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# CORNERSTONE WORKS FOR CATALYTIC 1,3-DIPOLAR CYCLOADDITION REACTIONS

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**Abstract** – This review covers the following subjects: (1) The chemistry of *N*-metalated azomethine ylide as a new 1,3-dipole containing a metal atom is studied. This 1,3-dipole, generated from (*N*-alkylideneamino)alkanoates upon treatment with a Lewis acid and amine base, undergoes rapid 1,3-dipolar cycloadditions toward electron-deficient alkenes. Especially, α,β-unsaturated carbonyl substrates show high rate acceleration to give pyrrolidine-2,4-dicarboxylates in a highly regio- and *endo*-selective manner. (2) This 1,3-dipolar cycloaddition reaction of (*N*-alkylideneamino)acetate can be switched into *anti*-selective Michael addition reaction by modification of substrate structures as well as reaction conditions. (3) Two types of heterocyclic chiral auxiliaries are demonstrated for the asymmetric 1,3-dipolar cycloadditions. One types are attached at the β-position of α,β-unsaturated esters. The resulting chiral α,β-unsaturated esters are successfully applied to the stereoselective asymmetric cycloadditions of *N*-metalated azomethine ylides. The other types include 4-benzyl-2,2,5,5-tetramethyloxazolidine-3-acrylamides which are based on the conformational control of the acrylamide reaction site and that of steric shielding of 4-benzyl amoiety. These are applied to the absolutely asymmetric nitrile oxide cycloadditions. (4) The nitrone cycloadditions to electron-deficient alkenes is attained in the presence of a Lewis acid catalyst. This provides the first catalytic stereo control of 1,3-dipolar cycloadditions. (5) The extremly effective rate enhancement of nitrile oxide 1,3-dipolar cycloadditions to the magnesium alkoxides of allylic alcohols. Maximum rate enhancement observed is 16,000 fold rate acceleration of the uncatalyzed reaction. This method offers the first successful rate acceleration in nitrile oxide 1,3-dipolar cycloadditions. (6) Use of magnesium alkoxide of allylic alcohols is also highly effectve in nitrone 1,3-dipolar cycloadditons, resulting in high stereo- and regioselectivities. (7) Catalytic enantioselective 1,3-dipolar cycloadditions are achieved by use of nitrones, nitronates, diazomethane, and nitrile oxides in the presence of tolerant chiral catalysts based on our *R,R*-DBFOX/Ph ligand.

**CONTENTS**



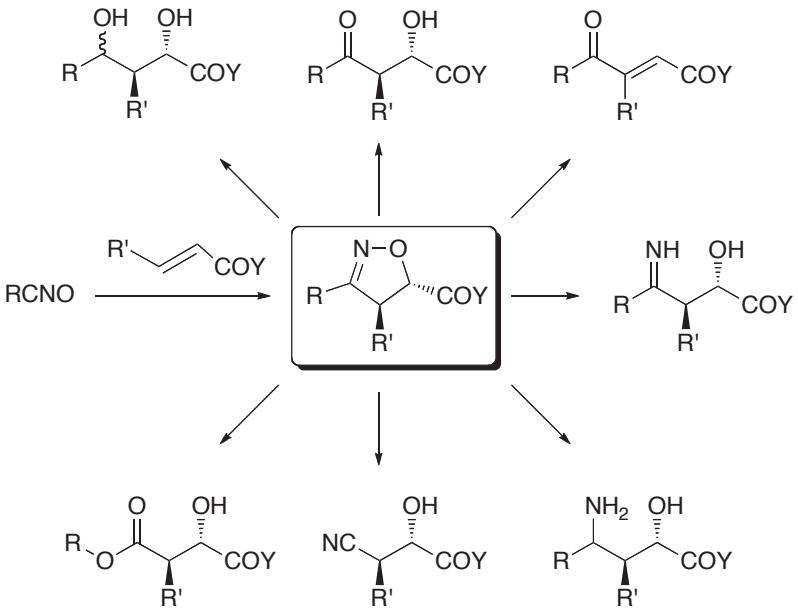
## 1. INTRODUCTION

1,3-Dipolar cycloaddition reaction includes interaction between 1,3-dipoles and unsaturated dipolarophiles. 1,3-Dipoles are 4π electron component consisting of onium-stabilized anionic species such as ylide, imine, oxide, and sulfide. Electron charges are formally located on the terminal 1,3-atoms so that it can undergo bond formation on these atoms. 1,3-Dipoles have mostly electron-rich reactive intermediates, but some stabilized 1,3-dipoles such as nitrones and some of nitrile oxides are isolable. Dipolarophiles are compounds having unsaturated bond such as alkenes, alkynes, and carbonyl compounds. Since dipolarophiles are activated by attachment with electron-withdrawing substituents, these are called as activated dipolarophiles. Five-membered heterocyclic compounds are the products obtained in 1,3-dipolar cycloaddition reactions.[1]

1,3-Dipolar cycloaddition reaction provides one of the most powerful synthetic reactions. Ring structures of the resulting heterocycles produced depend upon the combination of 1,3-dipoles and dipolarophiles employed. Wide variation of heterocyclic ring arrangements can be constructed through this reaction.

This is a major reason for the importantness of 1,3-dipolar cycloadditions. Usually some functional groups are needed to activate, or sometimes to stabilize, 1,3-dipoles and dipolarophiles and these functional groups are incoorporated in the ring structures of the cycloaddition products. Especially useful is the high stereospecificity of the reactions. Stereochemical relationship of 1,3-dipoles and alkene dipolarophiles can be stereospecifically maintained in the structure of cycloaddition products. This means that both substituents and functional groups can be arranged on the heterocyclic skeleton in a stereochemically defined manner.

As a result, the heterocyclic compouns produced in 1,3-dipolar cycloaddition reactions often have stereospecific structures with some functional groups. In addition, heterocyclic structure itself is regarded as functionalized building blocks. This is another reason for the high synthetic utility of 1,3-dipolar cycloadditions. Synthetic versatility of nitrile oxide cycloadditions to functionalized alkenes is shown below. 4,5-*trans*-2-Oxazoline is the cycloaddition product from *E*-alkene.




Through reductive cleavage of the nitrogen-oxygen bond of 2-oxazoline under hydrolytic conditions produces *anti*-isomer of β-hydroxy ketone, known as aldol. This indicates, *anti*-selective synthesis of aldols can be achieved through 1,3-dipolar cycloaddition reaction between nitrile oxides and *E*-alkenes. This method provides a stereoselective aldol synthesis based on a different concept. Other functional group transformations are also possible as shown above. It is apparent that the resulting derivatives are multi-functionalized and stereochemically defined synthetic blocks. A single step synthesis through 1,3-dipolar cycloaddition reactions afford 2-isoxazolines in a stereospecific manner. The heterocycle derivatives constructed by the 1,3-dipolar cycloaddition methodology provide complex functionalized framework of organic molecules in which many functional groups are masked in a protected form. If additional selectivity is given in 1,3-dipolar cycloadditions to alkenes, synthetic potential of this methodology should be much enhanced. This was the other point of our ideas. Probably "catalysis or mediation" of 1,3-dipolar cycloaddition reactions by the aid of external reagents was our answer.[2]

This review summarizes the researches, done by the group of Professor Shuji kanemasa in Kyushu University for these twenty years. The research object is to open a new synthetic methodology based on

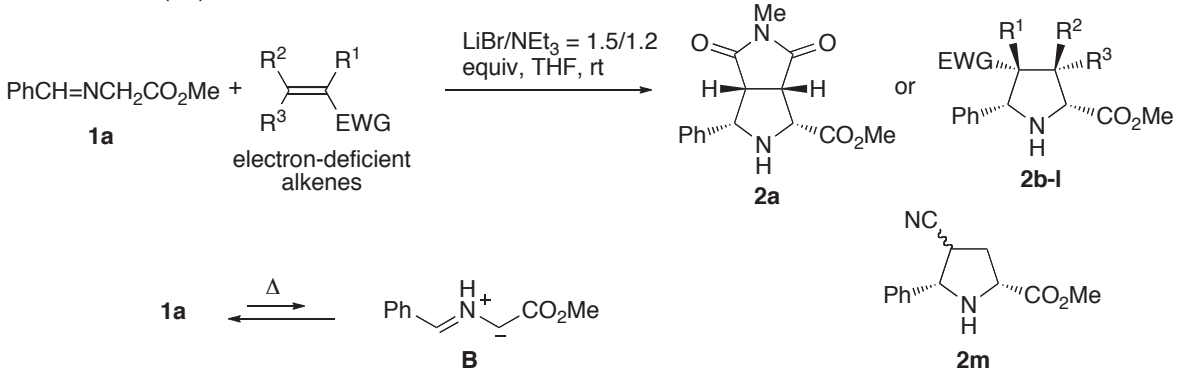
the catalytic 1,3-dipolar cycloaddition reactions. When he started this project, examples of catalytic stereo- and regiocontrol of 1,3-dipolar cycloadditions by use of external reagents are extremely rare. Use of a metal catalyst in 1,3-dipolar cycloaddition reactions was regarded as "a taboo" at that time.

## 2. AZOMETHINE YLIDES

### 2.1 *N*-Metalated azomethine ylides and cycloadditions

**Thermal Tautomerization of Imine Esters.**[3] Thermal tautomerization of imines of α-amino esters or nitriles, developed by Grigg[4] and Tsuge,[5] are known to provide a simple access to azomethine ylide 1,3-dipoles. By this process the *N*-unsubstituted azomethine ylides of ester- or cyano-stabilized types can be generated. The resulting 1,3-dipoles undergo stereoselective cycloadditions to highly activated cyclic dipolarophiles such as maleimides and maleic anhydride leading to the exclusive formation of *endo*-cycloadducts of the *E*,*E*-ylides (or *syn*-ylides). However, their cycloadditions to acyclic alkenes are not stereoselective. Although the cycloadditions to acrylates proceed in a regioselective manner, the *endo*-selectivity and/or the *E,E* specificity with respect to dipoles are poor. Furthermore reactivity, regio- and stereoselectivities, and stereospecificity of these azomethine ylide dipoles to other unsymmetrically substituted alkenes remained unsolved. We discovered that the treatment of *N*-(1-cyanoalkyl) imines with a metallic base such as LDA, *n*-BuLi, or EtMgBr generated highly reactive intermediates, which we believe are *N*-metalated azomethine ylides.[6] The cycloadditions of the *N*-metalated ylides to alkenes take place in a perfectly regio- and stereoselective manner to furnish 4,5-*cis*-l-pyrrolines after the elimination of the cyano moiety.

**Scheme 2-01** LiBr/$NEt_3$-induced 1,3-dipolar cycloadditions between methyl (*N*-benzylideneamino)acetate (**1a**) and electron-deficient alkenes




| Alkenes | Products | EWG | $R^1$ | $R^2$ | $R^3$ | Yield/% |
|---|---|---|---|---|---|---|
| *N*-methylmaleimide | **2a** | | | | | 45 |
| *N*-methylmaleimide[a] | | | | | | 83 |
| dimethyl maleate | **2b** | $CO_2Me$ | H | H | $CO_2Me$ | 44 |
| dimethyl fumarate | **2c** | $CO_2Me$ | H | $CO_2Me$ | H | 70 |
| methyl acrylate | **2d** | $CO_2Me$ | H | H | H | 82 |
| *t*-butyl acrylate | **2e** | $CO_2Bu$-*t* | H | H | H | 71 |
| methyl crotonate | **2f** | $CO_2Me$ | H | Me | H | 91 |
| methyl cinnamate | **2g** | $CO_2Me$ | H | Ph | H | 77 |
| methyl methacrylate | **2h** | $CO_2Me$ | Me | H | H | 91 |
| 3-buten-2-one | **2i** | COMe | H | H | H | 20 |
| 3-buten-2-one[a] | | | | | | 35 |
| (*E*)-3-penten-2-one | **2j** | COMe | H | Me | H | 77 |
| (*E*)-4-phenyl-3-buten-2-one | **2k** | COMe | H | Ph | H | 59 |
| (*E*)-l-(*p*-tolyl)-3-phenylpropenone | **2l** | $COC_6H_4Me$-*p* | H | Ph | H | 73 |
| acrylonitrile | **2m** | CN | H | H | H | 91[b] |

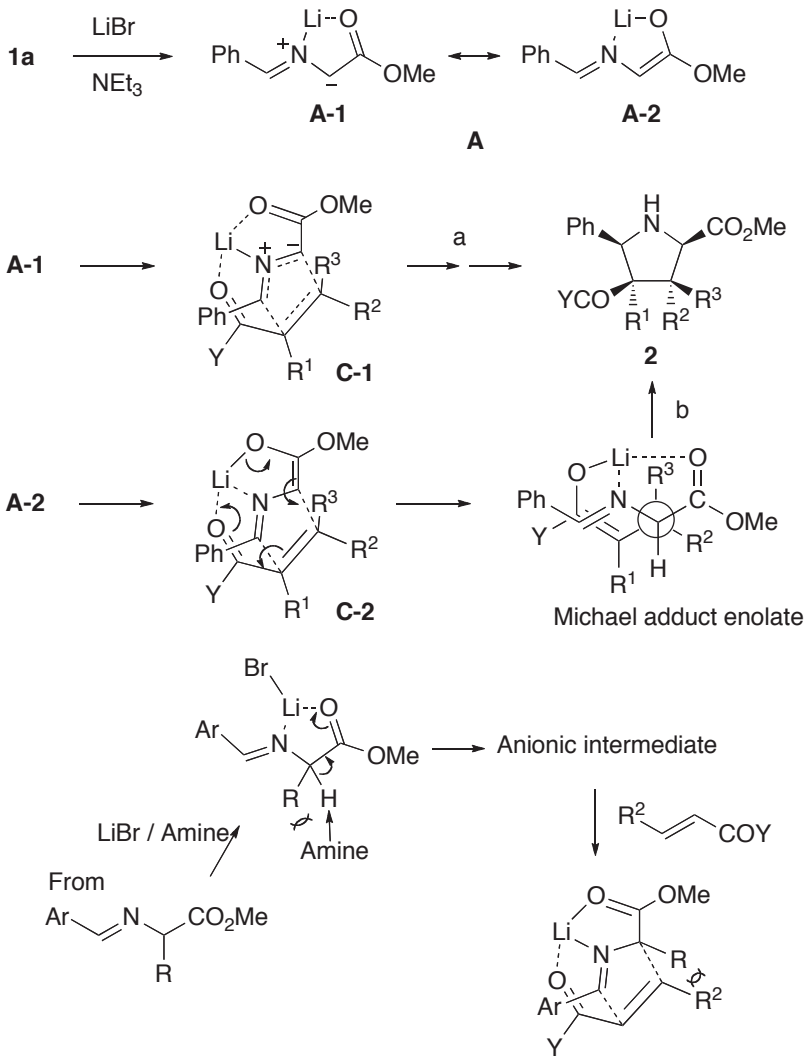
[a]LiBr/NEt3 = 0.1/0.1 equiv. [b]*cis:trans* = 26%/65%.

**Reversible generation of *N*-metalated azomethine ylides.**[3] Generation of ester-stabilized *N*-metalated azomethine ylides by deprotonation of methyl α-(*N*-benzylideneamino)acetate (**1a**) was difficult. Reactions of **1a** with a variety of bases such as potassium alkoxides, Triton B, LDA, *n*-BuLi, NaH, EtMgBr, and EtMgBr plus HN(*i*-Pr), followed by the trapping with methyl acrylate or *N*-methylmaleimide in dry THF at -78 °C, gave a complex reaction mixtures or poor yields of the expected cycloadducts. Presumably, lack of stability of alkene dipolarophiles under the reaction conditions would be a major reason for the failure. So, we examined to use a weaker base which is basic enough to deprotonate imine ester **1a** but does not initiate the undesired polymerization. Based on our previous successful experience of olefination using base-labile 2-oxoalkylphosphonates,[7] we examined a combination use of metal halide and tertiary amine. To our delight, the treatment of **1a** with "lithium bromide and triethylamine" in THF at room temperature successfully generated the anionic intermediate **A** which was captured by *N*-methylmaleimide leading to an excellent yield of the expected cycloadduct **2a** as a single isomer (Scheme 2-01).

Scheme 2-01 summarizes the reactions of **1a** with a variety of electron-deficient alkenes. Symmetrically and unsymmetrically substituted alkene esters and ketones all reacted with **1a** in a highly regio- and stereoselective manner to produce cycloadducts **2a-l** in excellent yields. The reactions were carried out in THF at room temperature by using a slight excess of lithium bromide (1.5 equiv) and triethylamine (1.2 equiv) to an equimolar mixture of imine ester **1a** and an alkene dipolarophile. The reaction rates seem to be independent upon reactivity of the alkenes used, indicating that the intermediate species are captured immediately after they are generated. In the reactions with *N*-methylmaleimide and 3-buten-2-one, which are very sensitive to base-catalyzed polymerization, use of catalytic amounts of lithium bromide and triethylamine (each 0.1 equiv) was effective.

On the basis of the spectral data, the cycloadduct **2a** was determined to be an *endo*-cycloadduct of the *syn*-form of lithiated anionic intermediate **A**. Exclusive *syn*- and *endo*-selectivity achieved is presumably a result of the lithium chelation involved in the two possible approaches (routes a and b) as illustrated in Scheme 2-02: (1) The concerted cycloaddition of *N*-lithiated azomethine ylide **A-1** via proposed transition structure **C-1** (route a) and (2) The stepwise reactions including Michael adduct enolate intermediate **C-2** (Y = OMe, $R^1 = R^2 = R^3 = H$) and subsequent cyclization steps of lithium enolate **A-2** (route b). However, discrimination between **A-1** and **A-2**, and hence **C-1** and **C-2**, is not possible thus far.

**Scheme 2-02** Two possible reacting intermediates **A-1** and **A-2** as well as steric congestion by the α-substituent R




High contribution of the lithium chelation is evidenced with the following two examples:

(1) The reaction of **1a** with acrylonitrile under similar conditions is highly *syn*-selective but poor in *endo*-selectivity. A mixture of two stereoisomeric cycloadducts **2m** was obtained (ds = 2:5 in Scheme 2-01).

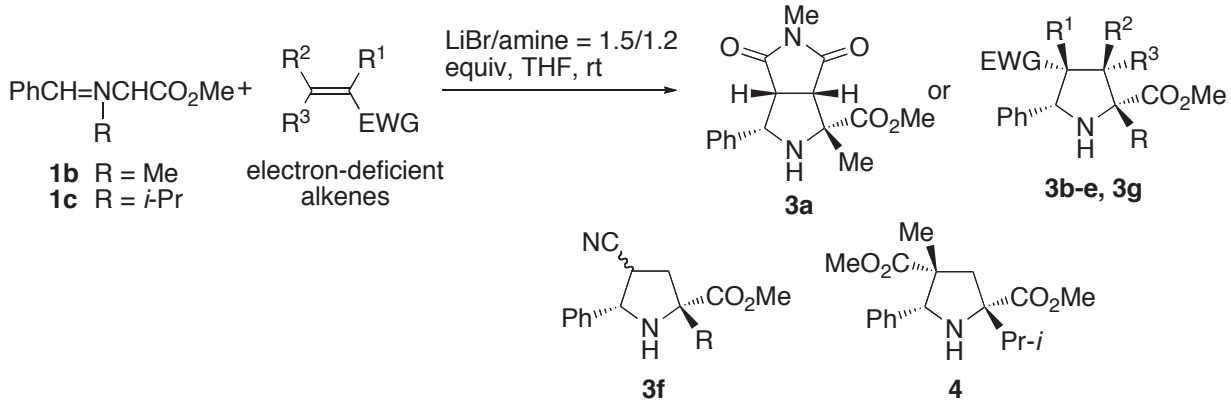
(2) Reaction of **1a** with methyl acrylate in the absence of lithium bromide was very poor in *syn*-selectivity. A mixture of two *endo*-cycloadducts **2d** (1:1) was produced.

Although such chelation control is structurally impossible in the reaction with *N*-methylmaleimide, a high *endo*-selection was still observed to give **2a**. The high selectivity was the same as that observed in the reaction of *N*-protonated azomethine ylide **B** with the maleimide.

α-Substitution of the imine ester **1a** with an alkyl moiety (methyl or isopropyl) makes it difficult for the remaining α-hydrogen to be deprotonated with lithium bromide and triethylamine. In addition, there is presumably some steric repulsion in the cycloaddition step of *N*-metalated azomethine ylide intermediates

bearing α-substituent R between the methyl or isopropyl group and the alkene substituent $R^2$ which is trans to the electron-withdrawing group EWG (EWG = COY, Scheme 2-02). Nonetheless, deprotonation of methyl 2-(*N*-benzylideneamino)propanoate (**1b**) with lithium bromide and triethylamine occured readily at room temperature as shown in Scheme 2-03. The intermediate was trapped with *N*-methylmaleimide, methyl acrylate, methacrylate ($R^2$ = H in all cases, so negligible steric congestion to the α-methyl substituent), to give diastereoselective cycloadducts **3a-c** and **3e,** respectively. The generation of the intermediate is still rate-determining.

**Scheme 2-03** LiBr/amine-induced cycloadditions between methyl 2-(*N*-benzylideneamino)propanoate (**1b**) or methyl 2-(*N*-benzylidene-amino)-3-methylbutanoate (**1c**) and electron-deficient alkenes

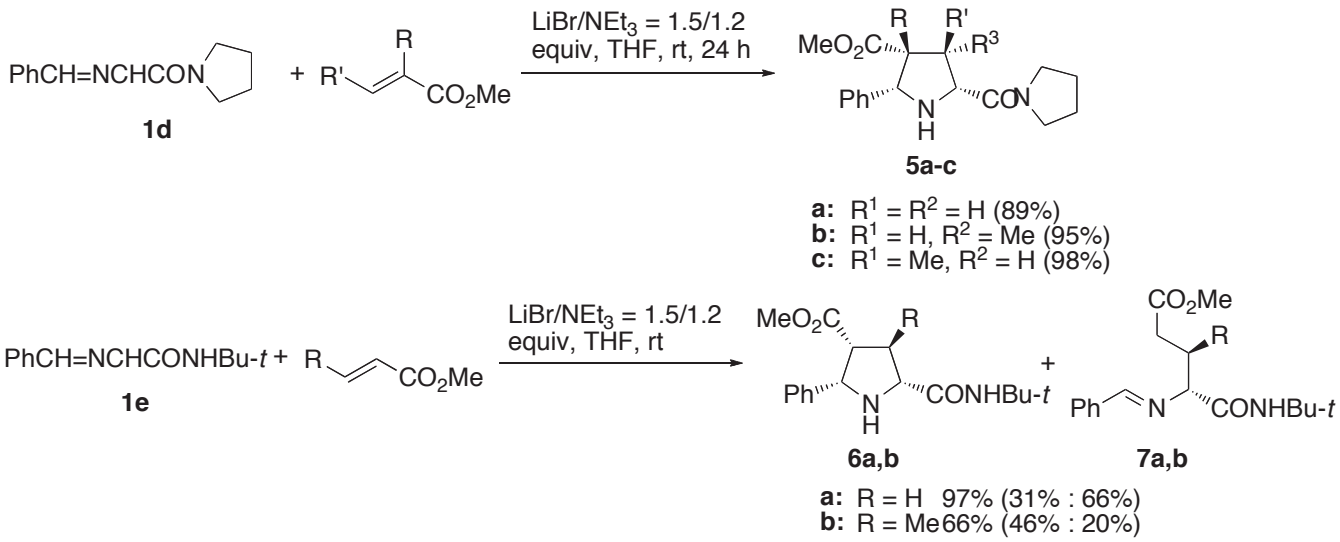



| **1** | Alkenes | Amine/equiv | Products | EWG | $R^1$ | $R^2$ | $R^3$ | Yield/% |
|---|---|---|---|---|---|---|---|---|
| **1b** | *N*-methylmaleimide | NEt, 0.1[a] | **3a** | | | $CO_2Me$ | | 86 |
| | dimethyl fumarate | $NEt_3$ 1.2 | **3b** | $CO_2Me$ | H | H | H | 87 |
| | methyl acrylate | $NEt_3$ 1.2 | **3c** | $CO_2Me$ | H | Me | H | 79 |
| | methyl crotonate | $NEt_3$ 1.2 | **3d** | $CO_2Me$ | H | | H | 33 |
| | methyl crotonate | $NEt_3$ 1.2[b] | | | | | | 50 |
| | methyl crotonate | DBU 1.0 | **3e** | $CO_2Me$ | Me | H | H | 82 |
| | methyl methacrylate | $NEt_3$ 1.2 | **3f** | CN | H | H | H | 81 |
| **1c** | acrylonitrile | $NEt_3$ 1.2 | **3g** | $CO_2Me$ | H | Me | H | 97[c] |
| | methyl crotonate | DBU 1.2 | **4** | $CO_2Me$ | Me | H | H | no reaction |
| | methyl methacrylate | DBU 1.2 | | | | | | 80 |

[a]$LiBr/NEt_3$ = 0.1/0.1 equiv. [b]Under reflux. [c]cis:trans = 25%/72%.

The *endo*-selective cycloaddition of anionic intermediate derived from **1b** to methyl crotonate ($R^2$ = Me) was extremely sluggish. This reaction was not complete under comparable conditions even using lithium iodide or under reflux in THF. However, use of DBU instead of triethylamine gave a satisfactory yield of *endo*-cycloadduct **3d**. The deprotonation and cycloaddition steps would be both sterically hindered, but the deprotonation step was rate-determing in the reaction using lithium bromide and triethylamine. When the *N*-metalated azomethine ylide was generated in a higher concentration with DBU, the cycloaddition reaction smoothly proceeded. On the other hand, the imine **1c** having an isopropyl substituent at the α-position did not react with methyl crotonate even in the presence of lithium bromide and DBU. The intermediate was generated but failed to be trapped with methyl crotonate (Scheme 2-03). Only alkenes bearing no α-substituent ($R^2$ = H) could be involved in the cycloaddition reaction. For example cycloadduct **4** was obtained in 80% yield as a single isomer in the reaction with methyl methacrylate.

**Scheme 2-04** LiBr/$NEt_3$-induced reaction of *N,N*-tetramethylene-2-(benzylideneamino)ethanamide(**1d**) or *N*-*tert*-butyl-2-(benzylideneamino)ethanamide (**ie**) with electron-deficient alkenes



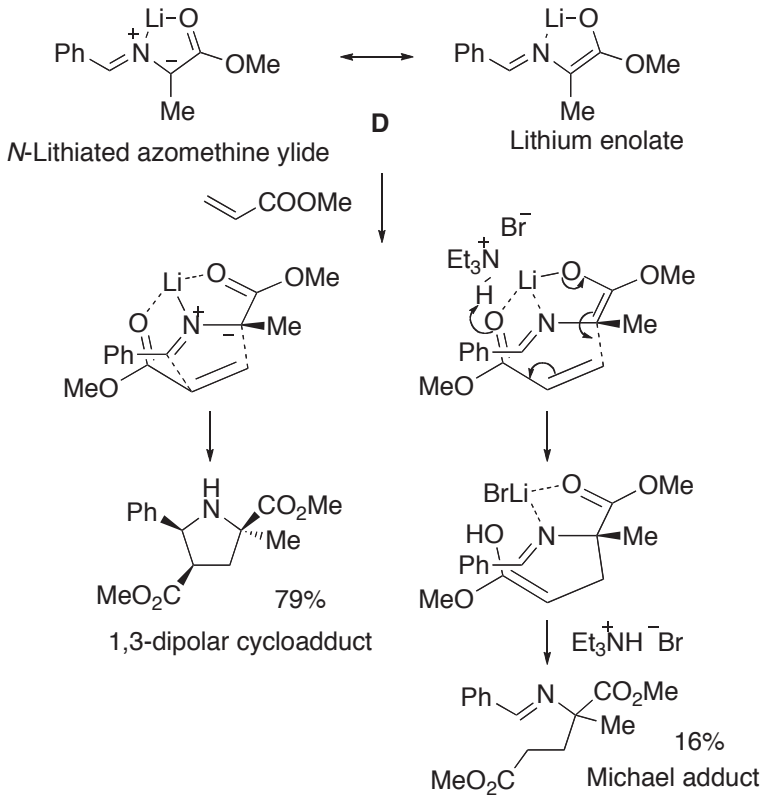

The imine of glycine amide, *N,N*-tetramethylene-2-(*N*-benzylideneamino)ethanamide (**1d**), underwent similar *syn*- and *endo*-selective cycloadditions to methyl acrylate, methacrylate, and crotonate to give **5a-c** in excellent yields, respectively (Scheme 2-04). On the other hand, the imine amide **1e** derived from a secondary amide produced a mixture of cycloadducts **6a,b** and the Michael adducts **7a,b**. Lithium chelation presumably exists in the latter amide case also, but the structure of reacting species is not clear.

*N*-Metalated azomethine ylides provide the first example of 1,3-dipolar intermediates containing a metal atom. This new ylide has the electronic structure of highly stabilized metal enolate derived from (*N*-alkylideneamino)acetates. This is why *N*-metalated azomethine ylides can be readily generated from (*N*-alkylideneamino)acetates on treatment with a Lewis acid and weak amine base such as triethylamine. Lithium bromide was used in tetrahydrofuran as reaction solvent, but other Lewis acids can be also utilized. Use of a stronger amine base such as DBU gives the ylide in higher concentration. The resulting 1,3-dipoles show high reactivity toward electron-deficient alkenes since they are strong nucleophiles. Especially high reactivity and stereoselectivity are observed when α,β-unsaturated carbonyl compounds are utilized in the reaction. The chelation transition structure is the origin of such high reactivity and stereoselectivity.

**Cycloaddition vs Michael addition.**[8] The reaction of methyl 2-(*N*-benzylideneamino)propanoate with methyl acrylate was further investigated under various reaction conditions for the in situ generation of *N*-metalated azometine ylides using lithium bromide/triethylamine.[3] Competitive production of 1,3-dipolar cycloaddition product (79%) and Michael addition product (16%) was observed under the standard reaction conditions using LiBr and $Et_3N$ (1.5 and 1.2 equiv of the imine ester substrate) in THF (Scheme 2-05). There are two reaction routes possible for the production of 1,3-dipolar cycloaddition products: (1) synchronous bond formation of two carbon-carbon bonds takes place via concerted transition state, and (2) one carbon-carbon bond formation undergoes earlier than the other one giving Michael adduct intermediate highly stabilized by a rigid lithium chelation.

When the latter intermediate goes further to cyclization through intramolecular imine aldol reaction, the cyclized product is produced which is the same to the 1,3-dipolar cycloadduct. However, the Michael adduct is produced if the intermediary Michael adduct enolate intermediate is protonated, probably with triethylammonium bromide, as shown in Scheme 2-05.

**Scheme 2-05** Competitive formation of 1,3-dipolar cycloaddion product and Michael addition product




In order to confirm the reaction route undergoing during the reaction course, we examined some factors which may affect the product ratios, between 1,3-dipolar cycloadduct and Michael adduct, in the reactions of methyl 2-(*N*-benzylideneamino)propanoate with methyl acrylate under the conditions for the in situ generation of *N*-metalated azomethine ylides using lithium bromide/triethylamine. All the results are given in Table 2-06.[8]

(1) Concentration effect: Protonation of the intermediary Michael adduct enolate with triethylammonium bromide is an intermolecular reaction, but the imino aldol reaction leading to the cyclized product, the same as the cycloadduct, is an intramolecular reaction which should have a reaction rate independent of the concentration of reaction. Accordingly, when the reaction is diluted with THF reducing the concentration, the intermolecular quenching of Michael adduct enolate should become slower. On the other hand, the concentration-independent reaction rate of intramolecular cyclization does not change by dilution. As a result, the relative ratio in favor for 1,3-dipolar cycloadduct should increase. This expectation was definitely correct, and the maximum ratio of 10:1 was recorded with the cycloadduct as major isomer when the concentration was reduced six times (entries 1-4 of Table 2-06).

(2) Effect of water addition: When a comparable amount of water is added, the Michael adduct becomes major product (entry 10).
(3) Catalytic use of LiBr and $Et_3N$: No reaction takes place without lithium bromide (entry 5). Both are catalytic (0.1 equiv), the reaction becomes awfully slow, and Michael adduct formation is favored when either of lithium bromide or triethylamine is catalytic (entries 6-8).
(4) Solvent effect: THF looks to be the best solvent giving the highest isomer ratio for the cycloadduct (entries 1, 11-13).

The best reaction conditions are given in entry 9 in which an excess amount of LiBr is used. This reaction is complete in 1 h at room temperature to give 91% total yield having 10:1 of the cycloadduct and Michael adduct.

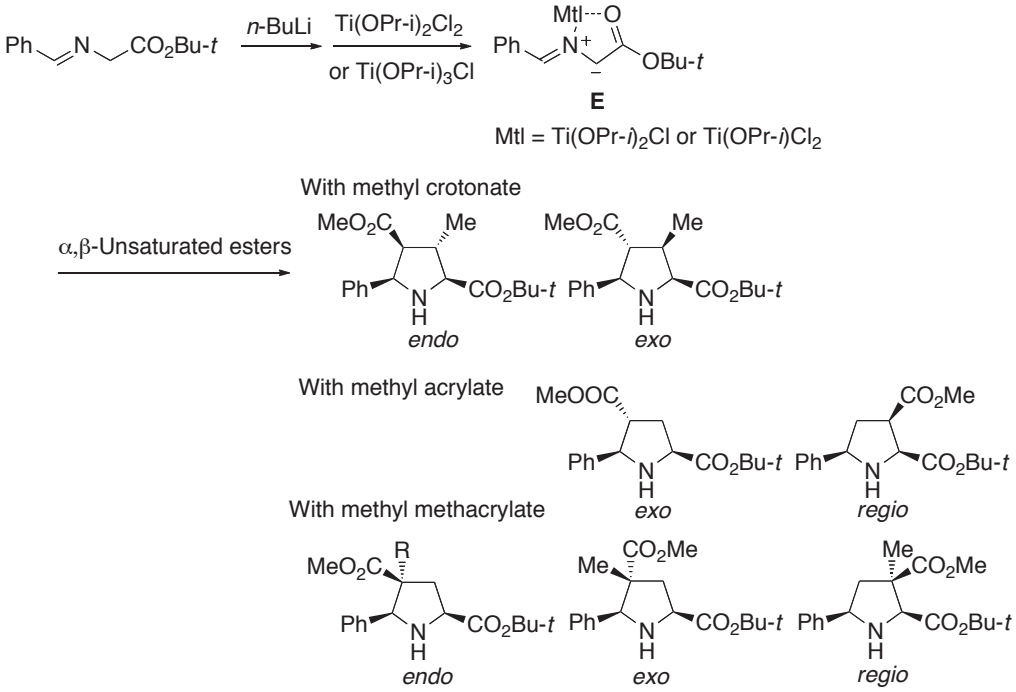
**Table 2-06** Reactions of methyl 2-(*N*-benzylideneamino)propanoate with methyl acrylate under various reaction conditions

| entry | LiBr equivalent | $NEt_3$ equivalent | Time/h | Solvent (conc)[a] | Additive | Yield/%[b] | 1,3-CA : M[c] |
|---|---|---|---|---|---|---|---|
| 1 | 1.5 | 1.2 | 10 min | THF (0.2 M) | | 51 | 5 : 1 |
| 2 | 1.5 | 1.2 | 15 | THF (0.4 M) | | 89 | 3 : 1 |
| 3 | 1.5 | 1.2 | 15 | THF (0.08 M) | | 81 | 6 : 1 |
| 4 | 1.5 | 1.2 | 15 | THF (0.03 M) | | 77 | 10 : 1 |
| 5 | 0 | 1.2 | 20 | THF (0.2 M) | | trace | |
| 6 | 0.1 | 1.2 | 14 | THF (0.2 M) | | 97 | 3 : 1 |
| 7 | 1.5 | 0.1 | 3 | THF (0.2 M) | | 67 | 2.2 : 1 |
| 8 | 0.1 | 0.1 | 48 | THF (0.2 M) | | 70 | 6 : 1 |
| 9 | 3.3 | 1.2 | 1 | THF (0.2 M) | | 91 | 10 : 1 |
| 10 | 1.5 | 1.2 | 1 | THF (0.2 M) | $H_2O$[d] | 52 | 1 : 2 |
| 11 | 1.5 | 1.2 | 3 | $Et_2O$ (0.2 M) | | 44 | 2.5 : 1 |
| 12 | 1.5 | 1.2 | 1 | MeCN (0.2 M) | | 79 | 1 : 1.4 |
| 13 | 1.5 | 1.2 | 3 | $CH_2Cl_2$ (0.2 M) | | 92 | 1 : 3.3 |

[a]With respect to imine ester. [a]Yield of isolated mixture. [c]1,3-CA: cycloadduct, M: Michael adduct, isomer ratio based on $^1$H NMR spectrum of isolated mixture. [d]0.17 mmol for the 1 mmol of substrate.

**Reactivity and selectivity of *N*-titanated azomethine ylide.**[9] Imines of α-amino esters can be transformed readily into *N*-metalated azomethine ylides, or the corresponding enolates, by action with metal salts and amine bases in THF at room temperature. The resulting ylides undergo highly stereoselective cycloadditions with α,β-unsaturated carbonyl compounds to produce 2-pyrrolidinecarboxylate derivatives, which correspond to the *endo*-cycloadducts to *E,E*-ylidic forms. A tight chelation would be responsible for the high stereoselection. We further continued to work on the research project of *N*-metalated azomethine ylides, with the aim of establishing the hitherto unknown asymmetric cycloaddition of azomethine ylides. In the course of our investigation along this line, we came across a successful generation of *N*-titanated azomethine ylides from *t*-butyl (*N*-benzylideneamino)acetate by action with dichlorodiisopropyloxytitanium, or chlorotriisopropyloxytitanium, and triethylamine; their cycloadditions with several α,β-unsaturated were been briefly investigated.

**Scheme 2-07** Cycloaddition reactions of methyl (*N*-benzylideneamino)acetate in the presence of titanium compounds




*t*-Butyl 2-(*N*-benzylideneamino)acetate was irreversibly lithiated into *N*-lithiated azomethine ylide by treatment with butyllithium at –78 °C in toluene, and then transmetalated with dichlorodiisopropyloxytitanium or chlorotriisopropyloxytitanium to generate the corresponding *N*-titanated azomethine ylide **E**. The same *N*-metalated azomethine ylide **E** was also generated reversibly by treatment of the imine with titanium chlorides and amine bases such as DBU or triethylamine. However, the ylide generation requires a little higher temperature when the latter weak amine base is employed. Capture of the resulting *N*-titanated azomethine ylide **E** was achieved with a variety of α,β-unsaturated esters such as methyl crotonate, methyl acrylate, and methyl methacrylate to give pyrrolidine-2-carboxylate derivatives (Scheme 2-07).

**Table 2-08** Generation and cycloaddition reactions of *N*-titanated azomethine ylides with α,β-unsaturated esters[a]

| entry | Dipolarophile | Metal halide | Base[b] | Solvent | Temp/°C | Time/h | Product yield/%[c] *endo* | *exo* | *regio* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Methyl crotonate | $Ti(OPr\text{-}i)_2Cl_2$ | *n*-BuLi[d] | toluene | –78/–30 | 1, 17 | 55 | | |
| 2 | | $Ti(OPr\text{-}i)_3Cl$ | *n*-BuLi[d] | toluene | –78/–31 | 4, 13.5 | 70 | | |
| 3 | | Ti(OPr-i)2Cl2 | DBU | $CH_2Cl_2$ | –78 | 24 | 53 | | |
| 4 | | $Ti(OPr\text{-}i)_2Cl_2$ | $NEt_3$ | $CH_2Cl_2$ | 0 | 2.5 | | 51 | |
| 5 | | $Ti(OPr\text{-}i)_2Cl_2$ | $NEt_3$ | $CH_2Cl_2$ | rt | 13 | | 65 | |
| 6 | | $Ti(OPr\text{-}i)_2Cl_2$ | DBU | $CH_2Cl_2$ | rt | 2 | | 75 | |
| 7 | | $Ti(OPr\text{-}i)_2Cl_2$ | $NEt_3$ | $CH_2Cl_2$ | reflux | 1 | | 65 | |
| 8 | Methyl acrylate | $Ti(OPr\text{-}i)_2Cl_2$ | DBU | $CH_2Cl_2$ | rt | 5 | | 75 | |
| 9 | | $Ti(OPr\text{-}i)_2Cl_2$ | DBU | $CH_2Cl_2$ | –20 | 24 | | | 55 |
| 10 | | $Ti(OPr\text{-}i)_2Cl_2$ | DBU | $CH_2Cl_2$ | –78 | 24 | | | 55 |
| 11 | Methyl methacrylate | $Ti(OPr\text{-}i)_2Cl_2$ | $NEt_3$ | $CH_2Cl_2$ | rt | 6 | | 70 | |
| 12 | | $Ti(OPr\text{-}i)_2Cl_2$ | $NEt_3$ | toluene | rt | 13 | | 83 | |
| 13 | | $Ti(OPr\text{-}i)_2Cl_2$ | $NEt_3$ | THF | rt | 4 | | 27 | 35 |
| 14 | | $Ti(OPr\text{-}i)_2Cl_2$ | $NEt_3$ | THF | –78 | 24 | | | 31 |

[a]All reactions were performed by employing 1 equivalent of a titanium salt and 1.1 equivalent of a base. [b]DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene. [c]Yield of the isolated product. [d]Imine was first treated with butyllithium (1 equiv) at –78 °C and then a titanium compound.

The *N*-titanated azomethine ylide **E** underwent exclusively stereoselective cycloadditions at -78 °C with methyl crotonate to produce the *endo*-cycloadduct (entries 1-3 of Table 2-08),[9] which has the same stereochemistry to that given in the reaction of *N*-lithiated azomethine ylide. However, dramatic change of stereoselectivity to *exo*-cycloadduct was observed when the reaction temperature was raised up to 0 °C or higher, both for the generation and cycloaddition steps. Thus, the absolutely *exo*-selective reaction was attained (entries 4-7). With methyl acrylate as monosubstituted alkene, the reaction of **E** at room temperature provided the *exo*-cycloadduct in a stereoselective manner (entry 8), however, the regioselectivity was completely reversed at -20 °C or lower (entries 9, 10). The reaction with methyl methacrylate as 1,1-disubstituted alkene at room temperature was also *exo*-selective in toluene or dichloromethane (entries 11, 12), and a similar reaction in THF was no longer selective, a mixture of *exo*-cycloadduct and regioisomeric cycloadduct in 27 and 35% yields, respectively. The reaction with methyl methacrylate at a low temperature of –78 °C also showed the completely reversed regioselectivity (entry 14).

### 2.2 Heterocyclic chiral auxiliaries for 1,3-dipolar cycloadditions

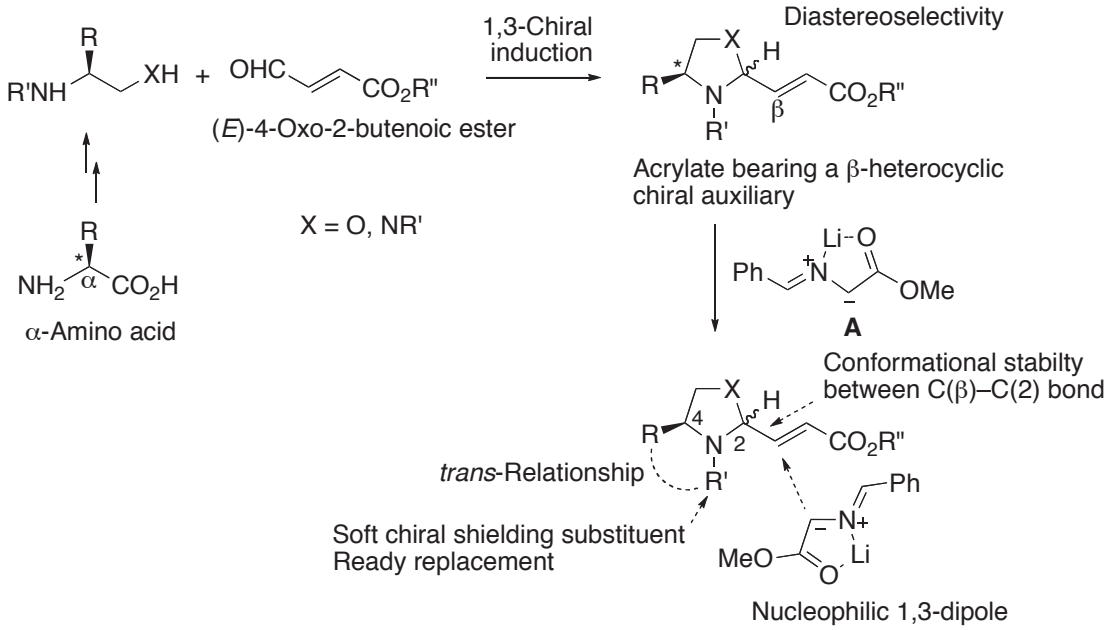
Effective stereocontrol of 1,3-dipolar cycloadditions by use of catalyst is extremely rare. Although some examples are known for asymmetric 1,3-dipolar cycloadditions by use of chiral 1,3-dipoles or dipolarophiles, the levels of diastereoselectivity achieved are often far from satisfaction. We discovered the generation of new reactive 1,3-dipoles, *N*-metalated azomethine ylides, by treatment of α-(*N*-alkylideneamino)acetates with metal salts in the presence of amines. The resulting 1,3-dipoles show high enhancement of reactivity toward α,β-unsaturated carbonyl compounds recording extremely high regio- and stereoselectivities. The reaction with a crotonate was complete even at -78 °C, and therefore the asymmetric cycloadditions utilizing *N*-metalated azomethine ylides are now ready in our research group. In this review, some details of our works along this line are described.

We planned to develop conceptually new chiral auxiliaries for the assymetric cycloadditions of *N*-metalated azomethine ylides (category 1).[10-12] Our concept of structural design for new chiral auxiliary of category 1 is given in Scheme 2-09. We selected α-amino acids as the chiral source since:

(1) α-Amino acids are readily available in optically pure forms and in a large quantity.
(2) The chiral center of α-amino acids is located at α-position of the amine substituent.
(3) These steric-shielding substrates can be readily transformed into γ-amino alcohols or 1,2-diamines without racemization.

The molecular structure of chiral dipolarophiles we designed consists of α,β-unsaturated esters bearing a heterocyclic chiral auxiliary at the β-position because such substrates can be readily accessible through the condensation reactions of chiral γ-amino alcohols or 1,2-diamines with methyl (*E*)-4-oxo-2-butenoate. A new chiral center is constructed adjacent to the β-terminus of α,β-unsaturated esters. Accordingly, the stereoselectivity of the 1,3-chiral induction in the condensation step should be critical. If this selectivity constructed as expected, then, the α,β-unsaturated esters bearing a heterocyclic chiral auxiliary at the β-position are in hand. Structure of the final target molecules are given in Scheme 2-09.

**Scheme 2-09** Chiral α,β-unsaturated esters bearing a β-heterocyclic chiral auxiliary for the asymmetric 1,3-dipolar cycloadditions of *N*-metalated azomethine ylides (category 1)




In our chiral α,β-unsaturated esters thus designed, a 5-membered heterocyclic chiral auxiliary is connected at the β-position with the α,β-unsaturated ester moiety. The distinctive structural features of our chiral auxiliaries are as follows:

(1) The *N*-substituent (R') is next to the substituent R at the original 4-chiral center so that the stereochemical relationship between R and R' should be *trans* to each other. So the ring nitrogen becomes "chiral". This would make it more effective the chiral shielding to the incoming *N*-metalated azomethine ylides.

(2) Such soft chiral shielding by the neighboring chiral *N*-substituent R' should work as induced fit type chirality control.

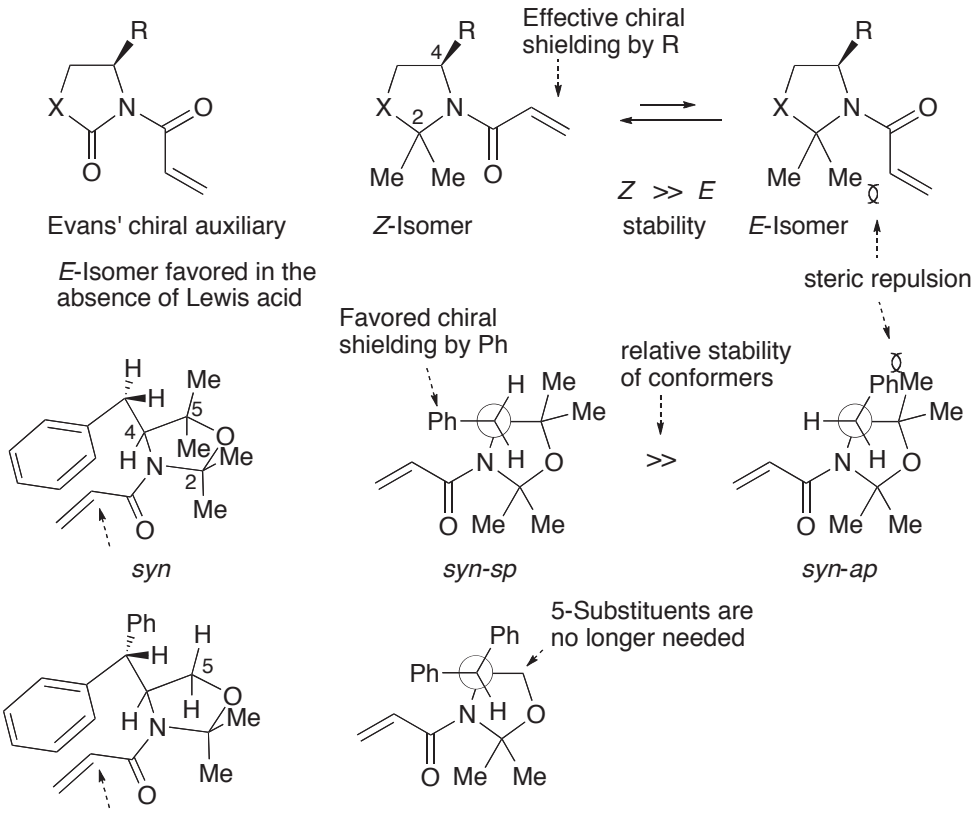
(3) If needed, the *N*-substituent R' can be replaced with others depending upon the structures and reactivity of *N*-metalated azomethine ylide 1,3-dipoles employed.

(4) The relative conformational stability between the C(2)–C(β) bond should be remarkably discriminated. Usually, the antiperiplanar (*ap*) conformation is thermodynamically much more favored than the synperiplanar (*sp*) conformation. Especially so in the case of five-membered heterocyclic chiral auxiliaries, the relative stability of synperiplanar conformation should be much less. Therefore, the less hindered face of *ap*-conformer of the α,β-unsaturated bond should be open in the transition state of the reaction.

(5) Since *N*-metalated azomethine ylides are highly nucleophilic 1,3-dipoles having the chemical property of metal enolate on the ground of resonance structures, the most nucleophilic α-carbon of ylides tends to attack the β-carbon of α,β-unsaturated esters.

(6) Accordingly, the nonbonding electron pair on the neighboring nitrogen atom and the steric hindrance by the *N*-substituent R' should both play effective roles in the transition structures. Thus, it is anticipated that strong electrostatic repulsion should result by controlling the hybridization of the ring nitrogen.

**Scheme 2-10** Chiral α,β-Unsaturated amides for the asymmetric 1,3-dipolar cycloadditions of nitrile oxides, based on the conformational control of chiral shielding substituents (category 2)




The chiral auxiliary designed for the asymmetric 1,3-dipolar cycloaddition reactions of nitrile oxides should be based on a different concept because of the quite big difference of chemical nature between *N*-metalated azomethine ylides and nitrile oxides. Nitrile oxides generally show high reactivity and regioselectivity toward monosubstituted alkenes to give isoxazoline derivatives with a substituent at 5-position regardless of the electronic nature of the substituent. However, the reactivity is extremely decreased when additional substituents are added. Therefore, the most convenient alkenes successfully applicable to nitrile oxide cycloadditions should be acrylic derivatives. Detail of the structural design of new chiral auxiliary for the asymmetric 1,3-dipolar cycloaddition reactions of nitrile oxides is given in Scheme 2-10 (category 2).[13-15]

4-Chiral 2-oxazolidinones, known as Evans' chiral auxiliary, have found wide applications in the synthetic works. This chiral auxiliary shows high diastereofacial selectivity in a variety of reactions in the presence of a Lewis acid catalyst. However without catalyst, the selectivity becomes awfully poor. This can be easily understood as follows: Because of the considerable electrostatic repulsion working between the carbonyl oxygens, the *E*-isomer is much more stabilized so that the alkene reaction site is located far from the shielding zone by the 4-substituent R at the chiral center. Nitrile oxide cycloaddition reactions to 2-acryloyl-4-benzyl-2-oxazolidinone gives only a mixture of two diastereomeric cycloadducts in a poor diastereomer ratio of 70:30.

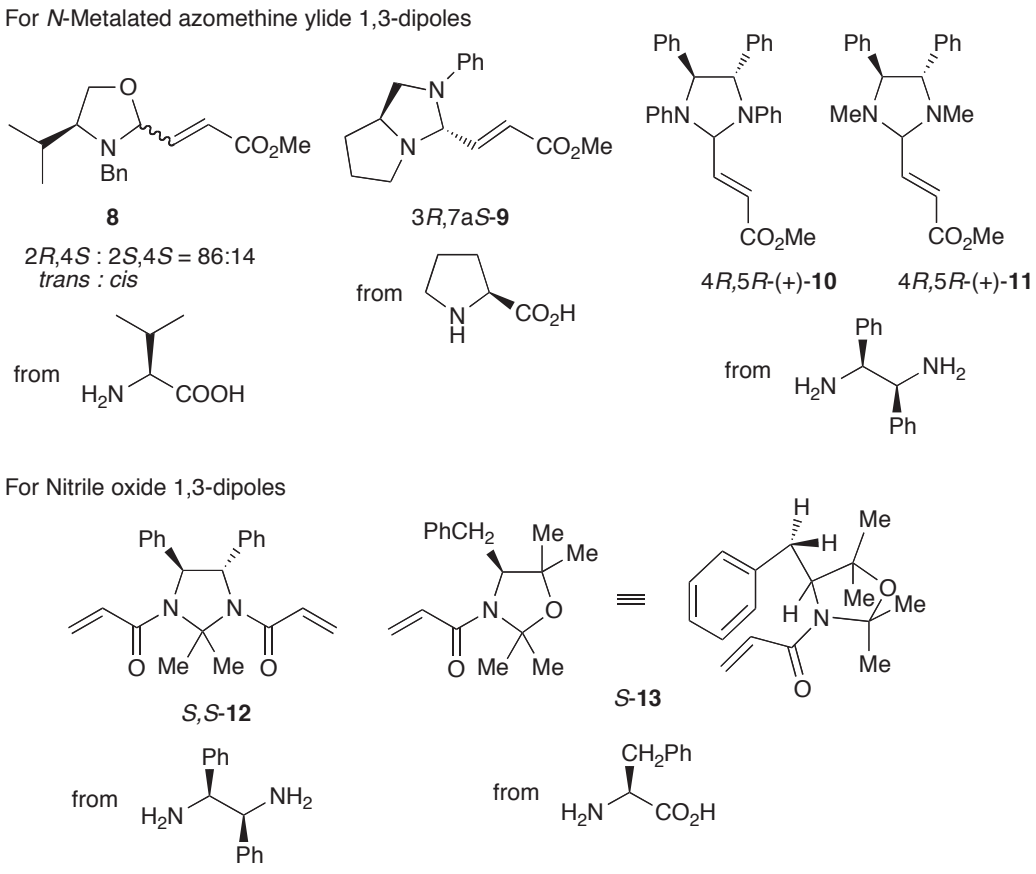
We focussed on the control of stereochemical preference for *Z*-isomer, or *anti*-isomer, in order to improve the chiral shielding by the 4-substituent. Our idea is based on the conformational control of the alkene

reaction site by introduction of two alkyl substituents, such as methyl or pentamethylene groups, at the 2-position of the oxazolidine ring. If this idea works well, the alkene moiety becomes closer to the steric-shielding substituent R so that the reaction should occur selectively at the face opposite of the shielding substituent R. Use of MM2 calculation as well as the $^1$H NMR study to see the magnetic deshielding effect on the vinyl protons provide us deep insights with respect to the steric shielding by the 4-substituent.

More informative is the additional idea; this is how to controll the conformation of steric shielding group of the 4-shielding substituent. When a benzyl group is introduced at 4-position as chiral steric-shielding substituent, its phenyl plane is expected to cover the top face of the reaction site. If so, let us introduce two more methyls at 5-position (Scheme 2-10). Thus, the phenyl group becomes outside of the heterocyclic ring so that it may cover the alkene face effectively. If one wants to use diphenylmethyl substituent instead of benzyl substituent at the 4-chiral center, 5-substituents are unnecessary.

