields and selectivities (entries 5-7). Reactions with primary alkyl substituted nitrones were also carried out to provide the cycloadducts in rather high yields with moderate stereoselectivities (entries 8-10).



entry	R	time (h)	yield (%)^b	endo/exo^c	ee (%)^d
1	Ph	13	91	>20/1	97
2	4-MePh	12	93	>20/1	98
3	4-MeOPh	15	99	11/1	98
4	4-ClPh	24	84	3.9/1	95
5	*t*-Bu	15	99	>20/1	97
6	cyclohexyl	20	96	>20/1	97
7	isopropyl	5	83	>20/1	97
8	isobutyl	24	88	2.9/1^e	34/70
9	$PhCH_2CH_2$	38	90	2.3/1^e	29/-
10	Et	64	79	4.3/1^e	45/85
11	Ph	20	96	>20/1	95^f

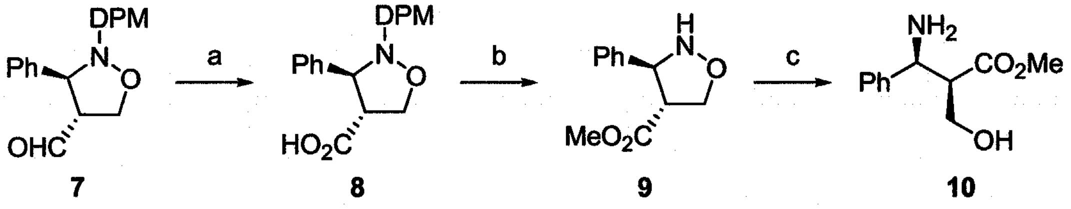
[a] Unless otherwise noted, the reaction of nitrones and acrolein (1.5 equiv) was carried out in the presence of chiral bis-Ti(IV) oxide (*S*,*S*)-**1** in CH_2Cl_2. [b] Isolated yield. [c] Determined by ^{1}H-NMR spectroscopy. [d] Determined by HPLC analysis using chiral columns. [e] Relative stereochemistry not determined. [f] Reaction performed with 5 mol % chiral bis-Ti(IV) oxide (*S*,*S*)-**1**.

Table 2.4

The remarkably reduced reaction time prompted us to attempt the reaction with a lower catalyst loading. Thus, the reaction of *N*-benzylidenediphenylmethylamine *N*-oxide and acrolein was performed in the presence of 5 mol % bis-titanium chiral Lewis acid, and the cycloadduct was obtained in 96% yield and 95% ee (entry 11).

The author then turned his attention to demonstrate the synthetic utility of thus formed *N*-diphenylmethyl isoxazolidine. After several unfruitful attempts to cleave

N-diphenylmethyl group and the N-O bond simultaneously under hydrogenation conditions, the author commenced a stepwise procedure to provide β-amino acid ester. Thus, 4-formyl isoxazolidine **7**, which was isolated from the reaction mixture without reducing the aldehyde, was oxidized to afford the carboxylic acid **8**. The diphenylmethyl group was then selectively cleaved under strongly acidic conditions to provide isoxazolidine carboxylic acid methyl ester **9**. With *N*-unsubstituted isoxazolidine in hand, reduction by the treatment with Raney-nickel was carried out to give β-amino acid methyl ester **10** in 46% yield (3 steps). It should be noted that selective reduction of the N-O bond in the presence of diphenylmethyl group on the nitrogen atom of the isoxazolidine was unexpectedly difficult.[11]



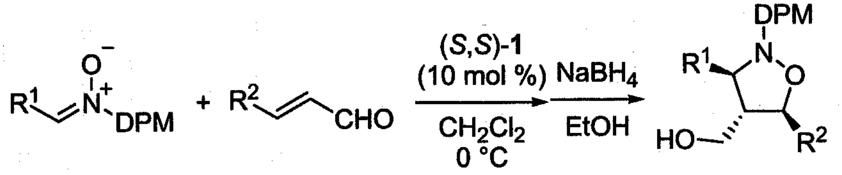
(a) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, ^{t}BuOH, H_2O, 91%; (b) conc. HCl, MeOH, 50%; (c) Raney-Ni, H_2, MeOH, quant.

Scheme 2.4

Catalytic Asymmetric 1,3-Dipolar Cycloaddition Reaction of Nitrones and β-Substituted Acroleins with a Bis-Titanium Chiral Lewis Acid

The metal-catalyzed asymmetric 1,3-dipolar cycloaddition reaction of nitrones and 3-substituted acroleins has been rarely reported to date and the most practical method to realize such a reaction is an organocatalytic methodology developed by MacMillan et al.[5] Since the enantioselectivity observed in the cycloaddition reaction of *N*-benzylidenebenzylamine *N*-oxide and crotonaldehyde was rather promising (Scheme 2.3), the author tested the replacement of the *N*-benzyl for *N*-diphenylmethyl, which showed a positive effect on the reactivity and enantioselectivity in the cycloaddition of nitrones and acrolein. Gratifyingly, the reaction took place smoothly to give the isoxazolidine in 83% yield with enhanced enantioselectivity of 87% ee (entry 1, Table 2.5).

The author then tested various *C*-substituted *N*-diphenylmethyl nitrones and β-substituted acroleins to explore the scope and limitation of this reaction (Table 2.5). Use of other nitrones bearing 4-tolyl, *t*-Bu and isopropyl groups was tolerated, providing the corresponding isoxazolidines in high yields and enantioselectivities (entries 2-4). Subjection of *trans*-2-hexenal to the reaction condition afforded the cycloadduct in diminished yield and enantioselectivity (entry 5). Additionally, cinnamaldehyde was completely unreactive, regardless of the reaction time and temperature (entry 6).



entry	R^1	R^2	time (h)	yield (%)[b]	endo/exo[c]	ee (%)[d]
1	Ph	Me	24	82	>20/1	87
2	4-MePh	Me	22	93	>20/1	89
3	*t*-Bu	Me	24	50	>20/1	89
4	isopropyl	Me	20	83	>20/1	92
5	Ph	*n*-Pr	28	47	>20/1	67
6	Ph	Ph	40	0	-	-

[a] Unless otherwise noted, 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. [b] Isolated yield. [c] Determined by ^{1}H-NMR spectroscopy. [d] Determined by HPLC analysis using chiral columns.

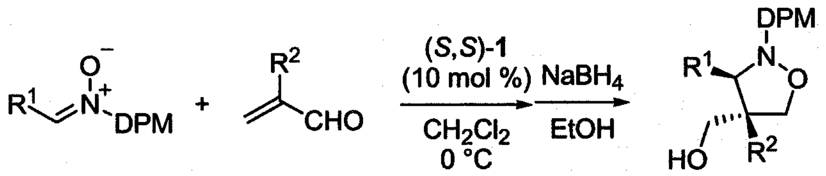
Table 2.5

Catalytic Asymmetric 1,3-Dipolar Cycloaddition Reaction of Nitrones and α-Substituted Acroleins with a Bis-Titanium Chiral Lewis Acid

Despite the fascinating feature of 1,3-dipolar cycloaddition reaction of nitrones and 2-substituted acrolein resulting in the formation of isoxazolidines with a quaternary carbon center, there have been only a few catalysts reported which facilitate these reactions in moderate to high regio- and stereoselectivity.[4] Especially, concerning about the reaction of acyclic nitrones and α-substituted acrolein, no report exists which provides the cycloadducts bearing an easily cleavable *N*-substituent in excellent levels of stereocontrol, and it still remains as a formidable challenge in the field of 1,3-dipolar cycloaddition reaction of nitrones.

In this context, the author conducted the 1,3-dipolar cycloaddition reaction of *N*-diphenylmethyl nitrones and methacrolein in the presence of the bis-titanium chiral Lewis acid. Gratifyingly, the reaction proceeded smoothly in sharp contrast to the preliminary experiment with *N*-benzyl nitrone (Scheme 2.3), and the isoxazolidine was obtained in 60% yield and 90% ee with exclusive control of the regio-, and diastereochemistry. However, the author could not obtain the cycloadduct in the better chemical yield even with prolonged reaction time.

The author then examined the generality of the present reaction with various *N*-diphenylmethyl nitrones and 2-substituted acroleins (Table 2.6). The reaction with *C*-aryl nitrones and methacrolein afforded the cycloadducts in moderate yields and high levels of enantiofacial discriminations (entries 1-4). *C*-Isopropyl nitrone was also subjected to the reaction condition; however, the reaction was sluggish and the regioisomeric 3,5-substituted isoxazolidine was obtained as a major product (data not shown). The reaction of α-ethyl acrolein was then performed to investigate the scope of the aldehyde part, which resulted in the disappointingly low reactivity. From these observations, the author speculates that substrate limitation may arise from the increased steric congestion between R^1 and R^2 groups.

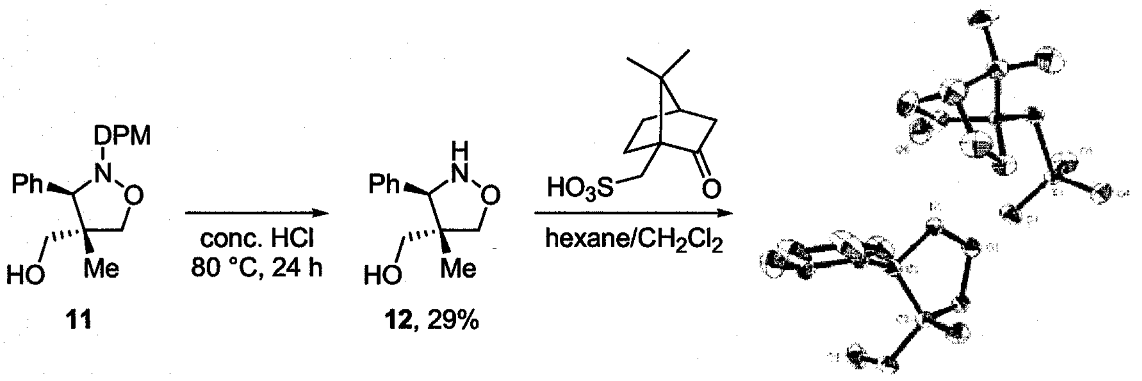


entry	R^1	R^2	time (h)	yield (%)[b]	endo/exo[c]	ee (%)[d]
1	Ph	Me	24	60	>20/1	90
2	4-MePh	Me	24	63	>20/1	88
3	4-MeOPh	Me	24	47	>20/1	89
4	2-naphthyl	Me	24	64	>20/1	92
5	Ph	Et	40	<10	-	-

[a] Unless otherwise noted, the reaction of nitrones and α-substituted acrolein (1.5 equiv) was carried out in the presence of chiral bis-Ti(IV) oxide (*S*,*S*)-**1** in CH_2Cl_2. [b] Isolated yield. [c] Determined by ^{1}H-NMR spectroscopy. [d] Determined by HPLC analysis using chiral columns.

Table 2.6

The relative and absolute stereochemistries of **11** were unequivocally determined by X-ray crystallographic analysis after deprotection of diphenylmethyl group and complexation with (+)-(*S*)-camphorsulfonic acid as shown in Scheme 2.5.



Scheme 2.5

Summary and Conclusions

To date, there has been no chiral catalyst reported which is applicable to α,β-unsaturated aldehydes of various substitution patterns, such as acrolein, crotonaldehyde and methacrolein. His research for the development of catalytic asymmetric 1,3-dipolar cycloaddition reactions of nitrones was culminated into the establishment of the most reliable method to provide optically enriched isoxazolidines with different substitutent patterns in a catalytic asymmetric manner.

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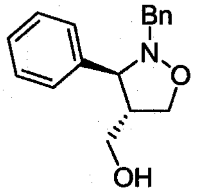
Experimental Section

General Information. Infrared (IR) spectra were recorded on a Shimadzu IRPrestige-21 spectrometer. ^{1}H NMR spectra were measured on a JEOL JNM-FX400 (400 MHz) spectrometer. Data were reported as follows: chemical shifts in ppm from tetramethylsilane as an internal standard, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = double-doublet, m = multiplet, br = broad, appt = apparent), coupling constants (Hz), and assignment. ^{13}C NMR spectra were measured on a JEOL JNM-FX400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. High performance liquid chromatography (HPLC) was performed on Shimadzu 10A instruments at 220 nm using 4.6 nm x 25 cm Daicel Chiralcel OD-H. High-resolution mass spectra (HRMS) were performed on Applied Biosystems Mariner 8295 API-TOF workstation. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. For thin layer chromatography (TLC) analysis 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 1.09386.9025, 230-400 mesh). CH_2Cl_2 was freshly distilled over CaH_2 and degassed before use. (*Z*)-*N*-benzylidenebenzylamine *N*-oxide, benzylhydroxylamine, diphenylmethylhydroxylamine and 2-methyl-1,3-dithian-2-carboxaldehyde were prepared according to the literature procedures. Aldehydes was freshly distilled before use. Other simple chemicals were purchased and used as such.

Preparation of Chiral Bis-Ti(IV) Oxide (*S*,*S*)-1. To a stirred mixture of Ag_2O (0.10 mmol, 23.2 mg) in CH_2Cl_2 (1.0 mL) was added 1.0 M hexanes solution of $ClTi(OPr^i)_3$ (0.20 mmol, 200 μL) at room temperature. After stirring 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 to the mixture, which was then stirred for 2 h at room temperature to afford the dark orange colored solution of chiral bis-Ti(IV) oxide (*S*,*S*)-**1**.

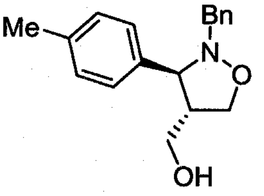
General Procedure. To the catalyst solution prepared as described above were added freshly distilled aldehyde (1.5 mmol) and a solution of nitrone (1.0 mmol) in CH_2Cl_2 (1.0 mL) dropwise at the temperature indicated in each Tables. The reaction mixture was stirred at the same temperature until the completion of the reaction. The mixture was then treated with ethanol solution of $NaBH_4$ (2.0 mmol) and allowed to warm to 0 °C. After stirring for 30 min, the mixture was quenched with aqueous NH_4Cl, filtered to remove insoluble materials and extracted with CH_2Cl_2. The combined organic layers were washed with 1N NaOH to remove (*S*)-BINOL, then dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate) to give the cycloadduct.



(3*S*,4*S*)-2-Benzyl-4-hydroxymethyl-3-phenylisoxazolidine (Table 2.2, entry 1). Prepared according to the general procedure with (*Z*)-*N*-benzylidenebenzylamine *N*-oxide (1.0 mmol, 211 mg) and acrolein (1.5 mmol, 100 μL) over the course of 24 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 2:1) to give the cycloadduct as a colorless oil [94% yield (253 mg), *endo*:*exo* = >20:1, *endo* 93% ee].

Enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 20:1, flow rate = 1.0 mL/min, retention time; 17.3 min (minor) and 20.0 min (major)).

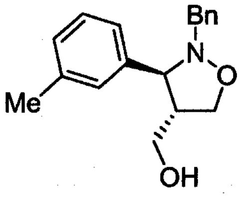
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.46 (10H, m, ArH), 4.17 (1H, dd, *J* = 8.4, 8.4 Hz, NOCHH), 3.93 (1H, d, *J* = 14.4 Hz, PhCHH), 3.88 (1H, dd, *J* = 4.4, 8.4 Hz, NOCHH), 3.69 (1H, d, 14.4 Hz, PhCHH), 3.65-3.74 (2H, m, CH_2OH), 3.46 (1H, d, *J* = 7.2 Hz, ONCH), 2.74 (1H, m, $CHCH_2OH$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 137.5, 128.6, 128.0, 127.9, 127.8, 127.0, 73.5, 69.1, 63.3, 60.0, 54.9 ppm; IR (neat) 3397, 3061, 3030, 2941, 2872, 1495, 1454, 1373, 1344, 1307, 1105, 1070, 1042, 1030, 1007, 972 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{17}H_{20}NO_2$: *m/z* 270.1489 ([M + H]$^+$), found: *m/z* 270.1492 ([M + H]$^+$); $[\alpha]_D^{31} = -84.9$ (*c* = 1.0, $CHCl_3$; 93% ee).



(3*S*,4*S*)-2-Benzyl-4-hydroxymethyl-3-(4-methylphenyl)isoxazolidine (Table 2.2, entry 2). Prepared according to the general procedure with (*Z*)-*N*-(4-methylbenzylidene)benzylamine *N*-oxide (1.0 mmol, 225 mg) and acrolein (1.5 mmol, 100 μL) over the course of 24 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 2:1) to give the cycloadduct as a colorless oil [81% yield (230 mg), *endo*:*exo* = >20:1, *endo* 94% ee].

Enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 20:1, flow rate = 1.0 mL/min, retention time; 14.4 min (minor) and 18.9 min (major)).

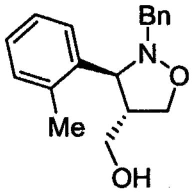
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16-7.36 (9H, m, ArH), 4.17 (1H, dd, *J* = 8.4, 8.4 Hz, NOCHH), 3.93 (1H, d, *J* = 14.4 Hz, PhCHH), 3.87 (1H, dd, *J* = 4.4, 8.4 Hz, NOCHH), 3.67 (1H, d, 14.0 Hz, PhCH**H**), 3.67-3.75 (2H, m, **CH$_2$**OH), 3.43 (1H, d, J = 7.6 Hz, ONC**H**), 2.74 (1H, m, C**H**CH$_2$OH), 2.35 (3H, s, C_6H_4**CH$_3$**) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 137.5, 129.3, 128.6, 128.0, 127.8, 127.0, 73.3, 69.1, 63.4, 59.9, 54.8, 21.2 ppm; IR (neat) 3385, 3028, 2941, 2870, 1514, 1497, 1454, 1342,1040, 1001, 802 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{18}H_{22}NO_2$: *m/z* 284.1645 ([M + H]$^+$), found: *m/z* 284.1646 ([M + H]$^+$); $[\alpha]_D^{30}$ = −82.0 (c = 1.0, $CHCl_3$; 93% ee).



(3*S*,4*S*)-2-Benzyl-4-hydroxymethyl-3-(3-methylphenyl)isoxazolidine (Table 2.2, entry 3). Prepared according to the general procedure with (*Z*)-*N*-(3-methylbenzylidene)benzylamine *N*-oxide (1.0 mmol, 225 mg) and acrolein (1.5 mmol, 100 μL) over the course of 24 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 3:1) to give the cycloadduct as a colorless oil [89% yield (253 mg), *endo*:*exo* = >20:1, *endo* 89% ee].

Enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time; 14.9 min (minor) and 16.9 min (major)).

