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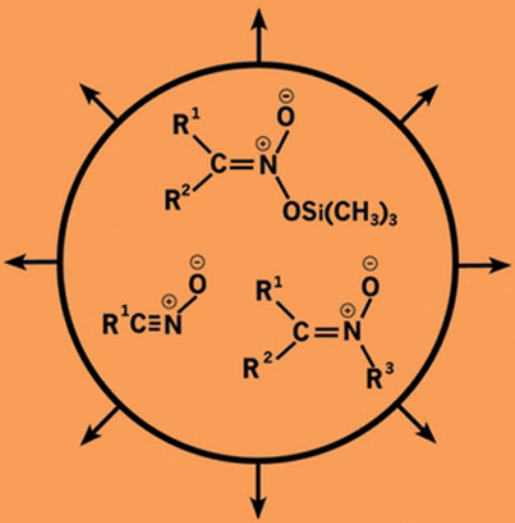
Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis

Novel Strategies in Synthesis

Second Edition



Edited by

HENRY FEUER

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Library of Congress Cataloging-in-Publication Data:

Nitrile oxides, nitrones & nitronates in organic synthesis : novel strategies in synthesis.—2nd ed. / edited by Henry Feuer.
p. cm.
Includes index.
ISBN 978-0-471-74498-6 (cloth)
1. Nitrogen oxides. 2. Organic compounds—Synthesis. I. Torssell, Kurt, 1926–. Nitrile oxides, nitrones and nitronates in organic synthesis. II. Feuer, Henry, 1912–
III. Title: Nitrile oxides, nitrones and nitronates in organic synthesis.
QD305.N8N53 2007
547′.2—dc22

2007024688

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

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SERIES FOREWORD

The beginning of aliphatic nitro chemistry goes back to 1872 when V. Meyer and O. Stueber achieved the synthesis of 1-nitropentane by reacting 1-iodopentane with silver nitrite. This report led to an impetus of research in the field, resulting in numerous publications.

Another important development in the field was the discovery of the vapor-phase nitration in the 1930s by H. Hass and his students at Purdue University. It led in 1940 to the commercial production of lower molecular weight nitroalkanes [C1 to C4] at a pilot plant of the Commercial Solvents Corporation in Peoria, Illinois. In the organic nitro chemistry era of the fifties and early sixties, a great emphasis of the research was directed towards the synthesis of new compounds that would be useful as potential ingredients in explosives and propellants.

In recent years, the emphasis of research has been directed more and more toward utilizing nitro compounds as reactive intermediates in organic synthesis. The activating effect of the nitro group is exploited in carrying out many organic reactions, and its facile transformation into various functional groups has broadened the importance of nitro compounds in the synthesis of complex molecules.

It is the purpose of the series to review the field of organic nitro chemistry in its broadest sense by including structurally related classes of compounds such as nitroamines, nitrates, nitrones and nitrile oxides. It is intended that the contributors, who are active investigators in various facets of the field, will provide a concise presentation of recent advances that have generated a renaissance in nitro chemistry research.

In this multi-authored volume are presented the important topics of nitronates, nitrones and nitrile oxides. Their significance in synthesis as starting materials and as reactive intermediates has grown considerably since 1988 in which year Dr. Torssell's monograph was published by Wiley-VCH.

Henry Feuer
Purdue University

LIST OF ABBREVIATIONS

AIBN	2,2'-azo-bis-iso-butyronitrile
AN	aliphatic nitro
AR	aminyl radical
ASIS	aromatic solvent induced shift
BIGN	*N*-benzyl-2,3-o-isopropylidene-D-glyceraldehyde nitrone
BINOL	2,2'-dihydroxy-1,1'-binaphthyl
Boc	*tert*-butyldimethylsilyl
BOX	bisoxazoline
BSTFA	N,O-bis(trimethylsilyl)trifluoroacetamide
CAN	cerium ammonium nitrate
Cbz	carbobenzyloxy
CIPE	complex Induced Proximity Effect
CRP	controlled radical polymerization
CVA	cyclic voltammogram
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DFT	density functional theory
DIBALH	diisobutylaluminium hydride
DIPT	diisopropyl (*R,R*)-tartrate
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DMD	dimethyldioxiran
DMF	dimethylformamide
DMPO	5,5-dimethylpyrroline *N*-oxide
DMSO	dimethylsufoxide
EDTA	ethylenediaminetetraacetic acid
EO	electrochemical oxidation
EPR	electron paramagnetic resonance
ES	embryonic stem
ESR	electron spin resonance
EWG	electron-withdrawing groups
FAB	fast atom bombardment
FMO	frontier molecular orbital
Fmoc	*N*-fluorenylmethoxycarbonyl
FSPE	fluorous solid phase extraction
HFI	hyperfine interaction
HIV	human immunodeficiency virus
HMDN	α-(2-hydroxy-4-methacryloyloxyphenyl)(2,6-dimethylphenyl)nitrone

HMPA	hexamethylphosphoramide
HMPN	α-(2-hydroxy-4-methacryloyloxyphenyl)-*N*-phenylnitrone
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
INAC	intramolecular nitrone-alkene cycloaddition
INEPT	insensitive nuclei enhanced by polarization transfer
INOC	intramolecular nitrile oxide cycloaddition
INR	iminonitroxyl radical
LA	Lewis acids
LDA	lithium diisopropylamine
LUMO	lowest unoccupied molecular orbital
MAD	methyl acetylenedicarboxylate
m-CPBA	*meta*-chloroperbenzoic acid
MEM	methoxyethoxymethyl
MIP	2-methoxyisopropyl
MMA	methyl methacrylate
MOMO	methoxymethoxy
Ms	mesyl
MTO	methyltrioxorhenium
MWD	molecular-weight distribution
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NDMA	*N*-methyl-D-aspartic acid
NIS	*N*-iodosuccinimide
NMO	methylmorpholine *N*-oxide
NMP	nitroxide-mediated polymerization
NMR	nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
NR	nitroxyl radical
OLED	organic light emitting diode
Oxone	potassium peroxymonosulfate
PBN	α-phenyl-*N*-*tert*-butylnitrone
PCWP	peroxotungstophosphate
PDC	pyridinium dichromate
PDT	photodynamic therapy
PEDC	1-phenyl-2-[(S)-1-aminoethyl]-*N,N*-diethylcyclopropanecarboxamide
PEG	polyethylene glycol
PET	photosensitive electron transfer
PMIO	1,2,2,5,5-pentamethyl-3-imidazoline-3-oxide
PPAR	peroxisome proliferator-activated receptor
PPC	polyperoxo complex
PSPO	2-phenylsulfonyl-3-phenyloxaziridine
PTK	protein tyrosine kinase
QSAR	quantitative structure-activity relationship
RA	radical anion

RC	radical cation
SA	spin adduct
SENA	silyl esters of nitronic acid
SET	single electron transfer
SMEAH	sodium bis(2-methoxyethoxy)aluminium hydride
ST	spin trap
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium triphenyldifluorosiliconate
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TMEDA	tetramethylethylenediamine
TMINO	isoindoline nitrone 1,1,3-trimethylisoindole *N*-oxide
TMIO	isoindoline nitroxide 1,1,3,3-tetramethylisoindolin-2-yloxy
TMPO	2,2,5,5-tetramethylpyrroline *N*-oxide
TMS	trimethylsilyl
TMSOTf	trimethylsilyltriflate
TOX	trioxazoline
TPAP	tetrapropylammonium perruthenate
TPS	*tert*-butyldiphenylsilyl
UHP	urea hydrogen peroxide

1 Nitrile Oxides

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The chemistry of nitrile oxides is well documented. Several important monographs either specially devoted to nitrile oxides or including corresponding comprehensive chapters should be mentioned (1–5). Several reviews appeared (6–8), which concern preparation, reactivity, and synthetic applications of nitrile oxides. Some books and reviews devoted to individual aspects of nitrile oxide chemistry will be cited elsewhere.

The topics of the present presentation is closest to that of the monograph written by Torssell (4). Therefore, the aim of this chapter is to update the information concerning nitrile oxides published after the monograph (4). The literature was followed by *Chemical Abstracts* database (1988–2001) and indices from Vol. 136 (2002) till Vol. 144 (2006). As to the period 1988–2002, references will be given practically only to data omitted in Reference 5.

1.1. PHYSICOCHEMICAL PROPERTIES

Nitrile oxides, RNCO, are derivatives of fulminic acid (R = H). They can be named as *fulmido-substituted parent molecules*, but usually their names are derived from corresponding nitriles, for example, benzonitrile oxide, mesitonitrile oxide, thiophene-2-carbonitrile oxide.

Specific properties of nitrile oxides depend on the structure of the functional group, which have highly polarized C–N and N–O bonds (Scheme 1.1).

Most nitrile oxides are unstable, some of them are explosive. This fact hinders the study of their physical properties. Nevertheless, there are a number of publications concerning not only stable but also unstable nitrile oxides. In particular, mass spectral data for nitrile oxides among other unstable compounds containing an $N^+–X^-$ bond are summarized in a review (9). In such studies, the molecular ions must be generated using indirect procedures, including dissociative electron ionization, online flash-vacuum pyrolysis mass spectrometry, or ion-molecular reactions. Their characterization is mainly based on collisional activation and ion-molecular reactions.

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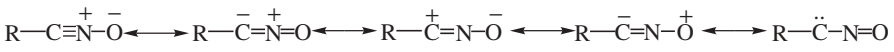


Scheme 1.1

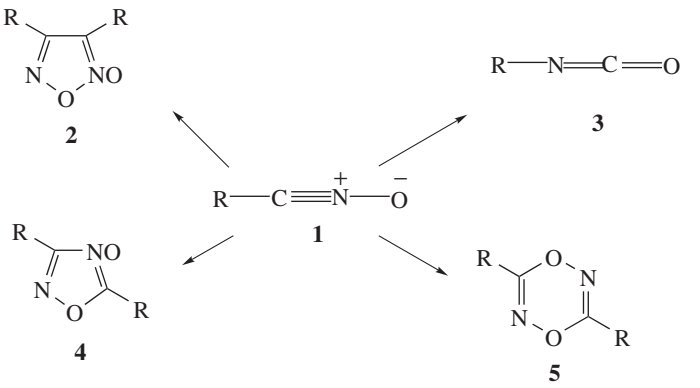
Unstable nitrile oxides XCNO, X = ONC, NC, Cl, Br, and Me, were generated and studied in the gas phase by He I photoelectron spectra (10) and by other methods, such as low resolution mid-IR, high-resolution IR, and microwave spectroscopy (11, 12). In particular, the unstable BrCNO molecule and its stable dibromofuroxan dimer were generated in the gas phase and studied by He I photoelectron, mid-IR, photoionization mass spectra as well as by *ab initio* calculations (13). Gas-phase IR and *ab initio* investigation were performed for the unstable CF_3CNO molecule and corresponding stable furoxan (14). Cyano- and isocyanofulminates were studied by *ab initio* calculations at the MP2/6−31G* level (15). It should also be noted that the electronic structure of fulminic acid was studied experimentally, using He I photoelectron and two-dimensional Penning ionization electron spectroscopies (16).

Thermochemical parameters of some unstable nitrile oxides were evaluated using corresponding data for stable molecules. Thus, for 2,4,6-trimethylbenzonitrile N-oxide and 2,4,6-trimethoxybenzonitrile N-oxide, the standard molar enthalpies of combustion and sublimation at 298.15 K were measured by static-bomb calorimetry and by microcalorimetry, respectively, this made it possible to derive the molar dissociation enthalpies of the N−O bonds, D(N−O) (17).

On the basis of published data for enthalpies of formation, sublimation, and vaporization, the dissociation enthalpies of terminal N−O bonds, DH°(N−O), in various organic compounds including nitrile oxides, were calculated and critically evaluated (18). The derived DH°(N−O) values can be used to estimate enthalpies of formation of other molecules, in particular nitrile oxides. N−O Bond energy in alkyl nitrile oxides was evaluated using known and new data concerning kinetics of recyclization of dimethylfurazan and dimethylfuroxan (19).

Evidently, stable nitrile oxides can be investigated by spectral and X-ray methods using ordinary procedures. As examples, X-ray diffraction studies of *o*-sulfamoylbenzonitrile oxides (20), 5-methyl-2-(methylsulfonyl)-3-thiophenecarbonitrile oxide (21), β,β-diphenylacrylonitrile oxide (22), and (dimorpholinophosphoryl) carbonitrile oxide (23) can be cited. It should be underlined that structures of the latter compounds differ from those of classical stable *o,o'*-disubstituted arylcarbonitrile oxides and *tert*-alkylcarbonitrile oxides. Therefore, not only purely steric shielding of the CNO group but also electrostatic or donor−acceptor interactions between the atoms of the latter and adjacent polar substituents (21, 23) and also electron delocalization in π-systems (20, 22) enhance the stability of nitrile oxide.

Main routes of chemical transformations of nitrile oxides **1** in the absence of other reagents with multiple bonds have been well generalized in Reference 4 and are presented in Scheme 1.2.



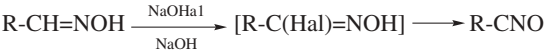
Scheme 1.2

These routes are dimerization to furoxans **2** proceeding at ambient and lower temperatures for all nitrile oxides excluding those, in which the fulmido group is sterically shielded, isomerization to isocyanates **3**, which proceeds at elevated temperature, is practically the only reaction of sterically stabilized nitrile oxides. Dimerizations to 1,2,4-oxadiazole 4-oxides **4** in the presence of trimethylamine (4) or BF_3 (**1**:$BF_3 = 2{:}1$) (24) and to 1,4,2,5-dioxadiazines **5** in excess BF_3 (1, 24) or in the presence of pyridine (4) are of lesser importance. Strong reactivity of nitrile oxides is based mainly on their ability to add nucleophiles and particularly enter 1,3-dipolar cycloaddition reactions with various dipolarophiles (see Sections 1.3 and 1.4).

1.2. METHODS FOR GENERATION AND PREPARATION OF NITRILE OXIDES

In this section, *generation* means formation, usually succeeded by *in situ* transformation of an unstable nitrile oxide, while *preparation* relates to stable nitrile oxides, which can be isolated and stored for a long time. A review including data on formation of nitrile oxides was published recently (25).