Our chiral α,β-unsaturated esters **8** to **13**, bearing a five-membered heterocyclic chiral auxiliary at the β-position, are given in Scheme 2-11.[10-12] These functionalized molecules are divided, as shown above, into two groups depending upon the 1,3-dipole types used in the diastereoface selective 1,3-dipolar cycloaddition reactions: alkenes **8** to **11** are for the reactions with *N*-metalated azomethine ylides; alkenes **12** and **13** are for the reactions with nitrile oxides.

**Scheme 2-11** A variety of chiral α,β-unsaturated ester derivatives **1** to **6** designed and synthesized for the diastereoface-selective asymmetric 1,3-dipolar cycloadditions



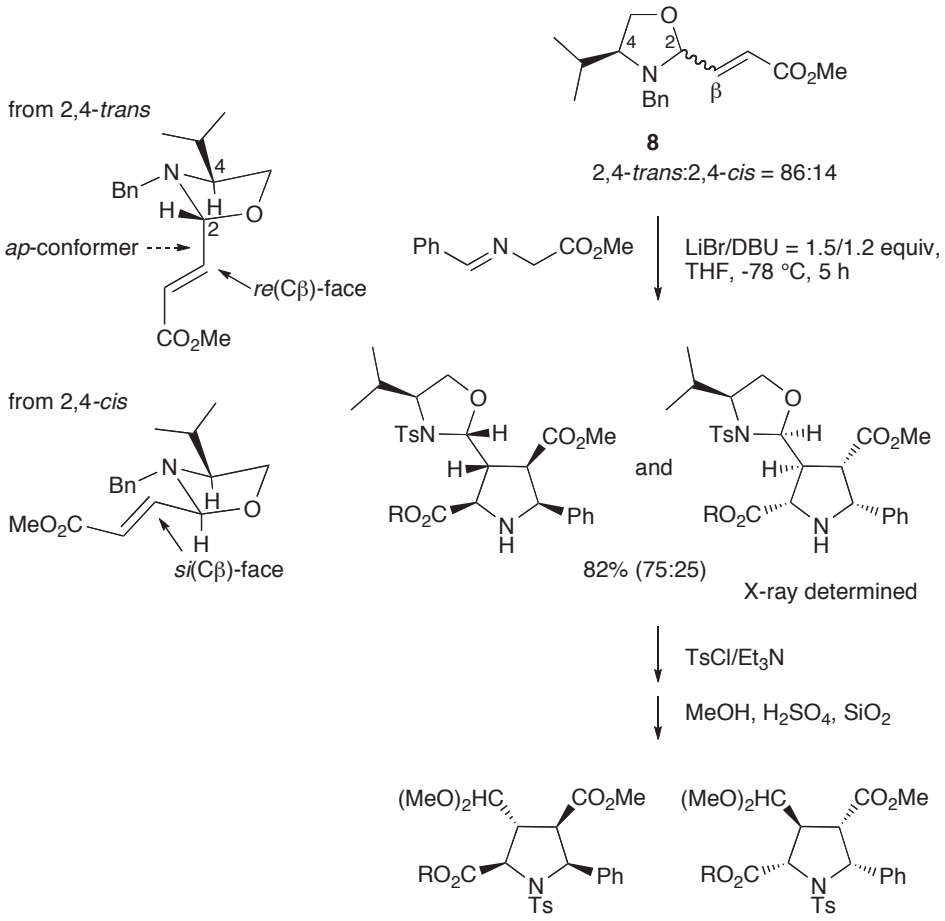
α,β-Unsaturated esters bearing chiral oxazolidine **8** and perhydropyrrolo[1,2-*c*]imidazole 3*R*,7a*S*-**9** auxiliaries were synthesized by condensation reactions of methyl (*E*)-4-oxo-2-butenoate with optical pure valine and prolin, respectively (Scheme 2-11). Compound **8** was obtained as an equilibrating mixture of 2,4-*trans*- and *cis*-diasteromers (86:14) which were used in the subsequent reactions without further separation procedure, however 3*R*,7a*S*-**9** was produced as single diastereomer and optically pure form. α,β-Unsaturated esters bearing a $C_2$-symmetric chiral imidazolidine auxiliary 4*R*,5*R*-**10** and 4*R*,5*R*-**11** were similarly prepared from *R,R*-1,2-dianilino-1,2-ethanediamine and *R,R*-1,2-bis(methylamino)-1,2-ethanediamine, respectively. Production of diastereomers is theoretically impossibile due to their $C_2$-symmetric structures. As shown below, these four chiral α,β-unsaturated esters **8** to **11** were employen in the 1,3-dipolar cycloaddition reactions of *N*-metalated azomethine ylides.

$C_2$-Symmetric 1,3-bisacryloylimidazolidine compound *S,S*-**12** was synthesized by the condensation of *R,R*-1,2-dianilino-1,2-ethanediamine with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid, followed by acylation with acryloyl chloride. The 4-benzyl-2,2,5,5-tetramethyloxazolidine chiral auxiliary of *S*-**13** was obtained by reaction of (*S*)-phenylalanine ethyl ester with a large excess amount of methylmagnesium iodide, followed by the acetalization with 2,2-dimethoxypropane and subsequent acylation with acryloyl chloride. The MM2 and $^1$H NMR spectral data of **12** and **13** are given in the original references.[14]

Methyl (*E*)-3-[(4*S*)-3-benzyl-4-isopropyl-2-oxazolidinyl]propenoate (**8**), as α,β-unsaturated ester bearing an oxazolidinyl chiral auxiliary, has some synthetic advantages[10] such as:

(1) This chiral α,β-unsaturated ester **8** is readily accessible from the readily available chiral β-amino alcohol and methyl (*E*)-4-oxo-2-butenoate.
(2) Two hetero substituents on the chiral carbon are very different both in bulkiness and electrostatic property, and the *N*-benzyl substituent should show much predominant shielding effect.
(3) A variety of *N*-substituents can be introduced on the asymmetric carbon at the stage of optically pure 2-amino alcohols. However, a rather disappointing disadvantage remaining unsolved is the poor diastereoselectivity at the stage of chiral oxazolidine ring construction.

**Scheme 2-12** Asymmetric cycloaddition reactions of an *N*-lithiated azomethine ylide with methyl (*E*)-3-[(4*S*)-3-benzyl-4-isopropyl-2-oxazolidinyl]propenoate **1**



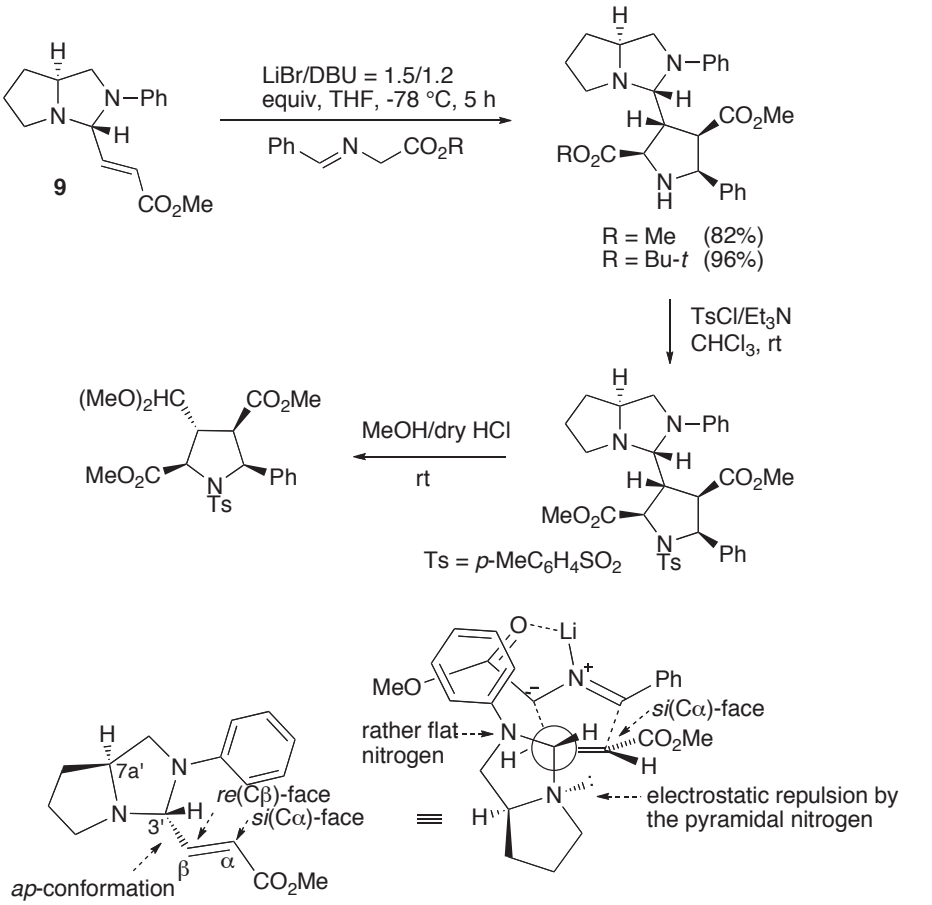

Thus, the condensation reaction of *N*-benzyl-(*S*)-valinol with methyl (*E*)-4-oxo-2-butenoate gave a mixture of two diastereomers, and the isomer ratio changed depending upon the reaction conditions (Scheme 2-12). Separation of isomers through column chromatography resulted serious weight loss, due to their susceptibility toward hydrolysis. Finally, we obtained an 86:14 diastereomer mixture in a similar reaction at room temperature in the presence of silica gel. This mixture (2,4-*trans* : 2,4-*cis* = 86:14) was used in the subsequent step of cycloaddition reactions.[10]

The reaction of **8** (an 86:14 diastereomer mixture) was treated with *N*-lithiated azomethine ylide intermediate, derived from methyl (*N*-benzylideneamino)acetate by action with LiBr/DBU at –78 °C for 3.5 h in THF, to give a 75:25 mixture of two diastereomeric cycloadducts in 82% yield (Scheme 2-12). Removal of the chiral oxazolidine auxiliary was performed for each diastereomer through the initial *N*-tosylation and the subsequent acetal exchange reaction under reflux in methanol in the presence of sulfuric acid. Structure as well as the absolute stereochemistry of the major cycloadduct isomer was found to have been produced from 2,4-*trans* major isomer of the α,β-unsaturated ester **8**.

The *re*(Cβ)-face selective cycloaddition reaction probably includes the participation of the synperiplanar (*sp*) conformation with respect to the C(2)–C(β) bond and the subsequent attack of *N*-lithiated azomethine

ylide from a diastereomeric face opposite side from the *N*-benzyl group. A similar face selection with the attack of *si*(Cβ)-face took place in the reaction of 2,4-*cis* isomer of **8**. When two hetero substituents on the chiral carbon are very different both in bulkiness and electrostatic property such as the case of α,β-unsaturated ester **8** bearing a chiral oxazolidine auxiliary, the *N*-benzyl substituent, including bulkier and pyramidal nitrogen atom, is found to show much stronger steric and electrostatic shielding effects than the etheral oxygen atom inducing the exclusive diastereofacial selectivity.[10]

**Scheme 2-13** Asymmetric cycloaddition reactions of an *N*-lithiated azomethine ylide with methyl (3*R*,7a*S*)-2-phenylperhydropyrrolo[1,2-*c*]imidazole-3-(*E*)-propenoate

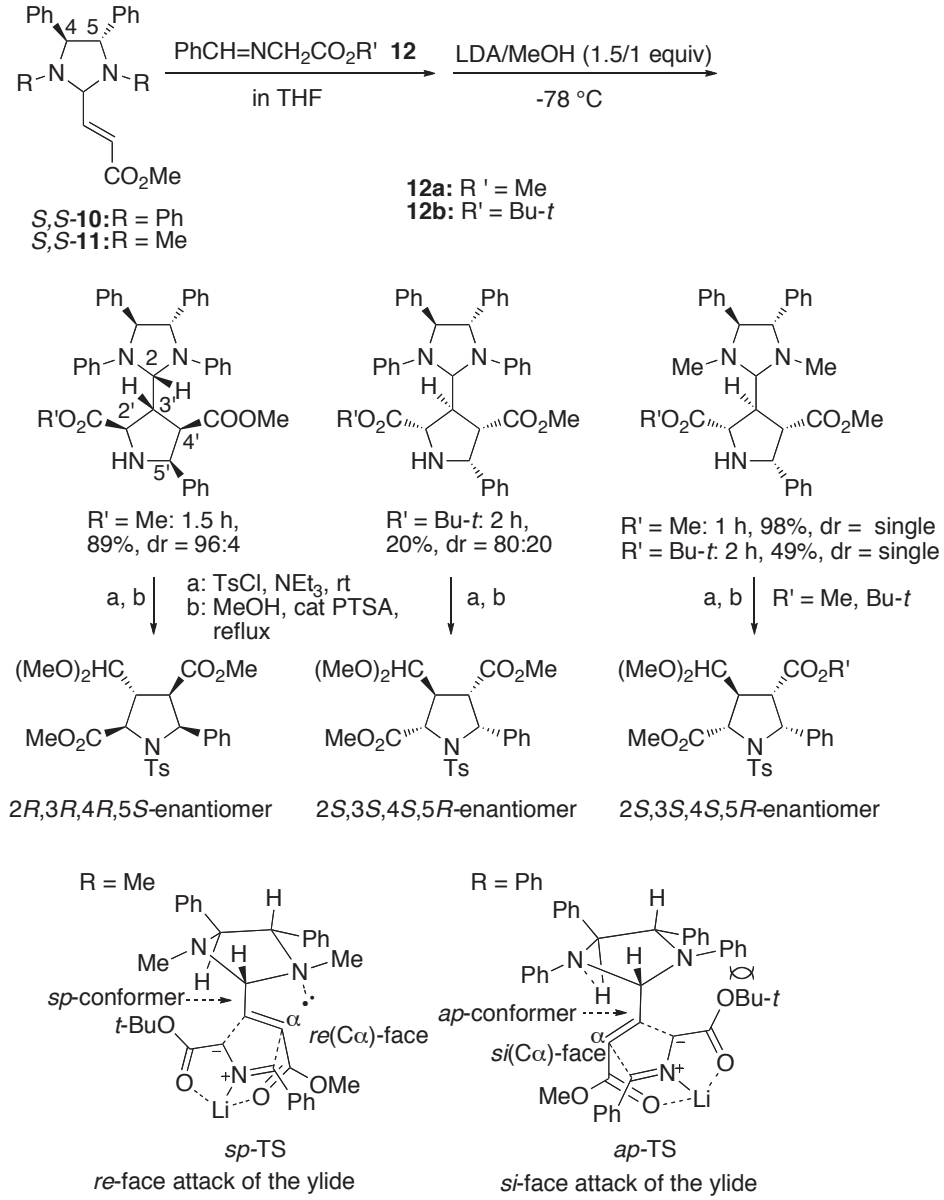



Methyl (3*R*,7a*S*)-2-phenylperhydropyrrolo[1,2-*c*]imidazole-3-(*E*)-propenoate (**9**) derived from *S*-prolin has 3,7a-*trans* structure so that the substituent newly introduced at the 3-position of the [3.3.0] bicyclic system is placed to be exo. Such stereoselective 1,3-chiral induction is a typical case for the formation of 5,5-ring condensation reactions. In the structure of the bicyclic chiral auxiliary of α,β-unsaturated ester **9**, the chiral center newly formed at the 3-position has two kinds of nitrogen atoms: one is rather flat anilino type nitrogen and the other is a pyramidal alkylated amine. It would be interesting which of these nitrogen atoms plays more desicive role in the diastereoface selection step of 1,3-dipolar cycloaddition reactions with *N*-metalated azomethine ylides.[11]

The reaction of (3*R*,7a*S*)-2-phenylperhydropyrrolo[1,2-*c*]imidazole-3-(*E*)-propenoate (**9**) with *N*-lithiated azomethine ylide, generated from (*N*-benzylideneamino)acetates by treatment with lithium bromide and

amine, gave a single diastereomer of cycloadduct in a quantitative yield (Scheme 2-13). When DBU was used as amine, the reaction was complete even at -78 °C for a few hours. However with triethylamine as weaker base, a higher reaction temperature of room temperature was needed to finish the cycloaddition reaction. The absolute configuration was determined after *N*-tosylation, acid catalyzed acetal exchange reaction with methanol, and comparison of the optical rotation with that of the authentic sample of dimethyl 2*R*,3*R*,4*R*,5*S*-(–)-3-dimethoxymethyl-5-phenyl-*N*-tosyl-2,4-dicarboxylate (Scheme 2-13).

**Scheme 2-14** Diastereoselective asymmetric cycloadditions of an *N*-lithiated azomethine ylide with (*E*)-3-((4*S*,5*S*)-4,5-diphenyl-2-imidazolidinyl)acrylates




Thus, the diastereofacial selectivity at the β-carbon of α,β-unsaturated ester was determined as the *re*(Cβ)-face of *ap*-conformation. This indicates that the pyramidal nitrogen atom behaving as extremely electrostatic nitrogen atom works much more predominant role than the sterically more hindered nitrogen atom.[11] 1,3-Dipolar cycloadditions of 4,5-disubstituted (*E*)-3-((4*S*,5*S*)-2-imidazolidiny)acrylates **10** (R = Ph) and **11** (R = Me), α,β-unsaturated esters bearing an imidazolidine chiral auxiliary derived from

enantiopure $C_2$-symmetric 1,2-diamines, were performed with *N*-lithiated azomethine ylide generated from methyl (*N*-benzylideneamino)acetate (**12a**).[12] Diastereofacial selectivity was found to depend upon the nature of *N*-substituents on the chiral controller and the bulkiness of ester moiety of **12**. Enantiopure methyl (*E*)-3-((4*S*,5*S*)-1,3,4,5-tetraphenyl-2-imidazolidinyl)acrylate **10**, having *N*-phenyl substituents on the auxiliary, was allowed to react with the *N*-lithiated azomethine ylide generated from methyl (*N*-benzylideneamino)acetate (**12a**) and LDA MeOH (1.5/1 equiv) in THF at –78 °C for 1.5 h and a 96:4 diastereomer mixture of cycloadducts was given in 89% yield (Scheme 2-14).

Separation and purification through silica-gel column chromatography provided two diastereomeric cycloadducts. *N*-Tosylation and subsequent acetal exchange reactions provided the 2*R*,3*R*,4*R*,5*S*- and 2*S*,3*S*,4*S*,5*R*-enantiomers as major and minor products, respectively, whose absolute configurations were determined by comparison of the optical rotations with those of authentic samples. However, it is interesting that the diastereofacial selectivity observed was reversed (20:80) when the *N*-lithiated azomethine ylide derived from *t*-butyl ester **12b** was employed in the reaction with *S,S*-**10** at –78 °C under similar reaction conditions. Thus, 2*S*,3*S*,4*S*,5*R*-enantiomer of methyl *t*-butyl *N*-tosylpyrrolidine-2,4-dicarboxylate cycloadduct was produced as the major product. Its structure was confirmed after conversion to dimethyl ester derivatives and comparison of chiral rotations with those of authentic references.

Enantiopure methyl (*E*)-3-((4*S*,5*S*)-1,3-dimethyl-4,5-diphenyl-2-imidazolidinyl)acrylate **11**, having *N*-methyl substituents on the ring nitrogen atoms of imidazolidine chiral auxiliary, was allowed to react with the *N*-lithiated azomethine ylide derived from methyl ester of imine ester **12a** under similar reaction conditions for 1 h to give a single diastereomer of cycloadduct in 98% yield. The cycloadduct exclusively produced was similarly transformed through *N*-tosylation and subsequent acetal exchange reactions to give the 2*S*,3*S*,4*S*,5*R*-enantiomer of dimethyl *N*-tosylpyrrolidine-2,4-dicarboxylate as antipode of the previous 2*R*,3*R*,4*R*,5*S*-enantiomer. The *N*-lithiated azomethine ylied derived from *t*-butyl ester of imine ester **12b** reacted with *S,S*-**11** to give the 2*S*,3*S*,4*S*,5*R*-enantiomer of methyl *t*-butyl *N*-tosylpyrrolidine-2,4-dicarboxylate in a low yield. The resulting methyl *t*-butyl ester was readily converted to the corresponding dimethyl ester and the their stereochemistry was determined to be the same. Thus, methyl and *t*-butyl esters of *S,S*-**11** both produced the cycloadducts in the exclusively high diastereofacial selectivities with the same chirarity.

The opposite diastereofacial selectivities were recorded in the reactions of chiral α,β-unsaturated esters *S,S*-**10** (R = Ph) by switching the ester group of *N*-metalated azomethine ylides from methyl to *t*-butyl ester (ds = 96:4 to 20:80),[12] but this is the only case for *S,S*-**10** having phenyl steric shielding substituent on the nitrogen atoms. Both *N*-metalated azomethine ylides of methyl and *t*-butyl esters of imine esters, **12a** and **12b** respectively, showed the absolute diastereofacial selectivities with the same chirality in the cycloaddition reactions of *S,S*-**11** (R = Me). Thus, the dependence of sensitivity of diastereofacial selectivity, that is induced chirality, was relatively much more fragile in the case of *S,S*-**10** (R = Ph) with

imidazolidine chiral auxiliary bearing *N*-phenyl substituent. On the other hand, dramatic change of selectivity resulted when the steric *N*-shielding substituent of $C_2$-symmetric imidazolidine chiral auxiliary was swiched from *S,S*-**10** (R = Ph) to *S,S*-**11** (R = Me) in the reaction of *N*-metalated azomethine ylide derived from methyl (*N*-benzylideneamino)acetate **12a** (ds = 96:4 to 0:100).

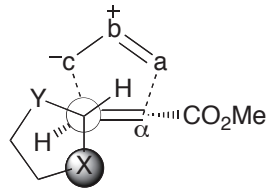
Based on the absolute configurations of major cycloadducts given in the reactions with *N*-lithiated azomethine ylide bearing a methyl ester group, the *re*(Cα)-face was selected in the reaction of *S,S*-**10** (R = Ph); the *si*(Cα)-face was selected in the reactions of *N*-lithiated azomethine ylide bearing a *t*-butyl ester group. We propose that a major reason for the swich of diastereofacial selection is due to the participation of different conformations with respect to the dipolarophile in the transition states. In the reaction of *N*-metalated azomethine ylide having methyl group with *S,S*-**10** (R = Ph), *ap*-conformation as much more stable conformation in the ground state selectively participated in the transition structure (*ap*-TS), but the reaction of *N*-metalated azomethine ylide having a bulky *t*-butyl group shows serious steric hindrance in a similar transition structure *ap*-TS. Consequently, *S,S*-**10** (R = Ph) is forced to take the rather unfavored *sp*-conformation in order to avoid the fatal steric repulsion between *t*-butyl/NPh. When the nitrogen atoms of imidazolidine chiral auxiliary are pyramidal as shown in *S,S*-**11**, *ap*-TS becomes always hindered due to either steric or electrostatic repulsion. As a result *sp*-TS becomes more favored. Detail is described in the next section of 2.3.

**2.3 Transition states in asymmetric azomethine ylide cycloadditions**

The *ap*-conformation should be more stabilized than the *sp*-conformation in the ground state of α,β-unsaturated esters bearing a five-menmbered heterocyclic chiral auxiliary at the β-carbon. Since the chiral heterocycle is constructed by condensation of (*E*)-4-oxo-2-propenoates with γ-amino alcohols or 1,2-diamines, the chiral center, which is a to the β-carbon of α,β-unsaturated ester group, is substituted with two hetero atoms X and Y including nitrogen and oxygen or two nitrogen atoms. The resulting alkenes are employed in the 1,3-dipolar cycloaddition reactions with highly nucleophilic *N*-metalated azomethine ylides. The transition state for the concerted dipolar cycloaddition should wear a five-membered rigid structure. Therefore, the α-carbon of ylide attacks to the β-carbon of dipolarophile from the direction of less sterically hindered or less electrostatic substituent located on the chiral center; the cycloaddition takes place anti to the most hindered hetero substituent X. Atom X is given for the substituent of either steric or electrostatic hindrance with the highest preference (Scheme 2-15).[10-12] In the cyclic transition structure of thermodynamically most stable *ap*-conformation, the negative center "c" atom of 1,3-dipole accesses from the face opposite of the most hindered hetero atom X so that the resulting c/Y repulsive interaction becomes critical. If this interaction works strongly repulsive, *ap*-TS can not be stabilized any more, then shifts to *sp*-TS at the cost of stabikization of *ap*-TS. Although the *sp*-conformation has less thermodynamic stability in the ground state than *ap*-conformation, the serious c/Y repulsion working in *ap*-TS is released in *sp*-TS in which the negative dipole terminus atom c becomes almost free from fatal steric or electrostatic hindrance. Accordingly, *sp*-TS remains to be the major route as shown in *sp*-TS of Scheme 2-15.

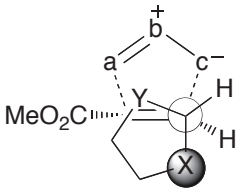
As a result, the diastereofacial selectivity of the reactions is determined by searching down from the top preference of *ap*-TS series to the bottom. If any of all preferences are not satisfactorily accepted, *ap*-TS should be discarded. Then, move to *sp*-TS series, and continue search down from the top preference to the bottom.

**Scheme 2-15** Preference of transition structure in the 1,3-dipolar cycloadditions to α,β-unsaturated esters bearing a heterocyclic five-membered chiral auxiliary




antiperiplanar TS (*ap*-TS)

stability >>

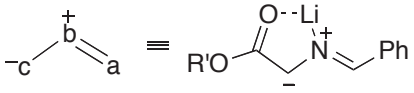



synperiplanar TS (*sp*-TS)

group of hindrance with the highest preference

PhCH=NCH$_2$CO$_2$R'

**12a:** R' = Me
**12b:** R' = Bu-*t*




1,3-dipole **A**

| X | Y | $CO_2R'$ | ds[a] |
|---|---|---|---|
| *ap*-TS | | | |
| $NCH_2Ph$ | O | $CO_2Me$ | single |
| $NCH_2$ | NPh | $CO_2Me$ | single |
| NPh | NPh | $CO_2Me$ | 96:4 |
| *syn*-TS | | | |
| NPh | NPh | $CO_2Bu$-*t* | – 80:20 |
| NMe | NMe | $CO_2Me$ | – single |
| NMe | NMe | $CO_2Bu$-*t* | – single |

[a]Minus sign of ds (diastereofacial selectivity) shows the reversal of chirality induced.

antiperiplanar TS (*ap*-TS)
1. *ap*-Conformer is more stable than *sp*-conformer in the ground state.
2. Anionic terminus "c" of 1,3-dipole attacks the β-carbon of dipolarophile.
3. 1,3-Dipole approaches from the opposite side of most hindered heteroatom X.
4. Cycloaddition occurs selectively if the repulsion between c/Y (= NPh) is minimized.
5. When R' is *t*-Bu, the c/Y (= NPh) repulsion becomes critical to reduce the stability of *ap*-TS.
6. Repulsion between c/Y (= NMe) is always critical to reduce the stability of *ap*-TS.

synperiplanar TS (*sp*-TS)
7. Repulsion of dipole terminus "c" becomes much less critical in *sp*-TS.
8. Dipole approaches from the opposite face of X.
9. *sp*-TS remains the only favored route at the cost of any possible *ap*-TS.

Start here of *ap*-TS series

(1) *ap*-Conformer is more stable than *sp*-conformer in the ground state.

(2) Anionic terminal atom "c" of 1,3-dipole attacks the β-carbon of dipolarophile.

(3) 1,3-Dipole approaches from the side opposite of the most hindered hetero atom X.

(4) Cycloaddition occurs selectively if the repulsion between c/Y (= NPh) is negligible.

(5) When R' is a bulky *t*-butyl, c/Y (= NPh) repulsion becomes critical to minimize the stability of *ap*-TS.

(6) Repulsion between c/Y (= NMe) is always critical to reduce the stability of *ap*-TS. Move to *sp*-TS series

(7) Repulsion of terminal atom "c" of 1,3-dipole is negligible in *sp*-TS.

(8) 1,3-Dipole approaches from the face opposite of the most hindered hetero atom X.
(9) *sp*-TS remains the only favored route at the cost of any possible approaches in *ap*-TS.

All the diastereofacial selectivities observed in the asymmetric 1,3-dipolar cycloadditions of *N*-lithiated azomethine ylides with a variety of chiral α,β-unsaturated ester dipolarophiles **8**-**11** are summarized in Scheme 2-15. The nucleophilic center "c" of 1,3-dipole binds with the β-carbon of α,β-unsaturated ester, on which a chiral heterocyclic auxiliary is substituted. Hetero atom X is more hindered, either sterically or electrostatically, than the other hetero atom Y. Accordingly, 1,3-dipole attacks the unsaturated bond of chiral α,β-unsuturated ester dipolarophiles from the side opposite of heteroatom X. When chiral auxiliary is an oxazolidine **8**, X = $NCH_2Ph$ and Y = O without any question. When chiral auxiliary is a 2-phenylperhydropyrrolo[1,2-*c*]imidazole **9**, X = 3a-N as alkyl-substituted pyramidal amine and Y = NPh since the bridgehead nitrogen 3a-N is typical pyramidal nitrogen being more strongly electrostatic and sterically bulkier than the rather flat anilino nitrogen. When chiral auxiliary is a $C_2$-symmetric imidazolidine **10** (R = Ph), X = Y = NPh. And finally when chiral auxiliary is a $C_2$-symmetric imidazolidine **11** (R=Me), X=Y=NMe. The difference of **10** and **11** is the rather flat anilino and typical pyramidal nitrogens, respectively. In the case of **11** (R = Me), the *ap*-TS always suffers from both so serious steric and electrostatic repulsions that the reaction through ap-TS may be totally inhibited. On the other hand, chiral auxiliary **10** (R = Ph) having rather flat nitrogen atoms would allow the cycloadditions through ap-TS, albeit in a lowered selectivity. The results of diastereofacial selectivities observed in the cycloaddition reactions of **8** to **11** to *N*-metalated azomethine ylides are found to be all consistent with the above anticipations (Scheme 2-15).

Especially interesting is that the mode of chirality induced was reversed when the methyl ester of imine ester **12** (R' = Me) was replaced with *t*-butyl ester (R' = Bu-*t*), indicating the dramatic swich of transition structure from *ap*-TS to *sp*-TS. In this case, the terminal atom c of 1,3-dipole bears a bulky *t*-butyl ester so that the steric hindrance becomes serious to inhibit *ap*-TS. When hetero atoms X and Y are alkylated amine NMe as pyramidal amine moiety in **11** (R = Me), both serious steric and electrostatic repulsion operates in the transition state. Especially strong repulsion works between c/X and between c/Y, through either steric or electrostatic repulsion, especially serious being the latter. Accordingly, the reaction through *ap*-TS is completely forbidden. On the contrary, the transition structure through *sp*-TS is free from such serious repulsive interactions to attain the absolute reversal of chiral induction regardless of the steric size of ester moieties.

## 3. NITRONES AND NITRONATES

### 3.1 Lewis acid catalysis

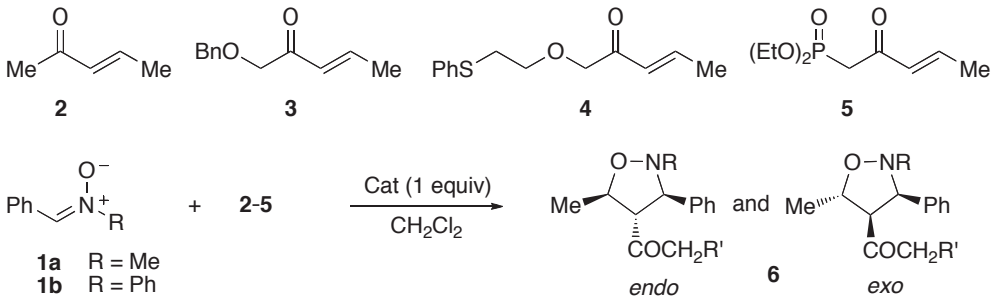
**Catalytic nitrone cycloadditions.**[16] Nitrile oxides and nitrones are among the most useful 1,3-dipoles ever used in organic synthesis. Thus, their cycloadditions, followed by functional group transformations including a reductive cleavage of the nitrogen-oxygen bond of cycloadducts, have found wide synthetic applications in elaboration of complex structures of natural products. Since nitrones are not so highly reactive 1,3-dipoles compared with nitrile oxides and their intermolecular cycloadditions are relatively lack of stereoselctivity, most of synthetic applications reported have consisted of intramolecular versions

of nitrone cycloadditions.

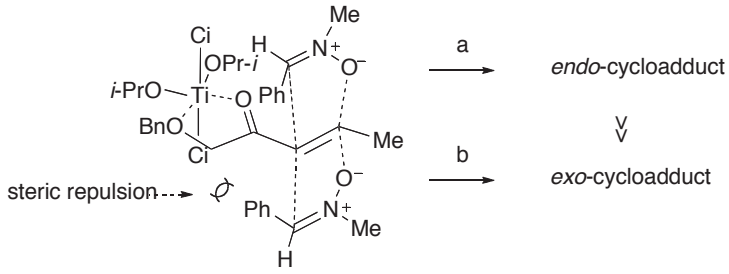
Based on numerous reports on successful Lewis acid-catalyzed stereoconttol of Diels-Alder reactions, similar Lewis acid catalysis can be also expected in 1,3-dipolar cycloadditions. However, few successful reactions are so far known. A serious problem is that 1,3-dipoles act as stronger bases than 1,3-dienes. Then 1,3-dipoles have a strong tendency to form inactive Lewis acid/1,3-dipole complexes and the catalytic activity of Lewis acid is extremely decreased. To overcome this difficulty we designed new electron-deficient alkene dipolarophiles that have a chelating ligand structure. Our expectation is that the incorporation of a Lewis acid should be equilibrating between 1,3-dipole and dipolarophile in the reaction, and that the reaction rate acceleration of cycloaddition will occur only in the Lewis acid/dipolarophile complex.

With the above expectation, some chelating enone types of dipolarophiles such as (*E*)-1-benzyloxy-3-penten-2-one (**3**), (*E*)-1-(2-phenylthioethoxy)-3-penten-2-one (**4**), and diethyl (*E*)-2-oxo-3-pentenylphosphonate (**5**) were employed in the nitrone 1,3-dipolar cycloadditions with *N*-benzylidenemethylamine *N*-oxide (**1a**) and *N*-benzylideneaniline *N*-oxide (**1b**); (*E*)-3-penten-2-one (**2**) as monodentate enone substrate was used as a reference substrate to compare the reaction rates in the absence or presence of Lewis acid catalysts (used of 1 equiv to the substrates).

**Scheme 3-01** Nitrone cycloaddition reactions to mono-, bi-, and tridentate enone dipolarophiles **2-4**




| Nitrones | Alkenes | Catalyst | Solvent | Temp/°C | Time/h | Yield/% | *endo:exo* |
|---|---|---|---|---|---|---|---|
| **1a** | **2** | $ZnCl_2$ | $CH_2Cl_2$ | rt | 144 | 39 | 20:80 |
| **1b** | **2** | - | toluene | 80 | 10 | 70 | 73:27 |
| **1b** | **2** | $Ti(OPr\text{-}i)_2Cl_2$ | $CH_2Cl_2$ | rt | 18 | 49 | 77:23 |
| **1a** | **3** | - | benzene | 80 | 8 | 76 | 40:60 |
| **1a** | **3** | $ZnCl_2$ | $CH_2Cl_2$ | rt | 52 | 77 | 87:23 |
| **1a** | **3** | $Ti(OPr\text{-}i)_2Cl_2$ | $CH_2Cl_2$ | 0 | 32 | 50 | >99:1 |
| **1b** | **3** | $Ti(OPr\text{-}i)_2Cl_2$ | $CH_2Cl_2$ | 0 | 17 | 74 | >99:1 |
| **1a** | **4** | - | benzene | 80 | 9 | 64 | 35:65 |
| **1a** | **4** | $Ti(OPr\text{-}i)_2Cl_2$ | $CH_2Cl_2$ | rt | 9 | 65 | 94:6 |



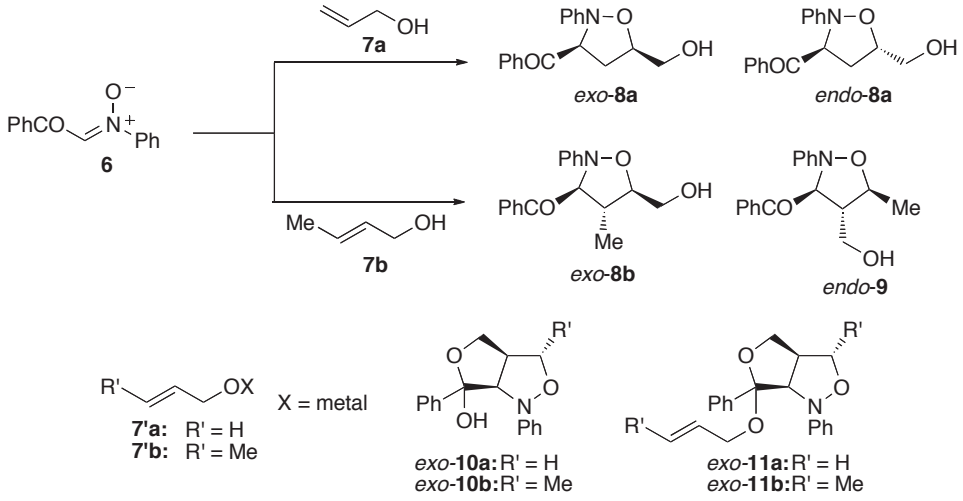
As shown in Scheme 3-01, these chelating enone substrates **3** and **4**, as well as the reference substrate **2**, showed only poor reactivity without Lewis acid in the cycloadditions with nitrones **1** at room temperature. Even at a higher reaction temperature of 80 °C, only slow reactions were observed giving a diastereomer mixture of the regioselective cycloadducts **6** in poor *endo:exo* selectivities of 35:65 to 40:60 (Scheme 3-01). However, to our delight, the reactions were accelerated in the presence of Lewis acid catalyst at room temperature, and some reactions were complete even at a lower temperature of 0 °C when catalyzed by either diisopropyloxytitanium dichloride or triisopropyloxytitanium chloride. High to exclusively high *endo*-selectivities were attained in the reactions of chelating enones **3** and **4**. The maximum *endo:exo* diastereoselectivities observed were >99:1 at 0 °C, and 94:6 at room temperature. On the other hand, zinc(II) chloride catalyst showed rather poor catalytic activity. Extremely improved selectivity was not observed in the reactions using reference substrate **2**. These results indicate that effective catalysis would be developed by the appropriate design of chelating 1,3-dipolarophiles and by the proper choice of effective Lewis acid catalysts showing a high catalytic activity.

### 3.2 Magnesium ion catalyzed nitrone cycloadditions to allylic alcohols

**Catalytic nitrone cycloadditions to allylic alcohols.**[17] In 1994 we reported the first successful regio- and diastereoselective nitrile oxide cycloadditions with allylic alcohols in the presence of magnesium ions.[39] Use of magnesium alkoxides of allyl alcohols is especially useful leading to the exclusive formation of 2-isoxaxoline-5-methanol derivatives through a chelated transition state. We report here the metallic base-induced and Lewis acid-catalyzed cycloadditions of nitrone 1,3-dipoles, with one oxidation level lower than nitrile oxides, to allyl alcohol dipolarophiles. The regio- and stereoselectivity depend upon the kind of metals included in the organometallics or Lewis acids employed. These reactions provide the first example of effective regio- and stereocontrol of nitrone cycloadditions to nonactivated alkenes.

*N*-(Benzoylmethylene)aniline *N*-oxide (**6**), one of the most reactive nitrones, was selected. This 1,3-dipole **6** reacted smoothly with 2-propen-l-ol (**7a**) as terminal allylic alcohol alkene at room temperature for 24 h giving a diastereomer mixture of isoxazolidine-5-methanol derivative **8a** in 78% yield (*endo* : *exo* = 97:3). On the other hand, reaction of the same nitrone **6** with (*E*)-2-buten-1-ol (**7b**) as internal allylic alcohol alkene needed a higher reaction temperature (Scheme 3-02). Under reflux in THF for 24 h, a regioisomeric mixture of isoxazolidine cycloadducts, isoxazolidine-5-methanol **8b** as *exo*-isomer and isoxazolidine-4-methanol **9** as *endo*-isomer, was produced (94%, *exo*-**8b**:*endo*-**9** = 18:82).

**Scheme 3-02** Lewis acid-catalyzed cycloaddition reactions of nitrones 6 to allylic alcohol derivatives 7




| Alkenes | Catalyst[a] | equiv | Solvent | Temp/°C | Time/h | Products | Yield/% | *endo*:*exo* |
|---|---|---|---|---|---|---|---|---|
| **7a** | - | - | $CH_2Cl_2$ | rt | 24 | *exo*-**8a** + *endo*-**8a** | 78 | 97:3 |
| **7a** | EtMgBr | 1 | $CH_2Cl_2$ | rt | 1 | *exo*-**8a** + *endo*-**8a** | 93 | 98:2 |
| **7a** | $Et_2Zn$ | 1 | $CH_2Cl_2$ | rt | 3 | *exo*-**10a** | 57 | single |
| **7a** | $MgBr_2$•$Et_2O$[b] | 1 | $CH_2Cl_2$ | rt | 5 | *exo*-**8a** | 81 | single |
| **7a** | $ZnBr_2$[b] | 1 | $CH_2Cl_2$ | rt | 5 | *exo*-**11a** | 65 | single |
| **7b** | - | - | THF | reflux | 24 | *exo*-**8b** + *endo*-**9** | 94 | 18:82 |
| **7b** | EtMgBr | 1 | $CH_2Cl_2$ | rt | 3 | *exo*-**8b** + *endo*-**9** | 97 | 98:2 |
| **7b** | $Et_2Zn$ | 1 | $CH_2Cl_2$ | rt | 5 | *exo*-**10b** | 57 | single |
| **7b** | $MgBr_2$•$OEt_2$[b] | 1 | $CH_2Cl_2$ | rt | 5 | *exo*-**8b** | 77 | single |
| **7b** | $MgBr_2$•$OEt_2$ | 0.1 | $CH_2Cl_2$ | rt | 6 | *exo*-**10b** | 59 | single |
| **7b** | $ZnBr_2$ | 1 | $CH_2Cl_2$ | rt | 5 | *exo*-**11b** | 65 | single |
| **7b** | Ti(OPr-*i*)$_2$$Cl_2$[b] | 0.1 | $CH_2Cl_2$ | rt | 5 | *exo*-**11b** | 82 | single |
| **7b** | | 0.1 | $CH_2Cl_2$ | rt | 12 | *exo*-**11b** | 58 | single |
| **7b** | Ti(OPr-*i*)$_3$Cl $BF_3$•$OEt_2$ | 0.1 | $CH_2Cl_2$ | rt | 10 | *exo*-**11b** | 75 | single |

[a]Organometallics were treated wlth allylic alcohols for 30 min prior to cycloaddition. [b]Five equivalents of allylic alcohols **7** were used.

When allylic alcohols were pretreated with ethylmagnesium bromide prior to cycloadditions, high rate enhancement and improved regioselectivity were attained: The reaction of benzoylnitrone **6** with magnesium ally alkoxide **7'a** (X = MgBr) in dichloromethane was complete within 1 h at room temperature giving isoxazolidine-5-methanol **8a** in 93% yield with an *exo*:*endo* ratio of 98:2. Effective rate acceleration was also achieved in the reaction of **6** with magnesium alkoxide of crotyl alcohol **7'b** (X = MgBr), where the regioselectivity observed in the thermal reaction using **7b** (X = H) was definitely reversed: Isoxazolidine-5-methanol *exo*-**8b** became the far major regioisomer rather than isoxazolidine-4-methanol *endo*-**9** (*exo*-**8b**:*endo*-**9** = 98:2, Scheme 3-02). To our surprise, zinc alkoxide dipolarophiles **7'a,b** (X = ZnEt), prepared in situ from allylic alcohols **7a,b** and diethylzinc in dichloromethane, showed the absolutely reversed regioselectivity on the reactions with benzoyl nitrone **6**, and the ring-fused hemiacetal derivatives of isoxazolidine-4-methanols *exo*-**10a,b** were produced both as single diastereomers.

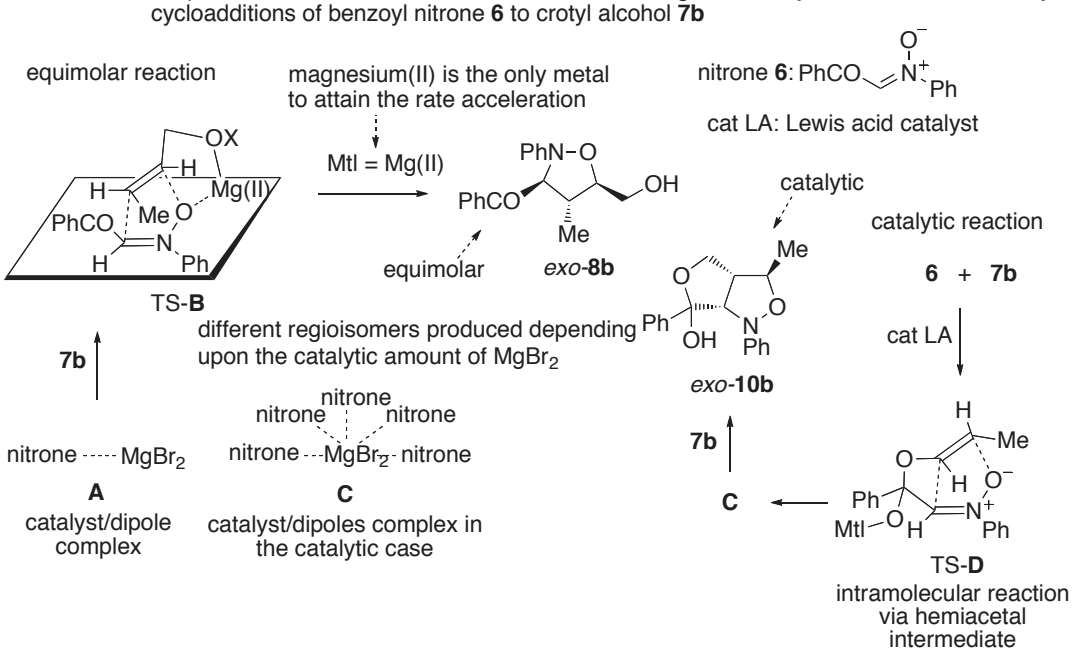
Thus, it is found that the regio- and diastereoselectivities achieved in the 1,3-dipolar cycloadditions of benzoyl nitrone **6** to metal alkoxides **7'** (X = metal) of allylic alcohol dipolarophiles depend upon the kind of alkoxide metals: Magnesium alkoxides **7'** (X = MgBr) mediated the production of isoxazolidine-5-methanol derivatives **8a,b**, as *exo*-isomers, but zinc alkoxides **7'** (X = metal) mediated the

production of ring-fused hemiacetals **10a,b** derived from 3,4-*cis*-isoxazolidine-4-methanol regioisomers (Scheme 3-02).

Instead of the reaction using metal alkoxides **7'** (X = metal) of allylic alcohols, the cycloaddition reactions using free alcohol substrates **7** (X = H) can be also effectively accelerated in the presence of Lewis acid. The regioselectivity again depends upon the kinds of metals included in the Lewis acid catalyst (Scheme 3-02). From magnesium bromide- and zinc(II) bromide-catalyzed reactions, *exo*-**8a,b** and *exo*-**11a,b** were produced as single diastereomers, respectively. Acetal products *exo*-**11a,b** may be derived from the originally produced the 3,4-*cis*-isoxazolidine-4-methanol cycloadducts, followed by subsequent formation of hemiacetals *exo*-**10a,b** and *O*-alkylation. *O*-Alkylation took place because a large excess of allylic alcohols **2** (X = H) exists under acidic conditions.

A catalytic amount of magnesium bromide (10 mol%) worked well in the reaction of benzoyl nitrone **6** with crotyl alcohol **7b**. However, the product *exo*-**10b** obtained in this catalytic case was regioisomeric to the isomer *exo*-**8b** produced in the reaction using equimolar or excess amount of catalyst (Scheme 3-02).[17] Use of dichlorodiisopropyloxytitanium, chlorotriisopropyloxytitanium, or boron trifluoride etherate, all in catalytic amounts, gave the equivalent product *exo*-**11b**.

**Scheme 3-03** Proposed reaction mechanism for the reversal of regioselectivity in the Lewis acid catalyzed cycloadditions of benzoyl nitrone **6** to crotyl alcohol **7b**




The molar ratio between nitrone **6** and magnesium bromide is an important factor that determines the regiochemistry of cycloadducts. When each equimolar amount was used, a 1:1 catalyst/dipole complex **A** was isolated as stable complex since nitrone **6** is a strong Lewis base. The hydroxyl oxygen of crotyl alcohol (**7b**) can coordinate to the metal ion of **A** to give a dipole/catalyst/dipolarophile(s) complex. Thus, nitrone **6** and diplarophile **7b** react through a chelated transition state TS-**B** to give *exo*-**8b** (Scheme 3-03).[17] When magnesium bromide is in a catalytic amount, several molecules of nitrone **6** combine with the metal ion of catalyst to form a catalyst/dipoles complex **C**. Accordingly, coordination of further molrcules of crotyl alcohol dipolarophile becomes to be limited. The exclusive production of *exo*-**8b** in

the reaction with crotyl alkoxide **2'b** (X = MgEt) may be on the same basis.

Two possible reaction mechanisms can be proposed for the dramatic reversal of regioselectivity, also diastereoselectivity as well:

(1) When magnesium bromide is used in a catalytic amount, several numbers of nitrone **1** coordinate to the metal of catalyst to form a catalyst/dipoles complex **C**. Accordingly, further coordination of crotyl alcohol dipolarophile is sterically hindered.
(2) The other reaction mechanism, probably more likely, includes the Lewis acid catalyzed formation of hemiacetal intermediate and subsequent intramolecular nitrone/alkene cycloaddition (mechanism TS-**D**). This reaction can explain the consistency for both regio- and stereoselectivities observed.

Although the isolated 1:1 catalyst/dipole complex **A** reacted with crotyl alcohol (**7b**) to give *exo*-**8b**, the reaction between equimolar amounts of **6** and **7b** in the presence of a catalytic amount (10 mol%) of **B** gave *exo*-**10b**. Presumably, complex **A** was rapidly transformed to complex **C** when treated with excess of nitrone **6**. The reason why the catalytic reaction via complex **C** was so accelerated in an regioselective and stereoselective manner remained unsolved.

As mentioned above, we developed the first successful synthetic method of regio- and stereoselective 1,3-dipolar cycloadditions between a carbonyl-conjugated reactive nitrone and allylic alcohols in the presence of a catalytic amount of Lewis acids. When allylic alcohols bearing a chirality at α-position are employed in the metal-mediated nitrone cycloadditions, a question of diastereofacial selectivity arises. Analysis of the stereochemical pathways of this reaction should provide us important informations to solve the reaction mechanism for the metal ion-dependent change of regioselectivity.

**Nitrone cycloadditions to α-chiral allylic alcohols.**[18] Accordingly, the metal ion-catalyzed nitrone cycloadditions to allylic alcohols bearing a chirality at α-positon were examined. Reaction of (*Z*)-*N*-(benzoylmethylene)aniline *N*-oxide (*Z*-**6**) with 3-buten-2-ol (**12a**), as terminal allylic alcohol bearing a small methyl substituent at the α-chiral center, proceeded smoothly at room temperature to give a 53:47 mixture of the 3,5-*cis* isomers of isoxazolidine-5-methanol cycloadduct **13a** and 1**3'a** (Scheme 3-04 and Table 3-05). Although the regio- and diastereoselectivities of this reaction were thus perfect even in the absence of metal ion, the diastereofacial selectivity with regard to the α-chirality (stereochemical relationship between C-5 and C-1') of **2a** was very poor. This is not surprising. When an equimolar amount of $MgBr_2$•$OEt_2$ is present, the reaction was highly accelerated to finish in 1 h under equivalent conditions, and the diastereofacial selectivity observed was not perfectly high (*syn:anti* = 84:16) even under such a rate enhancement.

Not so great improvement of selectivity was achieved even when the substituent $R^1$ at the α-chiral center was replaced with propyl and phenyl substituents as shown in the reactions with **12b,c** (*syn* : *anti* = 88:15 to 88:12). Allylic alcohol substrates **12a-c** are all terminal allylic alcohol dipolarophiles so that they show some enough reactivity to be highly reactive to benzoyl nitrone **6** even under noncatalyzed conditions. Accordingly, the observation of only moderate diastereofacial selectivities are due to the competitive noncatalyzed cycloadditions which are virtually stereorandom. Thus, the rate acceleration based on a

chelated transition state is somehow *saturated* in the reaction with terminally unsubstituted allylic alcohols.

To our delight, however, (*E*)-3-penten-2-ol (**2d**) as a disubstituted inner allylic alcohol reacted with benzoyl nitrone **6** in the presence of $MgBr_2$•$OEt_2$ to give a 96:4 stereoisomeric mixture of 3,5-*cis*-isoxazolidine-5-methanol **13d** and **13'd**. When the α-substituent is bulky isopropyl group, a single diastereomer of cycloadduct **13e** was produced. Stereostructure of the major diastereomer **13d** was determined to be the *syn*-isomer with regard to the α-chirality (between C-5 and C-1') on the basis of spectral data, especially the NOE spectrum measured in nonpolar deuteriobenzene.

**Scheme 3-04** 1,3-Dipolar cycloadditions of benzoyl nitrone **6** with α-chiral allylic alcohols **12** in the presence of a catalytic amount of Lewis acid catalysts

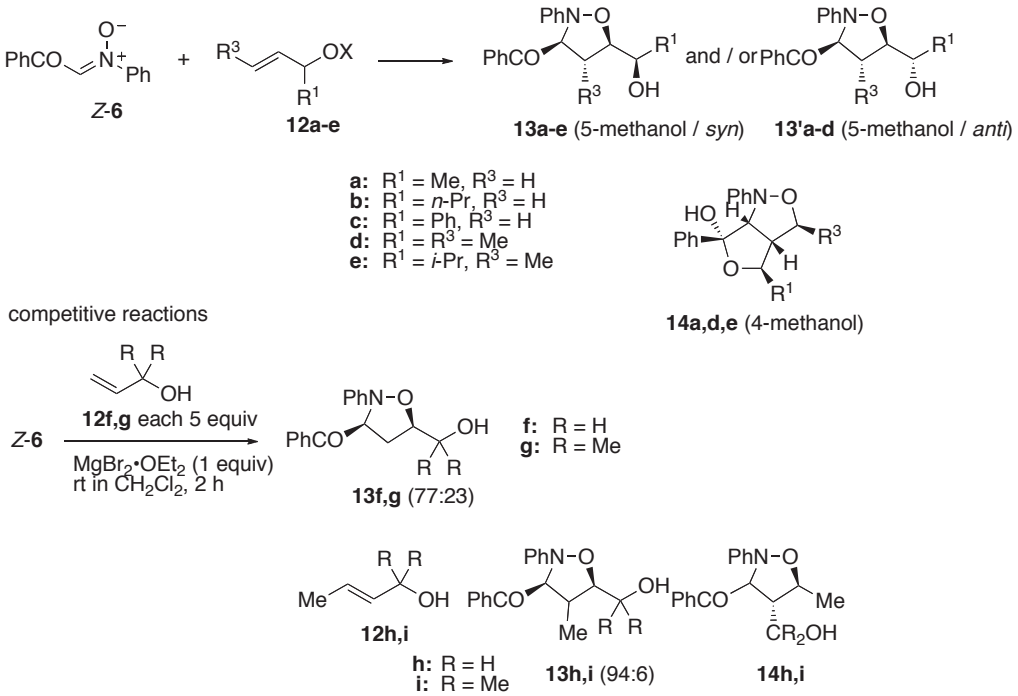



**Table 3-05** Lewis acid catalyzed diastereofacial cycloadditions of benzoylnitrone **6** with α-chiral allylic alcohols 1**2**

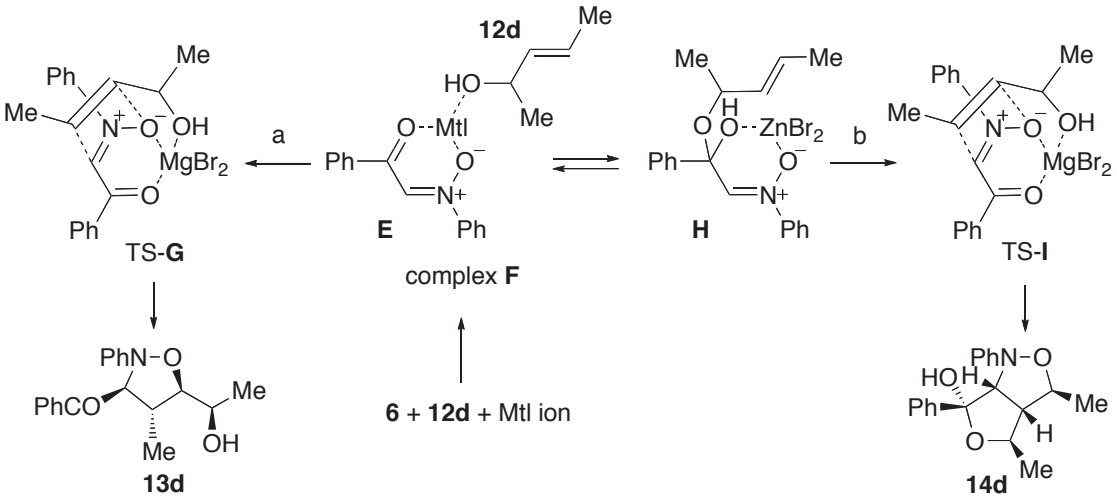
| Allylic alcohols 1**2** | | | Additives | Time/h | Products | Yield/% | Isomer ratio |
|---|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | | | | | |
| **12a** | Me | H | None | 10 | **13a** + 1**3'a** | quant | 53:47 |
| | | | $MgBr_2$•$OEt_2$ | 1 | **13a** + 1**3'a** | 89 | 84:16 |
| | | | $ZnBr_2$ | 5 | **13a** + 1**3'a** + **14a** | 73 (73:27) + 18 | |
| **12b** | n-Pr | H | None | 10 | **13b** + 1**3'b** | 95 | 55:45 |
| | | | $MgBr_2$•$OEt_2$ | 1 | **13b** + 1**3'b** | 96 | 85:15 |
| **12c** | Ph | H | $MgBr_2$•$OEt_2$ | 1 | **13c** + 1**3'c** | 91 | 88:12 |
| **12d** | Me | Me | $MgBr_2$•$OEt_2$ | 5 | **13d** + 1**3'd** | 85 | 96:4 |
| | | | $ZnBr_2$ | 5 | **14d** | 46 | single |
| **12e** | *i*-Pr | Me | $MgBr_2$•$OEt_2$ | 5 | **13e** | 47 | single |
| | | | $ZnBr_2$ | 20 | **14e** | 33 | single |
| **12g** | R = Me | | None | 24 | **13g** | 70 | single |
| | | | $MgBr_2$•$OEt_2$ | 2 | **13g** | 83 | single |
| | | | $ZnBr_2$ | 5 | **13g** | 49 | single |
| **12i** | R = Me | | None | 24 | **13i** + 1**4i** | 15 | 82:18 |
| | | | $MgBr_2$•$OEt_2$ | 5 | **13i** | 6 | single |

As described above, $ZnBr_2$ and $MgBr_2$•$OEt_2$ catalysts showed different catalysis in nitrone cycloadditions to such allylic alcohols as 2-propen-1-ol (**12f**) and (*E*)-2-buten-1-ol (**12h**). However, when the

α-substituted terminal allylic alcohol **12a** was used in the reaction catalyzed with $ZnBr_2$, the major product obtained was not the expected perhydrofuro[3,4-*c*]isoxazolole **14a** (18%) which corresponds to the cyclized product of an isoxazolidine-4-methanol regioisomer, but instead a mixture of the isoxazolidine-5-methanol cycloadducts **13a** and **13'a** was obtained (*syn:anti* = 73:27, 73%). This result indicates that the α-substitution of allylic alcohol dipolarophiles receives little benefit from the $ZnBr_2$-induced transition state so that the noncatalyzed reaction becomes the major reaction path producing **13a** and **13a'**. This was confirmned by the result that the $ZnBr_2$-catalyzed reactions of the inner allylic alcohols **12d,e** were perfectly regio- and *syn*-selective to give **14d,e** as single products, respectively.