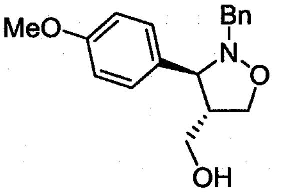
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09-7.32 (9H, m, Ar**H**), 4.12 (1H, appt t, J = 8.4 Hz, NOC**H**H), 3.94 (1H, d, J = 14.4 Hz, PhC**H**H), 3.89 (1H, dd, J = 4.8, 8.4 Hz, NOCH**H**), 3.71 (2H, m, **CH$_2$**OH), 3.69 (1H, d, 14.4 Hz, PhCH**H**), 3.43 (1H, d, J = 7.6 Hz, ONC**H**), 2.76 (1H, m, C**H**CH$_2$OH), 2.36 (3H, s, C_6H_4**CH$_3$**) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 138.3, 137.6, 128.62, 128.58, 128.52, 125.50, 128.0, 127.0, 125.0, 73.5, 69.2, 63.4, 60.0, 54.8, 21.5 ppm; IR (neat) 3397, 3028, 2941, 2870, 1607, 1493, 1454, 1375, 1339, 1034 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{18}H_{22}NO_2$: *m/z* 284.1645 ([M + H]$^+$), found: *m/z* 284.1645 ([M + H]$^+$); $[\alpha]_D^{30}$ = −76.1 (c = 1.0, $CHCl_3$; 89% ee).



(3*S*,4*S*)-2-Benzyl-4-hydroxymethyl-3-(2-methylphenyl)isoxazolidine (Table 2.2, entry 4). Prepared according to the general procedure with (*Z*)-*N*-(2-methylbenzylidene)benzylamine *N*-oxide (1.0 mmol, 225 mg) and acrolein (1.5 mmol, 100 μL) over the course of 24 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 3:1) to give the cycloadduct as a colorless oil [59% yield (167 mg), *endo*:*exo* = >20:1, *endo* 95% ee].

Enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time; 19.1 min (minor) and 21.2 min (major)).

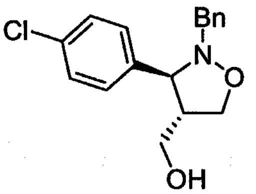
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.64 (1H, d, *J* = 7.2 Hz, Ar**H**), 7.14-7.30 (8H, m, Ar**H**), 4.23 (1H, appt t, *J* = 8.0 Hz, NOCH**H**), 3.87-3.94 (2H, m, PhC**H**H, NOC**H**H), 3.68-3.82 (4H, m, C**H$_2$**OH, PhCH**H**, ONC**H**), 2.82 (1H, m, C**H**CH$_2$OH), 2.40 (3H, s, C$_6$H$_4$C**H$_3$**) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ 137.7, 137.0, 136.3, 130.5, 128.5, 128.2, 128.0, 127.3, 127.0, 126.3, 69.7, 69.3, 63.4, 60.0, 54.8, 19.9 ppm; IR (neat) 3402, 3028, 2926, 2872, 1490, 1456, 1373, 1287, 1107, 1045, 1005 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{18}H_{22}NO_2$: *m/z* 284.1645 ([M + H]$^+$), found: *m/z* 284.1646 ([M + H]$^+$); $[\alpha]^{29}_{D} = -77.0$ (*c* = 1.0, CHCl$_3$; 95% ee).



(3*S*,4*S*)-2-Benzyl-4-hydroxymethyl-3-(4-methoxyphenyl)isoxazolidine (Table 2.2, entry 5). Prepared according to the general procedure with (*Z*)-*N*-(4-methoxybenzylidene)benzylamine *N*-oxide (1.0 mmol, 241 mg) and acrolein (1.5 mmol, 100 μL) over the course of 40 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 2:1) to give the cycloadduct as a colorless oil [85% yield (255 mg), *endo*:*exo* = >20:1, *endo* 88% ee].

Enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 20:1, flow rate = 1.0 mL/min, retention time; 23.5 min (minor) and 29.7 min (major)).

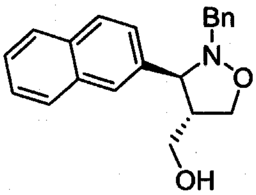
^{1}H NMR (400 MHz, CDCl$_3$) δ 6.88-7.37 (9H, m, Ar**H**), 4.16 (1H, dd, *J* = 8.4, 8.4 Hz, NOCH**H**), 3.92 (1H, d, *J* = 14.4 Hz, PhC**H**H), 3.86 (1H, dd, *J* = 4.8, 8.8 Hz, NOCH**H**), 3.80 (3H, s, OC**H$_3$**), 3.65 (1H, d, *J* = 14.4 Hz, PhCH**H**), 3.62-3.73 (2H, m, C**H$_2$**OH), 3.41 (1H, d, *J* = 7.6 Hz, ONC**H**), 2.72 (1H, m, C**H**CH$_2$OH) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.2, 137.6, 130.9, 129.0, 128.6, 128.0, 127.0, 114.0, 73.0, 69.1, 63.3, 59.8, 55.3, 54.6 ppm; IR (neat) 3385, 3030, 2938, 2872, 2835, 1610, 1512, 1454, 1302, 1175, 1031, 829 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{18}H_{22}NO_3$: *m/z* 300.1594 ([M + H]$^+$), found: *m/z* 300.1954 ([M + H]$^+$); $[\alpha]^{31}_{D} = -76.2$ (*c* = 1.0, CHCl$_3$; 88% ee).



(3*S*,4*S*)-2-Benzyl-3-(4-chlorophenyl)-4-hydroxymethylisoxazolidine (Table 2.2, entry 6). Prepared according to the general procedure with (*Z*)-*N*-(4-chlorobenzylidene)benzylamine *N*-oxide (1.0 mmol, 246 mg) and acrolein (1.5 mmol, 100 μL) over the course of 39 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 2:1) to give the cycloadduct as a colorless oil [76% yield (232 mg), *endo*:*exo* = >20:1, *endo* 88% ee].

Enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 20:1, flow rate = 1.0 mL/min, retention time; 17.4 min (minor) and 19.7 min (major)).

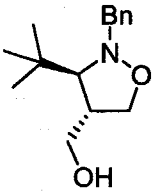
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.40 (9H, m, ArH), 4.16 (1H, dd, J = 8.0, 8.4 Hz, NOCHH), 3.90 (1H, d, J = 14.0 Hz, PhCHH), 3.87 (1H, dd, J = 4.4, 8.8 Hz, NOCHH), 3.72 (1H, d, 14.4 Hz, PhCHH), 3.68-3.78 (2H, m, CH_2OH), 3.49 (1H, d, J = 7.6 Hz, ONCH), 2.70 (1H, m, $CHCH_2OH$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 137.3, 133.5, 129.2, 128.8, 128.6, 128.1, 127.1, 72.8, 69.0, 63.2, 60.0, 55.0 ppm; IR (neat) 3391, 3030, 2926, 2872, 1493, 1454, 1410, 1371, 1090, 1041, 1015, 856, 823 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{17}H_{19}ClNO_2$: *m/z* 304.1099 ($[M + H]^+$), found: *m/z* 304.1099 ($[M + H]^+$); $[\alpha]_D^{30}$ = −70.5 (c = 1.0, $CHCl_3$; 88% ee).



(3*S*,4*S*)-2-Benzyl-4-hydroxymethyl-3-(2-naphthyl)isoxazolidine (Table 2.2, entry 7). Prepared according to the general procedure with (*Z*)-*N*-(2-naphthyl)methylidenebenzylamine *N*-oxide (1.0 mmol, 261 mg) and acrolein (1.5 mmol, 100 μL) over the course of 24 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 2:1) to give the cycloadduct as a colorless oil [92% yield (292 mg), *endo*:*exo* = >20:1, *endo* 93% ee].

Enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 20:1, flow rate = 1.0 mL/min, retention time; 27.0 min (minor) and 52.7 min (major)).

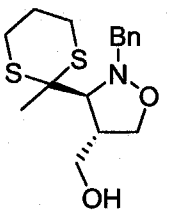
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17-7.85 (12H, m, ArH), 4.21 (1H, dd, J = 8.4, 8.0 Hz, NOCHH), 3.96 (1H, d, J = 14.0 Hz, PhCHH), 3.91 (1H, dd, J = 4.8, 8.8 Hz, NOCHH), 3.73 (1H, d, 14.8 Hz, PhCHH), 3.66-3.74 (2H, m, CH_2OH), 3.63 (1H, d, J = 7.6 Hz, ONCH), 2.82 (1H, m, $CHCH_2OH$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 136.7, 133.2, 133.0, 128.7, 128.5, 128.0, 127.7, 127.6, 127.2, 127.0, 126.1, 125.9, 125.4, 73.6, 69.2, 63.2, 60.1, 54.8 ppm; IR (neat) 3383, 3057, 3030, 2939, 2872, 1506, 1497, 1454, 1373, 1313, 1030, 1005, 856, 820 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{21}H_{22}NO_2$: *m/z* 320.1645 ($[M + H]^+$), found: *m/z* 320.1644 ($[M + H]^+$); $[\alpha]_D^{29}$ = −53.7 (c = 1.0, $CHCl_3$; 93% ee).



(3*S*,4*S*)-2-Benzyl-3-(*tert*-butyl)-4-hydroxymethylisoxazolidine (Table 2.2, entry 8). Prepared according to the general procedure with (*Z*)-*N*-*tert*-butylmethylidenebenzylamine *N*-oxide (1.0 mmol, 191 mg) and acrolein (1.5 mmol, 100 μL) over the course of 14 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 2:1) to give the cycloadduct as a white solid [90% yield (224 mg), *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 = 1.0 mL/min, retention time; 10.0 min (minor) and 13.5 min (major)).

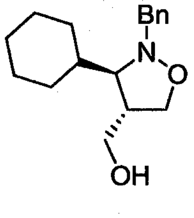
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.41 (5H, m, Ar**H**), 4.05 (1H, d, J = 13.6 Hz, PhC**H**H), 3.98 (2H, d, J = 6.4 Hz, C**H$_2$**OH), 3.91 (1H, d, J = 13.6 Hz, PhCH**H**), 3.80 (1H, m, NOC**H**H), 3.70 (1H, m, NOCH**H**), 2.65 (1H, m, C**H**CH_2OH), 2.45 (1H, d, J = 4.4 Hz, ONC**H**), 0.90 (9H, s, *t*-Bu) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 129.0, 128.1, 127.0, 75.6, 69.1, 64.8, 62.3, 48.0, 34.3, 26.6 ppm; IR (neat) 3420, 2953, 2868, 1476, 1454, 1395, 1362, 1074, 1045, 999 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{15}H_{24}NO_2$: *m/z* 250.1802 ([M + H]$^+$), found: *m/z* 250.1802 ([M + H]$^+$); $[\alpha]_D^{30}$ = –63.5 (*c* = 1.0, $CHCl_3$; 97% ee).



(3*S*,4*S*)-2-Benzyl-4-hydroxymethyl-3-(2-methyl-1,3-dithian-2-yl)isoxazolidine (Table 2.2, entry 9). Prepared according to the general procedure with (*Z*)-*N*-(2-methyl-1,3-dithian-2-yl)methylidenebenzylamine *N*-oxide (1.0 mmol, 267 mg) and acrolein (1.5 mmol, 100 μL) over the course of 24 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 2:1) to give the cycloadduct as a colorless oil [86% yield (280 mg), *endo*:*exo* = >97:3, *endo* 97% ee].

Enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 20:1, flow rate = 1.0 mL/min, retention time; 21.8 min (minor) and 29.7 min (major)).

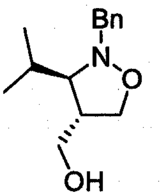
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.44 (5H, m, Ar**H**), 4.13 (2H, s, C_6H_5**CH_2**), 4.04 (2H, m, **CH_2**OH), 3.83 (1H, dd, J = 10.4, 5.6 Hz, NOC**H**H), 3.77 (1H, dd, J = 10.4, 6.8 Hz, NOCH**H**), 3.41 (1H, d, J = 4.0 Hz, ONC**H**), 2.59-3.00 (5H, m, S**CH_2**CHC**H_2**S, C**H**CH_2OH), 1.90 (2H, m, SCH_2**CH_2**CH_2S), 1.58 (3H, s, **CH_3**) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 129.2, 128.0, 127.1, 71.8, 69.0, 63.7, 61.7, 52.2, 48.9, 26.3, 26.0, 24.7, 24.1 ppm; IR (neat) 3419, 2926, 2870, 1748, 1454, 1418, 1373, 1061, 1028, 908,730, 696 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{16}H_{24}NO_2S_2$: *m/z* 326.1243 ([M + H]$^+$), found: *m/z* 326.1244 ([M + H]$^+$); $[\alpha]_D^{29}$ = –29.4 (*c* = 1.0, $CHCl_3$; 97% ee).



(3*R*,4*S*)-2-Benzyl-3-cyclohexyl-4-hydroxymethylisoxazolidine (Table 2.2, entry 10). Prepared according to the general procedure with (*Z*)-*N*-cyclohexylmethylidenebenzylamine *N*-oxide (1.0 mmol, 217 mg) and acrolein (1.5 mmol, 100 μL) over the course of 24 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 2:1) to give the cycloadduct as a white solid [52% yield (142 mg), *endo*:*exo* = >20:1, *endo* 70% ee].

Enantiomeric excess was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 20:1, flow rate = 0.5 mL/min, retention time; 22.5 min (minor) and 31.8 min (major)).

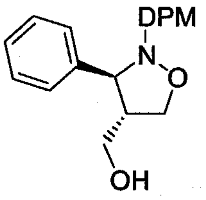
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.39 (5H, m, Ar**H**), 3.94 (2H, s, $PhCH_2$), 3.90 (2H, d, *J* = 6.0 Hz, CH_2OH), 3.70 (1H, dd, *J* = 5.2, 10.4 Hz, NOCH**H**), 3.62 (1H, dd, *J* = 8.4, 10.4 Hz, NOCH**H**), 2.57 (1H, m, $CHCH_2OH$), 2.40 (1H, dd, *J* = 4.4, 6.4 Hz, ONC**H**), 0.90-1.83 (11H, m, Cy) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 128.9, 128.1, 127.1, 72.4, 68.8, 64.7, 61.8, 49.1, 41.7, 30.6, 29.3, 26.7, 26.4, 26.3 ppm; IR (neat) 3385, 2922, 2851, 1497, 1450, 1339, 1055, 1030, 993, 966, 750, 729, 696 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{17}H_{26}NO_2$: *m/z* 276.1958 ([M + H]$^+$), found: *m/z* 276.1957 ([M + H]$^+$); $[\alpha]^{29}_{D}$ = –46.4 (*c* = 1.0, $CHCl_3$; 70% ee).



(3*R*,4*S*)-2-Benzyl-3-isopropyl-4-hydroxymethylisoxazolidine (Table 2.2, entry 11). Prepared according to the general procedure with (*Z*)-*N*-isopropylmethylidenebenzylamine *N*-oxide (1.0 mmol, 177 mg) and acrolein (1.5 mmol, 100 μL) over the course of 26 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 3:1) to give the cycloadduct as a colorless oil [43% yield (101 mg), *endo*:*exo* = >20:1, *endo* 54% ee].

Enantiomeric excess was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time; 13.6 min (minor) and 16.0 min (major)).

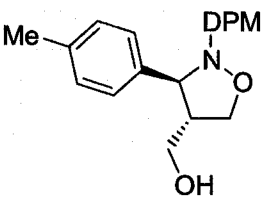
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.39 (5H, m, Ar**H**), 3.95 (2H, s, $PhCH_2$), 3.91 (2H, d, *J* = 5.6 Hz, CH_2OH), 3.62-3.73 (2H, m, $NOCH_2$), 2.53 (1H, m, $CHCH_2OH$), 2.42 (1H, dd, *J* = 4.4, 5.6 Hz, ONC**H**), 1.75 (1H, m, $(CH_3)_2CH$), 0.96 (3H, d, *J* = 6.8 Hz, $(CH_3)_2CH$), 0.95 (H, d, *J* = 6.8 Hz, $(CH_3)_2CH$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 128.9, 128.1, 127.1, 73.0, 68.9, 64.8, 61.7, 48.5, 31.3, 20.0, 18.3 ppm; IR (neat) 3397, 2955, 2926, 2870, 1497, 1458, 1368, 1211, 1072, 1034, 964 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{14}H_{21}NO_2$: *m/z* 236.1645 ([M + H]$^+$), found: *m/z* 236.1645 ([M + H]$^+$); $[\alpha]^{28}_{D}$ = –43.2 (*c* = 1.0, $CHCl_3$; 54% ee).



(3*S*,4*S*)-2-Diphenylmethyl-4-hydroxymethyl-3-phenylisoxazolidine (Table 2.4, entry 1). Prepared according to the general procedure with (*Z*)-*N*-benzylidenediphenylmethylamine *N*-oxide (1.0 mmol, 287 mg) and acrolein (1.5 mmol, 100 μL) over the course of 13 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 3:1) to give the cycloadduct as a white powder [91 % yield (314 mg), *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, retention time; 33.1 min (minor) and 37.7 min (major)).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41-7.03 (15H, m, ArH), 4.93 (1H, s, Ph$_2$CH), 4.22 (1H, appt t, J = 8.1 Hz, NOCHH), 3.90 (1H, dd, J = 8.6, 5.4 Hz, NOCHH), 3.65 (3H, m, CH$_2$OH, ONCH), 2.73 (1H, m, CHCH$_2$OH) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ 141.3, 141.0, 140.5, 128.6, 128.13, 128.07, 127.96, 127.8, 127.5, 127.0, 126.9, 126.8, 72.5, 69.7, 68.7, 63.1, 55.8 ppm; IR (neat) 3402, 3061, 3026, 2943, 2870, 1738, 1493, 1452, 1366, 1229, 1217, 1074, 1030, 999 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{23}H_{23}NO_2$: *m/z* 368.1621 ([M + Na]$^+$), found: *m/z* 368.1625 ([M + Na]$^+$); $[\alpha]_D^{27}$ = –53.8 (c = 1.0, CHCl$_3$; 97% ee).

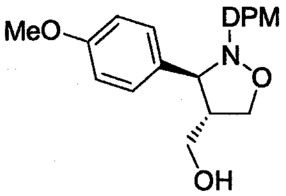


(3*S*,4*S*)-2-Diphenylmethyl-4-hydroxymethyl-3-(4-methylphenyl)isoxazolidine (Table 2.4, entry 2). Prepared according to the general procedure with (*Z*)-*N*-(4-methylbenzylidene) diphenylmethylamine *N*-oxide (1.0 mmol, 301 mg) and acrolein (1.5 mmol, 100 μL) over the course of 12 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 3:1) to give the cycloadduct as a white powder [93 % yield (334 mg), *endo*:*exo* = >20:1, *endo* 98% ee].

Enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 20:1, flow rate = 0.5 mL/min, retention time; 26.7 min (minor) and 37.1 min (major)).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.38-7.01 (14H, m, ArH), 4.90 (1H, s, Ph$_2$CH), 4.17 (1H, appt t, J = 8.0 Hz, NOCHH), 3.84 (1H, dd, J = 8.2, 5.6 Hz, NOCHH), 3.55 (3H, m, CH$_2$OH, ONCH), 2.67 (1H, m, CHCH$_2$OH), 2.29 (3H, s, ArCH$_3$) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ141.3, 140.2, 138.1, 136.7, 129.0, 128.9, 128.02, 127.96, 127.8, 127.5, 127.1, 126.8, 71.9, 69.3, 68.7, 63.4, 55.6, 21.2 ppm; IR (neat) 3395, 3024, 2941, 2868, 1514, 1492, 1452, 1180, 1109, 1076, 1030, 1003 cm^{-1}; HRMS (ESI) exact mass calcd.

