RECENT ADVANCES IN SYNTHETIC APPLICATIONS OF NITRILE OXIDE CYCLOADDITION (1981-1989).*

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Abstract —— The synthetic applications of nitrile oxide cycloadditions, developed in the 1980s, are briefly reviewed. Topics discussed in the present review are the modern developments on the generation methods of nitrile oxides, on the cycloadditions with multiple bonds other than carbon-carbon double and triple bonds, on reductive cleavage of the nitrogen-oxygen bonds of 2-isoxazolines, on the unmasking of functionalities, and on the asymmetric cycloadditions of nitrile oxides.

1. Introduction

1,3-Dipolar cycloaddition reaction offers one of the most powerful synthetic methodologies for heterocyclic compounds.[1] Nitrile oxide as an important member of many known 1,3-dipoles has greatly contributed to this field for a long time.[1,2] At least two answers would immediately come out to the question why nitrile oxide is the 1,3-dipole which has been most frequently and widely utilized in organic synthetic chemistry. One is its highly enhanced reactivity in 1,3-dipolar cycloadditions, with which it undergoes smooth reactions with a wide range of dipolarophiles such as electron-deficient, electron-rich, and nonactivated types. In other words, nitrile oxide involves a relatively high-lying highest occupied molecular orbital (HOMO) and a low-lying lowest unoccupied molecular orbital (LUMO).[3] The second answer is that the resulting heterocycles such as 2-isoxazolines and isoxazoles have various synthetically usuful functionalities masked in the rings. The central theme of the present review is the synthetic potential of nitrile oxide cycloadditions.

It is only 1984 when a comprehensive review[1] on the chemistry of nitrile oxides has been added to the preceding one,[2] however this latest review covers the literatures up to 1980. The 1980s are in the middle of the rapid development of synthetic organic chemistry, and quite much attention has been paid to the synthetic versatility of these heterocycles. Accordingly, many important findings and useful informations have been piled up in these years.

The present article reviews on the recent advances of synthetic applications of nitrile oxide cycloaddition, covering the literatures up to 1989. The readers might refer to an excellent review written by Kozikowski,[4] which mainly focuses on his own extensive works on the nitrile oxide cycloaddition chemistry as a tool for natural product total synthesis.

2. Generation and Cycloaddition

The following two are the most widely and frequently utilized methods of generating

* Dedicated to the late Professor Tetsuji Kametani.

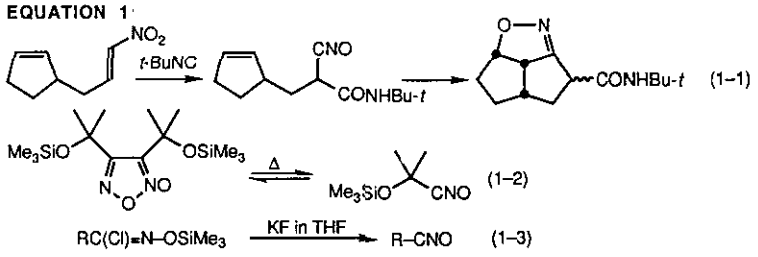
nitrile oxides:[1] 1) Triethylamine-mediated dehydrohalogenation of hydroxamoyl chlorides or bromides, both of which are readily accessible from the action of aldoximes with halogens, nitrosyl chloride, N-chlorosuccinimide, or N-bromosuccinimide, and 2) Mukaiyama reaction of primary nitroalkanes where phenyl isocyanate and a catalytic amount of triethylamine are the most commonly used dehydrating agents.

In the 1980s, a few conceptually new generation methods of nitrile oxides or some modified procedures have been reported. A variety of nitrile oxides including ArCNO, RCNO, and EtOOCCNO are effectively generated by dehydration of the corresponding primary nitoroalkanes with benzenesulfonyl chloride or ethyl chloroformate in the presence of triethylamine.[5] This method, a modified version of Mukaiyama reaction, does not need to separate the products resulting from the dehydrating agents.

2-Isoxazolines are prepared in 65-93% yields by heating a mixture of olefins and aldoximes with chloramine-T under reflux in ethanol.[6] Use of chloramine-T in this direct generation method from aldoximes would be deeply related with that of nitrosyl chloride or aqueous sodium hypochloride under phase-transfer catalysis.[1] Interesting is the photochemical generation of nitrile oxides where a mixture of hydroxamoyl chlorides and bis(tributyltin) as initiator is simply irradiated in the presence of a dipolarophile.[7]

Conjugate addition of t-butyl isocyanide to nitroalkenes occurs on heating under reflux in acetonitrile offering a convenient and direct generation procedure of nitrile oxides bearing an α-carbamoyl moiety (Eq. 1-1).[8] This generation route becomes a synthetically useful route since nitroalkenes are readily available by condensation of nitromethane with carbonyl compounds.

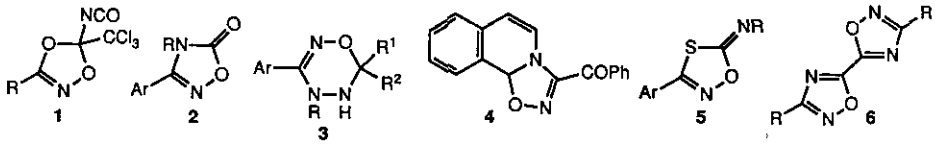
EQUATION 1



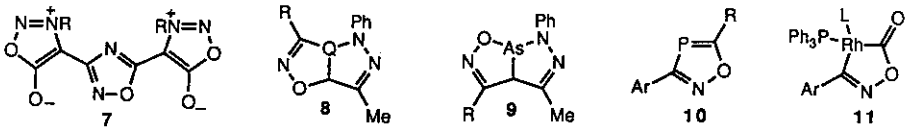
Regeneration of nitrile oxides from furoxans, cyclic dimers of nitrile oxides, by thermolysis usually requires severe reaction conditions, e.g. 450 ℃ on a flash vacuum pyrolysis apparatus. However, a fairly easy reversible cycloreversion reaction takes place when bis[1-methyl-1-(trimethylsilyloxy)ethyl]furoxan is heated at a relatively low temperature (165 ℃ in benzene in a sealed tube). The resulting 2-methyl-2-(trimethylsilyl)propanenitrile oxide undergoes smooth cycloadditions, under reversible conditions, even with less reactive di- and trisubstituted olefins to produce 3-[1-methyl-1-(trimethylsilyl)ethyl]-substituted 2-isoxazolines which are synthetical equivalent of β-hydroxy acids through a periodic acid oxidation procedure (Eq. 1-2).[9] Chlorotrimethylsilane adds to nitrile oxides to provide O-(trimethylsilyl)hydroxamoyl chlorides which regenerate the nitrile oxides on treatment with potassium fluoride in acetonitrile at room temperature (Eq. 1-3).[10] Cycloaddition reactions of nitrile oxide have been long examined most intensively

with olefin and acetylene dipolarophiles, because these reactions have collected much attention of synthetic chemists, and because 2-isoxazolines and isoxazoles have synthetically important properties as functionalized heterocycles. It is well known, however, that nitrile oxides show some increased reactivity to imines, carbonyls, and thiocarbonyls.[1] A few new reaction examples have been reported in the 1980s with respect to the nitrile oxide cycloadditions with multiple bonds other than carbon-carbon double and triple bonds.