When two substituents are introduced at the α-position of 2-propen-l-ol as shown with **12g**, the reactions with nitrone **6** gave the isoxazolidine-5-methanol **13g** as a single product, regardless of the difference of reaction conditions. This again indicates an extreme rate depression of the $ZnBr_2$-catalyzed reaction by steric effects. On the other hand, only a little rate deceleration resulted in the $MgBr_2$•$OEt_2$-catalyzed reaction where the relative reaction rate of 77:23 (= **13f**:**13g**) was recorded in the competitive cycloaddition reaction using each 5 equiv of 2-propen-l-ol (**12f**) and 2-methyl-3-propen-2-ol (**12g**) (Scheme 3-04). With less reactive (*E*)-2-methyl-3-penten-2-ol (**12i**) as substrate, however, an extremely decreased reactivity was observed. Thus, the competitve reaction of **6** with (*E*)-2-buten-l-ol (**12h**) and **12i** under the $MgBr_2$•$OEt_2$-catalyzed conditions gave a 94:6 mixture of **13h,i**.

**Scheme 3-06** Two reaction modes of $MgBr_2$•$OEt_2$-catalyzed (path a) and $ZnBr_2$-catalyzed (path b) cycloadditions of nitrone **6** to the α-chiral inner allylic alcohol **12d**




Based on the metal ion-mediated rate enhancement and diastereofacial selectivities observed above, two reaction modes could be figured out (modes a and b in Scheme 3-06).[18] The carbonyl-conjugated nitrone **6** interacts with a metal ion (Mtl) to form the *Z*-nitrone complex **E**, the metal part of which is further coordinated by an allylic alcohol dipolarophile leading to complex **F**. Although the nitrone cycloaddition via the transition state TS-**G** (mode a) can be accelerated to give **13d** when Mtl is $Mg^{2+}$ ion, $Zn^{2+}$ ion would not show such an accelerating effect. Accordingly, the second possible reaction is the Lewis acid-catalyzed carbonyl addition of the alcohol dipolarophile to give the hemiacetal intermediate **H** (path b). Intramolecular dipolar cycloaddition of **H** via the transition state TS-**I** leads to **14d**. These reaction mechanisms are consistent with the $Mg^{2+}$ ion-specific rate acceleration, the diastereofacial selectivities, and the serious rate sensibility to steric effects of the $ZnBr_2$-catalyzed reaction forming the sterically hindered intermediate **H**. Reaction of benzoyl nitrone **6** with **12h** in dichloromethane in the presence of

$Mg^{2+}$ led to the exclusive formation of **13h**, while a 34:66 regioisomeric mixture of **13h** and **14h** in THF. The stability of complex **F** would be reduced in THF since it is a highly coordinating solvent. When $Mg^{2+}$ ion is catalytic, the reaction via TS-**G** becomes slower to allow the competitive carbonyl addition.

### 3.3 Lewis acid catalyzed *E/Z*-isomerization of nitrones

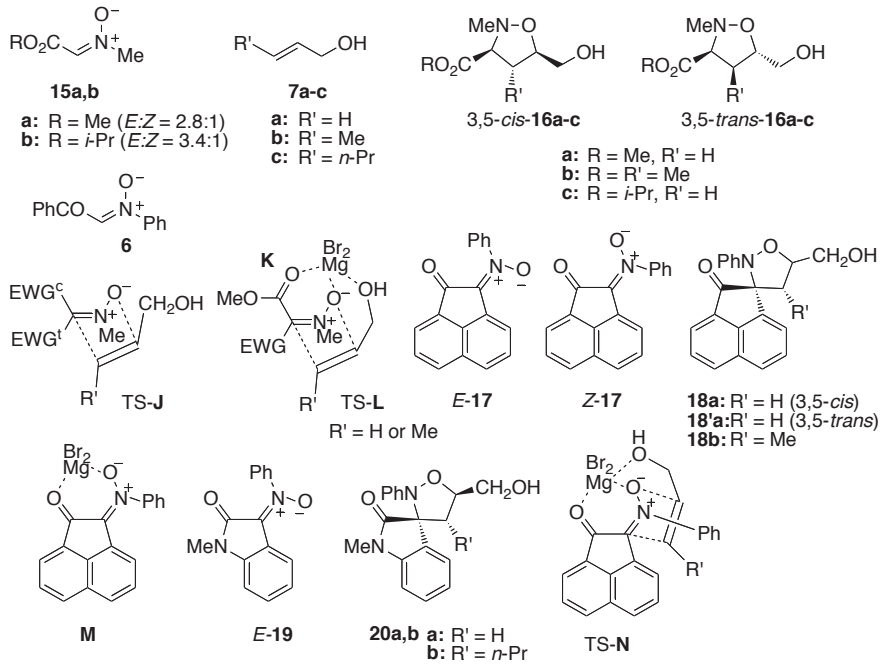
Two examples of Lewis acid-catalyzed 1,3-dipolar cycloadditions of nitrones were recently reported from our research group, which include:

(1) the *endo*- and regioselective nitrone cycloadditions to bidentate and tridentate α,β-unsaturated ketones catalyzed by $Ti(OPr\text{-}i)_nCl_{4-n}$ (n = 2, 3) and

(2) the *exo*-selective cycloadditions of a benzoylnitrone to allylic alcohols catalyzed by $MgBr_2 \bullet OEt_2$ or $ZnBr_2$.

In the latter case, high rate acceleration and the dramatic reversal of regioselectivity resulted depending upon the nature and amount of the Lewis acid used. On the other hand, it is well known titanium tetraisopropoxide $Ti(OPr\text{-}i)_4$ undergoes smooth ester exchange reactions with a variety of ester substrate, especially ready reaction takes place when the ester reagents have strong chelating ability. When ester-conjugated nitrones are used in the study of nitrone cycloadditions under the catalysis of Lewis acid catalysts, the possibility of Lewis acid catalyzed ester exchange has to be in consideration.

**Scheme 3-07** Lewis acid-catalyzed isomerization of nitrones **6, 15, 17, 19** and stereoselective cycloaddition reactions to allylic alcohol derivatives **7**




| Substrates[a] | Catalyst[b] | Temp/°C | Time/h | Products | Yield/% | Diasteromer ratio[c] |
|---|---|---|---|---|---|---|
| **15a** + **7a** | - | rt | 24 | **16a** | 41 | 44:56 |
| **15a** + **7a** | $MgBr_2 \bullet OEt_2$ | rt | 24 | **16a** | 71 | 3,5-*cis*-**16a** only |
| **15a** + **7b** | - | 83 | 48 | **16b** | 97 | 4 isomers |
| **15a** + **7b** | $MgBr_2 \bullet OEt_2$ | 40 | 48 | **16b** | 48 | 3,5-*cis*-**16b** only |
| *E*-**17** + **7a** | - | 110 | 12 | **18a** + **18'a** | 65 | 69:31 |
| *E*-**17** + **7a** | $MgBr_2 \bullet OEt_2$ | 61 | 2.5 | **18a** | 82 | single |
| *E*-**17** + **7b** | $MgBr_2 \bullet OEt_2$ | 61 | 8 | **18b** | 50 | single |
| *E*-**19** + **7a** | $MgBr_2 \bullet OEt_2$ | 83 | 2 | **20a** | 79 | single |
| *E*-**19** + **7c** | $MgBr_2 \bullet OEt_2$ | 83 | 5 | **20b** | 89 | single |

[a]5 Equivalents of allylic alcohols were used in all reactions. [b]One equivalent was used. [c]3,5-*cis* : 3,5-*trans* isomers.

However, no ester exchange reaction occurred in the $MgBr_2$•$OEt_2$-catalyzed cycloadditions of ester-conjugated nitrones to allyl alcohol, but instead the 3,5-*cis*-isomers of isoxazolidine-5-methanol derivatives were given as single isomers. Lewis acid catalyst $MgBr_2$•$OEt_2$ is effective for the *E*- and *Z*-isomerization of carbonyl-conjugated nitrones so that cycloadditions of the resulting nitrones are highly stereo- and regioselective under the catalyzed conditions.[19] Methyl (methylimino)acetate *N*-oxide (**15a**) as ester-conjugated nitrone is available as an *E:Z* mixture at room temperature, the isomer ratio changes depending upon the polarity of solvent used: *E/Z* = 6 in benzene, 3.6 in chloroform, and 0.67 in dimethyl sulfoxide. Ester-conjugated nitrone **15a** (*E/Z* = 2.8) reacted regioselectively with 2-propen-1-ol (**7a**) at room temperature to give a mixture of 3,5-*trans*- and 3,5-*cis*-isomers of 5-hydroxymethylisoxazolidine-3-carboxylate **16a** and the isomer ratio was again dependent upon the reaction solvent: 3,5-*trans*-**16a** : 3,5-*cis*-**16a** = 63:37 (48 h, 89%) in benzene, 56:44 (24 h, 41%) in dichlorimethane, and 22:78 (20 h, 4%) in dimethyl sulfoxide. Thus, the stereoselectivity observed in these nitrone cycloadditions reflects on the *E/Z* isomer ratio of nitrone **15a**, as expected from the assumed transition state TS-**J** (Scheme 3-07, R' = H) in which the hydroxylmethyl moiety is located *anti* to the *N*-methyl substituent. However, selectivities were not so exclusive.

A high rate acceleration was observed in the peresence of of an equimolar amount of $MgBr_2$•$OEt_2$ to give the 3,5-*cis*-isomer of **16a** as single stereoisomer in 71% yield.[19] With less reactive (*E*)-2-buten-1-ol (**7b**), the excellent improvement of both stereo- and regioselectivities was attained also in the presence of $MgBr_2$•$OEt_2$ (1 equiv) to give 3,5-*cis*-**16b** as a single product. Presumably, the catalyst $MgBr_2$•$OEt_2$ promoted the *E*- to *Z*-isomerization of nitrone **15a** (*E/Z* = 2.8), and the resulting *Z*-nitrone complex **K** would be the actual reacting species involved. The proposed transition state TS-**L** can explain the observed stereo- and regioselectivities (Scheme 3-07).

2-(Phenylimino)acenaphthenone *N*-oxide (**17**) as keto nitrone, existing exclusively in an *E*-form in chloroform solution, underwent isomerization in the presence of $MgBr_2$•$OEt_2$ under reflux in 1,2-dichloroethane to give a 91:9 mixture of *Z/E*-isomers. The *Z*-enriched mixture of **17** isomerized back to pure *E*-**17** in a few hours at room temperature. Under reflux in toluene, keto nitrone **17** showed only a limited reactivity to allylic alcohol **7a** to give a stereoisomeric mixture of spiro isoxazolidine **18a** and **18'a** (ds = 69:31). Under the $MgBr_2$•$OEt_2$-catalyzed conditions, however, cycloadduct **18a** was produced as a single isomer in an excellent yield; the exclusively stereo- and regioselective isomer **18b** was obtained from the less reactive dipolarophile **7b**. Presumably the *Z*-nitrone/$MgBr_2$ complex **M** would be involved in the transition state TS-**N** where the magnesium ion coordinates all to the alcohol oxygen, the nitrone oxygen, and the carbonyl oxygen atoms.

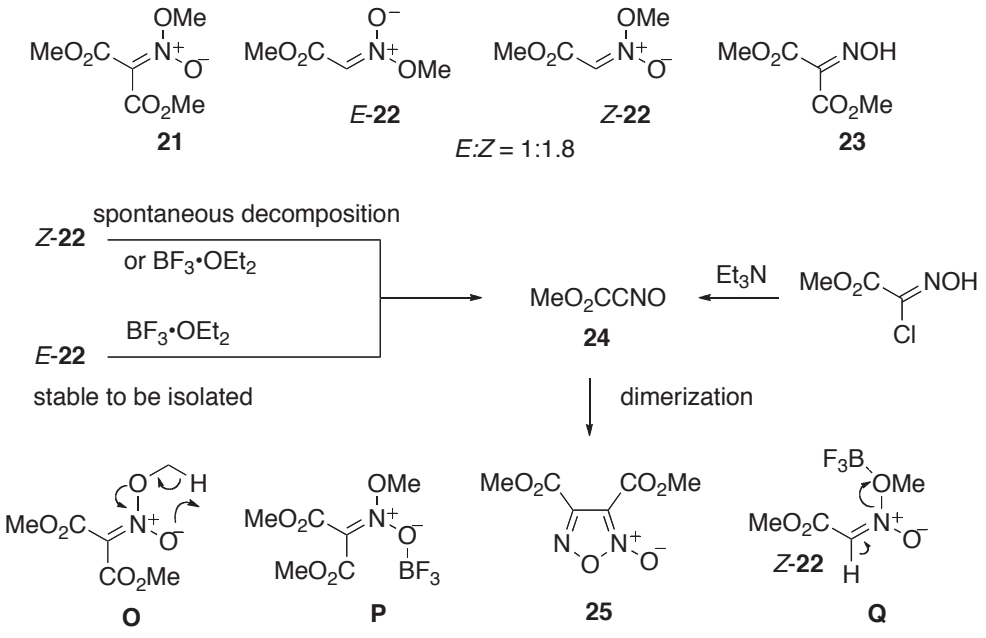
An amide type nitrone existing in an *E*-form, 1-methyl-3-phenylimino-2,3-dihydroindol-2-one *N*-oxide (**19**), also showed a poor reactivity to allylic alcohols. However, it reacted with **7a,c** under the $MgBr_2$•$OEt_2$-catalyzed conditions to give **20a,b** as single stereoisomers. Thus, Lewis acid-promoted *E*- to *Z*-isomerization of carbonyl-conjugated nitrones was achieved at the first time. The *Z*-nitrone/$MgBr_2$ complexes show an enhanced reactivity to allylic alcohols due to the metal coordination leading to excellent stereo- (*exo*-) and regioselectivities. Other Lewis acids such as $ZnBr_2$, $BF_3$•$OEt_2$, Ti(OPr-*i*)$_4$ did not show any activity for the isomerization of nitrones; $MgBr_2$ worked as the only effective promotor. No

clear interpretation is so far in hand for the magnesium ion specificity, but the above findings should contribute to the stereo- and regiocontrolled ring formation methodology through 1,3-dipolar cycloadditions.

**3.4 Lewis acid catalyzed nitronate cycloadditions.** Alkyl or silyl nitronates derived from primary nitroalkanes undergo cycloaddition reactions with activated alkenes to produce *N*-alkoxy- or *N*-silyloxyisoxazolidines which then undergo spontaneous or acid catalyzed β-elimination of alcohol (or silanol) to give 2-isoxazolines. Accordingly, through a cycloaddition/elimination sequence, *C*-monosubstituted nitronates become useful synthetic equivalents of nitrile oxides 1,3-dipoles. Nitronates show a reactivity similar to that of nitrones, and nitrones are one of the 1,3-dipoles which have been successfully developed to catalyzed asymmetric versions. So, catalyzed asymmetric nitronate cycloadditions could be open if an appropriate combination of nitronates and a chiral Lewis acid is selected. Like nitrones, nitronates would be activated by electron-withdrawing substituent(s) on the carbon even toward electron-poor alkenes, and such activated nitronates should be favored in the study of nitrile oxide cycloaddition equivalents. However, electron-deficient nitronates are often unstable; half life times are usually shorter than a few days, and sometimes a few hours. We examined the stability of ester-activated nitronates under uncatalyzed and Lewis acid catalyzed conditions and also tried to find reactive dipolarophiles toward these unstable nitronates.

We report the preparation, isolation, and characterization of methyl nitronates derived from methyl nitroacetate and dimethyl nitromalonate. The stability test under uncatalyzed or Lewis acid catalyzed conditions was investigated. Beside the known decomposition through irreversible sigmatropic fragmentation, a new nitrile oxide generation by β-elimination of nitronates under neutral conditions was discovered. This nitrile oxide generation is accelerated by a catalytic amount of Lewis acid catalyst. Magnesium alkoxides of allylic alcohols showed high reactivity to these electron deficient nitronates to give either isoxazolidines or isoxazolines depending upon the substituents of the allylic alcohols.

**Scheme 3-08** Decomposition of isomeric nitronates **22** under neutral or metal mediated conditions

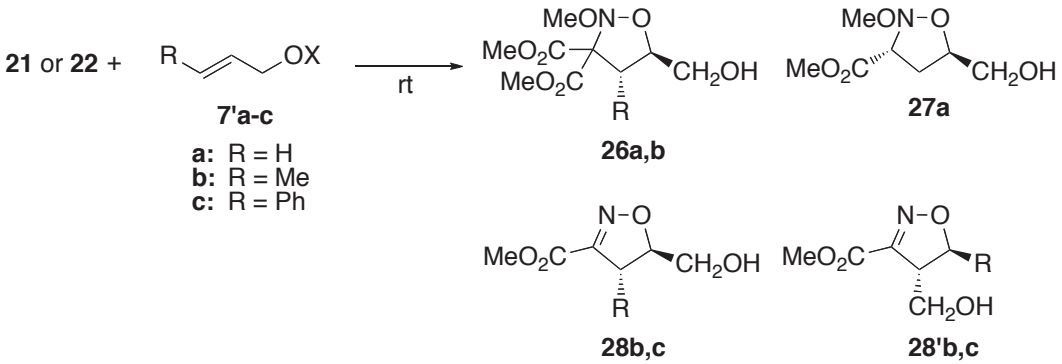


Nitronates are usually in situ generated and directly used in cycloadditions with an excess amount of dipolarophiles. The most convenient preparation method of nitronates is the *O*-methylation of "enolizable" nitroalkanes with diazomethane. Thus, two nitronic esters, *N*-methoxy-*N*-[bis-(methoxycarbonyl)methylene]amine *N*-oxide (**21**) and *N*-methoxy-*N*-(methoxycarbonylmethylene)amine *N*-oxide (**22**), were prepared by *O*-methylation, with diazomethane at a low temperature, of dimethyl nitromalonate and methyl nitroacetate, respectively. Diester nitronate **21** could be isolated as colorless solid, but a fairly rapid decomposition took place in chloroform at room temperature. In 2 days in deuteriochloroform, nitronate **21** was entirely consumed to give oxime **23** through an irreversible sigmatropic fragmentation (**O** in Scheme 3-08).[20] Because of its instability, cycloadditions of **21** with dipolarophiles were quite limited. Only poor yields of cycloadducts were produced in uncatalyzed reactions with a variety of dipolarophiles such as norbornene, methyl acrylate, dimethyl maleate, ethyl vinyl ether, and allyl alcohol (in all cases equivalent amounts were used). However, the magnesium alkoxide of allyl alcohol **7'a** (X = MgBr) showed an exceptionally high reactivity to **21** producing dimethyl isoxazolidine-3,3-dicarboxylate **26a** in a quantitative yield (Scheme 3-09). This indicates that the reaction of nitronates with allylic alcohols can be highly accelerated by the presence of magnesium ion. However, the magnesium alkoxide of crotonyl alcohol **7'b** (X = MgBr) was much less reactive. Increasing steric hindrance at the reaction site may be a major reason for the decreased reactivity.

The monoester nitronate **22** was also isolable, but quite labile. Especially, the major isomer of **22** (isomer ratio = 1.8:1) underwent a faster decomposition than the other isomer (decomposed in 4 days at room temperature in deuteriochloroform) than the minor isomer. Consequently, the minor isomer remained was isolated in a pure form after purification by column chromatography. Decomposition product of the major isomer was not sigmatropic fragmentation product, but 3,4-bis(methoxycarbonyl)-1,2,5-oxadiazole *N*-oxide (**25**), formed by the dimerization of methoxycarbonylformonitrile oxide (**24**) generated from **22** by the β-elimination of methanol. This will be discussed below. Due to the close resemblance of spectral data, structures of two geometrical isomers of nitronates **22** could not be distinguished. We temporarily assigned the more stable (minor) isomer to be the *E*-isomer *E*-**22** on the basis of the anticipated relative stability: the less stable (major) *Z*-isomer *Z*-**22** may have a geometry more favored for both β-elimination and fragmentation reactions.

Although the monoester nitronate **22** showed a higher reactivity than diester nitronate **21** toward ethyl acrylate, ethyl vinyl ether, allyl and crotyl alcohols, yields of cycloadducts were not satisfactory either. A mixture of isoxazolidines and/or isoxazolines was produced in less than 20% of combined yields when a mixture of stereoisomers of **22** was employed (equivalent amounts of dipolarophile). It should be noted that the pure *Z*-isomer *Z*-**22** isolated is inert to both allyl and crotyl alcohols (Scheme 3-09).[20] Presumably either the *E*-isomer *E*-**22** was more reactive than *Z*-**22** or nitrile oxide **24** as the decomposition product participated in the reaction. In this case also, the magnesium alkoxides of allylic alcohols **7'a-c** (X = MgBr) were excellent dipolarophiles to produce isoxazolidine **27a** (R = H) from allyl alkoxide (**7'a**) and regioisomeric mixtures of isoxazolines **28b,c** and **28'b,c** (R = Me and Ph) from crotyl and cinnammyl alkoxides (**7'b,c**, X = MgBr). Elimination of methanol from the initial isoxazolidines depends upon the existence of substituent at the 4 position. High rate acceleration in the magnesium ion mediated nitrone cycloadditions to allylic alcohols was previously reported by our group.

**Scheme 3-09** Metal mediated cycloaddition reactions of nitronates **21** and **22** with allylic alcohols **7'**




| Dipole | R | X | Time/h | Product | Yield/% | Ratio |
|---|---|---|---|---|---|---|
| **21** | H | MgBr | 1 | **26a** | quant | - |
| | Me | MgBr | 48 | **26c** | trace | - |
| **22** | H | MgBr | 3 | **27a** | 82 | - |
| | Me | MgBr | 5 | **28b** + **28'b** | 80 | 6.8:1 |
| *E*-**22** | H | H | 48 | **-** | 0 | - |
| | Me | H | 48 | **-** | 0 | - |
| | H | MgBr | 1 | **27a** | quant | - |
| | Me | MgBr | 3 | **28b** + **28'b** | quant | 7.1:1 |
| | Ph | MgBr | 5 | **28c** + **28'c** | 80 | 5.5:1 |

In the presence of a catalytic amount (10 mol%) of $BF_3$•$OEt_2$, decomposition of the diester nitronate **21** leading to oxime **23** was suppressed. This would be rationalized that coordination of the Lewis acid catalyst to the nitronate oxygen deactivates the irreversible sigmatropic fragmentation because of the lowered basicity of the coordinated oxygen atom (**B** in Scheme 3-08). On the other hand, both isomers of monoester nitronate **22** underwent a smooth decomposition in the presence of a catalytic amount of $BF_3$•$OEt_2$ at room temperature. The decomposition product formed in a quantitative yield was the nitrile oxide dimer **25**, the authentic sample of which was prepared from nitrile oxide **24**. Thus, the mono-substituted nitronate **22** undergoes either spontaneous or Lewis acid catalyzed β-elimination giving the corresponding nitrile oxide **24** (**C** in Scheme 3-08), the catalyzed reaction being much faster.

Coordination of Lewis acid to the methoxyl oxygen of nitronate **22** would accelerate the β-elimination of the methoxyl moiety. However, we believe that, in the reactions of **22** with the magnesium alkoxides of allylic alcohols **7'**, not nitrile oxide **24** but nitronate **22** is responsible for the formation of isoxazolines **28**. Reasons are that (1) the reaction with allyl substrate **7'a** (X = MgBr) produced isoxazolidine derivative **27a**, and (2) the reaction of nitrile oxide **24** with **7'b** (X = MgBr) is not a high yield reaction. Lewis acidity of the magnesium ion of the substrates **7'** (X = MgBr) would be insufficient to mediate such a nitrile oxide generation; the reactivity of magnesium alkoxides of allylic alcohols is faster than the rate of β-elimination. This indicates that use of a weak Lewis acid catalyst would lead to effective Lewis acid catalysis in nitronate cycloadditions.

1,3-Dipolar cycloadditions of *C*-monosubstituted nitronates to alkenes produce isoxazolidine derivatives which then undergo β-elimination to give 2-isoxazolines under acidic conditions. Accordingly, through this cycloaddition/β-elimination sequence, nitronates can be a useful synthetic equivalent of nitrile

oxides. Importance of nitrile oxide cycloaddition is based on the high synthetic potential of 2-isoxazolines in which a variety of important functionalities are masked such as β-hydroxy ketones, γ-amino alcohols, 1,3-diols, α,β-unsaturated ketones, and others. Nitrile oxides having an additional functionality are required in synthetic point of view, but such examples are quite limited.

Since nitronates should have a reactivity similar to nitrones, it is expected that their cycloadditions can be catalyzed by a Lewis acid catalyst. However, no successful examples are known so far for the Lewis acid catalyzed nitronate cycloadditions; in the presence of a strong Lewis acid such as $BF_3$•$OEt_2$, nitronates are converted to nitrile oxides through β-elimination. In the preceding paper, we already reported the facile cycloadditions of electron-deficient nitronates to the magnesium alkoxides of allylic alcohols, while the nitrile oxide generation is a fast reaction when catalyzed by $BF_3$•$OEt_2$.

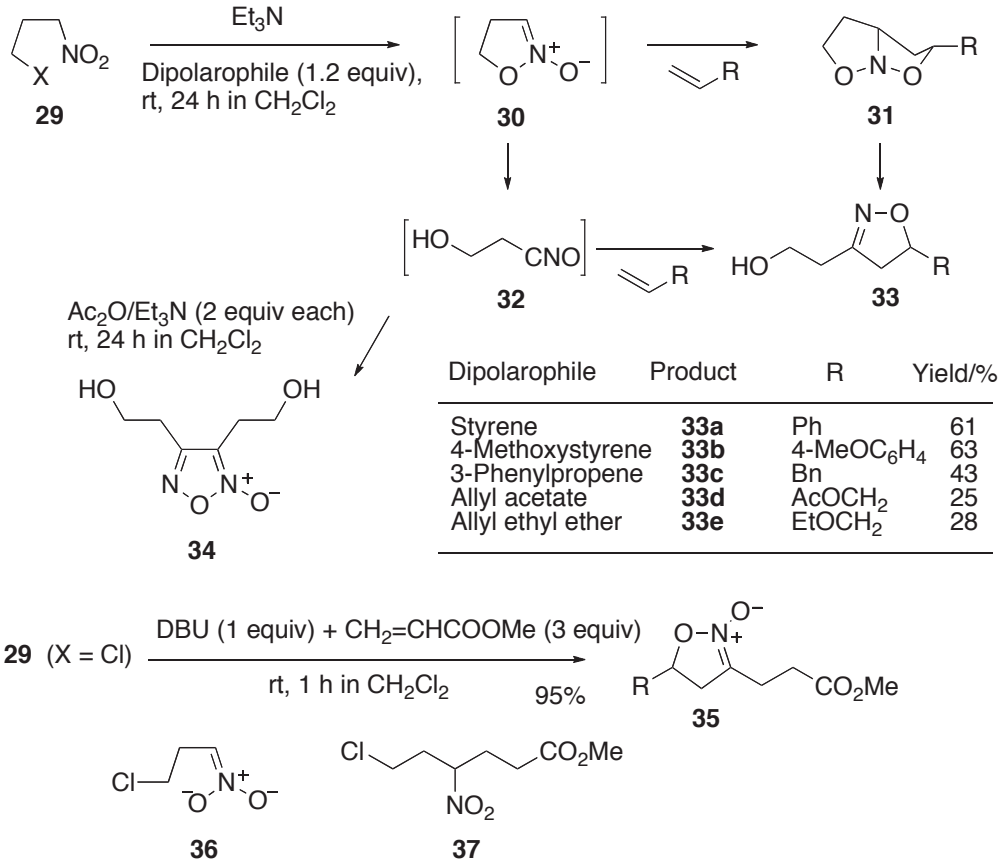
Therefore, reactive nitronates with a higher stability under Lewis acid catalyzed conditions are required to achieve the Lewis acid catalyzed nitronate cycloadditions. From these standpoints, we planed to utilize 3-unsubstituted cyclic nitronates; they would be a useful synthetic equivalent of nitrile oxides functionalized by a hydroxyalkyl group.[21] High synthetic utility of cyclic nitronates was well established by a series of pioneering works by Denmark. His reaction includes the initial step of [4+2] hetero Diels-Alder type cycloaddition of nitroalkenes with electron rich alkenes to form cyclic nitronates which are utilized for the subsequent 1,3-dipolar cycloadditions.[22] 3-Substituted cyclic nitronates are readily accessible by dehydrohalogenation of ω-halo-α-nitroalkanes with a base, but either synthesis or reaction of 3-unsubstituted cyclic nitronates is rare. We report the preparation of cyclic nitronates from 3-iodo-1-nitropropane and 4-iodo-l-nitrobutane by action with a base. These 1,3-dipoles can be trapped with a variety of monosubstituted ethenes to give 3-(2-hydroxyethyl)-2-isoxazolines or perhydroisoxazolo-[2,3-*b*]isoxazines depending upon the ring size of nitronates. The ring-fused isoxazolidines are transformed by treatment with an acid into 3-(3-hydroxypropyl)-2-isoxazolines in quantitative yields. Therefore, these cyclic nitronates are useful synthetic equivalents of functionalized nitrile oxides.

When 3-iodo-l-nitropropane (**29**, X = I) was treated with triethylamine (2 equiv) in dichloromethane in the presence of styrene (1.2 equiv) at room temperatyre for 24 h, 3-(2-hydroxyethyl)-5-phenyl-2-isoxazoline (**33a**) was obtained regioselectively in 61% yield (Scheme 3-10).[21] 4-Methoxystyrene as dipolarophile provided the best yield, but the maximum yield for cycloadduct **33b** was only 63%. Although single regioisomers were produced in all cases, trapping with less reactive alkenes such as 3-phenylpropene (43%), allyl acetate (25%), and allyl ethyl ether (28%) was rather ineffective (1.2 equiv in all cases). Two mechanisms are possible for the formation of **33**: By action with triethylamine, **29** cyclizes to form 2-isoxazoline *N*-oxide (**30**) which then undergoes either cycloaddition giving nitronate cycloadducts **31** or generation of nitrile oxide **32** through ring opening by β-elimination. We believe that the 2-isoxazoline cycloadducts **33** have been produced via a nitrile oxide route on the basis of the following informations:

(1) No trace of nitronate cycloadducts **31** was detected,
(2) β-Elimination of **31** should not be easy under the reaction conditions,
(3) Isoxazolidine ring is quite stable under basic conditions as observed for compounds **40**,

(4) The dimer of nitrile oxide **32** was produced as acetylated derivative **34** (30% yield) in the presence of acetic anhydride without dipolarophile.

**Scheme 3-10** Cycloaddition reactions of cyclic nitronate **30** with alkenes

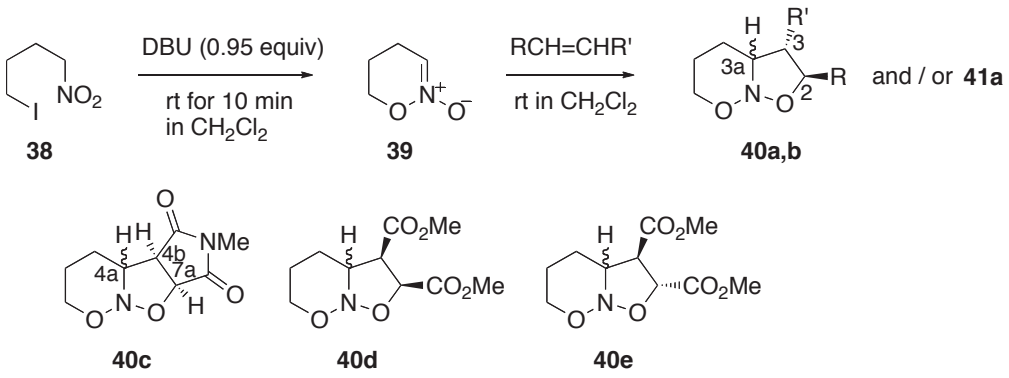



| Dipolarophile | Product | R | Yield/% |
|---|---|---|---|
| Styrene | **33a** | Ph | 61 |
| 4-Methoxystyrene | **33b** | 4-$MeOC_6H_4$ | 63 |
| 3-Phenylpropene | **33c** | Bn | 43 |
| Allyl acetate | **33d** | $AcOCH_2$ | 25 |
| Allyl ethyl ether | **33e** | $EtOCH_2$ | 28 |

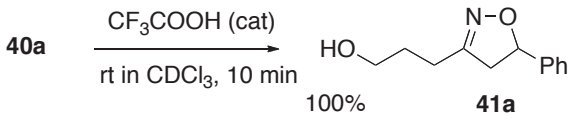
Electron deficient alkenes could not be used successfully to trap nitronate **30** (or nitrile oxide **32**). For example, when nitronate generation was carried out from 3-chloro-l-nitropropane (**29**, X = Cl) and DBU in the presence of methyl acrylate, the 3-alkylated nitronate **35** was produced quantitatively as highly stable compound. DBU and **29** (X = Cl) would generate a high concentration of nitronate anion **36** which can be smoothly trapped by the acrylate to give Michael adduct **37**; the subsequent base-mediated cyclization gives **35**.

High stability of **35** indicates that the unsubstitution at 3-position of **30** is the major reason for its instability under basic conditions. Actually, isolation of the 3-unsubstituted nitronate **30** was rather difficult. Since β-elimination of **30** leading to nitrile oxide **32** should be accelerated by a base, use of excess base should be avoided to isolate the base-labile nitronate **30**. Thus, **29** (X = I) was reacted with an amount slightly less than 1 equiv of DBU at room temperature for 10 min to give **30** (20% yield based on $^1$H NMR) together with the unreacted **29**. However, separation and isolation of pure **30** through column chromatography failed. This ready β-elimination may be favored because of its *Z*-geometry of the cyclic nitronate moiety of **30** in which the imine hydrogen at 3-position is antiperiplanar to the leaving oxygen group.

**Scheme 3-11** Cycloaddition reactions of cyclic nitronate **39** with alkenes

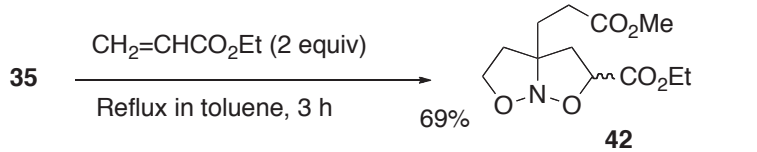



| Dipolarophile | Time/h | Product | R and R' in dipolarophile | Yield/% | Isomer ratio |
|---|---|---|---|---|---|
| Styrene | 18 | **40a** | R = H, R' = Ph | 52 | 3,3a-*trans* only |
| Methyl acrylate | 3 | **40b** | R = H, R' = $CO_2Me$ | 75 | 3,3a-*trans/cis* = 91:9 |
| *N*-Methykmaleimide | 10 min | **40c** | RR' = CON(Me)CO | 90 | 4a,4b-*trans/cis* = 78:22 |
| Dimethyl maleatte | 24 | **40d** | R = R' = $CO_2Me$ (*Z*) | 42 | 3,3a-*trans* only |
| Dimethyl fumarate | 3 | **40e** | R = R' = $CO_2Me$ (*E*) | 81 | 53:47 |




Six-mernbered nitronate, 5,6-dihydro-4*H*-1,2-oxazine *N*-oxide (**39**), was similarly generated and trapped with styrene: Reaction of 4-iodo-1-nitrobutane (**38**, X = I) with triethylamine (2 equiv) at room temperature for 72 h in the presence of styrene (1.2 equiv) gave a mixture of ring-fused isoxazolidine **40a** and 2-isoxazoline **41a** in 52 and 7% yields, respectively (Scheme 3-11).[21] The nitronate cycloadduct **40a** could be easily transformed into 3-(3-hydroxypropyl)-5-pheny-2-isoxazoline (**41a**) in a quantitative yield by treatment with a catalytic amount of trifluoroacetic acid at room temperature for a short time. When **38** (X = I) was treated with an amount slightly less than 1 equiv of DBU at room yemperature for 10 min, nitronate **39** was isolated in 80% yield. This nitronate **39**, a colorless liquid with a fairly high stability, was applied to the reactions with a variety of dipolarophiles. Monosubstituted alkenes such as styrene and methyl acrylate showed a moderate reactivity; 2,3a-*trans*-isomers of ring-fused isoxazolidines **40a,b** having a substituent at 2-position were produced as a single or major diastereomer. *N*-Methylmaleimide was highly reactive to give a stereoisomeric mixture of **40c** in a high yield, the major isomer of which was assigned as 4a,4b-*trans*-structure (*exo*-isomer) on the basis of the NOE spectrum between H-4a/H-4b of the minor diastereomer. Reactions with dimethyl maleate and fumarate were both absolutely stereospecific; although the maleate adduct **40d** was a single 3,3a-*trans*-stereoisomer, a low isomer ratio of stereoisomeric mixture of **40e** was produced from the fumarate.

**Scheme 3-12** Cycloaddition reactions of *C*-substituted cyclic nitrone **35** with an acrylate



As mentioned above, the 3-alkylated nitronate **35** was quantitatively obtained in the reaction of **29** (X = Cl) with methyl acrylate. Although this nitronate **35** was not highly reactive, it underwent cycloaddition with an excess amount of ethyl acrylate under reflux in toluene to give a stereoisomeric mixture (2,3a-*cis* : *trans* = 27:73) of 2,3a-disubstituted nitronate cycloadduct **42**.

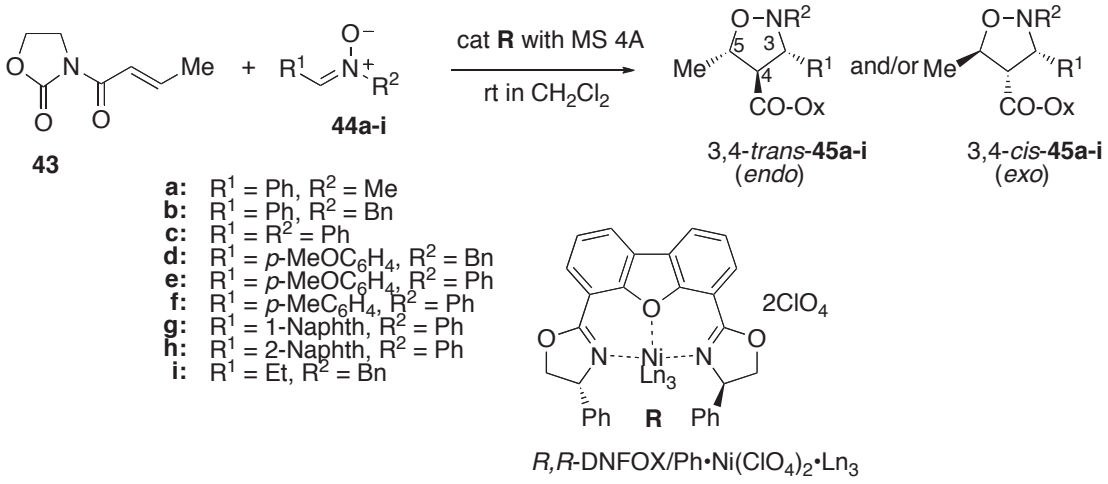
### 3.5 Catalytic enantioselective nitrone cycloadditions

A new tridentate *trans*-chelating chiral ligand, 4,6-dibenzofurandiyl-2,2'-bis(4-phenyloxazoline), was developed by us. Its complexes with transition metal perchlorates act as excellent chiral Lewis acid catalysts in the Diels-Alder reactions of cyclopentadiene to 3-alkenoyl-2-oxazolidinones.[23] We expected that the same combination of catalysts and alkenes would be applied to catalyzed asymmetric 1,3-dipolar cycloadditions. We report that the aqua complex derived from (*R,R*)-4,6-dibenzofurandiyl-2,2'-bis(4-phenyloxazoline) ligand (*R,R*-DBFOX/Ph) and $Ni(ClO_4)_2 \bullet 6H_2O$ acts as excellent chiral Lewis acid catalyst in asymmetric 1,3-dipolar cycloadditions of nitrones to 3-(2-alkenoyl)-2-oxazolidinones. The observed enantioselectivity of >99% and the minimum catalytic loading of 2 mol% are much more effective than previous examples.[24] The presence of MS 4A is essential to attain high selectivities. The results are satisfied by an *endo* approach of *Z*-isomers of nitrones leading to 3,4-*trans*-isoxazolidines with 4*R*,5*S* absolute configurations. The effect of water on both *endo*-selectivity and enantioselectivity can be explained by involving the transition structure including a substrate complex of trigonal bipyramid geometry.

In the presence of 10 mol % of the anhydrous nickel catalyst **R** (Ln = none), which can be prepared in situ from (*R*,*R*)-DBFOX/Ph ligand, $NiBr_2$, and two equimolar amounts of $AgClO_4$, the reaction of 3-crotonoyl-2-oxazolidinone (**43a**) with *N*-benzylidenemethylamine *N*-oxide (**44a**) produced 3,4-*trans*-isoxazolidine **45a** in near perfect *endo* selectivity (*endo:exo* = 99:1) and enantioselectivity for the 3*S*,4*R*,5*S*-enantiomer (>99% ee for the *endo*-isomer, Scheme 3-13).[24] The aqua nickel complex **R** (Ln = $H_2O$), which can be simply prepared in situ by stirring equimolar amounts of the (*R*,*R*)-DBFOX/Ph ligand and $Ni(ClO_4)_2,6H_2O$ in dichloromethane for a few hours, gives a comparable result in a similar reaction in the presence of MS 4A. The simple preparation procedure of the aqua catalyst should be attractive.

The presence of MS 4A is essential to attain high selectivities, especially in the reactions catalyzed by the aqua complex. In the absence of MS 4A, the *endo* selectivity and enantioselectivity for 3,4-*trans*-isoxazolidines are both lowered. Jørgensen was the first to observe a dramatic effect of MS 4A in Lewis acid-catalyzed nitrone cycloadditions. In his reaction, the chemical yield of the cycloadduct was not affected by the absence of MS 4A, but the *endo* selectivity was lowered (*endo:exo*, from 92:8 to 65:35) and the enantioselectivity almost disappeared (79 to 2% ee). Our results are comparable. Although the role of MS 4A cannot yet be fully explained, it certainly works as dehydrating agent. In a reaction catalyzed by the aqua nickel complex **R** (Ln = $H_2O$), anhydrous magnesium sulfate can replace MS 4A, but the reaction becomes a little slower. As shown in Scheme 313, reactions of other nitrones **43b-f** are also diastereoselective (*endo:exo* $\geq$ 95:5) and enantioselective for *endo*-**45b-f** (higher than 95% ee for **45a**,**b**,**d**,**f** and 89% ee for **45c**,**e**). High efficiency of the catalytic cycle can be demonstrated in the reactions of nitrone **44d**: a 99% ee for *endo*-**45d** is recorded with 2 mol% of the catalyst at room temperature and a 93% ee with 1 mol% even under reflux in dichloromethane.

**Scheme 3-13** Enantioselective cycloaddition reactions of nitrones **44a-i** to 3-crotonoyl-2-oxazolidinone **43** under the catalysis of *R,R*-DBFOX/Ph•Ni$(ClO_4)_2$•$Ln_3$



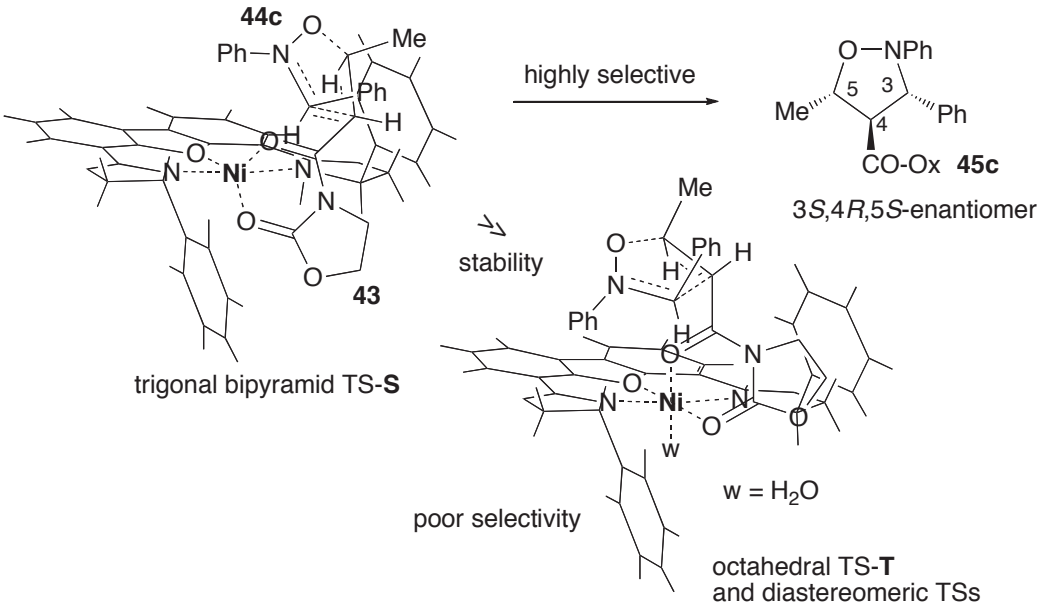

| 44 | Catalyst / mol% | MS 4A[a] | Product | Temp/°C | Yield/% | Ds[b] | % ee[c] |
|---|---|---|---|---|---|---|---|
| **44a** | $Ni(ClO_4)_2$ / 10 | 100 | **45a** | rt | 63 | 99:1 | >99 |
| **44a** | $Ni(ClO_4)_2/6H_2O$ / 10 | 100 | **45a** | rt | 72 | 98:2 | >99 |
| **44b** | $Ni(ClO_4)_2/6H_2O$ / 10 | 500 | **45b** | rt | 76 | >99:1 | 95 |
| **44c** | $Ni(ClO_4)_2/6H_2O$ / 10 | 300 | **45c** | rt | 96 | 98:2 | 89 |
| **44d** | $Ni(ClO_4)_2/6H_2O$ / 10 | 300 | **45d** | rt | 73 | >99:1 | >99 |
| **44d** | $Ni(ClO_4)_2/6H_2O$ / 2 | 500 | **45d** | rt | 75 | >99:1 | 99 |
| **44d** | $Ni(ClO_4)_2/6H_2O$ / 1 | 300 | **45d** | reflux | 37 | >99:1 | 93 |
| **44d** | $Ni(ClO_4)_2/6H_2O$ / 10 | 500[d] | **45d** | rt | 100 | 97:3 | 99 |
| **44e** | $Ni(ClO_4)_2$ / 10 | 100 | **45e** | 0 | 87 | 95:5 | 89 |
| **44e** | $Ni(ClO_4)_2/6H_2O$ / 10 | 300 | **45e** | rt | 100 | >99:1 | 87 |
| **44f** | $Ni(ClO_4)_2/6H_2O$ / 10 | 500 | **45f** | rt | 100 | 99:1 | >99 |
| **44g** | $Ni(ClO_4)_2/6H_2O$ / 10 | 500 | **45g** | rt | 25 | 74:26 | 9 |
| **44h** | $Ni(ClO_4)_2/6H_2O$ / 10 | 500 | **45h** | rt | 100 | 99:1 | 45 |
| **44i** | $Ni(ClO_4)_2/6H_2O$ / 10 | 500 | **45i** | rt | 92 | 94:6 | 97 |

[a]Weight of MS 4A (mg) per 1 mmol scale. [b]*endo/exo* ratio. [c]% ee for *endo*-isomers.
[d]In the presence of magnesium sulfate instead of MS 4A.

The nitrone having a bulky aromatic *C*-substituent such as *N*-(1-naphthylmethylene)aniline *N*-oxide (**44g**) shows a little decreased reactivity, the chemical yield, diastereoselectivity, and enantioselectivity being all poor, while the isomer *N*-(2-naphthylmethylene)aniline *N*-oxide (**44h**) is sufficiently reactive. It is pleasing that the nitrone **44i** derived from an aliphatic aldehyde also shows excellent diastereoselectivity as well as enantioselectivity for the *endo*-**45i**. Thus, the DBFOX/Ph•Ni$(ClO_4)_2$•$3H_2O$-catalyzed asymmetric nitrone cycloaddition in the presence of MS 4A has the most promising features with respect to the catalytic cycle, diastereoselectivity, and enantioselectivity among the catalyzed reactions yet reported.

Absolute configurations of isoxazolidines *endo*-**45b** and *endo*-**45c** were determined to be a 3*S*,4*R*,5*S* structure by comparison of the optical rotations as well as retention times in a chiral HPLC analysis with those of the authentic samples. Other 3,4-*trans*-isoxazolidines **45a** and **45d-i** were assigned by similarity of the proposed transition structures. Selection of the *si* face at the Cβ position of alkene **43a** in nitrone cycloadditions is the same as that observed in the Diels-Alder reactions of cyclopentadiene with **43a** in the presence of the (*R*,*R*)-DBFOX/Ph•Ni$(ClO_4)_2$•$3H_2O$ complex, and this indicates that the *s-cis* conformation of alkene **43a** has participated in the reaction.

**Scheme 3-14** Proposed transition structure TS-**S** for the *endo*-selective approach of (*Z*)-nitrones **44c** leading to (3*S*,4*R*,5*S*)-isoxazolidines **45c**




The simple structure of DBFOX complex catalysts facilitates discussion of transition structures and provides insight into the role of MS 4A. On the basis of ab initio molecular orbital calculations of a model nitrone cycloaddition, a variable-temperature $^1$H NMR study of the substrate complex derived from DBFOX/Ph•Zn($ClO_4$)$_2$ and 3-acetyl-2-oxazolidinone, and the observed high catalytic activity, the nitrone cycloaddition in the presence of MS 4A is most likely to proceed through the transition structure TS-**S** with a trigonal-bipyramid structure (Scheme 3-14).[24] Face shielding by one of the 4-phenyl substituents (the top 4-phenyl) becomes very effective, and the other 4-phenyl substituent (the bottom 4-phenyl) inhibits the exo approach of nitrone **44**. As a result, the reaction shows high *endo* and enantioselectivities in the absence of water. In the reactions catalyzed by the aqua DBFOX/Ph complex in the absence of MS 4A, a water molecule coordinates on the nickel ion so that octahedral transition structure TS-**T** becomes predominant. The reaction site of the coordinated substrate in TS-**T** is more open for the approach of nitrone **44**, and both the *si* and *re* faces (Cβ), showing low enantioselectivity. In addition, the *exo* approach of nitrone **3** leading to 3,4-*cis*-isoxazolidines is not difficult, and poor *endo* selectivity results. Even when a trace of water is present, TS-**S** may participate predominatly in the reaction since the octahedral complex catalyst should be less reactive than the trigonal bipyramid complex catalyst based on the trans effect by the aqua ligand.

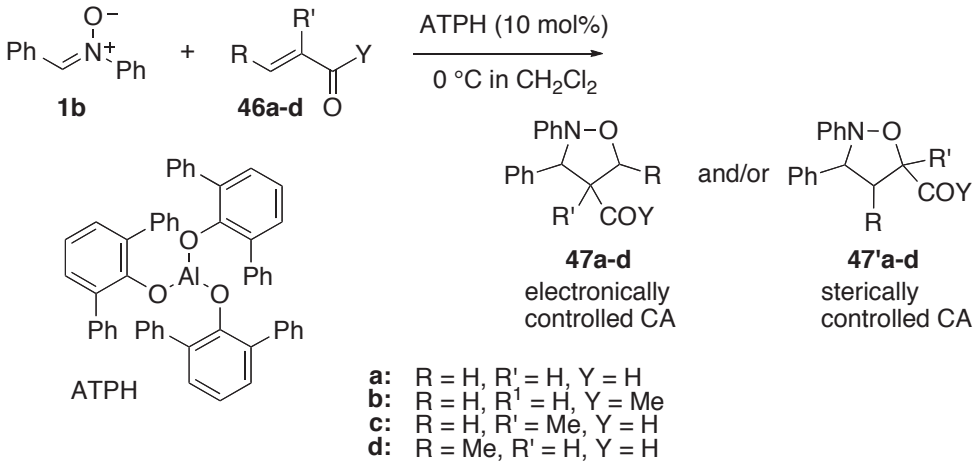
Thus, the aqua complex derived from the DBFOX/Ph ligand and Ni($ClO_4$)$_2$•6$H_2O$ is found to act as excellent chiral Lewis acid catalyst in the presence of MS 4A in asymmetric 1,3-dipolar cycloadditions of nitrones to 3-(2-alkenoyl)-2-oxazolidinones. Maximum enantioselectivities observed were as high as >99% ee, and the minimum catalytic loading was 2 mol %. The presence of MS 4A is essential to attain such high selectivities. These excellent diastereoselectivities and enantioselectivities for the 3,4-*trans*-isoxazolidines with 4*S*,5*R* absolute configurations arise from the transition structure involving a trigonal bipyramid substrate complex.

### 3.6 Catalytic enantioselective nitrone cycloadditions with pinhole catalysts

Based on our basic researches on the synthetic methodology through 1,3-dipolar cycloadditions of nitrones and nitrile oxides, the first catalyzed asymmetric nitrone cycloaddition was reported by Jørgensen in 1994.[25] Up to now, quite a number of examples are known for the catalyzed asymmetric nitrone cycloadditions using electron-deficient alkenes.[26] However, even when highly chelating alkenes are employed, the binding of nitrones to the catalyst is still more favored. Effective activation of 1,3-dipolar cycloaddition reactions by a Lewis acid catalyst still remains a challenging subject, and a new idea to inhibit the undesired formation of nitrone/catalyst complex is needed. When the metal center of a Lewis acid is surrounded by bulky ligand(s), a small opening exists in the ligand sphere. In such a case, dipolarophiles can be effectively activated if appropriately selected.