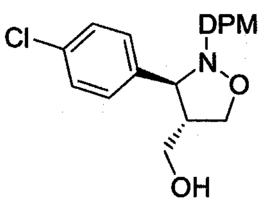
for $C_{24}H_{25}NO_2$: *m/z* 382.1778 ($[M + Na]^+$), found: *m/z* 382.1784 ($[M + Na]^+$); $[\alpha]_D^{26}$ = –69.2 (*c* = 1.0, $CHCl_3$; 98% ee).



(3*S*,4*S*)-2-Diphenylmethyl-4-hydroxymethyl-3-(4-methoxyphenyl)isoxazolidine (Table 2.4, entry 3). Prepared according to the general procedure with (*Z*)-*N*-(4-methoxybenzylidene) diphenylmethylamine *N*-oxide (1.0 mmol, 317 mg) in CH_2Cl_2 (5.0 ml) and acrolein (1.5 mmol, 100 μL) over the course of 15 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 3:1) to give the cycloadduct as a white powder [99 % yield (371 mg), *endo*:*exo* = 11.2:1, *endo* 98% ee].

Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol = 20:1, flow rate = 0.5 mL/min, retention time; 40.5 min (major) and 45.0 min (minor)).

^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.03 (14H, m, ArH), 6.73 (2H, d, *J* = 7.5 Hz, ArH), 4.88 (1H, s, Ph_2CH), 4.13 (1H, appt t, *J* = 8.0 Hz, NOCHH), 3.80 (1H, dd, *J* = 8.2, 5.8Hz, NOCHH), 3.71 (3H, s, OCH_3), 3.50 (3H, m, CH_2OH, ONCH), 2.62 (1H, m, $CHCH_2OH$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 141.1, 140.3, 133.0, 128.7, 128.6, 127.93, 127.87, 127.7, 127.0, 126.7, 113.6, 72.0, 69.0, 68.6, 63.0, 55.4, 55.2 ppm; IR (neat) 3418, 3061, 3026, 2936, 2870, 1611, 1510, 1452, 1302, 1246, 1173, 1030 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{24}H_{25}NO_3$: *m/z* 376.1907 ($[M + Na]^+$), found: *m/z* 376.1907 ($[M + Na]^+$); $[\alpha]_D^{27}$ = –76.7 (*c* = 1.0, $CHCl_3$; 98% ee).

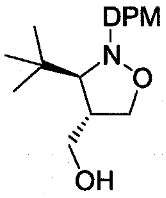


(3*S*,4*S*)-2-Diphenylmethyl-3-(4-chlorophenyl)-4-hydroxymethylisoxazolidine (Table 2.4, entry 4). Prepared according to the general procedure with (*Z*)-*N*-(4-chlorobenzylidene) diphenylmethylamine *N*-oxide (1.0 mmol, 322 mg) in CH_2Cl_2 (4.5 ml) and acrolein (1.5 mmol, 100 μL) over the course of 24 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 3:1) to give the cycloadduct as a white powder [84 % yield (320 mg), *endo*:*exo* = 3.9:1, *endo* 95% ee].

Enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 20:1, flow rate = 0.5 mL/min, retention time; 32.4 min (minor) and 42.7 min (major)).

^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.05 (14H, m, ArH), 4.92 (1H, s, Ph_2CH), 4.17 (1H, appt t, *J* = 8.0 Hz, NOCHH), 3.88 (1H, dd, *J* = 8.6, 5.7 Hz, NOCHH), 3.62 (3H, m,

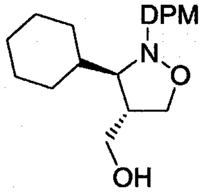
$\mathbf{CH_2OH}$, ONC**H**), 2.65 (1H, m, C**H**CH_2OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 140.6, 140.2, 132.4, 128.7, 128.14, 128.10, 128.0, 127.8, 127.0, 73.0, 69.2, 68.5, 62.8, 55.8 ppm; IR (neat) 3412, 3061, 3026, 2941, 2872, 1599, 1489, 1452, 1090, 1030, 1015 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{23}H_{22}ClNO_2$: *m/z* 402.1231 ([M + Na]$^+$), found: *m/z* 402.1236 ([M + Na]$^+$); $[\alpha]^{29}_{D} = -71.5$ (*c* = 1.0, $CHCl_3$; 95% ee).



(3*S*,4*S*)-3-(*tert*-Butyl)-2-diphenylmethyl-4-hydroxymethylisoxazolidine (Table 2.4, entry 5). Prepared according to the general procedure with (*Z*)- *N*-*tert*-butylmethylidenediphenylmethylamine *N*-oxide (1.0 mmol, 267 mg) and acrolein (1.5 mmol, 100 μL) over the course of 15 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 3:1) to give the cycloadduct as a white powder [99 % yield (323 mg), *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, retention time; 17.5 min (minor) and 20.0 min (major)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.15 (10H, m, Ar**H**), 5.10 (1H, s, Ph_2C**H**), 3.95 (1H, appt t, *J* = 8.3 Hz, NOC**H**H), 3.88 (1H, appt t, *J* = 8.2 Hz, NOCH**H**) 3.67 (2H, m, $\mathbf{CH_2}$OH), 2.71 (2H, m, ONC**H**, C**H**CH_2OH), 0.79 (9H, s, *t*-Bu) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 141.1, 129.5, 128.02, 127.96, 127.2, 126.6, 72.12, 72.08, 68.8, 64.7, 47.8, 34.4, 26.9 ppm; IR (neat) 3414, 2953, 2868, 1493, 1452, 1395, 1362, 1082, 1047 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{21}H_{27}NO_2$: *m/z* 348.1934 ([M + Na]$^+$), found: *m/z* 348.1936 ([M + Na]$^+$); $[\alpha]^{27}_{D} = 98.8$ (*c* = 1.0, $CHCl_3$; 97% ee).

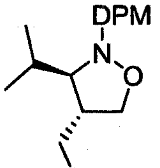


(3*R*,4*S*)-3-Cyclohexyl-2-diphenylmethyl-4-hydroxymethylisoxazolidine (Table 2.4, entry 6). Prepared according to the general procedure with (*Z*)-*N*-cyclohexylmethylidenediphenylmethylamine *N*-oxide (1.0 mmol, 293 mg) and acrolein (1.5 mmol, 100 μL) over the course of 20 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 3:1) to give the cycloadduct as a white powder [99 % yield (351 mg), *endo*:*exo* = >20:1, *endo* 97% ee].

Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol = 20:1, flow rate = 0.5 mL/min, retention time; 23.1 min (major) and 24.5 min (minor)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.15 (10H, m, Ar**H**), 5.03 (1H, s, Ph_2C**H**), 3.91 (1H, appt t, *J* = 8.2 Hz, NOC**H**H), 3.85 (1H, appt t, *J* = 7.7 Hz, NOCH**H**), 3.63-3.53 (2H, m,

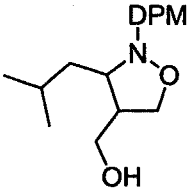
CH_2OH), 2.62 (1H, d, *J* = 6.2 Hz, ONC**H**), 2.58 (1H, m, C**H**CH_2OH) 0.73-1.92 (11H, m, Cy) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 141.3, 128.6, 128.1, 127.9, 127.8, 127.2, 126.7, 72.5, 69.2, 68.4, 64.4, 49.1, 42.3, 30.4, 28.8, 26.6, 26.30, 26.28 ppm; IR (neat) 3429, 2922, 2851, 1493, 1450, 1030 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{23}H_{29}NO_2$: *m/z* 374.2091 ([M + Na]$^+$), found: *m/z* 374.2090 ([M + Na]$^+$); $[\alpha]^{31}_{D}$ = 32.0 (*c* = 1.0, $CHCl_3$; 97% ee).



(3*R*,4*S*)-2-Diphenylmethyl-3-isopropyl-4-hydroxymethylisoxazolidine (Table 2.4, entry 7). Prepared according to the general procedure with (*Z*)-*N*-isopropylmethylidenediphenylmethylamine *N*-oxide (1.0 mmol, 253 mg) and acrolein (1.5 mmol, 100 μL) over the course of 5 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 3:1) to give the cycloadduct as a white powder [83% yield (259 mg), *endo*:*exo* = >20:1, *endo* 97% ee].

Enantiomeric excess was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 40:1, flow rate = 1.0 mL/min, retention time; 21.9 min (minor) and 24.4 min (major)).

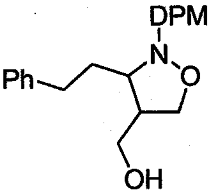
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.16 (10H, m, Ar**H**), 5.05 (1H, s, Ph_2C**H**), 3.97-3.87 (2H, m, NOC**H$_2$**), 3.67 (2H, dd, *J* = 12.8, 9.4 Hz, **CH_2**OH), 2.68 (1H, dd, *J* = 5.8, 3.9 Hz, ONC**H**), 2.58 (1H, m, C**H**CH_2OH), 1.54 (1H, m, $(CH_3)_2$C**H**), 0.86 (3H, d, *J* = 6.8 Hz, (**CH_3**)$_2$CH), 0.80 (3H, d, *J* = 6.8 Hz, (**CH_3**)$_2$CH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 141.4, 128.7, 128.2, 128.0, 127.8, 127.3, 126.8, 72.7, 69.8, 68.6, 64.7, 48.6, 32.1, 19.9, 18.0 ppm; IR (neat) 3431, 2955, 2870, 1493, 1452, 1072, 1030 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{20}H_{25}NO_2$: *m/z* 334.1778 ([M + Na]$^+$), found: *m/z* 334.1774 ([M + Na]$^+$); $[\alpha]^{27}_{D}$ = 50.7 (*c* = 1.0, $CHCl_3$; 97% ee).



2-Diphenylmethyl-4-hydroxymethyl-3-isobutylisoxazolidine (Table 2.4, entry 8). Prepared according to the general procedure with (*Z*)-*N*-isobutylidenediphenylmethylamine *N*-oxide (1.0 mmol, 267 mg) and acrolein (1.5 mmol, 100 μL) over the course of 24 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 3:1) to give the cycloadduct as a white powder [88 % yield (288 mg), d.r. = 2.9:1, 34% ee (major isomer)].

Enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 20:1, flow rate = 0.5 mL/min, retention time; 21.1 min (minor) and 27.1 min (major)).

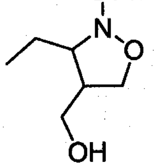
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.16 (10H, m, ArH), 5.03 (1H, s, Ph_2CH), 4.00 (1H, appt t, J = 8.2 Hz, NOCHH), 3.89 (1H, m, NOCHH), 3.77-3.67 (2H, m, CH_2OH), 2.98 (1H, m, ONCH), 2.41 (1H, m, $CHCH_2OH$), 1.53 (1H, m, $CH_2CH(CH_3)_2$), 1.34 (1H, m, $CHHCH(CH_3)_2$), 1.24 (1H, m, $CHHCH(CH_3)_2$), 0.64 (3H, d, J = 6.5 Hz, $CH_2CH(CH_3)_2$), 0.56 (3H, d, J = 6.5 Hz, $CH_2CH(CH_3)_2$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 141.2, 128.4, 128.2, 128.0, 127.5, 127.2, 126.7, 72.6, 68.2, 64.0, 63.0, 52.6, 45.5, 25.1, 22.7, 22.2 ppm; IR (neat) 3414, 2953, 2868, 1493, 1452, 1082, 1030, 993 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{21}H_{27}NO_2$: *m/z* 348.1934 ([M + Na]$^+$), found: *m/z*348.1934 ([M + Na]$^+$); $[\alpha]_D^{28} = -2.7$ (c = 1.0, $CHCl_3$; 34% ee).



2-Diphenylmethyl-4-hydroxymethyl-3-(2-phenylethyl)isoxazolidine (Table 2.4, entry 9). Prepared according to the general procedure with (*Z*)-*N*-(3-phenylpropylidene)diphenylmethylamine *N*-oxide (1.0 mmol, 315 mg) and acrolein (1.5 mmol, 100 μL) over the course of 38 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 3:1) to give the cycloadduct as a white powder [90 % yield (337 mg), d.r. = 2.3:1, 29% ee (major isomer)].

Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/Ethanol = 20:1, flow rate = 0.5 mL/min, retention time; 20.1 min (major) and 26.3 min (minor)).

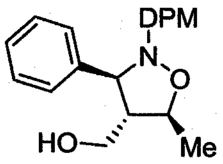
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-6.97 (15H, m, ArH), 5.02 (1H, s, Ph_2CH), 3.99 (1H, appt t, J = 8.1 Hz, NOCHH), 3.87 (1H, appt t, J = 7.5 Hz, NOCHH), 3.69-3.60 (2H, m, CH_2OH), 2.94 (1H, appt t, J = 2.7 Hz, ONCH), 2.59-2.44 (3H, m, $CHCH_2OH$, $PhCH_2CH_2$), 1.79 (1H, m, $PhCH_2CHH$), 1.60 (1H, m, $PhCH_2CHH$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 141.7, 141.2, 128.41, 128.38, 128.13, 128.08, 128.04, 127.6, 127.4, 126.8, 125.5, 73.0, 68.2, 64.8, 63.8, 52.1, 37.0, 32.5 ppm; IR (neat) 3406, 3026, 2932, 2864, 1495, 1452, 1074, 1030 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{25}H_{27}NO_2$: *m/z* 396.1934 ([M + Na]$^+$), found: *m/z* 396.1935 ([M + Na]$^+$); $[\alpha]_D^{26} = 3.2$ (c = 1.0, $CHCl_3$; 29% ee).



(3*R*,4*S*)-2-Diphenylmethyl-3-ethyl-4-hydroxymethylisoxazolidine (Table 2.4, entry 10). Prepared according to the general procedure with (*Z*)-*N*-propylidenediphenylmethylamine *N*-oxide (1.0 mmol, 239 mg) and acrolein (1.5 mmol, 100 μL) over the course of 64 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 3:1) to give the cycloadduct as a white powder [79 % yield (234 mg), d.r. = 4.3:1, 45% ee (major isomer)].

Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol = 15:1, flow rate = 0.5 mL/min, retention time; 18.9 min (major) and 20.2 min (minor)).

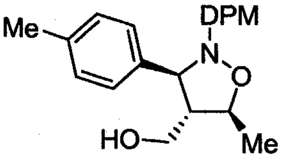
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.16 (10H, m, Ar**H**), 5.01 (1H, s, Ph_2C**H**), 3.98 (1H, appt t, *J* = 8.3 Hz, NOCH**H**), 3.87 (1H, dd, *J* = 8.7, 6.3 Hz, NOC**H**H), 3.72-3.62 (2H, m, **CH₂**OH), 2.78 (1H, m, ONC**H**), 2.45 (1H, m, **C**HCH₂OH), 1.38 (2H, m, **CH₂**CH₃), 0.79 (3H, t, *J* = 7.4 Hz, CH₂**CH₃**) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 141.4, 128.3, 128.1, 127.7, 127.2, 126.8, 72.9, 68.3, 66.5, 64.1, 51.6, 28.1, 10.6 ppm; IR (neat) 3416, 3026, 2961, 2932, 2874, 1493, 1452, 1078, 1030 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{19}H_{23}NO_2$: *m/z* 320.1621 ([M + Na]$^+$), found: *m/z* 320.1630 ([M + Na]$^+$); $[\alpha]_D^{28}$ = –9.1 (*c* = 1.0, $CHCl_3$; 45% ee).



(3*S*,4*S*,5*S*)-2-Diphenylmethyl-3-phenyl-4-hydroxymethyl-5-methylisoxazolidine (Table 2.5, entry 1). Prepared according to the general procedure with (*Z*)-*N*-benzylidenediphenylmethylamine *N*-oxide (1.0 mmol, 287 mg) and crotonaldehyde (1.5 mmol, 124 μL) over the course of 24 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 3:1) to give the cycloadduct as a white solid [82% yield (318 mg), *endo*:*exo* = >20:1, *endo* 87% ee].

Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/ethanol = 50:1, flow rate = 0.5 mL/min, retention time; 21.6 min (major) and 25.1 min (minor)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.03 (15H, m, Ar**H**), 5.05 (1H, s, Ph_2C**H**), 4.23-4.17 (1H, m, NOC**H**), 3.82 (1H, d, *J* = 7.0 Hz, ONC**H**), 3.72-3.61 (2H, m, **CH₂**OH), 2.29 (1H, m, **C**HCH₂OH), 1.39 (3H, d, *J* = 6.0 Hz, OCH**CH₃**) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 141.3, 141.2, 128.5, 128.2, 128.0, 127.9, 127.3, 126.9, 126.8, 75.5, 72.7, 70.5, 62.7, 62.1, 19.4 ppm; IR (neat) 3418, 3061, 3028, 2972, 2928, 2870, 1601, 1493, 1452, 1371, 1304, 1074, 1028 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{24}H_{25}NO_2$: *m/z* 360.1958 ([M + H]$^+$), found: *m/z* 360.1959 ([M + H]$^+$); $[\alpha]_D^{23}$ = –68.8 (*c* = 1.0, $CHCl_3$; 87% ee).

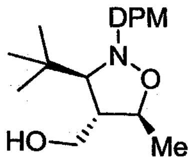


(3*S*,4*S*,5*S*)-2-Diphenylmethyl-3-(4-tolyl)-4-hydroxymethyl-5-methylisoxazolidine (Table 2.5, entry 2). Prepared according to the general procedure with (*Z*)-*N*-benzylidenediphenylmethylamine *N*-oxide (1.0 mmol, 301 mg) and crotonaldehyde

(1.5 mmol, 124 μL) over the course of 22 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 3:1) to give the cycloadduct as a white solid [93% yield (348 mg), *endo*:*exo* = >20:1, *endo* 89% ee].

Enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 20:1, flow rate = 0.5 mL/min, retention time; 15.9 min (minor) and 26.3 min (major)).

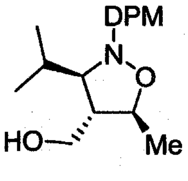
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (14H, m, Ar**H**), 5.03 (1H, s, Ph_2C**H**), 4.17 (1H, m, NOC**H**), 3.77 (1H, d, *J* = 7.3 Hz, ONC**H**), 3.73-3.61 (2H, m, C**H**$_2$OH), 2.34-2.25 (1H, m, C**H**CH_2OH), 2.31 (3H, s, PhC**H**$_3$), 1.40 (3H, d, *J* = 6.0 Hz, OCHC**H**$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 140.9, 138.8, 136.5, 128.9, 128.7, 128.1, 127.9, 127.8, 127.3, 126.9, 126.7, 75.5, 72.2, 70.2, 62.6, 62.2, 21.2, 19.5 ppm; IR (neat) 3422, 3059, 3026, 2972, 2924, 2868, 1599, 1512, 1493, 1450, 1371, 1304, 1078, 1026 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{25}H_{27}NO_2$: *m/z* 374.2115 ($[M + H]^+$), found: *m/z* 374.2117 ($[M + H]^+$); $[\alpha]_D^{27} = -95.7$ (*c* = 1.0, $CHCl_3$; 89% ee).