Thus, 5-isocyanato-1,4,2-dioxazolines 1 are produced by the reaction with the carbonyl moiety of trichloroacetyl isocyanate.[11] Carbon-nitrogen double bonds[12-18] which undergo cycloaddition with nitrile oxides are isocyanates leading to 1,2,4-oxadiazolin-5-ones 2 (R = H,[16] COCl[18]), hydrazones leading to 1,2,4,5-oxatriazines 3,[14] and isoquinoline giving fused 1,2,4-oxadiazoline 4.[17]



Thiocarbonyl group is also reactive to nitrile oxides as shown by the reaction examples with the thiocarbonyl group of thioaldehydes,[19] dithiooxalate,[20] and isothiocyanates;[21] 5-imino-1,4,2-oxathiazolines 5 are products from isothiocyanates. Nitriles[22-24] such as thiocyanates, malononitrile, cyanogen, and diazo cyanides undergo cycloadditions with nitrile oxides. Especially interesting is the formation of bi(1,2,4-oxadiazoles) 6[24] and 1,2,4-oxadiazoles 7 bearing two sydnone substituents.[25] A few reaction examples to the carbon-phosphorus or carbon-arsenic bond are known.[26-29] The reaction with a 1,2,3-diazaphosphole or a 1,2,3-diazaarsole at a low temperature takes place regioselectively to give 8 (Q = As, P) as kinetically controlled cycloadducts. Arseic derivative 8 (Q = As) isomerizes

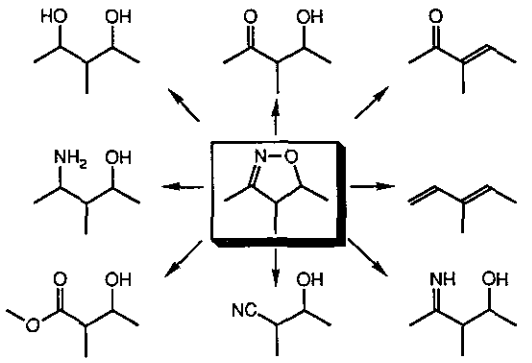


into thermodynamically more stable regioisomer 9.[26] The carbon-phosphorus bond of phosphaethenes such as 1-silyl-2-silyloxy-[27] and 1-chloro-2-silylphosphaethenes[28] also reacts with nitrile oxides to give 1,2,4-oxazaphospholes 10 through a cycloaddition-elimination sequence. An unusual cycloaddition of nitrile oxides with low-valent metal carbonyl complexes giving five-membered metallacycles 11 is known.[30]

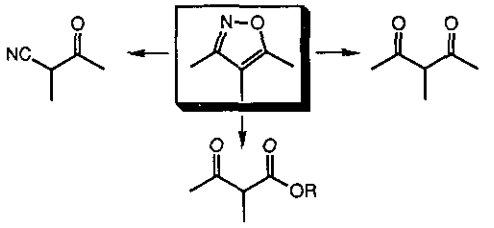
3. Ring Opening:

The known transformations of 2-isoxazoline rings are summarized in Eq. 2, leading to 1) β-hydroxy ketones (further to α,β-unsaturated ketones, 1,3-dioles, and 1,3-dienes), 2) γ-amino alcohols, 3) β-hydroxy imines, 4) β-hydroxy nitriles, and 5) β-hydroxy acids. On the other hand, the following functionalities are masked in an isoxazole ring: 1) 1,3-diketones, 2) β-keto esters, and 3) β-keto nitriles (Eq. 3). Since nitrile oxides show high reactivity toward the olefinic and acetylenic dipolarophiles bearing a wide range of functionalized substituents, one would be

EQUATION 2



EQUATION 3



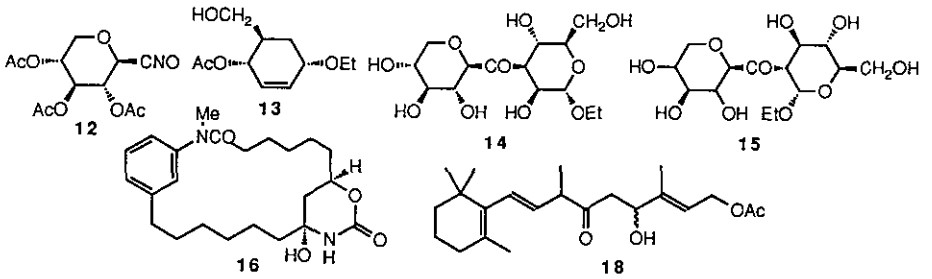
able to create polyfunctionalized synthetic block by combining the functionalities introduced from dipolarophiles with the ones derived from the unmasking of the heterocyclic ring.

3-1. β-Hydroxy Ketones and Related Functionalities

Reductive cleavage of the nitrogen-oxygen bond of 2-isoxazolines followed by acid hydrolysis leads to β-hydroxy ketones which are important in organic synthesis because this functional group, called aldol, can be further transformed into a variety of related functionalities such as α,β-unsaturated ketones, 1,3-dioles, and 1,3-dienes. Catalytic hydrogenation on Raney Ni[31] in aqueous methanol in the presence of boric acid is now most widely employed for this purpose, while rhodium on alumina[32] works as well. When an olefinic substituent is present on 2-isoxazoline rings, $Mo(CO)_6$-mediated ring-opening[33] and reduction by Al(Hg)[34] in aqueous tetrahydrofuran (THF) are conveniently applied. The coexisting olefinic moiety remains untouched under these conditions. Sodium in liquid ammonia[35] is successfully employed to reduce the nitrogen-oxygen bond of a 2-isoxazoline into β-hydroxy ketone which, on Raney Ni reduction under acidic conditions, suffers from a ready acid-catalyzed dehydration to give the corresponding α,β-unsaturated ketone. Two newly merged methods for the ring cleavage of isoxazolines involve the titanium(Ⅲ) chloride-mediated reduction[36-38] and ozonolysis.[39] The latter method is especially useful when any epimerization of the resulting β-hydroxy ketones (aldols) should be avoided.