We report effective activation of α,β-unsaturated aldehydes by use of aluminum tris(2,6-diphenylphenoxide), ATPH as a pinhole catalyst.[27] ATPH has been utilized as useful carbonyl protecting reagents, and only a limited number of reports have appeared for the catalytic use. We anticipated that ATPH would work well as a Lewis acid catalyst in nitrone cycloadditions, since the cycloaddition reaction of nitrones to the carbon-carbon double bond of α,β-unsaturated aldehydes leads to the formation of bulky isoxazolidines.

**Scheme 3-15** Nitrone cycloaddition reactions to α,β-unsaturated aldehydes **46a-d** in the presence of ATPH as pinhole catalyst




| Dipolarophile | Catalyst | Time/h | Yield/% | **47** : **47'** |
|---|---|---|---|---|
| Acrolein (**46a**) | None | 8 | 5 | 20:80 |
| | ATPH | 8 | quant | >99:1 |
| 3-Buten-2-one (**46b**) | None | 24 | 7 | 8:92 |
| | ATPH | 24 | 82 | 100:0 |
| Methacrolein (**46c**) | None | 22 | 5 | 0:100 |
| | ATPH | 22 | quant | 91:9 |
| Crotonaldehyde (**46d**) | None | 24 | 2 | 100:0 |
| | ATPH | 24 | quant | 100:0 |

*N*-Benzylideneaniline *N*-oxide (**1b**) shows only a poor reactivity towards acrolein (**46a**) in the absence of catalyst. When nitrone **1b** is allowed to react with **46a**, in dichloromethane at room temperature for 8 h in the absence of a catalyst, a 20:80 mixture of regioisomeric cycloadducts, 2,3-diphenylisoxazolidine-4-carbaldehyde (**47a**) and -5-carbaldehyde (**47'a**), was obtained in 5% total yield. The starting **1b** was

mostly recovered unchanged (Scheme 3-15). On the other hand, when the same reaction was performed in the presence of a catalytic amount of ATPH (10 mol%) at 0 °C in 8 h, isoxazolidine-4-carbaldehyde derivative **47a** was given as a single regioisomer in a quantitative yield (rs > 99:1), albeit in a poor diastereoselectivity (ds = 77:23). Thus, ATPH catalyst was so effective both for rate enhancement and improvement of regioselectivity.[27] Especially, the exclusive formation of the regioisomer **47a** as the electronically controlled product was surprising. Nitrone cycloadditions with electron deficient mono-substituted alkenes give isoxazolidine-5-carbaldehydes as major regioisomer, as shown in the reaction between **1b** and **46a**. Such dramatic shift of regioselectivity giving the electronically favored 4-substituted isoxazolidines is rare even in Lewis acid catalyzed reactions. Another point is the effective catalysis of ATPH.

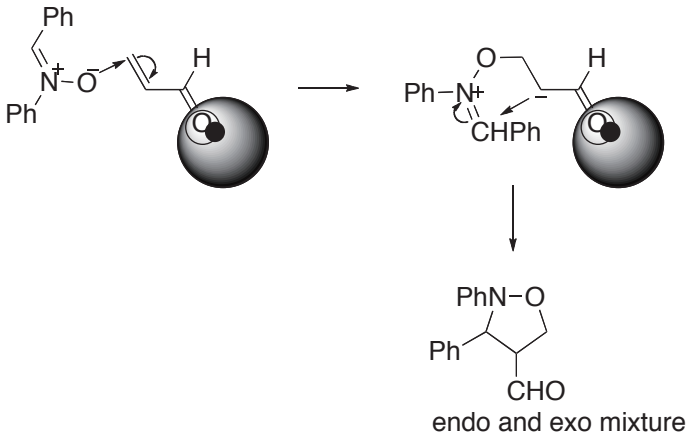
Although only a fair diastereoselectivity (ds = 77:23) could be observed in the ATPH-catalyzed reaction between **1b** and **46a**, the major diastereomer **47a** formed was characterized to be the *endo*-cycloadduct on the basis of $^1$H NMR spectrum. The major *endo*-diastereomer of **47a** shows 3-methine and 4-methine protons in higher fields and formyl proton in a lower field than those of the minor *exo*-cycloadduct of **47a** whose formyl group is magnetically shielded by the adjacent *cis*-phenyl group. The regiochemistry of **47a** was easily characterized by the lower chemical shifts for 5-methylene protons than those of **47'a**.

Dramatic change of regioselectivity was observed in the reaction of nitrone **1b** with 3-buten-2-one (**46b**). Without catalyst, the sterically controlled cycloadduct **47'b** was given as far major regioisomer after 24 h at room temperature (7%, **3b:4b** = 8:92). However, isoxazolidine-4-carbaldehyde **47b** was produced as a single isomer in 82% yield under catalytic conditions. Thus, not only the formyl group but also the rather bulky acetyl group can coordinate to the aluminum ion of ATPH catalyst.

Methacrolein (**46c**) and nitrone **1b** gave 5,5-disubstituted isoxazolidine **47'c** as a single regioisomer (5% yield). Under ATPH-catalysis, however, this reaction was accelerated at 0 °C to give a quantitative yield of mixture of regioisomeric cycloadducts **47c** and **47'c** (**rs** = 91:9). On the other hand, crotonaldehyde (**46d**) as a 1,2-disubstituted inner alkene reacted with nitrone **1b** in an exclusively regioselective manner under both noncatalyzed and ATPH-catalyzed conditions to give the isoxazolidine-4-carbaldehyde **47d** as the electronically controlled product. Methyl acrylate was not reactive both under noncatalyzed and ATPH-catalyzed conditions. Although the coordination of methyl esters to ATPH is known, a sufficient activation for nitrone cycloadditions was not attained.
In conclusion, the following new findings have been obtained:

(1) ATPH acts effectively as pinhole catalyst in 1,3-dipolar cycloaddition reactions of nitrones leading to reaction rate acceleration and an improvement of regioselectivity.
(2) ATPH selectively activates the alkene dipolarophiles with a relatively small electron-withdrawing substituent such as a formyl or acetyl group.
(3) α,β-Unsaturated esters cannot be activated effectively by ATPH, probably due to the steric bulkiness of ester group.
(4) The electronically controlled regioisomers are produced as major regioisomers in the ATPH-catalyzed nitrone cycloadditions.

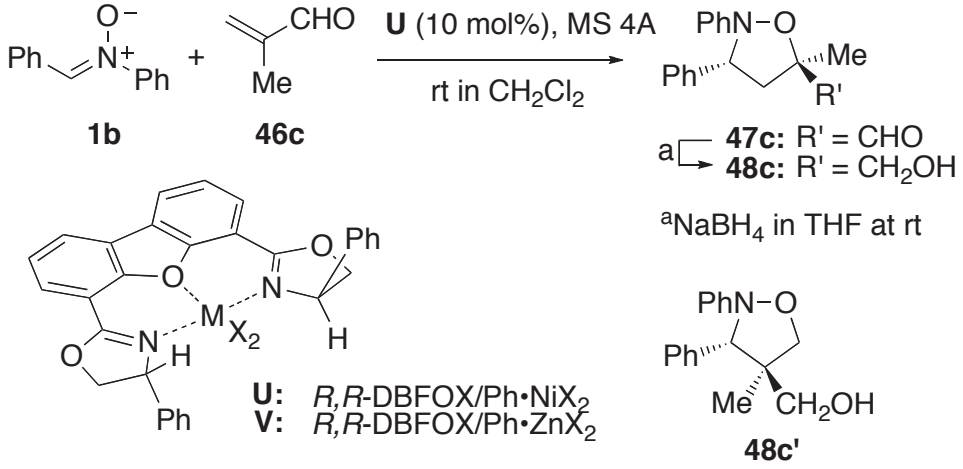
**Scheme 3-16** A possible reaction pathway including twitterionic intermediate




This effective catalytic cycle of ATPH should be noteworthy. Participation of betaine intermediates is likely to effect the catalytic cycle (Scheme 3-16): 1,3-dipolar cycloadditions possibly would proceed stepwise when catalyzed by a strong Lewis acid catalyst. Especially in the catalyzed reactions via the ATPH/dipolarophile complex, the α-position of dipolarophiles is sterically so hindered that the concerted bond formation in the 1,3-dipolar cycloadditions becomes difficult since it contains bond formation at the congested α-position. The betaine intermediate formed through the stepwise reaction is followed by cyclization which results in serious steric hindrance. Then, the free cycloadducts are liberated from the ATPH/cycloadduct complexes. If this is the case, ATPH would work as effective catalyst in 1,3-dipolar cycloaddition reactions using other 1,3-dipoles and α,β-unsaturated aldehydes.

Nitrones coordinate predominantly to the catalyst in Lewis acid-catalyzed nitrone cycloadditions. However, if the resulting Lewis acid/nitrone complexes still have a catalytic capability, the complexes would work as chiral pinhole catalysts (Scheme 3-17, **U** and **V**, Ln = nitrone(s) and/or anionic counterion(s)) and effective activation of α,β-unsaturated aldehydes can be expected. This expectation was actually realized.

**Scheme 3-17** The DBFOX/Ph nickel(II) complex catalyzed enantioselective nitrone cycloaddition reactions to α,β-unsaturated aldehyde **46c**

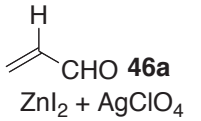
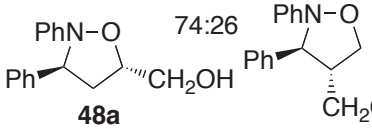
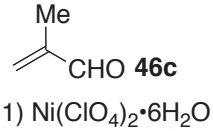
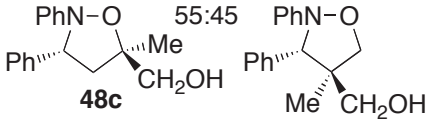
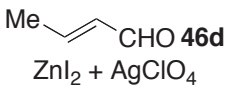
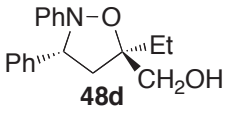
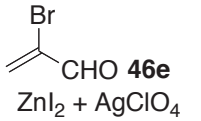
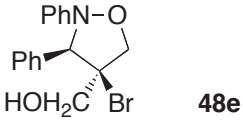
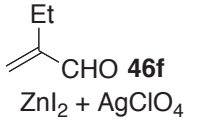
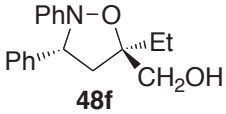
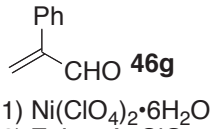
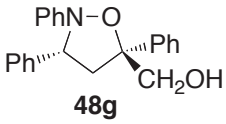
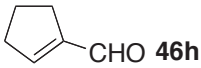
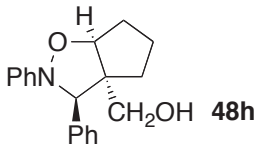


We describe the DBFOX/Ph complex-catalyzed enantioselective nitrone reactions to α,β-unsaturated aldehydes. The sterically controlled isoxazolidine-5-carbaldehydes are produced in the reactions of α-alkyl- and α-arylacroleins in the presence of either nickel(II) or magnesium complexes, while the electronically controlled isoxazolidine-4-carbaldehydes are given in the zinc(II) complex-catalyzed reactions with α-bromoacrolein. The reactions with other aldehydes such as acrolein, crotonealdehyde, and 1-cyclopentenecarbaldehyde have been examined under the catalysis of nickel(II), zinc(II), and cobalt(II) complexes. It has been found that a variety of DBFOX/Ph complexes of zinc(II) salts are isolable and storable in open air without loss of catalytic activity, and replacement of one iodide anion of the $ZnI_2$ complex with a noncoordinating anion leads to the most powerful catalysts. Enantioselectivities up to 99.5% ee have been observed in the reactions performed at room temperature.[28]

Reaction of *N*-benzylideneaniline *N*-oxide (**1b**) with methacrolein (**46c**) in dichloromethane at room temperature (48 h) in the presence of MS 4A (500 mg/mmol) and 10 mol% of the nickel(II) complex **U**, prepared by stirring equivalents of *R,R*-DBFOX/Ph and $Ni(ClO_4)_2•6H_2O$ in the same solvent for a few hours, gave a single diastereomer of isoxazolidine-5-carbaldehyde **47c** as a sterically controlled regioisomer as shown in Scheme 3-17. Reduction of **47c** with $NaBH_4$ produced isoxazolidine-5-methanol **48c** (73% based on **1b**) whose enantiopurity was determined to be 96% ee. Although the zinc(II) complex catalyst **V** (X = $ClO_4$) was more active than the nickel(II) complex **U**, the product obtained after the reduction of **47c** with $NaBH_4$ was a 55:45 regioisomeric mixture of **48c** (95% ee) and **48'c** (83% ee) as shown in Table 3-18. Thus, the zinc complex **V** tends to activate the formation of electronically controlled cycloadduct **48'c**. In our previous theoretical work on Lewis acid catalyzed nitrone cycloadditions, a stronger Lewis acid favors the preferred formation of electronically controlled cycloadducts.

1,3-Dipolar cycloadditions of nitrone **1b** with a variety of α,β-unsaturated aldehydes were examined, and results are listed in Table 3-18. In all cases of nitrone cycloadditions to α,β-unsaturated aldehydes, the use of MS 4A was essential in order to attain high reactivity and selectivities. For example, reaction of **1b** with **46e** catalyzed by the zinc(II) complex **V** (X = OTf) at –40 °C in the absence of MS 4A resulted in much lower chemical yields and selectivities (46 h, 36%, *endo/exo* = 87:13 for **47e**, 86% ee for **48e**). Accordingly, all the reactions shown in Table 3-18 were performed in the presence of MS 4A (500 mg/mmol).[28]

**Table 3-18** Enantioselective nitrone cycloaddition reactions to α,β-unsaturated aldehydes[a]

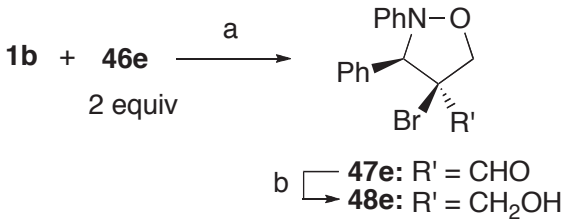
| Aldehydes | Conditions and results[b] | Products[c] |
|---|---|---|
|  CHO **46a** $ZnI_2 + AgClO_4$ | –10 °C, 72 h<br>75%<br>rs = 74:26<br>98 / 91% ee |  74:26  **48a** **48'a** (dr = 95:5) |
|  CHO **46c** 1) $Ni(ClO_4)_2 \cdot 6H_2O$ 2) $ZnI_2 + AgClO_4$ | 1) rt, 48 h<br>73%<br>96% ee<br>2) rt, 4 h<br>98%<br>rs = 55:45<br>95 / 83% ee |  55:45 **48c** **48'c** |
|  CHO **46d** $ZnI_2 + AgClO_4$ | rt, 69 h<br>78%<br>ds = 80:20<br>49 / 84% ee |  **48d** |
|  CHO **46e** $ZnI_2 + AgClO_4$ | rt, 3 h<br>85%<br>ds = 95:5<br>98 / 89% ee |  **48e** |
|  CHO **46f** $ZnI_2 + AgClO_4$ | rt, 48 h<br>98%<br>rs = 98:2<br>77 / 55% ee |  **48f** |
|  CHO **46g** 1) $Ni(ClO_4)_2 \cdot 6H_2O$ 2) $ZnI_2 + AgClO_4$ | 1) rt, 22 h<br>quant<br>80% ee<br>2) rt, 22 h<br>quant<br>78% ee |  **48g** |
|  CHO **46h** $Co(ClO_4)_2 \cdot 6H_2O$ | rt, 24 h<br>46%<br>92% ee |  **48h** |

[a] In dichloromethane in the presence of MS 4A and 10 mol% of the *R,R*-DBFOX/Ph complex catalyst. [b] rs: regioselectivity. ds: diastereoselectivity. [c] Products were obtained by reduction of the crudecycloadducts with sodium borohydride in ethanol.

The cycloaddition of nitrone **1b** with α-bromoacrolein (**46e**), which is more electrophilic than **46c**, is sluggish under uncatalyzed conditions, and the electronically controlled isoxazolidine-4-carbaldehyde regioisomer **47e** was given as a 51:49 diastereoisomeric mixture only in a poor yield (41 h, 23%). Switch of the regioselectivity observed is dipolarophile-controlled due to the strongly electron-withdrawing nature of α-bromine moiety of **46e**. The nickel(II) complex catalyst **U** (X = $ClO_4$) was not effective to activate this reaction showing poor catalytic activation and enantioselectivity (31% after 41 h at room temperature, *endo/exo* = 90:10, 42% ee for the major *endo*-**47e**). However, the zinc(II) complex **V** was found to be the most effective catalyst. Thus, the catalyzed reaction was completed in 1 h at room temperature in the presence of the zinc(II) complex **V** (X = OTf, 10 mol%) and MS 4A, producing a 95:5 diastereomeric mixture of **47e** in 85% yield (Table 3-18).

Enantioselectivity of the major *endo*-cycloadduct **47e** was determined to be 98% ee after its $NaBH_4$ reduction to isoxazolidine-4-methanol **48e**. Thus, the electronically controlled regioisomer **47e** was the sole product in the reaction of **1b** with **46e**, regardless of the presence or absence of catalyst. The reaction of nitrone **1b** with acrolein (**46a**) showed a low regios electivity (rs = 74:26) even under the catalysis of the nickel(II) complex **U** (X = $ClO_4$), but enantioselectivities were excellent both for regioisomers **48a** and **48'a**. Reactions to α-ethylacrolein (**46f**) and α-phenylacrolein (**46g**), having an α-substituent bulkier than that of **46c**, were exclusively regioselective in favor of the sterically controlled isoxazolidine-5-methanols **48f** and **48g**, respectively, under the catalysis of the nickel(II) and magnesium(II) complexes, followed by the sodium borohydride reduction. However, enantioselectivities in these cases were only moderate. Crotonaldehyde (**36d**) as 1,2-disubstituted alkene was successfully activated with the zinc(II) complex **B** ($X_2$ = IOTf) to show the exclusive regioselectivity, but both diastereoselectivity and enantio-selectivity were low. Although other catalysts failed to activate cyclopentene-1-carbaldehyde (**46h**), high enantioselectivity was attained only by catalysis of the cobalt(II) perchlorate complex.

**Scheme 3-19** High efficiency of the cationic DBFOX/Ph Zinc(II) complexes




[a] **V** (10 mol%), $AgClO_4$ (n mol%), MS 4A, rt in $CH_2Cl_2$.
[b] $NaBH_4$ in THF at rt.

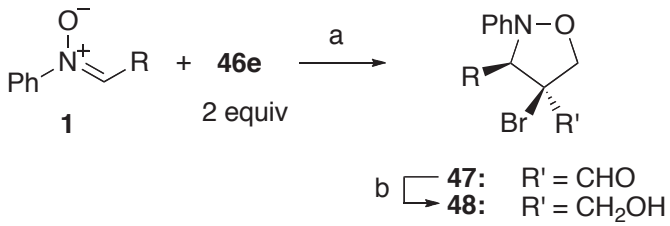
| | n mol% | Time/h | Yield/% | endo/exo | ee % |
|---|---|---|---|---|---|
| $ZnBr_2$ | 0 | 10 | 65 | 81/19 | 16/3 |
| | 10 | 3 | 90 | 95/5 | 94/51 |
| $ZnI_2$ | 0 | 3 | 72 | 94/6 | 95/84 |
| | 10 | 0.5 | 94 | 98/2 | 97/89 |
| | 20 | 6 | 91 | 88/12 | 97/94 |

Yield and diastereoselectivities are for **47e**, ee % for **48e**.

A dramatic difference of catalytic effectiveness was observed depending upon the halide counteranions of the zinc complex catalysts (Scheme 3-19).[28] Thus, the zinc(II) iodide complex **V** (X = I) effectively activated the reaction of nitrone **1b** with α-bromoacrolein **46e** showing excellent selectivities (3 h at room temperature, 72%, *endo/exo* = 94:6 for **47e**, 95% ee for **48e**). However, to our surprise, the zinc(II) bromide complex **V** (X = Br) gave much lower selectivities (10 h, 65%, *endo/exo* = 81:19 for **47e**, 16% ee for **48e**). Based on the difference of bond energies between the Zn-I and Zn-Br bonds, we believe that at least one of the iodide anions of complex **V** (X = I) is dissociated from the metal center of the complex under the reaction conditions, while both bromide ions of complex **V** (X = Br) stay on the zinc metal.

When one of the bromide ions of **V** (X = Br) was replaced with a less coordinating perchlorate anion by treatment with 1 equiv of $AgClO_4$, a great improvement of both reactivity and selectivities resulted as shown in Scheme 3-19 (3 h, 90%, *endo/exo* = 95:5 for **47e**, 94% ee for **48e**). This indicates that the zinc(II) bromide complex **V** (X = Br), which has only one vacant position on the metal center, shows insufficient catalytic activity in the nitrone cycloadditions with α-bromoacrolein; two vacant positions are essential for both high catalytic activity and selectivity. These observations provide us important information for the consideration of reaction mechanism.

**Scheme 3-20** Enantioselective nitrone cycloaddition reactions to 2-bromoacrolein



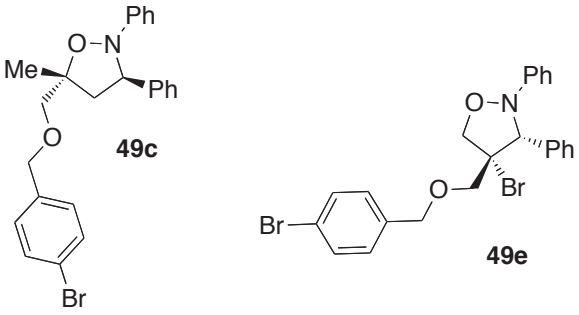

[a] *R,R*-DBFOX/Ph•$ZnI_2$, $AgClO_4$ (10 mol% each), MS 4A (500 mg/mmol) in $CH_2Cl_2$. [b] $NaBH_4$ in THF at rt.

| R | | Time/h | Yield/% | ds | ee % |
|---|---|---|---|---|---|
| Ph | **b** | 0.5 | 94 | 98/2 | 97 |
| 4-$MeC_6H_4$ | **d** | 1 | 96 | 98/2 | 97 |
| 1-Naph | **g** | 1 | 98 | 98/2 | 88 |
| 2-Naph | **h** | 1 | 97 | 90/10 | 99.5 |
| 4-$BrC_6H_4$ | **j** | 0.5 | 95 | 91/9 | 97 |
| 4-$NO_2C_6H_4$ | **k** | 2 | 97 | >99/1 | >99 |
| 2-Furyl | **l** | 18 | 76 | 91/9 | 90 |

Yields and diastereoselectivities are for **47**, ee % for **48**.

It should be noted that the zinc(II) halide complexes **V** (X = I and Br) were isolable and storable in open air without loss of catalytic activity. Exchange of either one or both of the iodide ions of complex **V** (X = I) with noncoordinating counteranions such as perchlorate, tetrafluoroborate, and triflate ions leads to the corresponding zinc(II) complexes which are more reactive catalysts. All of the resulting complexes were again stable enough to be isolated and stored. Thus, when the catalysts either in situ-prepared or isolated were employed in the reactions of **1b** with **46e** and the catalytic activity was compared, comparable results were observed to confirm the high stability of all these complex catalysts. Especially active were the *R,R*-DBFOX/Ph complexes of zinc salts having the formula of $ZnIClO_4$ and $ZnIBF_4$, which can be derived by treatment of the diiodide complex **V** (X = I) with one equivalent amount of silver ions bearing a less coordinating anion. When the reaction temperature was lowered to –40 °C (40 h) either in the reaction catalyzed by the complex derived from **V** (X = I) and $AgClO_4$ (1 equiv, 10 mol%) or that catalyzed by the complex **V** (X = OTf), *endo*-cycloadduct **47e** was produced in 83 or 94% with an enantioselectivity of 99.5 or 99.7% ee for **48e**, respectively.

**Scheme 3-21** Absolute configurations of **48c** and **48e** were determined by X-ray crystalographic analysis of **49c** and **49e**, respectively




After optimization, the reactions of nitrones **1** having a variety of *C*-substituents with α-bromoacrolein **46e** were examined in the presence of a catalytic amount (10 mol%) of the zinc(II) complex **V** ($X_2$ = $IClO_4$) at room temperature (Scheme 3-20).[28] In almost all the cases, excellent *endo*-selectivities and enantioselectivities were obtained for isoxazolidine-4-carbaldehydes **47** and isoxazolidine-4-methanols **48**. In particular, *N*-(2-naphthylmethylene)aniline *N*-oxide (**1g**) produced the isoxazolidine-4-methanol derivative in an absolutely high enantioselectivity of 99.5% ee in the reaction performed at room temperature. Such high generality of *C*-substituents of nitrones **1** in the reactions to **46e** is also a synthetic advantage of our enantioselective nitrone cycloadditions.

The absolute configurations of **48c** and **48e** were determined to be the 3*R*,5*R*- and 3*R*,4*R*-enantiomers on the basis of X-ray crystal structures of the *p*-bromobenzoate derivatives **49c** and **49e** of isoxazolidine methanols, respectively. This indicates that the preferred attack of nitrones to the *re*(Cα)-faces of α,β-unsaturated aldehydes **2** and **5** took place in the transition structure of these nitrone cycloadditions. The absolute configurations of **48f** and **48g** were temporarily assigned as shown in Table 3-18 on the basis of the expected structural similarity of **46f** and **46g** to the starting material **46c**. Absolute configuration of the cycloadduct **48h** to cyclopentene-1-carbaldehyde (**46h**) was detremined to be 3*R*,3a*S*,6a*S*-enantiomer by comparison of its optical rotation of the authentic sample. Other cycloadducts **48a** and **48d** derived from **46a** and **46d**, respectively, remained uncharacterized.

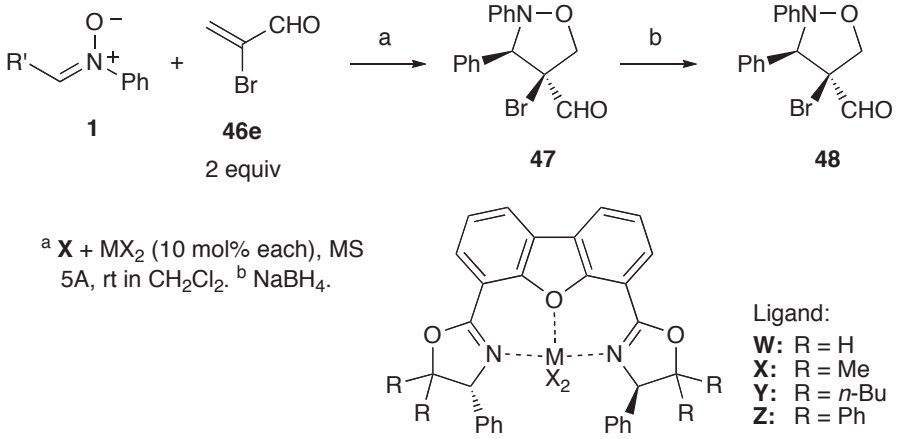
Nitrone cycloadditions to a variety of α,β-unsaturated aldehydes were thus effectively catalyzed by the nickel(II), zinc(II), magnesium(II), and cobalt(II) complexes derived from the *R,R*-DBFOX/Ph ligand. Highly useful were the nickel(II) and magnesium(II) complexes for the reactions of methacrolein, and the zinc(II) complexes for the reactions of α-bromoacrolein. Especially active were the catalysts derived from the $ZnI_2$ complex by replacement of an iodide anion with a noncoordinating anionic ligand. The highest enantioselectivity up to 99.5% ee was observed in the reaction with α-bromoacrolein performed at room temperature. Other α-substituted acrolein derivatives as well as 1-cyclopentenecarbaldehyde were also effectively catalyzed. Thus, the reactions of acyclic nitrones with α,β-unsaturated aldehydes, catalyzed by DBFOX/Ph complexes, provided much higher enantioselectivities than the reported examples.

The complex derived from DBFOX/Ph and zinc(II) triflate showed a high catalytic activity in the enantioselective nitrone cycloadditions with α-bromoacrolein, regardless of its extremely small solubility in dichloromethane. In general, solubility of catalystis lowered when strong attractive interactions are

workng among complex molecules. Therefore, the resulting tight aggregation causes the decreased catalytic activity. Therefore, much more efficient catalysis can be expected if the above negative aggregation issue can be solved. Steric protection of the metal center of complexes would be one of the most effective solutions. We demonstrated the steric protection of the metal center based on the structural modification of DBFOX/Ph ligand.[29] Excellent enantioselectivities of up to 99% were achieved in the nitrone cycloadditions to α,β-unsaturated aldehydes at room temperature.

Treatment of DBFOX/Ph ligand **W** with $Zn(OTf)_2$ in dichloromethane (10 mol% each) led to a densely heterogeneous solution, but the resulting suspension shows a high catalytic activity in the reaction of *N*-benzylideneaniline *N*-oxide (**1b**) to α-bromoacrolein (**46e**). The cycloadduct **47e**, obtained in 85% yield as the far major diastereomer, was converted into isoxazolidine-4-methanol **48e**, whose enantioselectivity was 97% ee. In the preparation step of the DBFOX/Ph - zinc complex catalyst, the insoluble materials were all filtered off and then the filtrate was evaporated. The residue obtained was analyzed by $^1$H NMR spectroscopy; the free DBFOX/Ph ligand used was almost quantitatively recovered, indicating that the complex formation was difficult due to the extremely small solubility of $Zn(OTf)_2$ in dichloromethane. Addition of nitrone **1b** to this suspension did not improve the solubility at all. Thus, the chiral catalyst **W** ($MX_2 = Zn(OTf)_2$) should be more active in the nitrone cycloadditions to **46e** if it is soluble.

**Scheme 3-22** Enantioselective cycloaddition reactions of nitrones **1** to 2-bromoacrolein **46e** under the catalysis of *R,R*-tetramethylDBFOX/Ph complex **X**




| Compnd | R | $MX_2$ | Time/h | Yield/%[c] | ds | ee %[d] |
|---|---|---|---|---|---|---|
| **b** | Ph | $Ni(ClO_4)_2 \cdot 6H_2O$ | 4.5 | 59 | 94/6 | 18/-1 |
| **b** | Ph | $Co(ClO_4)_2 \cdot 6H_2O$ | 2 | 90 | 99/1 | 95/- |
| **b** | Ph | $Co(BF_4)_2 \cdot 6H_2O$ | 1 | 92 | >99/1 | 98 |
| **b** | Ph | $ZnBr_2$ | 20 | 73 | 85/15 | 26/9 |
| **b** | Ph | $ZnI_2$ | 1.5 | 98 | >99/1 | 99 |
| **b** | Ph | $Zn(ClO_4)_2$ | 0.75 | 96 | 99/1 | 99/69 |
| **b** | Ph | $Zn(OTf)_2$ | 2 | quant | >99/1 | 97/- |
| **d** | 4-$MeC_6H_4$ | $Zn(OTf)_2$ | 1 | 94 | 99/1 | 94 |
| **g** | 1-Naphthyl | $Zn(OTf)_2$ | 1 | 98 | >99/1 | >99 |
| **h** | 2-Naphthyl | $Zn(OTf)_2$ | 1 | 96 | >99/1 | 98 |
| **j** | 4-$BrC_6H_4$ | $Zn(OTf)_2$ | 1 | 89 | >99/1 | 98 |
| **k** | 4-$NO_2C_6H_4$ | $Zn(OTf)_2$ | 2 | 88 | >99/1 | >99 |
| **l** | 2-Furyl | $Zn(OTf)_2$ | 20 | 67 | 95/5 | 97 |

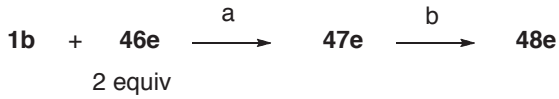
[c] Yield of **47**. [d] Determined for **48**.

Coplanarity of the heterocyclic rings of DBFOX/Ph ligand **W** may be a major reason for the tight aggregation of complex. Introduction of substituents at the 5-positions of the oxazoline rings of **W** would suppress the undesired aggregation to improve the catalytic activity. Substituted DBFOX/Ph derivatives, called the second generation of DBFOX/Ph series, were synthesized via straightforward synthetic routes; the starting methyl phenylglycinate was converted into β-amino tertiary alcohols by treating with excess Grignard reagents, and the resulting alcohols were converted to the substituted DBFOX/Ph derivatives according to the usual synthetic route to bisoxazolines.

When the tetramethyl ligand **X** was treated with $Zn(OTf)_2$ under stirring in dichloromethane, a clear solution resulted within a few minutes. The complex formation was definitely confirmed by a $^1H$ NMR spectral study. Other metal salts could also be successfully applied to prepare the corresponding complexes **X** and these were effectively used in the cycloadditions of nitrone **1b** to α-bromoacrolein **46e** (Scheme 3-22). Except for the complexes derived from $Ni(ClO_4)_2 \cdot 6H_2O$ and $ZnBr_2$, those derived from metal salts such as $Co(ClO_4)_2 \cdot 6H_2O$, $Co(BF_4)_2$, $Zn(ClO_4)_2$, and $Zn(OTf)_2$ were all highly effective catalysts when applied to the reactions at room temperature in the presence of 10 mol% of the catalyst. Especially, it should be emphasized that *endo*-selectivities were exclusively high in all cases.

Other nitrones **1** having several aryl substituents on the nitrone carbon were examined in the 1,3-dipolar cycloaddition reactions with α-bromoacrolein **46e** in the presence of 10 mol% of complex **X** ($MX_2$ = $Zn(OTf)_2$) to give the corresponding cycloadducts **47** with exclusive enantioselectivity and *endo*-selectivity (Scheme 3-22).[29] The highest enantioselectivity of 99.9% ee was observed with the exclusive *endo*-selectivity in the reaction with *N*-(4-nitrobenzylidene)aniline *N*-oxide (**1k**).

**Scheme 3-23** Enantioselective cycloaddition reactions of nitrone **1b** to **46e** under the catalysis of other ligand complexes **W-Y**




[a] Ligand + $MX_2$, MS 4A, in $CH_2Cl_2$, rt. [b] $NaBH_4$.

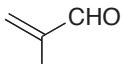
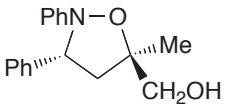
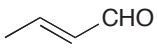
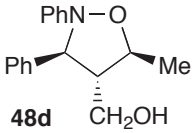
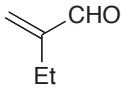
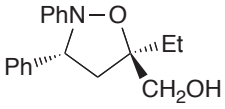
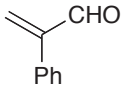
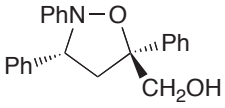
| Ligand (mol%) | Temp/°C[c] | Time/h | Yield/% of **47e** | ds | ee % of **48a** |
|---|---|---|---|---|---|
| **W** + $Zn(OTf)_2$ | | | | | |
| 2 | rt | 21 | 56 | 86/14 | 23/12 |
| 2 | rt | 1 (SA) | 37 | 86/14 | 78/43 |
| 2 | rt | 1 (SA) | 59 | 91/9 | 92/25 |
| **X** + $Zn(OTf)_2$ | | | | | |
| 2 | rt | 17.5 | 61 | 84/16 | 57/3 |
| 2 | rt | 1 (SA) | 73 | 98/2 | 97/4 |
| 1 | -20 | 91 (SA, 10) | 41 | 96/4 | 95/26 |
| **Y** + $Zn(OTf)_2$ | | | | | |
| 2 | rt | 1 (SA) | 68 | 99/1 | 96/- |

[c] SA: slow addition of nitrone **1b** in the period of time shown.

When the catalytic loading was reduced to 2 mol% for nitrone **1b**, the reaction catalyzed by the complex **X** ($MX_2$ = $Zn(OTf)_2$) became rather slow giving a lowered enantioselectivity of 57% ee (Scheme 3-23).[29]

However, the reaction was completed within 1 h under slow addition (SA) conditions at room temperature giving **47e** in 73% yield with an enantioselectivity of 97% ee for **48e**. Even with the decreased catalytic loading of 1 mol%, an excellent enantioselectivity of 95% ee was achieved. The tetrabutyl DBFOX/Ph complex **Y** derived from $Zn(OTf)_2$ showed a catalytic activity similar to that of the tetramethyl DBFOX/Ph complex **X**, while the tetraphenyl DBFOX/Ph complex **Z** was much less active. Thus, highly efficient catalytic activity of the complexes derived from the second generation of DBFOX/Ph ligands **X** and **Y** is clear.

**Table 3-24** Enantioselective nitrone cycloaddition reactions of **1b** to a variety of α,β–unsaturated aldehydes **46**[a]

| Aldehydes | Conditions and results | Products |
|---|---|---|
|  **46c** | **X** + $Ni(ClO_4)_2$•$6H_2O$ (10 mol%), rt, 22 h, 98% single, 99% ee<br>**X** + $Ni(ClO_4)_2$•$6H_2O$ (2 mol%), 0 °C, 48 h, 91% single, 96% ee |  **48c** |
|  **46d** | **X** + $Zn(COTf)_2$ (10 mol%), rt, 14 h, SA, 74%, 99:1, 77% ee |  **48d** |
|  **46f** | **X** + $Ni(ClO4)_2$•$^6H_2O$ (10 mol%), rt, 29 h, quant single, 92% ee |  **48f** |
|  **46g** | **X** + Ni(ClO4)2•$6H_2O$ (10 mol%), rt, 24 h, 67% single, 84% ee |  **48g** |

[a] All the reactions were performed in $CH_2Cl_2$ in the presence of catalysts **X** and MS 4A. [b] Products **48** were obtained by reduction of the cycloadducts with $NaBH_4$ in ethanol.

Combination of the second generation of DBFOX/Ph ligand with nickel(II) salts was also effective. Thus, the reaction of nitrone **1b** with methacrolein (**46c**) in the presence of 10 mol% of the complex **X** ($MX_2$ = $Ni(ClO_4)_2$•$nH_2O$) gave isoxazolidine-5-methanol **48c** as a single product in 98% yield (*endo* only, 99% ee, Table 3-24).[29] Even a catalytic loading of 2 mol% worked well at 0 °C giving *endo*-**48c** in an excellent enantioselectivity of 96% ee, while the reaction catalyzed by complex **W** ($MX_2$ = $Ni(ClO_4)_2$•$nH_2O$, 2 mol%) provided a relatively low enantioselectivity of 75% ee. The cycloadditions of **1b** with both α-ethylacrolein (**46f**) and α-phenylacrolein (**46g**), in the presence of the nickel(II) complex **Y** ($MX_2$ = $Ni(ClO_4)_2$•$nH_2O$, 10 mol%), were highly enantioselective producing **48f** (quant, *endo* only, 92% ee) and **48g** (53%, *endo* only, 95% ee), respectively. Although enantioselectivity was not very high (77% ee for **48d**), the reaction of **1b** with crotonaldehyde (**46d**) was almost exclusively *endo*-selective in the presence of the zinc(II) complex **X** ($MX_2$ = $Zn(OTf)_2$, 10 mol%).

Thus, we successfully solved the aggregation issue of the DBFOX/Ph - transition metal complexes by use of the second generation of chiral ligand DBFOX/Ph. These new chiral ligands worked well to improve catalysis in the nitrone cycloadditions using a variety of α,β-unsaturated aldehyde dipolarophiles. Excellent enantioselectivities up to 99% ee were demonstrated with a catalytic loading of 2 mol%.

## 4. DIAZOALKANE

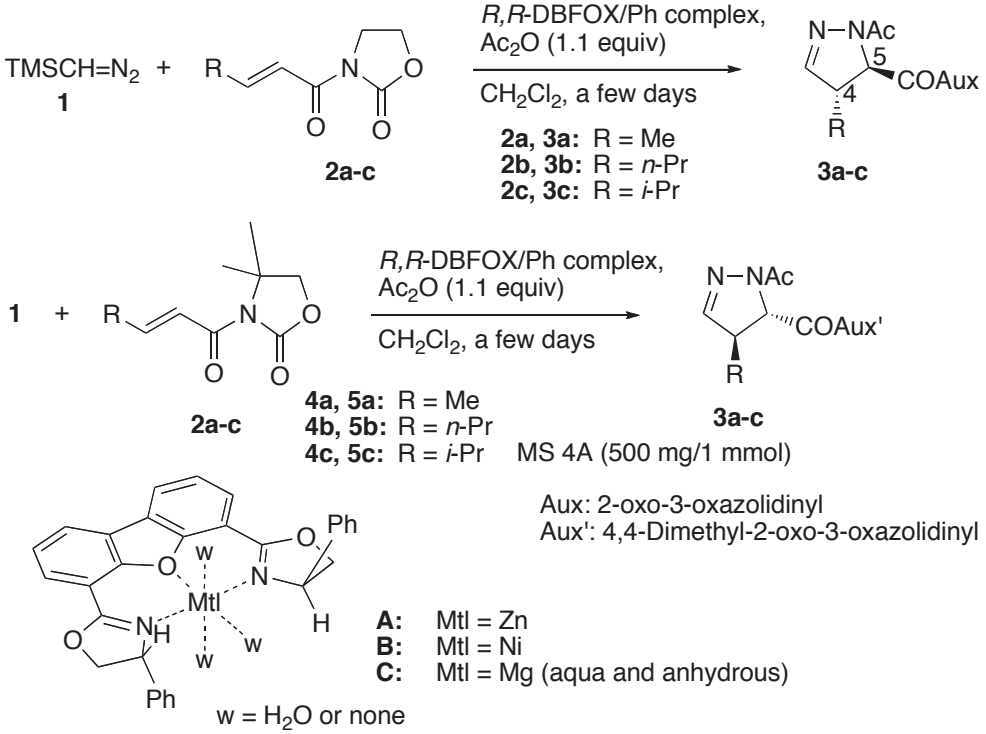
### 4.1 Catalytic enantioselective diazo cycloadditions

No single examples are known for the Lewis acid-catalyzed enantioselective 1,3-dipolar cycloaddition reactions of diazoalkanes. However, based on the kinetic data on the relative reaction rates reported by Huisgen in the competitive cycloadditions of diazomethane between 1-alkene and acrylic ester, it is clear that diazomethane is one of the most nucleophilic 1,3-dipoles ever examined ($k_{acrylate}/k_{1\text{-alkene}}$ = 250,000). So, diazoalkanes can be a strong candidate which should be most successfully applied to Lewis acid-catalyzed reactions. We were aware of this possibility and started to study the catalyzed enantioselective diazoalkane cycloadditions to 3-(2-alkenoyl)-2-oxazolidinones.[30]

Diazoalkane cycloadditions to alkenes produce 1-pyrazolines as the initial cycloadducts which are usually not so stable that these undergo spontaneous 1,3-proton migration leading to thermodynamically more stable 2-pyrazoline derivatives. Usually more acidic hydrogen migrates and consequently the chirality at this position disappears. Carreira and co-workers reported the diastereoselective diazoalkane cycloadditions of trimethylsilyldiazomethane to chiral alkenes. Upon treatment with protonic acid or acid chloride/silver triflate after the completion of reaction, regioselective protodesilylation or acyldesilylation is found to occur at the 2,3-diazaallylsilane moiety masked in the 1-pyrazoline rings to produce 2-pyrazolines.[31] We expected that the *R,R*-DBFOX/Ph - transition metal aqua complexes would be a powerful catalyst in ever unprecedented enantioselective diazoalkane cycloadditions.

After several chiral catalysts were screened, the nickel(II) and zinc(II) aqua complexes (**A** and **B**) of *R,R*-DBFOX/Ph ligand were found to be effective in catalytic amounts (10 mol%), especially the zinc(II) complex being the best catalyst of all examined. When trimethylsilyldiazomethane (**1**, 1.1 equiv) was treated with 3-crotonoyl-2-oxazolidinone (**2a**), acetic anhydride (1.1 equiv), and MS 4A in dichloromethane in the presence of the *R,R*-DBFOX/Ph•$Zn(ClO_4)_2$•$3H_2O$ (10 mol%) at -40 °C for 72 h, the desilylacetylated 2-pyrazoline cycloadduct **3a** was produced in 87% yield in 99% ee (Scheme 4-01).[30] The role of MS 4A is simply a dehydrating agent in this case since the comparable results were obtained in the reaction catalyzed by the anhydrous complex catalyst **A** (w = none) prepared from *R,R*-DBFOX/Ph, $ZnI_2$, and $2AgClO_4$ (81%, 97% ee). However, use of the aqua complex is more preferable because its simple preparation procedure is an advantage. The nickel(II) aqua complex **B** was a little less effective in enantioselectivity than the zinc(II) aqua complex **A**. The reactions catalyzed by the magnesium complex **C** showed the maximum enantioselectivity of 82% ee at -20 °C, while the selectivity was lowered at a lower reaction temperature (37% ee at -40 °C).

**Scheme 4-01** Reactions of trimethylsilyldiazomethane (**1**) with dipolarophiles **2** and **4** leading to **3** or **5**




| Metal salt / mol% | **1**/equiv | **2** | Temp/°C | **3** | Yield/% | % ee |
|---|---|---|---|---|---|---|
| $Zn(ClO_4)_2 \cdot 6H_2O$ / 10 | 2 | **2a** | rt | **3a** | 49 | 40 |
| $Zn(ClO_4)_2 \cdot 6H_2O$ / 10 | 2 | **2a** | -20 | **3a** | 85 | 92 |
| $Zn(ClO_4)_2 6H_2O$ / 10 | 2 | **2a** | -40 | **3a** | 85 | 96 |
| $Zn(ClO_4)_2$ / 10 | 2 | **2a** | -40 | **3a** | 81 | 97 |
| $Zn(ClO_4)_2 \cdot 6H_2O$ / 10 | 1.2 | **2a** | 40 | **3a** | 87 | 99 |
| $Zn(ClO_4)_2 \cdot 6H_2O$ / 10 | 1.2 | **2a** | -40 | **3a** | 79 | 96 |
| $Ni(ClO_4)_2 \cdot 6H_2O$ / 10 | 1.2 | **2a** | -40 | **3a** | 79 | 93 |
| $Mg(ClO_4)_2$ / 10 | 1.2 | **2a** | rt | **3a** | 61 | 64 |
| $Mg(ClO_4)_2$ / 10 | 1.2 | **2a** | -20 | **3a** | 64 | 82 |
| $Mg(ClO_4)_2 \cdot 6H_2O$ / 10 | 1.2 | **2a** | -40 | **3a** | 75 | 37 |
| $Zn(ClO_4)_2 \cdot 6H2O$ / 10 | 2 | **2b** | -55 | **3b** | 81 | 47 |
| $Zn(ClO_4)2 \cdot 6H2O$ / 10 | 2 | **2c** | -40 | **3c** | 89 | 71 |
| $Mg(ClO_4)_2$ / 10 | 1.5 | **4a** | -40 | **5a** | 71 | 89 |
| $Mg(ClO_4)_2$ / 10b | 1.5 | **4a** | -40 | **5a** | 63 | 82 |
| $Mg(ClO_4)_2$ / 10 | 1.5 | **4a** | -78 | **5a** | 75 | 97 |
| $Mg(ClO_4)_2$ / 10 | 1.5 | **4b** | -60 | **5b** | 62 | 98 |
| $Mg(ClO_4)_2$ / 10 | 1.5 | **4c** | -60 | **5c** | 93 | 98 |

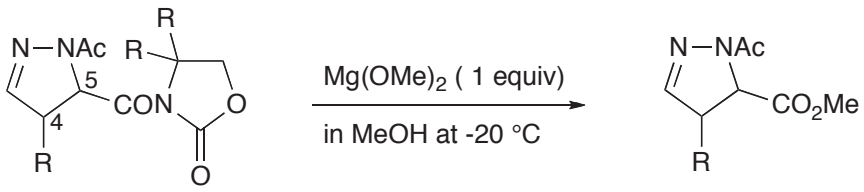
[a] All of the reactions were performed in dichloromethane in the presence of acetic anhydride (1.1 equiv), MS 4A (500 mg/1 mmol scale), and the catalysts derived from *R,R*-DBFOX/Ph and metal salts. [b] In the absence of MS 4A.

Unfortunately the reaction of **1** with 3-acryloyl-2-oxazolidinone catalyzed by the zinc aqua complex **A** (10 mol%) led to a racemic result. It was surprising that both 3-(2-hexenoyl)-2-oxazolidinone (**2b**) and 3-(4-methyl-2-pentenoyl)-2-oxazolidinone (**2c**) were much less enantioselective than the methyl-substituted dipolarophile **1a**. Especially, the reaction of **2b** as the primary alkyl-substituted dipolarophile never exceeded an enantioselectivity of 50% ee. These β-substituents, isopropyl and propyl moieties, have higher mobility than the methyl substituent, and therefore, some steric hindrance should exist against one of the shielding phenyl groups so that the reaction site departs from the shielding zone of the 4-phenyl group. As a result, efficiency of chiral shielding became rather ineffective.

On the other hand, use of 4,4-dimethyl-2-oxazolidinone as chiral auxiliary was very effective. It was found that the *R,R*-DBFOX/Ph•Mg($ClO_4$)$_2$ complex **C** was the catalyst of choice to mediate the reactions of 3-crotonoyl-4,4-dimethyl-2-oxazolidinone (**4a**), while both the *R,R*-DBFOX/Ph-zinc(II) and -nickel(II) complexes, **A** and **B**, were totally inactive. Thus, the *R,R*-DBFOX/Ph•Mg($ClO_4$)$_2$-catalyzed reaction of **1** with **4a** in the presence of MS 4A proceeded smoothly even at -78 °C to give the corresponding cycloadduct **5a** in 75% yield with the enantioselectivity of 97% ee.[30] Other dipolarophiles **4b,c** having 2-hexenoyl and 4-methyl-2-pentenoyl substituents at the nitrogen atom of the oxazolidinone chelating auxiliary, showed similarly high enantioselectivities of 98% ees regardless of the β-substituents of dipolarophiles.

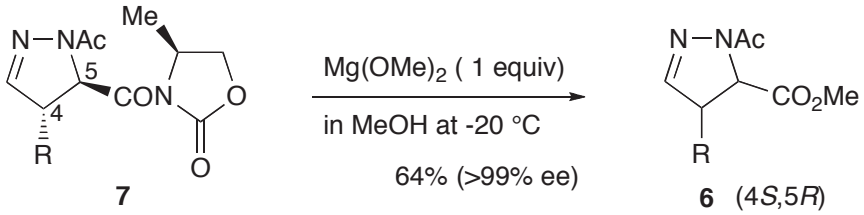
The desilylacetylated cycloadducts **3a** and **5a**, which were derived from **2a** and **4a**, respectively, were transformed to the methyl esters, methyl *trans*-1-acetyl-4-methyl-1-pyrazoline-5-carboxylates **6**, through the reactions with dimethoxymagnesium at -20 °C (Scheme 4-02). When optical rotations and chiral HPLC data of these two esters were compared, these two products **3a** and **5a** were found to have the opposite absolute stereochemistry. The absolute configuration of **3a** was determined on the basis of the X-ray-determined structure of the major diastereomer of cycloadduct **7** which was derived from the reaction of **1** to (*S*)-3-crotonoyl-4-methyl-2-oxazolidinone.

**Scheme 4-02** Absolute configuration determination of **3a** and **5a**




**3a** or **5a** **6**

| Sbstrates | R | % ee | Yield/% of **6** | % ee | Chirality |
|---|---|---|---|---|---|
| **3a** | H | 76 | 68 | 74 | 4*S*,5*R* |
| **5a** | Me | 89 | 73 | 84 | 4*R*,5*S* |




**7** **6** (4*S*,5*R*)

X-Ray determined as *S*-4*S*,5*R*

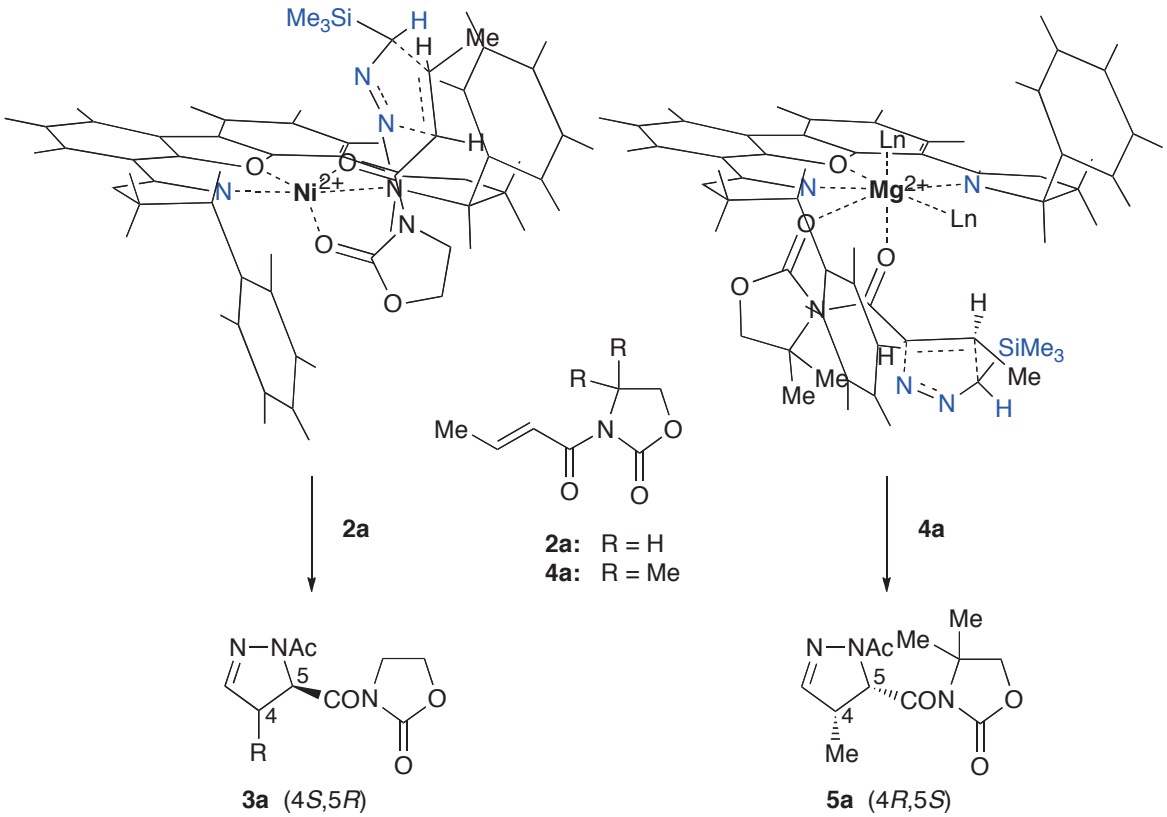
$[\alpha]_{23}^{D}$ -70.9 (c = 1.1, $CHCl_3$)

The cycloaddition product **3a** derived from 3-crotonoyl-2-oxazolidinone (**2a**) was identified to be the 4*S*,5*R*-enantiomer of 2-pyrazoline cycloadduct, indicating that the *re,si*-enantioface of the unsaturated bond of dipolarophile **2a** was attacked by **1** as a result of the chiral shielding by the top 4-phenyl substituent, as shown in the trigonal bipyramid transition structure **TS-D** (Scheme 4-03).[30] The selected

enantioface of 3-crotonoyl-2-oxazolidinone (**2a**) was the same to that involved in the transition structure of the *R,R*-DBFOX/Ph•Mg($ClO_4$)$_2$•3$H_2O$ - catalyzed Diels−Alder reaction of cyclopentadiene with the same dienophile. Consequently, the absolute configuration of the cycloaddition product **5a** produced in the diazo cycloaddition reaction of 3-crotonoyl-4,4-dimethyl-2-oxazolidinone (**4a**) was the 4*R*,5*S*-enantiomer, which resulted from the selection of *si,re*-enantioface of the reacting site of oxazolidinone dipolarophile **4a**. Steric effects of the two methyl groups at the oxazolidinone ring probably force the substrate into a different coordination geometry as shown in Scheme 4-03, but the reason only the Mg complex is active is unclear.

Thus, the first effective enantioselective 1,3-dipolar cycloaddition reactions of trimethylsilyldiazomethane were attained in the presence of the *R,R*-DBFOX/Ph-metal perchlorate complexes. The reaction of 3-crotonoyl-2-oxazolidinone, catalyzed by the *R,R*-DBFOX/Ph•Zn($ClO_4$)$_2$•3$H_2O$ at -40 °C, produced the 4*S*,5*R*-enantiomer of 1-acetyl-5-(2-oxo-3-oxazolidinylcarbonyl)-2-pyrazoline in 99% ee, while the reaction of 3-crotonoyl-4,4-dimethyl-2-oxazolidinone, catalyzed by the *R,R*-DBFOX/Ph•Mg($ClO_4$)$_2$ at -78 °C, gave the 4*R*,5*S*-enantiomer of 1-acetyl-5-(4,4-dimethyl-2-oxo-3-oxazolidinylcarbonyl)-2-pyrazoline in 97% ee. Thus, almost complete switch of enantioselectivity was performed simply by adding substituents to the same achiral chelating auxiliary.