(3*S*,4*S*,5*S*)-2-Diphenylmethyl-3-*tert*-butyl-4-hydroxymethyl-5-methylisoxazolidine (Table 2.5, entry 3). Prepared according to the general procedure with (*Z*)-*N*-*tert*-butylmethylidenediphenylmethylamine *N*-oxide (1.0 mmol, 267 mg) and crotonaldehyde (1.5 mmol, 124 μL) over the course of 24 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 3:1) to give the cycloadduct as a white solid [50% yield (169 mg), *endo*:*exo* = >20:1, *endo* 89% ee].

Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol = 20:1, flow rate = 0.5 mL/min, retention time; 11.8 min (minor) and 13.0 min (major)).

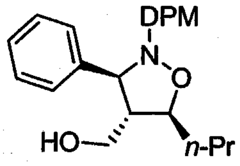
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (2H, d, *J* = 7.49 Hz, Ar**H**), 7.38 (2H, d, *J* = 7.5 Hz, Ar**H**), 7.31-7.14 (6H, m, Ar**H**), 5.20 (1H, s, Ph_2C**H**), 4.26 (1H, m, NOC**H**), 3.84 (2H, m, C**H**$_2$OH), 2.74 (1H, d, *J* = 4.1 Hz, ONC**H**), 2.19 (1H, m, C**H**CH_2OH), 1.22 (3H, d, *J* = 5.8 Hz, OCHC**H**$_3$), 0.74 (9H, s, *t*-Bu) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 141.2, 129.9, 128.01, 127.99, 127.7, 127.3, 126.4, 75.8, 73.5, 72.5, 64.5, 54.6, 34.6, 27.0, 18.2 ppm; IR (neat) 3447, 3028, 2953, 2870, 1597, 1452, 1366, 1082, 1026 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{22}H_{29}NO_2$: *m/z* 340.2271 ($[M + H]^+$), found: *m/z* 340.2272 ($[M + H]^+$); $[\alpha]_D^{28} = 111.8$ (*c* = 1.0, $CHCl_3$; 89% ee).



(3R,4S,5S)-2-Diphenylmethyl-3-isopropyl-4-hydroxymethyl-5-methylisoxazolidine (Table 2.5, entry 4). Prepared according to the general procedure with (*Z*)-*N*-isopropylmethylidenediphenylmethylamine *N*-oxide (1.0 mmol, 253 mg) and crotonaldehyde (1.5 mmol, 124 μL) over the course of 20 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 3:1) to give the cycloadduct as a white solid [83% yield (271 mg), *endo*:*exo* = >20:1, *endo* 92% ee].

Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol = 20:1, flow rate = 0.5 mL/min, retention time; 14.3 min (minor) and 15.5 min (major)).

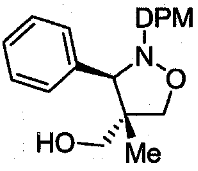
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (2H, d, J = 7.7 Hz, Ar**H**), 7.41 (2H, d, J = 7.7 Hz, Ar**H**), 7.29-7.14 (6H, m), 5.17 (1H, s, Ph_2C**H**), 4.27 (1H, m, NOC**H**), 3.79 (2H, m, **CH_2**OH), 2.73 (1H, dd, J = 6.8, 4.4 Hz, ONC**H**), 2.07 (1H, m, **CH**CH_2OH), 1.70 (1H, m, $(CH_3)_2$**CH**), 1.24 (3H, d, J = 6.0 Hz, OCH**CH_3**), 0.81 (6H, d, J = 6.5 Hz, **$(CH_3)_2$**CH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 141.7, 128.8, 128.3, 128.1, 127.5, 127.2, 126.5, 75.6, 72.6, 70.8, 64.2, 56.1, 33.2, 20.0, 18.8, 18.7 ppm; IR (neat) 3445, 3061, 3026, 2957, 2928, 2870, 1493, 1452, 1385, 1369, 1072, 1028 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{21}H_{27}NO_2$: *m/z* 326.2115 ($[M + H]^+$), found: *m/z* 326.2116 ($[M + H]^+$); $[\alpha]_D^{24}$ = 49.6 (c = 1.0, $CHCl_3$; 92% ee).



(3S,4S,5S)-2-Diphenylmethyl-3-phenyl-4-hydroxymethyl-5-propylisoxazolidine (Table 2.5, entry 5). Prepared according to the general procedure with (*Z*)-*N*-benzylidenediphenylmethylamine *N*-oxide (1.0 mmol, 287 mg) and *trans*-2-hexenal (1.5 mmol, 174 μL) over the course of 28 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 3:1) to give the cycloadduct as a viscous oil [47% yield (180 mg), *endo*:*exo* = >20:1, *endo* 67% ee].

Enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 20:1, flow rate = 0.5 mL/min, retention time; 14.4 min (minor) and 15.9 min (major)).

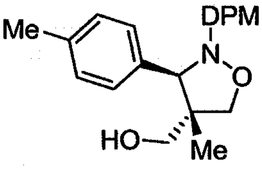
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.04 (15H, m, Ar**H**), 5.01 (1.0H, s, Ph_2C**H**), 3.99 (1H, m, NOC**H**), 3.76-3.62 (3H, m, ONC**H**, **CH_2**OH), 2.35 (1H, m, **CH**CH_2OH), 1.86 (1H, m, CH_3CH_2CH**H**), 1.66 (1H, m, CH_3CH_2CH**H**), 1.47-1.27 (2H, m, CH_3**CH_2**CH_2), 0.91 (3H, t, J = 7.4 Hz, **CH_3**CH_2CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 141.4, 140.7, 128.9, 128.21, 128.16, 127.84, 127.76, 127.5, 126.88, 126.86, 126.7, 79.2, 72.2, 70.5, 62.7, 61.3, 36.6, 19.7, 14.2 ppm; IR (neat) 3420, 3061, 3026, 2957, 2930, 2870, 1601, 1493, 1452, 1076, 1030 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{26}H_{29}NO_2$: *m/z* 388.2271 ([M + H]$^+$), found: *m/z* 388.2272 ([M + H]$^+$); $[\alpha]_D^{27}$ = –67.5 (*c* = 1.0, $CHCl_3$; 67% ee).



(3*R*,4*S*)-2-Diphenylmethyl-3-phenyl-4-hydroxymethyl-4-methylisoxazolidine (Table 2.6, entry 1). Prepared according to the general procedure with (*Z*)-*N*-benzylidenediphenylmethylamine *N*-oxide (1.0 mmol, 287 mg) and methacrolein (1.5 mmol, 124 μL) over the course of 24 h. The crude material was further treated with lithium aluminum hydride (0.5 mmol) to remove inseparable nitrone by converting to less polar and separable hydroxylamine and the residue was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 4:1) to give the cycloadduct as a white powder [60% yield (214 mg), *endo*:*exo* = >20:1, *endo* 90% ee].

Enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 50:1, flow rate = 0.5 mL/min, retention time; 35.3 min (major) and 38.1 min (minor)).

1H NMR (400 MHz, CDC13) δ 7.32-7.08 (15H, m, Ar**H**), 4.99 (1H, s, Ph_2C**H**), 3.99 (1H, d, *J* = 8.2 Hz, NOCH**H**), 3.79 (1H, s, ONC**H**), 3.74 (1H, d, *J* = 8.5 Hz, NOCH**H**), 3.45 (2H, br, C**H$_2$**OH), 0.68 (3H, s, C**H$_3$**) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 139.4, 129.5, 128.6, 128.1, 127.9, 127.8, 127.7, 127.2, 127.0, 126.7, 74.8, 72.0, 71.7, 69.2, 51.9, 18.5 ppm; IR (neat) 3422, 3026, 2967, 2932, 2868, 1600, 1493, 1450, 1030 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{24}H_{25}NO_2$: *m/z* 360.1958 ([M + H]$^+$), found: *m/z* 360.1958 ([M + H]$^+$); $[\alpha]_D^{27}$ = –63.2 (*c* = 1.0, $CHCl_3$; 90% ee).

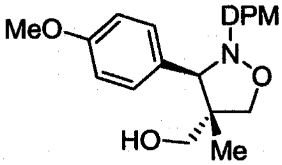


(3*R*,4*S*)-2-Diphenylmethyl-3-(4-tolyl)-4-hydroxymethyl-4-methylisoxazolidine (Table 2.6, entry 2). Prepared according to the general procedure with (*Z*)-*N*-(4-methylbenzylidene) diphenylmethylamine *N*-oxide (1.0 mmol, 301 mg) and methacrolein (1.5 mmol, 124 μL) over the course of 24 h. The crude material was further treated with lithium aluminum hydride (0.5 mmol) to remove inseparable nitrone by converting to less polar and separable hydroxylamine and the residue was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 4:1) to give the cycloadduct as a white powder [63% yield (235 mg), *endo*:*exo* = >20:1, *endo* 88% ee].

Enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 20:1, flow rate = 0.5 mL/min, retention time; 17.6 min (major) and

19.6 min (minor)).

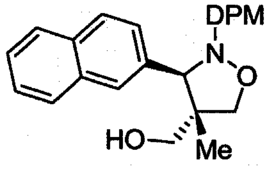
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.06 (14H, m, Ar**H**), 4.97 (1H, s, Ph_2C**H**), 3.97 (1H, d, *J* = 7.3 Hz, NOCH**H**), 3.73 (1H, s, ONC**H**), 3.72 (1H, d, *J* = 8.0 Hz, NOC**H**H), 3.42 (2H, br, $\mathbf{CH_2}OH$), 2.32 (3H, s, $Ar\mathbf{CH_3}$), 0.70 (3H, s, $\mathbf{CH_3}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 139.0, 136.7, 129.8, 128.6, 128.0, 127.8, 127.7, 127.2, 126.6, 74.8, 71.7, 71.0, 69.3, 51.6, 21.2, 18.6 ppm; IR (neat) 3420, 3059, 3026, 2967, 2924, 2866, 1601, 1512, 1493, 1450, 1179, 1109, 1032 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{25}H_{27}NO_2$: *m/z* 374.2115 ($[M + H]^+$), found: *m/z* 374.2115 ($[M + H]^+$); $[\alpha]_D^{29}$ = –86.9 (*c* = 1.0, $CHCl_3$; 88% ee).



(3*R*,4*S*)-2-Diphenylmethyl-3-(4-methoxyphenyl)-4-hydroxymethyl-4-methylisoxazolidine (Table 2.6, entry 3). Prepared according to the general procedure with (*Z*)-*N*-(4-methoxybenzylidene)diphenylmethylamine *N*-oxide (1.0 mmol, 317 mg) in CH_2Cl_2 (3 mL) and methacrolein (1.5 mmol, 124 μL) over the course of 24 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 4:1) to give the cycloadduct as a white powder [46% yield (178 mg), *endo*:*exo* = >20:1, *endo* 89% ee].

Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol = 20:1, flow rate = 0.5 mL/min, retention time; 22.1 min (major) and 24.1 min (minor)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-6.78 (14H, m, Ar**H**), 4.95 (1H, s, Ph_2C**H**), 3.98 (1H, d, *J* = 6.5 Hz, NOCH**H**), 3.79 (3H, s, $O\mathbf{CH_3}$), 3.73 (1H, s, ONC**H**), 3.72 (1H, d, *J* = 7.5 Hz, NOC**H**H), 3.43 (2H, br, $\mathbf{CH_2}OH$), 0.70 (3H, s, $\mathbf{CH_3}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 141.3, 139.2, 129.6, 128.0, 127.8, 127.7, 127.2, 126.6, 113.4, 74.8, 71.5, 71.2, 69.3, 55.2, 51.6, 18.6 ppm; IR (neat) 3443, 3059, 3026, 2961, 2868, 1610, 1510, 1452, 1300, 1246, 1175, 1032 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{25}H_{27}NO_3$: *m/z* 390.2064 ($[M + H]^+$), found: *m/z* 390.2061 ($[M + H]^+$); $[\alpha]_D^{29}$ = –86.3 (*c* = 1.0, $CHCl_3$; 89% ee).



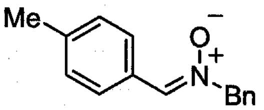
(3*R*,4*S*)-2-Diphenylmethyl-3-(2-naphthyl)-4-hydroxymethyl-4-methylisoxazolidine (Table 2.6, entry 4). Prepared according to the general procedure with (*Z*)-*N*-(2-naphthylmethylidene) diphenylmethylamine *N*-oxide (1.0 mmol, 337 mg) in CH_2Cl_2 (3 mL) and methacrolein (1.5 mmol, 124 μL) over the course of 24 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate

= 4:1) to give the cycloadduct as a white powder [64% yield (263 mg), *endo*:*exo* = >20:1, *endo* 92% ee].

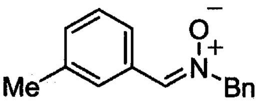
Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol = 20:1, flow rate = 0.5 mL/min, retention time; 19.7 min (major) and 22.9 min (minor)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81-7.01 (17H, m, ArH), 5.04 (1H, s, Ph_2CH), 4.05 (1H, d, J = 8.5 Hz, NOCHH), 3.98 (1H, s, ONCH), 3.80 (1H, d, J = 8.2 Hz, NOCHH), 3.51 (2H, br, CH_2OH), 0.70 (3H, s, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 139.4, 133.0, 132.7, 129.5, 128.0, 127.9, 127.7, 127.5, 127.4, 127.2, 126.8, 126.7, 125.8, 125.6, 74.9, 72.1, 71.7, 69.2, 52.2, 18.6 ppm; IR (neat) 3422, 3057, 2965, 2932, 2868, 1601, 1493, 1452, 1377, 1269, 1179, 1125, 1032 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{28}H_{27}NO_2$: *m/z* 410.2115 ($[M + H]^+$), found: *m/z* 410.2115 ($[M + H]^+$); $[\alpha]^{29}_D = -87.0$ (*c* = 1.0, $CHCl_3$; 92% ee).

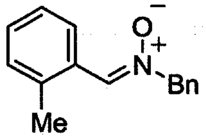
General Procedure for the Synthesis of Nitrones. To the solution of benzylhydroxylamine or diphenylmethylhydroxylamine was added 1.5 equiv of aldehyde respectively and the mixture was stirred at room temperature. After the consumption of the hydroxylamine, solvent was evaporated *in vacuo* and the residue was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate/CH_2Cl_2) to give the corresponding nitrone.



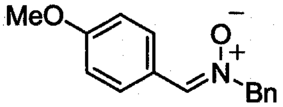
(*Z*)-*N*-(4-Methylbenzylidene)benzylamine *N*-Oxide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (2H, d, J = 8.4 Hz, ArH), 7.38-7.49 (5H, m, ArH), 7.34 (1H, s, N=CH), 7.20 (2H, d, J = 8.0 Hz, ArH), 5.04 (2H, s, $PhCH_2$), 2.36 (3H, s, $ArCH_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 134.2, 133.2, 129.1, 128.8, 128.5, 127.7, 71.0, 21.7 ppm; IR (neat) 3066, 3032, 1609, 1497, 1458, 1431, 1180, 1146, 939, 849, 829 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{15}H_{16}NO$: *m/z* 226.1226 ($[M + H]^+$), found: *m/z* 226.1224 ($[M + H]^+$).



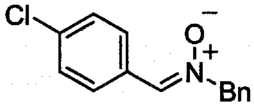
(*Z*)-*N*-(3-Methylbenzylidene)benzylamine *N*-Oxide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (1H, s, ArH), 7.91 (1H, d, J = 7.6 Hz, ArH), 7.37-7.49 (4H, m, ArH), 7.36 (1H, s, N=CH), 7.20-7.30 (3H, m, ArH), 5.04 (2H, s, $PhCH_2$), 2.36 (3H, s, $ArCH_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 134.2, 133.2, 131.2, 130.2, 129.1, 128.9, 128.8, 128.2, 125.8, 71.2, 21.5 ppm; IR (neat) 3065, 3032, 2947, 1578, 1456, 1429, 1302, 1169, 1142 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{15}H_{16}NO$: *m/z* 248.1046 ($[M + Na]^+$), found: *m/z* 248.1050 ($[M + Na]^+$).



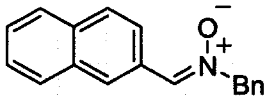
(*Z*)-*N*-(2-Methylbenzylidene)benzylamine *N*-Oxide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (1H, m, Arb), 7.54 (1H, s, N=CH), 7.39-7.50 (5H, m, ArH), 7.16-7.28 (3H, m, ArH), 5.10 (2H, s, $PhCH_2$), 2.28 (3H, s, $ArCH_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 133.2, 131.2, 130.1, 130.0, 129.1, 128.9, 128.6, 127.8, 126.2, 71.7, 19.8 ppm; IR (neat) 3065, 3032, 1701, 1564, 1468, 1296, 1202, 1152 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{15}H_{16}NO$: *m/z* 248.1046 ([M + Na]$^+$), found: *m/z* 248.1045 ([M + Na]$^+$).



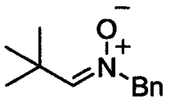
(*Z*)-*N*-(4-Methoxybenzylidene)benzylamine *N*-Oxide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (2H, d, *J* = 8.8 Hz, ArH), 7.37-7.48 (5H, m, ArH), 7.31 (1H, s, N=CH), 5.02 (2H, s, $PhCH_2$), 3.83 (3H, s, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 133.7, 133.3, 130.4, 129.1, 128.8, 128.7, 123.3, 113.7, 70.7, 55.3 ppm; IR (neat) 3065, 2979, 2939, 1603, 1566, 1506, 1458, 1321, 1252, 1200, 1173, 1146, 1023, 937, 841, 829 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{15}H_{16}NO_2$: *m/z* 242.1176 ([M + H]$^+$), found: *m/z* 242.1175 ([M + H]$^+$).



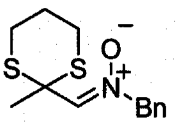
(*Z*)-*N*-(4-Chlorobenzylidene)benzylamine *N*-Oxide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (2H, d, *J* = 8.8 Hz, ArH), 7.25-7.48 (8H, m, ArH, N=CH), 5.05 (2H, s, $PhCH_2$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 132.9, 129.6, 129.2, 129.0, 128.8, 128.6, 71.4 ppm; IR (neat) 3068, 3032, 1584, 1557, 1487, 1458, 1431, 1194, 1148, 1088, 1015, 907, 854, 831 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{14}H_{13}ClNO$: *m/z* 246.0680 ([M + H]$^+$), found: *m/z* 246.0678 ([M + H]$^+$).



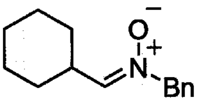
(*Z*)-*N*-(2-Naphthyl)methylidenebenzylamine *N*-Oxide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (1H, s, N=CH), 7.78-7.90 (4H, m, ArH), 7.40-7.54 (8H, m, ArH), 5.11 (s, 2H, $PhCH_2$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.2, 134.0, 133.1, 133.0, 129.2, 129.1, 128.9, 128.5, 127.8, 127.5, 127.4, 127.2, 126.4, 125.7, 71.3 ppm; IR (neat) 3397, 3057, 3032, 1566, 1497, 1456, 1423, 1354, 1179, 1150, 1140, 945, 907, 864, 827 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{18}H_{16}NO$: *m/z* 262.1226 ([M + H]$^+$), found: *m/z* 262.1225 ([M + H]$^+$).