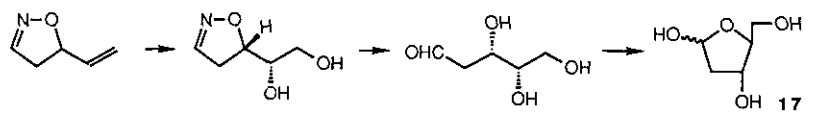
The reductive nitrogen-oxygen bond cleavage of 2-isoxazoline rings, formed as cycloadducts, is the most frequently utilized reaction in the reported examples of synthetic applications of the nitrile oxide cycloaddition methodology. Since the nitrile oxide cycloaddition reaction takes place strictly with the retension of configuration of olefin dipolarophiles, stereoselective synthesis of β-hydroxy

ketones (aldols) is achieved by starting from a wide variety of olefins.[40-42] As one example, the xylose-mannose and xylose-glucose carbon-linked disaccharides, 14 and 15, are synthesized from two regioisomers of the diastereoface-selective cycloadducts of nitrile oxide 12 with olefin 13.[42] Apparently, in this case, the

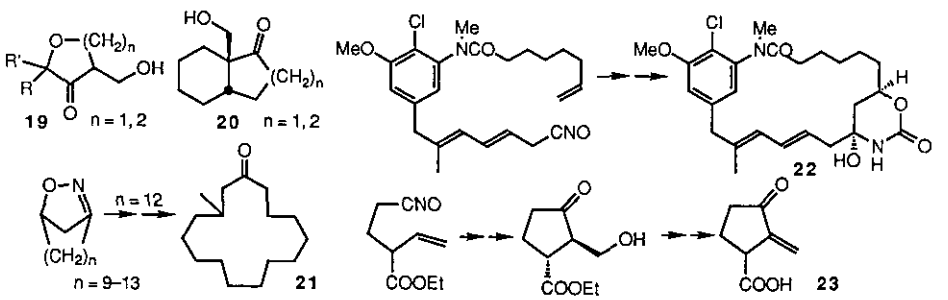


cyclic structure of dipolarophile 13 is responsible for the absolutely high diastereoselectivity. Regioselective nitrile oxide cycloadditions to terminal olefins, which lead to the exclusive formation of β-hydroky ketones of the secondary alcohol types, have been effectively utilized to assemble the ansa-macrolide skeleton 16,[43] 2-deoxyribose 17 and related sugars,[44] and the retinoid carbon skeleton 18.[33] The reaction sequence employed for the synthesis of dl-2-deoxyribose 17 consists of the regioselective nitrile oxide cycloaddition with 1,3-butadiene producing 5-vinyl-2-isoxazoline, the diastereoselective hydroxylation of the vinyl moiety with osmium tetroxide giving the anti-diol, and the final stage of catalytic reduction of the heterocycle on deactivated palladium (Eq. 4).

EQUATION 4

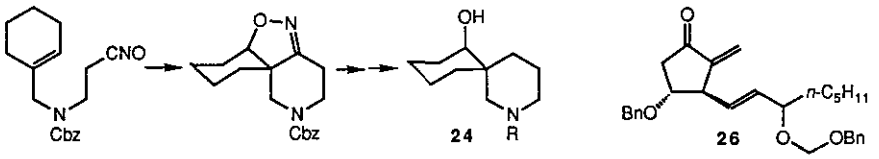


However, diastereoselectivity including regioselectivity is often far from the satisfactory level in the intermolecular versions of nitrile oxide cycloadditions, especially so for the purpose of stereoselective assembling of the skeletons of structurally complex and highly functionalized natural products. It is easy to expect that much higher diastereoselectivity would be achieved in intramolecular cycloadditions of nitrile oxides. In addition, one additional ring system is added



in a manner of fusion to the 2-isoxazoline ring, the size of ring member depending upon the length of chain intervening between the nitrile oxide functionality and olefin moieties.

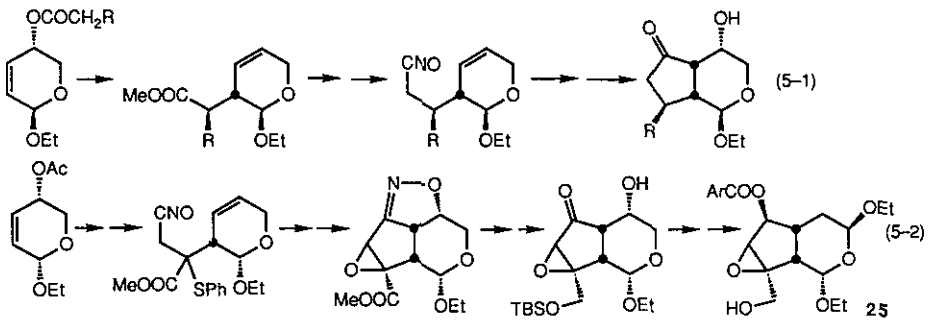
Simple applications of the intramolecular cycloaddition methodology are seen in the synthetic examples of functionalized cyclic ethers 19,[45] bicyclic ketones 20[46] with functionalized angular methyl groups, macrocarbocycles including muscone 21,[47] maytansinoid skeletons 22,[43-48] and sarkomycin 23.[49] The synthesis of sarkomysin 23 is one of the first application examples, *which has demonstrated the synthetic* versatility of the intramolecular nitrile oxide cycloaddition methodology.



Spirocyclic alkaloides 24 such as isonitamine (R = H) and sibirine (R = Me) are successfully assembled through the intramolecular nitrile oxide cycloaddition.[50] Reductive cleavage of the nitrogen-oxygen bond of the tricyclic cycloadduct is followed by the removal of the resulting carbonyl moiety after thioacetalization. Adjustment of N-substituent is carried out at the same time depending upon the hydrogenation conditions.

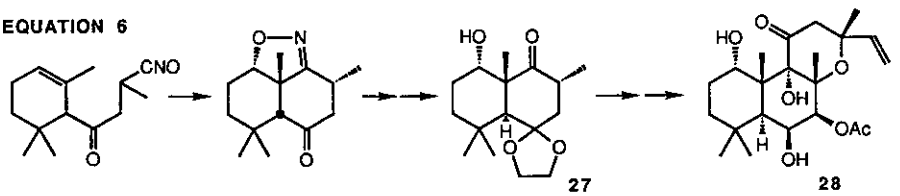
The combination of Claisen rearrangement with nitrile oxide cycloaddition offers a convenient entry for the intramolecular nitrile oxide cycloaddition procedure. Preparation of bicyclic β-hydroxy ketones is shown in Eq. 5-1.[51] A successful application of this methodology is the elaboration of (-)-specionin 25, which starts from (D)-xylal (Eq. 5-2).[52] Therein, a useful method for the introduction of an enol acetal functionality based on ruthenium-catalyzed olefin migration has been developed, and the enol acetal is utilized to introduce C-3β-ethoxy moiety of 25.