**Scheme 4-03** Proposed transition structures for the dramatic switch of the modes of induced chiralities in the reactions of 3-crotonoyl-2-oxazolidinone (**2a**) and 3-crotonoyl-4,4-dimethyl-2-oxazolidinone (**4a**)




**3a** (4*S*,5*R*) **5a** (4*R*,5*S*)

## 5. NITRILE OXIDES AND NITRILE IMINES

### 5.1 Asymmetric nitrile oxide cycloadditions to chiral alkenes

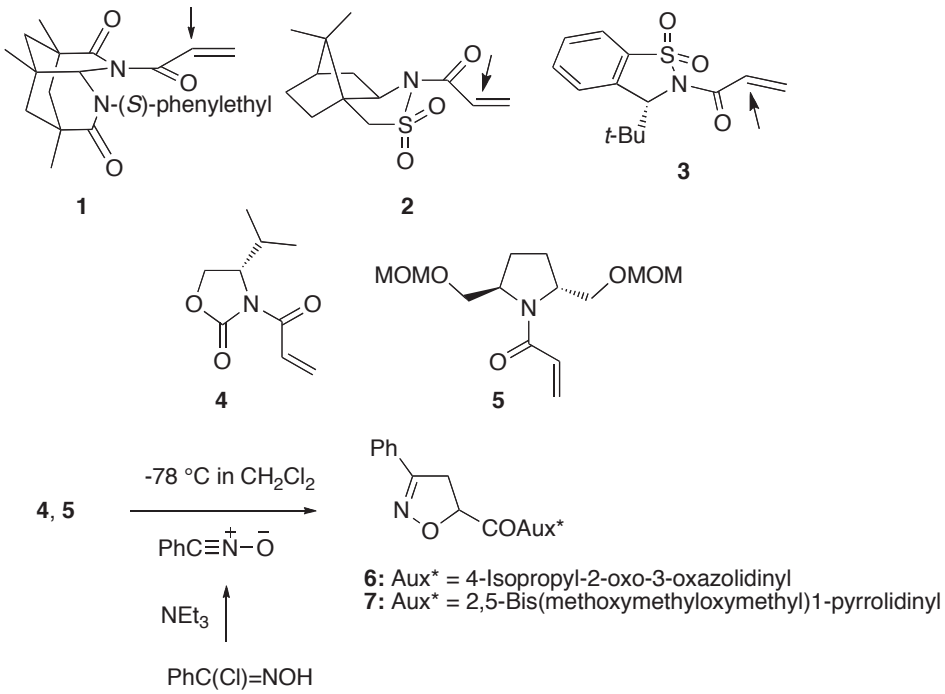
1,3-Dipolar cycloaddition reactions of nitrile oxides to alkenes produce 2-isoxazolines, in which a variety of multifunctionalized synthetic building blocks are masked. β-Hydroxy ketone known as aldol is a typical example. Aldols are synthesized through the carbon-carbon bond forming reactions of enols or metal enolates with carbonyl compounds such as aldehydes or ketones. Therefore, nitrile oxide cycloaddition reactions provide a synthetically equivalent methodology of aldol reactions via 2-isoxazolines, but concep is different. An advantage of nitrile oxide cycloaddition method is the high stereospecificity of the reaction; stereochemistry of 2-isoxazolines depends upon stereochemistry of the starting alkene substrates.

Synthetically useful dipolarophiles in nitrile oxide cycloadditions are limited to monosubstituted alkenes since other multisubstituted alkenes show either extremely decreased reactivity or awfully low regioselectivity. On the other hand, this 1,3-dipole shows very high regioselectivity in the reaction with monosubstituted alkenes producing 5-substituted 2-isoxazolines as single products. Unfortunately, the chirality control of 1,3-dipolar cycloadditions of nitrile oxides has remained one of the most difficult subjects. At the early stage of our work on assymetric 1,3-dipolar cycloaddition reactions of nitrile oxides, we had to start with the synthetic methodology depending upon chiral auxiliaries, since no single methods for chirality control by use of external reagents were known. Accordingly, it is desired to develop a new chiral auxiliary that can be effectively used in noncatalyzed, or without the aid of metallic additive, asymmetric 1,3-dipolar cycloaddition reactions.

Acrylamide **1** was the best among electron-deficient dipolarophiles ever used in asymmetric 1,3-dipolar cycloadditions (Scheme 5-01). The exclusive diastereoselectivity is recorded in its cycloaddition with benzonitrile oxide.[32] A disadvantage would be the complicated synthetic route starting from the naturally occurring Kemp's triacid. This discourages its wide use in asymmetric reactions. The acrylamides derived from the Oppolzer's chiral sultams **2** and **3** are satisfactory both for high diastereoselectivity and acceptably short synthesis.[33] In these cases, chiral discrimination is based on its *anti*-conformations by the electrostatic repulsion operating between nucleophiles and the pseudoaxial sulfonamide oxygen. This point should be emphasized because it makes a striking contrast with the Curran's chiral acrylamide **1** in which face selection is simply based on the steric shielding in the *anti*-conformation.

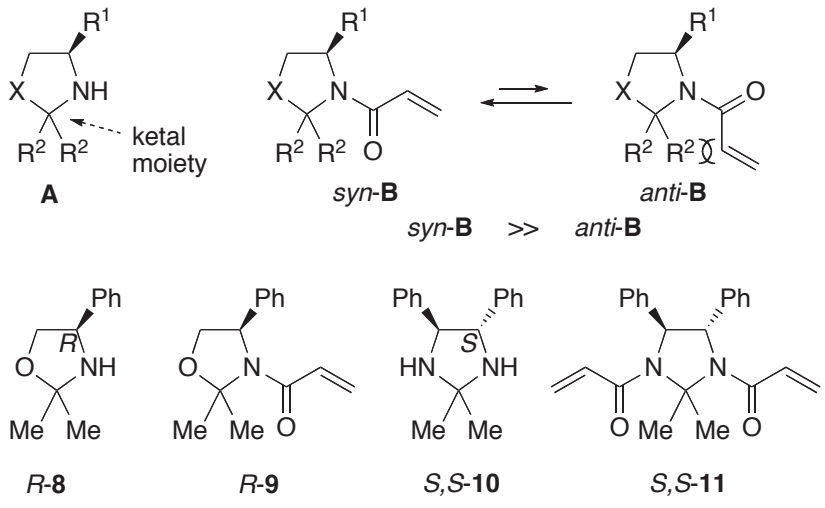
Two acrylamides **4** and **5**, derived from the chirality-controlling heterocycles such as 4-isopropyl-2-oxazolidinone[34] and *trans*-2,5-bis(methoxymethoxymethyl)pyrrolidine,[35] known as Evans' and Katsuki's auxiliaries, found wide synthetic applications. In the nitrile oxide 1,3-dipolar cycloadditions of **4** and **5**, it is of special interest what diastereoselectivity these will be able to record under noncatalyzed conditions (or without the aid of metallic additive). We first employed the se two chiral acrylamides **4** and **5** in nitrile oxide cycloadditions (Scheme 5-01). Benzonitrile oxide, generated in situ from benzohydroximoyl chloride and triethylamine, reacted with **4** or **5** at a low temperature to give a mixture of diastereomers of regioselective cycloadduct **6** (94% at -30 °C) and **7** (78% at -78 °C). The diastereoselectivities (ds) observed were not higher than 75% for both **6** (ds = 73%) and **7** (ds = 70%). It is apparent that synthetic potential of **4** and **5** in asymmetric nitrile oxide cycloadditions in the absence of metallic additive is not excellent.

**Scheme 5-01** A variety of chiral auxiliaries ever used for the highly diastereoselective asymmetric reactions



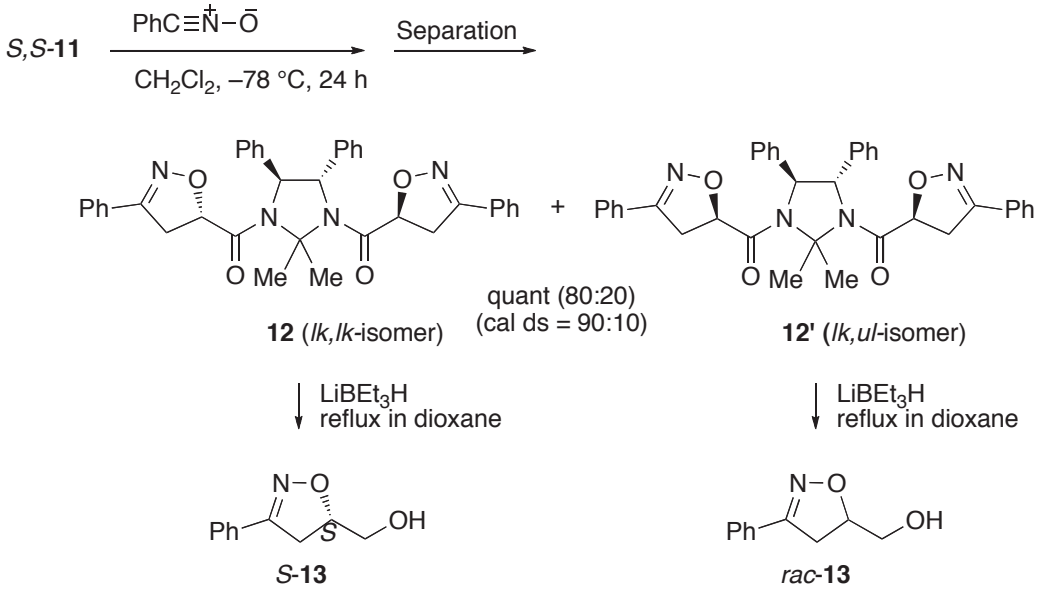

**Chirality control based on the ketal formation.** We started the project of molecular design of new chiral dipolarophiles on the basis of a new concept of diastereofacial discrimination. Our work is based on the use of conformation-controlled *N*-acryloyl derivatives of chiral heterocycles such as 4-chiral oxazolidines *R*-**8** (X = O) or $C_2$-symmetric imidazolidine *S,S*-**9** (X = NH) as shown in Scheme 5-02.[13] In saturated chiral nitrogen heterocycles **A**, the carbon atom adjacent to the nitrogen is highly substituted so that the acrylamide derivatives may occupy the more stable Z-configuration *syn*-**B**. One of the diastereotopic alkene faces can be effectively hindered on the attack of a nucleophile. Their synthetic use as chiral auxiliaries should be promising since a variety of derivatives can be readily accessible in optically pure forms when X is a heteroatom.

**Scheme 5-02** New chiral auxiliaries based on conformational control of the chiral shielding groups



Oxazolidine acrylamide (*R*)-**9** and imidazolidine bisacrylamide (*S,S*)-**11** were readily prepared from 2,2-dimethyl-4-phenyloxazolidine (*R*)-**8** and $C_2$-symmetric 2,2-dimethyl-4,5-diphenylimidazolidine (*S,S*)-**10**, respectively. These amides could be safely purified by column chromatography on silica gel. As expected, they exist as single *syn*- and *syn,syn*-configurations in the $^1$H NMR spectra recorded in $CDCl_3$ at room temperature.[13]

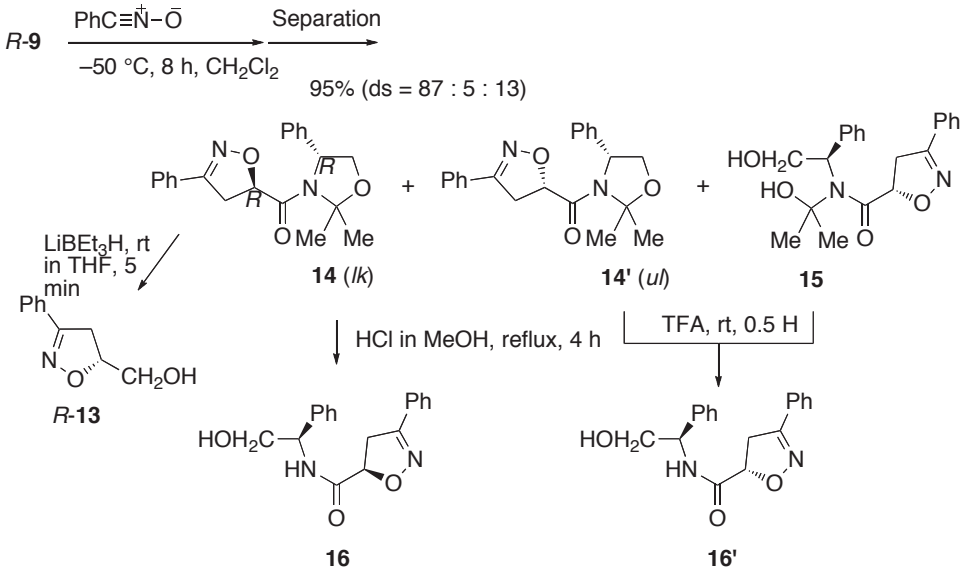
**Scheme 5-03** Assymetric diastereoselective nitrile oxide cycloadditions using $C_2$-symmetric imidazolidine bisacrylamide *S,S*-**11**




Reaction of optically pure (*S,S*)-**11** with benzonitrile oxide (3 equiv) at –78 °C produced a mixture of diastereomeric cycloadducts **12** and **12'** (97%, 80:20) which were easily separated from each other by column chromatography on silica gel (**12**: mp 309-310 °C; **12'**: mp 220-221 °C). The reaction temperature was not important since essentially the same selectivities (ds = 80:20) resulted in both reactions at 0 °C and at rt (Scheme 5-03). Based on the fact that the major diastereomer **12** was symmetric and the minor one **12'** unsymmetric diastereomers (by $^1$H NMR), the total diastereoselectivity in this reaction was calculated to be 90:10. Reductive removal of the chiral auxiliary from **12** was performed by treatment with lithium triethylborohydride (reflux in dioxane, 0.5 h) to give (*S*)-**13** (42%) whose optical purity was 98:2 (HPLC on Daicel Chiralcel OB with hexane/2-propanol 3:1 v/v).

Similar reaction of optically pure oxazolidine acrylamide (*R*)-**9** with benzonitrile oxide at –50 °C gave a mixture of **14** and **14'** together with a side product **15** (95%, 82:5:13 by $^1$H NMR) as shown in Scheme 5-04. Hydrolysis of **14'** and **15** was catalyzed with trifluoroacetic acid (TFA in $CH_2Cl_2$, rt, 0.5 h) to give the same compound **16'** in quantitative yields, but the major isomer **14** was stable under these conditions. Heating under reflux of **14** in methanol in the presence of conc HCl gave **16** (81%, 4 h), an antipode **16'**. When the crude reaction mixture was treated with TFA, a 80:20 mixture of **14** and **16'** was obtained. After separation through column chromatography on silica gel, **14** was reduced with lithium triethylborohydride (rt in THF, 5 min) to give optically pure 2-isoxazoline-5-methanol (*R*)-**13** as confirmed by a chiral HPLC. Thus, the diastereoselectivity in this reaction was 82:18.

**Scheme 5-04** Asymmetric diastereoselective nitrile oxide cycloadditions using oxazolidine acrylamide *R*-**9**

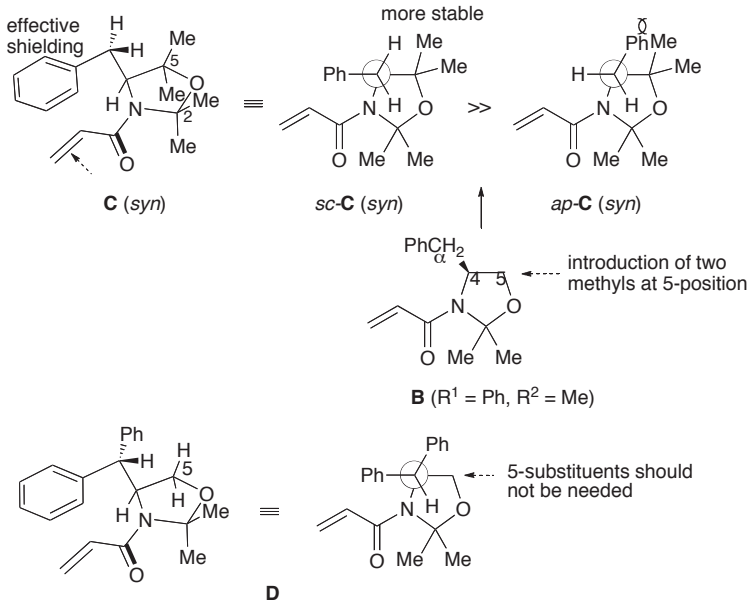



Thus, acrylamides (*S,S*)-**11** and (*R*)-**9** predominantly occupy *syn,syn*- and *syn*-configurations and *s-cis*-conformation with regard to C(CO)-C(α) single bond in the transition state. Benzonitrile oxide attacked the alkene face from a side opposite to the 4-phenyl substituent, *si*(Cα,Cα')- and *re*(Cα)-faces for (*S,S*)-**11** and (*R*)-**9**, respectively, to give **12** and **14** as major diastereomers. Although diastereoselectivities were not exclusively high, the major diastereomers can be readily separated to give optically pure isoxazolines after reductive removal of the chiral auxiliary.

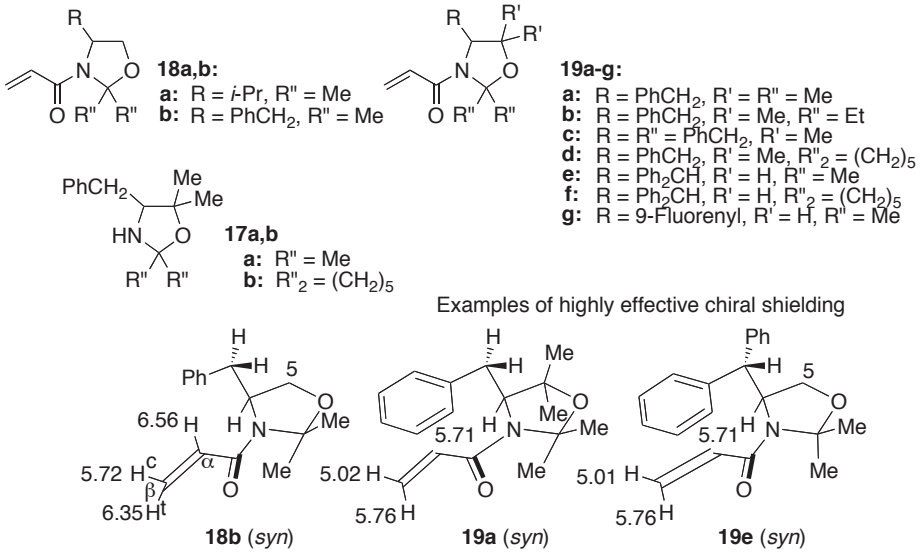
**Additional conformation control based on the 5,5-disubstitution.** The amide bond of 3-acryloyl-4-phenyl-2,2-dimethyloxazolidine **B** ($R^1$ = Ph, $R^2$ = Me) can be controlled in favor of *syn*-isomer by introduction of two methyl substituents at 2-position (Scheme 5-02). However, the diastereofacial selectivity in nitrile oxide cycloadditions was not excellent. Probably the 4-phenyl substituent was not the steric shielding substituent of choice. We decided to replace the 4-phenyl group with a benzyl group. The phenyl plane of 4-benzyl group of **B** ($R^1$ = $PhCH_2$, $R^2$ = Me) should work as effective shielding substituent if the conformation around the C(α)-C(4) single bond is controlled so that the benzylic phenyl plane can cover the top face of the vinyl moiety (Scheme 5-05).

For this purpose, another pair of methyl groups was added at the 5-position resulting in a new chiral auxiliary **C**. Two pairs of methyl substituents are expected to work as effective buttress for the control of each reaction site or chiral steric shielding. In the case of 3-acryloyl-4-benzyl-2,2,5,5-tetramethyloxazolidine **C**, the antiperiplanar conformation *ap*-**C** across the C(4)-C(α) bond becomes much less stabilized than the synclinal conformer *sc*-**C** due to the serious steric repulsion against the 5,5-dimethyl substituents (stability: *sc*-**C** >> *ap*-**C**, Scheme 5-05). If the effective steric shielding by the benzylic phenyl plane of **C** is the case actually happened, this situation may be visible in the $^1$H NMR analysis as well as molecular mechanics calculation using MM2 program.[14] When the 4-benzyl moiety is replaced with diphenylmethyl moiety as seen in the case of **D**, 5,5-dimethyl substituents would be no longer needed. Thus, we synthesized a variety of acrylamide derivatives **18a,b** and **19a-g** having various chiral oxazolidine auxiliaries as shown in Scheme 5-06.

**Scheme 5-05** Stabilization of the *synclinal* conformation *sc*-**C** (*syn*) through the introduction of 5,5-dimethyl substituents as buttress




**Scheme 5-06** Effective chiral shielding effect due to the buttress effect of 5,5-dimethyl substituents can be evaluated through the magnetic deshielding by the 4-benzyl or 4-diphenylmethyl substituent




| | Chemical shifts[a] | | | *syn* / *anti* ratio at varius temperature | | | | | MM2 calculation[b] |
|---|---|---|---|---|---|---|---|---|---|
| | $=CH_2^t$ | $=CH_2^c$ | =CH- | 27°C | 0°C | -30°C | -50°C | -80°C | DG = $G_{anti}$-$G_{syn}$ |
| **18a**[c] | 6.42 | 5.68 | 6.41 | | | | | | 1.25 |
| **18b** | 6.35 | 5.72 | 6.56 | 91:9 | 92:8 | 94:6 | 95:5 | | 2.92 |
| | 6.41 | 5.74 | 6.58 | | | | | | |
| **19a** | 5.76 | 5.02 | 5.71 | 94:6 | 95:5 | 97:3 | 97:3 | | 2.59 |
| | 6.34 | | 6.57 | | | | | | |
| **19b** | 6.13 | 5.47 | 6.31 | | 81:19 | 81:19 | | | 2.34 |
| | 6.38 | 5.69 | 6.54 | | | | | | |
| **19c** | 6.53 | 5.71 | 6.50 | single | single | single | single | single | 2.71 |
| **19d** | 5.76 | 5.01 | 5.71 | | 96:4 | 96:4 | 97:3 | | 2.81 |
| | 6.31 | 5.69 | 6.65 | | | | | | |
| **19e** | 5.70 | 4.91 | 5.62 | 94:6 | 94:6 | 96:4 | 98:2 | 98:2 | 2.67 |
| | 6.20 | | 6.42 | | | | | | |
| **19f** | 5.67 | 4.86 | 5.61 | | 95:5 | 96:4 | 97:3 | | 2.82 |
| | 6.12 | | 6.47 | | | | | | |
| **19g** | 6.22 | 5.47 | 6.17 | 70:30 | 71:29 | 74:26 | 79:21 | | 2.98 |
| | 6.52 | 5.86 | 6.70 | | | | | | |

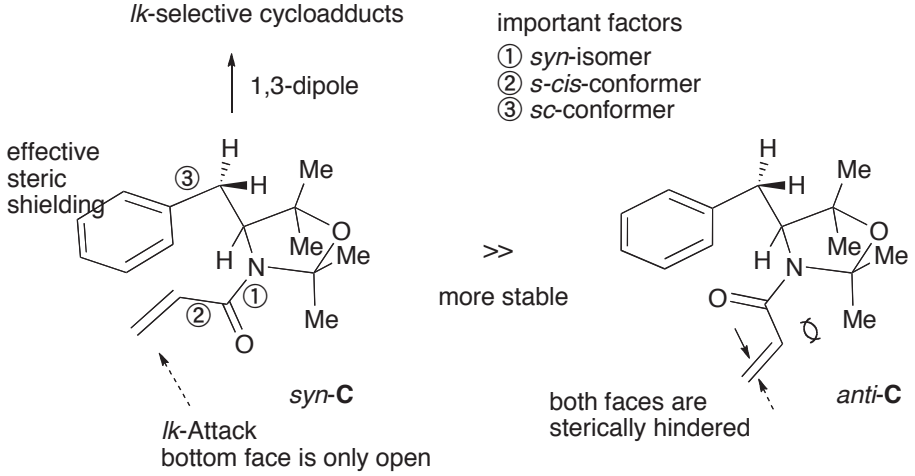
[a]The upper and lower lines are for major and minor isomers, respectively. $^1$H NMR spectrum recorded at -30°C in $CD_2Cl_2$ solution. [b]Energy calculation made for the most stable conformer each for the *syn*- and *anti*-isomers (kcal/mole). [c]Measured only at 27°C. solvent = $CDC_3$.

Among all the bonds involved in a new version of chiral auxiliary of **C**, the amide N-C(CO) bond must be no doubt most restricted, and the C(CO)-C(α) single bond of the *N*-acryloyl moiety may be the second. With respect to the amide configuration, *syn*-isomer *syn*-**C** should be much more stabilized than *anti*-isomer *anti*-**C**. Even if some of the unfavored *anti*-**C** is involved, contribution to the diastereofacial selectivity would be negligible. Both faces of *N*-acryloyl moiety of *anti*-**C** should be sterically hindered due to the steric repulsion by 2,2-dimethyl groups (Scheme 5-07). With respect to the conformation across the C(CO)-C(α) single bond, *s-cis*-conformation should be involved in the reaction, since *s-trans*-conformation causes unfavorable steric repulsion against the 4-substituent at the adjacent chiral center. The preference for *syn*-isomer and *s-cis*-geometry as well as effective steric shielding by the steric shielding of 4-benzyl group to the vinyl reaction site can be confirmed by $^1$H NMR spectroscopy as well as molecular mechanics calculation based on the MM2 program (the bottom table of Scheme 5-06). This will be discussed below. As a result, the least sterically hindered approach of 1,3-dipolar reagent to *syn*-**C** must take place from the bottom side of the vinyl reaction site of the *s-cis*-conformer, and it is expected to work as effective chiral auxiliary.

Finally, the level of diastereoselectivity should depend upon the following preference (Scheme 5-07):[14]
(1) the isomerization stability of *syn/anti* amide,
(2) the stability of *s-cis*-conformation of the C(CO)-C(α) single bond of the *N*-acryloyl moiety,
(3) the efficiency of chiral shielding by the 4-substituent.

When X is oxygen atom, so oxazolidine cases, such chiral olefins **C** bearing a variety of substituents R$^4$ are readily available by starting from optically pure α-amino acids. This is a high synthetic advantage.

**Scheme 5-07** The bottom face of acrylamide of *syn*-**C** is only open for the *lk*-attack of 1,3-dipoles, so diastereofacial selectivity of this reaction should be absolutely high




**Synthesis of chiral auxiliaries.**[13,14] 4-Phenyl-2,2-dimethyloxazolidine *R*-**8** and 4,5-diphenyl-2,2-dimethylimidazolidine $C_2$-symmetric chiral auxiliary *S,S*-**10** were readily synthesized from the corresponding β-amino alcohol and 1,2-diamine, which are both commercially available in optical pure forms. Optically pure β-amino alcohol were also readily prepared without racemization by reduction of the corresponding α-amino esters with sodium borohydride or the corresponding α-amino acids with sodium borohydride in the presence of chlorotrimethylsilane. Condensation of diamine with acetone took

palce readily at room temperature in the presence of anhydrous $MgSO_4$ in dichloromethane to produce *S,S*-**10** in a quantitative yield. On the other hand, the β-amino alcohol was condensed with acetone under reflux in the presence of a catalytic amount of *p*-toluenesulfonic acid (PTSA). However, purification of the condensation product by column chromatography on silica gel caused partial hydrolytic decomposition, the crude product was employed without further purification to the subsequent *N*-acryloylation with acryloyl chloride and $Et_3N$ in dichloromethane at room temperature to give diacrylamide *R*-**9** and *S,S*-**11**. These acrylamide derivatives have high chemical stability enough to be purified by silica gel column chromatography without trouble. 4-Benzyl-2,2,5,5-tetranethyloxazolidine *S*-**17a** and 4-benzyl-5,5-dimethyl-2,2-pentamethyleneoxazolidine *S*-**17b** were synthesized through similar synthetic method. The starting substituted β-amino alcohol was obtained by action of a large excess amounts of methylmagnesium iodide onto methyl (*S*)-benzylglycinate, followed by the condensation with acetone under reflux or with cyclohexanone under reflux in dichloromethane, both in the presence of a catalytic amount of PTSA, respectively. *N*-Acryloylation was performed under similar reaction conditions as descrived above.

**Conformational analysis.**[14] The $^1$H NMR spectra recorded at -30 °C in $CD_2Cl_2$, summarized in the bottom table of Scheme 5-06, showed that some of 3-acryloyl-2,2-dialkyloxazolidines **18a,b** and **19a-g** existed as mixtures of *syn*- and *anti*-isomers. Such isomerism must have arisen from the restricted rotation around the amide linkage N-C(CO). Fixation of the amide bond as *syn*-isomer should be essential to attain highly diastereoselective reactions at one of the diastereomeric acryloyl faces; the contribution by *anti*-isomers is not desired.

Effective chiral shielding can be expected when a benzyl moiety is introduced at the 4-position and the phenyl plane is forced to cover the top face of *N*-acryloyl reacting site. In such case, chemical shifts of the acrylic protons can be used as a convenient indicator for the effectiveness of chiral shielding. The only structural difference between **18b** and **19a** is that the existence of 5,5-dimethyl substituents in **19a**. If the 5,5-dimethyl substituents work as effective buttress, the phenyl plane of 4-benzyl substituent should cover the top face of acryl unsaturated bond more effectively than the case without 5,5-dimethyl substituents. This expectation was actually realized. Both the ternminal olefinic β-protons as well as α-proton (δ = 6.13, 5.47, and 6.31 for $=CH_2^t$, $=CH_2^c$, and –CH=) are all magnetically shielded in the major *syn*-isomer of **19a** than those of **18b** (δ = 6.35, 5.72, and 6.56) , but the corresponding protons in the minor isomers appeared about the same chemical shifts (6.34, 6.57 for **19a**; 6.41, 5.74, 6.58 for **18b**). The major/minor isomer ratios are not so different for **19a** (97:3) and **18b** (94:6) in the $^1$H NMR spectra taken at -30 °C. The big difference of steric shielding by the 4-benzyl substituent strongly indicates that the effective chiral shielding was achieved in **19a**. The buttress effect by the 5,5-dimethyl substituents is apparent. Based on these $^1$H NMR observation, the major isomer of 3-acryloyl-4-benzyl-2,2,5,5-tetramethyloxazolidine (**19a**) was clearly assigned to be *syn*-stereochemistry and *s-cis*-conformation. The isomer ratio of 97:3 at –30 °C is very satisfied since the reactivity of minor *anti*-isomer would be much less than of major *syn*-isomer as already discussed in Scheme 5-07.

When the 4-benzyl group is replaced with a diphenylmethyl substituent, one of the two phenyl groups should be induced to cover the acryloyl plane as shown with the examples of **19e** in Scheme 5-06. No

substituents are necessary at 5-position to direct the chiral shielding substituent toward the *N*-acryloyl moiety. However, it was feared that the relative stability of *syn*-conformers, e.g. *syn*-**19e**, would decrease due to the increased steric repulsion since the diphenylmethyl moiety is a secondary and bulky substituent. Nevertheless, almost identical *syn*/*anti* ratios (96:4 at –30 °C) were actually observed. This is consistent with the MM2 calculations. Chiral shielding, evaluated by magnetic shielding, by the dipheylmethyl moiety was also about the same to that of **19a** at –30 °C.

**Conclusion.**[14]

A variety of new chiral auxiliaries based on conformation control have been described in the present work. Important factors to effect the chiral shielding at the *N*-acryloyl faces by a substituent at 4-position are:

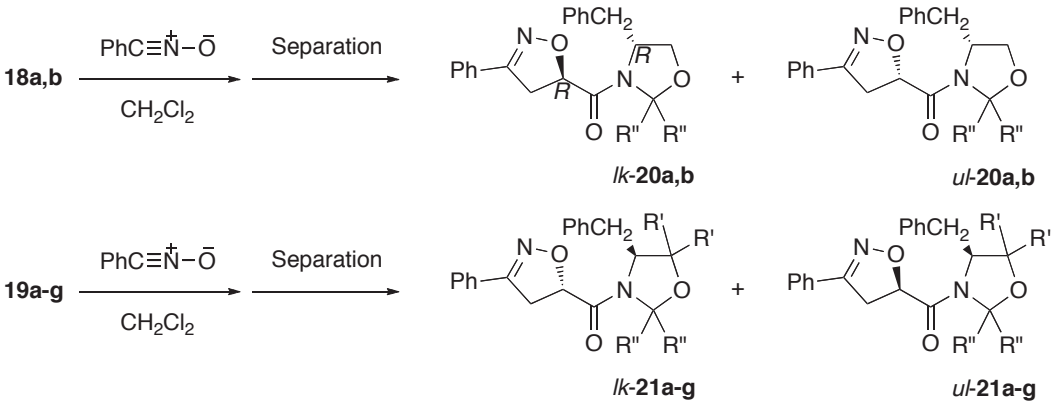
(1) High *syn/anti* conformer ratio can be accomplished enough by introduction of two methyl groups or a pentamethylene group at 2-position. Substituents bulkier than methyl group at 2-position improve neither *syn/anti* conformer ratio nor chiral shielding.
(2) A benzyl group at 4-position works as excellent chiral shielding substituent if two two methyl groups are introduced at 5-position.
(3) Introduction of a bulky substituent at 4-position does not always affect the stability of *syn*-conformation.
(4) A diphenylmethyl substituent at 4-position is effective even when no substituents are introduced at the 5-position.

**Application to asymmetric nitrile oxide cycloadditions.**[15] We examined nitrile oxide 1,3-dipolar cycloadditions of acrylamides **19a-g** in order to evaluate its utility in asymmetric synthesis in the absence of metal additive. Several 4-benzyloxazolidine acrylamide derivatives **19a-g** were employed for this purpose (Scheme 5-08). When no substituent exists at 5-position as seen in **18b**, the selectivities *lk*-**20b**/*ul*-**20b** were extremely poor ($lk:ul \leq 70:30$). However, the reactions of 4-benzyloxazolidine **19a,d** bearing two methyl groups at 5-position afforded satisfactory selectivities. The best value was $lk:ul = 93:7$ at 0 °C, and the same ratio at –30 °C. Such improvement of selectivity was, though not perfect but, mostly consistent with the expectation made above on the basis of conformational analysis. Two methyl substituents introduced at 5-position presumably stablized the synclinal conformation with respect to the rotation around the C(4)-C($\alpha$) bond. Acrylamides **19a,d** carrying methyl and pentamethylene substituents at 2-position, respectively, showed the identical diastereoselectivities (Scheme 5-08).

The 4-benzyloxazolidine **19b** bearing ethyl groupes at 2 position showed much lower selectivities (ds = 86-81%). It was expected at the early stage of this work that bulky substituents at 2-position would increase the *syn*/*anti* conformer ratio and decrease the reaction rate in the *anti*-conformation. We anticipated that the both factors would work to improve diastereoselectivity in favor for *lk*-attack. However, the isomer ratio of **19b** was as poor as 81:19 at –30 °C and the magnetic shielding by the 4-benzyl moiety was insufficient (see Scheme 5-06). Consequently, it came out that the observed poor diastereoselectivities were again predictable on the basis of the result of conformational analysis. The acrylamide **19c** bearing benzyl groups at 2 position was single conformer in the temperature range from

room temperature to –80 °C, but magnetic shielding by the 4-benzyl substituent was not effective (Scheme 5-06). This was explained by the steric instability of the flat amide structure. Its cycloaddition reaction with benzonitrile oxide was actually very poor in selectivity (ds = 83%), indicating that the distorted ground state structure is not useful to accomplish a high diastereofacial selectivity. The acrylamide **19g** bearing a 9-fluorenyl substituent exists as a 71:29 *syn/anti* isomer mixture in the $^1$H NMR analysis measured at 0 °C. Its reaction with benzonitrile oxide at the same temperature resulted in the diastereoselectivity of 76:24. It is certain that not only the low *syn/anti* conformer ratio but also the insufficient magnetic shielding by the 4-(9-fluorenyl) substituent lowered the diastereoselectivity. As observed above, the achievement of exclusively high diastereofacial selectivity in the 1,3-dipolar cycloadditions of nitrile oxide to 3-acryloyl-4-benzyl-2,2,5,5-tetramethyloxazolidine (**19a**) ended with a little unsatisfactory results. Small molecular size as well as relatively low activation energy of nitrile oxide molecules would be one of the major reasons.

**Scheme 5-08** Asymmetric diastereoselective nitrile oxide cycloadditions using a variety of chiral oxazolidine acrylamides **18a,b** and **19a-g**




| Dipolarophile | PhCNO[b] equiv | Temp/°C | Time/h | Product | Yield/%[c] | Isomer ratio[d] *lk:ul* |
|---|---|---|---|---|---|---|
| **18a** | 1.25 | rt | 0.5 | **20a** | 94 | 83:17 |
| **18b** | 1 | 0 | 8 | **20b** | 95 | 68:32 |
| **18b** | 1 | -30 | 41 | **20b** | 78 (23) | 70:30 |
| **19a** | 1 | -30 | 42 | **21a** | 77 (21) | 93:7 |
| **19a** | 1 | 0 | 16 | **21a** | 99 | 93:7 |
| **19a** | 1 | 0 | 2 | **21a** | 99[f] | 93:7 |
| **19b** | 1 | -50 | 83 | **21b** | 88 | 86:14 |
| **19b** | 1 | 0 | 5 | **21b** | 88 | 81:19 |
| **19b** | 1 | 0 | 5.5 | **21b** | 87[g] | 82:18 |
| **19c** | 1 | 4 | 4 | **21c** | 99 | 83:17 |
| **19d** | 1 | 0 | 4 | **21d** | 87 | 93:7 |
| **19d** | 1 | rt | 1 | **21d** | 99 | 90:l0 |
| **19e** | 1 | 0 | 3 | **21e** | 99 | >99: 1 |
| **19f** | 1 | 0 | 3 | **21f** | quant | >99: 1 |
| **19f** | 1 | -50 | 70 | **21f** | 90 | >99: 1 |
| **19g** | 1 | 0 | 7 | **21g** | quant | 76:24 |

[a]All reactions were performed in dichloromethane unless otherwise stated. [b]Generated in situ from benzohydroximoyl chloride and triethylamine. [c]Yield of the isolated mixture of diastereomers. The recovered dipolarophile in parenthesis. [d]Determined by $^1$H NMR spectrum (270 MHz) or HPLC (Hibar LiChrosorbR Si 60, Cica-Merck) of the crude reaction mixture. [e]Based on the benzohydroximoyl chloride used. [f,g]Solvent: [f]hexane. [g]acetonitrile.

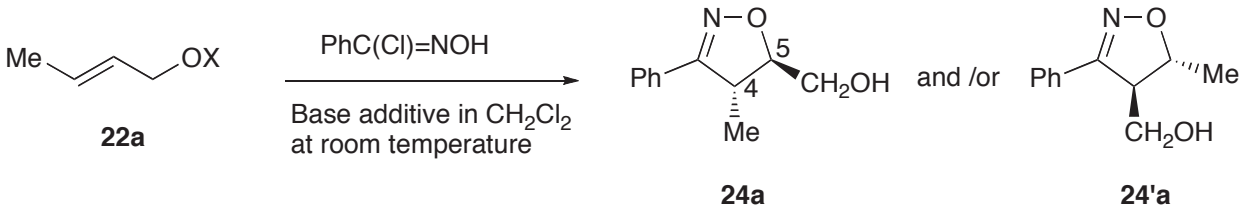
However, to our great delight, 3-acryloyl-4-(diphenylmethyl)oxazolidines **19e,f** provided the absolute diastereofacial selectivities in favor for *lk*-**21e,f** when the reactions with benzonitrile oxide were performed at 0 °C or below (Scheme 5-08).[15] Single diastereomers of **21e,f** were produced in quantitative yields, regardless of the 2-substituents. These isoxazolines *lk*-**21e,f** were used as racemates because optically resolution of *rac*-**19e,f** were not successful yet.

It was found that polarity of reaction solvent was not so important in the above asymmetric nitrile oxide cycloadditions. The benzonitrile oxide employed in this work was generated in situ from benzohydroximoyl chloride and triethylamine. Since most of cycloadditions were performed in dichloromethane solution, the reaction was homogeneous and the triethylammonium chloride was always in solution. Use of hexane or acetonitrile as reaction solvent gave essentially the equivalent results. A more polar medium certainly stabilizes the polarized amide structure so that the rotation barrier with respect to the amide nitrogen-carbonyl carbon bond may increase. In the asymmetric nitrile oxide cycloadditions using chiral acrylamides **18** and **19**, however, the most important is the efficiency of chiral shielding by the 4-substituent. It is not surprising that no polarity effect is working in the conformation of such nonfunctionalized 4-substituents. Probably, the charge transfer from the benzylic substituent at 4-position to the *N*-acryloyl moiety is not important in the present reactions.

### 5.2 New generation method of nitrile oxide/Lewis acid complexes

Nitrile oxides undergo ready cycloadditions with terminal alkenes producing the 5-substituted 2-isoxazolines in an exclusively regioselective manner, regardless of the nature of substituent (electron-withdrawing, -donating, alkyl, aryl, heteroatom type substituents, etc.). However, reactions with 1,2-disubstituted alkenes show disappointingly decreased reactivity and low regioselectivity. Situation is even worse in the reactions with 1,1,2-trisuhstituted ethenes. We found the chelation-controlled highly diastereoselective cycloadditions of nitrile oxides to the magnesium alkoxides of allylic alcohols, this offered the first example of the Lewis acid-assisted stereocontrol of 1,3-dipolar cycloadditions. The nitrile oxide/Lewis acid complexes, generated from hydroximoyl chlorides and organometallics, undergo *syn*-selective cycloadditions to the allyl alcohols bearing an α-chirality.[36]

**Scheme 5-09** Magnesium ion mediated regiselectivity control of nitrile oxide cycloadditions to (*E*)-2-buten-1-ol **22a**[a]




PhC≡N⁺−O⁻ **23**

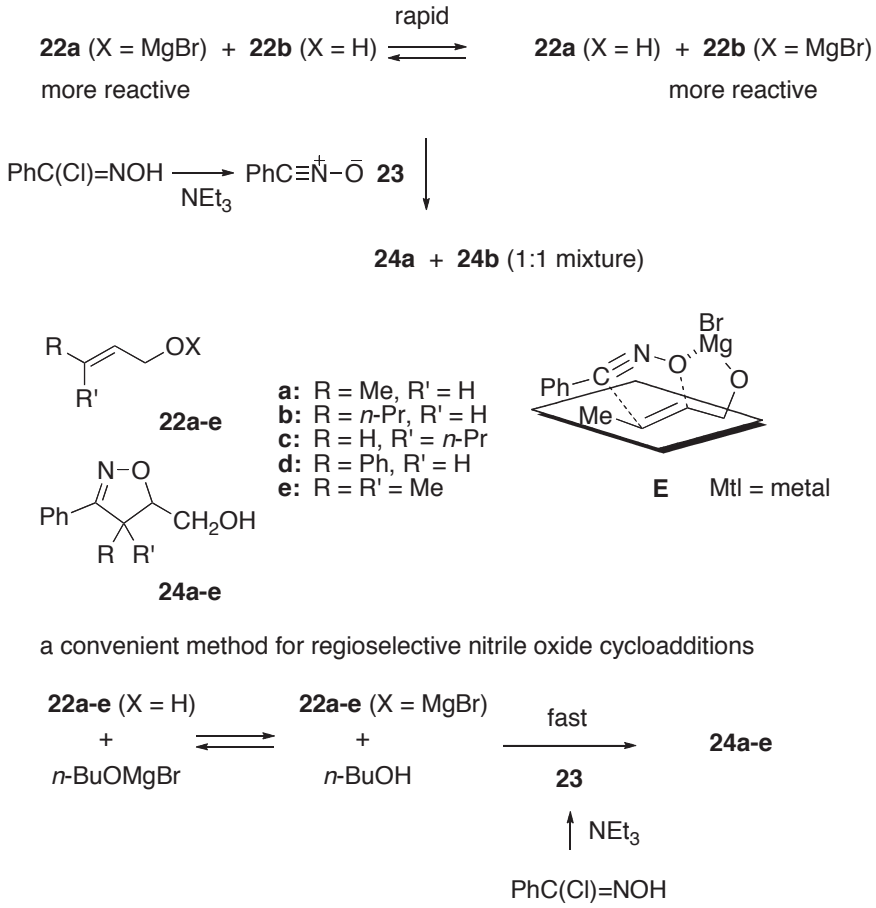
PhC≡N⁺−O⁻·····MgBrCl **23**•MgBrCl

| X of **22a** (equiv) | Base (equiv) | Additive (equiv) | Temp/°C | Time/h | Yield/%[b] | **24a : 24'a** |
|---|---|---|---|---|---|---|
| H (1) | $NEt_3$ (1) | - | rt | 1.5 | 46 | 46:54 |
| H (1) | EtMgBr (1) | - | 30 | 17 | 20 | 55:45 |
| Li (1) | $NEt_3$ (1) | | rt | 0.5 | 10 | 49:51 |
| Li (1) | *n*-BuLi (1) | - | rt | 0.5 | 13 | 60:40 |
| EtZn (1) | $NEt_3$ (1) | - | rt | 0.5 | 9 | 46:54 |
| $Et_2Al$ (1) | $NEt_3$ (1) | | rt | 0.5 | 14 | 48:52 |
| MgBr (1) | $NEt_3$ (1) | - | rt | 0.5 | 62 | 96:4 |
| MgBr (1) | - | - | rt | 27 | 9 | 88:12 |
| MgBr (2) | - | | -30 | 66 | 63 | 98:2 |
| MgBr (2) | | - | rt | 0.5 | 82 | 99:1 |
| MgBr (2) | - | *i*-PrOH (2) | rt | 0.5 | 92 | 97:3 |
| MgBr (2) | - | *n*-BuOH (2.2) | rt | 3.5 | 75 | 98:2 |
| MgCl (1) | *t*-BuMgCl (1) | - | rt | 0.5 | 47 | 96:4 |
| MgBr (1) | EtMgBr (1) | - | rt | 0.5 | 62 | 96:4 |
| MgI (1) | MeMgI (1) | - | rt | 0.5 | 10 | 98:2 |
| MgBr (1) | n-BuLi (1) | - | rt | 0.5 | 55 | 95:5 |
| MgBr (1) | *i*-PrOLi (1) | | rt | 0.5 | 62 | 96:4 |
| Li (1) | EtMgBr (1) | - | rt | 2.5 | 66 | >99:1 |
| Li (1) | EtMgBr (1) | [c] | rt | 5 | 41 | 93:7 |

[a]All reactions were performed in $CH_2Cl_2$. [b]Isolaed yield. [c]Solvent: THF.

Reaction of (*E*)-2-butenol (**22a**, X = H) with benzonitrile oxide (**23**) produced a mixture of regioisomeric cycloadducts **24a** and **24'a**. (1) Both the regioselectivities and the yields of products were very poor (1 : 1 regioselectivity in ca 50% yield) when free alkene alcohol **22a** (X = H) was reacted with nitrile oxide **23** generated from benzohydroximoyl chloride/$NEt_3$ or EtMgBr, (2) alkoxides **22a** (X = Li, EtZn, $Et_2Al$) were reacted with **23** generated from the benzohydroximoyl chloride/$NEt_3$, or (3) alkoxide **22a** (X = Li) was reacted with nitrile oxide **23** generated from benzohydroximoyl chloride/*n*-BuLi (Scheme 5-09). However, it was surprising that reaction of magnesium alkoxide **22a** (X = MgBr) with the nitrile oxide **23** generated from benzohydroximoyl chloride/$NEt_3$ resulted in a satisfactory yield and a high regioselectivity (82%, at rt in 30 min, **24a** : **24'a** > 99:1).

**Scheme 5-10** Rapid alcohol / alkoxide exchange reaction can be applied to a convenient procedure for the rapid regioselective nitrile oxide cycloadditions to allylic alcohols




When a mixture of **22a** (X = MgBr) and **22b** (X = H), each 2 equivalents, was allowed to react with nitrile oxide **23** generated from benzohydroximoyl chloride/$NEt_3$, a 53:47 regioisomeric mixture of cycloadducts **24a** and **24b** was obtained in 98% of total yield (Scheme 5-10).[36] This indicates that the magnesium alkoxide **22a** (X = MgBr) underwent a rapid alkoxide exchange reaction with free alcohol **22b** (X = H) and the resulting 1:1 mixture of alkoxides **22a,b** (X = MgBr) participated in the reaction with nitrile oxide **23**. On the basis of these results and the fact that the free nitrile oxide **23** is more reactive than the complex **23**•MX (MX: Lewis acid), a more convenient simple procedure was achieved as shown below. Nitrile oxide **23** generated from benzohydroximoyl chloride/$NEt_3$ was reacted with a mixture of free alcohol **22a** (X = H) and *n*-BuOMgBr. When more than one equivalent of *n*-BuOMgBr was employed, the 2-isoxazoline-5-methanol **24a** was only obtained in a high yield. Both the selectivity and the yield were found to depend upon the equimolar amount of *n*-BuOMgBr used so that the catalytic reaction could not be attained (Scheme 5-11).

Finally, the nitrile oxide cycloadditions with a variety of substituted allylic alcohols were performed under the reaction conditions that the generation of nitrile oxide **23** from benzohydroximoyl chloride/$Et_3N$ was followed to react with allylic alcohols **22a-e** (X = H) at room temperature in dichloromethane in the presence of *n*-BuOMgBr (1.3 equiv). The results are listed in Scheme 512. To be emphasized are[36]

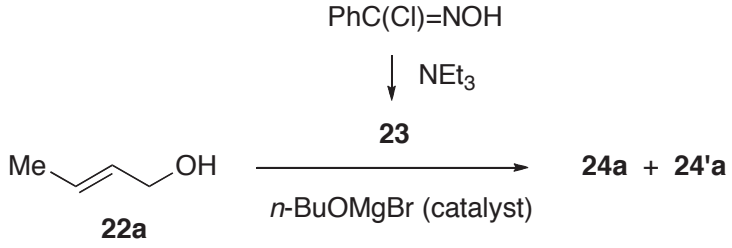
(1) the exclusively high regioselectivities producing 2-isoxazoline-5-methanols **24a-e**,

(2) the excellent yields of **24**,

(3) the effective rate acceleration of cycloadditions,

(4) the reversed regiosclcctivity in reactions with (*E*)-3-phenyl-2-propenol **(22d)** and 3-methyl-2-butenol (**22e**).

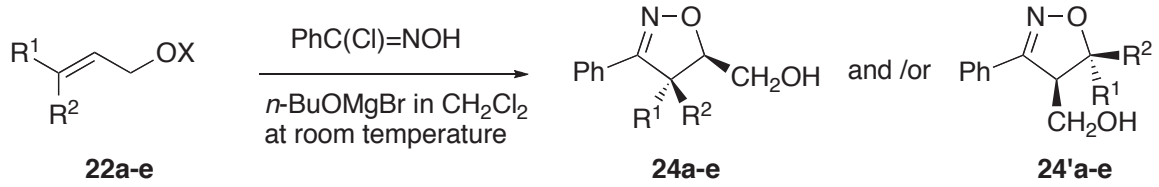
**Scheme 5-11** Effect of catalytic amounts of magnesium butoxide on the regioselectivity of nitrile oxide cycloadditions to **22a** (X = H)




| *n*-BuOMgBr | Time/h | Yield/% | **24a : 24'a** |
|---|---|---|---|
| 0.1 equiv | 24 | 37 | 57:43 |
| 0.3 | 24 | 29 | 68:32 |
| 0.5 | 24 | 59 | 82:18 |
| 0.8 | 12 | 53 | 97:3 |
| 1.1 | 2.5 | 83 | **24a** only |
| 1.3 | 1 | 87 | **24a** only |

About one equiv of magnesium alkoxide is needed.

**Scheme 5-12** Regioselective cycloadditions of nitrile oxide to substituted allylic alcohols **21a-e** (X = H)[a]




PhC≡N⁺-O⁻ **23**

**a:** $R^1$ = Me, $R^2$ = H
**b:** $R^1$ = *n*-Pr, $R^2$ = H
**c:** $R^1$ = H, $R^2$ = *n*-Pr
**d:** $R^1$ = Ph, $R^2$ = H
**e:** $R^1$ = $R^2$ = Me

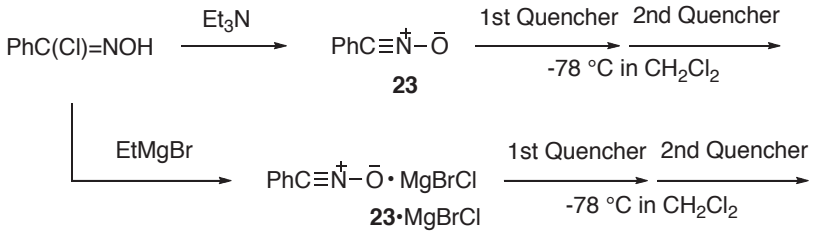
| Allyl alcohol | $R^1$ | $R^2$ | Time/h | Product | Yield/% [b] | **24 : 24'** [c] |
|---|---|---|---|---|---|---|
| **22a** (X = H) | Me | H | 1 | **24a** | 90 | single (46:54) |
| **22b** (X = H) | *n*-Pr | H | 1 | **24b** | 90 | single (55:45) |
| **22c** (X = H) | H | *n*-Pr | 1.5 | **24c** + **24'c** | 100 | 98:2 (-) [d] |
| **22d** (X = H) | Ph | H | 1.5 | **24d** | 92 | single (20:80) |
| **22e** (X = H) | Me | Me | 13 | **24e** + **24'e** | 47 | 99:1 (1:99) [e] |

[a] *n*-BuOMgBr (1.3 equiv) at rt. [b] The ratio in parenthesis is that observed in the reaction of **23** without magnesium alkoxide. [d] No cycloadduct was produced. [e] Yield: 15% (15 h at rt).

Thus, the highly effective regiocontrol to produce 2-isoxazoline-5-methanol derivatives could be accomplished by the reactions of nitrile oxides, generated through a usual method using hydroximoyl chloride precursors and triethylamine, with substituted allyl alcohols in the presence of more than one equimlar amount of magnesium alkoxide derived from an 1-alkanol. It is no doubt that the chelated transition state **E** (Scheme 5-10) is responsible for the high regiocontrol as well as the rate enhancement. However, the extensive magnesium specificity remains unsolved.

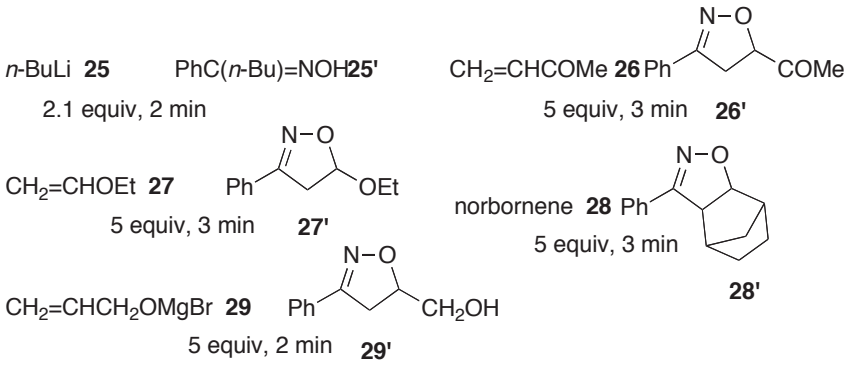
In the course of our kinetic study on the rate acceleration in chelation-controlled nitrile oxide cycloadditions, we needed an effective termination method of nitrile oxide cycloadditions. Quenching with aqueous salts such as ammonium chloride is most widely employed. However, this procedure often arouses criticisms when one tries to terminate the nitrile oxide reactions performed at a low temperature such as -78 °C. Quenching becomes ineffective due to the freeze of aqueous quencher at this temperature. Nitrile oxides are not always instaneously consumed under these conditions, and hence cycloaddition to the remaining dipolarophile still proceeds under the workup conditions. Especially, the cycloaddition rate increases as the reaction mixture is concentrated in a condensation procedure. On the hydrolytic termination of the chelation-controlled cycloadditions to electron-deficient dipolarophiles, free nitrile oxides, presumably more reactive than the complex, are liberated. They are hydrolyzed, but at the same time they undergo a competitive cycloaddition with the unreacted dipolarophile during the workup procedure. We present a highly effective quenching method of nitrile oxide cycloadditions by the aid of 2-propenyloxymagnesium bromide. This termination method can be applied to a wide variety of nitrile oxide cycloadditions to any kinds of dipolarophiles. A very reactive dipolarophile is suitable as an efficient quencher for nitrile oxide cycloadditions. Inexpensive and volatile compounds are desired so that they can be employed in a large excess and removal of the remaining quencher may be readily undertaken by evaporation. Also desirable is the ready separation of the cycloadduct derived from the quencher employed from the target cycloadduct.