It is quite natural to consider that nitrile oxides could be generated or prepared from fulminic acid or fulminates. However, until recently, only one example of such a reaction is known, namely *the formation of stable triphenylacetonitrile oxide* from trityl chloride and silver fulminate. Other attempts to generate nitrile oxides from organic halides and metal fulminates gave the corresponding isocyanates (1, 4). In 1982, a successful synthesis of trimethylsilanecarbonitrile oxide from trimethylsilyl bromide and Hg(II) fulminate was reported (26). This nitrile oxide possesses all of the characteristic properties of nitrile oxides and, moreover, its use is equivalent to that of fulminic acid, owing to the hydrolytic cleavage of the Si–C bond. In addition the conditions were elaborated, which



Hal = Cl, Br

Scheme 1.3

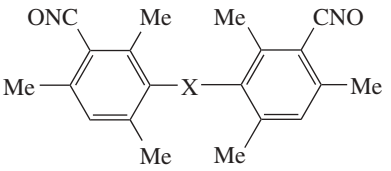
allowed one to hydrolyse the mentioned organosilicon nitrile oxide (27) and to introduce fulminic acid generated in some reactions (28). Nevertheless, because of the explosive nature of metal fulminates, their synthetic use is very limited and no data on their application for generation or formation of nitrile oxides were found in the literature published through the last 20 years.

1.2.1. Formation from Aldoximes

The transformation of aldoximes to nitrile oxides is essentially a dehydrogenation process.

Different procedures of this dehydrogenation are thoroughly discussed in the monograph (4). It is only necessary to note here that the process is carried out mainly as halogenation–dehydrohalogenation. The intermediate hydroximoyl halide is frequently not isolated (Scheme 1.3). The reaction is convenient for both the generation of unstable nitrile oxides (in the presence of a dipolarophile) and the preparation of stable nitrile oxides. It is usually carried out in a two-phase water–organic solvent system with methylene dichloride as the preferred solvent.

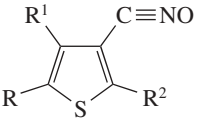
The latter procedure was used in syntheses of stable nitrile oxides such as β,β-diphenylacrylonitrile oxide and 2,6-diphenylbenzonitrile oxide (22), a series of functionally substituted 2,6-dimethylbenzonitrile oxides (29), as well as 2,4,6-triethylbenzene-1,3-dicarbonitrile oxide (29), stable bis(nitrile oxides) of a novel structure **6**, in which two benzene rings, bearing hindered fulmido groups are connected with a bridge (30), tetrachloroisophthalo- and terephthalonitrile oxides (31). Stable *o*-sulfamoylbenzonitrile oxides with only one shielding substituent were also prepared using NaOCl/NaOH in a two-phase system (20, 32).



6

X = $(CH_2)_n$, where n = 0, 1, 2, 6; S; C=CH_2; C=CHEt

Stable 2,4-disubstituted thiophene-3-carbonitrile oxides **7** and 3,5-di(*t*-butyl)-thiophene-2-carbonitrile oxide **8** were synthesized from respective aldoximes by the similar one-pot procedure (33–35).



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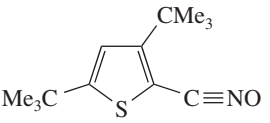


8

$R = R^2 = Me$, $R^1 = H$, Alk;
$R = H$, Me, MeO, $MeSO_2$, $R^2 = H$, Br, $R^1 = SMe$, SO_2Me, OMe

The above-mentioned procedure and some of its modifications were also used for the generation of various unstable nitrile oxides. In this section, only those reactions in which nitrile oxides were isolated or identified by physical methods will be discussed in detail. References will be given only if nitrile oxides are transformed *in situ* to other products.

Thus, the bromoformonitrile oxide BrCNO was generated in the gas phase from dibromoformaldoxime by pyrolysis or by a chemical reaction with HgO(s) or NH_3(g) (13). Polyfluoroalkanecarbonitrile oxides were generated from the respective hydroximoyl bromides and triethyl amine (36). Generation of ethoxycarbonylformonitrile oxide from ethyl chloro(hydroxyimino)acetate in the ionic liquids (1-butyl-3-methyl-1*H*-imidazolium tetrafluoroborate or hexafluorophosphate) and its *in situ* reaction with ethyl acrylate gave 4,5-dihydro-3,5-isoxazoledicarboxylic acid diethyl ester (37). Recently, a procedure was used for the generation of nitrile oxides from aldoximes, in water or in aqueous tetrahydrofuran (THF), and subsequent *in situ* transformations by intra- or intermolecular 1,3-cycloaddition reactions. This simple though prolonged (18–72h) procedure gives practically quantitative yields (38).

Hydroximoyl halides can be readily prepared by halogenation of oximes using various reagents. As one of rather new reagents, the hydrogen chloride/N, N-dimethylformamide/ozone system (39) was used for the preparation of different hydroximoyl chlorides RCCl=NOH (R = Ar, 5-nitro-2-furyl, PhCO, *t*-Bu) as precursors of nitrile oxides. However, most useful for both two-step and one-step (usually in the presence of Et_3N) procedures are N-bromo- (40, 41) and N-chlorosuccinimides (42–44). Other N-halogen-substituted compounds such as chloramine-T (45), trichloroisocyanuric acid (46), and N-(*t*-butyl)-N-chlorocyanamide (47) were also used for the oxidative dehydrogenation of aldoximes.

Dehydrochlorination of hydroximic acid chlorides for generation of nitrile oxides can also be performed using organotin compounds such as $(SnBu_3)_2O$ or $SnPh_4$ (48, 49). The reaction proceeds under mild conditions, O-stannylated aldoximes like $RCH{=}NOSnBu_3$ being thought to be key intermediates.

Thermal dehydrochlorination of hydroximoyl chlorides affords nitrile oxides (50–52). O-Ethoxycarbonylbenzohydroximoyl chloride, generating benzonitrile oxide, was used as a stable nitrile oxide precursor, which was efficiently used in 1,3-cycloaddition reactions with alkenes (53).

Direct oxidation of oximes is prospective promising procedure for the generation of nitrile oxides. Mercury(II) acetate (54), dimethyldioxirane (55), ceric

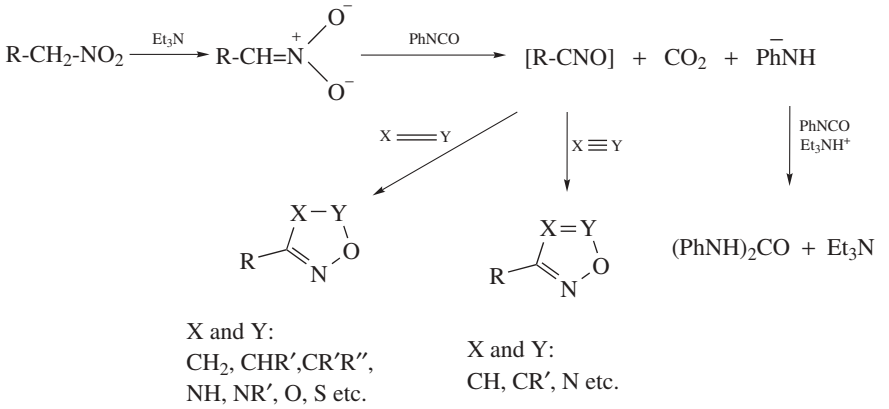
ammonium nitrate (56), and hypervalent iodine compounds, such as iodobenzene dichloride (57), iodosylbenzene (58), diacetoxy iodobenzene (59) were used as oxidants. Manganese(IV) oxide was also found to oxidize aldoximes to nitrile oxides, the best results being obtained with hydroximinoacetates as nitrile oxide precursors (60).

1.2.2. Formation from Aliphatic Nitro Compounds

Generation of nitrile oxides by the Mukaiyama procedure, *viz*., dehydration of primary nitroalkanes with an aryl isocyanate, usually in the presence of Et_3N as a base, is of high importance in nitrile oxide chemistry. Besides comprehensive monographs (4, 5), some data concerning the procedure and its use in organic synthesis can be found in References 61 and 62.

Dehydration of primary nitroalkanes results in unstable nitrile oxides and, therefore, is limited by *in situ* transformation of the latter, for the preparation of various stable products, mainly those of 1,3-dipolar cycloaddition (Scheme 1.4).

As an example of the "classic" Mukaiyama procedure, one might mention cycloaddition of nitrile oxides, generated by reaction of primary nitroalkanes with *p*-chlorophenylisocyanate in the presence of a catalytic amount of Et_3N, to diethyl vinylphosphonate or diethyl propargylphosphonate affording the corresponding 2-isoxazolines or isoxazole, bearing the phosphonate group, in good yields (63). Many reagents, other than arylisocyanates, have been tested for the dehydration of nitroalkanes, among them $POCl_3$, AcCl, Ac_2O, BzCl, and $MeSO_2Cl$ (64). A rather "exotic" *p*-toluenesulfonyl chloride – K_2CO_3 – 18-crown-6 system was used in the synthesis of annulated Δ^2-isoxazolines starting from primary nitroalkanes (including functionalized ones) and cyclopentenes (65). There was also reported (66) the successful generation of nitrile oxides from primary nitro compounds by using thionyl chloride and triethylamine. Generation of nitrile oxides from nitromethyl ketones by the action of Ce(III) or Ce(IV) ammonium



Scheme 1.4

nitrates in the presence of formic acid has been described (67). Formation of nitrile oxides was also reported for the action of Mn(III) acetate on nitroacetate esters (68) and for the reaction of phosphorus trichloride with nitronate anion generated from β-nitrostyrene (69).

Nitrile oxides can be generated not only from primary but also from some functionalized secondary nitroalkanes. Thus, ethyl 2-nitroacetoacetate readily eliminates the acetic acid moiety using a $AcOH-Ac_2O$ mixture in the presence of a catalytic amount of strong mineral acid, for example, H_2SO_4, at room temperature to give ethoxycarbonylformonitrile oxide (70). Aroylformonitrile oxides were generated in a nitrating mixture from 1,3-diketones such as 1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1,3-butanedione and its 4,4-difluoro and 4,4,4-trifluorosubstituted derivatives (71).

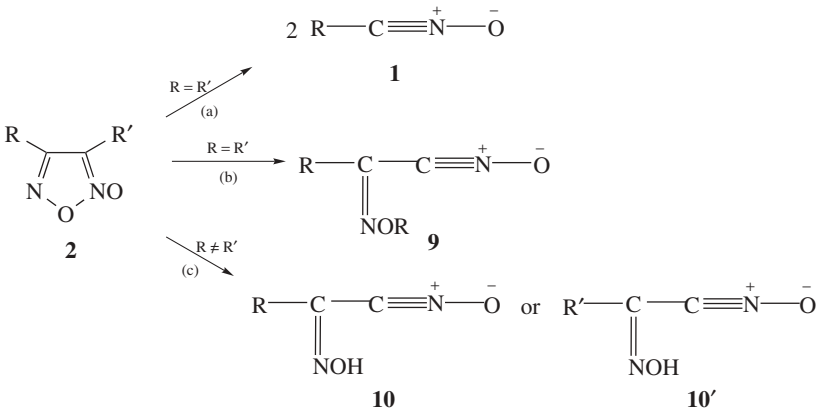
Generation of nitrile oxides can also proceed by the action of "neutral" or basic reagents, for example, *tert*-butyl carbonate (72) or 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride, both in the presence of a catalytic amount of 4-(dimethylamino)pyridine (73), the latter with microwave activation. Some primary nitro compounds, are activated by electron-withdrawing substituents in a vicinal position such as in acetylnitromethane, benzoylnitromethane, ethyl nitroacetate, and nitro(phenylsulfonyl)methane generate nitrile oxides by the action of tertiary amines, preferably, 1,4-diazabicyclo[2.2.2]octane (DABCO) (74).

Highly efficient modifications of Mukaiyama's procedure, convenient for combinatorial syntheses, were reported recently, namely *the polymer-supported synthesis of isoxazolines via* nitrile oxides, starting from primary nitroalkanes, in a one-pot process (75) and by microwave activation of the process (73).

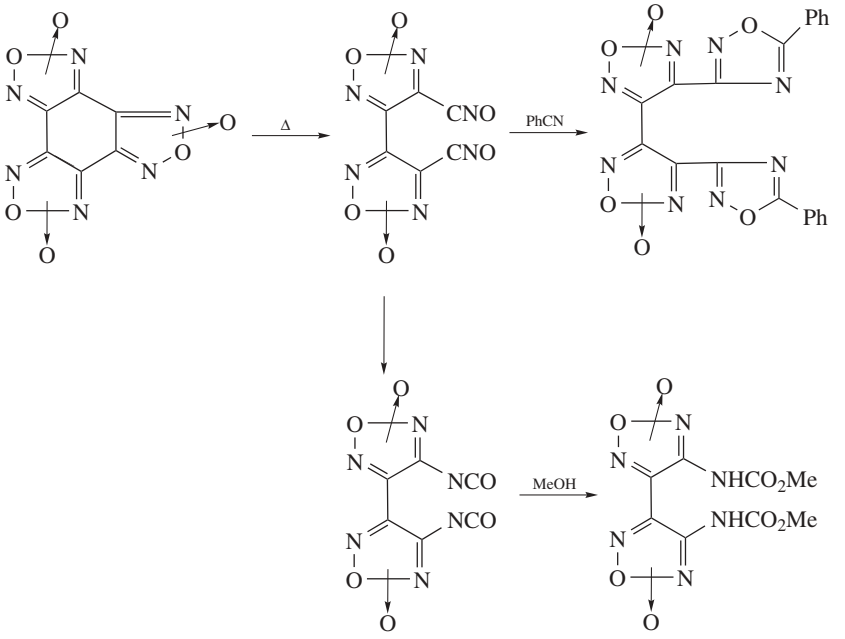
1.2.3. Formation by Cycloreversion

Dimerization of nitrile oxides to furoxans (Scheme 1.2) becomes reversible at elevated temperatures, by photolysis or electron impact, the first two methods being used in synthesis. The data concerning vacuum pyrolysis and photolysis of furoxans summarized in (76) are of great interest. Both formation of furoxans and their thermolytic transformation to nitrile oxides are comprehensively presented in a two-volume monograph (77, 78) and in a review (79). Three modes of the cycloreversion, depending on the nature of substituents in the furoxan molecule (5) are shown in Scheme 1.5. The cycloreversion of furoxan **2** to form two nitrile oxides **1** molecules [route (a)] is of main interest. Rearrangement [route (b)], which occurs mainly in diacylfuroxans affording α-acyloximinonitrile oxides **9** as well as fragmentation [route (c)] leading to a mixture of α-hydroximinonitrile oxides **10** and **10′** are of limited interest.

Stable furoxans are convenient starting compounds for generating short-lived nitrile oxides XCNO (X = ONC, NC, Cl, Br, and Me) by thermolysis (10, 11, 80, 81). The thermolysis of benzotrifuroxan (200°, in excess PhCN) proceeds (Scheme 1.6) with the cleavage of the C–C and O–N(O) bonds in only one furoxan ring to give bifuroxan bis(nitrile oxide). The latter undergoes further reactions such as cycloaddition with PhCN or conversion to bisisocyanate (82).