EQUATION 5



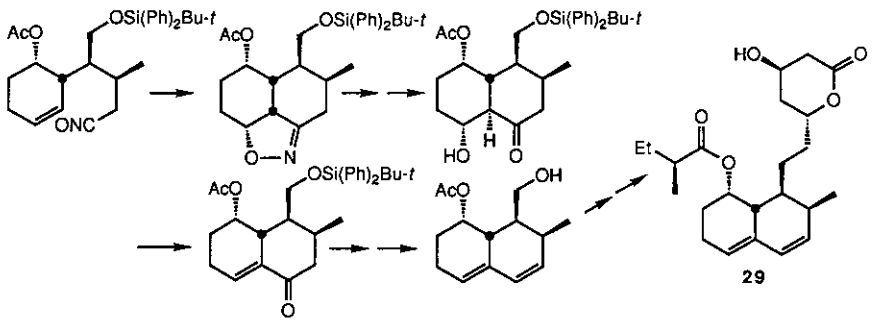
Some other examples are known for the synthesis of complex natural products using the intramolecular cycloaddition methodology, involing methylenecyclopentanone 26[52] as a PGF_2 synthon and ketone 27[53] as a potential precursor of forskolin 28. In the latter case, the 2-isoxazoline-fused cycloadduct is subjected to acetalization before the unmasking of β-hydroxy ketone functionality, and the subsequent epimerization leads to the desired key compound 27 (Eq. 6). The total synthesis of compactin 29,[55] known for potent hypocholesterolemic activity, utilizes 2-

EQUATION 6



isoxazoline ring as masked 1,3-diene functionality. The hexahydronaphthalene ring of compactin 29 has been correctly assembled by the diastereoselective intramolecular nitrile oxide cycloaddition. Reductive unmasking of β-hydroxy ketone moiety, acid-catalyzed dehydration into α,β-unsaturated ketone, and the final step of Shapiro transformation lead to the desired 1,3-diene (Eq. 7).

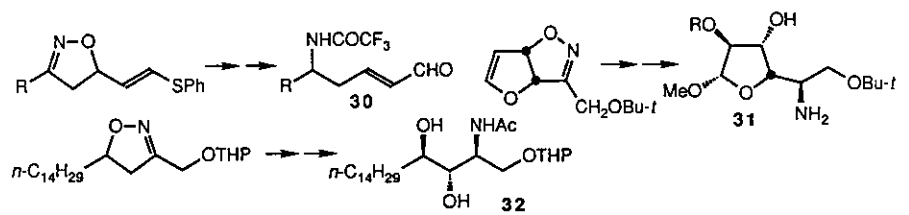
EQUATION 7



3-2. γ-Amino Alcohols

Reduction of 2-isoxazolines under severe conditions leads to a γ-amino alcohol functionality. In most cases, lithium aluminum hydride (LAH) is employed as reducing agent for this purpose.

Nitrile oxide cycloadditions with 1-phenylthio-1,3-butadiene take place at the monosubstituted olefin to produce 5-[2-(phenylthio)ethenyl]-2-isoxazolines which are readily transformed to 5-amino-2-pentenals 30 through the LAH reduction and subsequent mercury(II) chloride-mediated hydrolysis.[55] The regioselective cycloadditions of nitrile oxides with furan producing fused 5,5-ring systems are followed by the stereoselective epoxidation with m-chloroperoxybenzoic acid (MCPBA) and then reduction with LAH. This sequence offers a highly stereoselective entry to amino sugars, which is successfully applicable to synthesize β-xylo-furanside 31.[56]

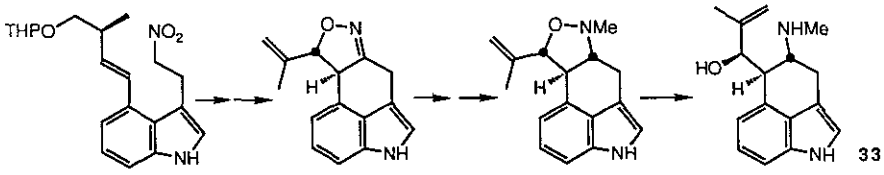


An effective method for introducing a hydroxyl group at the 4-position of 2-isoxazolines has been established by action of the 4-anions with a borate and oxidative work-up.[57] Stereoselective reduction of the resulting trans-4-hydroxy-2-

isoxazolines with LAH, where the hydride attack occurs exclusively from the side of the 4-hydroxyl group, leads to the stereoselective synthesis of a protected derivative of phytosphingosine 32.[57]

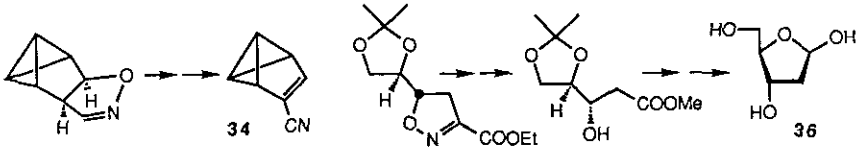
A modified procedure for the reductive cleavage of 2-isoxazolines leading to β-amino alcohols consists of the initial N-alkylation and subsequent reduction of the resulting iminium products under mild conditions. As shown in Eq. 8, the intramolecular cycloaddition of a nitrile oxide to a neighboring olefinic appendage bearing an allylic asymmetric center produces two diastereoisomeric cycloadducts, one of which is N-methylated with trimethyloxonium fluoroborate in acetonitrile and reduced with LAH. Subsequent reductive cleavage of the nitrogen-oxygen bond with aluminum amalgam gives paliclavine 33[34] in optically pure form.