**Scheme 5-13** Reactions of benzonitrile oxide **23** or Its MgBrCl complex **23**•MgBrCl with various quenching agents **25**-**29**[a]




| Nitrile oxide or complex | 1st Quencher[b,c] | 2nd Quencher[b,c] | Products (yield)[d] |
|---|---|---|---|
| PhC≡N+–O− **23**[e] | **25** | none | **25'** (76%) |
| | **26** | none | **26'** (97%) |
| | **25** | **26** | **25'** (95%) + **26'** (5%) |
| | **26** | **25** | **26'** (85%) + **25'** (6%) |
| | **26** + **28**[f] | none | **26'** + **28'** (100%, 42:58) |
| | **27** | **25** | **25'** (92%) |
| | **28** + **29** | none | **29'** (97%) |
| PhC≡N+–O−• MgBrCl **23**•MgBrCl[e] | **25** | **26** | **25'** (15%) + **26'** (50%) |
| | **26** | **25** | **26'** (86%) + **25'** (trace) |
| | **26** + **28**[f] | none | **26'** + **28'** (78%, 45:55) |
| | **27** | **25** | **27'** (25%) + **25'** (16%) |
| | **28** + **29** | none | **28'** + **29'** (86%, 2:98) |

[a]All reactiones were performed in $CH_2Cl_2$ in the upper 7 experiments and $CH_2Cl_2$/THF (10:1 v/v, in the down five experiments). [b]Unless otherwise referred, a quencher was added and allowed to stir at -78 °C for 2-3 min. [c]Quencher **25** was used in 2.1 equivalent and the other ones **26**-**29** in 5 equivalents. [d]Yield of isolated products. Product ratio was based on the $^1$H NMR spectrum of the crude reaction mixture. [e]Hydroximoyl chloride was treated with $Et_3N$ (0 °C , 3 min) or EtMgBr (1 M in THF, 0 °C, 5 min) and then cooled down to -78 °C. [f]A mixture of each 5 equivalents was used.




Selected quenchers here in the present work include butyllithium (**25**). 3-buten-2-one (**26**), ethyl vinyl ether (**27**), bicyclo[2.2.1]hept-2-ene (norbornene **28**), and 2-propenyloxymagnesium bromide (**29**). Dipolarophiles **26-28** are each the most reactive dipolarophiles of the electron-deficient, electron-rich, and strained types. Nucleophile **25** adds to nitrile oxides to give alkylated oximes; alkoxide **29** undergoes a rapid cycloaddition to give 2-isoxazoline-5-methanols. One anxious thing is that termination with **25** as a strong base may cause some undesired serious decomposition of cycloadducts, especially when a leaving group is attached at 5-position of 2-isoxazoline ring.

**Magnesium allyl alkoxide as strong quenching agent.** In general, termination of a reaction is desired to be done in a few minutes at a low temperature, more desirably in a few second. Accordingly, appropriate

two quenchers of the above **25**-**29**, in excess as much as 5 equivalents (2.1 equivalents for **25**), were employed in any orders in an interval of 3 min (2 min for **25**, **29**). As a general procedure, nitrile oxide was allowed to react with the first quencher for 3 min at –78 °C and this reaction was terminated with the second quencher. The efficiency of quenchers was evaluated based on the product ratios. Results are summarized in Scheme 5-13.[37] Free benzonitrile oxide (**23**), generated from hydroximoyl chloride and triethylamine at 0 °C, was first examined in quenching experiments. In reactions with **23**, nucleophile **25** and enone **26** are smoothly consumed in a few minutes at -78 °C to give adduct **25'** and cycloadduct **26'**, respectively, in good yields (Scheme 5-13). The successive use of **25** and **26** in an interval of 2 or 3 min indicates that these two can be excellent quenchers at –78 °C; the competitive cycloaddition between **26** and **28** indicates that they have nearly equal reactivities to nitrile oxide **23**. However, vinyl ether **27** does not show a sufficient reactivity toward **23** in a reaction within a few minutes at –78 °C.

To our great surprise, the competitive cycloaddition of free nitriie oxide **23** between norbornene (**28**) and 2-propenyloxymagnesium bromide (**29**, each 5 equiv, at –78 °C results in the exclusive formation of cycloadduct **29'** as the sole product in a quantitative yield. It is later found that the latter is about 130 times more reactive than the former. As a result, allyl alkoxide **29** is recognized to be the best quenching agent for nitrile oxide cycloadditions so as to be effectively utilized in the nitrile oxide cycloadditions to any kinds of dipolarophiles.

Quenching of the cycloadditions of a nitrile oxide/Lewis acid complex has to be done carefully. Among the quenching agents employed in the cycloadditions of benzonitrile oxide/MgBrCl complex, as a representative for nitrile oxide/Lewis acid complexes, alkyllithium **25** and vinyl ether **27** are not promising: Vinyl ether **27** is a little more activated in the reaction with **23**•MgBrCl than in the reaction with **23**, but still too poor in reactivity. In the case of **25**, two equivalents are consumed in the transmetalation with the Lewis acid part (MgBrCl) of complex **23**•MgBrCl, but yet use of a large excess of such a strong base **25** would cause some undesired side reactions. Nucleophilic addition to carbonyl-functionalized 2-isoxazolines may be a case. As a trouble actually observed, when **27** and **25** are employed in this order. the reaction produces mixture of complex products and part of cycloadduct **27'** suffers from the elimination of ethanol.

Enone **26** and strained olefin **28** show reactivities comparably high enough to consume complex **23**•MgBrCl within a few minutes at -78 °C. However, ally1 alkoxide **29** is much more reactive than norbomene (**28**), and hence than **26** as well, indicating that **29** may be effectively utilized again as a powerful terminating agent for the cycloadditions of nitrile oxide/Lewis acid complexes to any kinds of dipolarophiles.

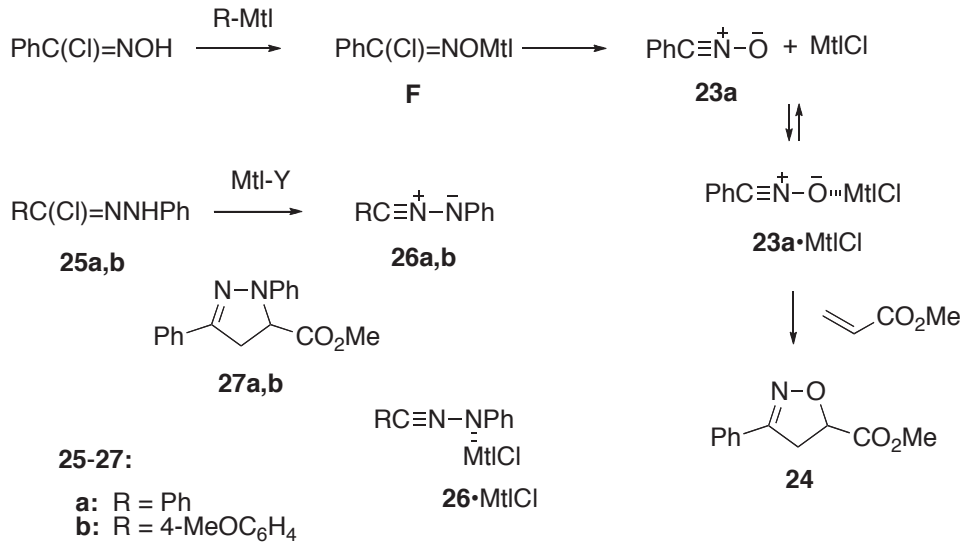
### 5.3 *syn*-Selective and regioselective cycloadditions of nitrile oxides or imines to allylic alcohols

**Magnesium catalysis in nitrile oxide and imine cycloadditions.** Nitrile oxides and nitrile imines, especially the formers, are one of the most widely utilized 1,3-dipoles in organic synthesis since the cycloadducts produced through their cycloadditions have high synthetic potentials as functionalized heterocycles. The general method of generating such 1,3-dipoles consists of the treatment of precursor chlorides such as carbohydroximoyl and carbohydrazonoyl chlorides with tertiary amines such as triethy-

lamine. Such in situ generated 1,3-dipoles show high reactivities toward alkene dipolarophiles having either electron-withdrawing and -donating substituents to offer a convenient route to 2-isoxazoline and pyrazoline heterocycles.

In the course of our study on the chelation-mediated stereo- and regiocontrol of 1,3-dipolar cycloadditions we needed an effective entry to the facile generation of 1,3-dipole/Lewis acid complexes. The conventional generation method always provides the 1,3-dipoles accompanied by undesired triethylammonium chloride. Our idea for the new generation of 1.3-dipole/Lewis acid complexes is based on the direct treatment of precursors with organometallics. For example, *O*-metalation of a carbohydroximoyl chloride to generate the corresponding nitrile oxide. Thus formed dipole and Lewis acid should combine each other to give the nitrile oxide/magnesium chloride complex. A new generation method of Lewis acid-coordinated nitrile oxide and nitrile imine 1,3-dipoles by treatment of carboximoyl chlorides with organometallics or carbohydrazonoyl chlorides with metal alkoxides or amides, respectively.[38] These 1,3-dipole/Lewis acid complexes undergo *syn*-selective cycloaddition reactions to 2-(1-hydroxyalkyl)-acrylates through a chelated transition state, while free dipoles show anti-selectivities.

**Scheme 5-14** 1,3-Dipolar cycloadditions of nitrile oxides **23** and imines **26** in the presence of magnesium ion




Treatment of benzohydroximoyl chloride with butyllithium, ethylmagnesium bromide, or diethylzinc at –30 to –50 °C in tetrahydrofuran (THF), followed by interaction with methyl acrylate as acceptor molecule, gave methyl 3-phenyl-2-isoxazoline-5-carboxylate (**24**) in good yields, indicating the successful generation of benzonitrile oxide (**23a**) (Scheme 5-14 and Table 5-15).[38] No formation of ketone oximes as nucleophilic substitution products was delightful. The first step involved is the *O*-metalation of highly acidic oxime proton to form the metalated hydroximoyl chloride intermediate **F** which then undergoes smooth 1,3-elimination of the corresponding metal chloride MtlCl to generate **23a**. Half an equimolar amount of diethylzinc was sufficient. For example, ethylzinc chloride which is the elimination product in the first generation of **23a** can further react with benzohydroximoyl chloride to generate the second molecule of nitrile oxide **23a**.

Metal chloride MtlCl, produced together with **23a** in the elimination step, is classified to be a Lewis acid.

The resulting Lewis acid should be attacked by nitrile oxide as a strong Lewis base to form the nitrile oxide/Lewis acid complex **23a**•MtlCl. In the nitrile oxide cycloadditions to electron-deficient dipolarophiles, the highest occupied molecular orbital (HOMO) of nitrile oxide generally interacts with the lowest unoccupied molecular orbital (LUMO) of dipolarophile. Accordingly, it is assumed that deactivation of nitrile oxide **23a** occurs by the formation of Lewis acid complex **23a**•MtlCl. The lithium complex **23a**•LiCl (Mtl = Li) suffers from little deactivation because LiCl is a weak Lewis acid, while the magnesium complex **23a**•MgBr (Mtl = MgBr) is extremely deactivated because MgBrCl is a strong Lewis acid. However, even the complex **23a**•MgBr (Mtl = MgBr) showed some sufficient reactivity toward methyl acrylate. Use of alkylaluminum chlorides such as diethylaluminum chloride and ethylaluminum dichloride failed to generate **23a**.

**Table 5-15** Generation of nitrile oxide **23a** and nitrile imines **26a,b** from benzohydroximoyl chloride and carbohydrazoyl chlorides **25a,b** followed by trapping with methyl acrylate.[a]

| Precursor | R | Base[b] | Equiv | Dipole | Temp/°C | Time/h | Product | Yield/%[c] |
|---|---|---|---|---|---|---|---|---|
| PhC(Cl)=NOH | | $Et_3N$ | 1 | **23a** | -30 | 7 | **24** | 94 |
| | | *n*-BuLi | 1 | | -50 | 61 | | 89 |
| | | EtMgBr | 1 | | -30 | 39 | | 90 |
| | | $Et_2Zn$ | 1 | | -30 | 15 | | 94 |
| | | $Et_2Zn$ | 0.5 | | -30 | 48 | | 91 |
| **25a** | Ph | $Et_3N$ | 1 | **26a** | rt | 3 | **27a** | 97 |
| | | LDA | 1 | | rt | 2 | | 57 |
| | | $(i\text{-}Pr)_2NMgBr$ | 1 | | rt | 2 | | 89 |
| **25b** | 4-$MeOC_6H_4$ | LDA | 1 | **26b** | -50 | 3 | **27b** | 63 |
| | | EtOLi | 1 | | -50 | 20 | | 83 |
| | | $(i\text{-}Pr)_2NMgBr$ | 1 | | rt | 2 | | 98 |
| | | EtOMgBr | 1 | | rt | 24 | | 29 |

[a]All reactions were performed in THF with methyl acrylate. [b]A precursor was treated with a base at -78 °C, methyl acrylate was added, and then the reaction was continued under the reaction conditions shown in Table. [c]Isolated yield.

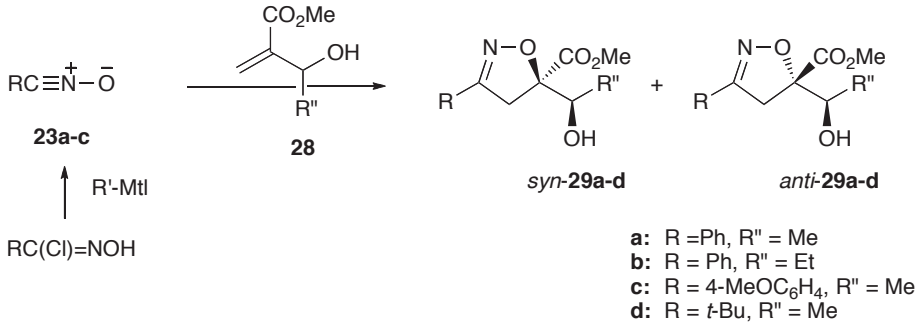
It should be emphasized that the clean and high yield formation of cycloadduct **24** can conpensate for decreased reactivity of dipole. No dimeric product, 4,5-diphenyl-2,1,5-oxadiazol-1-oxide in the case of **23a**, was even detected. This makes a striking contrast with the fact that **23a**, when generated by the normal method using triethylamine, undergoes ready dimerization if no acceptor molecule is present or acceptor molecules are sluggish. However, nitrile oxide complexes **23a**•MtlCl are stable under the reaction conditions and they slowly react with acceptor molecules.

The above *O*-metalation/1,3-elimination procedure was simply applied to generate nitrile imine 1,3-dipoles from hydrazonoyl chloride precursors **25**. However, treatment of (1-chlorobenzylidene)-phenyl-hydrazine (**25a**) with organometallics such as butyllithium, ethylmagnesium bromide, and diethylzinc failed to generate benzonitrile *N*-phenylimide (**26a**). Formation of complex mixture of many products resulted, in which alkylation of **25a** is partly responsible. This is presumably because the *N*-metalation of hydrazonoyl chloride **25a** is relatively more difficult than the *O*-metalation of hydroxi-

moyl chloride. The organometallic nucleophile still remains unreacted when some nitrile imine **26a** is generated so that they react immediately to give the alkylated products. However, such difficulty was solved by use of metal alkoxides or amides instead of organometallics. For example, lithium diisopropylamide, magnesium bromide diisopropylamide, and magnesium bromide ethoxide worked well. The nitrile imines **26a,b** generated from **25a,b** were trapped with methyl acrylates to give cycloadducts **27a,b** (Scheme 5-14).

When a chiral center consisting of a hydroxyl group is introduced to the acrylate skeleton, this hetero substituent will coordinate to the metal atom of complex **23a**•MtlCl in the transition state of nitrile oxide cycloaddition. Accordingly, high diastereofacial selection can be expected in the reactions of the nitrile oxide / Lewis acid complex **23a**•MtlCl. Methyl 2-(1-hydroxyalkyl)acrylates **28** were the electron-deficient olefinic dipolarophiles of our choice. Similar chelated transition state will operate as well in the cycloaddition reactions of nitrile imine/Lewis acid complexes **H** (Scheme 5-19). Benzonitrile oxide **23a** generated from benzohydroximoyl chloride and triethylamine reacted with methyl 2-(1-hydroxyethyl)-acrylate (**28a**, R" = Me) in dichloromethane at –30 °C to give a 70:30 mixture of diastereomers of cycloadduct **29a** (Scheme 5-16). The major and minor diastereomers were determined to be *anti*-**29a** and *syn*-**29a**, respectively, on the basis of chemical conversions and $^1$H NMR analysis. This will be described below. Such *anti*-selectivity observed in the reaction of **23a** to **28a** is opposite to the *syn*-selectivity usually observed in nitrile oxide cycloadditions to 1-chiral allyl alcohols.

**Scheme 5-16** Reactions of nitrile oxides **23a-c** with methyl 2-(1-hydroxyalkyl)acrylate **28a,b**




**a:** R =Ph, R" = Me
**b:** R = Ph, R" = Et
**c:** R = 4-MeOC$_6$H$_4$, R" = Me
**d:** R = *t*-Bu, R" = Me

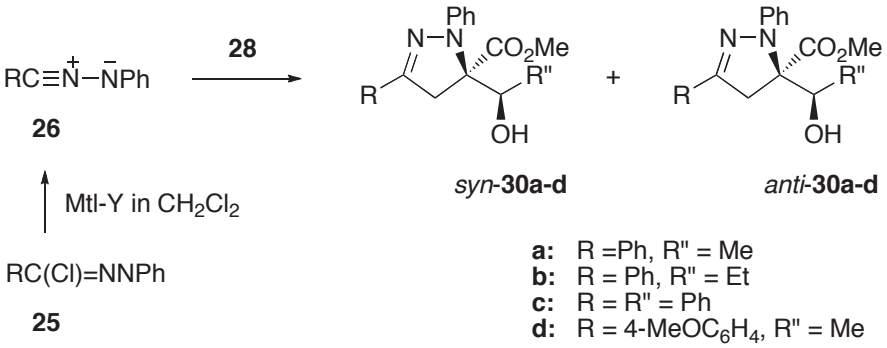
| RC(Cl)=NOH | Base[a] | Dipolarophile | R" | Solvent | Method[b] | Temp/°C | Time/h | Product | Yield/% | *syn:anti*[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| R = Ph | $Et_3N$ | **28a** | Me | $CH_2Cl_2$ | A | -30 | 12 | **29a** | 90 | 30:70 |
| | *n*-BuLi | | | | B | -30 | 13 | | 78 | 47:53 |
| | $Et_2Zn$ | | | | B | -30 | 12 | | 92 | 74:26 |
| | $EtAlCl_2$ | | | | A | rt | 24 | | trace | - |
| | EtMgBr | | | | B | -30 | 21 | | 86 | 81:19 |
| | EtMgBr | | | | C | -30 | 21 | | 100 | 92:8 |
| | EtMgBr | | | | C | rt | 1 | | 100 | 89:11 |
| | EtMgBr | | | THF | B | -30 | 24 | | 93 | 63:37 |
| | $Et_3N$ | **28b** | Et | $CH_2Cl_2$ | A | -30 | 18 | **29b** | 87 | 24:76 |
| | EtMgBr | | | | B | -30 | 16 | | 81 | 86:14 |
| | EtMgBr | | | | C | -30 | 13 | | 100 | 96:4 |
| R = 4-MeOC$_6$H$_4$ | $Et_3N$ | **28a** | | | B | rt | 4 | **29c** | 97 | 46:54 |
| | EtMgBr | | | | B | rt | 4 | | 63 | 83:17 |
| R = *t*-Bu | $Et_3N$ | | | | A | rt | 3 | **29d** | 84 | 34:66 |
| | EtMgBr | | | | B | rt | 5 | | 83 | 83:17 |

[a]All reactions were performed in THF with methyl acrylate. [b]Method A: the precursor + $Et_3N$ and then **28** was added. B: the precursor + organometallic compound at -78 °C prior to the addition of **28**. C: Each two equimolar amounts of the precursor + EtMgBr at -78 °C and then **28** was added. [d]Determined by $^1$H NMR spectrum of the crude product.

When nitrile oxide complex **23a**•LiCl (Mtl = Li) was employed instead of **23a** itself, the *anti*-selectivity was much lowered. And further, the reversal of selectivity took place by use of magensium and zinc complexes **23a**•MtlCl (Mtl = MgBr and Mtl = EtZnCl and/or ZnBr) to provide *syn*-selective cycloadducts *syn*-**29a**. The best *syn*-selectivity of 92:8 was obtained when the magnesium alkoxide of **28a** (2 equiv) was used as a base for the generation of 1,3-dipole **23a** from benzoydroximoyl chloride. This method was useful in the reaction carried out at room temperature. Use of THF instead of dichloromethane lowered selectivity. It is no doubt that chelation transition state is responsible for the high *syn*-selectivity. Generation of similar nitrile oxide complexes **23**•MtlCl (R = 4-$MeOC_6H_4$ and *t*-Bu) was carried out and used in *syn*-selective reactions with **28a** and methyl 2-(1-hydroxypropyl)acrylate (**28b**) as shown in Scheme 5-16.[38]

Reactions of the nitrile imines **26a,b**, generated from **25a,b** and a variety of metallic bases, with methyl 2-(1-hydroxyalkyl)acrylates **28a-c** were examined (Scheme 5-17).[38] When **26a** was generated from **25a** by the usual triethylamine method, the selectivity of reaction was only moderate in favor for *anti*-cycloadduct *anti*-**30a** (70:30). Structures of *anti*-**30a** and *syn*-**30a** were again confirmed by their conversions to a spiro derivative **34** and its diastereomer through a sequence of ester reduction and acetalization followed by an NOE analysis (Scheme 5-18).

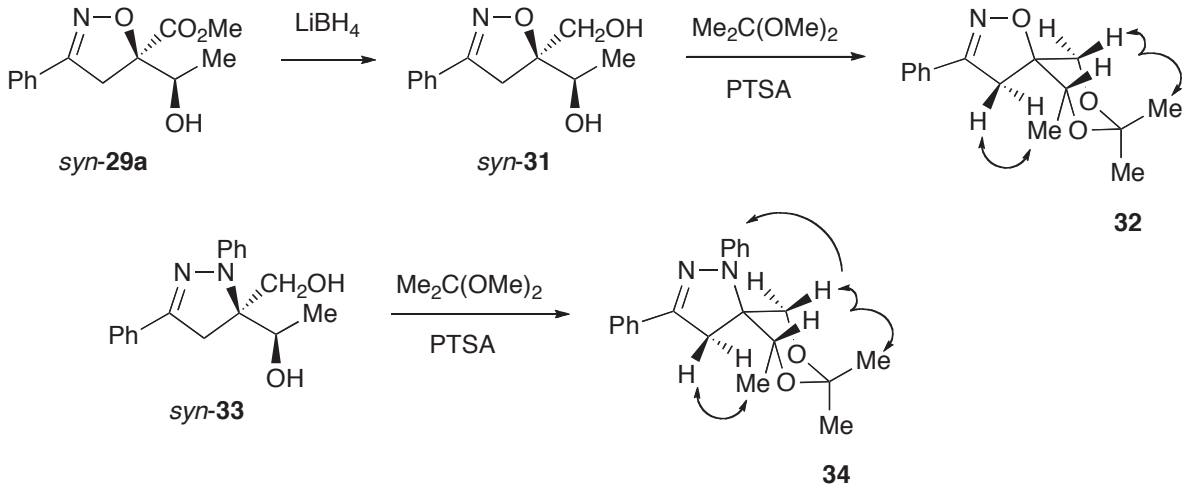
**Scheme 5-17** Reactions of nitrile imines **26a,b** with methyl 2-(1-hydroxyalkyl)acrylates **28a-c**




| Dipole | R | Base[a] | Dipolarophile | R" | Method[b] | Temp/°C | Time/h | Product | Yield/% | *syn*:*anti*[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| **26a** | Ph | $Et_3N$ | **28a** | Me | A | rt | 18 | **30a** | 90 | 30:70 |
| | | LDA | | | B | -50 | 1 | | 53 | 46:54 |
| | | LiOEt | | | B | -50 | 25 | | 90 | 63:37 |
| | | LDA | | | D | -50 | 7 | | 100 | 79:21 |
| | | $(i\text{-}Pr)_2NMgBr$ | | | B | rt | 41 | | 70 | 87:13 |
| | | EtOMgBr | | | B | rt | 87 | | 20 | 96:4 |
| | | EtOMgBr | | | B | reflux | 18 | | 60 | 95:5 |
| | | EtMgBr | | | D | rt | 48 | | 37 | 96:4 |
| | | $Et_3N$/EtMgBr | | | C | rt | 18 | | 18 | 93:7 |
| | | $Et_3N$ | **28b** | Et | A | rt | 10 | **30b** | 90 | 24:76 |
| | | $Et_3N$/EtMgBr | | | C | rt | 25 | | 66 | 82:18 |
| | | $Et_3N$ | **28c** | Ph | A | rt | 21 | **30c** | 94 | 27:73 |
| | | $Et_3N$/EtMgBr | | | C | rt | 40 | | 47 | 95:5 |
| **26b** | 4-$MeOC_6H_4$ | $Et_3N$ | **28a** | Me | B | rt | 20 | **30d** | 94 | 26:74 |
| | | MeOMgBr | | | B | reflux | 37 | | 50 | 91:9 |

[a]Used for the generation of **26a,b** fom precursors. [b]Method A: the precursor + $Et_3N$ and then **28** was added. B: the precursor + a base, and the addition of **28** was followed. C: the precursor + $Et_3N$ and then treated with a mixture of **28** and EtMgBr. D: Each two equimolar amounts of the precursor + a base and then **28** was added to the resulting solution. [c]Determined by $^1H$ NMR spectrum of the crude product.

**Scheme 5-18** Structure determination of diastereoisomers *syn*-**29a** and *syn*-**33** through acetalization followed by the NOE spectrum

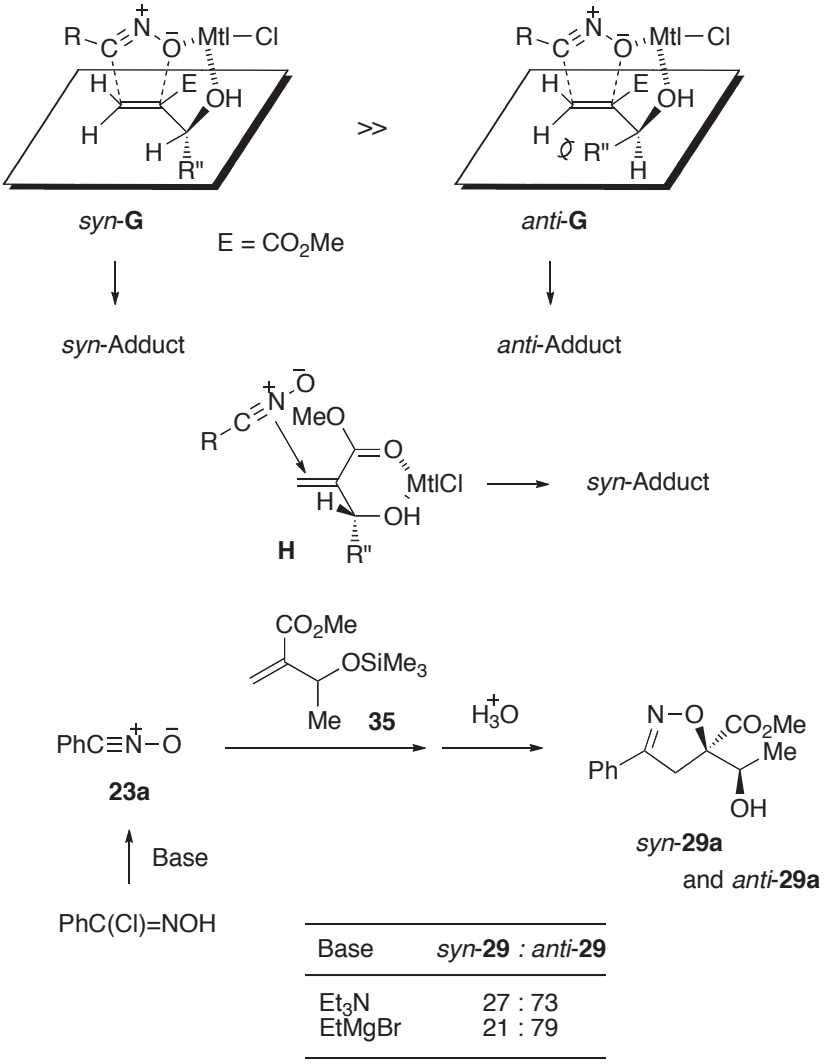



The lithium complex of nitrile imine **26a** showed either no selectivity or *anti*-selectivities. Especially when two equivalents of the lithium alkoxide derived from **28a** and lithium diisopropylamide (LDA) were used as the base for generation of **26a** and also as the dipolarophile, good *anti*-selectivity (79:21) was observed. The magnesium complex (R = Ph, Mtl = MgBr) provided much better *syn*-selectivities, while the yields are usually poor. Other dipoles **26b** and dipolarophiles **28b,c** reacted to show similar selectivities.

Structures of two diastereomeric cycloadducts **29a** and those of other derivatives **29b-d** as well by comparison of spectral data, were determined on the basis of their chemical conversions. A 76:24 mixture of *syn*-**29a** and *anti*-**29a** was reduced with lithium borohydride leading to diols **31** and its diastereomer. Acetalization of this mixture with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid (PTSA) gave a 76:24 mixture of spiro compound **32** and its diastereomer in a total yield of 98%. The major isomer **32**, after separation from the minor one by column chromatography, was determined to be *syn*-product on the basis of NOE spectrum. Notable NOE was observed between 4-Me of the 1,3-dioxane ring and one of H-4 of the isoxazoline ring. Based on the stable conformation of the 1,3-dioxane ring in which the 4-Me moiety must occupy the equatorial position, the *syn*-structure of **32** was assigned. Accordingly, the minor isomer was identified to be *anti*-**29**.

The transition state leading to *syn*-selectivity is explained in Scheme 5-19 with the example of nitrile oxide cycloaddition. The metal atom of nitrile oxide/Lewis acid complex can coordinate to the alcoholic oxygen atom of dipolarophile **28**. The transition state takes the fused five-five ring system. When the substituent R' at the chiral center is located inside of the concave of fused ring system (*anti*-**G**), serious allylic strain works. Accordingly, the reactioon proceeds through sterically less hindered transition state *syn*-**G**. In such reaction mechanism, chelating ability of the metal atom of the nitrile oxide/Lewis acid complex **23**•MtlCl is important. Lithium and zinc metals do not form stable complexes. When the dipolarophiles are ionized, they become better ligands to the metal Mtl so that *syn*-selectivity becomes higher.[38]

**Scheme 5-19** Chelation transition structure for the *syn*-selective cycloadditions of nitrile oxides to magnesium allylic alkoxides




| Base | *syn*-**29** : *anti*-**29** |
|---|---|
| $Et_3N$ | 27 : 73 |
| EtMgBr | 21 : 79 |

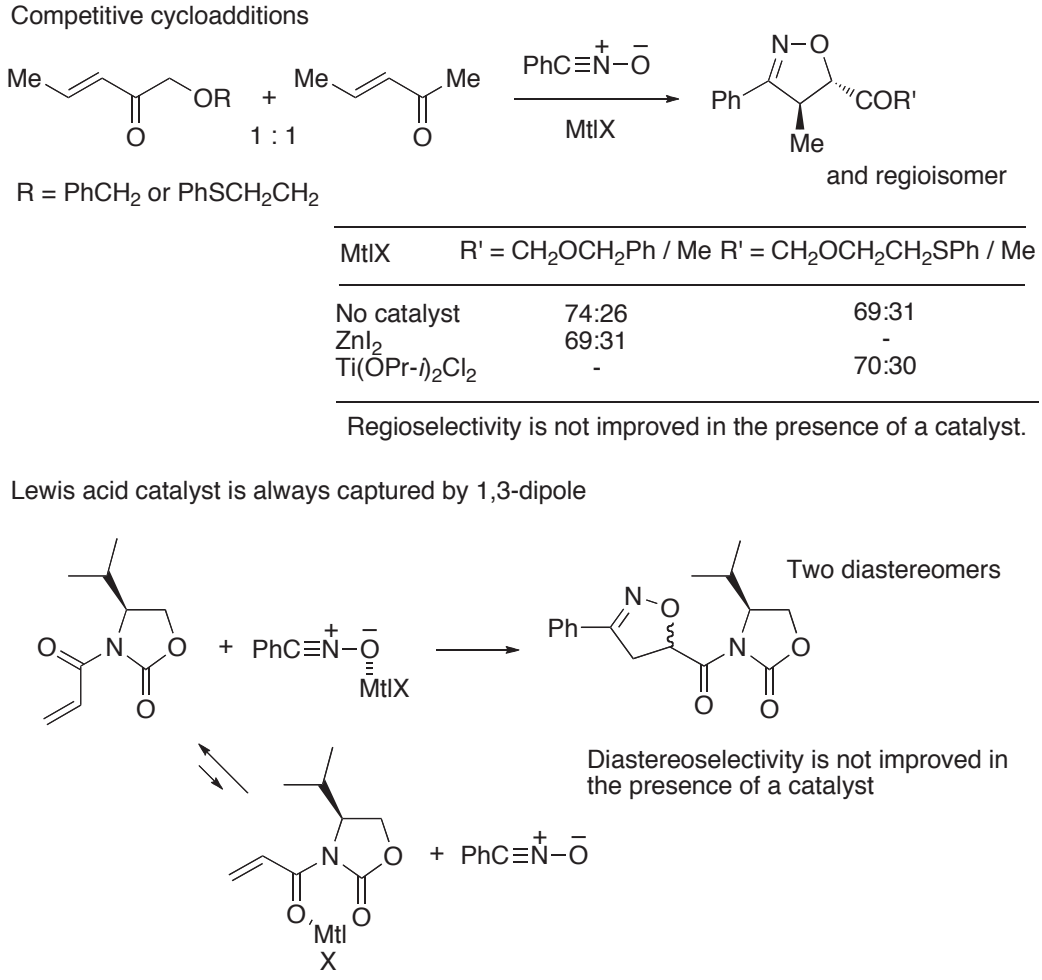
Although it would be possible to explain that the Lewis acid MtlCl only bind between the carbonyl oxygen and the alcoholic oxygen of **28**. In that case cycloaddition reactions should occur with the attack of nitrile oxide to the face opposite to the substituent R'. However, this is not the case actually happened. The decrease of reactivity of nitrile oxide cycloaddition indicates that nitrile oxide must be decelerated by the coordination to the Lewis acid. It is most likely that the chelating metal atom is stabilized by the additional coordination by the carbonyl oxygen as shown in transition *syn*-**G'**.

When the hydroxyl group is protected with a bulky trimethylsilyl moiety, the chelated transition must be destabilized. This anticipation is true. The reacton of benzonitrile oxide with methyl 2-[(1-trimethylsilyl-oxy)ethyl]acrylate (**35**) resulted in moderate anti-selectivities (ds = 71 to 73%) regardless of the generation method.

A new general method to control the stereoselectivity of nitrile oxide cycloadditions was needed. In the course of our study on regio- and stereocontrol of 1,3-dipolar cycloadditions, the effect of Lewis acid catalysis was examined in nitrile oxide cycloadditions. Specifically designed bidentate (or tridentate)

α,β-unsaturated ketones and a chiral α,β-unsaturated amide were used as dipolarophiles (Scheme 5-20) in order to minimize the undesired coordination of nitrile oxides to the Lewis acid. However, all of these attempts failed to improve the reactivity and selectivity of cycloaddition reactions. Probably the Lewis acids were coordinating predominantly to the nitrile oxide to form stabilized and unreactive dipole/Lewis acid complexes, and such complex formation deactivated cycloaddition to electron-deficient olefins. If this were true, use of electron-rich alkenes would solve the problem.

**Scheme 5-20** Nitrile oxide cycloadditions to chelating electron-deficient alkenes in the absence and presence of metal ion




Interaction of hydroximinoyl chlorides with organometallic compounds offered a new method to generate nitrileoxides. The *O*-metalation is followed by 1,3-elimination of a metal chloride, MtlC1, to liberate nitrile oxides. They combine immediately to form nitrile oxide/Lewis acid complexes which still show some reactivity toward electron-deficient alkenes. Cycloadditions using these complexes to 2-(1-hydroxyalkyl)acrylates are highly *syn*-selective. Accordingly, cycloadditions of nitrile oxide/Lewis acid complexes with heterosubstituted electron-rich alkenes, such as allylic alcohols, would be promising since some activation is expected by the formation of dipolarophile/Lewis acid complexes.

The first successful example of stereo- and regiocontrol of 1,3-dipolar cycloadditions by metal coordination is described. In nitrile oxide dipolar cycloadditions to allylic alcohols, use of the magnesium

alkoxides leads to a large acceleration of the reaction rate. Cycloadditions to the allylic magnesium alkoxides also proceed exclusively in a *syn*-selective manner. The magnesium ion-mediated cycloadditions to internal alkenes provide a useful method for the regioselective preparation of 5-hydroxymethyl-2-isoxazolines.[39] Kinetic and theoretical studies indicate that the high stereo- and regiocontrol are due to the rate enhancement of the cycloadditions proceeding through a chelated transition state.

***syn*-Selectivity.** Treatment of benzohydroximinoyl chloride with EtMgBr in $CH_2Cl_2$ at -78 °C (method B) formed the nitrile oxide/MgBrCl complex **23a**•MtlCl (Mtl = MgBr). The reaction of this complex with 1-pentene-3-ol (**36a**, X = H) gave a 95:5 mixture of *syn*- and *anti*-isomers of 5-(1-hydroxypropyl)-3-phenyl-2-isoxazoline (**37a** (Scheme 5-21 and Table 5-22). The free nitrile oxide **23a**, generated from benzohydroximinoyl chloride and triethylamine (method **A**), showed only a poor *syn*-selectivity (*syn:anti* = 67:33). When THF was the reaction solvent, *syn*-selectivity disappeared completely. This result suggests that the reaction proceeds via an intermediate in which one of the two reactants, nitrile oxide **23a** or allylic alcohol **36a**, or both of them coordinate to the magnesium ion. However, this high *syn*-selectivity was not observed when other metal ions were used in the reaction. For example, although nitrile oxide complexes **23a**•MtlCl (Mtl = Li, EtZn, $Et_2Al$) could be generated from benzohydroximinoyl chloride by deprotonation with *n*-BuLi, $Et_2Zn$, $Et_3Al$ (method B), respectively, these complexes showed low *syn*-selectivities. The complexes **23a**•MtlCl generated from $Et_2AlCl$ and $EtAlCl_2$ failed to react with **36a**.

**Scheme 5-21** *syn*-Selective nitrile oxide cycloadditions to 1-substituted 1-propen-3-ols in the presence of magnesium ions

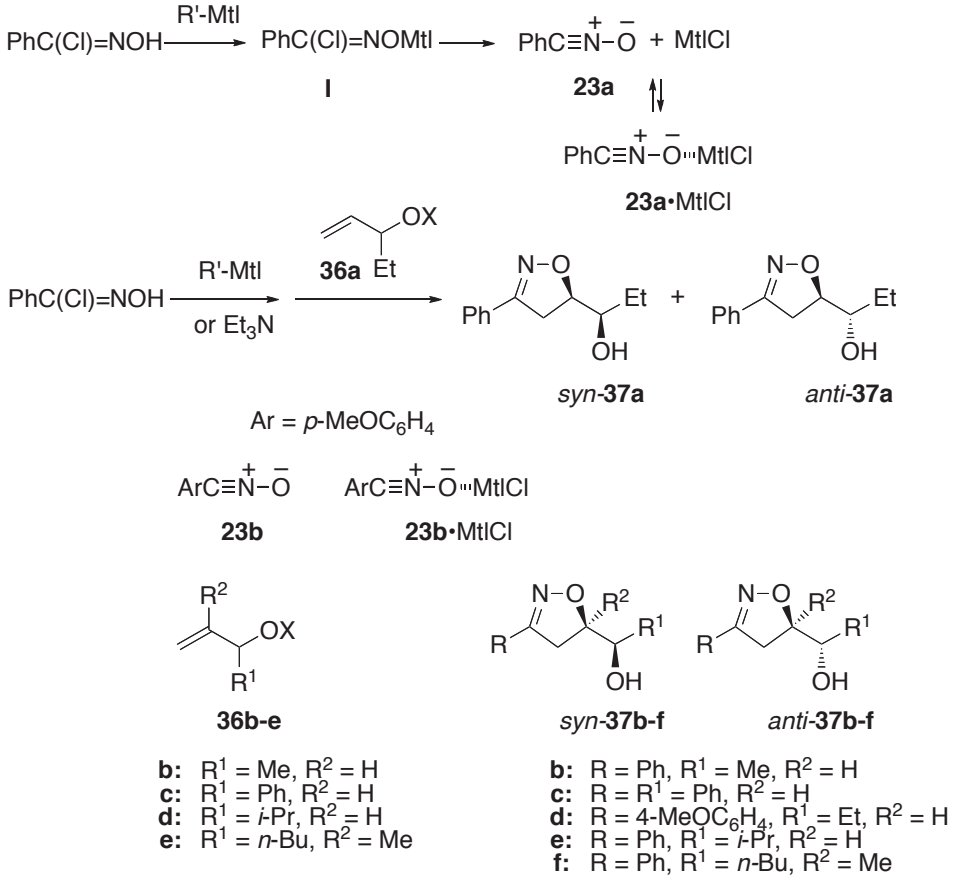


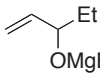
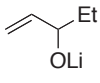
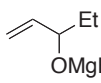
**Table 5-22** Cycloadditions of benzonitrile oxides **23** or benzonitrile oxide / Lewis acid complexes **23**•MtlCl with 1-substituted allylic alcohols **36**

| entry | **36** | $R^1$ | $R^2$ | X | Precursor[a] | Base | Method[b] | Solvent | Temp/°C | Time/h | Product | Yield/% | *syn : anti* [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **36a** | Et | H | H | Ph | $Et_3N$ | A | $CH_2Cl_2$ | -30 | 19 | **37a** | 40 | 67 : 33 |
| 2 | **36b** | Me | H | H | Ph | $Et_3N$ | A | $CH_2Cl_2$ | -30 | 9 | **37b** | 60 | 61 : 39 |
| 3 | **36c** | Ph | H | H | Ph | $Et_3N$ | A | $CH_2Cl_2$ | -30 | 24 | **37c** | 84 | 56 : 44 |
| 4 | **36a** | Et | H | H | Ph | EtMgBr[c] | B | $CH_2Cl_2$ | -30 | 41 | **37a** | 75 | 95 : 5 |
| 5 | **36a** | Et | H | H | Ph | EtMgBr[c] | B | $CH_2Cl_2$ | rt | 1 | **37a** | 63 | 95 : 5 |
| 6 | **36a** | Et | H | H | Ph | EtMgBr[c] | B | THF | -30 | 41 | **37a** | 66 | 60 : 40 |
| 7 | **36a** | Et | H | H | Ph | *n*-BuLi[d] | B | $CH_2Cl_2$ | -30 | 96 | **37a** | 54 | 75 : 25 |
| 8 | **36a** | Et | H | H | Ph | $Et_2Zn$[e] | B | $CH_2Cl_2$ | -30 | 71 | **37a** | 79 | 77 : 23 |
| 9 | **36a** | Et | H | H | Ph | $Et_3Al$[f] | B | $CH_2Cl_2$ | -40 | 17 | **37a** | 32 | 71 : 29 |
| 10 | **36a** | Et | H | H | Ph | $EtAlCl_2$[g] | B | $CH_2Cl_2$ | rt | 16.5 | | 0 | |
| 11 | **36b** | Me | H | H | Ph | EtMgBr[c] | B | $CH_2Cl_2$ | -30 | 12 | **37b** | 42 | 87 : 13 |
| 12 | **36c** | Ph | H | H | Ph | EtMgBr[c] | B | $CH_2Cl_2$ | -30 | 50 | **37c** | 63 | 64 : 36 |
| 13 | **36a** | Et | H | H | *p*-$MeOC_6H_4$ | EtMgBr[c] | B | $CH_2Cl_2$ | -30 | 5.5 | **37d** | 65 | 95 : 5 |

[a]Precursor is RC(Cl)=NOH, R = Ph or *p*-$MeOC_6H_4$. [b]Method A: A mixture of hydroximinoyl chloride and allylic alcohol **36** (X = H) was treated with $Et_3N$ (an equimolar amount). Method B: Hydroximinoyl chloride was treated with an organometallic compound, and the reaction with allylic alcohol **36** (X = H) was followed. [c]Based on $^1H$ NMR. [d-h]The following solution was used: d, 1 M in THF; e, 1.6 M in hexane; f,g, 1 M in hexane; h, 1.8 M in hexane.

Allylic alkoxides **36** (X = Mtl) were used to generate complexes **23**•MtlCl from hydroximinoyl chloride. Treatment of benzohydroximinoyl chloride with **36a** (X = Mtl) at -30 °C in $CH_2Cl_2$ generated complex **23a**•MtlCl, which then reacted with allylic alcohol **36a** (X = H) to give cycloadduct **37a** (method C, Table 524). Under these conditions, the *syn*-selectivity depended upon the molar equivalents of alkoxide **36a** (X = MgBr) used. For example, the *syn:anti* ratio gradually rose as the molar amounts of alkoxide **36a** (X = MgBr) increased, and the highest *syn*-selectivity was observed when 2 molar equiv of magnesium alkoxide **36a** (X = MgBr) were employed (*syn* : *anti* = 95:5, entries 1-4). The selectivity was not seriously affected by the reaction temperature, but vanished when THF was used as reaction solvent (entry 6). The presence of 2 equimolar amounts of isopropyl alcohol made the reaction cleaner and improved the yield of **37a** (almost quantitative), but did not improve the *syn*-selectivity (Table 5-22, entries 4,7). However, the use of a large excess of coordinating additive certainly reduced the *syn*-selectivity. For example, the reaction performed in THF gave **37a** as a roughly 2:1 mixture of *syn*- and *anti*-isomers.

**Table 5-23** *syn* : *anti* Selectivity observed in the nitrile oxide cycloadditions to 1-penten-3-ol **36a** under various conditions (at –30 °C)

| | | in $CH_2Cl_2$ | in THF |
|---|---|---|---|
| Method B | PhCNO•MgBrCl +  | 95:5 | 60:40 |
| Method A | PhCNO•$HNEt_3Cl$ +  | 67:33 | |
| | PhCNO•$HNEt_3Cl$ +  | 96:4 | |
| | PhCNO•LiCl +  | 74:26 | |
| Method D | PhCNO•MgBrCl +  | 94:6 | |
| | PhCNO•EtZnCl +  | 77:23 | |
| Method C | PhCNO•MgBrCl +  | 97:3 | 68:32 |
| | PhCNO•$Et_2AlCl$ +  | 68:32 | |
| Method C | ROH* + PhCNO•MgBrCl +  | >99:1 | 69:31 |

*ROH: $CH_2$=CHCH(Et)OH or *i*-PrOH

**Table 5-24** Cycloadditions of benzonitrile oxide / Lewis acid complexes **23a**•MtlCl with alkoxides of 1-penten-3-ol **36a** (X = Mtl)

| entry | R'Mtl (equiv)[a] | X in **36a** | Method[b] | Solvent | Temp/°C | Time/h | Product | Yield/% | *syn : anti* [c] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | EtMgBr (1.0) | MgBr/H | C | $CH_2Cl_2$ | -30 | 12 | **37a** | 82 | 93 : 7 |
| 2 | EtMgBr (1.2) | MgBr/H | C | $CH_2Cl_2$ | -30 | 12 | **37a** | 82 | 95 : 5 |
| 3 | EtMgBr (1.5) | MgBr/H | C | $CH_2Cl_2$ | -30 | 12 | **37a** | 92 | 97 : 3 |
| 4 | EtMgBr (2.0) | MgBr/H | C | $CH_2Cl_2$ | -30 | 12 | **37a** | 92 | >99 : 1 |
| 5 | EtMgBr (2.0) | MgBr/H | C | $CH_2Cl_2$ | rt | 20 min | **37a** | 95 | 98 : 2 |
| 6 | EtMgBr (2.0) | MgBr/H | C | THF | -30 | 12 | **37a** | 85 | 69 : 31 |
| 7 | EtMgBr (2.0) | MgBr/H | C | $CH_2Cl_2$ | -30 | 12 | **37a** | 97 | >99 : 1 |
| 8 | *n*-BuLi (2.0) | Li/H | C | $CH_2Cl_2$ | -30 | 12 | **37a** | 46 | 74 : 26 |
| 9 | $Et_2Zn$ (2.0) | EtZn/H | C | $CH_2Cl_2$ | -30 | 12 | **37a** | 71 | 77 : 23 |
| 10 | $Et_3Al$ (2.0) | $Et_2Al$/H | C | $CH_2Cl_2$ | -30 | 215 | **37a** | 39 | 68 : 32 |
| 11 | EtMgBr | Li | D | $CH_2Cl_2$ | -30 | 17 | **37a** | 74 | 94 : 6 |
| 12 | EtMgBr | MgBr | D | $CH_2Cl_2$ | -30 | 13 | **37a** | 71 | 97 : 3 |

[a]Unless otherwise indicated in parentheses, an equimolar amount of organometallic compound was used. [b]Method C: hydroximinoyl chloride was treated with allylic alkoxide **36a** (X = Mtl). Method D: hydroximinoyl chloride was treated with an organometallic compound, and the reaction with allylic alkoxide **36a** (X = Mtl) was followed. [c]Based on $^1$H NMR. [d]In the presence of isopropyl alcohol (2 molar amounts) as an additive.

On the basis of these results, the characteristics of the reaction can be summarized:[39]

(1) Nitrile oxide cycloadditions to allylic alcohols can be controlled in a *syn*-selective manner in the presence of magnesium ions. The selectivity is improved by using 2 equimolar amounts of allylic magnesium alkoxide (method C).

(2) Allylic magnesium alkoxide **36a** (X = MgBr) is much more reactive than the free alcohol **36a** (X = H).

(3) Existence of a small excess of the free alcohol **36a** (X = H) does not affect the *syn*-selectivity.

Since a 1 M THF solution of EtMgBr was used to prepare the allylic magnesium alkoxide **36a** (X = MgBr) in $CH_2Cl_2$, a small amount of THF always existed in the reaction system. The nitrile oxide cycloadditions were usually performed in a 0.05 M solution of the 1,3-dipole. When 2 equimolar amounts of EtMgBr was used in method C, 10 volume percent of THF, or about 15 molar equiv based on complex **23a**•MtlCl (Mtl = MgBr), was present in the reaction mixture. Nevertheless, the very high selectivity (>99: 1) under these conditions indicated that the existence of a small excess of THF does not affect the *syn*-selectivity at all.

**Table 5-25** *syn*-Selective cycladditions of benzonitrile oxide / MgBrCl complex **23a**•MgBrCl with alkoxides **36a-e** (Mtl = Mtl)[a]

| entry | **3** | $R^1$ | $R^2$ | Precursor | RCNO | Time/h | Product | Yield/% | *syn : anti* [b] | *syn : anti* [c] |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **36a** | Et | H | Ph | PhCNO | 12 | **37a** | 92 | >99 : 1 | 67 : 33 |
| 2 | **36b** | Me | H | Ph | PhCNO | 12 | **37b** | 95 | 96 : 4 | 61 : 39 |
| 3 | **36c** | Ph | H | Ph | PhCNO | 12 | **37c** | 94 | 89 : 11 | 56 : 44 |
| 4 | **36a** | Et | H | *p*-$MeOC_6H_4$ | *p*-$MeOC_6H_4CNO$ | 12 | **37d** | 92 | >99 : 1 | d |
| 5 | **36d** | *i*-Pr | H | Ph | PhCNO | 20 min | **37e** | 95 | 97 : 3 | 65 : 35 |
| 6 | **36e** | *n*-Bu | Me | Ph | PhCNO | 12 | **37f** | 85 | 96 : 4 | 60 : 40 |

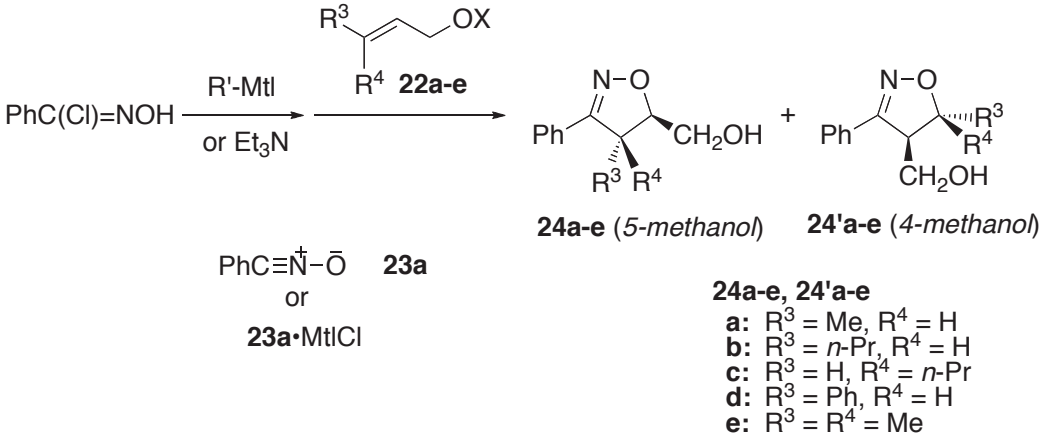
[a]All reactions were performed with 2 molar equiv of magnesium alkoxides **36** (X = MgBr) and hydroximoyl chlorides in dichloromethane at -30 °C according to method C (refer to the footnote of Table 524). [b]Based on $^1$H NMR. [c]The *syn : anti* selectivity observed in reactions by method A. [d]No isomer ratio is given since the 1:l adduct **37d** is contaminated by the 1:2 adduct.

The high *syn*-selectivity for the reaction is presumed to come from a chelation-controlled transition state involving the magnesium ion. In contrast, the reactions of nitrile oxide complex **23a**•MtlCl, generated by the use of *n*-BuLi, $Et_2Zn$, or $Et_3Al$ in method B or C, showed only poor *syn*-selectivities (entries 8-10 of Table 5-22), very similar to that for the reaction of free nitrile oxide **23a** with allylic alcohol **36a** (X = H). The high *syn*-selectivity, observed in the reaction of **23a**•MtlCl (Mtl = MgBr) with lithium alkoxide **36a** (X = Li) is presumably due to a rapid metal exchange.

Other chiral allylic alcohols **36b-e** showed similar excellent *syn*-selectivities under conditions where 2 molar equiv of alkoxide **36a** (X = MgBr) were used (method C, Table 5-25).[39] The *syn*-selectivity for **36c** was somewhat lower (*syn:anti* = 75:25) than for the other cases. This reaction in the absence of THF exhibited a slightly better *syn*-selectivity (*syn:anti* = 89:11).

**Regioselectivity.** Nitrile oxide cycloadditions to internal alkenes give rise to two serious synthetic problems. Firstly, internal alkenes are much less reactive than terminal alkenes. The cycloadducts are usually obtained in moderate to low yields since the nitrile oxides prefer to form their dimers, the furoxanes. Secondly, regiochemical control of the cycloaddition is poor. For example, a mixture of regioisomeric cycloadducts **24a** and **24'a** was formed in a poor ratio and in a low yield in the reaction of free benzonitrile oxide (**23a**) with (*E*)-2-buten-l-ol (**22a**, X = H, Scheme 5-26). A number of unsuccessful attempts remained to improve these results. We therefore attempted to solve these problems by the application of metal coordination control.

**Scheme 5-26** Generation of nitrile oxides by treatment of hydroximoyl chloride with allyl magnesium alkoxides **22a-e** and subsequent cycloadditions




Initially, metal coordination control was applied to the reaction of (*E*)-2-buten-1-ol (**22a**) (Table 5-27). The use of 1 molar equiv of a Grignard reagent gave poor results (entries 2, 3). However, when an excess amount of magnesium alkoxide **22a** (X = MgBr) was employed in the reaction with nitrile oxide **23a**, not only the regioselectivity but also the reactivity was dramatically improved. For example, the cycloaddition promoted by the presence of 2 molar equiv of **22a** (X = MgBr) gave (*E*)-4-methyl-3-phenyl-2-isoxazoline-5-methanol (**24a**) as a single product in 82% yield (method C). The presence of isopropyl alcohol (2 molar equiv) increased the yield of **24a** and **24'a** to 92% combined yield, and the regioselectivity was 97:3 (entry 5 of Table 5-27).