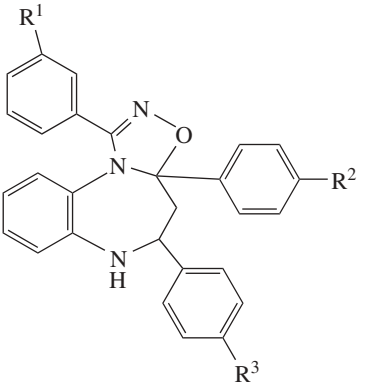


Scheme 1.5



Scheme 1.6

Cycloreversion with nitrile oxide formation is known not only in furoxans but also in isoxazolines, 1,2,4-oxadiazoles, furazans, and some other five-membered heterocycles (76). Such process, eliminating nitrile oxide fragment 3-$R^1C_6H_4C{\equiv}N^+O^-$, was observed mass spectrometrically in 3a,4,5,6-tetrahydro-[1,2,4]oxadiazolo[4,5-*a*][1,5]benzodiazepine derivatives **11** (83).



11

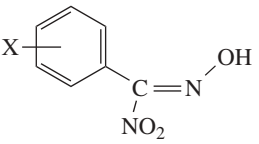
(R^1 = H, Br; R^2= H, OMe; R^3 = H, OMe)

1.2.4. Other Methods

The methods considered in this section concern mainly reactions of nitro compounds.

The reaction of dinitrogen tetroxide with substituted dinitromethane salts $RC(NO_2)=NO_2K$ [R = Ph, 3-$O_2NC_6H_4$, 3,5-$(O_2N)_2C_6H_3$, 4-MeO-3,5-$(O_2N)_2C_6H_2$, EtO_2C, Me, MeO_2C] was carried out in the generation of nitrile oxides RCNO (84, 85). Using ^1H, ^{13}C and ^{14}N nuclear magnetic resonance (NMR) spectroscopy, it was shown that this reaction proceeds through dinitronitrosomethyl intermediates, of which one was isolated. The reaction occurs only when substituents capable of conjugation with the nitrile oxide fragment are present.

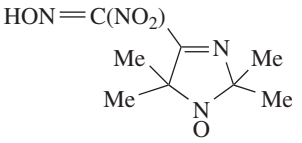
Z-Acetonitrolic acid rapidly loses NO_2^- to form unstable acetonitrile oxide, which could be detected by monitoring its subsequent reactions (86). Arylnitrolic acids **12** (X = *p*-Cl, *m*-NO_2, *o*-NO_2) exist in the *E*-configuration and undergo slow loss of NO_2^- to give nitrile oxides. Subsequently it was shown (87) that nitrolic acids are converted to nitrile oxides in practically quantitative yields under neutral conditions (heating in THF).



12

(X = *p*-Cl, *m*-NO_2, *o*-NO_2)

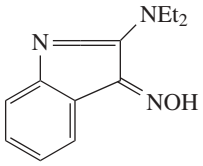
Thermolysis of a stable radical 4-[(hydroxyimino)nitromethyl]-2,2,5,5-tetramethyl-3-imidazolin-1-oxyl **13** gives the corresponding spin-labeled nitrile oxide. It was also identified in isoxazolines formed in cycloadditions with olefins (88).



13

Nitrile oxides are generated by photolysis of 1,2-diaryl-substituted nitroethylenes through the formation of an oxazetine 2-oxide and its fragmentation (Scheme 1.7) (89).

Nitro(imidoyl)ketene $PhN{=}C(NEt_2)C(NO_2){=}CO$ eliminates CO_2 on heating and rearranges to 2-diethylamino-3-hydroximino-3*H*-indole **14**, presumably via nitrile oxide $PhN{=}C(NEt_2)C{-}N^+O^-$ (90).

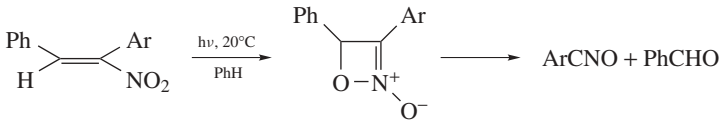


14

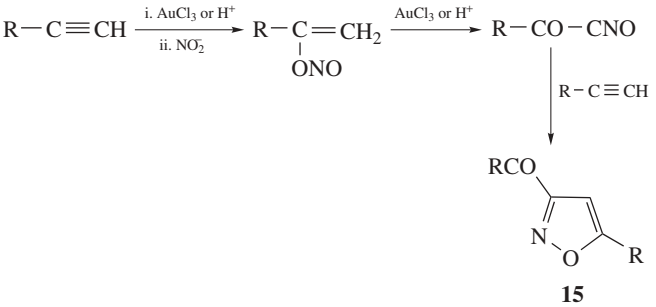
In alkali solutions, 5-nitro-2-furaldehyde forms an anion of (5-nitrofuran-2-yl)methanediol, which undergoes an irreversible redox ring-opening reaction to give mono(nitrile oxide) of α-ketoglutaconic acid $HO_2CCOCH{=}CH{-}CNO$,° the latter was identified as furoxan (91).

Very interesting transformations were reported in terminal alkynes $RC{\equiv}CH$ (R = alkyl, aryl, alkoxy, carboxylate, etc.). They react readily with nitric acid, in aqueous nitromethane (1:1) and in the presence of catalytic amounts of tetrabutylammonium tetrachloroaurate to give 3,5-disubstituted isoxazoles **15** in 35% to 50% isolable yield (92). The reaction might proceed via a nitrile oxide intermediate by attack of an electrophile ($AuCl_3$ or H^+) and of a nucleophile (NO_2^-) on the triple bond to form a vinyl nitrite, which is converted to a nitrile oxide by the action of gold(III) or of nitric acid (Scheme 1.8).

Intermediate formation of nitrile oxides is, also proposed in reactions of nitroacetylene with furan and vinyl ethers (Scheme 1.9) (93) and of lithium (phenyl)acetylide with N_2O_4 (94).



Scheme 1.7



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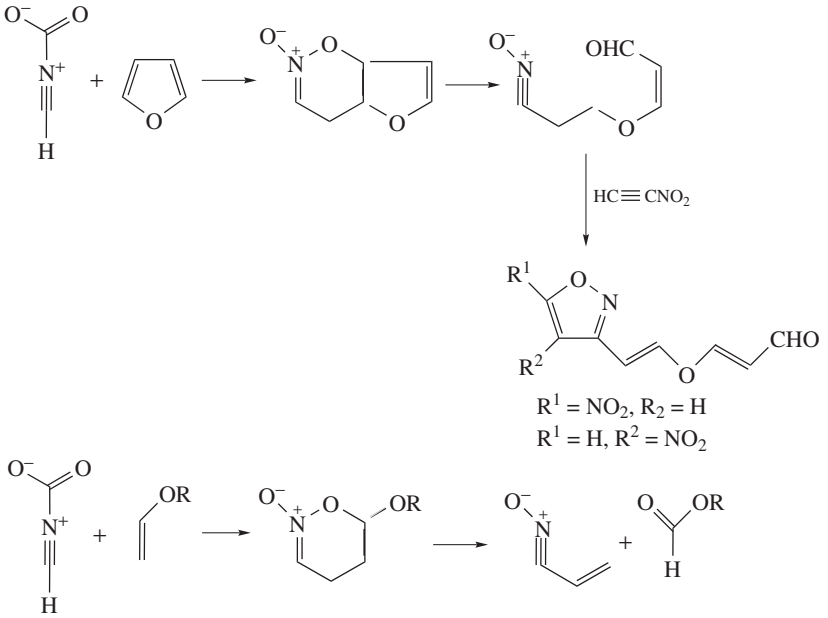
Scheme 1.8



Scheme 1.9

Dehydration of O-silylated hydroxamic acids is used as a general method in the synthesis of nitrile oxides (95) in the presence of trifluoromethanesulfonic anhydride and triethylamine.

Methoxycarbonylformonitrile oxide is smoothly generated by β-elimination of methanol from *E*-N-methoxy-N-(methoxycarbonylmethylene)amine N-oxide, $MeO_2CCH{=}N(OMe)O$, in the presence of a catalytic amount of boron trifluoride etherate (96).

Phosphorylated and thiophosphorylated diazo compounds, $i\text{-}Pr_2P(X)C(N_2)SiMe_3$ (X = O, S) react with nitrosyl chloride to give α-nitroso-diazo derivatives

which rapidly eliminate nitrogen to form i-$Pr_2(X)CNO$ (97). Similarly phosphorylated nitrile oxide, $R_2P(O)CNO$ (R = morpholino) was prepared by treatment of $R_2P(O)CHXCHO$ (R = morpholino; X = Cl, Br) with HNO_2 in AcOH (98).

Ammonium cerium(IV) nitrate on reaction with acetone or acetophenone generates acetyl- or benzoylformonitrile oxides, respectively (99). These nitrile oxides dimerize to furoxans and give, in the presence of alkenes and alkynes, 3-acetyl- or 3-benzoyl-4,5-dihydroisoxazoles and 3-acetyl- or 3-benzoylisoxazoles, respectively; the yield of the isoxazole derivatives was improved on using ammonium cerium(III) nitrate tetrahydrate–formic acid (99).

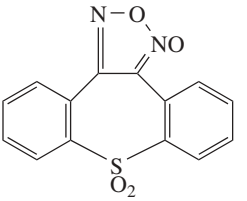
1.3. REACTIONS OF NITRILE OXIDES

Some routes of chemical transformations of nitrile oxides connected with the problem of their stability were briefly discussed in Section 1.2. Here only two types of such reactions, proceeding in the absence of other reagents, *viz*., dimerization to furoxans and isomerization to isocyanates, will be considered. All other reactions of nitrile oxides demand a second reagent (in some cases the component is present in the same molecule, and the reaction takes place intramolecularly): namely, *deoxygenation, addition of nucleophiles*, and *1,3-dipolar cycloaddition reactions*. Also, some other reactions are presented, which differ from those mentioned above.

Probably, the diversity of nitrile oxide chemistry is not conducive to writing reviews related to all aspects of their reactivity. Therefore, only several references can be mentioned, which are connected with several topics in this section. Among these are the reviews devoted to the photochemistry of N-oxides (including nitrile oxides) (100) and reactions of nitrilium betaines with heteroaromatic compounds (101). Other references on reviews will be given in corresponding subsections or paragraphs.

1.3.1. Dimerization and Isomerization

Dimerization and isomerization are conveniently considered together, since reaction routes for the same group of nitrile oxides frequently depends on reaction conditions or differences in substituent(s). Dimerization of unstable nitrile oxides proceeds during their generation, when another reaction partner is absent, while isomerizations demand, thermal or photostimulation (97). As a rule, sterically stabilized nitrile oxides do not give furoxans, and their heating leads to isomeric isocyanates. This is the case, for example, for stable bis(nitrile oxides) of the benzene series (30). However, there are stable nitrile oxides, which can dimerize. Thus, stable o-sulfonylbenzonitrile oxides undergo thermal dimerization to furoxans, (2,2′-sulfonylbis(benzonitrile oxide) on heating rearranges to tetracyclic furoxan **16**, a dibenzothiepinofurazane derivative (32). Similarly, 2-thienylphenylsulfon-3,2′-dicarbonitrile oxides give benzothienothiepinofurazan trioxides **17** (R = H, Me) at reflux in benzene (102).



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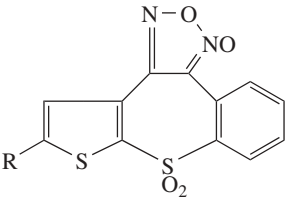
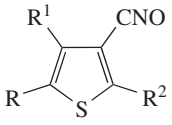


17

The stability of *o*-sulfonylbenzonitrile oxides and their thiophene analogs probably depends on electronic factors. The same factors do not prevent dimerization, as can be seen from data concerning several differently substituted nitrile oxides of the thiophene series (103). Sterically stabilized 3-thiophenecarbonitrile oxides **18** ($R = R^1 = R^2 = Me$; $R = R^2 = Me$, $R^1 = i$-Pr), when boiled in benzene or toluene, isomerized to isocyanates (isolated as ureas on reaction with aniline) while nitrile oxides **18** with electron-withdrawing substituents (R^1 and/or $R^2 = SO_2Me$, Br) dimerized to form furoxans **19**.



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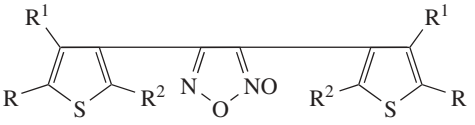
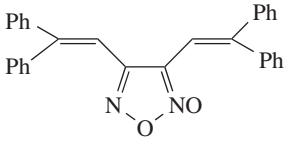


19

3,3-Diphenylacrylonitrile oxide, exhibiting unexpected stability, presumably due to delocalization, dimerized to furoxan **20** or 1,4,2,5-dioxadiazine **21** (22).



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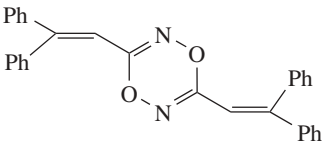
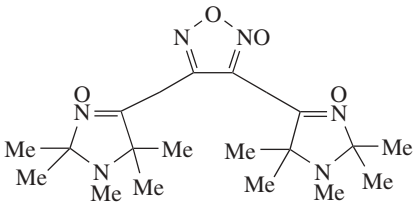


21

Diaryl- (85), diaroyl- (71), bis(4-substituted-1,2,5-oxadiazol-3-yl)furoxans (104) as well as "exotic" 1,2,2,5,5-pentamethyl-4-(nitromethyl)-3-imidazoline 3-oxide-derived furoxan **22** (105) were obtained via corresponding nitrile oxides.



22

Dimethyl furoxan-3,4-dicarboxylate was obtained from methoxycarbonylformonitrile oxide (96). Treatment of nitroacetamides $RR^1NCOCH_2NO_2$ [R, R^1 = H, Me; Me, Me; H, Ph; $RR^1 = (CH_2)_4$] with $SOCl_2$ afforded furoxan-3,4-dicarboxamides (106).

The nitrile oxide dimerization mechanism was subjected to quantum chemical investigation. Semiempirical methods MNDO for acetonitrile oxide and AM1 for dimethoxyphosphorylformonitrile oxide (107) as well as density functional theory (DFT) calculations (B3LYP/6–31G*) for acetonitrile oxide and *p*-chlorobenzonitrile oxide (108) agree that these reactions proceed in two steps. They involve dinitroso alkene intermediates, the limiting stage depending on C–C bond formation. The retardation of dimerization in aromatic nitrile oxides arises from the interruption of conjugation between the nitrile oxide and aryl groups in the C–C bond formation step (108).