EQUATION 8



3-3. β-Hydroxy Nitriles

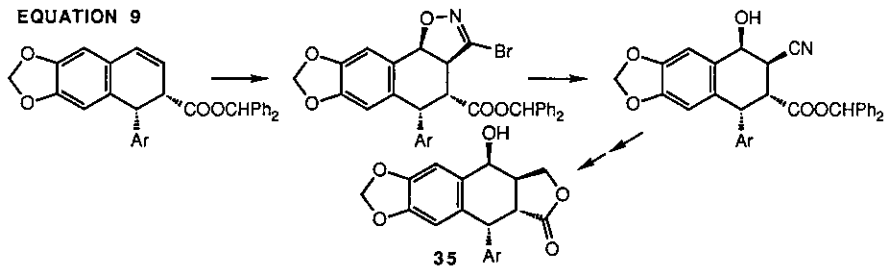
2-Isoxazolines unsubstituted at 3-position undergo a novel ring-opening reaction by the action of a base, β-hydroxy nitriles being formed. One simple application is the introduction of a cyano group at the olefinic carbon of a molecule. Thus, benzvalene is subjected to the cycloaddition with the parent carbonitrile oxide, and the resulting cycloadduct is treated with sodium methoxide causing a smooth ring cleavage producing the β-hydroxy cyanide. Subsequent dehydration is carried out through an O-tosylation and elimination sequence to give cyano-substituted benzvalene 34.[58] The transformation reaction of 1,3-butadiene to 3-hydroxy-4-pentenenitrile and further to 1-cyano-1,3-butadiene is performed by a similar method where ring-opening is effected by triethylamine.[38]



3-Bromo- or 3-chloro-substituted isoxazolines are also convertible to β-hydroxy nitriles. This methodology has been applied to the total synthesis of epipodophyllotoxin 35 (Eq. 9).[59] Thus, the diastereoface- and regioselective cycloadduct between bromonitrile oxide and a dihydronaphthalene is reduced on Raney Ni to produce the cis-β-hydroxy nitrile in 90% yield, which is converted into 35 by a sequence of the LAH reduction to β-amino alcohol, diazotization, and the final lactonization. 2-Isoxazolines bearing a 3-silyl moiety are so labile that heating at 100 ℃ is enough to cause the ring cleavage furnishing β-hydroxy nitriles.[60]

A decarboxylation-induced ring-opening of isoxazolines also offers an alternative method[61] for the stereoselective cis cyanohydroxylation methodology. Isoxazoline-3-esters, used as substrates in the present method, are readily accessible by the cycloadditions of (ethoxycarbonyl)carbonitrile oxide which is easily prepared from

EQUATION 9



ethyl glycinate. The 3-ester group is first hydrolyzed by 10% sodium hydroxide, and the resulting isoxazoline-3-carboxylic acids are heated without solvent at a temperature 5-10 ℃ above their melting points.

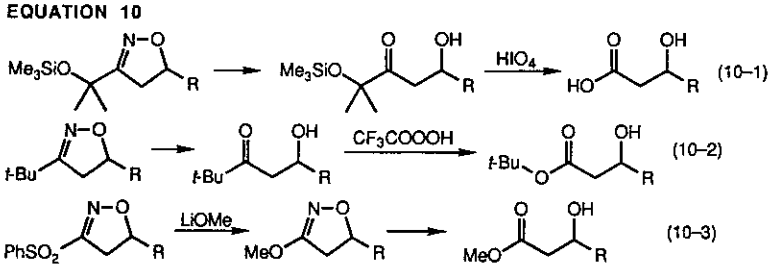
This methodology has been successfully applied to the synthesis of 2-deoxy-D-ribose 36.[62] The major diastereomer (80:20) of the cycloadduct of (ethoxycarbonyl)carbonitrile oxide with (S)-(+)-isopropylidene-3-butene-1,2-diol is subjected to the decarboxylative cyanohydroxylation procedure. Alkaline hydrolysis is followed by esterification with diazomethane to give the β-hydroxy ester. Lactonization and subsequent reduction with bis(3-methyl-2-butyl)borane leads to 36.

3-4. β-Hydroxy Acids and Derivatives

Since β-hydroxy nitriles can be converted into β-hydroxy acids through alkaline hydrolysis, the decarboxylative cyanohydroxylation methodology mentioned above offers an indirect route to β-hydroxyl acids from 2-isoxazolines. One example has been already shown in the synthetic work[62] of deoxyribose 36.

The tetrahydropyranyl (THP) ether of 2-nitroethanol generates the nitrile oxide bearing a protected hydroxylmethyl functionality.[61] 2-Isoxazolines derived from cycloadditions using this nitrile oxide are readily transformed into β-hydroxy acids in excellent yields. After removal of THP protecting group, the nitrogen-oxygen bond is reduced by catalytic hyrogenation on Raney Ni in the presence of acetic acid. The resulting α-hydroxy ketone function is readily cleaved by oxidation with periodic acid at room temperature.[61] For the same purpose, 2-methyl-

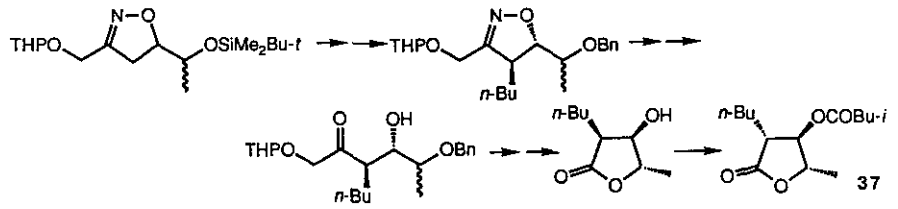
EQUATION 10



2-(trimethylsilyloxy)propanenitrile oxide[63] is also employed as well (Eq. 10-1).

One application of this methodology in the total synthesis of blastmycinone 37 (Eq. 11)[64] starts with the cycloaddition of THP-protected 2-hydroxyacetonitrile oxide with 3-(t-butyldimethylsilyloxy)-3-butene. A diastereoisomeric mixture (4:1) of the cycloadduct is alkylated via metallation at 4-position, after exchange of the O-protecting group to a benzyl, to lead to the exclusive formation of a trans 4-alkylated 2-isoxazoline. Reductive cleavage of the nitrogen-oxygen bond affords the β-hydroxy ketone, the major diastereomer of which is subjected to periodide

EQUATION 11



oxidation. The resulting acid is lactonized to epi-blastmycinol which is epimerized and acylated to give the desired blastmycinone 37.

The second method to get β-hydroxy acid functionality involves the utilization of Baeyer-Villiger reaction as oxidation step (Eq. 10-2).[63] Highly α-hindered nitrile oxide, 2,2-dimethylpropanenitrile oxide, is employed in cycloadditions with olefins to prepare 3-(t-butyl)-2-isoxazolines, which are reduced into β-hydroky t-butyl ketones. Subsequent Baeyer-Villiger oxidation with trifluoroacetic peracid affords t-butyl esters of β-hydroxy acids.

3-Phenylsulfonyl-substituted 2-isoxazolines are smoothly converted into 3-methoxy-2-isoxazolines by displacement with lithium methoxide (Eq. 10-3).[63] The Raney Ni reduction of the 3-methoxy-substituted 2-isoxazolines directly provides methyl esters of β-hydroxy acids.