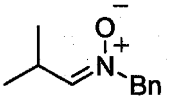
(*Z*)-*N*-*tert*-Butylmethylidenebenzylamine *N*-Oxide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (5H, br, ArH), 6.49 (1H, s, N=CH), 4.84 (2H, s, $PhCH_2$), 1.26 (1H, s, *t*-Bu) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 133.4, 128.7, 128.6, 128.5, 70.6, 32.9, 26.1 ppm; IR (neat) 2959, 2914, 1583, 1497, 1483, 1456, 1423, 1360, 1227, 1204, 1144, 937 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{12}H_{18}NO$: *m/z* 192.1383 ([M + H]$^+$), found: *m/z* 192.1382 ([M + H]$^+$).



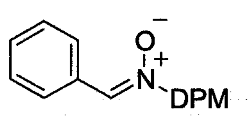
(*Z*)-*N*-(2-Methyl-1,3-dithian-2-yl)methylidenebenzylamine *N*-Oxide. The mixture of benzylhydroxylamine and 2-methyl-1,3-dithian-2-carboxaldehyde in benzene was azeotroped for 12 h. Benzene was then removed *in vacuo* and the residue was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate/CH_2Cl_2 = 5:5:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.43 (5H, m, ArH), 7.03 (1H, s, N=CH), 4.93 (2H, s, PhCH_2), 2.78-2.85 (m, 2H, SCH_2), 2.65-2.2.70 (m, 2H, SCH_2), 2.03-2.09 (m, 1H, $SCH_2CH_2CH_2S$), 1.63-1.93 (1H, m, $SCH_2CH_2CH_2S$), 1.88 (3H, s, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 133.1, 128.9, 70.9, 45.9, 28.2, 24.7, 23.4ppm; IR (neat) 3063, 2930, 2901, 1564, 1456, 1420, 1194, 1141, 1069, 905, 729, 702cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{13}H_{18}NOS_2$: *m/z* 268.0824 ([M + H]$^+$), found: *m/z* 268.0823 ([M + H]$^+$).



(*Z*)-*N*-Cyclohexylmethylidenebenzylamine *N*-Oxide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (5H, br, ArH), 6.46 (1H, d, *J* = 7.6, N=CH), 4.86 (2H, s, PhCH_2), 2.99 (1H, m, N=CHCH), 1.08-1.87 (10H, m, CyH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 133.1, 128.9, 128.7, 128.6, 69.4, 35.1, 28.9, 26.0, 25.3 ppm; IR (neat) 2920, 2849, 1591, 1497, 1447, 1427, 1188, 1173, 1121, 937 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{14}H_{20}NO$: *m/z* 218.1539 ([M + H]$^+$), found: *m/z* 218.1540 ([M + H]$^+$).

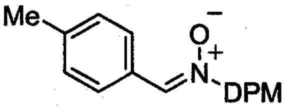


(*Z*)-*N*-Isopropylmethylidenebenzylamine *N*-Oxide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (5H, br, ArH), 6.48 (1H, d, *J* = 7.6, N=CH), 4.86 (2H, s, PhCH_2), 3.17 (1H, m, N=CHCH), 1.08 (6H, d, *J* = 6.8 Hz, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 132.9, 128.9, 128.7, 128.6, 69.3, 26.0, 18.9 ppm; IR (neat) 3063, 2965, 2930, 2872, 1593, 1460, 1198, 1115 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{11}H_{15}NO$: *m/z* 200.1046 ([M + Na]$^+$), found: *m/z* 200.1046 ([M + Na]$^+$).

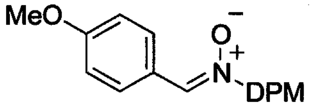


(*Z*)-*N*-Benzylidenediphenylmethylamine *N*-Oxide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25-8.22 (2H, m, ArH), 7.48 (1H, s, N=CH), 7.41-7.33 (13H, m, ArH), 6.36 (1H, s, Ph_2CH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 134.7, 130.4, 130.2, 128.7, 128.63, 128.61, 128.44, 128.35, 83.7 ppm; IR (neat) 3061, 3030, 2926, 1560, 1584, 1495, 1447, 1319, 1288, 1134, 1028 cm^{-1};

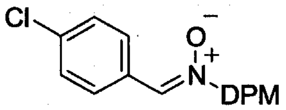
HRMS (ESI) exact mass calcd. for $C_{20}H_{17}NO$: *m/z* 310.1202 ([M + Na]$^+$), found: *m/z* 310.1202 ([M + Na]$^+$).



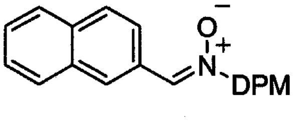
(*Z*)-*N*-(4-Methylbenzylidene)diphenylmethylamine *N*-Oxide. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.14 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.43 (1H, s, N=C**H**), 7.38-7.34 (10H, m, Ar**H**), 7.21 (2.H, d, *J* = 8.2 Hz, Ar**H**), 6.34 (1H, s, Ph_2C**H**), 2.37 (3H, s, ArC**H**$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 137.1, 134.8, 129.1, 128.7, 128.6, 128.4, 127.6, 83.4, 21.8 ppm; IR (neat) 3061, 3028, 2920, 1574, 1495, 1449, 1285, 1180, 1140, 1032 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{21}H_{19}NO$: *m/z* 324.1359 ([M + Na]$^+$), found: *m/z* 324.1357 ([M + Na]$^+$).



(*Z*)-*N*-(4-Methoxybenzylidene)diphenylmethylamine *N*-Oxide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (2H, d, *J* = 8.9 Hz, Ar**H**), 7.39 (1H, s, N=C**H**), 7.34 (10H, m, Ar**H**), 6.90 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.32 (1H, s, Ph_2C**H**), 3.81 (3H, s, OC**H**$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 137.1, 134.3, 130.6, 128.6, 128.5, 128.3, 123.2, 113.7, 83.0, 55.3 ppm; IR (neat) 3061, 3005, 2965, 2909, 2837, 1602, 1566, 1497, 1464, 1447, 1420, 1304, 1250, 1172, 1136, 1030 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{21}H_{19}NO_2$: *m/z* 340.1308 ([M + Na]$^+$), found: *m/z* 340.1307 ([M + Na]$^+$).

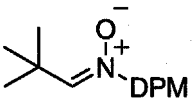


(*Z*)-*N*-(4-Chlorobenzylidene)diphenylmethylamine *N*-Oxide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (2H, m, Ar**H**), 7.46 (1H, s, N=C**H**), 7.38 (12H, m, Ar**H**), 6.35 (1H, s, Ph_2C**H**) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 135.8, 133.6, 129.8, 128.7, 128.61, 128.57, 128.55, 83.8 ppm; IR (neat) 3065, 3028, 2924, 1585, 1555, 1495, 1483, 1462, 1447, 1398, 1298, 1280, 1260, 1103, 1086, 1030, 1011 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{20}H_{16}ClNO$: *m/z* 344.0813 ([M + Na]$^+$), found: *m/z* 344.0812 ([M + Na]$^+$).

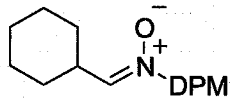


(*Z*)-*N*-(2-Naphthyl)methylidenediphenylmethylamine *N*-Oxide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (1H, s, Ar**H**), 7.88 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.80 (3H, m, Ar**H**), 7.64 (1H, s, N=C**H**), 7.52-7.35 (12H, m, Ar**H**), 6.42 (1H, s, Ph_2C**H**) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 134.8, 134.1, 133.0, 129.2, 128.7, 128.6, 128.5, 127.7, 127.4, 127.2, 126.4, 126.0 ppm; IR (neat) 3059, 3032, 1690, 1557, 1495, 1450, 1271, 1177, 1142, 1115, 1031 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{24}H_{19}NO$: *m/z* 360.1359 ([M +

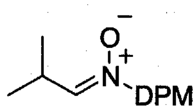
Na]$^+$), found: *m/z* 360.1363 ([M + Na]$^+$).



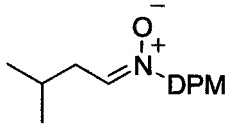
(*Z*)-*N*-*tert*-Butylmethylidenediphenylmethylamine *N*-oxide. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.38-7.28 (10H, m, Ar**H**), 6.54 (1H, s, N=C**H**), 6.13 (1H, s, Ph$_2$C**H**), 1.28 (9H, s, *t*-Bu) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ 145.4, 137.2, 128.5, 128.4, 128.2, 82.8, 33.0, 26.2 ppm; IR (neat) 3063, 2959, 2866, 1580, 1497, 1454, 1225, 1136, 1030 cm^{-1}; HRMS (ESI) exact mass calcd. for C$_{18}$H$_{21}$NO: *m/z* 290.1515 ([M + Na]$^+$), found: *m/z* 290.1516 ([M + Na]$^+$).



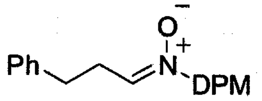
(*Z*)-*N*-Cyclohexylmethylidenediphenylmethylamine *N*-oxide. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.38-7.27 (10H, m, Ar**H**), 6.55 (1H, d, *J* = 7.3 Hz, N=C**H**), 6.14 (1H, s, Ph$_2$C**H**), 3.07 (1H, m, N=CHC**H**), 1.92-1.88 (2H, m, Cy), 1.67 (3H, m, Cy), 1.36 (2H, m, Cy), 1.18 (3H, m, Cy) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ 143.7, 137.0, 128.49, 128.45, 128.2, 81.8, 35.1, 28.9, 26.0, 25.3 ppm; IR (neat) 3063, 2920, 2851, 1578, 1495, 1447, 1294, 1258, 1163, 1123, 1103, 1032 cm^{-1}; HRMS (ESI) exact mass calcd. for C$_{20}$H$_{23}$NO: *m/z* 316.1672 ([M + Na]$^+$), found: *m/z* 316.1672 ([M + Na]$^+$).



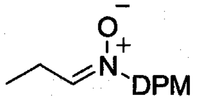
(*Z*)-*N*-Isopropylmethylidenediphenylmethylamine *N*-oxide. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39-7.28 (10H, m, Ar**H**), 6.55 (1H, d, *J* = 7.0 Hz, N=C**H**), 6.15 (1H, s, Ph$_2$C**H**), 3.25 (1H, m, C**H**(CH$_3$)$_2$), 1.12 (3H, d, *J* = 2.2 Hz, CH(**CH$_3$**)$_2$), 1.10 (3H, d, *J* = 1.9 Hz, CH(**CH$_3$**)$_2$) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ 145.2, 136.9, 128.6, 128.5, 128.3, 81.8, 26.1, 19.0 ppm; IR (neat) 3063, 2957, 2868, 1576, 1497, 1450, 1283, 1196, 1171, 1117, 1030 cm^{-1}; HRMS (ESI) exact mass calcd. for C$_{17}$H$_{19}$NO: *m/z* 276.1359 ([M + Na]$^+$), found: *m/z* 276.1354 ([M + Na]$^+$).



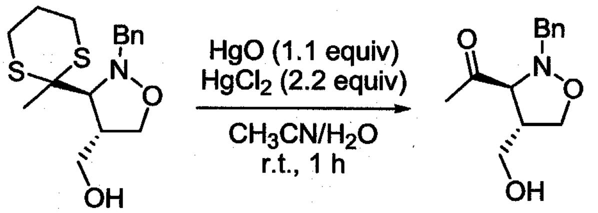
(*Z*)-*N*-Isobutylmethylidenediphenylmethylamine *N*-oxide. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39-7.28 (10H, m, Ar**H**), 6.73 (1H, appt t, *J* = 5.8 Hz, N=C**H**), 6.20 (1H, s, Ph$_2$C**H**), 2.47 (2H, appt t, *J* = 6.5 Hz, **CH$_2$**CH(CH$_3$)$_2$), 1.89 (1H, m, CH$_2$C**H**(CH$_3$)$_2$), 0.94 (3H, d, *J* = 0.5 Hz, CH$_2$CH(**CH$_3$**)$_2$), 0.92 (3H, d, *J* = 0.5 Hz, CH$_2$CH(**CH$_3$**)$_2$) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ 139.3, 136.9, 128.6, 128.5, 128.3, 82.1, 35.5, 26.1, 22.7 ppm; IR (neat) 3063, 2955, 2870, 1587, 1495, 1454, 1294, 1260, 1155, 1128, 1030 cm^{-1}; HRMS (ESI) exact mass calcd. for C$_{18}$H$_{21}$NO: *m/z* 290.1515 ([M + Na]$^+$), found: *m/z* 290.1510 ([M + Na]$^+$).



(*Z*)-*N*-(3-Phenylpropylidene)diphenylmethylamine *N*-oxide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.13 (15H, m, ArH), 6.69 (1H, appt t, *J* = 5.1 Hz, N=CH), 6.14 (1H, s, Ph_2CH), 2.88 (4H, m, $PhCH_2CH_2$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 138.9, 136.7, 128.6, 128.5, 128.4, 128.3, 129.2, 126.2, 82.1, 31.4, 28.0 ppm; IR (neat) 3061, 3026, 2928, 1580, 1495, 1452, 1281, 1142, 1030 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{22}H_{21}NO$: *m/z* 338.1515 ([M + Na]$^+$), found: *m/z* 338.1511 ([M + Na]$^+$).



(*Z*)-*N*-Propylidenediphenylmethylamine *N*-oxide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.23 (10H, m, ArH), 6.71 (1H, dd, *J* = 5.7, 5.0 Hz, N=CH), 6.18 (1H, s, Ph_2CH), 2.54 (2H, m, $C{=}NCH_2CH_3$), 1.08 (3H, dd, *J* = 9.3, 5.9 Hz, $C{=}NCH_2CH_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 136.7, 128.38, 128.35, 128.1, 81.5, 20.2, 9.9 ppm; IR (neat) 3061, 2970, 2880, 1634, 1589, 1497, 1450, 1281, 1165, 1113, 1028 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{16}H_{17}NO$: *m/z* 262.1202 ([M + Na]$^+$), found: *m/z* 262.1201 ([M + Na]$^+$).

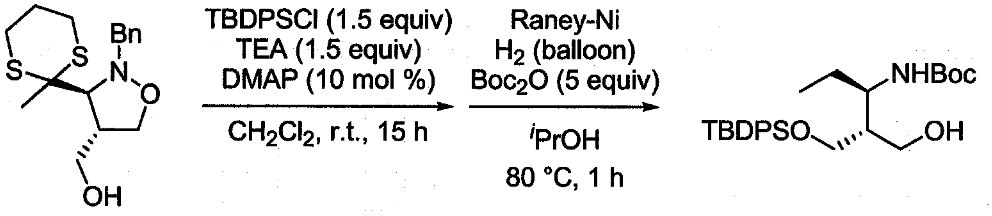


4

(3*S*,4*S*)-3-Acetyl-2-benzyl-4-hydroxymethylisoxazolidine (Scheme 2.2, 4). To a solution of (3*S*,4*S*)-2-benzyl-4-hydroxymethyl-3-(2-methyl-1,3-dithian-2-yl)isoxazoline (0.20 mmol, 65.1mg) in CH_3CN (1.6 mL) and H_2O (0.4 mL) were added HgO (0.22 mmol, 47.6 mg) and $HgCl_2$ (0.44 mmol, 120 mg). The suspension was then stirred for 1 h at room temperature, filtered through Celite and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 1:1) to afford the isoxazoline **4** as a colorless oil [63% (29.8 mg), *endo*:*exo* = >97:3, *endo* 97% ee].

Enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 20:1, flow rate = 1.0 mL/min, retention time; 23.0 min (minor) and 24.6 min (major)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.39 (5H, m, ArH), 4.18 (1H, d, *J* = 12.8 Hz, PhCHH), 4.07 (1H, dd, J = 8.0, 8.8 Hz, NOCHH), 3.94 (1H, d, J = 12.8 Hz, PhCHH), 3.92 (1H, dd, J = 6.8, 8.8 Hz, NOCHH), 3.78 (2H, m, CH_2OH), 3.31 (1H, d, J = 6.0 Hz, ONCH), 2.90 (1H, m, $CHCH_2OH$), 2.15 (1H, s, $COCH_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.0, 136.0, 129.3, 128.4, 127.7, 76.3, 68.3, 62.7, 61.6, 50.1, 26.6 ppm; IR (neat) 3391, 2918, 2849, 1709, 1354, 1236, 1030, 800, 700 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{13}H_{18}NO_3$: m/z 236.1281 ($[M + H]^+$), found: m/z 236.1293 ($[M + H]^+$); $[\alpha]_D^{30} = -55.1$ (c = 1.0, $CHCl_3$; 97% ee).

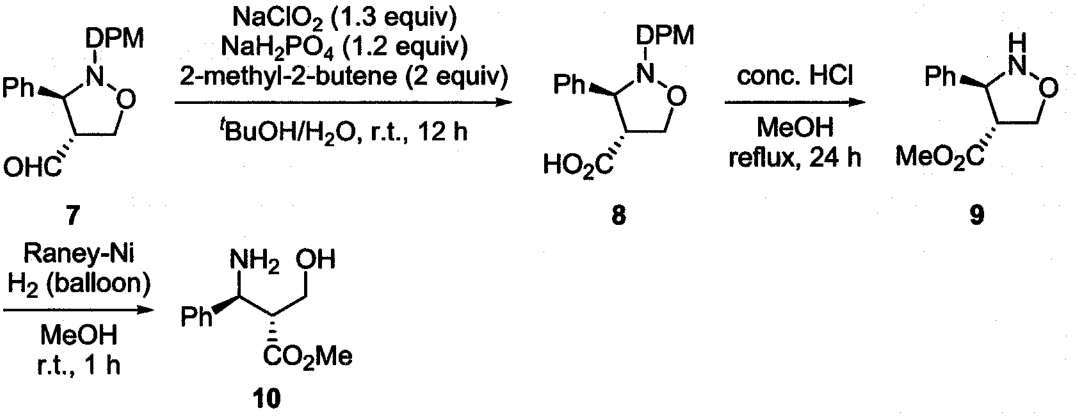


4 5

(2*R*,3*R*)-*N*-(*tert*-Butoxycarbonyl)-3-amino-2-(*tert*-butyldiphenylsiloxymethyl)-1-pentanol (Scheme 2.2, 5). To a solution of **4** (0.166 mmol, 54.0 mg) in CH_2Cl_2 (2 mL) were added triethylamine (0.232 mmol, 32.3 μL), *tert*-butylchlorodiphenylsilane (0.232 mmol, 59.4 μL) and catalytic amount of *N*,*N*-dimethylaminopyridine (0.017 mmol, 2.0 mg) at room temperature. After stirring for 15 h, the reaction was quenched by aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give a crude material. The residue was passed through a short plug of silica gel (eluting with hexane/ethyl acetate = 10:1) to remove highly polar impurities and used in the next step without further purification.