There are very interesting experimental data demanding theoretical interpretations: both dimerization and cycloaddition with dipolarophiles of some aromatic nitrile oxides RCNO (R = Ph, 2-ClC_6H_4, 2,6-$Cl_2C_6H_3$) can be inhibited by a catalytic amount of $(4\text{-}BrC_6H_4)_3N^+$ $SbCl_6^-$ (109).

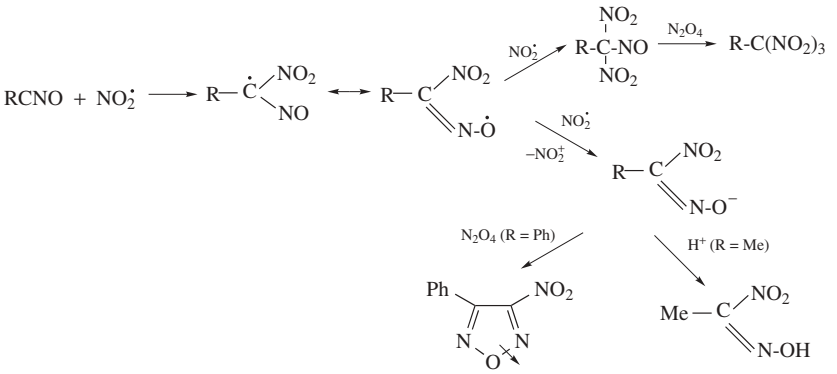
1.3.2. Deoxygenation

Deoxygenation of nitrile oxides demands a reducing agent. Amongst those, compounds of phosphorus(III) like PPh_3 (97) are useful. The reaction gives respectively, nitrile and P-oxide. Reactions of nitrile oxides with phospholes is of special interest. Phospholes undergo Diels–Alder reactions at high pressure rather than 1,3-dipolar cycloadditions with nitrile oxides but the latter are deoxygenated in the process (110).

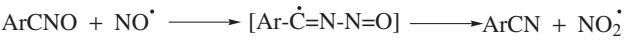
Intriguing results, concerning both deoxygenation and dimerization of nitrile oxides were obtained on investigation of reactions of the latter and of furoxannitrolic acids with nitrogen oxides (111–113). Reaction of acetonitrile oxide with N_2O_4 in CH_2Cl_2 led to the corresponding nitrolic acid MeC(:NOH)NO_2 while hydroxyiminonitrile oxide PhC(:NOH)CNO gave a mixture of 4-nitro-3-phenyl- and 3-nitro-4-phenylfuroxans (111). Under similar conditions, benzonitrile oxides RC_6H_4CNO (R = H, 3-, 4-O_2N, 4-Br) afforded aryltrinitrosomethanes $RC_6H_4C(NO)_3$ (111). A probable mechanism of the reactions, taking into account the radical nature of nitrogen dioxide (111), is presented in Scheme 1.10.

Previously unknown deoxygenation was reported with *o*-, *m*-, and *p*-nitrobenzonitrile oxides on reactions with NO (112); this was interpreted as being due to the radical nature of the latter (Scheme 1.11).

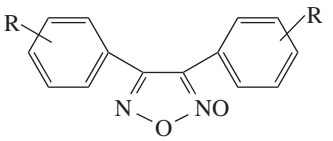
Deoxygenation by NO proceeds rather slowly, and nitrile oxides take part simultaneously in two other reactions: (a) dimerization to furoxans **23** and (b) interaction with NO_2 which is formed in the reaction, to give aryltrinitromethanes. The most unstable of the known arenecarbonitrile oxides, benzonitrile oxide, owing to its fast dimerization gives no phenyltrinitromethane but only furoxans. Products similar to both cited reactions are formed with N_2O_3 because of its known equilibrium with NO and NO_2 (112).



Scheme 1.10



Scheme 1.11

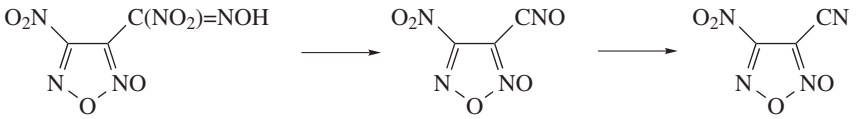


23 (R = H, 2-, 3-, 4-O_2N)

Investigation of the reaction of furoxannitrolic acids with nitrogen tetroxide (113) showed that the first step is the formation of the corresponding intermediate nitrile oxides followed by their transformations. Thus, treating nitrolic acid **24** with N_2O_4 in $CHCl_3$ resulted in furoxancarbonitrile **25** via intermediate nitrile oxide **26** (Scheme 1.12). It seems probable that nitrogen tetroxide plays the role of a reducing agent in the nitrile oxide deoxygenation.

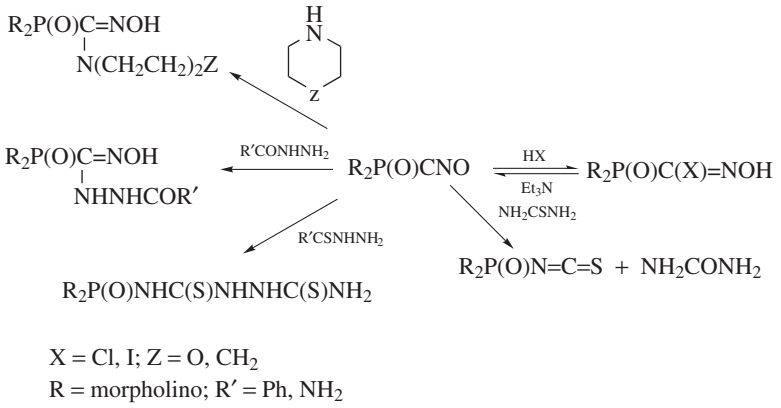
1.3.3. Addition of Nucleophiles and Further Tranformations

Nucleophiles react with nitrile oxides in a 1,3-nucleophilic addition pattern. The carbon atom of the CNO group is being attacked by the negatively polarized part



24 **26** **25**

Scheme 1.12



X = Cl, I; Z = O, CH_2
R = morpholino; R′ = Ph, NH_2

Scheme 1.13

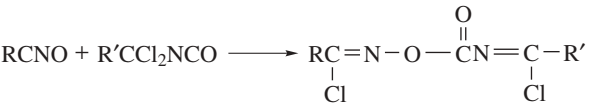
of the nucleophile (by an anion as a limiting case), while its positively polarized or charged part (proton in the simplest case) adds to the oxygen atom of the fulminate moiety. 1,3-Addition reactions proceed with halogen, N-, O-, S-, C-, and other nucleophiles. The adducts formed might undergo further transformations.

Thus, (dimorpholinophosphoryl)formonitrile oxide undergoes 1,3-addition reactions with HCl, HI, primary and secondary amines, acylhydrazines, and even with thiourea or thiosemicarbazide (Scheme 1.13) (98). The former gives (dimorpholinophosphoryl)isothiocyanate and urea. Those products might arise from a retro destruction of the unstable 1,3,5-oxathiazoline. The latter transforms to the isothiocyanate, the product of addition of a second molecule of thiosemicarbazide. (98).

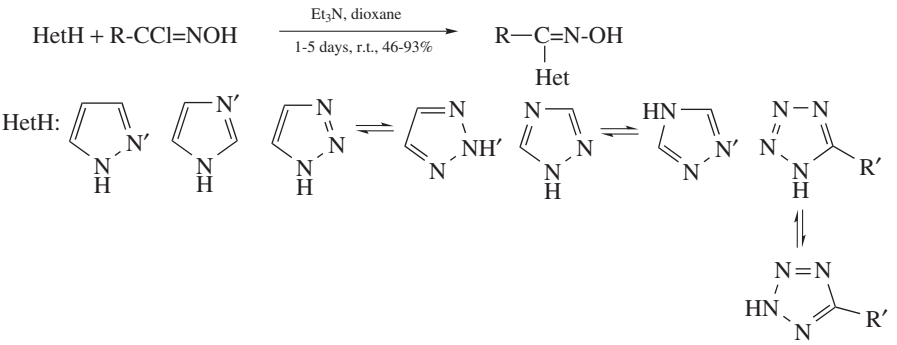
Related (diisopropoxyphosphoryl)- and (diisobutoxyphosphoryl)formonitrile oxides (114), generated in basic media from the corresponding oximes react *in situ* with alcohols, phenols, alkanethiols, thiophenols, aliphatic and aromatic primary amines, hydrazines and hydrazides as well as 4-aminoantipyryne to give hydroxymates, thiohydroxymates, and amidoximes, respectively. It is important to note that the addition is stereoselective and gives *E*-adducts with the exception of $(i\text{-PrO})_2P(O)C(:NOH)OMe$, which is formed as a 1:1 mixture of *E* and *Z* isomers.

3-Arylsydnone-4-carbonitrile oxides add hydrogen chloride to give the corresponding hydroximoyl chlorides on treatment with HCl/EtOH (115). Reactions of nitrile oxides, RC−NO (R = mesityl, duryl, $p\text{-}O_2NC_6H_4$, PhCO) with 1,1-dichloroalkyl isocyanates, $R'CCl_2NCO$ ($R' = CCl_3$, CF_3) in benzene containing Et_3N lead by [2 + 3] cycloaddition (116) to the corresponding O-acylated chlorooximes $RCCl{=}NO_2CN{=}CClR$ in 58% to 89% yield, rather than to oxadiazolidinone adducts (Scheme 1.14).

Nitrile oxides add to various N-nucleophiles, bearing N-H bonds to give amidoximes. These nucleophiles comprise primary and secondary amines, amides, N-heterocycles and so on. Thus, N-unsubstituted pyrazole, imidazole, 1,2,3- and



Scheme 1.14



R = *t*-Bu,Ph_2CH, Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, 2,4,6-$Me_3C_6H_2$, 2-pyridyl

R′ = H, Me, Et, *i*-Pr, Ph, 2-$O_2NC_6H_4$, PhH_2, MeO, MeS, EtS, Me_2NH, PhNH, NH_2

Scheme 1.15

1,2,4-triazoles or tetrazoles and its 5-substituted derivatives give hydroximoylazoles (Scheme 1.15) on addition to nitrile oxides, which are generated from the corresponding hydroximoyl chlorides (117).

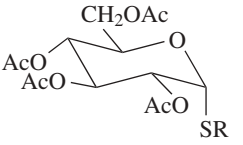
The 1,3-dipoles were generated by the addition of Et_3N' in 20% excess. Only imidazole was basic enough to generate a nitrile oxide in the absence of triethylamine. Due to prototropic tautomerism, reactions of triazoles and tetrazoles led to mixtures of two isomers. With unsubstituted pyrazole and imidazole only one hydroximoylazole was formed (117).

Interesting examples of the addition of N-nucleophiles to nitrile oxides are syntheses of chelated *Z*-amidoxime, N-[2-(dimethylaminomethyl)phenyl]mesitylenecarboamidoxime (118), and pyranosyl amidoximes (119) from the respective nitrile oxides and amines. Aromatic aldoximes undergo unusual reactions with chloramine-T (4 equiv, in refluxing MeOH). N-(*p*-tolyl)-N-(*p*-tosyl)benzamides are formed via addition of 2 equiv of chloramine-T to the intermediate nitrile oxide followed by elimination of sulfur dioxide (120).

Addition of ammonia as a model nucleophile to nitrile oxides was studied by a semiempirical MNDO method, for fulminic acid and acetonitrile oxide (121). The reaction is exothermic and proceeds in two steps. The first (and rate-determining) step is the formation of a zwitterionic structure as intermediate. The second step, which involves transfer of a proton, is very fast and leads to the formation of *Z*-amidoximes in accordance with experimental data. Similar results were

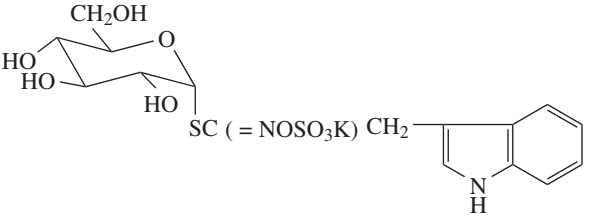
obtained by the same authors, for nitrile oxides, cited above, and for benzonitrile oxide considering water as an O-nucleophile (122).

S-Nucleophiles are very reactive in 1,3-addition reactions with nitrile oxides. A series of α-glucosinolates **27** ($R = CR^1{=}NOH$; $R^1 = Ph$, CH_2Ph, CH_2CH_2Ph, (*E*)-CH=CHPh, 3-indolylmethyl) was prepared by addition reactions of thiol **27** (R = H) with nitrile oxides (123). The indolyl-substituted glucosinolate was then converted to α-glucobrassicin **28**.



27

$R = CR^1 = NOH$; R^1= Ph, CH_2Ph, CH_2CH_2Ph, (*E*)-CH = CHPh, 3-indolylmethyl



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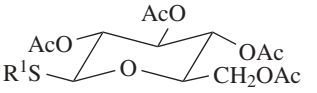
Similarly, adducts **29** were prepared starting from 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranose (124).



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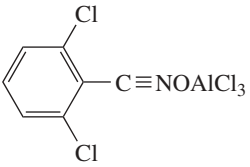
Nitrile oxides were generated from oximes RCH:NOH by successive treatment with chlorine and Et_3N and used *in situ* without further purification. Only benzonitrile oxide and phenylacetonitrile oxide afforded normal adducts in high yields. The reactions generated from nitrile oxides with *p*-, *m*-, and *o*-methoxybenzaldehyde oximes gave adducts, chlorinated in the benzene ring, while the reactions with nitrile oxides, generated from *p*-chloro- and *p*-nitrobenzaldehyde oximes gave no adducts.

Addition of C-nucleophiles to nitrile oxides is of special interest. There are examples of reactions with both carbanions and neutral carbon nucleophiles. To the former group belong reactions of nitrile oxides with organometallic

compounds leading to corresponding oximes (125). These reactions proceed with or without the aid of a Lewis acid depending on the nucleophilic nature. Thus, reactions of aromatic nitrile oxides with BuLi, without a Lewis acid catalyst or with Et_2Zn catalyzed by $BF_3.OEt_2$ afford ketoximes ArC(:NOH)R (Ar = 2,6-$Cl_2C_6H_3$, R = Bu, Et) in 94% to 99% yield.