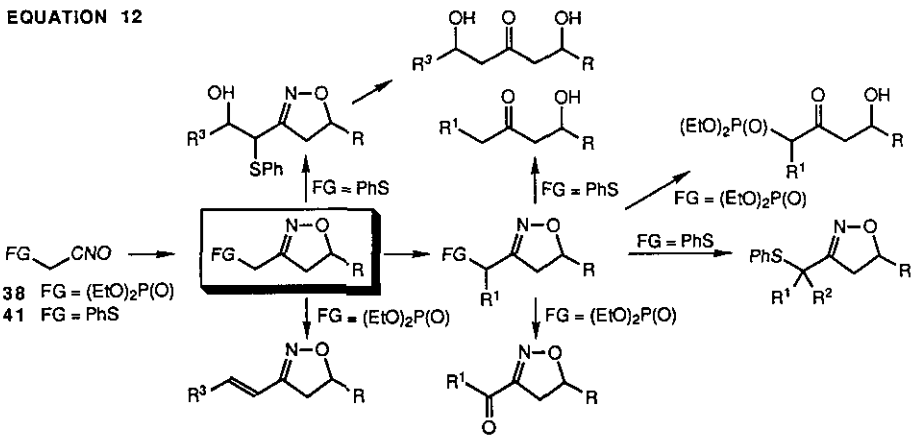
3-5. Functionalized Nitrile Oxides

In nitrile oxide cycloadditions, the substituents introduced from dipoles and terminal dipolarophiles occupy the 3- and 5-positions of 2-isoxazolines, respectively. As well known, a wide variety of functionalized substituents can be introduced from dipolarophiles, while nitrile oxides bearing functionalized substituents are quite limited. Some known examples are listed below.

Nitrile oxides whose carbon atom is directly substituted by a functional group (FG) are as follows: FG-CNO: FG = Me_3Si, Br, Cl, CN, RCO, ROOC, and RSO_2. Several examples of the α-functionalized types are known: FG-CNO: FG = $THPOCH_2$, $t\text{-}BuOCH_2$, $Me_3SiOC(Me)_2$, $(EtO)_2P(O)CH_2$, and $PhSCH_2$. The nitrile oxide with a mesoionic heterocycle has been described above.

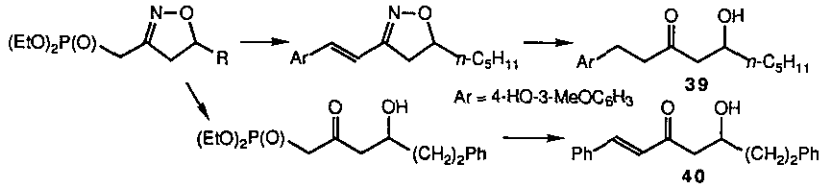
(Diethoxyphosphoryl)acetonitrile oxide 38 as α-functionalized dipole is readily

EQUATION 12



accessible from (diethoxyphosphoryl)acetoaldehyde oxime[65] and N-bromosuccinimide (NBS), which shows a high synthetic versatility (Eq. 12).[66] After cycloadditions with a wide range of olefinic dipolarophiles, the cycloadducts are lithiated with butyllithium selectively at the carbon substituted by the phosphorus group. The resulting anions smoothly react with aldehydes and alkyl halides to give 3-(1-alkenyl)- and 3-(1-phosphorylalkyl)-2-isoxazolines, respectively. The alkylated 2-isoxazolines are transformed into 3-acyl derivatives by a sequence of lithiation and air oxidation. The phosphorus moiety is stable under the conditions of Raney Ni reduction leading to phosphorus-functionalized β-hydroxy ketones, 4-hydroxy-2-oxoalkylphosphonates,[67] whose Horner-Emmons olefinations are successfully carried out by use of a weak base such as lithium bromide/triethylamine. Change of order for the Horner-Emmons olefination and the Raney Ni reduction enables a short synthesis[67] of gingerol 39 and yashabushiketol 40 as shown in Eq. 13. Thus, the 2-

EQUATION 13

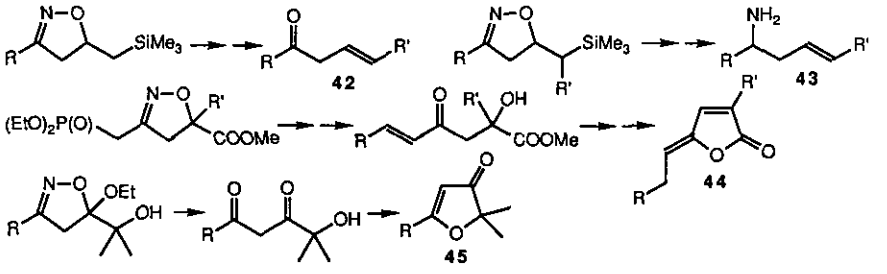


isoxazolines derived from nitrile oxide 38 serve as useful agents for the nucleophilic introduction of a 2-isoxazolin-3-yl unit as functionalized heterocycle. (Phenylthio)acetonitrile oxide 41[68] can be used for a similar purpose (Eq. 12). The 2-isoxazolines derived from 41 are also lithiated at the carbon of 3-side chain. Alkylation can be easily repeated at the same position, and reactions with aldehydes and α,β-unsaturated esters also work as well. On the reductive ring cleavage with Raney Ni, the phenylthio moiety is removable at the same time to provide β-hydroxy ketones bearing a variety of functionalities.

3-6. Combination of Functionalities

The functionalities introduced from nitrile oxides and/or dipolarophiles would be effectively combined with those derived from unmasking of 2-isoxazoline ring.

Nitrile oxide cycloadditions of allylsilanes furnishes 5-silylmethyl-2-isoxazolines. These 2-isoxazolines are important as synthetic equivalents of β,γ-unsaturated ketones 42[69] and homoallylamines 43[70] through the reductive ring cleavage into β-hydroxy ketones followed by the elimination of silanol.

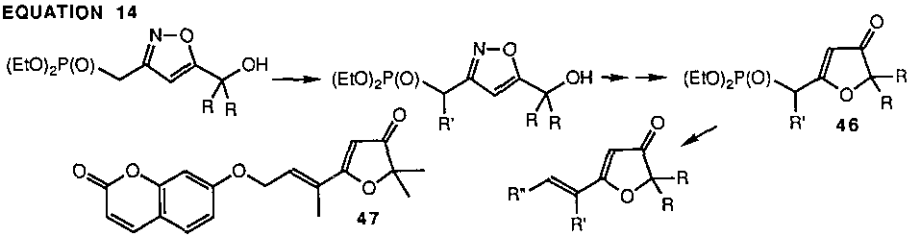


Cycloaddducts of nitrile oxide 38 with α,β-unsaturated esters undergo the reductive ring cleavage into 2-hydroxy-4-oxo-5-phosphoryl esters whose Horner-Emmons

olefinations produce 2-hydroxy-4-oxo-5-alkenoates. Sodium borohydride reduction of the conjugated carbonyl is followed by lactonization to give 2-hydroxy lactones which are further transformed into (Z)-5-alkylidene-2(5H)-furanones 44[71] via dehydration and double bond migration.