To the residue in 2-propanol (4 mL) were added Boc_2O (0.830 mmol, 191 μL) and Raney-Ni (1.7 g). Hydrogen gas (balloon) was then charged to the reaction flask. After stirring for 1 h at 80 °C, Raney-Ni was filtered off and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 4:1) to afford **5** as a colorless oil [43% yield (33.7 mg), 97% ee]. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 50:1, flow rate = 0.5 mL/min, retention time; 16.0 min (major) and 18.0 min (minor)).

^1H NMR (400 MHz, $CDCl_3$) δ 7.58-7.65 (4H, m, ArH), 7.36-7.45 (6H, m, ArH), 4.80 (1H, d, J = 9.2 Hz, NH), 3.71-3.86 (4H, m, CH_2OH and CH_2OSi), 3.52 (1H, m, NCH), 2.55 (1H, m, $CHCH_2OH$), 1.30-1.57 (2H, m, CH_3CH_2), 1.41 (9H, s, t-Bu) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 135.5, 135.4, 133.2, 133.1, 129.6, 127.6, 79.2, 63.6, 61.1, 51.5, 46.6, 28.5, 27.0, 25.8, 19.2, 10.5 ppm; IR (neat) 3408, 2962, 2930, 2878, 2859, 1686, 1506, 1366, 1244, 1173, 1111, 1076, 824, 741, 702, 613 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{27}H_{41}NNaO_4Si$: *m/z* 494.2697 ([M + Na]$^+$), found: *m/z* 494.2697 ([M + Na]$^+$); $[\alpha]^{25}_{D}$ = 12.4 (*c* = 1.0, $CHCl_3$; 97% ee).



(3*R*,4*S*)-3-Phenylisoxazolidine-4-carboxylic acid methyl ester (Scheme 2.4, 9). To a solution of 2-methyl-2-butene (182 μL, 1.72 mmol) and **7** (0.86 mmol, 295 mg), which was isolated from the reaction of *N*-benzylidenediphenylamine *N*-oxide and acrolein without reducing the aldehyde, in ^{t}BuOH (52 mL) was added aqueous solution of $NaClO_2$ (101 mg, 1.12 mmol) and $NaH_2PO_4{\cdot}H_2O$ (1.0 mmol, 138 mg). The reaction mixture was stirred for 12 h at room temperature before the solvent was removed in vacuo. The crude mixture was passed through silica gel columns (eluting with ethyl acetate) to give the carboxylic acid **8** in 91% yield (0.78 mmol, 282 mg).

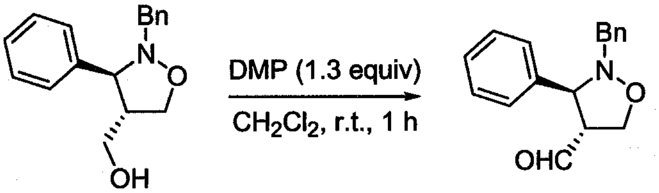
To a solution of the carboxylic acid **8** (0.20 mmol, 71.9 mg) thus obtained in MeOH (0.60 mL) was added conc. HCl (0.30 mL) and the reaction solution was refluxed for 24 h. The solution was then poured into aqueous $NaHCO_3$ and organic materials were extracted with ethyl acetate. The organic phase was then dried over Na_2SO_4 and concentrated in vacuo. The residue was then purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 4:1) to give **9** as a white solid [50% yield (20.7 mg)].

^{1}H NMR ($CDCl_3$) δ 7.42-7.24 (5H, m, ArH), 5.78 (1H, s, NH), 4.75 (1H, br, PhC**H**), 4.27 (1H, br, NOC**H**H), 4.11 (1H, br, NOCH**H**), 3.78 (3H, s, C**H**$_3$), 3.51 (1H, m, C**H**CO_2Me) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 128.8, 127.8, 126.6, 73.7, 67.2, 56.2, 52.5, 29.7 ppm; IR (neat) 3219, 2953, 2332, 1730, 1495, 1435, 1368, 1204, 1173, 1074, 1028 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{11}H_{13}NO_3$: *m/z* 230.0788 ([M + Na]$^+$), found: *m/z* 230.0789 ([M + Na]$^+$); $[\alpha]^{28}_{D}$ = 108.7 (*c* = 1.0, $CHCl_3$).

(2*R*,3*S*)-3-Amino-2-hydroxymethyl-3phenylpropionic acid methyl ester (Scheme

2.4, 10). To a stirred solution of **9** (0.10 mmol, 20.7 mg) in MeOH was added spatula tip of Raney-Ni and the reaction flask was then charged with hydrogen gas (balloon). The reaction solution was stirred for 1 h at room temperature and filtered to remove insoluble materials. The filtrate was concentrated under reduced pressure to give the crude material of **10**. The residue was then purified by column chromatography on silica gel (eluting with CH_2Cl_2/MeOH = 10:1) to give **10** as a colorless oil in quantitative yield (0.10 mmol, 21.4 mg).

^{1}H NMR (400 MHz, CD_3OD) δ 7.22-7.12 (5H, m, ArH), 4.04 (1H, d, J = 8.5 Hz, $CHNH_2$), 3.79 (2H, dd, J = 6.4, 3.0 Hz, CH_2OH), 3.36 (3H, s, OCH_3), 2.80 (1H, m, $CHCH_2OH$) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 174.8, 144.4, 129.4, 128.5, 128.0, 62.5, 57.2, 57.0, 51.9 ppm; IR (neat) 3358, 3296, 2951, 1728, 1593, 1454, 1435, 1362, 1265, 1196, 1167, 1032 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{11}H_{15}NO_3$: *m/z* 210.1125 ($[M + H]^+$), found: *m/z* 210.1128 ($[M + H]^+$); $[\alpha]_D^{28}$ = 10.9 (c = 0.80, CH_3OH).



Determination of the Absolute Configuration of (3*S*,4*S*)-2-Benzyl-4-hydroxymethyl-3-phenylisoxazoline (Table 2.1, entry 6). To a solution of (3*S*,4*S*)-2-benzyl-4-hydroxymethyl-3-phenylisoxazolidine (0.20 mmol, 53.9 mg) in CH_2Cl_2 was added Dess-Martin periodinane (0.26 mmol, 110 mg) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction was then quenched by the addition of aqueous Na_2SO_3, washed with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 3:1) to give (3*S*,4*R*)-2-benzyl-4-formyl-3-phenylisoxazolidine as a colorless oil in 82% yield (0.16 mmol, 43.8 mg); $[\alpha]_D^{22}$ = –59.6 (c = 1.0, $CHCl_3$; 93% ee).

The absolute configuration was assigned by the comparison with the data in the literature[4a].

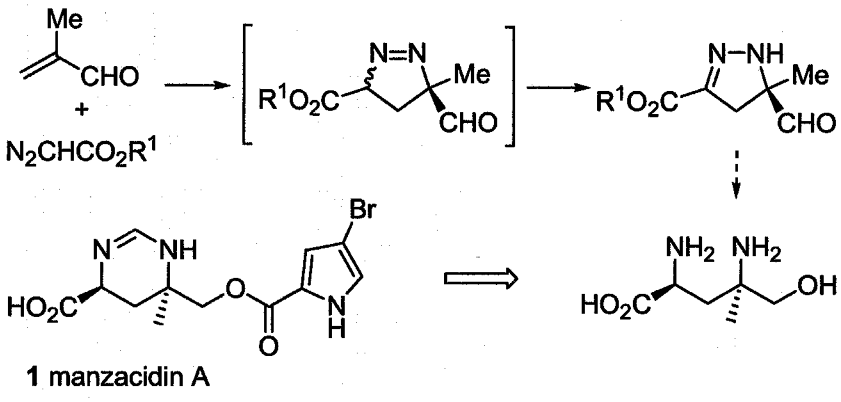
Chapter 3

1,3-Dipolar Cycloaddition Reaction of Diazoacetates and α-Substituted Acroleins: Total Synhthesis of Manzacidin A

Introduction

Diazoalkanes have been widely utilized in 1,3-dipolar cycloaddition reactions with various olefins to construct synthetically useful pyrazolines and pyrazoles, which are easily derivatized to various types of nitrogen-containing molecules.[1] The asymmetric variants of this transformation were previously effected by a chiral auxiliary-based approach.[2,3] Among these researches, Carreira and co-workers elegantly showed the usefulness of such an approach by the construction of a complex natural product, in which camphor sultam-derived dipolarophiles and $TMSCHN_2$ were combined in excellent diastereoselectivities.[4] Following their reports, Kanemasa and co-workers disclosed that the catalytic asymmetric 1,3-dipolar cycloaddition reaction between 3-(2-alkenoyl)-2-oxazolidinones and $TMSCHN_2$ could be facilitated by the use of chiral Lewis acid exploiting a unique tridentate ligand to furnish optically active 2-pyrazolines in remarkably high enantiomeric excess.[5] To the best of his knowledge, this report is the only successful example of Lewis acid catalyzed asymmetric 1,3-dipolar cycloaddition reaction of diazoalkanes and α,β-unsaturated carbonyl compounds.[6]

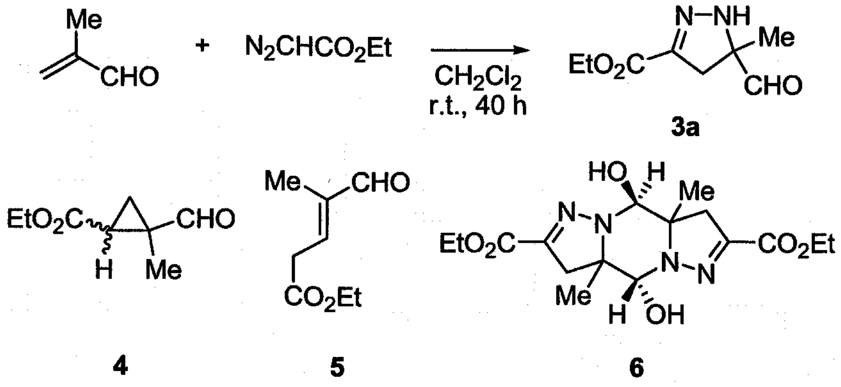
In this context, the author is interested in the possibility of developing the unprecedented enantioselective 1,3-dipolar cycloaddition of readily available substrates with broad applicability such as diazoacetates and monodentate α-substituted acroleins. Here, the author wishes to describe such an asymmetric transformation by using certain chiral titanium-BINOLate Lewis acids, one of which has recently been found to effectively catalyze the enantioselective 1,3-dipolar cycloaddition between acrolein and nitrones.[7] The resulting highly functionalized pyrazolines with a quaternary stereogenic center can be transformed by reduction into the pharmacologically intriguing 1,3-diamino carboxylic acids.[8] Indeed, the utility of this methodology is illustrated by the expedient synthesis of manzacidin A (Scheme 3.1).



Scheme 3.1

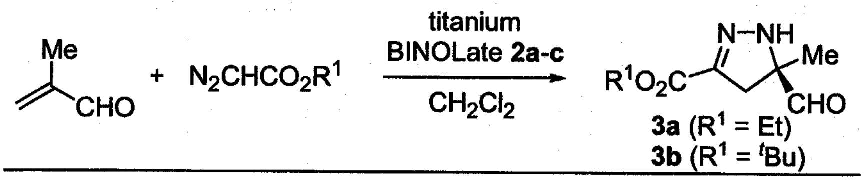
Results and Discussion

Initially, the author examined the reaction[9] between ethyl diazoacetate and methacrolein, which was reported to give a diastereomeric mixture of cyclopropanes, ethyl 4-formyl-3-pentenoate and 2-pyrazoline dimer. When the reaction was re-investigated in CH_2Cl_2 at room temperature, 2-pyrazoline monomer **3a** could be isolated in 16% yield as a labile compound, which is gradually transformed to a dimmer **6** under high concentration, accompanied with the formation of cyclopropanes **4** (37%) and ethyl 4-formyl-3-pentenoate **5** (11%) after column chromatography on silica gel (Scheme 3.2).



Scheme 3.2

Encouraged by this observation, the author then set out a survey of asymmetric transformation using a catalytic amount of titanium BINOLates.[10] Unfortunately, the reaction performed with 10 mol % (*S*)-BINOL/Ti(O^{i}Pr)$_4$ (1:1 molar ratio) complex **2a** at 0 °C gave a complex mixture through extrusion of nitrogen. Gratifyingly, this problem was circumvented by lowering the temperature to –40 °C, and consequently, the author obtained the 2-pyrazoline **3a** in moderate yield with high enantioselectivity of 88% after the usual work up procedure. Moreover, the use of (*S*)-BINOL/Ti(O^{i}Pr)$_4$ (2:1 molar ratio) complex **2b**[11] afforded the cycloadduct in 54% yield and 90% ee. In the case of bis{((*S*)-binaphthoxy)(isopropoxy) titanium} oxide **2c**,[12] which was recently developed in our laboratory, **3a** was obtained with excellent enantioselectivity (95% ee). Changing the ester moiety of diazoacetate from ethyl to *tert*-butyl led to the enhanced reactivity, although the chemical yield of the 2-pyrazoline **3b** remained moderate.



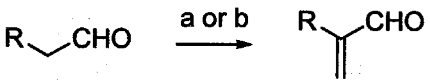
3a (R^1 = Et)
3b (R^1 = ^{t}Bu)

entry	R^1	catalyst (mol %)	conditions [°C, h]	yield (%)[b]	ee (%)[c]
1	Et	**2a** (10)	0, 1	-	-
2	Et	**2a** (10)	–40, 4	42	88
3	Et	**2b** (10)	–40, 2	54	90
4	Et	**2c** (5)	–40, 3	52	95
5	*t*-Bu	**2b** (10)	–40, 1	52	91
6	*t*-Bu	**2c** (5)	–40, 1	43	94

[a] Reactions were performed with methacrolein (1.0 mmol) and alkyl diazoacetates (1.5 mmol) in the presence of a chiral titanium catalyst in CH_2Cl_2. [b] Isolated yield. [c] Determined by chiral HPLC analysis after the reduction of the aldehyde.

Table 3.1

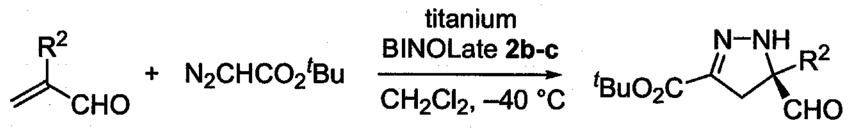
To evaluate the substrate scope of this methodology, the author then examined the 1,3-dipolar cycloaddtion reactions of *tert*-butyl diazoacetate and various 2-substituted acroleins. It should be noted that these 2-substituted acroleins were easily prepared from readily available aldehydes in one step according to literature procedures (Scheme 3.3).[13]



(a) $Me_2NCH_2NMe_2$ and AcCl then TEA, aldehyde, CH_2Cl_2
(b) Me_2NH_2Cl, aqueous HCHO

Scheme 3.3

As shown in Table 3.2, titanium BINOLates **2b** and **2c** could be applied to a reasonable range of olefinic substrates and provided corresponding 2-pyrazolines in fairly good yields with high to excellent enantioselectivities. Considering the other possible reaction pathways, such as 1,2- and 1,4-addition of *tert*-butyl diazoacetate to α-substituted acroleins[14] in addition to the cyclopropanation,[15] the yield of cycloadducts is quite remarkable.



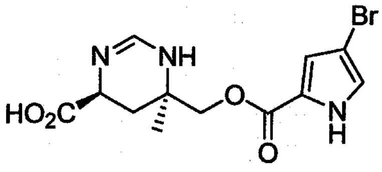
entry	R^2	catayst (mol %)	time (h)	yield (%)[b]	ee (%)[c]
1	Me	**2b** (10)	1	52	91[d]
2	Me	**2c** (5)	1	43	94[d]
3	Et	**2b** (10)	3	63	83
4	Et	**2c** (5)	3	48	84
5	$BnOCH_2CH_2$	**2b** (10)	1	81	80
6	$PhCH_2CH_2$	**2b** (10)	4	63	82
7	isopropyl	**2b** (10)	3	82	92
8	Cy	**2b** (10)	5	77	94
9	Cy	**2c** (5)	5	75	94

[a] Reactions were performed with a-substituted acroleins (1.0 mmol) and *tert*-butyl diazoacetate (1.5 mmol) in the presence of a chiral titanium catalyst in CH_2Cl_2. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Determined by chiral HPLC analysis after the reduction of the aldehyde.

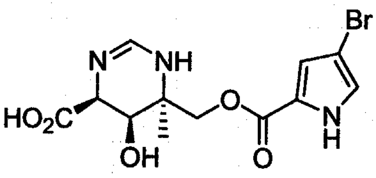
Table 3.2

Total Synthesis of Manzacidin A

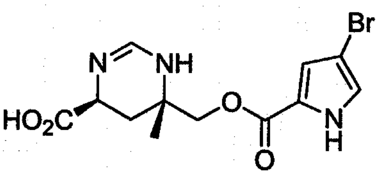
Manzacidins are a class of bromopyrrole alkaloids, which were isolated from Okinawan sponge *Hymeniacidon* sp.[16] Biological activities in such bromopyrrole alkaloids, such as α-adrenoceptor blockage, antagonism of serotonergic receptor, and activation of actomyosin ATPase, prompted synthetic chemists to construct these challenging structures containing unique tetrahydropyrimidine core with one asymmetric tetrasubstituted carbon center.[17]



1 manzacidin A



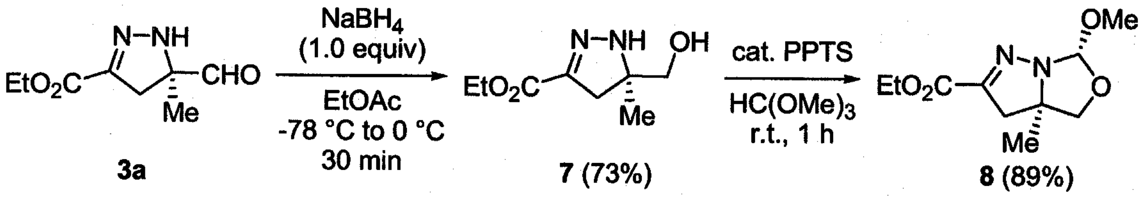
manzacidin B



manzacidin C

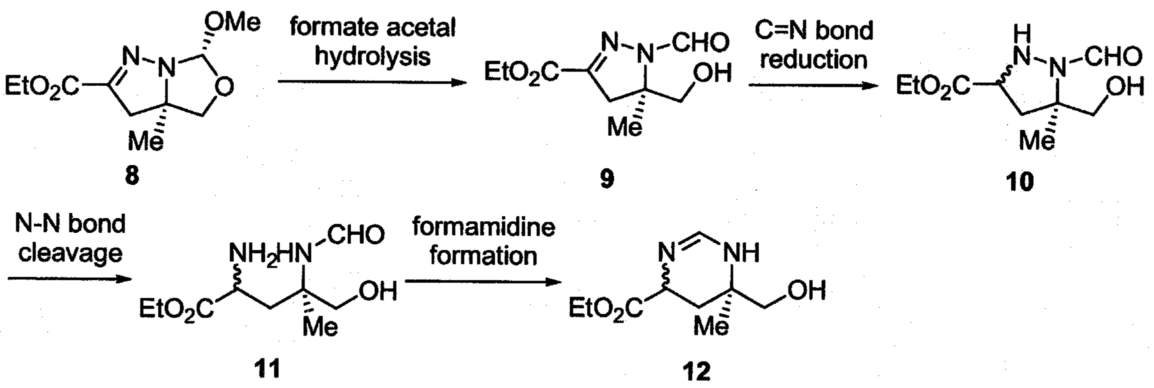
Kobayashi et al. proposed that these alkaloids might be generated from unusual γ-amino-δ-hydroxyleucine and formic acid.[16] The author envisioned that 2-pyrazoline provided by his catalytic asymmetric approach was a suitable precursor to construct such an unusual amino acid in short steps.