Similar reactions proceeding with aromatic and heteroaromatic compounds can be classified as unconventional types of aromatic electrophilic substitution. Extremely reactive aromatic substrates react with nitrile oxides without a catalyst. In other cases reactions demand stimulation with a Lewis acid. Thus, ethyl cyanoformate N-oxide $EtO_2CC{\equiv}NO$ reacts at the 3-position of 2,5-dimethyl- and 2,5-diphenylpyrrole to give the corresponding hydroxyimino esters (126). Nitrile oxides complexed with Lewis acids have increased electrophilic character at the nitrile carbon atom and are used as hydroxynitrilium ion equivalents with common aromatic compounds. Thus, treating 2,4-$Cl_2C_6H_3CCl{=}NOH$ with $AlCl_3$ gives the nitrile oxide–Lewis acid complex **30**, which reacts with benzene to afford oxime **31** in 70% yield (127).



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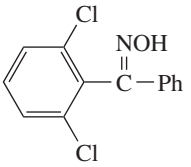


31

Nitrile oxide–BF_3 complexes can also be used as electrophilic moieties with aromatic systems. Introducing BF_3 into a mixture of 2,6-dichlorobenzonitrile oxide and mesitylene in hexane, gave 88% *Z*-2′,6′-dichloro-2,4,6-trimethylbenzophenone oxime (128).

Nitrile oxides react *in situ* with formaldehyde dimethylhydrazone (129) to give oxime-hydrazones RC(:NOH)CH:$NNMe_2$ (R = 4-$O_2NC_6H_4$, MeCO, MeC(:NOH)). The reaction is performed on treatment of oximes with CH_2:$NNMe_2$ in the presence of Et_3N without isolation of the intermediate nitrile oxides.

1.3.4. 1,3-Dipolar Cycloaddition Reactions

1,3-Dipolar cycloaddition reactions are of main interest in nitrile oxide chemistry. Recently, reviews and chapters in monographs appeared, which are devoted to individual aspects of these reactions. First of all, problems of asymmetric reactions of nitrile oxides (130, 131), including particular aspects, such as asymmetric metal-catalyzed 1,3-dipolar cycloaddition reactions (132, 133), development of new asymmetric reactions utilizing tartaric acid esters as chiral auxiliaries (134), and stereoselective intramolecular 1,3-dipolar cycloadditions (135) should be mentioned. Other problems considered are polymer-supported 1,3-dipolar cycloaddition reactions, important, in particular, for combinatorial chemistry

(136, 137), application of cyclodextrin-based catalysts and molecular reactors in 1,3-dipolar cycloaddition reactions of nitrile oxides (138, 139).

In the scope of this subsection, competitive 1,3-cycloaddition of nitrile oxides to carbon–carbon and carbon–heteroatom multiple bonds are of special interest. Competition between carbon–carbon and carbon–nitrogen double bonds in 1,3-cycloaddition reactions with benzonitrile oxides is the subject of a review (140). 1,3-Dipolar cycloaddition reactions of *o*-benzoquinones are summarized in Reference 141. Depending on the nature of the substrates and of the substituents, benzonitrile oxides add to both C=C and C=X bonds.

Several papers concerning modern modifications of 1,3-cycloaddition reactions of nitrile oxides should be also mentioned. An efficient solution-phase combinatorial synthesis of isoxazolines and isoxazoles, using [2 + 3] cycloaddition reaction of nitrile oxides with olefins and alkynes, followed by precipitation of the products as HCl salts has been developed (142). A general method for the liquid-phase syntheses of isoxazoles and isoxazolines via a 1,3-dipolar cycloadditions is elaborated. Poly(ethylene glycol)-supported alkyne or alkene react with nitrile oxides, generated *in situ* from aldoximes followed by elimination from the poly(ethylene glycol) support, to give target products in good yield and purity (143).

One-pot 1,3-dipolar cycloaddition of nitrile oxides generated *in situ* on solid phase, in the presence of a variety of dipolarophiles, provided a library of isoxazolines and isoxazoles (144). (4*S*)-*p*-Hydroxybenzyl-1,3-oxazolidin-2-one was used as a solid-supported chiral auxiliary in asymmetric 1,3-dipolar cycloadditions (145). It was also shown that Mg(II) cation (from magnesium perchlorate) catalyzes asymmetric 1,3-dipolar cycloaddition reactions using solid-supported oxazolidinone chiral auxiliaries (146). The results obtained support a reaction mechanism, which proposes the coordination of the Mg(II) to the dicarbonyl fragment of the chiral auxiliary. The resin-bound chiral auxiliaries could be recycled once, with little loss in regio- or stereoselectivity, but a second recycle gave products with significantly decreased regio- and stereoselectivities.

It was found that 2-propenyloxymagnesium bromide reacts much more readily with nitrile oxides than other known dipolarophiles of electron-deficient, electron-rich, and strained types, including 3-buten-2-one, ethyl vinyl ether, and norbornene, respectively (147). Therefore, this BrMg-alkoxide is highly effective in various nitrile oxide cycloaddition reactions, including those of nitrile oxide/Lewis acid complexes.

An unusual solvent effect was observed in cycloadditions of aromatic nitrile N-oxides with alkyl-substituted *p*-benzoquinones in ethanol-water (60:40): the reaction rates were 14-fold greater than those in chloroform (148). The use of ion pairs to control nitrile oxide cycloadditions was demonstrated. A chiral auxiliary bearing an ionic group and an associated counterion provides enhanced selectivity in the cycloaddition: the intramolecular salt effect controls the orientation of the 1,3-dipolar reagent (149).

Microwave irradiation promotes the 1,3-dipolar activity of nitrile oxides generated from hydroximoyl chlorides. They interacted *in situ* over alumina with alkenes and alkynes (150). The effect was demonstrated in reactions of

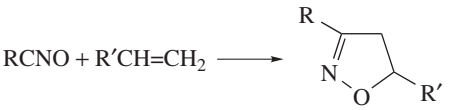
4-chlorobenzhydroximoyl chloride with dimethyl 2-butenedioate and dimethyl acetylenedicarboxylate. Cycloadditions of mesitonitrile oxide to various dipolarophiles in supercritical carbon dioxide were studied. The magnesium bromide-mediated cycloaddition to pent-1-en-3-ol gave higher stereoselectivity than reactions in most conventional solvents (151).

1,3-Dipolar cycloaddition reactions of nitrile oxides were studied using various computational methods. Thus, tendency of some thiophene nitrile oxides to undergo intramolecular 1,3-dipolar cycloaddition was evaluated by quantitative structure-activity relationship (QSAR) indices (152), and some nitrile oxides and dipolarophiles were characterized quantitatively by the global electrophilicity power, ω (153). For several nitrile oxides, *ab initio* (4−31G*) and semiempirical (MNDO, AM1) quantum chemical calculations demonstrated that all the nitrile oxides including phosphoryl nitrile oxides are electron-donating dipoles, for which in their competing electronic and steric interactions in [2 + 3] cycloaddition reactions, the latter are determinant (154). Theoretical studies of stereoselectivity of intramolecular 1,3-dipolar cycloaddition using *ab initio* methods, semiempirical methods, and a tandem quantum mechanic-molecular mechanic method were also performed (155). In a review (156) data, concerning transition-state modeling with empirical force fields were analyzed for various reactions including nitrile oxide cycloaddition.

1.3.4.1. Intermolecular Cycloaddition at the C=C Double Bond Addition at the C=C double bond is the main type of 1,3-cycloaddition reactions of nitrile oxides. The topic was treated in detail in Reference 157. Several reviews appeared, which are devoted to problems of regio- and stereoselectivity of cycloaddition reactions of nitrile oxides with alkenes. Two of them deal with both inter- and intramolecular reactions (158, 159). Important information on regio- and stereochemistry of intermolecular 1,3-dipolar cycloaddition of nitrile oxides to alkenes was summarized in Reference 160.

Individual aspects of nitrile oxide cycloaddition reactions were the subjects of some reviews (161−164). These aspects are as follows: preparation of 5-hetero-substituted 4-methylene-4,5-dihydroisoxazoles by nitrile oxide cycloadditions to properly chosen dipolarophiles and reactivity of these isoxazolines (161), 1,3-dipolar cycloaddition reactions of isothiazol-3(2*H*)-one 1,1-dioxides, 3-alkoxy- and 3-(dialkylamino)isothiazole 1,1-dioxides with nitrile oxides (162), preparation of 4,5-dihydroisoxazoles via cycloaddition reactions of nitrile oxides with alkenes and subsequent conversion to α,β-unsaturated ketones (163), and [2 + 3] cycloaddition reactions of nitroalkenes with aromatic nitrile oxides (164).

Cycloaddition with nitrile oxides occur with compounds of practically any type with a C=C bond: alkenes and cycloalkenes, their functional derivatives, dienes and trienes with isolated, conjugated or cumulated double bonds, some aromatic compounds, unsaturated and aromatic heterocycles, and fullerenes. The content of this subsection is classified according to the mentioned types of dipolarophiles. Problems of relative reactivities of dienophiles and dipoles, regio- and stereoselectivity of nitrile oxide cycloadditions were considered in detail by Jaeger and



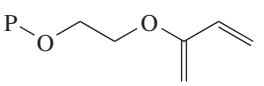
Scheme 1.16

Colinas (5). These aspects are not treated here separately but data omitted in Reference 5 or published after 2001 are included in individual reactions and types of dipolarophiles.

1.3.4.1.1. Alkenes Unsubsituted ethylene, though highly reactive as a dipolarophile (5), is not conveniently used because of its physical state. Its adducts are of lower interest compared to those formed from other olefins. Terminal alkenes (R′ is various alkyl, cycloalkyl, aryl groups) add to nitrile oxides regioselectively to give 3,5-disubstituted isoxazolines (Scheme 1.16) and frequently serve for trapping unstable and characterizing stable nitrile oxides. Styrene is one of the most popular dipolarophiles. (30–33, 105, 165–167).

This regioselectivity is practically not influenced by the nature of subsituent R. 3,5-Disubstituted isoxazolines are the sole or main products in [3 + 2] cycloaddition reactions of nitrile oxides with various monosubstituted ethylenes such as allylbenzene (99), methyl acrylate (105), acrylonitrile (105, 168), vinyl acetate (168) and diethyl vinylphosphonate (169). This is also the case for phenyl vinyl selenide (170), though subsequent oxidation–elimination leads to 3-substituted isoxazoles in a one-pot, two-step transformation. 1,1-Disubstituted ethylenes such as 2-methylene-1-phenyl-1,3-butanedione, 2-methylene-1,3-diphenyl-1,3-propanedione, 2-methylene-3-oxo-3-phenylpropanoates (171), 2-methylene-1,3-dichloropropane, 2-methylenepropane-1,3-diol (172) and 1,1-bis(diethoxyphosphoryl) ethylene (173) give the corresponding 3-R-5,5-disubstituted 4,5-dihydrooxazoles.

An efficient one-pot synthesis of isoxazolines, using soluble polymer-supported acrylate has been described (174). Thus, the addition of 1,4-benzenedicarbonitrile N,N'-dioxide (generated from *N*,*N*'-dihydroxy-1,4-benzenedicarboximidoyl dichloride) to polyethylene glycol-supported 2-propenoic acid 2-hydroxyethyl ester **32** (**P** = polyethylene glycol support) followed by cleavage of the bond with the support gave 3,3′-(1,4-phenylene)bis[4,5-dihydro-5-isoxazolecarboxylic acid] di-Me ester (**33**) in 97% yield.



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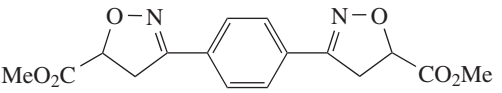

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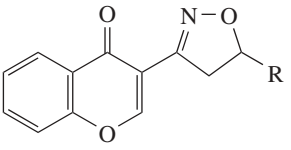
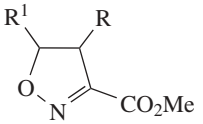
Chromone-3-carbonitrile oxide obtained from 3-formylchromone oxime by bromination and subsequent dehydrobromination underwent cycloaddition reactions with terminal alkenes to give isoxazolines **34** (175).



34 (R = CN, Ph, *p*-Tol, CH_2Br, Ac)

Reaction of methoxycarbonylformonitrile oxide (generated from $MeO_2CCCl{=}NOH$ in the presence of Et_3N in Et_2O) with methyl undec-10-enoate gave 90% of isoxazoline **35** [$R = (CH_2)_8CO_2Me$, $R^1 = H$] whereas a similar reaction with methyl oleate gave a 40% isomeric mixture of **35** [R = 1-octyl, $R^1 = (CH_2)_7CO_2Me$ and $R = (CH_2)_7CO_2Me$, R^1 = 1-octyl] (176).



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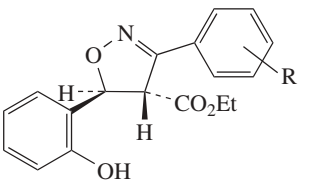
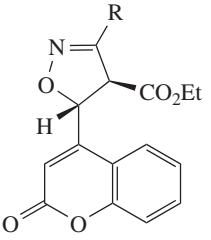
Formation of mixtures of the above type, which is common with internal olefins, do not occur with many functionalized alkenes. Thus, tertiary cinnamates and cinnamides undergo cycloadditions with benzonitrile oxides to give the 5-Ph and 4-Ph regioisomers in a 25–30:75–70 ratio. This result is in contrast to that obtained when methyl cinnamate was used as the dipolarophile (177). 1,3-Dipolar cycloaddition of nitrile oxides to ethyl *o*-hydroxycinnamate proceeds regioselectively to afford the corresponding ethyl *trans*-3-aryl-4,5-dihydro-5-(2-hydroxyphenyl)-4-isoxazolecarboxylates **36** (178). Reaction of 4-[(*E*)-(2-ethoxycarbonylvinyl)] coumarin with acetonitrile oxide gives **37** (R = Me) and **38** in 73% and 3% yields, respectively, while reaction of the same dipolarophile with 4-methoxybenzonitrile oxide affords only **37** ($R = 4\text{-}MeOC_6H_4$) (85%) (179).