5-Ethoxy-5-(2-hydroxyalkyl)-2-isoxazolines, readily available by the nitrile oxide cycloaddition to 2-ethoxyallyl alcohols, are reduced into 1,3-diketones which undergo cyclization to give 3(2H)-furanones 45.[72] The nitrile oxide cycloaddition strategy by another combination of dipoles and dipolarophiles offers a general synthetic method of 2,2-dimethyl-5-(1-methyl-1-alkenyl)-2(3H)-furanones, a central skeleton of furanone natural products (Eq. 14). Nitrile oxide 38 and unprotected propargyl alcohols undergo smooth cycloadditions to furnish 3-(1-phosphorylalkyl)-substituted isoxazoles. An alkyl group is introduced at the 3-side chain via

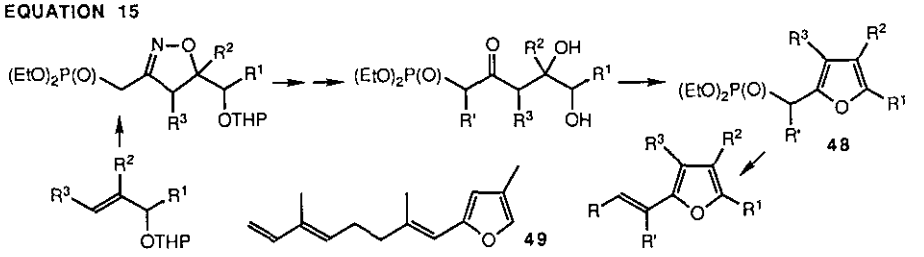
EQUATION 14



lithiation. The Raney Ni reduction is followed by work-up under acidic conditions to produce 5-(1-phosphorylalkyl)-2(3H)-furanones 46[73] which undergo Horner-Emmons olefinations in the presence of lithium bromide/triethylamine leading to the corresponding olefins in high E-selectivity. Synthesis of geiparvarin 47 has been readily achieved by this methodology. In these cases, the key intermediates are highly functionalized carbonyl compounds.

When the cycloaddition-reductive ring cleavage methodology is applied to allyl alcohols, a β,γ-dihydroxy ketone functionality is assembled. Thus, the reactions of nitrile oxide 38 with the THP ethers of allyl alcohols afford 4,5-dihydroxy-2-oxoalkylphosphonates after the side chain alkylation and the Raney Ni reduction, which are then treated with sodium acetate in acetic acid at 100 ℃ to give 2-

EQUATION 15



(phosphorylmethyl)furans 48 (Eq. 15). Horner-Emmons olefination of 48 leads to 2-(1-alkenyl)furans. A furanosesquiterpene 49,[74] produced in Australian soft coral, has been synthesized by this route.

4. Asymmetric Cycloaddition

Synthetic versatility and potential of the nitrile oxide cycloaddition methodology would be greatly enhanced if 2-isoxazolines could be prepared in optically pure form. However, a nitrile oxide behaves as sterically tiny addend in the

cycloadditions with terminal olefins since any effective overlapping of each substituent is not expected in the transition state leading to more favored regioisomers of cycloadducts. No any example for the Lewis acid-catalyzed nitrile oxide cycloadditions is known. Accordingly, the development of highly selective asymmetric cycloadditions of nitrile oxides is a challenging goal.

Three types of diastereoselective nitrile oxide cycloadditions have been examined so far, including 1) intermolecular cycloadditions by use of acrylic derivatives bearing a chiral auxiliary, 2) use of olefinic dipolarophiles of the ally ether types, and 3) intramolecular cycloadditions using internal olefins of the allyl ether types.

CHART 1

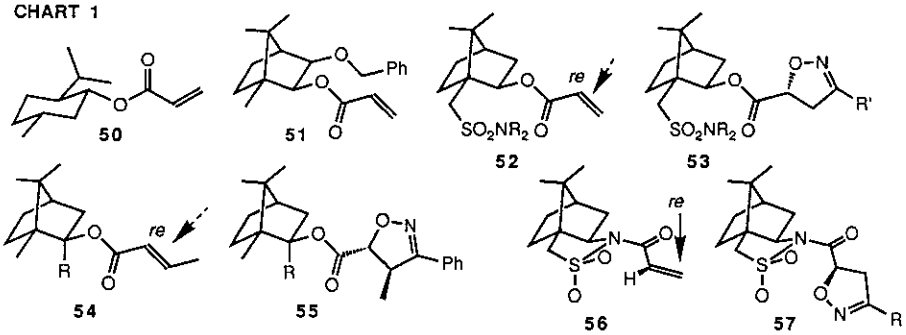


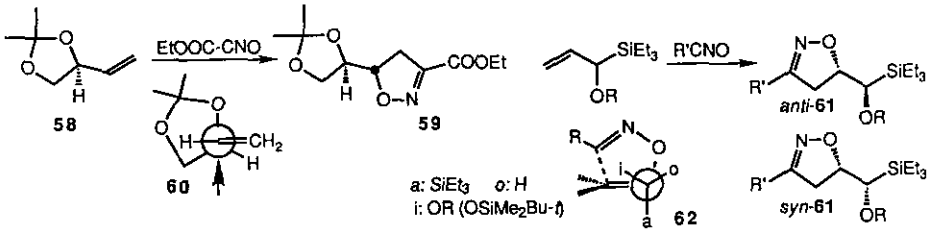
Chart 1 collects one of the most straightforward approaches to prepare optically active 2-isoxazolines, which consists of the diastereoface-selective cycloaddition to chiral acrylic dipolarophiles. Of chiral acrylates ever examined, menthyl acrylate 50 (4% de to p-nitrobenzonitrile oxide) and acrylate 51 (10% de to the same dipole) show only low magnitudes of diastereoface-selectivity, no stereochemical assignment of the major diastereomers being made. Oppolzer's chiral sulfonamide 52 provides a significant level of diastereoselectivity (R = cyclohexyl, 56% de to benzonitrile oxide),[75] much better than the previous two cases. Based on the structural analysis of the major diastereomers 53, the approach of a nitrile oxide to the re-face of acrylate 52 is confirmed, suggesting the participation of an s-cis conformation of the acrylate in the transition state leading to 53. Nitrile oxide cycloadditions using bornyl crotonates 54 are also known,[75] where formation of two regioisomeric 2-isoxazolines is possible. When the borneol skeleton bears a sterically bulky 1-naphthyl group (R = 1-Nap), 2-isoxazoline-5-carboxylate 55 is produced as major diastereomer with a satisfactory level of diastereoselectivity (80% de). However, 55 is the minor regioisomer (28% yield), and the degree of diastereoselectivity of the major regioisomer, the 2-isoxazoline-4-carboxylate type, is disappointingly low (63% yield, 5% de).