The synthesis of manzacidin A began with reduction of formyl group of 2-pyrazoline under the influence of $NaBH_4$, followed by treatment with methyl orthoformate to afford the bicyclic compound **8** as a single diastereomer (Scheme 3.4).



Scheme 3.4

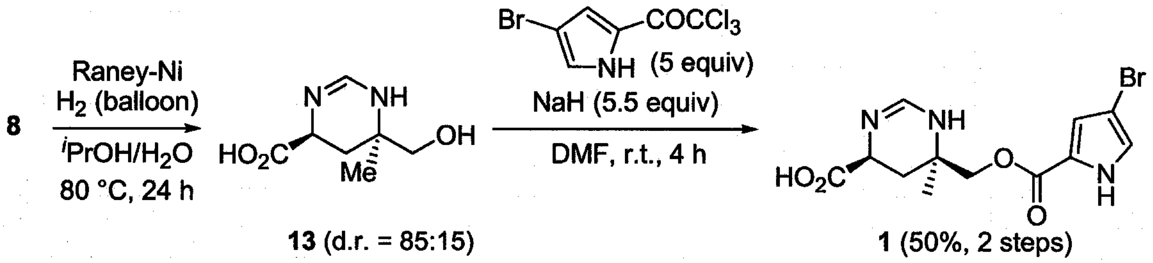
Notable features of his strategy to protect the alcohol **7** with orthoformate are as follows; a) **8** was obtained as a bench stable compound in contrast to the instability of **3a** and **7**; b) hydrolysis of **8** will provide the *N*-formyl compound **9**, which is susceptible to reduction due to the electron withdrawing nature of formyl group; c) the *N*-formyl group may be incorporated into the tetrahydropyrimidine core after reduction of the N-N bond and the C=N double bond (**11** to **12**, Scheme 3.5).



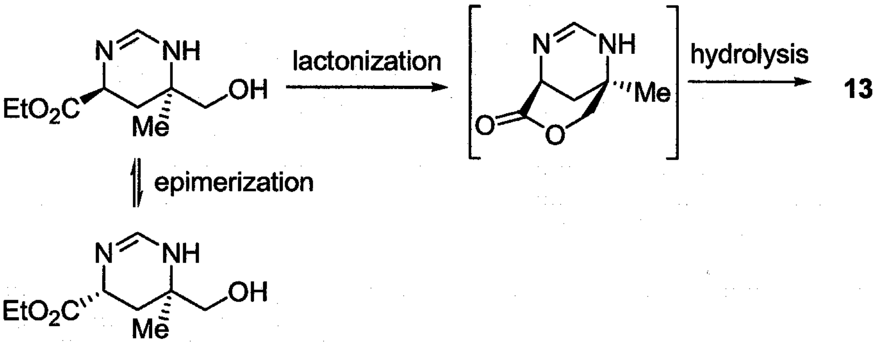
Scheme 3.5

With the expectation described above, the author attempted simultaneous reduction of the N-N bond and the C=N double bond of **8**. After screening of several conditions, such as reaction temperatures and solvents, it turned out that treatment of ethyl ester **8** with Raney-nickel under hydrogen atmosphere resulted in the formation of pyrimidine carboxylic acid **9** in a good diastereoselectivity of 85:15. Indeed, the formate acetal group was incorporated in the pyrimidine core of **13,** and to his surprise, the ester moiety was hydrolyzed under the reaction condition at a time.

The LC-MS analysis of the reaction showed the *m*/*z* peaks at 239.2 (**10** + Na^+) and 195.1 (**13** + Na^+), indicating that the N-N bond cleavage is the rate determining step of this tandem reaction. The reaction conducted without use of water as co-solvent was found to be sluggish and therefore, the first hydrolysis of **8** to yield the intermediate **9** was experimentally supported in accordance with his proposed reaction sequence (Scheme 3.5). Considering the unexpected ester hydrolysis, the stereochemical outcome might be rationalized by the preferential lactonization of one diastereomer of **12** followed by hydrolysis concomitant with the epimerization at α-position of the ester, rather than the stereoselective hydrogenation of the C=N double bond (Scheme 3.7).



Scheme 3.6



Scheme 3.7

Thus obtained pyrimidine core in hand, the bromopyrrole moiety was incorporated to finish the total synthesis of manzacidin A, following the reported procedure.[17a] The crude mixture of manzaicidin A and its diastereo isomer (*ent*-manzacidin C) was separated by reverse phase HPLC (cosmosil 5C18-AR-II, eluting with $H_2O/CH_3CN/TFA$ = 75:25:0.1) to give pure manzacidin A, which was identical in spectral data ($[\alpha]_D^{29} = -23.0$ ($c = 0.50$, CH_3OH)) to naturally occurring manzacidin A (lit. $[\alpha]_D^{27} = -28$ ($c = 0.67$, CH_3OH)).

Summary and Conclusion

In summary, the author has developed a catalytic asymmetric formation of 2-pyrazoline with a quaternary asymmetric stereogenic center. Such an asymmetric variant of 1,3-dipolar cycloaddition reactions of diazo compounds is still scarce in the literatures and the practical aspect of this methodology was successfully delineated by the short total synthesis of manzacidin A in 5 steps starting from readily available starting materials without laborious protection and deprotection steps.

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Experimental Section

General Information. Infrared (IR) spectra were recorded on a Shimadzu IRPrestige-21 spectrometer. ^{1}H NMR spectra were measured on a JEOL JNM-FX400 (400 MHz) spectrometer. Data were reported as follows: chemical shifts in ppm from tetramethylsilane (in the case of $CDCl_3$) or CD_2HOD ($\delta = 3.30$, in the case of CD_3OD) as an internal standard, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = double-doublet, m = multiplet, br = broad, app = apparent), coupling constants (Hz), and assignment. ^{13}C NMR spectra were measured on a JEOL JNM-FX400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. High performance liquid chromatography (HPLC) was performed on Shimadzu 10A instruments at 280 nm using 4.6 nm x 25 cm Daicel Chiralpak and Chiralcel. High-resolution mass spectra (HRMS) were performed on Applied Biosystems Mariner 8295 API-TOF workstation. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. For thin layer chromatography (TLC) analysis 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 1.09386.9025, 230-400 mesh). 2-Substituted acroleins were purchased or prepared according to the procedures[13] and used after distillation or column chromatography on silica gel.

Preparation of (*S*)-BINOL/Ti(OPr^{i})$_4$ (1:1 molar ratio) Complex (2a).

To a stirred mixture of (*S*)-BINOL (0.10 mmol, 28.6 mg) in CH_2Cl_2 (1.0 mL) was added Ti(OPr^{i})$_4$ (0.10 mmol, 29.5 μL) at room temperature under argon. The mixture was then stirred for 2 h at room temperature to afford a orange solution of titanium (*S*)-BINOLate (**2a**).

Preparation of (*S*)-BINOL/Ti(OPr^{i})$_4$ (2:1 molar ratio) Complex (2b).

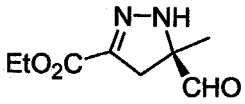
To a stirred mixture of (*S*)-BINOL (0.20 mmol, 57.2 mg) in CH_2Cl_2 (1.0 mL) was added Ti(OPr^{i})$_4$ (0.10 mmol, 29.5 μL) at room temperature under argon. The mixture was then stirred for 2 h at room temperature to afford a dark orange solution of titanium (*S*)-BINOLate (**2b**).

Preparation of Bis{((*S*)-binaphthoxy)(isopropoxy) titanium} Oxide (2c).

To a stirred mixture of Ag_2O (0.05 mmol, 11.6 mg) in CH_2Cl_2 (0.9 mL) was added 1.0 M CH_2Cl_2 solution of ClTi(OPr^{i})$_3$ (0.10 mmol, 100 μL) at room temperature under argon. After stirring for 5 h at room temperature, (*S*)-BINOL (0.10 mmol, 28.6 mg) was added to the mixture, which was then stirred for 2 h at room temperature to afford a dark orange colored solution of chiral bis-Ti(IV) oxide (**2c**).

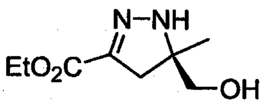
General Procedure

To a catalyst solution prepared as described above were added the corresponding α-substituted acrolein (1.0 mmol) and alkyl diazoacetate (1.5 mmol) dropwise at −40 °C under argon. The reaction mixture was stirred at the same temperature until complete consumption of the aldehyde. The mixture was quenched with ice-cooled aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give the cycloadduct.



(*R*)-Δ^2-5-Formyl-5-methyl-3-pyrazolinecarboxylic acid ethyl ester (Table 3.1, entry 3). Prepared according to the general procedure with methacrolein (1.0 mmol, 82.8 μL) and ethyl diazoacetate (1.5 mmol, 158 μL) over the course of 2 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 1:1) to give the title cycloadduct as a pale yellow oil [54% yield (99.4 mg)].

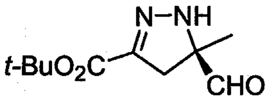
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (1H, s, CHO), 6.42 (1H, s, NH), 4.31 (2H, q, *J* = 7.2 Hz, OCH_2), 3.30 (1H, d, *J* = 17.6 Hz, CH**H**), 2.83 (1H, d, *J* = 17.6 Hz, C**H**H), 1.42 (3H, s, CH_3), 1.35 (3H, t, *J* = 7.2 Hz, OCH_2CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 161.7, 142.4, 73.3, 61.5, 39.5, 19.8, 14.3 ppm; IR (neat) 3318, 2980, 2932, 1701, 1568, 1422, 1375, 1337, 1265, 1111, 818 cm^{-1}; $[\alpha]_D^{27} = -283.9$ (*c* = 1.0, C_6H_6; 90% ee). Full characterization including HRMS and HPLC analysis was carried out after reduction of the aldehyde to the corresponding alcohol. The absolute configuration was deduced from a total synthesis of manzacidin A.



(*R*)-Δ^2-5-Hydroxymethyl-5-methyl-3-pyrazolinecarboxylic acid ethyl ester (7). To a stirred solution of (*R*)-Δ^2-5-formyl-5-methyl-3-pyrazolinecarboxylic acid ethyl ester (0.25 mmol, 46.5 mg) in ethyl acetate was added $NaBH_4$ (0.25 mmol, 10.5 mg) at −78 °C, and the reaction mixture was warmed to 0 °C within 30 min. The reaction solution was then quenched with aqueous NH_4Cl and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 1:3) to give the title alcohol as a colorless oil [73% yield (34.0 mg)].

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time; 25.3 min (minor) and 27.4 min (major)).

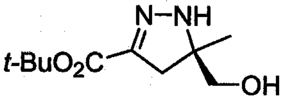
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18 (1H, s, NH), 4.29 (2H, q, J = 7.2 Hz, **OCH_2**), 3.51 (2H, s, **CH_2**OH), 2.98 (1H, d, J = 17.6 Hz, **C**H**H**), 2.67 (1H, d, J = 17.2 Hz, CH**H**), 1.34 (3H, t, J = 7.2 Hz, OCH_2**CH_3**), 1.27 (3H, s, **CH_3**) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 142.5, 68.4, 67.0, 61.1, 39.7, 22.9, 14.3 ppm; IR (neat) 3327, 2980, 2934, 2874, 1697, 1558, 1422, 1377, 1339, 1277, 1117, 1051 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_8H_{14}N_2O_3$: m/z 209.0897 ($[M + Na]^+$), found: m/z 209.0897 ($[M + Na]^+$); $[\alpha]_D^{29}$ = −17.4 (c = 1.0, C_6H_6; 90% ee).



Δ^2-5-Formyl-5-methyl-3-pyrazolinecarboxylic acid *tert*-butyl ester (Table 3.1, entry 6). Prepared according to the general procedure with methacrolein (1.0 mmol, 82.8 μL) and *tert*-butyl diazoacetate (1.5 mmol, 213 mg) over the course of 1 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 1:1) to give the title cycloadduct as a pale yellow oil [52 % yield (109.6 mg)].

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (1H, s, **CHO**), 6.47 (1H, s, **NH**), 3.25 (1H, d, J = 17.6 Hz, **C**H**H**), 2.78 (1H, d, J = 18.0 Hz, CH**H**), 1.54 (9H, s, t-Bu), 1.41 (3H, s, **CH_3**) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 160.9, 143.7, 82.3, 73.1, 39.6, 28.1, 19.7 ppm; IR (neat) 3308, 2978, 2934, 1697, 1572, 1368, 1273, 1250, 1072, 845, 814 cm^{-1}; $[\alpha]_D^{28}$ = −169 (c = 1.0, C_6H_6; 91% ee).

Full characterization including HRMS and HPLC analysis was carried out after reduction of the aldehyde to the corresponding alcohol.

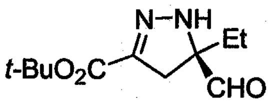


Δ^2-5-Hydroxymethyl-5-methyl-3-pyrazolinecarboxylic acid *t*-butyl ester. To the stirred solution of Δ^2-5-formyl-5-methyl-3-pyrazolinecarboxylic acid *tert*-butyl ester (0.52 mmol, 109.6 mg) in ethyl acetate was added $NaBH_4$ (0.25 mmol, 21.0 mg) at 0 °C and the reaction mixture was stirred for 10 min at the same temperature. The reaction solution was then quenched with aqueous NH_4Cl and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 1:2) to give the title alcohol as a white solid [44% yield (49.2 mg)].

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time; 16.3 min (minor) and

19.0 min (major)).

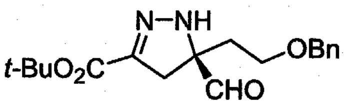
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (1H, s, NH), 3.50 (2H, s, CH_2OH), 2.98 (1H, d, J = 17.6 Hz, CHH), 2.64 (1H, d, J = 17.6 Hz, CHH), 1.54 (9H, s, *t*-Bu), 1.25 (3H, s, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 144.0, 81.8, 68.1, 66.9, 39.8, 28.2, 22.9 ppm; IR (neat) 3325, 2976, 2932, 1694, 1562, 1368, 1281, 1250, 1123, 1051, 843, 812, 750 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{10}H_{18}N_2O_3$: *m/z* 237.1210 ([M + Na]$^+$), found: *m/z* 237.1211 ([M + Na]$^+$); $[\alpha]_D^{29}$ = –9.4 (c = 1.0, C_6H_6; 91% ee).



Δ^2-5-Formyl-5-ethyl-3-pyrazolinecarboxylic acid *tert*-butyl ester (Table 3.2, entry 3). Prepared according to the general procedure with 2-ethylacrolein (1.0 mmol, 84.1 mg) and *tert*-butyl diazoacetate (1.5 mmol, 213 mg) over the course of 3 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/diethyl ether = 1:1) to give the title cycloadduct as a pale yellow oil [63% yield (157.2 mg)].

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OJ-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time; 17.7 min (major) and 19.4 min (minor)).

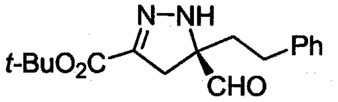
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (1H, s, CHO), 6.48 (1H, s, NH), 3.22 (1H, d, J = 18.0 Hz, CHH), 2.83 (1H, d, J = 18.0 Hz, CHH), 1.83 (2H, m, CCH_2CH_3), 1.53 (9H, s, *t*-Bu), 0.93 (3H, t, J = 7.2 Hz, CCH_2CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 161.0, 143.9, 82.3, 76.7, 37.0, 28.2, 26.6, 8.1 ppm; IR (neat) 3316, 2976, 2936, 1697, 1570, 1458, 1416, 1368, 1258, 1128, 843, 812, 750, 696 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{11}H_{18}N_2O_3$: *m/z* 249.1210 ([M + Na]$^+$), found: *m/z* 249.1209 ([M + Na]$^+$); $[\alpha]_D^{25}$ = –151.6 (c = 1.0, C_6H_6; 83% ee).



Δ^2-5-Formyl-5-(2-benzyloxyethyl)-3-pyrazolinecarboxylic acid *tert*-butyl ester (Table 3.2, entry 5). Prepared according to the general procedure with 2-(2-benzyloxyethyl)acrolein (1.0 mmol, 190 mg) and *tert*-butyl diazoacetate (1.5 mmol, 213 mg) over the course of 1 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/diethyl ether = 1:1) to give the title cycloadduct as a pale yellow oil [81% yield (270.5 mg)].

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol = 10:1, flow rate = 1.0 mL/min, retention time; 15.5 min (minor) and 17.2 min (major)).

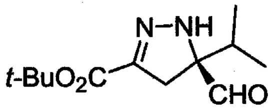
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.55 (1H, s, CHO), 7.26-7.37 (5H, m, ArH), 6.85 (1H, s, NH), 4.42 (2H, app dd, *J* = 11.6, 16.8 Hz, $PhCH_2$), 3.57 (2H, m, **$BnOCH_2$**), 3.18 (1H, d, *J* = 18.0 Hz, C**H**H), 2.82 (1H, d, *J* = 18.0 Hz, CH**H**), 2.19 (1H, m, $BnOCH_2C$**H**H), 2.10 (1H, m, $BnOCH_2CH$**H**), 1.52 (9H, s, *t*-Bu) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 161.0, 143.4, 137.2, 128.4, 127.8, 127.7, 82.2, 75.3, 73.4, 65.8, 39.4, 35.1, 28.2 ppm; IR (neat) 3327, 2978, 2930, 2866, 1724, 1697, 1576, 1368, 1256, 1125, 845, 810, 746, 698 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{18}H_{24}N_2O_4$: *m/z* 355.1628 ([M + Na]$^+$), found: *m/z* 355.1620 ([M + Na]$^+$); $[\alpha]_D^{29}$ = –87.0 (*c* = 1.0, C_6H_6; 80% ee).



Δ^2-5-Formyl-5-(2-phenylethyl)-3-pyrazolinecarboxylic acid *tert*-butyl ester (Table 3.2, entry 6). Prepared according to the general procedure with 2-(2-phenylethyl)acrolein (1.0 mmol, 160.2 mg) and *tert*-butyl diazoacetate (1.5 mmol, 213 mg) over the course of 4 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/diethyl ether = 1:1) to give the title cycloadduct as a pale yellow oil [63% yield (189.9 mg)].