36 (R = H, 4-Me, 2,4,6-Me_3)



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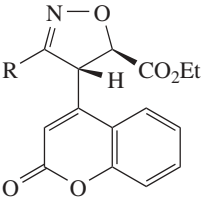
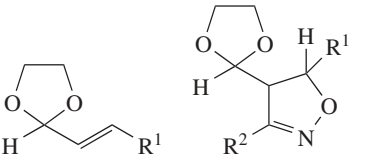


38

1,3-Dioxolanes **39** derived from α,β-unsaturated aldehydes react with nitrile oxides R^2CNO to give the corresponding isoxazolines **40** with the 1,3-dioxolan-2-yl substituent in position 4 as main products, and their 5-isomers as minor products with good regioselectivity and synthetically useful yields. The corresponding

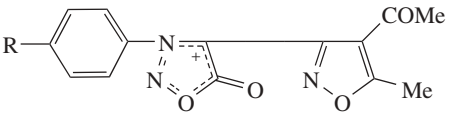
aldehydes are being inactive as dipolarophiles (180). The 1,3-dipolar cycloaddition reactions of nitrile oxides and α,β-unsaturated 1,3-dioxolanes **39** are effectively accelerated by ultrasound irradiation to give isoxazolines **40** with yields and regioselectivities surpassing those from the corresponding thermal reactions (181).



39 **40**

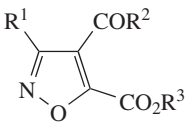
R^1 = Ph, Me, Pr; R^2 = Ph, CO_2Et, Et

Reactions of nitrile oxides with 1,3-dicarbonyl compounds are of a specific character: the latter enter the interaction in enol form, and cycloaddition is followed by dehydration to give isoxazole derivatives. Thus, 3-arylsydnone-4-carbohydroximic acid chlorides react with acetylacetone in the presence of Et_3N to give arylisoxazolyl sydnones **41** (182). Cycloaddition of nitrile oxides R^1CNO with β-acylpyruvates, $R^2COCH{=}C(OH)CO_2R^3$, results in izoxazole derivatives **42** (183). β-Acylpyruvates, unlike ordinary β-diketones, show high dipolarophilic reactivity toward nitrile oxides in the absence of base.



41

R = H, Me, EtO



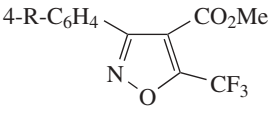
42

R' = CF_3, Ac, CO_2Et, Bz, Ph, 3-$O_2NC_6H_4$, 4-ClC_6H_4, 2,5-$Cl(O_2N)C_6H_3$, 2-ClC_6H_4, 2,6-$Cl_2C_6H_3$, $R^2 = R^3$ = Me; R^1 = 2,6-$Cl_2C_6H_3$, R^2 = Ph, Et, R^3 = Me

Other compounds, with C=C bond activated by an electron-withdrawing group and bearing a good leaving group in the β-position also give isoxazoles, rather than oxazolines, on 1,3-dipolar cycloaddition reactions with nitrile oxides. Thus, methyl 3-(*p*-nitrobenzoyloxy)acrylate was used as a methyl propiolate equivalent with reverse regioselectivity, giving 3-aryl-4-methoxycarbonylisoxazoles on reactions with a variety of substituted benzonitrile oxides, in moderate to good yields (184). A reversal in regioselectivity was also observed when β-dimethylamino-

vinyl phenyl sulfone was used as a dipolarophile in cycloadditions with nitrile oxides. The sulfone gives rise mainly to 4-substituted isoxazoles, after elimination of dimethylamine, while phenyl vinyl sulfone is known to give 5-substituted isoxazolines (185).

A Wang resin-bound β-bromo-β-trifluoromethylacrylate, (*Z*)-$F_3CCBr{=}CHCO_2Me$, was used in the solid-phase synthesis of trifluoromethylated isoxazolecarboxylates using aromatic nitrile oxides generated *in situ* from hydroxymoyl chlorides ($4\text{-}RC_6H_4C(Cl){=}NOH$) and Et_3N, followed by removing the resin with trifluoroacetic acid. Methylation of the free acid with diazomethane in diethyl ether gave aryltrifluoromethylisoxazolecarboxylates **43** as major products in 21% to 48% yields and in 8:1–14:1 regioselectivities (186).



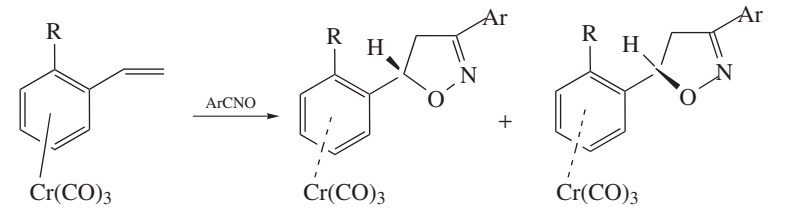
43

R = MeO, EtO, Me, H, Cl, PhO, $PhCH_2O$

A promising magnesium ion catalysis in nitrile oxide cycloadditions has been observed, using allylic alcohols and stable mesitonitrile oxide as models (187). Such a catalysis was applied to asymmetric syntheses of a variety of isoxazolines from achiral nitrile oxides using chiral alkenes with $MgBr_2$ (188, 189), achiral alkenes with Lewis acid complexes with chiral ligands, the role of Lewis acid being played by $MgBr_2$ (190), Et_2Zn (191, 192), and ytterbium triflate (193). Recently, a novel chiral reaction strategy was designed by the intensive assembling of characteristically functionalized metals, which play specific roles in controlling the stereochemical course. In particular, 1,3-dipolar cycloaddition of nitrile oxides to allylic alcohols was achieved by using zinc and magnesium metal and diisopropyl (*R,R*)-tartrate as a chiral auxiliary to afford the corresponding 2-isoxazolines with excellent enantioselectivity (194).

However, most asymmetric 1,3-dipolar cycloaddition reactions of nitrile oxides with alkenes are carried out without Lewis acids as catalysts using either chiral alkenes or chiral auxiliary compounds (with achiral alkenes). Diverse chiral alkenes are in use, such as camphor-derived chiral N-acryloylhydrazide (195), C_2-symmetric 1,3-diacryloyl-2,2-dimethyl-4,5-diphenylimidazolidine, chiral 3-acryloyl-2,2-dimethyl-4-phenyloxazolidine (196, 197), sugar-based ethenyl ethers (198), acrylic esters (199, 200), C-bonded vinyl-substituted sugar (201), chirally modified vinylboronic ester derived from D-(+)-mannitol (202), (1*R*)-menthyl vinyl ether (203), chiral derivatives of vinylacetic acid (204), (*E*)-1-ethoxy-3-fluoroalkyl-3-hydroxy-4-(4-methylphenylsulfinyl)but-1-enes (205), enantiopure γ-oxygenated-α,β-unsaturated phenyl sulfones (206), chiral (α-oxyallyl)silanes (207), and (*S*)-but-3-ene-1,2-diol derivatives (208). As a chiral auxiliary, diisopropyl (*R,R*)-tartrate (209, 210) has been very popular.

A rather rare case is the use of chiral nitrile oxide, derived from N-glyoxyloyl-(2*R*)-bornane-10,2-sultam (211). Several nitrile oxides of the latter type, bearing



44 **45**

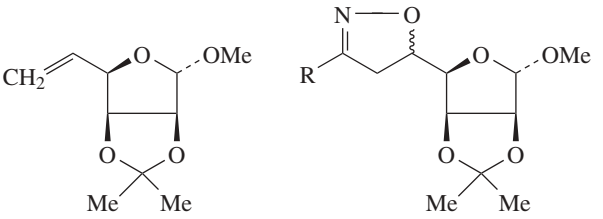
Ar = 3,5-$Cl_2C_6Me_3$	R =				
	MeO	80	:	20
	Me	98	:	2
	Cl	96	:	4

Scheme 1.17

a chiral terpene-based unit X, were generated from oximes and nitro compounds and were subjected to 1,3-dipolar cycloaddition with (*E*)-hex-3-ene to give the corresponding 2-isoxazolines in good yields. However, stereoselectivities were only moderate (212).

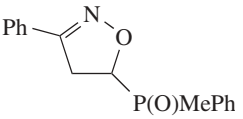
The cycloaddition of 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide to tricarbonylchromium complexed styrenes proceeds with high stereoselectivity (Scheme 1.17), thus offering a new synthetic route to optically active 3,5-disubstituted 4,5-dihydroisoxazoles (213). The preferred formation of cycloadducts **44** rather than **45** shows that nitrile oxide attacks the π face opposite to $Cr(CO)_3$ and the reactive rotamer of the dipolarophile is transoid (213).

π-Facial selectivity occurs in regio- and diastereoselective cycloaddition reactions of benzonitrile oxide and ethoxycarbonylformonitrile oxide to α-methyl dideoxy-D-lyxo-hexenofuranoside **46** giving isoxazolines **47** (R = Ph, CO_2Et), respectively (214).



46 **47**

Considerable (ca 40% de) diastereofacial selectivity was found in 1,3-dipolar cycloaddition reactions of nitrile oxides with racemic methylphenylvinylphosphine oxide, providing phosphinylisoxazolines in high yields. The five substituted regioisomers, for example, **48**, either prevailed or were the only product formed (215). The crystal structure of **48** showed, in agreement with spectral assignments, that it has the *erythro* configuration and exists in a conformation with *anti*-arranged C–O and P = O bonds.

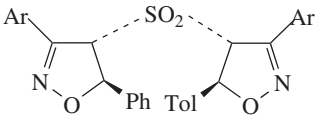


48

An interesting antibody-catalyzed intermolecular asymmetric 1,3-dipolar cycloaddition reaction between 4-acetamidobenzonitrile N-oxide and N,N-dimethylacrylamide generating the corresponding 5-acylisoxazoline was observed (216). Reversed regioselectivity of nitrile oxide cycloaddition to a terminal alkene was reported in the reaction of 4-*tert*-butylbenzonitrile oxide with 6A-acrylamido-6A-deoxy-β-cyclodextrin in aqueous solution, leading to the formation of the 4-substituted isoxazoline, in contrast to the predominance of the 5-substituted regioisomer from reactions of monosubstituted alkenes (217).

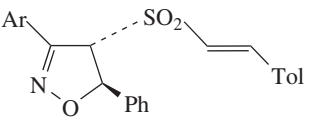
Baker's yeast catalyzed the regioselective cycloaddition of stable aromatic nitrile oxides ArCNO [Ar = 2,6-$Cl_2C_6H_3$, 2,4,6-$Me_3C_6H_2$, 2,4,6-$(MeO)_3C_6H_2$] to ethyl cinnamate, ethyl 3-(*p*-tolyl)acrylate, and *tert*-butyl cinnamates (218). Reactions of dichloro- and trimethoxybenzonitrile oxides with all three esters proceeded regio- and stereoselectively to form exclusively alkyl *trans*-3,5-diaryl-4,5-dihydrooxazole-4-carboxylates. However, mesitonitrile oxide gave an analogous result, only with *tert*-butyl cinnamate, whereas from the two other esters mixtures of isomeric 3,4-diaryl-4,5-dihydrooxazole-5-carboxylate (65:35) were obtained. An attempt to improve regioselectivity of the reactions of ethyl cinnamates with mesitonitrile oxide, by using β-cyclodextrin as an artificial enzyme along with baker's yeast resulted in the reversal of regioselectivity (218). Baker's yeast also catalyzed the asymmetric cycloaddition reactions of above-mentioned nitrile oxides to 2- and 4-vinylpyridines to afford optically active 3-aryl-5-pyridyl-4,5-dihydroisoxazoles. The stereoselectivity was enhanced by directing the geometry of both the dipole and dipolarophile, using β-cyclodextrin as an additional binding cavity along with baker's yeast (219).

1.3.4.1.2. Alkadienes and -trienes 1,3-Dipolar cycloaddition of bis(styryl) sulfone (*E,E*)-PhCH=$CHSO_2$CH=CHC_6H_4Me-4 with 4-$MeOC_6H_4$CH=NOH, in the presence of chloramine-T, gave a mixture of bis(isoxazolinyl) sulfone **49** and (styrylsulfonyl)isoxazoline **50** (220).



49

Ar = 4-$MeOC_6H_4$

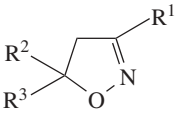


50

1,3-Dipolar cycloaddition of 2,6-dichlorobenzonitrile oxide to unsymmetrical 1,5-hexadien-3-ol proceeds regioselectively to some extent due to the hydrogen

bonding effect. The chelation of Mg metal instead of H bonding, in the same reaction, results in excellent regioselectivity in addition to a good diastereoselectivity (221).

Cycloaddition of 2-alkoxy-1,3-butadienes, $H_2C{=}C(OAlk)CH{=}CH_2$, and nitrile oxides to give isoxazolines **51** proceeds with the participation of only one of the conjugated C=C bonds. With benzonitrile oxide, only the vinyl group in alkoxydienes participates in cycloaddition reactions while in the case of phenylglyoxylonitrile oxide both double bonds react (222). Nitrile oxides RC≡NO react with iron complexed trienes **52**. The reaction proceeds with good yield and diastereoselectivity (~90/10) to give isoxazolines **53** (223).

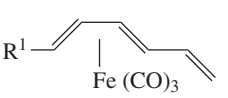


51

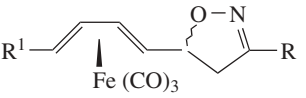
R^1 = Ph, R^2 = C(OAlk)=CH_2, R^3 = H

R^1 = PhCO; R^2 = C(OAlk)=CH_2, R^3 = H + R^2 = CH=CH_2, R^3 = OAlk

Alk = Me, Et, *i*-Pr, *t*-Bu



52



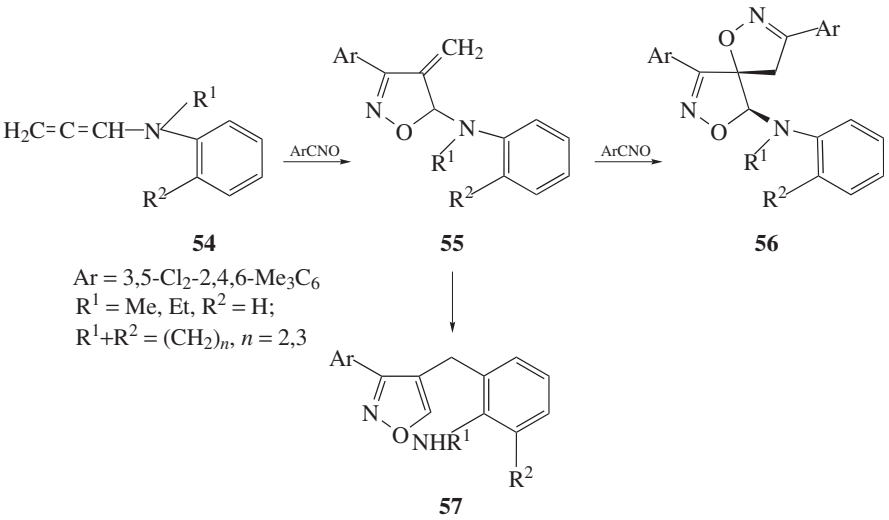
53

R = Me, Et, CMe_3, Ph; R^1 = CO_2Me, Me, Si(CMe_3), Ph_2OCH_2

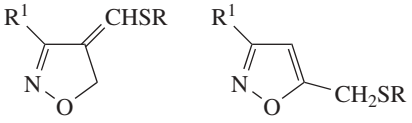
Allenes add nitrile oxides either to one or two double bonds. For mono- and 1,1-disubstituted allenes, relative activity of the two bonds depends on the nature of substituents. The reaction (Scheme 1.18) of N-propadienylanilines **54** with 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide proceeds site- and regioselectively to give 5-substituted 4-methylene-4,5-dihydroisoxazoles **55**, which add a second molecule of nitrile oxide to afford 4,5′-spirobi-(4,5-dihydroisoxazoles) **56**. Dihydroisoxazoles **55** isomerize to 4-(2-aminobenzyl)isoxazoles **57** via a Claisen-type rearrangement (224).