An excellent diastereoselectivity as high as 90% de has been achieved[77] in the cycloadditions employing Oppolzer's chiral sultam 56. Major diastereomers 57 (R = Ph, t-Bu: 90% de; R = Me, Et: 80% de) have 5R stereochemistry, similar to the above cases. Conformation model 56 is proposed to explain the stereochemical outcome. s-trans Conformation with respect to N-CO bond is due to the unfavorable dipole-dipole interaction working between S-O and C=O; again s-cis conformation of the acrylate part is involved. Reason for the top attack of nitrile oxides remains unsolved.

In the course of synthetic work of 2-deoxy-D-ribose 36, the diastereoselectivity in

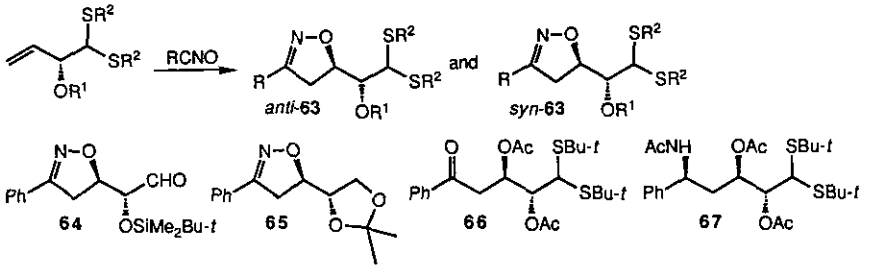
the intermolecular cycloadditions of nitrile oxides has been investigated.[62] A satisactory level of diastereoselectivity (80:20) is achieved in cycloaddition of (ethoxycarbonyl)carbonitrile oxide with (S)-(+)-isopropylidene-3-butene-1,2-diol 58 producing anti-2-isoxazoline 59 as major diastereomer (Eq. 16). An approach model 60 has been proposed, in which the anti-directing effect of an allyl oxygen, called "anti-periplanar effect", is operating.

EQUATION 16



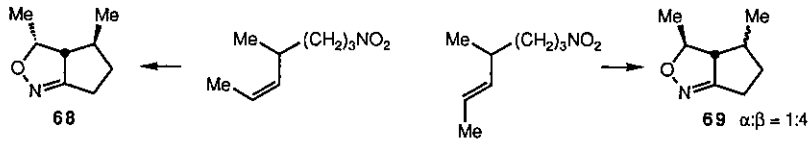
Nitrile oxide cycloadditions of α-oxyallylsilanes have been studied where the direction and magnitude of asymmetric induction depend upon the allylic oxygen substituent: A free hydroxyl provides a modest excess of the syn diastereomer syn-61; a silyl ether shows good selectivity for the anti diastereomer anti-61.[79] The maximum diastereoselectivity, achieved when R is t-butyldimethylsilyl, is 88% de for anti-61 in the reaction with benzonitrile oxide. The major product anti-61 is predicted to arise from transition state 62 which places the largest silyl group anti ("a"), the medium oxy group inside ("i"), and the smallest hydrogen outside ("o").

EQUATION 17

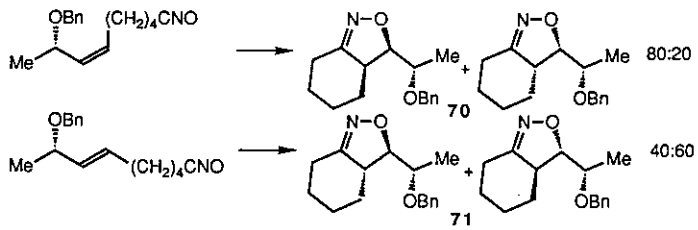


High diastereoselectivity has been achieved recently in the nitrile oxide cycloadditions with (R)-2-silyloxy-3-butenal dithioacetals, anti isomers anti-63 being favored again (Eq. 17). The magnitude of selectivity for anti-63 is as high as 96% de when the dithioacetal group is bulky (R^2 = $SiMe_2Bu$-t),[80] and does not differ by the size of nitrile oxides. Stereoselective elaboration of several polyfunctional compounds 64-67 as optically pure forms is demonstrated.

Effect of an inside allylic asymmetric center on the course of the intramolecular nitrile oxide cycloaddition reactions has been studied.[81] Both E- and Z-isomers of 4-methyl-7-nitro-2-heptene are the model substrates employed. Cycloaddition of the Z-isomer exclusively leads to 3,4-trans cycloadduct 68, while only a significant level of diastereoselectivity is achieved from the E-isomer (69: $\beta:\alpha$ = 4:1). These results are explained in terms of $A^{1,3}$ strain present in the transition state for cycloaddition.



Effect of an outside allylic asymmetric center on the diastereoselectivity of intramolecular nitrile oxide cycloadditions is also known. Cycloadditios of each three Z- and E-chiral allyl ethers occur with poor to good diastereoselectivity, up to 72% de, which depends upon the double bond configuration as well as on steric and stereoelectronic effects.[82] Higher selectivity for anti-cycloadducts is achieved from the Z-allyl ethers. For example, the 80:20 ratio of anti-70 and syn-70 results from the Z-allyl ether, while the 40:60 ratio of anti-71 and syn-71 from the E-isomer.



5. Concluding Remarks

The present concise review has focussed on the recent advances in synthetic applications of the nitrile oxide cycloaddition methodology. Cycloadditions of functionalized nitrile oxides with functionalized olefinic dipolarophiles lead to 2-isoxazolines bearing numerous functional groups, and it is important that 2-isoxazoline ring itself corresponds to a wide variety of functional groups of the masked (or protected) types. Unmasking is carried out under some specified conditions under which most of functional groups survive. Combination of these functionalities would be especially useful for elaborating polyfunctionalized complex molecules. Establishment of an effective method to construct optically pure 2-isoxazoline rings is a theme of great urgency, and also more nitrile oxides with functional groups, or protected forms, are required. The authors strongly wish that the readers will notice the importance of this field of chemistry from the standpoint of organic synthesis, and that they would employ this methodology effectively in their synthetic projects.

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