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 20:1, flow rate = 1.0 mL/min, retention time; 29.8 min (minor) and 47.7 min (major)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (1H, s, CHO), 7.14-7.31 (5H, m, Ar**H**), 6.53 (1H, s, NH), 3.26 (1H, d, *J* = 18.0 Hz, C**H**H), 2.88 (1H, d, *J* = 18.0 Hz, CH**H**), 2.62 (2H, m, Ph**CH_2**), 2.12 (2H, m, $PhCH_2$**CH_2**), 1.53 (9H, s, *t*-Bu) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 160.9, 143.8, 140.2, 128.6, 128.1, 126.4, 82.3, 76.1, 37.8, 35.7, 30.2, 28.2 ppm; IR (neat) 3318, 2976, 2930, 1703, 1572, 1447, 1364, 1260, 1126, 839, 748, 700 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{17}H_{22}N_2O_3$: *m/z* 325.1523 ([M + Na]$^+$), found: *m/z* 325.1522 ([M + Na]$^+$); $[\alpha]_D^{27}$ = –85.8 (*c* = 1.0, C_6H_6; 82% ee).

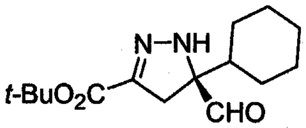


Δ^2-5-Formyl-5-isopropyl-3-pyrazolinecarboxylic acid *tert*-butyl ester (Table 3.2, entry 7). Prepared according to the general procedure with 2-isopropylacrolein (1.0 mmol, 98.1 mg) and *tert*-butyl diazoacetate (1.5 mmol, 213 mg) over the course of 3 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/diethyl ether = 3:1 to 1:1) to give the title cycloadduct as a pale yellow oil [82% yield (209.1 mg)].

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time; 14.4 min (minor) and 16.1 min (major)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.55 (1H, s, CHO), 6.56 (1H, s, NH), 3.21 (1H, d, *J* =

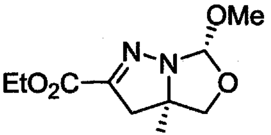
18.4 Hz, CH**H**), 2.88 (1H, d, J = 18.0 Hz, C**H**H), 2.14 (1H, m, C**H**(CH$_3$)$_2$), 1.53 (9H, s, *t*-Bu), 0.98 (6H, app dd, J = 6.8, 11.2 Hz, CH(C**H**$_3$)$_2$) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ 200.0, 161.1, 143.7, 82.2, 79.4, 34.6, 32.0, 28.2, 17.6, 17.1 ppm; IR (neat) 3302, 2972, 1724, 1699, 1568, 1368, 1267, 1258, 1138, 843 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{12}H_{20}N_2O_3$: *m/z* 263.1366 ([M + Na]$^+$), found: *m/z* 263.1369 ([M + Na]$^+$); $[\alpha]^{27}_{D}$ = –213.2 (c = 1.0, C_6H_6; 92% ee).



Δ^2-5-Formyl-5-cyclohexyl-3-pyrazolinecarboxylic acid *tert*-butyl ester (Table 3.2, entry 8). Prepared according to the general procedure with 2-cyclohexylacrolein (1.0 mmol, 138 mg) and *tert*-butyl diazoacetate (1.5 mmol, 213 mg) over the course of 5 h. The crude material was purified by column chromatography on silica gel (eluting with hexane/diethyl ether = 2:1 to 3:2) to give the title cycloadduct as a pale yellow oil [77% yield (215.9 mg)].

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 20:1, flow rate = 0.5 mL/min, retention time; 23.0 min (minor) and 31.3 min (major)).

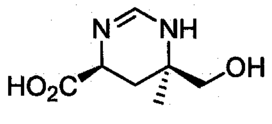
^{1}H NMR (400 MHz, CDCl$_3$) δ 9.52 (1H, s, CHO), 6.55 (1H, s, NH), 3.19 (1H, d, J = 18.0 Hz, CH**H**), 2.90 (1H, d, J = 18.0 Hz, C**H**H), 1.69-1.83 (5H, m, Cy), 1.53 (9H, s, *t*-Bu), 1.00-1.26 (6H, m, Cy) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ 200.3, 161.1, 143.8, 82.1, 79.3, 42.2, 34.8, 28.2, 27.9, 27.4, 26.3, 26.1, 26.0 ppm; IR (neat) 3310, 2928, 2857, 1713, 1570, 1447, 1364, 1260, 1125, 835, 743 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{15}H_{24}N_2O_3$: *m/z* 303.1679 ([M + Na]$^+$), found: *m/z* 303.1679 ([M + Na]$^+$); $[\alpha]^{28}_{D}$ = –143 (c = 1.0, C_6H_6; 94% ee).



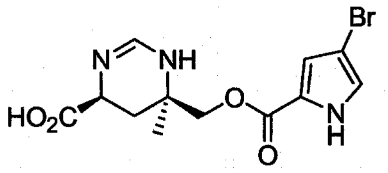
(3a*R*,6*R*)-6-Methoxy-3a-methyl-3a,4-dihydro-3H-pyrazolo[1,5-c]oxazole-2-carboxylic acid ethyl ester (8). To a stirred solution of (*R*)-Δ^2-5-hydroxymethyl-5-methyl-3-pyrazolinecarboxylic acid ethyl ester (0.18 mmol, 33.5 mg, 90% ee) in methyl orthoformate (1.0 mL) was added a catalytic amount of pyridinium *p*-toluenesulfonate. After stirring for 1 h at room temperature, the reaction mixture was treated with aqueous NaHCO$_3$ and the organic phase was extracted with ethyl acetate. The residue was concentrated under reduced pressure and purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 2:1) to give the title bicyclic compound **6** as a colorless oil [89% yield (36.4 mg)].

^{1}H NMR (400 MHz, CDCl$_3$) δ 5.95 (1H, s, CH$_3$OC**H**), 4.33 (2H, m, OC**H**$_2$CH$_3$), 3.94

(1H, d, J = 8.4 Hz, OCHH), 3.81 (1H, J = 8.4 Hz, OCH**H**), 3.44 (3H, s, OC**H**$_3$), 3.18 (1H, d, J = 18.0 Hz, N=CC**H**H), 2.90 (1H, d, J = 18.0 Hz, N=CCH**H**), 1.59 (3H, s, CC**H**$_3$), 1.36 (3H, t, 7.2 Hz, OCH$_2$C**H**$_3$) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ 161.5, 148.2, 112.9, 76.5, 69.9, 61.8, 53.8, 45.5, 25.9, 14.3 ppm; IR (neat) 2974, 2931, 1711, 1585, 1450, 1290, 1242, 1157, 1092, 1009 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{10}H_{16}N_2O_4$: *m/z* 229.1183 ([M + H]$^+$), found: *m/z* 229.1184 ([M + H]$^+$); $[\alpha]^{25}_{D}$ = –467.0 (c = 1.0, CHCl$_3$).



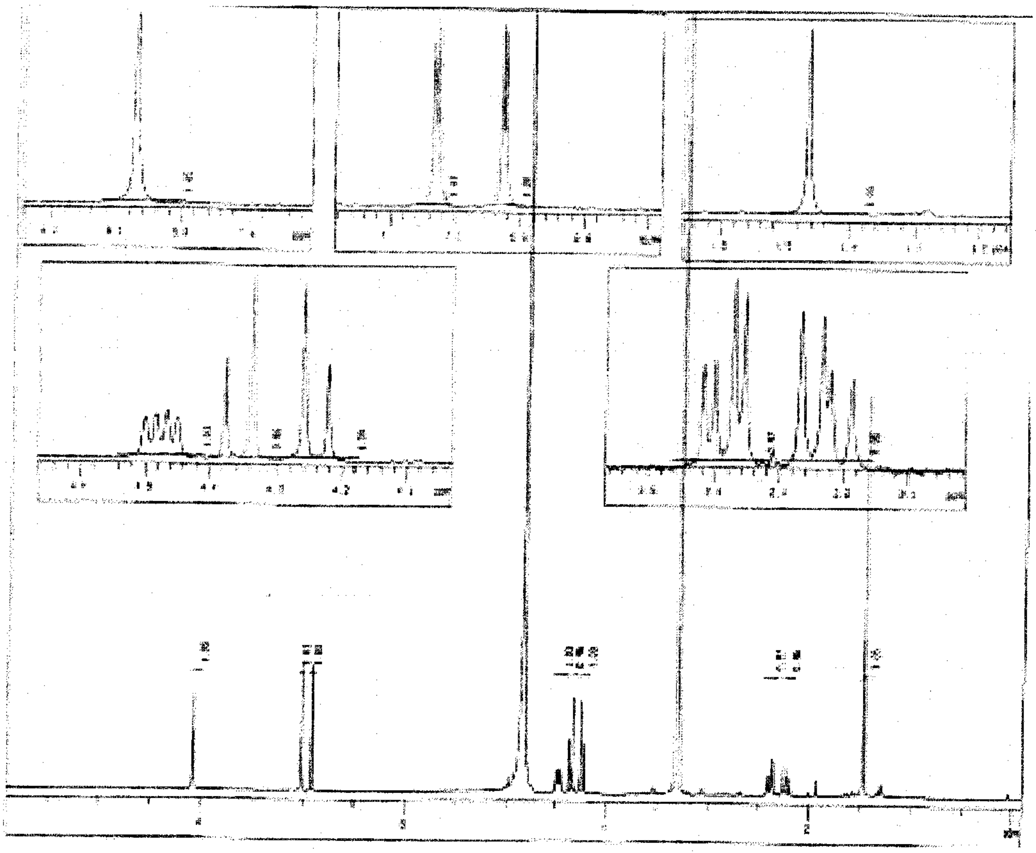
(4*S*,6*R*)-6-Hydroxymethyl-6-methyl-1,4,5,6-tetrahydro-pyrimidine-4-carboxylic acid (13). To a solution of **6** (0.159 mmol, 36.4 mg) in isopropanol/H$_2$O (1.5 mL/0.5 mL) was added Raney nickel (50 mg, purchased from Aldrich). Hydrogen gas (balloon) was then charged to the reaction flask, and the mixture was stirred at 80 °C for 24 h. The reaction mixture was filtered, and the residue was washed with methanol. After concentration *in vacuo*, the residue was passed through column chromatography on Dowex 50W × 8 (100~200 mesh, H$^+$ form, eluting with H$_2$O then 1N aqueous NH$_3$) to give the title compound 8 as a mixture of diastereomers (85:15), which was used for the next step without further purification.

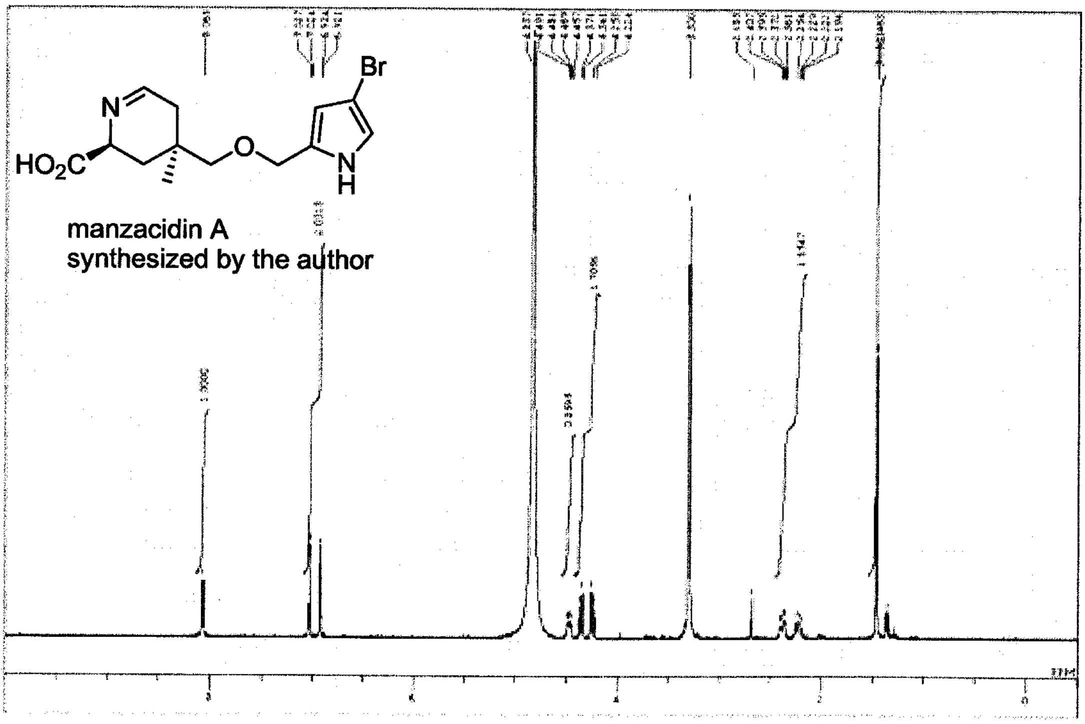


Manzacidin A (1). Prepared according to the literature procedure. The crude product was purified by reverse phase HPLC (cosmosil 5C18-AR-II, eluting with H$_2$O/CH$_3$CN/TFA = 75:25:0.1) to give pure manzacidin A [50% yield in 2 steps (27.4 mg)].

^{1}H NMR (400 MHz, CD$_3$OD) δ 8.07 (1H, s, N=C**H**-NH), 7.03 (1H, d, J = 1.2 Hz, BrCC**H**), 6.92 (1H, d, J = 1.2 Hz, BrCC**H**), 4.47 (1H, dd, J = 5.2, 10.0 Hz, NC**H**CO$_2$H), 4.36 (1H, d, J = 12.0 Hz, OC**H**H), 4.24 (1H, d, J = 11.6 Hz, OCH**H**), 2.38 (1H, dd, J = 5.2, 14.0 Hz, C**H**HCHCO$_2$), 2.22 (1H, dd, J = 10.4, 14.0 Hz, CH**H**CHCO$_2$), 1.46 (3H, s, C**H**$_3$) ppm; ^{13}C NMR (100 MHz, CD$_3$OD) δ 172.8, 160.4, 151.9, 125.2, 123.1, 118.4, 98.1, 68.7, 53.8, 31.2, 24.1 ppm (one ^{13}C peak remains unidentified, which overlapped with the solvent peak)[17a]; IR (neat) 3198, 2982, 1670, 1589, 1456, 1400, 1387, 1188, 1138, 1078 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{12}H_{14}BrN_3O_4$: *m/z* 344.0240 ([M + H]$^+$) and 346.0221 ([M + H]$^+$), found: *m/z* 344.0231 ([M + H]$^+$) and 346.0223 ([M + H]$^+$); $[\alpha]^{29}_{D}$ = –23.0 (c = 0.50, CH$_3$OH).

Manzacidin A: Synthesized by Ohfune's group





Publication List

1. Catalytic, Enantioselective Hetero-Diels-Alder Reaction with Novel, Chiral Bis-Titanium(IV) Catalyst
   Satoshi Kii, Takuya Hashimoto, and Keiji Maruoka *Synlett* **2002**, 6, 931-932.

2. Bis(((*S*)-binaphthoxy)(isopropoxy)titanium) Oxide as a μ-Oxo Type Chiral Lewis Acid: Application to Catalytic Asymmetric Allylation of Aldehydes
   Hideo Hanawa, Takuya Hashimoto, and Keiji Maruoka *J. Am. Chem. Soc.* **2003**, *125*, 1708-1709.

3. Substituent Effect of Binaphthyl-Modified Sprio-Type Chiral Phase-Transfer Catalysts
   Takuya Hashimoto, and Keiji Maruoka *Tetrahedron Lett.* **2003**, *44*, 3313-3316.

4. Symmetrical 4,4',6,6'-Tetraphenylbinaphthyl-substituted Ammonium Bromide as a New, Chiral Phase-Transfer Catalyst
   Takuya Hashimoto, Yohei Tanaka, and Keiji Maruoka *Tetrahedron: Asymmetry* **2003**, *14*, 1599-1602.

5. Catalytic Asymmetric Allylation of Aldehydes and Related Reactions with Bis(((*S*)-binaphthoxy)(isopropoxy)titanium) Oxide as a μ-Oxo Type Chiral Lewis Acid
   Hideo Hanawa, Daisuke Uraguchi, Shunsuke Konishi, Takuya Hashimoto, and Keiji Maruoka *Chem. Eur. J.* **2003**, *9*, 4405-4413.

6. Asymmetric 1,3-Dipolar Cycloaddition Reaction of Nitrones and Acrolein with a Bis-Titanium Catalyst as Chiral Lewis Acid
   Taichi Kano, Takuya Hashimoto, and Keiji Maruoka *J. Am. Chem. Soc.* **2005**, *127*, 11926-11927.

7. Enantioselective 1,3-Dipolar Cycloaddition Reaction between Diazoacetates and α-Substituted Acroleins: Total Synthesis of Manzacidin A
   Taichi Kano, Takuya Hashimoto, and Keiji Maruoka *J. Am. Chem. Soc.* **2006**, *128*, 2174-2175.

Acknowledgment

This research project was accomplished at the Department of Chemistry, Graduate School of Science, Kyoto University with the invaluable contributions made by many people. First and foremost, I would like to thank Professor Keiji Maruoka for supporting this research and for providing an environment to make it possible to purse the scientific interest freely and deeply. In addition, I would also like to thank to Professor Atsuhiro Osuka, Professor Norihito Tokitoh and Professor Tamio Hayashi for serving on my Dissertation committee.

I am thankful to Dr. Taichi Kano and Dr. Takashi Ooi, both of whom provided lucid and valuable insights into my work and contributed to its development in numerous ways.

Among all of Maruoka group members, I would like to show my best gratitude for Dr. Satoshi Kii, who had trained me to be a good chemist when I joined Maruoka's group. I am also indebted to my labmates I used to have, Dr. Makoto Takahashi, Dr. Tomoya Miura, and Dr. Hideo Hanawa. I learned so many things from their remarkable aptitudes for chemistry. I firmly believe that the stimulating colleagues are quite important to achieve excellent works and in that point, I am grateful to Mika Taniguchi, Yukitaka Uematsu, and Shingo Fujioka. Needless to say, I would like to thank all of the other Maruoka group members, including some visiting associates, especially, Turet Laurent and Osamu Tokuda.

I would like to express special appreciation to Professor Erick M. Carreira, who kindly gave me an exciting opportunity to learn his elegant chemistry at ETH Zurich. Also thanks to his group members, especially, Takumi Watanabe, Junichi Yasuoka, Takeyuki Suzuki, Takashi Ichikawa, Thomas Knöpfel, and Christian Defieber for their warm hospitality and friendship.

Professor Jérôme Lacour and his group members are also acknowledged, who offered me a wonderful collaboration, and gave me an chance to have a talk in his group seminar at Genève University during my stay in Switzerland.

I am grateful to the fellowship of the Japan Society for the Promotion of Science for Young Scientists.

Last but not least, I would like to thank my grandma Mineko, my parents Katsuyuki and Harumi, my brother Takashi, and my sister Yukie for their love and support.

-Special Thanks to Saki Takada-