N,N-diarylaminoallenes **54** (R^1 = 2-R^3-3-R^4-C_6H_3, $R^2 = R^3 = R^4$ = H; $R^2 + R^3$ = CH=CH, CH_2CH_2, R^4 = H), undergo similar transformations with 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide affording methyleneisoxazolines **55** and 4,5′-spirobi-(4,5-dihydroisoxazoles) **56**, respectively (225). The difference is that only **55** (R^1 = Ph, R^2 = H) undergoes a Claisen rearrangement to **57** on treatment with Lewis acids while under similar conditions complicated rearrangements and degradation reactions are observed with other compounds **55**.

Allenyl sulfides RSCH=C=CH_2 and the same nitrile oxide undergo cycloadditions which occur exclusively or predominantly at the external double bond to give 4-alkylidenedihydroisoxazoles **58** and 5-(methylthio)isoxazoles **59** (226).

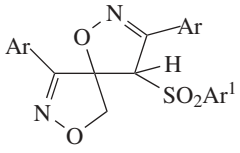


Scheme 1.18



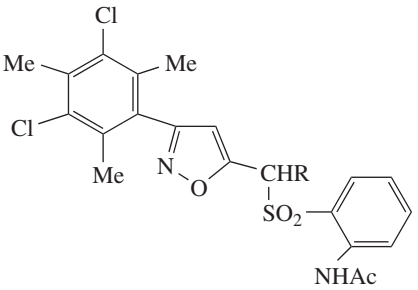
R = 2-AcNHC$_6$H$_4$, 2,4-(O$_2$N)$_2$C$_6$H$_3$, benzothiazol-2-yl; R^1 = 3,5-Cl$_2$C$_6$Me$_3$

Reactions of arylsulfonylallenes with 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide (227) proceed in a manner similar to that of the above-mentioned sulfides. Probably, both 4- and 5-alkylidene-4,5-dihydroisoxazole cycloadducts are initially formed which then undergo different transformations. 4-Alkylidene isomers give spiro adducts such as **60** with an additional molecule of nitrile oxide, while 5-isomers convert to isoxazoles **61**, products of their prototropic rearrangement.



60

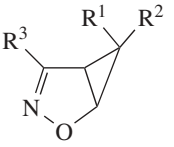
Ar = 3,5-Cl$_2$C$_6$Me$_3$; Ar^1 = 2-AcNHC$_6$H$_4$



61 (R=H, Me)

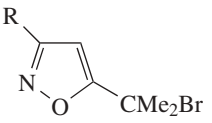
Selective nitrile oxide addition at the internal $C_{(4)}$=Cα double bond, to give the spiro compound, is described for 4-vinylideneoxazolidin-2-one (228).

1.3.4.1.3. Cycloalkene Derivatives Cyclopropenes readily interact with nitrile oxides. Reactions of a broad series of 3,3-disubstituted cyclopropenes with 4-substituted benzonitrile, methoxycarbonyl- and cyanoformonitrile oxides (229) as well as with di(isopropoxy)phosphorylformonitrile oxide (230) give 2-oxa-3-azabicyclo[3.1.0]hexene derivatives **62**. Stereoselectivity of the cycloaddition is governed by both steric and polar factors. In particular, steric factors are supposed to prevail for 3-methyl-3-phenylcyclopropene affording **62** [R^1 = Me, R^2 = Ph, R^3 = $(Me_2CHO)_2P(O)$] with *endo*-Ph, whereas electrostatic factors control cycloadditions to 3-methyl-3-cyanocyclopropene leading to adducts **62** [R^1 = CN, R^2 = Me, R^3 = $(Me_2CHO)_2P(O)$] with an *exo*-oriented cyano group (230). 1,2-Dichloro-3-(chloromethyl)-3-methylcyclopropene undergoes dipolar cycloadditions with nitrile oxides to produce 2-oxa-3-azabicyclo[3.1.0]hex-3-enes, **62**, in which the 6-$ClCH_2$ substituent occupies the *endo* position (231). It should be noted that reactions of (diisopropoxyphosphoryl)formonitrile oxide with 1-bromo-3,3-dimethylcyclopropene and 3,3-dimethyl-1,2-dichlorocyclopropene lead to isoxazole **63** and oxazine **64** [R = $(Me_2CHO)_2PO$], respectively (232).

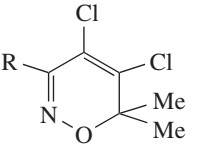


62

R^1 = Me, R^2 = Me, Ph, 4-BrC_6H_4, CH:CH_2, CH_2:CMe, Me_2C:CH, CN;
R^1 = R^2 = Ph; R^1 = Ph, R^2 = CN; R^3 = CN, $(Me_2CHO)_2P(O)$

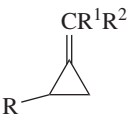


63

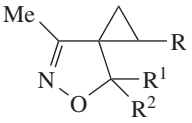


64

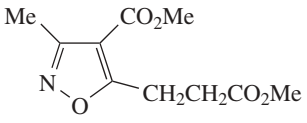
1,3-Dipolar cycloadditions of acetonitrile oxide to alkylidenecyclopropanes **65** (R = H; R^1 = H, R^2 = Ph; R^1 = Me, R^2 = CH_2CH_2Ph) give mainly or exclusively spirocyclopropaneisoxazolines **66**. However, **65** (R = R^1 = CO_2Me; R^2 = H) affords isoxazole **67** originating from the rearrangement of the regioisomer of **66** (233).



65



66

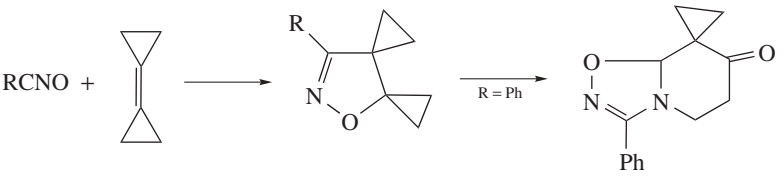


67

Bicyclopropylidene smoothly undergoes 1,3-dipolar cycloaddition to nitrile oxides to give rather stable bisspirocyclopropaneisoxazolines **68** (Scheme 1.19). Formation of side product **69** was observed for **68** (R = Ph). The yield of **69** depended on temperature and duration of the reaction rising from 5% (THF, 66°C, 7h) to 14% (PhH, 80°C, 14h). Two routes were suggested for the side reaction: (a) rearrangement of **68** to **70** followed by reaction of the latter with a second molecule of PhCNO to give **69**, and (b) reaction with a second molecule of PhCNO to give **70** with subsequent rearrangement of the latter to **69** (234).

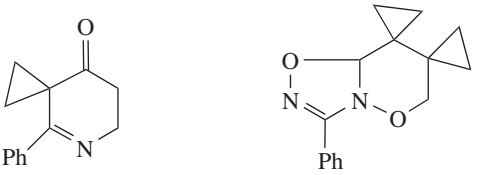
On the basis of previously published data (235), concerning thermal rearrangement of **68** (R = Ph and mesityl) to furo[3,2-*c*]pyridine derivatives, reactions of mesitonitrile oxide and triphenylacetonitrile oxides were carried out (*o*-$Cl_2C_6H_4$, 170°C, 5 days) leading to compounds **72** (R = 2,4,6-$Me_3C_6H_2$, Ph_3C) in 7% and 21% yields, respectively (Scheme 1.20) (234).

Facial selectivity in 1,3-dipolar cycloadditions to cis-3,4-dimethylcyclobutene (**73**) (Scheme 1.21) was studied. Only phenylglyoxylo- and pyruvonitrile oxides lacked facial selectivities (*anti*:*syn* = 1:1). All other nitrile oxides formed preferably *anti*-**74**. The *anti/syn* ratio increased from 60:40 (R = *p*-$O_2NC_6H_4$) and 65:35 (R = Ph) to 87:13 and 92:8 for bulky *tert*-Bu and mesityl substituents, respectively. The transition-state structure of the cycloaddition of formonitrile oxide was determined using both HF/6−31G* and B3LYP/6−31G* methods. The



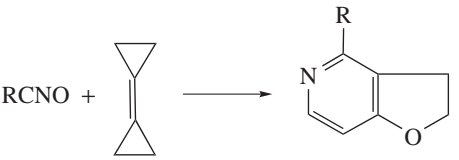
68 **69**

R = Ph, Me, 2,4,6-$Me_3C_6H_2$, Ph_3C



70 **71**

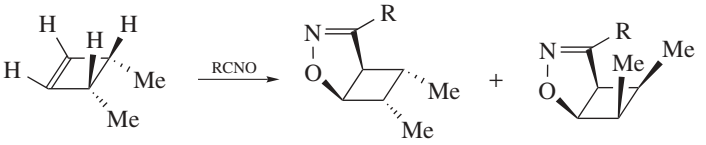
Scheme 1.19



72

R = 2,4,6-$Me_3C_6H_2$, Ph_3C

Scheme 1.20



73 *anti*-**74** *syn*-**74**

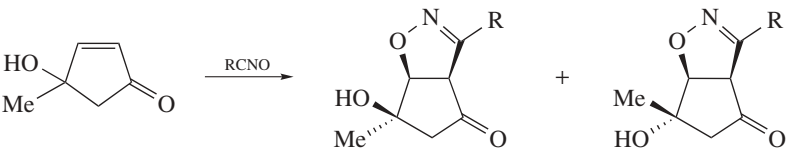
R = Ph, *p*-$O_2NC_6H_4$, PhCO, MeCO, Me_3C, 2,4,6-$Me_3C_6H_2$

Scheme 1.21

calculated relative free enthalpies of these transition states satisfactorily reproduce, at both levels the observed facial selectivity (236).

Dimethyl 7-10-tetrahaptotricyclo[4.2.2.$0^{2,5}$]deca-3,7,9-triene-7,8-dicarboxylate tricarbonyliron reacted readily with several 1,3-dipoles nitrile oxides, at the cyclobutene double bond, to give adducts from which the tricarbonyliron group could be easily removed by oxidative decomplexation with trimethylamine N-oxide (237).

Regio- and diastereoselectivity in 1,3-dipolar cycloadditions of nitrile oxides to 4-substituted cyclopent-2-enones was studied (238, 239). The reactions are always regioselective, while the diastereofacial selectivity depends on the nature of the substituents. Thus, 4-hydroxy-4-methylcyclopent-2-enone (**75**) gives preferably adducts **76a**, the **76a**:**76b** ratio warying from 65:35 to 85:15 (Scheme 1.22).

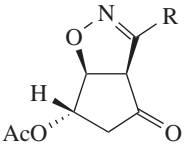


75 **76a** **76b**

R = 2,6-$Cl_2C_6H_3$, *p*-Tol, *p*-ClC_6H_4, Ph, Me

Scheme 1.22

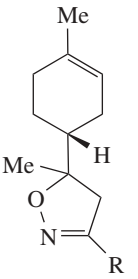
It was also shown that for some other related 4-substituted cyclopent-2-enone derivatives the regiofacial selectivity is lower, and completely reversed in the case of 4-acetoxycyclopent-2-enone, giving 100% of the adduct **77**.



77

The study of benzonitrile oxide additions to 4-benzoylaminocyclopent-2-en-1-ol and its derivatives (240) demonstrated that mainly anti-adducts are formed. This was interpreted as the result of the *syn*-directing ability of the cyclopentene substituents by strong intramolecular hydrogen bonding. Indeed, removal of the intramolecular hydrogen bond, by OH protection or oxidation, activates the *syn*-directing ability of the amido substituent and provides a route for obtaining *syn*-adducts (240).

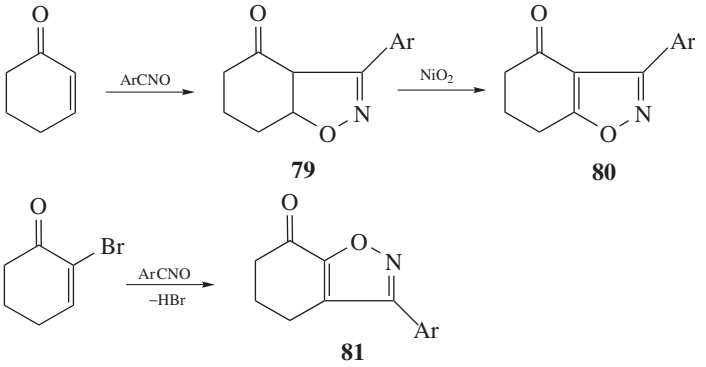
The cycloaddition of nitrile oxides RCNO (R = alkyl, alkenyl, aryl), generated *in situ* from either RCH_2NO_2/PhNCO or RCH=NOH/NaOCl to (*R*)-(+)-limonene, proceeds regioselectively at the extracyclic double bond, but not stereospecifically, to form (5*R/S*)-isoxazoles **78** in 64% to 81% isolated yield (241).



78

Isoxazolines **79**, obtained from aromatic nitrile oxide cycloadditions to cyclohex-2-enone, reacted with nickel peroxide to give 3-aryl-6,7-dihydro[1]benzoisoxazol-4(5*H*)-ones **80**. In contrast, the corresponding 2-bromocyclohex-2-enone underwent nitrile oxide cycloaddition, followed by dehydrobromination, to afford the regioisomeric 3-aryl-4,5-dihydro[1]benzoisoxazol-7(6*H*)-ones **81** (Scheme 1.23) (242).