**Table 5-27** Regioselective cycloadditions of benzonitrile oxide **23a** or benzonitrile oxide/Lewis acid complex **23**•MgBrCl with 2-buten-1-ol **22a**[a]

| entry | X in **22a** | Base (equiv)[b] | Additive (equiv) | Method[c] | Temp/°C | Time/h | Product | Yield/% | **24a : 24'a**[d] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | H | $Et_3N$ | | A | rt | 1.5 | **24a + 24'a** | 46 | 46 : 54 |
| 2 | H | EtMgBr | | B | -30 | 17 | **24a + 24'a** | 20 | 55 : 45 |
| 3 | MgBr/H | **22a** (X = MgBr, 1.0) | | C | rt | 0.5 | **24a + 24'a** | 9 | 65 : 35 |
| 4 | MgBr/H | **22a** (X = MgBr, 2.0) | | C | rt | 0.5 | **24a** | 82 | >99 : 1 |
| 5 | MgBr/H | **22a** (X = MgBr, 2.0) | *i*-PrOH (2.0)[e] | C | rt | 0.5 | **24a + 24'a** | 92 | 97 : 3 |
| 6 | MgBr | *i*-PrOLi | | D | rt | 0.5 | **24a + 24'a** | 76 | 96 : 4 |
| 7 | Li | EtMgBr | | D | rt | 2.5 | **24a** | 66 | >99 : 1 |
| 8 | Li | EtMgBr | | D[f] | rt | 5 | **24a + 24'a** | 41 | 93 : 7 |
| 9 | Li | *n*-BuLi | | D | rt | 0.5 | **24a + 24'a** | 13 | 60 : 40 |

[a]All reactions were performed in dichloromethane. [b]Unless otherwise indicated in parentheses, an equimolar amount of base was used to generate nitrile oxide **23a**. [c]Methods A-D: refer to the footnote in Tables 522 and 524. [d]Based on $^1$H NMR. [e]To a mixture of *i*-PrOH and **22a** was added **22a** (X = MgBr, 2 equiv). [f]In THF.

We tested three combinations of reagents for accelerating the cycloaddition:

(1) the nitrile oxide/magnesium halide complex **23a**•MtlCl (Mtl = MgBr) with lithium alkoxide **22a** (X = Li),

(2) the nitrile oxide/lithium chloride complex **23a**•MtlCl (Mtl = Li) with magnesium alkoxide **22a** (X = MgBr), and

(3) the nitrile oxide/lithium chloride complex **23a**•MtlCl (Mtl = Li) with lithium alkoxide **22a** (X = Li).

The first two conditions gave the cycloadducts regioselectively (entries 6, 7 of Table 5-27). The third cycloaddition, however, occurred with poor regioselectivity. Accordingly, the use of magnesium ion is essential to achieve a high regioselectivity and rate enhancement. Alkoxides **22a** (X = Li, ZnEt, $AlEt_2$) other than magnesium were totally ineffective, resulting in poor regioselectivities and poor yields (10%, 49:51 for X = Li; 9%, 46:54 for X = ZnEt; 14%, 48:52 for X = $AlEt_2$). The regioselectivity was not lowered as drastically when using THF as a highly coordinating solvent (entries 7, 8).

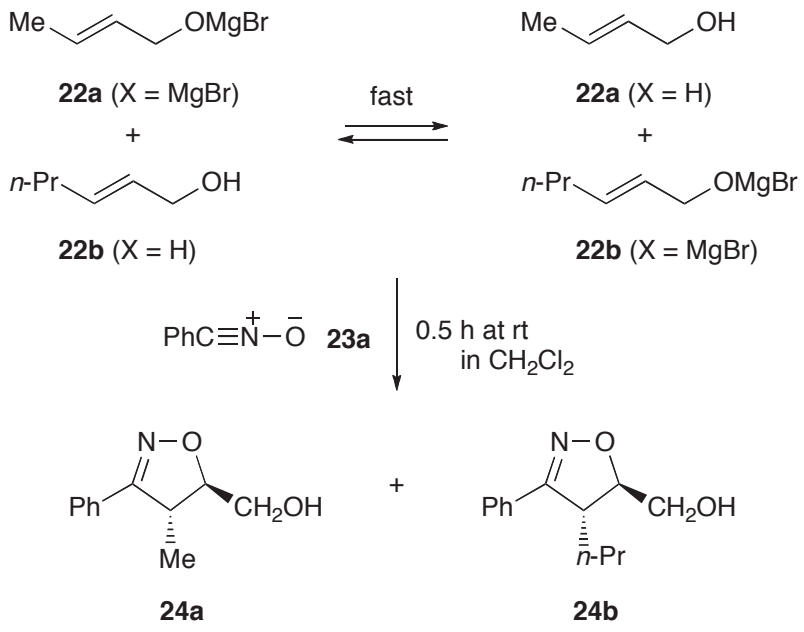
**Table 5-28** Regioselective cycloadditions of benzonitrile oxide/Lewis acid complex **23a**•MtlCl with alkoxides of allylic alcohols **22a-e** (X = Mtl)[a]

| entry | **22** | $R^3$ | $R^4$ | X | Base (equiv) | Method[b] | Time/h | Product | Yield/% | **24 : 24'** [c,d] |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **22a** | Me | H | H | **22a** (X = MgBr, 2.0) | C | 0.5 | **24a** | 82 | >99 : 1 (46:54, 46%) |
| 2 | **22a** | | | Li | EtMgBr (1.0) | D | 2.5 | **24a** | 66 | >99 : 1 |
| 3 | **22b** | *n*-Pr | H | H | **22b** (X = MgBr, 2.0) | C | 2.5 | **24b + 24'b** | 73 | 98 : 2 (55:45, 44%) |
| 4 | **22b** | | | Li | EtMgBr (1.0) | D | 2.5 | **24b** | 68 | >99 : 1 |
| 5 | **22c** | H | *n*-Pr | H | **22c** (X = MgBr, 2.0) | C | 2.5 | **24c + 24'c** | 63 | 94 : 6 e |
| 6 | **22c** | | | Li | EtMgBr (1.0) | D | 1.5 | **24c + 24'c** | 67 | 96 : 4 |
| 7 | **22d** | Ph | H | H | **22d** (X = MgBr, 2.0) | C | 1.5 | **24d** | 68 | >99 : 1 (20:80, 46%) |
| 8 | **22d** | | | Li | EtMgBr (1.0) | D | 3 | **24d** | 43 | >99 : 1 |
| 9 | **22e** | Me | Me | H | **22e** (X = MgBr, 2.0) | C | 15 | **24e + 24'e** | 14 | 95 : 5 (1:99, 19%) |
| 10 | **22e** | | | Li | EtMgBr (1.0) | D | 17 | **24e + 24'e** | 20 | 97 : 3 |

[a]All reactions were performed in dichloromethane. [b]Methods C, D: refer to Table 524. [c]Based on $^1$H NMR. [d]Results by use of benzohydroximoyl chloride generated by method A are shown in parentheses. [e]N0 reaction took place at room temperature for 24 h.

The present method was applied to a variety of 3-substituted and 3,3-disubstituted allylic alcohols **5a-e** (Scheme 5-26). The results are summarized in Table 5-28.[39] Generation of the nitrile oxide/magnesium complex **23a**•MtlCl (Mtl = MgBr) was performed by the application of methods C and D. The regioselectivity of cycloaddition did not depend upon the method of the generation. It is interesting that a complete reversal of regioselectivity was observed for certain allylic alcohols. For example, in the reactions of free nitrile oxide **23a** with (*E*)-3-phenyl-2-propenol (**22d**, X = H) and 3-methyl-2-butenol (**22e**, X = H), the 2-isoxazoline-4-methanol regioisomers **24'd,e** were produced in poor yields (**24 : 24'** = 20:80 for **22d** and 1:99 for **22e**). Presumably, the phenyl group (**22d**) and two methyl groups (**22e**) play an important role in regiocontrol for 2-isoxazoline-4-methanols. On the other hand, magnesium alkoxides **22d,e** (X = MgBr) showed reversed regioselectivities to provide 2-isoxazoline-5-methanol derivatives **24d,e** as major products (entries 7-10 of Table 5-28).

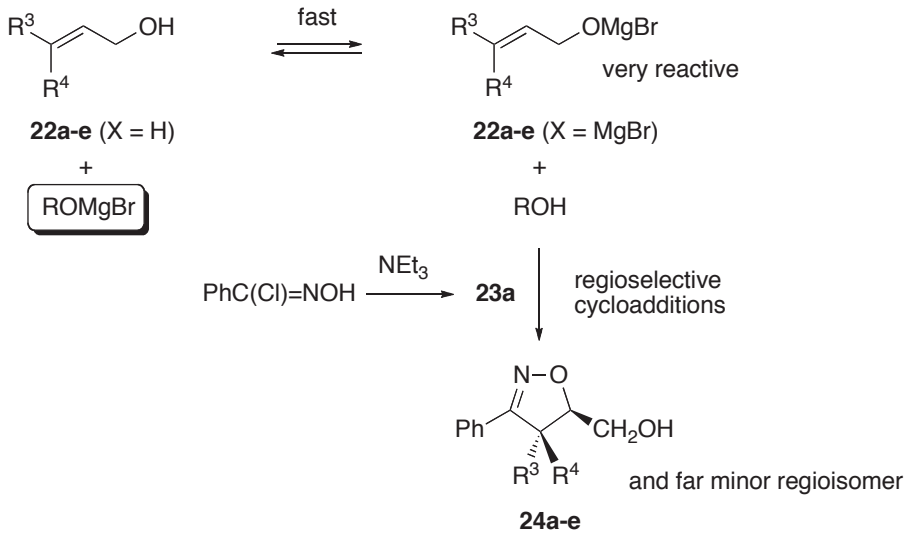
**Scheme 5-29** Competitive cycloadditions of benzonitrile oxide between *E*-2-buten-1-ol and *E*-2-hexene-1-ol, one of which was converted to magnesium alkoxide




98% (**24a** : **24b** = 53 : 47)

In order to get more information about metal alkoxide exchange, we examined the competitive cycloaddition of nitrile oxide **23a** to two different allylic dipolarophiles (Scheme 5-29). Exposure of free nitrile oxide **23a** to a 1:1 mixture of the magnesium alkoxide of (*E*)-2-butenol **22a** (X = MgBr) and free (*E*)-2-hexenol **22b** (X = H) gave two 2-isoxazoline-5-methanol derivatives **24a,b** in the ratio 53:47. No regioisomers **24'a** and **24'b** were detected. A rapid metal exchange presumably occurred between **22a** (X = MgBr) and **22b** (X = H) to form a 1:1 mixture of two allylic magnesium alkoxides **22a,b** (X = MgBr) along with a 1:1 mixture of free alcohols **22a,b** (X = H). The nitrile oxide reacted with the magnesium complexes to give cycloadducts **24a** and **24b**, regioselectively.

**Scheme 5-30** Regioselective nitrile oxide cycloadditions to allylic alcohols **22a-e** (X = H) in the presence of magnesium alkoxides




On the basis of this rapid alkoxide exchange, we propose the following simple procedure for the effective regiocontrol of nitrile oxide cycloadditions to allylic alcohols: Free nitrile oxide **23a**, which is generated from benzohydroximoyl chloride and triethylamine (method A), is treated with free allylic alcohols **22a-e** (X = H) in the presence of the appropriate magnesium alkoxide ROMgBr (method E).[39] A rapid equilibration takes place between **22a-e** (X = H) and ROMgBr to generate the reactive magnesium alkoxide dipolarophiles **22a-e** (X = MgBr), which then undergo regioselective cycloadditions (Scheme 5-30). As Table 531 shows, regioselectivity increases with the incremental addition of magnesium bromide butoxide (Table 5-31, entries 1-6). An alternative procedure to the one above is accomplished by the successive addition of the following materials to butyl alcohol: EtMgBr in $CH_2Cl_2$, an allylic alcohol **22** (X = H), triethylamine, and finally hydroximinoyl chloride as precursor of nitrile oxide **32** (method E'). We achieved highly regioselective nitrile oxide cycloadditions to allylic alcohols **22** (X = H) by this simple method (entries 7-11).

**Table 5-31** Highly regioselective cycloadditions of benzonitrile oxide **2a** with free allylic alcohols **22a-e** (X = H) in the presence of butoxymagnesium bromide[a]

| entry | **22** | $R^3$ | $R^4$ | *n*-BuOMgBr (equiv) | Method[b] | Time/h | Product | Yield/% | **24 : 24'** [c,d] | |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **22a** | Me | H | 0.1 | E | 24 | **24a + 24'a** | 37 | 57 : 43 | (46:54, 46%) |
| 2 | | | | 0.3 | E | 24 | **24a + 24'a** | 24 | 68 : 32 | |
| 3 | | | | 0.5 | E | 24 | **24a + 24'a** | 59 | 82 : 18 | |
| 4 | | | | 0.8 | E | 12 | **24a + 24'a** | 53 | 97 : 3 | |
| 5 | | | | 1.05 | E | 2.5 | **24a** | 83 | >99 : 1 | |
| 6 | | | | 1.3 | E | 1 | **24a** | 87 | >99 : 1 | |
| 7 | | | | 1.3 | E' | 1 | **24a** | 90 | >99 : 1 | |
| 8 | **22b** | *n*-Pr | H | 1.3 | E' | 1 | **24b** | 90 | >99 : 1 | (55:45, 44%) |
| 9 | **22c** | H | *n*-Pr | 1.3 | E' | 1.5 | **24c + 24'c** | 100 | 98 : 2 | e |
| 10 | **22d** | Ph | H | 1.3 | E' | 1.5 | **24d** | 92 | >99 : 1 | (20:80, 46%) |
| 11 | **22e** | Me | Me | 1.3 | E' | 13 | **24e** | 47 | >99 : 1 | (1:99, 19%) |

[a]All reactions were performed in dichloromethane. [b]Method E free nitrile oxide **23a** was allowed to react with a free allylic alcohol **22** (X = MgBr) in the presence of *n*-BuOMgBr. Method E': to a solution of butanol are added EtMgBr, an alcohol **22**, $Et_3N$, and benzphydroximoyl chloride in this order. [c]Based on $^1H$ NMR. [d]Results in the presence of *n*- BuOMgBr are shown in parentheses. [e]No reaction took place at room temperature for 24 h.

**Homoallylic alcohols.** We investigated an extension of the present methodology to homoallylic alcohol dipolarophiles. Although reaction of free nitrile oxide **23a** with terminal alkene 4-penten-2-ol (**38a**, X = H) was completely regioselective, the diastereoselectivity was very poor (Scheme 5-32), giving a 1:1 mixture of stereomeric cycloadducts of **8a** (Table 5-33). Introduction of a bulkier substituent at the α-chiral center of the homoallylic dipolarophile, such as the *t*-butyl substituent, did not improve the selectivity, either (entries 4-6).

**Scheme 5-32** Nitrile oxide cycloadditions to magnesium homoallylic alkoxides **38a,b** and **40** (both X = MgBr) in the presence of magnesium alkoxides

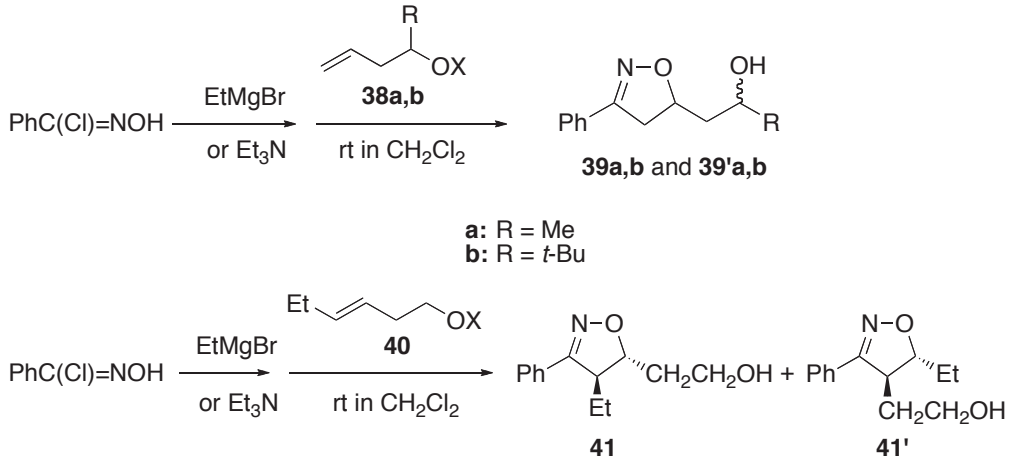



**Table 5-33** Cycloadditions of benzonitrile oxide **23a** or benzonitrile oxide/Lewis acid complex **23a**•MICl with homoallylic alcohols **38a,b** and **40**[a]

| entry | Homoallyl alcohols | X | Base (equiv) | Method[b] | Temp/°C | Time/h | Product | Yield/% | Selectivity[c] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **38a** R = Me | H | $Et_3N$ | A | -30 | 11 | **39a** + **39'a** | 47 | 50 : 50 |
| 2 | **38a** | MgBr | **38a** (X = MgBr, 2.0) | C | -30 | 12 | **39a** + **39'a** | 64 | 51 : 49 |
| 3 | **38a** | Li | EtMgBr | D | -30 | 12 | **39a** + **39'a** | 48 | 52 : 48 |
| 4 | **38b** R = *t*-Bu | H | $Et_3N$ | A | -78 | 36 | **39b** + **39'b** | 88 | 51 : 49 |
| 5 | **38b** | MgBr | **38b** (X = MgBr, 2.0) | C | -30 | 20 | **39b** + **39'b** | 8 | 55 : 45 |
| 6 | **38b** | Li | EtMgBr | D | -30 | 23 | **39b** + **39'b** | 52 | 53 : 47 |
| 7 | **40** | H | $Et_3N$ | A | rt | 2.5 | **41** + **41'** | 47 | 54 : 46 |
| 8 | **40** | MgBr | **40** (X = MgBr, 2.0) | C | rt | 43 | **41** + **41'** | 15 | 82 : 18 |
| 9 | **40** | Li | EtMgBr | D | rt | 2.5 | **41** + **41'** | 5 | 96 : 4 |

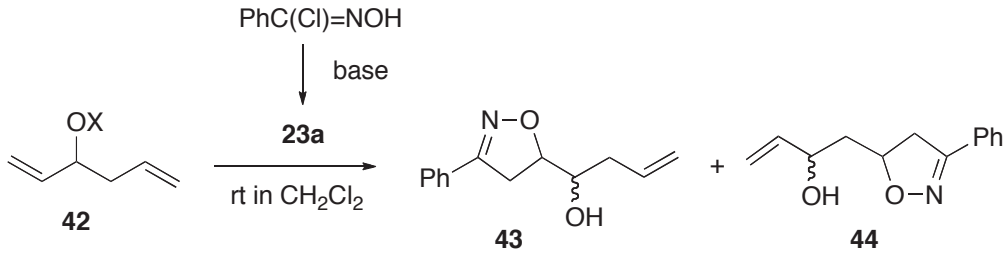
[a]All reactions were performed in dichloromethane. [b]Methods A, C, D: refer to the footnote in Tables 522 and 524. [c]Based on $^1$H NMR.

Improvement of regioselectivity in the presence of magnesium ions was observed in cycloaddition to the internal homoallylic alcohol **40**. The reaction of free nitrile oxide **23a** to a 4-substituted homoallylic alcohol, (*E*)-3-hexen-1-ol (**40**, X = H), proceeded nonregioselectively (Scheme 5-32, Table 5-33). The use of magnesium alkoxide **40** (X = MgBr) generated by either method C or D dramatically improved their regioselectivities to the level of 96:4 (entries 8, 9), though the yields of **41** and **41'** remained very low.

**Chemoselectity and combination of regio- and stereoselectivity.**[39] Diene **42**, which has a hydroxyl group in both an allylic and homoallylic position, seemed an attractive probe for the relative effectiveness

of magnesium ion catalysis on these two homologous moieties. Treatment of 1,5-hexadien-3-ol (**42**, X = H) with free benzonitrile oxide (**23a**) gave a 67:33 mixture of cycloadducts **43** (67:33) and **44** (59:41) (Scheme 5-34). This indicated that the allylic alcohol moiety was only slightly more reactive than the homoallylic one. On the other hand, the reaction using magnesium alkoxide **42** (X = MgBr) by method C showed an absolute chemoselectivity for cycloaddition at the allylic moiety (**43** was the only cycloadduct) and good diastereoselectivity (*syn:anti* = 99:1 for **43**). Thus, the magnesium alkoxide methodology is much more effective for allylic alcohols than homoallylic alcohols.

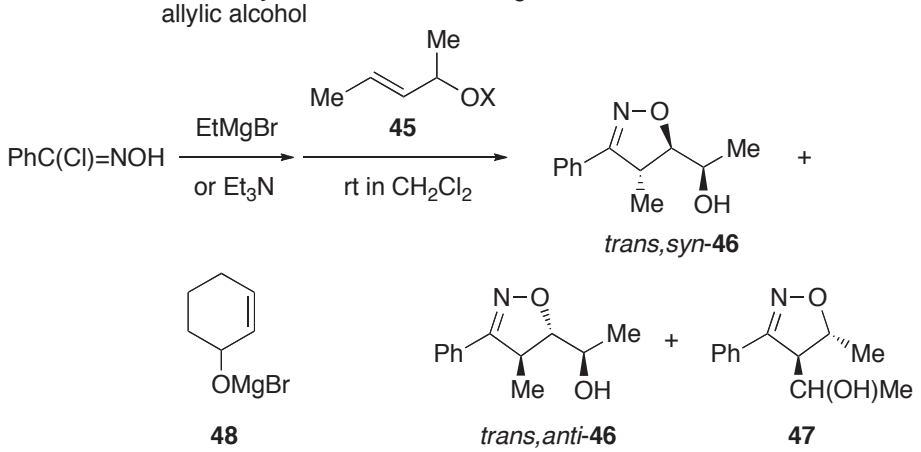
**Scheme 5-34** Competitive nitrile oxide cycloadditions to magnesium alkoxides of allylic and homoallylic terminal alcohol **42** (X = MgBr)




| Base | X | Time/h | Yield/% | **43** : **44** |
|---|---|---|---|---|
| **42** [X = MgBr (2 equiv)] | MgBr | 0.15 | 94 | **43** only[a] |
| $Et_3N$ | H | 3 | 100 | 67 : 33[b] |

[a] **43** consists of each two stereoisomers (*syn : anti* = 99:1).
[b] **43** (67:33) and **44** (53:47) consists of each two stereoisomers.

**Scheme 5-35** Nitrone cycloadditions to the magnesium alkoxide of inner and α-chiral allylic alcohol

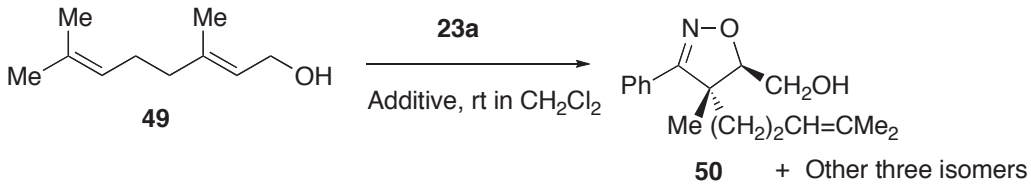



| Base | X | Time/h | Yield/% | **46** (*syn:anti*) : **47** |
|---|---|---|---|---|
| **45** [X = MgBr (2 equiv)] | MgBr | 1 | 53 | 100 (94:6) : 0 |
| $Et_3N$ | H | 2 | 28 | 83 (55:27) : 18 (12:6) |

A problem of both stereo- and regioselectivity arises in the cycloaddition to the internal allylic alcohol **45** bearing α-chirality. A mixture of four possible isomers of cycloadducts – *anti*- and *syn*-diastereomers for regioisomeric cycloadducts **46** and **47** – in poor combined yield was predicted from the reaction between

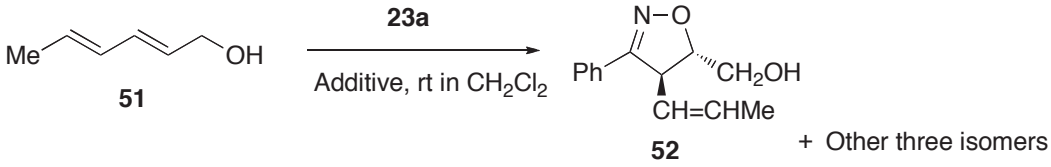
the free nitrile oxide **23a** and **45** (X = H) (Scheme 5-35). Indeed, the cycloaddition of free nitrile oxide **23a** gave a mixture of the four possible diastereomers. In contrast, the application of method C, employing 2 molar equiv of magnesium alkoxide **45** (X = MgBr), gratifyingly produced a complete regioselective cycloaddition in favor of **46**, in which the *syn*-selectivity was as high as 94:6. Surprisingly, a similar reaction with the magnesium alkoxide of 3-cyclohexenol **48** led to the formation of a complex mixture of many products.

**Scheme 5-36** Nitrile oxide cycloadditions to both trisubstituted and separated alkenes **49**




| Additive | Time/h | Yield/% | **50** : Isomers |
|---|---|---|---|
| *n*-BuOMgBr (1.3 equiv) | 2.5 | 26 | **50** only |
| none (**22a**: 5 equiv) | 29 | 67 | 0 : 40 : 33 : 27 |

With 2,4-dienol **51**




| Additive | Time/h | Yield/% | **52** : Isomers |
|---|---|---|---|
| *n*-BuOMgBr (1.3 equiv) | 2.5 | 88 | **52** only |
| none | 16 | 67 | 7 : 42 : 44 : 7 |

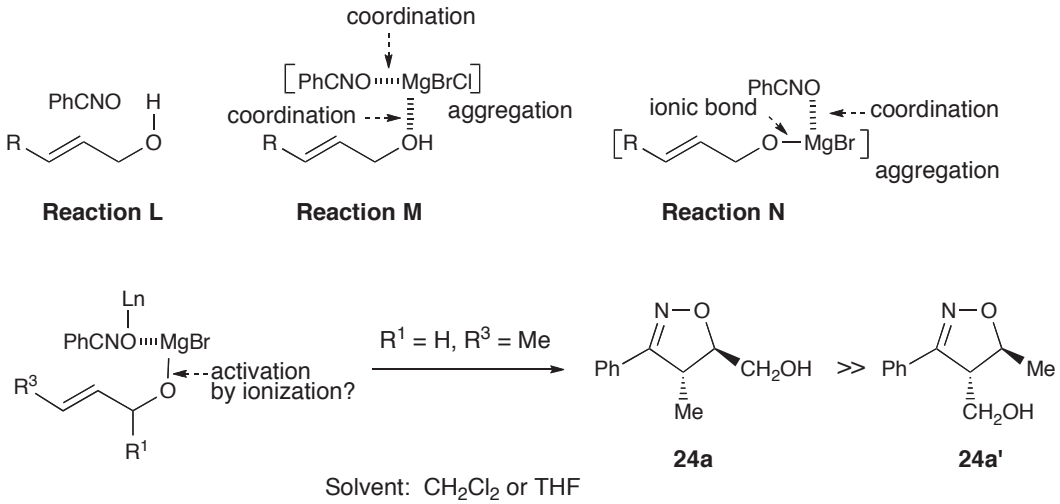
Questions of both chemo- and regioselectivity arise for the two unsymmetrically trisubstituted alkene moieties of the diene alcohol **49**. As expected, free benzonitrile oxide (**23a**) showed a low regioselectivity to **49**. The cycloaddition gave a mixture of three isomeric cycloadducts in a comparable ratio only when a large excess of free nitrile oxide **23a** was used (Scheme 5-36). However, in the presence of *n*-BuOMgBr (1.3 molar equiv) the reaction proceeded with absolute chemo- and regioselectivity to lead to exclusive formation of **50**, a product not seen in the uncatalyzed reaction.

The cycloaddition to conjugated diene alcohol, (*E,E*)-2,4-hexadien-1-ol (**51**), was moderately regioselective for each double bond, with 5-alkenyl-substituted 2-isoxazoline regioisomers having been obtained as major isomers (Scheme 5-36). Reactivities of the two double bonds of **51** were comparable. The regiochemical preference favoring introduction of the unsaturated substituent at the 5-position is similar to the reaction of the phenyl-substituted allylic alcohol **22d** (Tables 5-28, 5-31). When the same reaction was performed in the presence of *n*-BuOMgBr (1.3 equiv), however, this substrate-based regiocontrol was completely overcome and gave 2-isoxazoline-5-methanol **52** as the single isomer.

**Kinetic studies.**[39] For our kinetic studies, three types of nitrile oxide cycloadditions were examined (Scheme 5-37):
(1) the reaction of free nitrile oxide with free dipolarophile alcohols (reaction L),
(2) that of a benzonitrile oxide /Lewis acid complex with free dipolarophile alcohols (reaction M),
(3) that of free benzonitrile oxide with the magnesium alkoxides of dipolarophile alcohols (reaction N).

As mentioned above, reaction N gave the best stereo- and regiocontrol. The stabilized benzonitrile oxide/MgBrCl complex **23a**•MgBrCl must be formed initially in reaction M. The cycloaddition reaction proceeds when the oxygen atom of the dipolarophile coordinates to the magnesium ion. In reaction N, ionic bonding between the magnesium ion and the alkoxide oxygen is formed first, and then nitrile oxide coordinates to this complex. As the negatively charged alkoxide ion coordinates to magnesium, its Lewis acidity becomes weaker. Accordingly, higher acceleration of cycloaddition is expected for reaction N.

**Scheme 5-37** Possible interactions working among dipoles, dipolarophiles, and metals in nitrile oxide cycloadditions to allylic alcohols




Since the rates of reactions M and N are very fast, relative rate accelerations in reaction M and N were estimated by competitive nitrile oxide cycloadditions using two dipolarophiles. Norbornene was selected as the reference dipolarophile. This strained and reactive olefin bears no additional functional group, so little influence by the presence of a Lewis acid is expected in nitrile oxide cycloadditions. Competitive cycloadditions were performed using 5 molar equiv each of norbornene and of a dipolarophile alcohol at room temperature in $CH_2Cl_2$. The relative rate was estimated on the basis of product ratios.

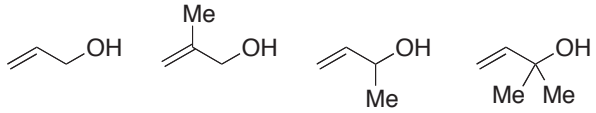
For reaction L, in which a free nitrile oxide **23a** was reacted with free dipolarophile alcohols, reaction rates depended upon the substitution pattern of the dipolarophiles (Table 5-38).[39] Terminal olefins showed reaction rates about equal to that of the nonfunctionalized terminal alkene 3-phenylpropene (3/100 to 6/100 the rate of norbornene, entries 2-5, 11, 12, 17), indicating that hydrogen-bonding interactions, if any, hardly enhanced the reaction rates. *vic*-Disubstituted internal olefins and a trisubstituted olefin were much less reactive than terminal alkenes (2/10000 to 1/1000 the rate of norbornene, entries 6-10, 13, 14). Reaction M pits an alkene alcohol and norbornene (5 molar equiv each in $CH_2Cl_2$, Table 5-38) in competition for the nitrile oxide/MgBrCl complex **23a**•MtlCl (Mtl = MgBr). These reactions showed low

acceleration factors of 3-14 (ratios M/L in Table 5-38). The acceleration ratios M/L were even lower when substituents were introduced at the α-position of the dipolarophiles (entries 4, 5, 12).

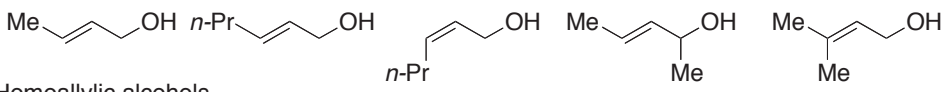
A much greater rate enhancement was observed for reaction N, in which the magnesium alkoxides of dipolarophiles and free nitrile oxide **23a** were used in $CH_2Cl_2$ (Table 5-38). A rate acceleration by a factor of more than 2000 was recorded in the reaction of the magnesium alkoxide of 2-propen-1-ol, the parent allylic alcohol (ratio N/L in entry 2). Existence of a substituent at the α-position caused a significant decrease in the rate enhancement (entries 4, 5)

**Table 5-38** Relative reaction rates in nitrile oxide cycloadditions to allylic and homoallylic alcohol dipolarophiles, terminal allylic alcohols (TA), internal allylic alcohols (IA) and homoallylic alcohols (HA).[a,b]

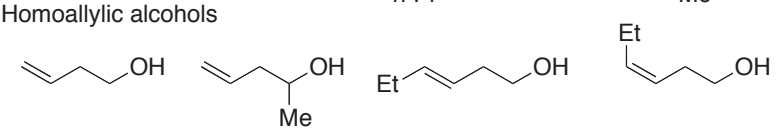
Terminal allylic alcohols



Internal allylic alcohols



Homoallylic alcohols



| entry | dipolarophile[c] | reaction L[d,e] | reaction M[f,g] | reaction N[h] | M/L | N/L |
|---|---|---|---|---|---|---|
| 1 | norbornene | 1 | 1 | 1 | | |
| | Terminal Allylic Alcohols | | | | | |
| 2 | 2-propen-1-ol | 0.064 (1) | 0.79 | 130 (1) | 12 | 2030 |
| 3 | 2-methyl-2-propen-1-ol | 0.031 (0.5) | 0.42 | 19 (0.1) | 14 | 610 |
| 4 | 3-buten-2-ol | 0.059 (0.9) | 0.46 | 14 (0.1) | 8 | 240 |
| 5 | 2-methyl-3-buten-2-ol | 0.048 (0.8) | 0.14 | 3.6 (0.03) | 3 | 75 |
| | Internal Allylic Alcohols | | | | | |
| 6 | (*E*)-2-buten-1-ol | 0.0013 (0.02) | 0.014 | 9 (0.07) | 11 | 6900 |
| 7 | (*E*)-2-hexen-1-ol | 0.0012 (0.02) | 0.012 | 3.8 (0.03) | 10 | 3170 |
| 8 | (*Z*)-2-hexen-1-ol | 0.00056 (0.009) | 0.0063 | 3 (0.02) | 11 | 5360 |
| 9 | (*E*)-3-penten-2-ol | 0.0009 (0.01) | 0.0079 | 0.76 (0.006) | 9 | 840 |
| 10 | 3-methyl-2-buten-1-ol | 0.00022 (0.003) | 0.0013 | 3.6 (0.03) | 6 | 16000 |
| | Homoallylic Alcohols | | | | | |
| 11 | 3-buten-1-ol | 0.041 (0.6) | 0.34 | 20 (0.2) | 8 | 490 |
| 12 | 4-penten-2-ol | 0.034 (0.5) | 0.18 | 1.3 (0.01) | 5 | 40 |
| 13 | (*E*)-3-hexen- 1-ol | 0.00098 (0.02) | 0.0072 | 0.1 (0.0008) | 7 | 100 |
| 14 | (*Z*)-3-hexen-1-ol | 0.00032 (0.005) | 0.0024 | 0.2 (0.002) | 8 | 625 |
| | Other Olefins | | | | | |
| 15 | 3-buten-2-one | 0.82 | 0.82 | | 1 | |
| 16 | methyl acrylate | 0.39 | 0.44 | | 1 | |
| 17 | 3-phenylpropene | 0.012 | 0.018 | | 2 | |

[a]All reactions were performed in dichloromethane at room temperature using a mixture of two dipolarophiles (each 5 molar amounts). [b]The relative rates are determined by $^1H$ and/or $^{13}C$ NMR spectra of the crude reaction mixture. [c]Dipolarophiles were used either in free alcoholic forms (in reactions L and M) or in the forms of magnesium alkoxides (in reaction N). [d]Reaction L: between free nitrile oxide **23a** and free allylic alcohols. [e]The relative rates based on 2-propen-1-01 are shown in parentheses. [f]Reaction M: between nitrile oxide complex **23a**•MtlCl (Mtl = MgBr) and free allylic alcohols. [g]Complex **23a**•MtlCl was in situ generated from benzohydroximoyl chloride and EtMgBr so that the solvent contains some THF ($CH_2Cl_2$ : THF = 40 : 1 v/v). [h]Reaction N: free nitrile oxide **23a** and the magnesium alkoxides of allylic alcohols.

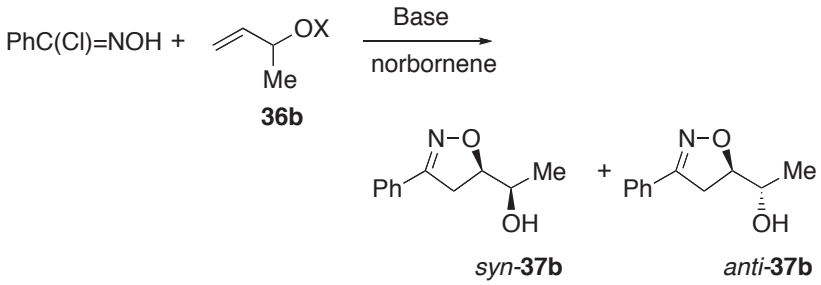
Cycloadditions to internal allylic magnesium alkoxides were interesting (entries 6-10). Reactions of these *vic*-disubstituted olefins are very sluggish under noncatalyzed conditions (6/10000 to 1/1000 the rate of norbornene in reaction L), but rate enhancements of more than 3000 times resulted from the use of magnesium alkoxides (ratios N/L in Table 5-38). Reactivities of the magnesium alkoxides of allylic alcohols are even greater than that of norbornene in reaction N. With the 1,1,2-trisubstituted olefin **22e**, a rate acceleration of as much as 16000 times was recorded (entry 10), this providing the maximum accelerating factor in the series.

A homoallylic alcohol was also activated by its conversion to the magnesium alkoxide (490 times, entry 11, a little smaller than the acceleration factor for 2-propen-1-ol), and α-substitution reduced the enhancement ratio to 1/20 (entry 12). The rate acceleration of the internal homoallylic alkoxide was quite small (100 times, entry 13).

Surprisingly, free nitrile oxide **23a** and its complex with MgBrCl **23a**•MtlCl (Mtl = MgBr) showed similar reactivities to nonactivated olefins (norbornene and 3-phenylpropene) and electron-deficient olefins (3-buten-2-one and methyl acrylate) (entries 1, 15-17). In reactions of **23a**•MtlCl (Mtl = MgBr) with 3-buten-2-one and methyl acrylate, we assume that the metal-promoted rate acceleration with respect to the dipolarophile effectively competes with the rate deceleration by the complex formation with the dipole.

**Solvent effect on selectivity and reaction rate.**[39] The high rate enhancement observed in the kinetic studies above is no doubt the major reason for the excellent stereo- and regiocontrol. However, use of a noncoordinating solvent such as $CH_2Cl_2$ was necessary to achieve excellent selectivities. *syn*-Selectivities were especially sensitive to the nature of the solvent. Accordingly, the effect of a coordinating additive, THF, on both reaction rate and selectivity was examined. The relative rate of reaction of the free nitrile oxide **23a** in a competitive experiment between 3-buten-2-ol (**36b**, X = H) and norbornene was 0.059 (Scheme 5-39), while the stereoselectivity was *syn*-**37b** : *anti*-**37b** = 61:39. On the other hand, a similar reaction of **23a** with the magnesium alkoxide **36b** (X = MgBr) in $CH_2Cl_2$ was highly accelerated (relative rate = 14) and gave a 96:4 ratio of *syn*-**37b** : *anti*-**37b**. In THF both the selectivity and the reaction rate were lowered to the level of the uncatalyzed reaction (relative rate = 0.09, *syn*-**37b** : *anti*-**37b** = 68:32). This indicates that in the cases of nitrile oxide cycloadditions using magnesium alkoxides of terminal allylic alcohols, the rate enhancement, and therefore the high *syn*-selectivity, mainly comes from the effective coordination of nitrile oxide dipoles to the magnesium ion rather than the ionization of dipolarophile alcohols.

**Scheme 5-39** Relative rates and *syn/anti* selectivities in the nitrile oxide cycloadditions in various reaction solvents




**36b** *syn*-**37b** *anti*-**37b**

| Solvent | X | Base | Relative rate[a] | *syn*-**37b** : *anti*-**37b** |
|---|---|---|---|---|
| $CH_2Cl_2$ | MgBr | **36b** | 14 | 96 : 4 |
| THF | MgBr | **36b** | 0.09 | 68 : 32 |
| $CH_2Cl_2$ | H | $Et_3N$ | 0.059 | 61 : 39 |

[1]Relative rate to that of norbornene. Each five equimolar amounts of norbornene and **36b** were used.

**Table 5-40** Effect of polar additives on the relative rates and regiosclectivities of nitrile oxide cycloadditions to **22a** (X = MgBr)

| Dipolarophile | Additive (equiv to the alkoxide) | Relative rate | Regioselectivity |
|---|---|---|---|
| **22a** (X = MgBr) | none | 9 | **23a** only |
| **22a** (X = MgBr) | *n*-BuOH (1) | 13 | **23a** only |
| **22a** (X = MgBr) | *i*-PrOH (1) | 19 | **23a** only |
| **22a** (X = MgBr) | *t*-BuOH (1) | 19 | **23a** only |
| **22a** (X = MgBr) | THF ($CH_2Cl_2$ : THF = 10:1 v/v | 1 | **23a** only |
| **22a** (X = MgBr) | THF (as solvent) | 0.1 | **23a** only |
| **22a** (X = H) | none | 0.0013 | **23a** : **23'a** = 46 : 54 |

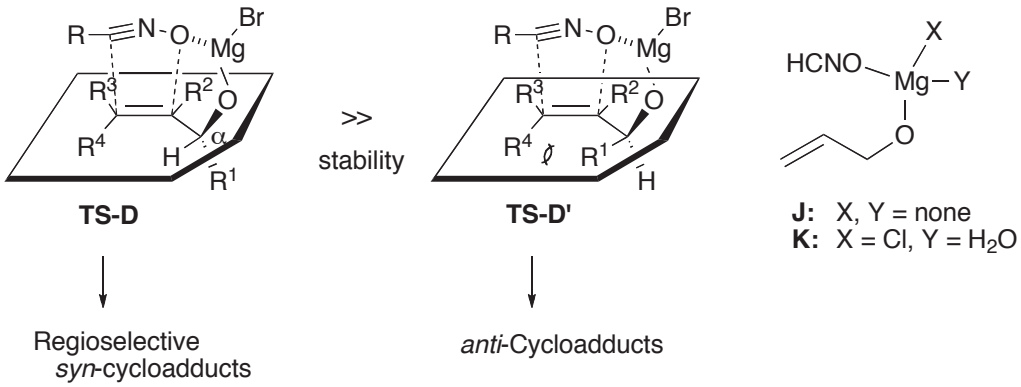
[a]Benzonitrile oxide (**23a**) generated from benzohydroximoyl chloride and triethylamine was allowed to react with a mixture of **22a** (X = MgBr) and norbornene (each 5 molar amounts) in dichloromethane at room temperature. [b]Relative rate to that of norbornene. [c]THF corresponds to about 15 molar amounts to the alkoxide.

Reaction of free nitrile oxide **23a** with 2-buten-1-ol (**22a**, X = H), as an internal allylic alcohol substrate, showed a relative rate of 0.0013 and a regioselectivity **24a:24'a** of 46:54 (Table 5-40). When the magnesium alkoxide **2a** (X = MgBr) was employed in $CH_2Cl_2$, the reaction was accelerated by a factor of 6900 (relative rate = 9) to give **24a** as a single isomer. The same reaction performed either in the presence of THF ($CH_2Cl_2$ : THF = 10:1 v/v) or in THF itself again sharply decreased the relative rate. In both reactions, however, rates were still much greater than that of the uncatalyzed reaction and **24a** was the only regioisomer produced. This striking contrast with the reactions of terminal allylic alcohols will be discussed below.

The presence of an alcoholic additive, if not much more than 1 molar equiv, did not affect the reaction with respect to both rate enhancement and regioselectivity (Table 5-40). Interestingly, the reaction in the presence of 1 molar equiv of *i*-PrOH or *t*-BuOH was even faster than the reaction without additive. This is why the procedure using the magnesium alkoxides of dipolarophile alcohols (2 molar equiv) works so well (method C).

**Transition state and MO calculations.**[39] The presence of magnesium ions dramatically improves the reaction rate, regioselectivity, and *syn*-selectivity of nitrile oxide cycloadditions to allylic alcohols. We believe that a chelated transition model **TS-D** or **TS-D'**, where a nitrile oxide and an allylic alcohol coordinate to the magnesium ion, is responsible for the observed high *syn*-selectivities and regioselectivities (Scheme 5-41). The transition state that contains less steric hindrance from allylic strain between the terminal substituent $R^4$ and the α-substituent $R^1$ should be more favored. Thus, the stereoselective formation of *syn*-stereoisomers would arise via the transition state **TS-D**. This chelated transition state explains the observed high regioselectivities as well.

**Scheme 5-41** Proposed chelating transition structure for the high *syn*-selective and regioselective nitrile oxide cycloaddition

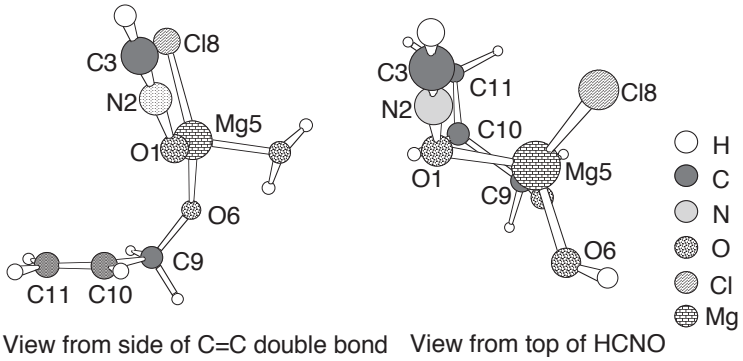



In order to investigate the nature of the magnesium complex in detail, we executed ab initio molecular orbital (MO) calculations. Initially, a mono cation complex **J** composed of a formonitrile oxide ligand (HCNO) and an allyl alcohol ligand ($CH_2$=$CHCH_2OH$) (Scheme 5-41) was adopted as a simplified model. After optimization, the O-Mg-O angle was estimated to be 180°, indicating that two reacting units, HCNO and $CH_2$=$CHCH_2OH$ ligands, are located too far to interact with each other. However, complex **J** with only two ligands is not an appropriate candidate for a reactive intermediate in the cycloaddition process. In fact, a tetrahedral or octahedral environment is more plausible for the magnesium complex. We then modified our initial model by adding chloride ion ($Cl^-$) and THF as presumed ligands (complex **K**, Scheme 5-41). A $C1^-$ is likely to coordinate to the magnesium ion of the complex and would arise from the Grignard reagent or magnesium alkoxide chloride employed to generate the nitrile oxides. THF might also serve as a ligand because a THF solution of the Grignard reagent was used. For simplicity of calculation, the THF was replaced with an $H_2O$ molecule, and we optimized the tetrahedral complex **K** (Scheme 5-42). Although this structure may not be the global minimum of the complex, it is good enough for the analysis of the cycloaddition as discussed below.

As shown in Scheme 5-42, C(3)-N(2) and N(2)-O(1) lengths of HCNO were estimated to be 1.12 and 1.33 Å, respectively. The Mg(5)-O(6) length was estimated to be 1.84 Å, which was shorter by 0.18 Å than the O(1)-Mg(5) length (2.02 Å). The nitrile oxide unit has a linear structure since the C(3)-N(2)-O(1) angle was 179.4°. The magnesium atom is not located just behind HCNO but at the side of HCNO, since the Mg(5)-O( 1)-N(2) angle was estimated to be 118.1°. The dihedral angle of τ-C(11)-C(10)-C(9)-O(6) was estimated to be 122.2°. A view from the top of HCNO shows that all atoms consisting of the reaction centers, C(3) and O( 1) in the dipole unit and C(10) and C(11) in the dipolarophile unit, are located almost

in the same plane. The C(10)-O(1) and C(11)-C(3) distances in the structure are 3.88 and 6.04 Å, respectively.

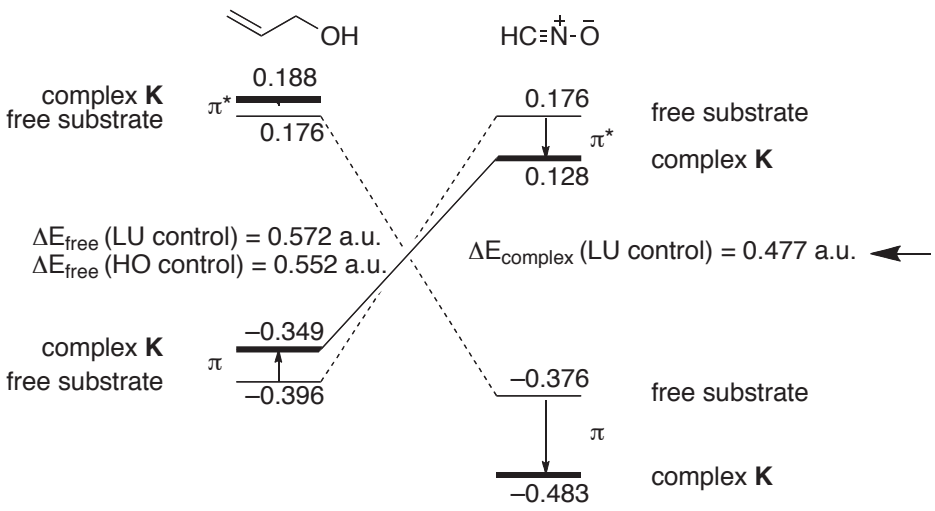
**Scheme 5-42** The tetrahedral structure optimized for complex **K**




Thus, the optimized conformation for complex **K** should be advantageous for accelerating cycloaddition between the two reacting ligands, dipole and dipolarophile. It is interesting to consider the orbital interactions between the two reactive ligands in complex **K**. We call the frontier molecular orbitals (FMOs) in the HCNO unit $\pi_{dipole}$ and $\pi^*_{dipole}$ and those in the allyl alcohol unit $\pi_{dipolarophile}$ and $\pi^*_{dipolarophile}$. According to Sustmann's classification, the following two interactions should govern nitrile oxide cycloadditions: one working between $\pi_{dipole}$ and $\pi^*_{dipolarophile}$ (HO control) and the other between $\pi^*_{dipole}$ and $\pi_{dipolarophile}$ (LU control). As discussed below, the LU-controlled interaction is calculated to be more important in the nitrile oxide cycloadditions to the magnesium alkoxide of allylic alcohols. The contour maps of $\pi_{dipolarophile}$ and $\pi^*_{dipole}$ orbitals in complex **K** show that these molecular orbitals of the two reacting units, HCNO and allyl alcohol, involved in complex **K** can interact well with each other to promote the cycloaddition.

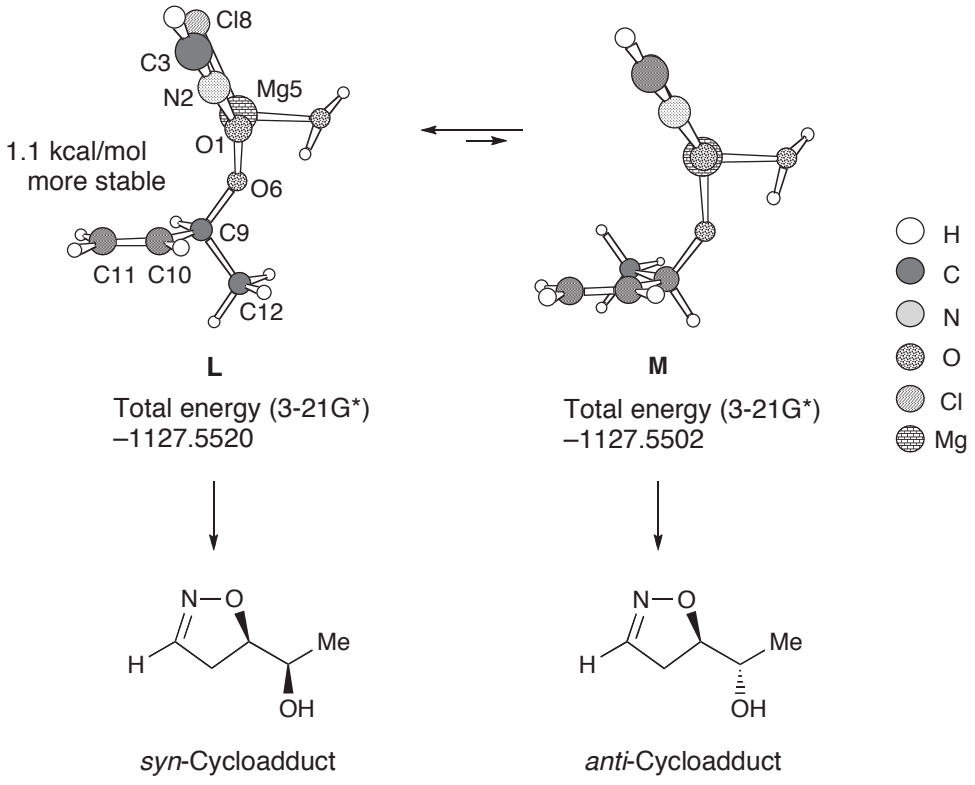
Scheme 5-43 summarizes the orbital energy diagram of the related MOs. In order to compare orbital energies in complex **K** with those in the free substrates, energy levels of free HCNO and allyl alcohol are also depicted in the same figure.

**Scheme 5-43** Orbital energies of HCNO and allyl alcohol either in free forms or in magnesium complex **K**



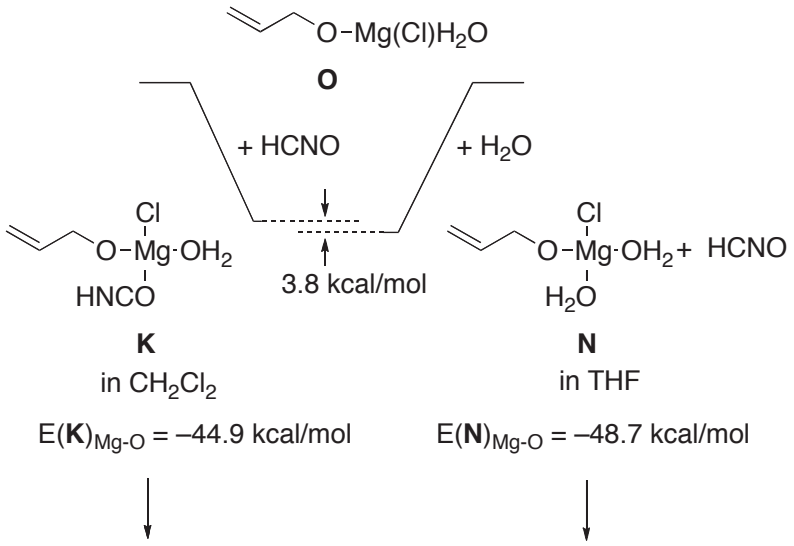
The orbital energies of $\pi_{dipolarophile}$ and $\pi^*_{dipole}$ in the free allyl alcohol are calculated to be -0.396 and 0.176 hartree, respectively, and the complex formation raises these energies to -0.349 and 0.188 hartree. In the absence of magnesium ion, the energy gap between $\pi_{dipole}$ and $\pi^*_{dipolarophile}$ for the HO-controlled interaction is estimated to be 0.552 hartree, while that between $\pi^*_{dipole}$ and $\pi_{dipolarophile}$ for the LU-controlled interaction is 0.572 hartree. Formation of complex **K** has frontier orbital energies for HCNO lowered by 0.107 and 0.048 hartree for $\pi_{dipole}$ and $\pi^*_{dipole}$, respectively. Change of orbital energies by complex formation causes a great decrease in the energy gap of the LU-controlled interaction from 0.572 to 0.477 hartree. This energy gap is much smaller than that of the HO-controlled interaction (0.671 hartree). As a result, the cycloaddition via complex **K** will be accelerated by the LU-controlled interaction. Formation of the magnesium complex **K** reduces the orbital energy gap and increases the overlap between FMOs, and hence the cycloaddition via the magnesium complex is accelerated compared to the reaction without magnesium. In the LU-controlled cycloadditions (reaction N), more substituted alkene dipolarophiles should show higher acceleration factors. This is the case observed in the reactions of 1,2-disubstituted and 1,1,2-trisubstituted alkenes.

**Scheme 5-44** Optimized conformers of 1-methylallyl alkoxide complexes **L** and **M**




The excellent *syn*-selectivity observed in the cycloadditions of magnesium alkoxides **36** (X = MgBr) prompted us to perform other MO calculations for the two complexes, **L** and **M**, which can be regarded as transition-state models for the formation of *syn*- and *anti*-cycloadducts. The optimized geometries and total energies are shown in Scheme 5-44.

**Scheme 5-45** Calculated stabilization energy (3-21G*) by complexation




The dihedral angle τ-C(11)-C(10)-C(9)-C(12) in L was calculated to be 117.6°. Its methyl group C(12) exists out of the plane of the C(10)=C(11) double bond, and the methyl group and vinylic hydrogen at C(10) are far apart, minimizing the steric repulsion between them. On the other hand, in complex **M**, the dihedral angle is estimated at 1.2°. The methyl carbon C(12) is placed almost in the plane of the C(10)=C(11) double bond. This complex **M** contains serious repulsive steric interactions between the methyl group and the vinylic hydrogen because a hydrogen of the methyl group and the vinylic hydrogen are located as close as 2.436 Å. The total energy of **L** and **M** are calculated to be -1127.5520 and -1127.5502 hartrees, respectively. Thus, the complex **L** is more stable by 1.1 kcal/mol than complex **M**. Cycloadditions proceeding through **L** are therefore more favored to give *syn*-adducts stereoselectively than those via **M**.

Levels of stereoselectivity observed in the nitrile oxide cycloadditions to magnesium allylic alkoxides depend upon the nature of the solvent employed. For example, the cycloaddition of the magnesium alkoxide of an α-chiral terminal allylic alcohol **36a** (X = MgBr) in $CH_2Cl_2$ occurs stereoselectively to give the *syn*-isomer of 5-(1-hydroxypropyl)-2-isoxazoline **37a** (Table 5-24, entry 4, *syn* only). However, the same reaction in THF affords a mixture of *syn*- and *anti*-cycloadducts (Table 5-22, entry 6, *syn : anti* = 60 : 40). This diastereomeric ratio is close to that observed in the reaction without magnesium ion (Table 5-24, entry 1, *syn : anti* = 67 : 33). Such a dramatic change of stereoselectivity suggests that the effective formation of magnesium complex **K** is quite difficult in THF solution. The magnesium ion would favor coordination to the oxygen atom of THF rather than the oxygen atom of the nitrile oxide.

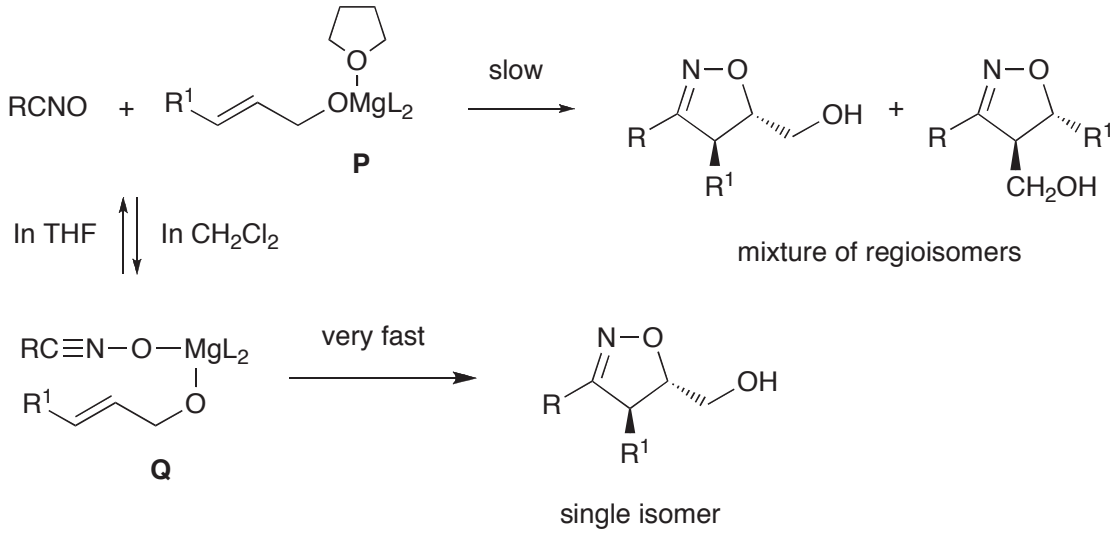
In order to quantify this solvent effect on the stereoselectivity, we optimized complex **N** (Scheme 5-45) by using *ab initio* MO calculations with the 3-21G* basis sets. This is a model for the magnesium complex, in which HCNO of **K** is replaced with THF. We sought to determine which ligand, THF or

HCNO, would coordinate more strongly to magnesium ion by calculating the stabilization energies due to Mg-O bond formation, $\Delta E(X)_{Mg\text{-}O}$. This energy can be estimated by the following equation:
$D E(X)_{Mg\text{-}O} = E_Y + E_H - E_X$ (X = **K** or **N**)

where $E_Y$ is the total energies of $H_2O$ for **N** or HCNO for **K**, and $E_H$ is that of **O**, $\Delta E(\mathbf{K})_{Mg\text{-}O}$ and $\Delta E(\mathbf{N})_{Mg\text{-}O}$ were calculated to be 44.9 and 48.7 kcal/mol, respectively. This indicates that $H_2O$ coordinates to magnesium ion stronger than HCNO by 3.8 kcal/mol. The magnesium ion forms mostly complex **N**, while very little complex **K** exists in the reaction mixture. Intermolecular cycloaddition of free nitrile oxide to a terminal alkene, such as that of complex **N**, takes place at a high rate. But since **N** imparts no diastereofacial selectivity to the nitrile oxide attack on the C=C double bond, both possible diastereomers for the cycloadduct are formed. Since THF coordinates to magnesium more strongly than $H_2O$, the above arguments are equally applicable to the reactions when performed in THF.

While this explains the lack of stereoselectivity toward terminal allyloxymagnesium species in THF, it does not explain why THF has no effect on the regioselectivity of addition to internal allylic alkoxides (Table 5-27, entries 7, 8). Regioselectivity in THF-free $CH_2Cl_2$ is governed by geometrical constraints in the nitrile oxide / allyloxymagnesium complex **Q** (Scheme 5-46). Even though THF disrupts this complex to form **P**, a small equilibrium concentration of **Q** still exists. As the reaction of uncomplexed nitrile oxide with internal alkenes is slow (and coincidentally nonregioselective), the rapid formation of product via **Q** is dominant. Thus, regardless of the presence of THF, reaction occurs regioselectively from a nitrile oxide complex.

**Scheme 5-46** Solvent effect on nitrile oxide cycloaddition to allylic alcohols




Metal coordination methodology in nitrile oxide cycloadditions to the magnesium alkoxides of allylic and homoallylic dipolarophiles was extremely useful for the stereoselective synthesis of 2-isoxazoline derivatives. Although the question of high magnesium specificity has not been solved so far, the great rate acceleration of dipolar cycloadditions and highly effective stereo- and regiocontrol showed synthetic

promise. In addition, this novel methodology should be generally applicable to 1,3-dipolar cycloadditions using dipoles other than nitrile oxides, providing a versatile regio- and stereoselective synthetic route to five-membered heterocyclic compounds.

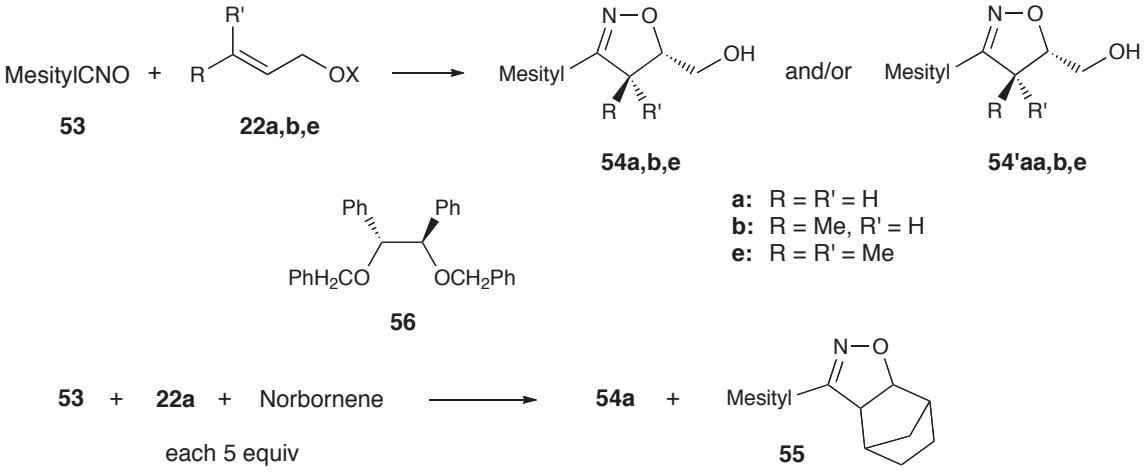
**5.4 Catalytic magnesium ion mediated nitrile oxide cycloadditions to allylic alcohols**

Nitrile oxide cycloadditions to allylic alcohols are highly accelerated in the presence of magnesium ion leading to the dramatic improvement of reactivity, regio- and *syn*-selectivity. The chelation transition state arising from the coordination of both 1,3-dipole and allylic alcohol dipolarophile on the same magnesium ion should be responsible for the high rate enhancement. Although this new stereocontrolling method has offered the first successful example for the metal ion catalysis in 1,3-dipolar cycloadditions, the achievement of effective catalytic cycle in the above magnesium catalyzed reactions is apparently very difficult to attain. The oxazoline-4-methanol cycloadducts are the types of chelating ligands so that release of the magnesium ion incorporated in cycloadducts by their transfer to free allylic alcohols must be extremely disfavored. This always happens in the metal ion catalyzed nitrile oxide or nitrone cycloadditions, or even for most of 1,3-dipoles, using hetero-substituted dipolarophiles such as allylic alcohols. In addition, informations on the catalytic efficiency in the magnesium catalyzed cycloadditions of ordinary nitrile oxides, such as benzonitrile oxide, are hardly available because there are known no effective quenching agents better than the magnesium alkoxides of allylic alcohols. Use of isolable and sluggish derivatives of nitrile oxides, such as mesitonitrile oxide or derivatives, may open an entry to solve the problem.

Based on the competitive reaction method, moderate levels of catalytic efficiency, ligand acceleration effect, and concentration effect were examined in the magnesium ion mediated 1,3-dipolar cycloadditions of mesitonitrile oxide to allylic alcohols.[40] These results should be important to analyze the possibility of a catalytic version of 1,3-dipolar cycloaddition reactions.

Although mesitonitrile oxide (**53**) shows a moderate reactivity to 2-propen-1-ol (**22a**) at room temperature (6% after 5 h at room temperature), higher temperatures are needed for the completion of reactions with bulkier dipolarophiles such as (*E*)-2-buten-1-ol (**22b**) and 3-methyl-2-buten-1-ol (**22e**) (Scheme 547). Because of bulkiness of the mesityl substituent of dipole **53**, regioselectivities of these reactions are sensitively dependent upon the steric size of substituents attached on the unsaturated moiety of **22**. A rate enhancement was observed in the reactions between **53** and **22a** when catalyzed by magnesium ion, one equivalent to the dipole. Competitive cycloadditions of **53** between **22a** and norbornene, both excess amounts (5 equiv each), were performed at room temperature to estimate the rate enhancement. The relative rates between **22a** and norbornene were estimated on the basis of the product ratio **54a**/**55**, and then each relative rate was adjusted to the standard ratio of **54a/55** recorded in the uncatalyzed competitive reaction. The reaction in the presence of $MgBr_2$•$OEt_2$ (1 equiv) gave a moderate rate enhancement, while use of zinc bromide was totally ineffective.

**Scheme 5-47** Cycloadditions of mesitonitrile oxide (**53**) to allylic alcohols **22a,b,e**[a]




| 21 | X | Solvent | Additive | M[b] | Temp/°C | Time/h | Product | Yield/%[c] | Ratio[d] | Relative rate |
|---|---|---|---|---|---|---|---|---|---|---|
| **22a** | H | toluene | - | 0.05 | rt | 62 | **54a** | 100 | | |
| **22b** | H | toluene | - | 0.05 | 65 | 17 | **54b** + **54'b** | 83 | 57:43 | |
| **22e** | H | toluene | - | 0.05 | 80 | 10 | **54'e** | 51 | | |
| **22a**[e] | H | $CH_2Cl_2$ | - | 0.05 | rt | 5 | **54a** + **55** | 97 | 1:5.9 | 1 |
| **22a**[e] | H | $CH_2Cl_2$ | $MgBr_2$•$OEt_2$[f] | 0.05 | rt | 5 | **54a** + **55** | 100 | 3.1:1 | 18 |
| **22a**[e] | H | $CH_2Cl_2$ | $MgBr_2$•$OEt_2$[f] | 0.005 | rt | 5 | **54a** + **55** | 95 | 12.2:1 | 72 |
| **22a**[e] | MgBr[g] | $CH_2Cl_2$ | - | 0.005 | rt | 5 | **54a** + **55** | 99 | 71:1 | 419 |
| **22a**[e] | H | $CH_2Cl_2$ | $ZnBr_2$[f] | 0.05 | rt | 5 | **54a** + **55** | 87 | 1:6 | 1 |
| **22a**[e] | H | $CH_2Cl_2$ | $MgBr_2$•$OEt_2$[f] + **56**[h] | 0.05 | rt | 5 | **54a** + **55** | 92 | 8.5:1 | 50 |
| **22a**[e] | MgBr[g] | $CH_2Cl_2$ | **56**[h] | 0.005 | rt | 5 | **54a** + **55** | 100 | 116:1 | 684 |

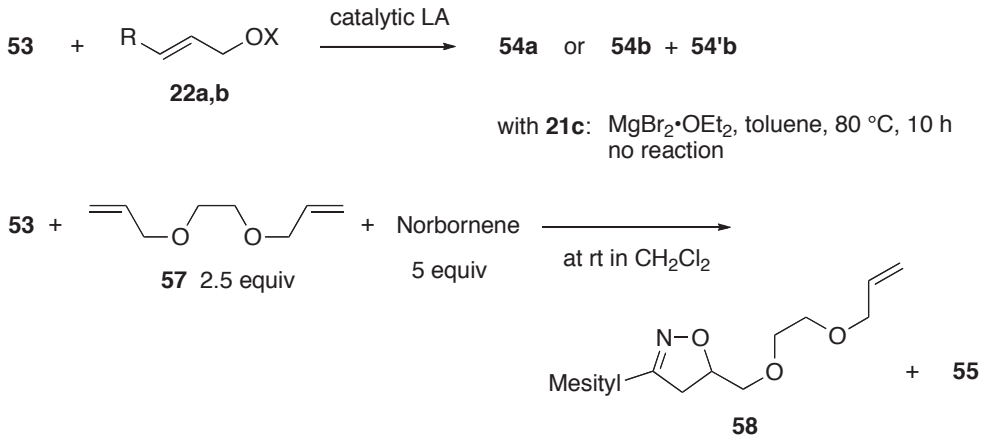
[a]All reactions were performed at rt. [b]Molar concentration of nitrile oxide **1**. [c]Yield of isolated products. [d]Calculated on the basis of the relative reaction rate between **22a** and norbornene (by $^1$H NMR). [e]Five equivalents each of **22a** and norbornene were used in the competitive cycloadditions. [f]An equimolar amount of metal salt was used. [g]One equivalent of the magnesium alkoxide was employed together with free alcohol (4 equiv). [h]Ligand **56** was equivalent to the magnesium ion.

Dilution with dichloromethane (0.05 M to 0.005 M solution) resulted in a higher rate enhancement (from 18 to 72 times faster than the uncatalyzed reaction, and hence 4 fold acceleration), confirming the responsibility of chelation transition state previously proposed for the rate enhancement. A much more increased reaction rate (418 times) was observed in the reaction using the magnesium alkoxide of dipolarophile **22a** (1 equiv). On the other hand, in the cycloaddition to **22b** as 1,2-disubstituted alkene, the rate acceleration should result in the improvement of regioselectivity between isoxazoline-5-methanol **54b** and -4-methanol cycloadduct **54'b**, since the uncatalyzed reaction is very poor in regioselectivity (**54b**:**54'b** = 57 : 43). Thus, the reaction of **53** with **22b** in the presence of $MgBr_2$•$OEt_2$ (1 equiv) gave the cycloadduct **3b** as a single regioisomer (Scheme 5-48). However, no evidence for rate acceleration was observed in the magnesium mediated reactions using bulkier alcohol **22e**.

The addition of a chelating ligand of the 1,2-diether type such as *rac*-1,2-bis(benzyloxy)-1,2-diphenylethane (**57**) in the magnesium catalyzed reactions did not reduce the reaction rate of the ligand-free reactions but the relative rate was even increased. When magnesium ion is coordinated by the 1,2-diether

ligand **57**, the magnesium ion should become sterically more hindered. Neverthless, the enhancement of reaction rate was observed. Thus, the rate deceleration by the increased steric hindrance is compensated with the entropy-based rate acceleration. In the present cases, the entropy-based rate acceleration was more favored. This shows a possibility for the ligand acceleration methodology in metal ion catalyzed asymmetric 1,3-dipolar cycloaddition reactions, which is now in progress.

**Scheme 5-48** Catalytic cycle in magnesium ion catalyzed nitrile oxide cycloadditions between nitrile oxide **53** and allylic alcohols **22a,b**.[a]




| 21 | X | Solvent | Catalyst | M[b] | Time/h | Product | Yield/% | Ratio | TON[c] |
|---|---|---|---|---|---|---|---|---|---|
| **22a** | H | $CH_2Cl_2$ | - | 0.05 | 5 | **54a** | 6 | | |
| **22a** | H | $CH_2Cl_2$ | $MgBr_2$•$OEt_2$ / 0.1 | 0.05 | 5 | **54a** | 37 | | 3.1 |
| **22a** | H | $CH_2Cl_2$ | $MgBr_2$•$OEt_2$ / 0.3 | 0.05 | 5 | **54a** | 68 | | 2.1 |
| **22a** | H | $CH_2Cl_2$ | **22a** (X = MgBr) / 0.1 | 0.05 | 5 | **54a** | 89 | | 8.3 |
| **22a**[d] | H | $CH_2Cl_2$ | **22a** (X = MgBr) / 0.1 | 0.05 | 5 | **54a** | 100 | | >9.4 |
| **22a** | H | $CH_2Cl_2$ | **22a** (X = MgBr) / 0.05 | 0.05 | 5 | **54a** | 50 | | 8.8 |
| **22a** | H | $CH_2Cl_2$ | **22a** (X = MgBr) / 0.01 | 0.05 | 5 | **54a** | 40 | | 34 |
| **22a** | H | $CH_2Cl_2$ | $MgBr_2$•$OEt_2$ / 0.1 + **56** | 0.05 | 5 | **54a** | 39 | | 3.3 |
| **22b** | H | toluene | $MgBr_2$•$OEt_2$ / 1 | 0.1 | 70 | **54b** + **54'b** | 36 | 99:1 | 3.6[e] |
| **22b** | H | $CH_2Cl_2$ | **22b** (X = MgBr) / 0.1 | 0.003 | 72 | **54b** + **54'b** | 45 | 96:4 | 4.5 |
| **22b**[f] | H | $CH_2Cl_2$ | **22b** (X = MgBr) / 0.1 | 0.003 | 72 | **54b** + **54'b** | 14 | 70:30 | 1.4 |

[a,b]See the previous table. [c]Turn over number was calculated by deducting the contribution of uncatalyzed reaction. [d]To the mixture of **1** and the catalyst, was added **22a** slowly by the aid of a syringe pump (1 h). [e]No cycloadducts were formed in the uncatalyzed reaction at rt. [f]Three equivalents of **22b** were used.

Catalytic cycle in the magnesium ion mediated nitrile oxide cycloadditions to allylic alcohols was next investigated. The reactivity of **53** to **22a** in the uncatalyzed reaction at room temperature is so sluggish giving 6% of cycloadduct **54a** after 5 h that this reaction can be used for the examination of catalytic efficiency (Scheme 5-47 and Table 5-48). Although only moderate catalytic efficiencies were observed in the reactions using 10 mol% of $MgBr_2$•$OEt_2$ catalyst (TONs = 3.1), as expected, the reaction catalyzed by the magnesium alkoxide of **22a** was much more effective. For example, use of 10 mol% of the alkoxide resulted in the formation of **54a** in 89% yield, and slow addition of dipolarophile **22a** was even more effective. The maximum turnover number observed was 34.

When (*E*)-2-buten-1-ol (**22b**, X = H) was used in the presence of the magnesium alkoxide of **22b** (X = MgBr, 10 mol%), a regioisomeric cycloadduct mixture was obtained in 45% yield (**3b**:**3b'** = 96:4). Use of a large excess of free alcohol **22b** (X = H), 30 times excess to the magnesium alkoxide of **22b**, led to both

the decreased reaction rate and the poor regioselectivity. This contrasts with the result observed in the reaction. On the basis of these results, it is certain that allylic alcohols **22a,b** should be better ligands than nitrile oxide **53** to magnesium ion. The presence of a large excess of dipolarophile **22a,b** prevents the effective coordination of dipole **53** to the magnesium ion resulting the decrease of reaction rate. In the case of less reactive **22b** such a rate decrease affected the yields of products, while more reactive **22a** maintained the reaction rate with better catalytic cycle.

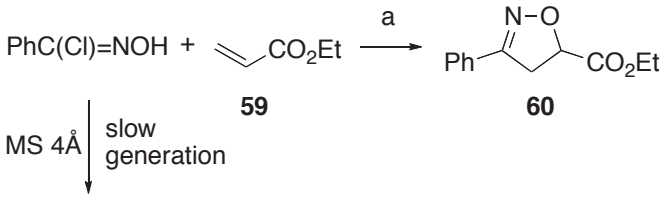
As mentioned above, the ligand acceleration effect was observed in the magnesium ion (1 equiv) mediated reaction in the presence of ligand **56**. In the reaction using a catalytic loading of magnesium ion, the efficiency of catalytic cycle was not seriously affected either by the addition of the same diether ligand **56**. On the basis of the following experimental result, it is certain that the 1,2-diether ligand **56** is coordinating with the magnesium ion as effective chelating ligand: The reaction of **1** with 1,2-bis(2-propenyloxy)ethane (**57**), a dipolarophile of the 1,2-diether type, was significantly accelerated in the presence of $MgBr_2$•$OEt_2$, where rate of the catalyzed reaction was 18 times faster than that of the uncatalyzed reaction. The level of rate acceleration obsereved here was equivalent to that recorded in the reaction between **53** and 2-propen-1-ol (**22a**) in the presence of $MgBr_2$•$OEt_2$ (Scheme 5-47). This fact also suggests that the allylic 1,2-diether **57** can be used as effective dipolarophile in the magnesium ion mediated nitrile oxide cycloadditions.

### 5.5 Catalyic enantioselective nitrile oxide cycloadditions[41]

A new synthetic application of Molecular Sieves, designated MS hereafter, was discovered in the effective catalytic generation of metalated nucleophiles. Reaction of nucleophile precursors with MS 4A in the presence of a catalytic amount of chiral Lewis acid generates metal enolates or related nucleophiles; alcohols are the far most appropriate solvents. MS 4A(Na) acts as strong base through ion exchange with protonic acid. The ion exchange reaction should be favored in alcohol media.[42] With such a success, we examined the MS-mediated dehydrohalogenation under nearly neutral conditions. We aimed to demonstrate was the MS-mediated 1,3-dipolar cycloadditions using hydroximoyl chlorides. We found that powdered MS 3A and 4A worked as mild solid bases to react with hydroximoyl chlorides generating nitrile oxides. The rate of nitrile oxide generation depends upon the choice of reaction solvent and alcohols are the best choice. This new synthetic method can be successfully applied to the first successful catalytic enantioselective nitrile oxide cycloaddition reactions with monosubstituted alkenes.

**MS 4A Mediated nitrile oxide generation.**[41] A solution of benzohydroximoyl chloride (0.22 M), ethyl acrylate (**59**, 1.5 equiv) as dipolarophile and fluorene as internal reference (0.2 equiv of the precursor) in several deuterated reaction solvents, such as dimethyl sulfoxide-$d_6$, acetonitrile-$d_3$, methanol-$d_4$, dichloromethane-$d_2$, and toluene-$d_8$, in the presence of powdered Molecular Sieves 4A (MS 4A, 500 mg/mmol scale) at room temperature. The reaction was monitored after 2 and 5 hours by sampling part of it. The MS 4A used was removed off by filtration through membrane filter. The filtrate was submitted to $^1$H NMR spectroscopic analysis to determine the yield of cycloadduct **60** between nitrile oxide **23a** and dipolarophile **59** on the basis of relative ratio to the internal reference. The results are listed in the table of Scheme 5-49.

**Scheme 5-49** Effect of the reaction solvent on the rate of generation of nitrile oxide **23a** from benzohydroximoyl chloride

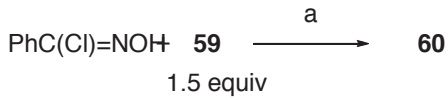



| Solvent | Yield/% of **60** 2 h | 5 h |
|---|---|---|
| DMSO-$d_6$ | 42 | 57 |
| $CD_3CN$ | 68 | 80 |
| $CD_3OD$ | 77 | 94 |
| $CD_2Cl_2$ | 13 | 36 |
| Toluene-$d_8$ | 12 | 26 |

[a]MS 4Å (500 mg/mmol), solvent (0.22 M), rt

Both for the reaction times of 2 and 5 hours, methanol was the most effective solvent and acetonitrile was the second. On the other hand, dichloromethane and toluene were poor solvents providing only low yields of **60**. Thus, MS 4A worked as effective base in the generation of nitrile oxide **23a** from benzohydroximoyl chloride in methanol. However, the MS 4A mediated generation of nitrile oxide **23a** from hydroximoyl chloride is much slower than the reaction with triethylamine, and it should be even more important to notice that the rate of generation can be easily controlled by the choice of reaction solvents. A variety of MSs were examined as solid base for the generation of **23a** in methanol as shown in the upper table of Scheme 5-50. Among MS 3A, 4A, and 5A which have the same aluminosilicate framework structure and Si/Al ratio of 1, MS 4A was found to be most effective, and MS 3A was the next. MS 13X having bigger aluminum content (Si/Al = 1.4) worked as stronger base than MS 13Y (Si/Al = 20).

**Scheme 5-50** Type of molecular sieves and amount in the generation of nitrile oxide **23a** from benzohydroximoyl chloride



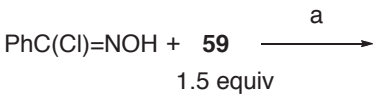

| MS | Si/Al Ratio | Yield/% of **60** 2 h | 5 h |
|---|---|---|---|
| 3A | 1 | 50 | 70 |
| 4A | 1 | 77 | 94 |
| 5A | 1 | 39 | 54 |
| 13X | 1.4 | 68 | 81 |
| 13Y | ca 20 | 16 | 20 |

[a]MS (500 mg/mmol), $CD_3OD$ (0.22 M), rt

| MS 4Å mg/mmol | equiv/Na* | Yield/% of **60** 2 h | 5 h |
|---|---|---|---|
| 250 | 1.37 | 60 | 66 |
| 500 | 2.74 | 77 | 94 |
| 750 | 4.11 | 86 | 98 |

[a]MS Type (upper table) and amount (lower table), $CD_3OD$ (0.22 M), rt

**Scheme 5-51** Type of molecular sieves and amount in the generation of nitrile oxide **23a** from benzohydroximoyl chloride




| MS | Si/Al Ratio | Yield/% of **60** 2 h | 5 h |
|---|---|---|---|
| 3A | 1 | 50 | 70 |
| 4A | 1 | 77 | 94 |
| 5A | 1 | 39 | 54 |
| 13X | 1.4 | 68 | 81 |
| 13Y | ca 20 | 16 | 20 |

[a]MS (500 mg/mmol), $CD_3OD$ (0.22 M), rt

| MS 4Å mg/mmol | equiv/Na* | Yield/% of **60** 2 h | 5 h |
|---|---|---|---|
| 250 | 1.37 | 60 | 66 |
| 500 | 2.74 | 77 | 94 |
| 750 | 4.11 | 86 | 98 |

[a]MS Type (upper table) and amount (lower table), $CD_3OD$ (0.22 M), rt

A question arises how much of MS 4A would be enough for the complete generation of nitrile oxide **23a** from the hydroximoyl chloride precursor in methanol. If MS 4A works as base through ion exchange between proton and sodium cations, MS 4A of ca 182.5 mg is equivalent to 1 mmol of benzohydroximoyl chloride. When 500 mg of MS 4A (ca 2.74 equiv) is used for the reaction of 1 mmol scale, nitrile oxide **23a** was generated at least in 94% yield after 5 h in methanol at room temperature (the lower table of Scheme 5-50). With a small excess amount (1.37 equiv to **1a**) of MS 4A, the reaction generating **23a** remained incomplete even after 5 h.

The genaration of nitrile oxide **23a** from benzohydroximoyl chloride becomes catalytic in terms of amine in the presence of MS 4A (Scheme 5-51).[41] Thus, the reaction between hydroximoyl chloride and **59** was much more accelerated with a catalytic amount (5 mol%) of triethylamine even in toluene in the presence of MS 4A (500 mg/mmol) to give cycloadduct **60** in 94% yield after 5 h at room temperature. Triethylamine is known to react with hydroximoyl chloride to undergo smooth generation of nitrile oxide **23a**, and the resulting triethylammonium chloride then undergoes ion exchange with MS 4A to regenerate free triethylamine catalyst. This catalytic cycle is probably repeated in the amine catalyzed reaction. It is likely that the rate of ion exchange reaction of triethylammonium ion with MS 4A is much faster in toluene than the direct deprotonation of hydroximoyl chloride with MS 4A. Even 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), a much stronger base than triethylamine, worked as amine catalyst in the presence of MS 4A, indicating that MS 4Å works as stronger base than DBU.

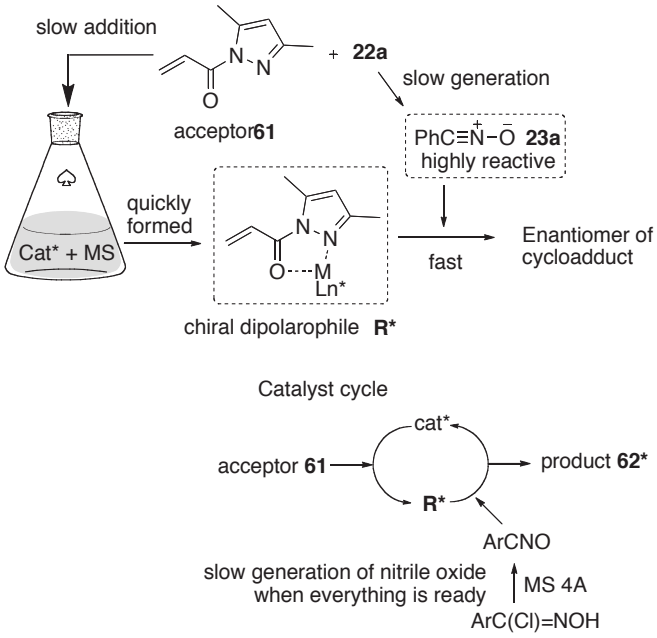
Thus, a generation method of nitrile oxides **23** was developed by use of MS 4A and hydroximoyl chlorides. The rate of generation of 1,3-dipoles can be effectively controlled by the appropriate choice of reaction solvent. As discussed above in this chapter, nitrile oxide 1,3-dipoles show extremely high reactivity to monosubstituted alkenes regardless of the electronic nature of the substituent. In addition, no effective catalysts are known so far for nitrile oxide cycloadditions indicating that uncatalyzed reactions

producing racemic products can never be removed. Usual catalytic methodology can not solve this difficulty. However, the MS 4A based new generation methodology of 1,3-dipoles is available to us. We noticed that another possibility comes out to attain the enantioselective version of nitrile oxide cycloadditions.

**Enantioselective nitrile oxide cycloadditions.**[41] Our idea includes a procedure that an equimolar mixture of nitrile oxide precursor and dipolarophile **61** is slowly added to a mixture of MS 4A and chiral catalyst (Scheme 5-52). With this procedure, one can expect the quick formation of chiral dipolarophile complex **R** is folloed by the relatively slow generation of nitrile oxide **23**. By adjusting the proper rate of slow addition of the both substrates, dipolarophile **61** becomes chiral as soon as it is exposed to the catalyst, and less amount of nitrile oxide **23** is gradually generated. Thus, the reactive 1,3-dipole **23** quickly reacts with the chiral dipolarophile complex **R** providing the cycloadduct in high selectivities. Therefore, our procedure should work well. This can be called *'a synthetic method for the production of highly enantio-enriched product with repeated stoichiometric reactions'* as shown in the lower catalyst cycle in Scheme 5-52.

We used the nickel(II) aqua complex of *R,R*-DBFOX/Ph ligand **S** (X = $ClO_4$) as chiral Lewis acid catalyst and 1-acryloyl-3,5-dimethylpyrazole (**61**) as dipolarophile, since the substrate **61** is known to form a strong coordination structure to the chiral nickel(II) catalyst **S**. In the preliminary experiment, to a mixture of commercially available MS 4A (120 mg) and catalyst **S** (X = $ClO_4$, 0.024 mmol, 10 mol%) in 2-propanol/dichloromethane (1/5 v/v, 0.5 mL) was added slowly a solution of benzohydroximoyl chloride and chelating dipolarophile substrate **61** at room temperature in dichloromethane (0.24 mmol each, 0.2 mL) by use of a syringe. This procedure took 30 min. After the addition was complete, stirring was continued for additional 30 min at room temperature. The MS 4A was filtered off through Celite. Purification of the crude product through silica-gel column chromatography gave **62a** in 81% yield with the enantioselectivity of 81% ee.

**Scheme 5-52** A possibility of enantiomer synthesis through repeated stoichiometric enantioselective reactions

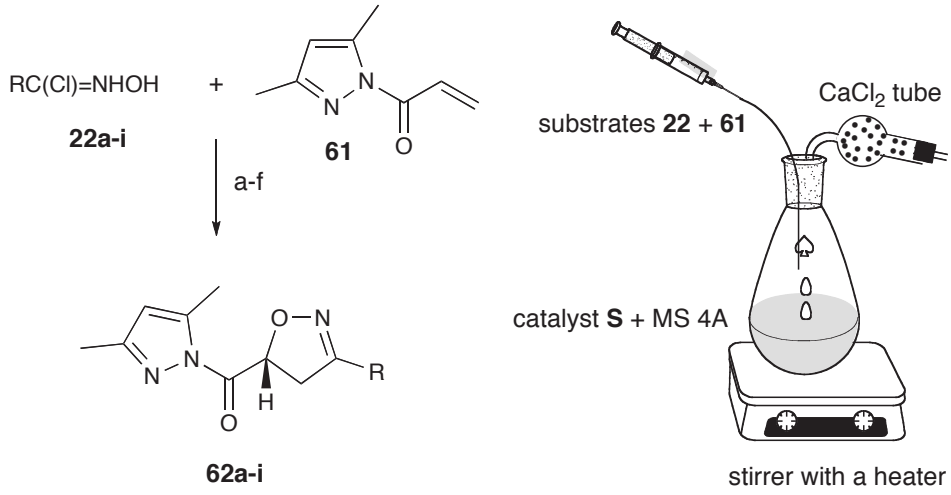


With such success of the preliminary exp eriment in hand, the reaction conditions were optimized in terms of the chiral catalyst **A** (X = $ClO_4$ and $BF_4$) under dry argon, the preactivation of MS 4A by heating with a heat gun under vacuum, use of the dry mixed solvent of 2-propanol/1,2-dichloroethane (1/5 v/v, 0.5 mL), the reaction temperature at 30 or 40 °C, and the spontaneous removal of low-boiling solvent such as dichloromethane. Consequently, better yield (95%) and enantioselectivity (96% ee) were observed for **7a** under the optimized reaction conditions (conditions shown in Scheme 5-53).

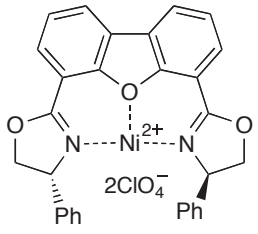
When the pyrazole amide dipolarophile **61** is used together with aqua complex catalyst **S** in a water-soluble solvent like alcohol, the amide linkage of both alkene substrate **61** and product cycloadducts **62** tends to be hydrolyzed so that the yield of cycloadduct **62** is significantly lowered. However, the drying procedure of alcoholic solution of catalyst **S** by stirring with the preactivated MS 4A, under dry argon at room temperature for 30 min, is found very effective to minimize water content in the reaction mixture. With an expectation of shortening the reaction time, the mixed solvent of 2-propanol/dichloromethane is replaced with 2-propanol/1,2-dichloroethane (1/5 v/v, 0.5 mL), and the reaction temperature can be raised to either 30 or 40 °C. With this procedure, dichloromethane as a low-boiling solvent is mostly removed by spontaneous evaporation through the drying tube attached to the reaction vessel. As a result, the solvent contained in the reaction vessel could be kept to be constant in volume so that the rate of catalytic reaction should be mostly steady.

Under the optimized reaction conditions of 'synthetic method for the generation of highly enantioenriched product with repeated stoichiometric reactions', was performed as follows: An equimolar solution of 2-propanol and 1,2-dichloroethane (1/5 v/v, 2 mL/mmol) containing a catalytic amount of chiral catalyst **S** (X = $BF_4$, 10 mol%) was allowed to stir with the preactivated MS 4A powder (500 mg/mmol) at room temperature under dry argon for 30 min. Then, a dichloromethane solution (2 mL/mmol) of hydroximoyl chlorides and pyrazole dipolarophile **61** was slowly added in a period of 30 min, at 40 °C in some cases using less reactive 1,3-dipoles. After the addition of both substrates hydroximoyl chlorides and **61** was complete, the resulting mixture was stirred at the same temperature for 30 min. Purification of the crude product through silica gel column chromatography with dichloromethane/ethyl acetate (4/1 v/v) gave isoxazoline cycloadducts **62b-i** in excellent yields with perfect regioselectivities and enantioselectivities. As shown in the table of Scheme 5-53, the highest yield of **62** was 94% and the maximized enantioselectivity was up to 97% ee.

**Scheme 5-53** The DBFOX/Ph Ni(II) complex catalyzed enantioselective 1,3-dipolar cycloadditions of nitrile oxides




a: Preactivation of MS 4Å (120 mg). b: *R,R*-DBFOX/Ph + $Ni(BF_4)_2$•$6H_2O$ (0.024 mmol each) in *i*-PrOH/$ClCH_2CH_2Cl$ (1/5 v/v, 0.5 mL). c: stirring at rt, 0.5 h. d: **22** + **61** (0.24 mmol each) in $CH_2Cl_2$ (0.5 mL) is slowly added (0.5 mL/h) at 30 or 40 °C. e: stirring for 0.5 h. f: filtration through Celite, short column ($CH_2Cl_2$/ethyl acetate = 4/1 v/v).




**S**

*R,R*-DBFOX/Ph + $NiX_2$•$6H_2O$

| **22** | R | temp/°C | **62** | yield/% | % ee |
|---|---|---|---|---|---|
| **22a** | Ph | 40 | **62a** | 94 | 96 |
| **22b** | *p*-$MeC_6H_4$ | 30 | **62b** | 92 | 97 |
| **22c** | *p*-$MeOC_6H_4$ | 30 | **62c** | 88 | 95 |
| **22d** | *p*-$BrC_6H_4$ | 30 | **62d** | 94 | 93 |
| **22e** | *p*-NO2$C_6H_4$ | 40 | **62e** | 74 | 90 |
| **22f** | *o*-$ClC_6H_4$ | 40 | **62f** | 65 | 93 |
| **22g** | *m*-$ClC_6H_4$ | 40 | **62g** | 88 | 92 |
| **22h** | *p*-$C_6H_4$ | 40 | **62h** | 81 | 92 |
| **22i** | *t*-Bu | 30 | **62i** | 67 | 90 |

One of the cycloaddition products **62a** was treated with sodium borohydride in methanol to give a quantitative yield of (5*R*)-3-phenylisoxazoline-5-methanol whose absolute sturucture was assigned by comparison with the authentic sample. Other isoxazoline derivatives **62b-i** were determined to be 5*R*-enantiomers on the basis of the absolute stereochemistry of **62a**. The stereochemistry observed in the present catalytic cycloaddition reactions producing **62** involves the selective attack of nitrile oxides at the *Re*-face of dipolarophile **61**. This is consistent with the mode of enantioselectivity observed in our previous reactions using chelating acceptor molecules.

We developed the effective use of Molecular Sieves 4A for the rate-controlled slow generation of nitrile oxide 1,3-dipoles from hydroximoyl chlorides in alcohol media. Less than 3 equivalents of MS 4A were sufficient enough for the quantitative generation of nitrile oxides in a few hours. This MS 4A mediated generation method of nitrile oxide can be effectively applied to the catalytic enantioselective nitrile oxide cycloadditions with monosubstituted alkene dipolarophiles. Such highly enantioselective synthesis of isoxazoline enantiomers is otherwise difficult to attain.

## 6. CONCLUSION AND FUTURE ASPECT

This review describes the advanced progress of 1,3-dipolar cycloaddition chemistry performed in the group of professor Shuji Kanemasa in Kyushu University. Some important informations found and studies during the research are summarized below. The author sincerely hopes that organic chemists working on 1,3-dipolar cycloaddition chemistry, especially on the synthetic methodology using 1,3-dipolar cycloaddition methodology under catalytic conditions would have studied something useful to them.

(1) A simple and general activation method of (*N*-alkylideneamino)acetates was developed on treatment with lithium bromide and triethylamine (or DBU). The resulting species show high reactivity to a wide variety of carbonyl-conjigated alkene substrates. Such mediators are usually needed in a little more than one equimolar amounts, but use of a catalytic amount is enough in the reactions with electron deficient terminal alkens. The cycloaddition reactions are quite fast enough to be complete in a few hours even at a temperature lower than room temperature. Regioselectivity, stereoselectivity, and stereospecificity are perfect with respect to all the carbon atoms of pyrrolidine-2-carboxylates. A reactive species of *E,E*-configuration combines with the alkenes of either *E*- or *Z*-geometry, depending upon the alkene substrates employed, in an *endo*-selective manner to give pyrrolidine-2-carboxylates as a single product. We believe that *N*-lithiated azomethine ylide 1,3-dipoles are generated.

The *N*-lithiated azomethine ylide provides the first example of 1,3-dipoles containing a metal atom in the molecule. This new 1,3-dipole has the electronic structure of chelation stabilized metal enolate derived from (*N*-alkylideneamino)acetates. This is why *N*-metalated azomethine ylides can be readily generated from (*N*-alkylideneamino)acetates on treatment with a weak Lewis acid such as lithium bromide and a weak amine base such as triethylamine. Lithium bromide is generally used, but other Lewis acids can be also utilized. Use of a stronger amine base such as DBU generates the *N*-metalated azomethine ylide in a higher concentration at a low temperature of -78 °C. The resulting 1,3-dipoles show high reactivity toward electron-deficient alkenes, but the alkenes bearing noncarbonyl type electron-withdrawing substituents such as acrylonitrile produce a mixture of diastereomers. Highly stereoselective cycloadducts are produced in the reactions with α,β-unsaturated esters and amides as dipolarophiles. Similar situation can be applied to the side of 1,3-dipoles, so the proper choice of electron-withdrawing substituents is important for the ylide precursors. In order to generate *N*-lithiated azomethine ylides from (*N*-alkylideneamino)acetonitrile, irreversible deprtonation with strong bases such as LDA, *n*-BuLi, and EtMgBr is needed for ylide generation at -78 °C. The resulting ylides are not always single geometry. However, the ylide generation from (*N*-alkylideneamino)acetates or -amides can be performed under much milder revrsible conditions as shown above; the resulting ylides are exclusively W-shaped due to the internal chelation. Accordingly, ylide generation, stabilized structure, as well as selectivity of cycloadditions are all perfect in the case of *N*-metalated azomethine ylides derived from (*N*-alkylideneamino)acetates. Especially, when α,β-unsaturated carbonyl compounds are utilized in the reaction, high reactivity and perfect stereoselectivity are observed. Thus, the chelation transition structure is the origin of such enhanced reactivity and exclusive stereo-selectivity.

(2) The 1,3-dipolar cycloaddition reactions of *N*-metalated azomethine ylides proceed through the stepwise mechanism via the chelated transition structure. The chelation in the resulting intermediates becomes more effective after the initial carbon-carbon bond is formed, between the nucleophilic α-carbon of the imine esters and the β-carbon of dipolarophiles. Accordingly, the remaining carbon-carbon bond formation is quickly followed in a intramolecular fashion between the imine carbons and the carbons of metal enolates under the chelated conditions. If any proton quenchers are present in the reaction or the meal salt is catalytic for the reaction using less reactive α,β-unsaturated dipolarophiles, the intermediates are readily protonated giving Michael adducts instead of cycloadducts. This Michael addition reaction also shows the same stereoselectivity as the 1,3-dipolar cycloaddition reactions since the step of initial carbon-carbon bond formation is common inbetween these two reactions. When bulky aldehydes or ketones are used for the imine ester synthesis, the Michael addition products are only produced in a stereoselective manner.

(3) Based on the enhanced reactivity and excellent stereoselectivity, *N*-metalated azomethine ylide 1,3-dipoles are the most favolable candidate to demonstrate the effective asymmetric 1,3-dipolar cycloaddition reactions using chiral α,β-unsaturated esters. In order to utilize the characteristic transition structure of 1,3-dipolar cycloadditions of *N*-metalated azomethine ylides, new heterocyclic chiral auxiliaries are designed to attach at the β-position of α,β-unsaturated esters. Chiral oxazolidines and perhydropyrrolo[1,2-*c*]imidazoles are derived from α-amino esters; $C_2$-symmetric chiral imidazolidines bearing different substituents (*N*-Ph and *N*-Me) on the nitrogen atoms are available from $C_2$-symmetric 1,2-diamines. The chiral α,β-unsaturated esters can be prepared in situ by the condensation reactions with 4-oxo-2-propenoates.

The 1,3-dipolar cycloadditions of the above chiral α,β-unsaturated esters are mostly highly diastereofacially selective. Although the chiral oxazolidine auxiliary is rather fragile under the reaction conditions to give the equilibrating 86:14 mixture of two diastereomers. This mixture can be used without separation in the cycloadditions with *N*-metalated azomethine ylides. Each diatereomer undergoes exclusively diastereoselective cycloadditions. The reaction with α,β-unsaturated esters bearing the perhydropyrrolo[1,2-*c*]imidazole chiral auxiliary at the β-position produces a single diastereomer, so the perfect selectivity is attained both for the condensation and cycloaddition steps. Cycloadditions with the α,β-unsaturated ester bearing the $C_2$-symmetric chiral imidazolidine with *N*-phenyl substituents show the only stereoselectivities lower than 100% ds. Diastereoselectivity is found to depend upon the bulkiness of the ester moiety of *N*-metalated azomethine ylides. Methyl and *t*-butyl esters show the dramatic change of selectivity (ds = 96:4 to 20:80). On the other hand, the cycloadditions with the α,β-unsaturated ester bearing the $C_2$-symmetric chiral imidazolidine bearing *N*-methyl substituents are absolutely diastereoselective regardless of the switch of ester substituents of *N*-metalated azomethine ylides or the reaction conditions. In addition, these two $C_2$-symmetric chiral imidazolidines substituted with the different chiral shielding *N*-substituents (*N*-phenyl and *N*-methyl) induce the opposite mode of stereochemistry.

The diastereofacial selectivities observed in the above asymmetric cycloaddition reactions to *N*-metalated azomethine ylides can be successfully rationalized with the proposed transition structures.

The most important factor determing the transition structures is the conformational isomers with respect to the C(2)–C(β) single bond; *ap*-Conformer is more stable than the *sc*-conformer in the ground state. The next two factors are both steric hindrance of the steric shielding *N*-substituents as well as electrostatic repulsion to the highly nucleophilic α-position of *N*-metalated azomethine ylides. The shape of pyramid structure of the nitrogen atom adjacent to the chiral center of auxiliary is also important. In the case of *N*-phenyl auxiliary both steric and electrostatic hindrance are much less than the case of *N*-methyl auxiliary.

(4) Nitrone cycloadditions to bidentate chelating enones was undertaken either in the absence or presence of a Lewis acid. It is found that titanium alkoxide chloride catalysts worked well to induce the high *endo*-selective cycloadditions (*endo:exo* = 40:60 to >99:1) under the Lewis acid catalyst. This shows that the proper selection of chelating α,β-unsaturated carbonyl substrates as well as Lewis acid catalysts in nitrone cycloadditions enables the effective catalytic stereo control of nitrone 1,3-dipolar cycloadditions. Similar cycloadditions of benzoyl nitrone to crotyl alcohol are effectively catalyzed with magnesium bromide to give the *exo*-cycloadduct of isoxazolidine-5-methanol derivative in 94% yield with a regioselectivity of 98:2. The reaction is magnesium ion specific, other Lewis acids are much less effective. Lewis acids also work to the effective nitrone isomerization from *E*- to *Z*-nitrone isomers. Under the catalysis of magnesium bromide, the nitrone cycloadditions show rate enhancement and high regio and stereoselectivities. Nitrone cycloadditions to 3-crotonoyl-2-oxazolidinone under the catalysis of the cationic *R,R*-DBFOX/Ph complexes of aqua nickel(II) and iron(II) ions in a catalytic amount (10 mol%). MS 4A should be present for exclusively high diastereoselectivity (ds: up to >99:1) as well as enantioselectivity (% ee: >99:1).

We proposed to utilize a unique catalyst for the nitrone 1,3-dipolar cycloadditions in order to avoid the undesired coordination of 1,3-dipoles to the catalyst. When the metal center of a Lewis acid is surrounded by bulky ligand(s), a small opening exists in the ligand sphere. In such a case, dipolarophiles can be effectively activated if appropriately selected. Catalytic activation of α,β-unsaturated aldehydes and methyl ketone by use of aluminum tris(2,6-diphenylphenoxide), ATPH as a pinhole catalyst we propose to call, is observed leading to regioselective 1,3-dipolar cycloadditions of nitrones. The zinc(II) complexes derived from *R,R*-DBFOX/Ph ligand works well in a catalytic amount in the nitrone cycloadditions to a variety of α,β-unsaturated aldehydes. Especially useful are the zinc(II) and nickel(II) complexes derived from 5,5,5',5'-tetramethyl derivative of *R,R*-DBFOX/Ph ligand. The resulting zinc(II) complexes are highly soluble in the reaction solvent, and more important we believe, they work to activate α,β-unsaturated aldehydes as chiral pinhole catalyst. The reaction was effectively activated by the zinc(II) catalyst even in a small catalytic amount (1 to 2 mol%) giving enantiomers of isoxazolidine derivatives with excellent enantioselectivities and diastereoselectivities.

(5) With some powerful chiral Lewis acid catalysts derived from the *R,R*-DBFOX/Ph cationic complexes of transition metal aqua complexes in hand, we challenged the ever unknown catalytic enantioselective 1,3-dipolar cycloaddition reactions of a synthetic equivalent of diazomethane since diazomethine is known as one of the most nucleophilic 1,3-dipoles. We selected trimethylsilyldiazomethane as a stable synthetic equivalent of rather explosive diazomethane and β-substituted derivatives of 3-acryloyl-2-

oxazolidinone as chelating dipolarophiles. The initial cycloadducts are 3-trimethylsilyl-1-pyrazolines in which 2,3-diazaallylsilane moiety is masked. This intermediates undergo either 1,3-proton migration or protodesilylation to give the final 2-pyrazoline products. With expectation of the selective occurerence of acyldesilylation, acetic anhydride is employed. After screening of some chiral catalysts, both the *R,R*-DBFOX/Ph complexes of nickel(II) and zinc(II) ions were selected.

The effective enantioselective 1,3-dipolar cycloaddition reactions of trimethylsilyldiazomethane were attained in the presence of the *R,R*-DBFOX/Ph-metal perchlorate complexes. The reaction of 3-crotonoyl-2-oxazolidinone catalyzed by the *R,R*-DBFOX/Ph•$Zn(ClO_4)_2 \cdot 3H_2O$ at -40 °C produced 4*S*,5*R*-enantiomer of 1-acetyl-5-(2-oxo-3-oxazolidinylcarbonyl)-2-pyrazoline in 99% ee. The nickel(II) complex catalyst was similarly active, but the magnesium(II) catalyst was less effective. On the other hand, when the dipolarophile with two methyl substituents introduced at 4-position of the oxazolidine ring was employed, the magnesium complex *R,R*-DBFOX/Ph•$Mg(ClO_4)_2$ was the best catalyst was the magnesium complex. The reaction of 3-crotonoyl-4,4-dimethyl-2-oxazolidinone proceeds even at -78 °C. The product obtained in 97% ee was the 4*R*,5*S*-enantiomer of 1-acetyl-5-(4,4-dimethyl-2-oxo-3-oxazolidinylcarbonyl)-2-pyrazoline. Thus, almost complete switch of enantioselectivity was performed simply by adding substituents to the same achiral chelating auxiliary.

(6) In the chapter 2, it is described the design and synthesis of some new chiral auxiliaries in order to apply to the asymmetric nitile oxide cycloaddition reactions. Nitrile oxides correspond to the 1,3-dipoles whose chirality control is extremely difficult by use of external chiral reagents. Our idea is based on the structural design for the effective conformational control of chirality shielding. The heterocycle selected is chiral 4-benzyloxazolidine in which each two methyl substituents are introduced at 2- and 5-positions. The former two methyls are to fix the amide linkage of 3-acryloyl group to *syn*-isomer, and the latter two for the coverage of the vinyl reaction site of 3-acryloylamide by the 4-benzyl group. The 3-acrylamide of 4-benzyl-2,2,5,5-tetramethyloxazolidine is found to show effective chiral shielding effect on the reaction site of 3-acrylamide on the basis of $^1$H NMR analysis as well as MM2 calculation. When a diphenylmethyl group is replaced with the 4-benzyl substituent, the 5,5-dimethyls are not needed any more. It shows even better chiral shielding effect.

Two new chiral acrylamides, the 3-acrylamides of 4-benzyl-2,2,5,5-tetramethyloxazolidine and 2,2-dimethyl-4-(diphenylmethyl)oxazolidine, were examined in asymmetric nitrile oxide cycloadditions. Benzonitrile oxide 1,3-dipolar cycloadditions of the chiral acrylamide having 4-benzyl shielding substituent gave a 93:7 diastereomer mixtures. Without 5,5-dimethyl substituents, the diastereomeric selectivity is lowered to 83:17, so that the 5,5-dimethyls are playing to improve the selectivity. However, 3-acryloyl-4-(diphenylmethyl)oxazolidines provided the absolute diastereofacial selectivities when the reactions with benzonitrile oxide are performed at 0 °C or below. Single diastereomer was produced in quantitative yields, regardless of the 2-substituents. These isoxazolines were used as racemates since optically resolution of the auxiliary was not successful yet.

(7) We find the first successful example of stereo- and regiocontrol of 1,3-dipolar cycloadditions by metal coordination. In nitrile oxide dipolar cycloadditions to allylic alcohols, use of the magnesium alkoxides leads to a large acceleration of the reaction rate. Cycloadditions to the allylic magnesium alkoxides also proceed exclusively in a *syn*-selective manner. The magnesium ion-mediated cycloadditions to internal alkenes provide a useful method for the regioselective preparation of 5-hydroxymethyl-2-isoxazolines. Kinetic and theoretical studies indicate that the high stereo- and regiocontrol are due to the rate enhancement of the cycloadditions proceeding through a chelated transition state. Chemoselectity and combination of regio- and stereoselectivity are also examined.

The magnesium ion mediated 1,3-dipolar cycloadditions of mesitonitrile oxide to allylic alcohols are studied. Based on the competitive reaction method, moderate levels of catalytic efficiency, ligand acceleration effect, and concentration effect were observed. These results provide some important informations for the possibility of a catalytic version of 1,3-dipolar cycloaddition reactions.

(8) A new generation method of nitrile oxides, discovered by us, include the treatment of hydroximoyl chlorides with powdered MS 4A in alcohol solvents. Although the reaction is very slow in toluene as nonpolar solvent, the nitrile oxide generation becomes much more accelerated with a catalytic amount (5 mol%) of triethylamine even in toluene in the presence of MS 4A. This new method can be successfully applied to the catalytic enantioselective nitrile oxide cycloadditions to electron-deficient alkenes. An equimolar mixture of hydroximoyl chloride and 1-acryloyl-3,5-dimethylpyrazole as dipolarophile is slowly added to a mixture of MS 4A and chiral catalyst (10 mol%). The chiral catalyst of our choice is the *R,R*-DBFOX/Ph/nickel(II) perchlorate complex. This procedure provides the successful enantioselective nitrile oxide cycloadditions with the best enantioselectivity of 96% ee.

The rate enhancement is the most important factor, the author believes, in the advanced progress of catalytic 1,3-dipolar cycloadditions. Nitrones as rather sluggish 1,3-dipoles are relatively easy to control the catalysis, but highly reactive nitrile oxides are extremely difficult to yield to a catalyst. Even now, highly effective enantioselective nitrile oxide cycloadditions under catalytic conditions are a tough subject. The author wants to say that the basic research aiming to develop the chemical science of 1,3-dipolar cycloadditions is strongly needed. Useful informations are extremely lacking in this field. Although it takes time to understand the chemical interaction between 1,3-dipoles and catalysts, the research on this field must be steady. The superficial knowledge is not helpful. This must be the most important attitude of chemists who can make big contribution to the chemistry of 1,3-dipolar reactions.

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