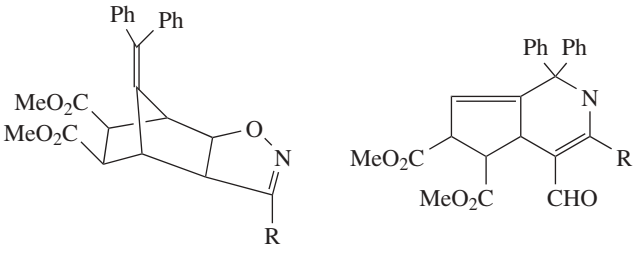
The 1,3-dipolar cycloaddition reactions of nitrile oxides to unsymmetrically substituted norbornenes (243) and to dicyclopentadiene and its derivatives (244) proceed with complete stereoselectivity. The approach of the dipole takes place exclusively from the exo-face of the bicycloheptane moiety, generally



Scheme 1.23

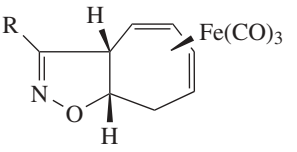
providing mixtures of regioisomers; however some substituted norbornene and dicyclopentadiene derivatives give a single isomer. Experimental observations concerning dicyclopentadiene derivatives were investigated via a gas phase and solvent model, MO calculations on the transition-state geometries at semiempirical (PM3), and hybrid *ab initio*-DFT levels (244).

Reactions of methoxycarbonylformonitrile, furonitrile and substituted benzonitrile oxides (4-Me, 4-OMe, 3-OMe, 4-Cl, 3-Cl, 2,4-di-Cl, 4-F as substituents) with dimethyl 7-(diphenylmethylene)bicyclo[2.2.1]hept-2-ene-5,6-dicarboxylate led exclusively to exo cycloadducts **82** (R = CO_2Me, 2-furyl, substituted phenyl), which, on irradiation with a low-pressure mercury lamp, afforded 3-azabicyclo [4.3.0]nonadiene-7,8-dicarboxylates **83** as the only products. The 1,3-dipolar cycloaddition, followed by a photorearrangement, provides a new method for obtaining tetrahydro-2*H*-pyridine derivatives from cyclopentadiene (245).



82 **83**

Nitrile oxides react with cycloheptatriene and its tricarbonyliron complex to give mixtures of adducts. In particular, for the complex, these adducts are **84**, **85** (regioisomers at the uncomplexed double bond) and bisadduct **86**. The regioselectivity of the reactions of cycloheptatriene is similar to that of the reactions of its tricarbonyliron derivative (246).



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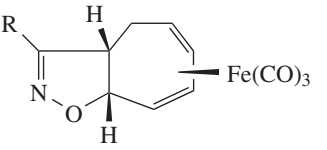

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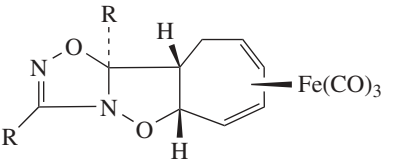
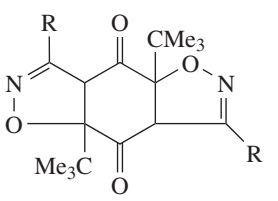


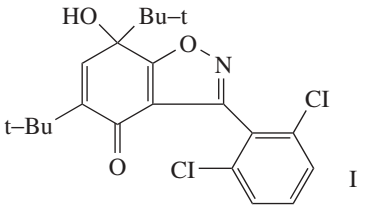
86

1.3.4.1.4. Aromatic and Related Compounds The main part of aromatic compounds, able to undergo 1,3-dipolar cycloaddition reactions with nitrile oxides, are polycyclic hydrocarbons and their derivatives. Dipolarophilic reactivity toward nitrile oxides is known for phenanthrene and pyrene (247). Microwave irradiation in the absence of a solvent improves product yields and reduces reaction times compared with classical heating with and without refluxing solvents (248). Quantum chemical DFT calculations at the B3LYP/6−31G(d) level for reactions of mesitonitrile oxide with anthracene and its aza-analog, acridine, are in agreement with the observed regioselectivity and do not agree with the predictions of frontier molecular orbital (FMO) theory (249).

p-Quinones are active dipolarophiles, used in particular in natural product syntheses (250). 2,5-Di(*tert*-butyl)-*p*-benzoquinone is well known as a dipolarophile in reactions with a series of substituted benzonitrile oxides (251, 252). This quinone gives not only 1:1 but also 1:2 cycloadducts, the latter, for example, **87**, with *p*-substituted benzonitrile oxides, probably, because of less steric hindrances (251). Normal 1:1 and 1:2 adducts of the 1,3-cycloaddition at C=C bond(s) are, however, rather unstable and, in particular, undergo base-induced transformations. The structure of one of the final products **88**, obtained from 1,3-dipolar 1:1 cycloadduct of 2,5-di(*tert*-butyl)-*p*-benzoquinone with 2,6-dichlorobenzonitrile oxide was determined by X-ray diffraction analysis. The *t*-Bu group at



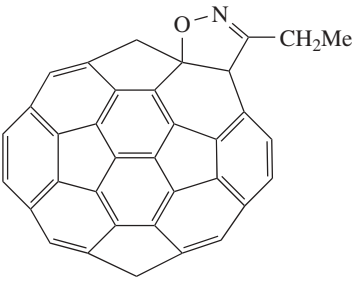
87 (R = 4–BrC_6H_4, 4–ClC_6H_4)



88

the bridgehead position of the 1,3-dipolar cycloadduct migrated to the neighboring carbonyl carbon atom. This base-induced rearrangement takes place with a bulky group, that is, Et, *i*-Pr, *t*-Bu, and Bn at the bridgehead position of nitrile oxide—quinone cycloadducts in an alcohol media. The driving force of this reaction is stabilization by aromatization from isoxazoline derivatives to isoxazole-fused *p*-quinol derivatives (252).

1.3.4.1.5. Fullerenes Cycloaddition reactions are very popular for functionalization of fullerenes. Such reactions of fullerenes are compiled and discussed in detail in Reference 253. During the last 10 to 15 years, several communications appeared concerning [3 + 2] cycloaddition of nitrile oxides to fullerene C_{60}. Nitrile oxides, generated in the presence of C_{60}, form products of 1,3-cycloaddition, fullerene isoxazolines, for example, **89**. The products were isolated by gel permeation chromatography and appear by ^{1}H and ^{13}C NMR spectroscopy to be single isomers. Yields of purified products are ca 30%. On the basis of ^{13}C NMR, structures with C_s symmetry are proposed. These products result from addition of the nitrile oxide across a 6,6 ring fusion (254).



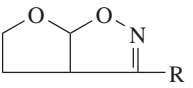
89

Similarly, other cycloadducts of nitrile oxides with C_{60} were synthesized. The cycloadducts were characterized by ^{13}C NMR spectroscopy and high-resolution fast atom bombardment (FAB) mass spectrometry. It should be mentioned that X-ray structure determination of the 3-(9-anthryl)-4,5-dihydroisoxazole derivative of C_{60}, with CS_2 included in the crystals, was achieved at 173 K (255). Cycloaddition of fullerene C_{60} with the stable 2-(phenylsulfonyl)benzonitrile oxide was also studied (256). Fullerene formed with 2-$PhSO_2C_6H_4CNO$ 1:1 and 1:2 adducts. The IR, NMR, and mass spectra of the adducts were examined. Di(isopropoxy)phosphorylformonitrile oxide gives mono- and diadducts with C_{60} (257). Structures of the adducts were studied using a combination of high performance liquid chromatography (HPLC), semiempirical PM3 calculations, and the dipole moments.

1,3-Dipolar cycloaddition of C_{60} with nitrile oxides was modeled at the B3LYP/6−31G(d,p)//AM1 level, and its mechanism and regiochemistry were investigated. Theoretically, the reaction can proceed by four types of additions, *viz*., closed [6,6], open [5,6], closed [5,6], and open [6,6] additions. Analysis of

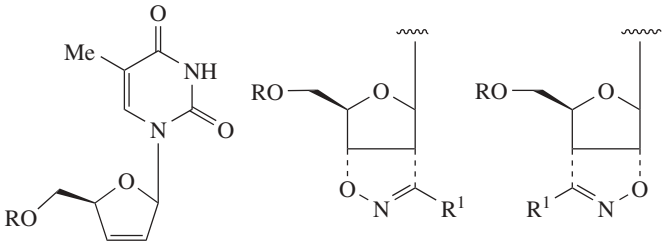
these reactions showed that closed [5,6] and open [6,6] additions are not probable and that closed [6,6] addition is the most favored one (258).

1.3.4.1.6. Heterocycles Both non-aromatic unsaturated heterocycles and heteroaromatic compounds are able to play the role of ethene dipolarophiles in reactions with nitrile oxides. 1,3-Dipolar cycloadditions of various unsaturated oxygen heterocycles are well documented. Thus, 2-furonitrile oxide and its 5-substituted derivatives give isoxazoline adducts, for example, **90**, with 2,3- and 2,5-dihydrofuran, 2,3-dihydropyran, 1,3-dioxep-5-ene, its 2-methyl- and 2-phenyl-substituted derivatives, 5,6-bis(methoxycarbonyl)-7-oxabicyclo[2.2.1]hept-2-ene, and 1,4-epoxy-1,4-dihydronaphthalene. Regio- and *endo-exo* stereoselectivities have also been determined (259).



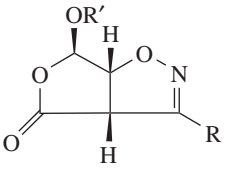
90 (R = H, NO_2, 4-, 3-nitrophenyl)

1,3-Dipolar cycloaddition reactions of 2,6-dichlorobenzonitrile oxide with 2′,3′-didehydro-2′,3′-dideoxythymidine **91** (R = H, Me_3CMe_2Si), at its 2,5-dihydrofuran double bond, gave nucleosides **92** and **93** in 67% yield and 3:2 ratio and 96% yield and 3:1 ratio, respectively (260).



91 **92** **93**

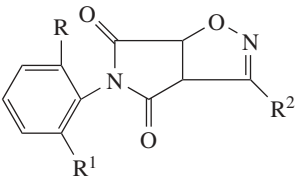
1,3-Dipolar cycloadditions of benzonitrile oxide, its substituted derivatives as well as 9-anthro- and 2-furonitrile oxides to 5-alkoxy- and 5-hydroxy-2(5*H*)-furanones afforded regiospecifically furoisoxazoles **94**. 5-Methoxy- and 5-ethoxyfuranones gave exclusively *exo*-**94**, whereas 5-hydroxyfuranone gave a 52:48 mixture of *exo*-**94** (R = Ph, R′ = H) and its *endo* diastereomer (261). Reaction of benzonitrile oxide with 5-(*R*)-(1-menthyloxy)-2(5*H*)-furanone proceeds regioselectively to give (3a*S*,6*R*,6a*R*)-3a,6a-dihydro-4-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyloxy]-3-phenylfuro[3,4-*d*]isoxazol-4(3a*H*)-one and its regioisomer, (3a*R*,4*R*,6a*S*)-3a,6a-dihydro-4-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyloxy]-3-phenylfuro[3,4-*d*]isoxazol-6(4*H*)-one, in a 68:32 ratio (262).



94

1,3-Dipolar cycloaddition of 2,4-(trimethylsilyl)- and 2,4-(trimethylgermyl)-substituted thiophene-1,1-dioxides as well as silylated 2,2′-bithiophene-1,1-dioxides was investigated. It was shown that only the $C_{(4)}=C_{(5)}$ double bond of 2,4-disubstituted thiophene-1,1-dioxides interacts with acetonitrile oxide to give thienoisoxazoline dioxides. Bithiophene derivatives were inactive or their reaction with nitrile oxide was accompanied by desilylation. Cycloaddition of benzonitrile oxide with all mentioned sulfones did not occur. The molecular structure of 3a-methyl-5,6a-bis(trimethylgermyl)-3a,6a-dihydrothieno[2,3-*d*]isoxazole 4,4-dioxide was established by X-ray diffraction (263) .

N-Arylmaleimides are useful reagents for trapping and characterization of nitrile oxides (see, e.g., Ref. 165). However, their cycloadducts can also be target products. Thus, a series of 3,5-diaryl-4,6-dioxo-3a,4,6,6a-tetrahydropyrrolo-[3,4-*d*]isoxazoles **95** was obtained by 1,3-dipolar cycloaddition of substituted benzonitrile oxides with N-(2,6-dialkylphenyl)maleimides. Certain compounds **95** showed bactericidal and fungicidal activity (264).



95

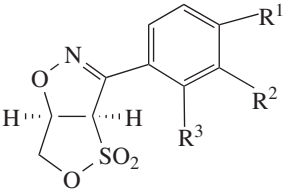
$R = R^1 = Me, Et; R = Me, R^1 = Et;$

$R^2 = Ph, 2\text{-}MeOC_6H_4, 4\text{-}MeOC_6H_4, 4\text{-}ClC_6H_4, 2,4\text{-}Cl_2C_6H_3, 3\text{-}O_2NC_6H_4,$
$4\text{-}O_2NC_6H_4, 4\text{-}FC_6H_4, 4\text{-}MeC_6H_4, 2\text{-}ClC_6H_4, 3,4\text{-}Cl_2C_6H_3, 3,4\text{-}(OCH_2O)C_6H_3,$
$3\text{-}MeOC_6H_4, 3,5,2\text{-}Cl_2(MeO)C_6H_2, 3,4,5\text{-}(MeO)_3C_6H_2$

4-[Chloro(hydroxyimino)methyl]-3-phenyl-1,2,3-oxadiazolium-5-olate-(3-phenylsydnone-4-carbohydroximoyl chloride) reacts *in situ* (through nitrile oxide) with N-arylmaleimides or 2-methyl-N-phenylmaleimide to give 5-aryl-3-(3-phenylsydnon-4-yl)-3a,6a-dihydropyrrolo[3,4-*d*]isoxazole-4,6-diones or 6a-methyl-5-phenyl-3-(3-phenylsydnon-4-yl)-3a,6a-dihydropyrrolo[3,4-d]isoxazole-4,6-diones, respectively (265).

The cycloaddition of prop-1-ene-1,3-sultone to a variety of nitrile oxides (generated from corresponding α-chlorobenzaldoximes and used *in situ*) afforded

oxathioloisoxazolines **96** ($R^1 = H$, Cl, F, Me, MeO; $R^2 = R^3 = H$; $R^1 = R^3 = H$; $R^2 = Cl$, Br, O_2N, Me; $R^1 = R^2 = H$; $R^3 = Cl$; $R^1 = R^3 = Cl$; $R^2 = H$; $R^1R^2 = OCH_2O$; $R^3 = H$) in good yield and with excellent regioselectivity (266). The scope and limitations of dipolar cycloaddition reactions between nitrile oxides and prop-1-ene-1,3-sultone was also studied by other authors (267), who observed a remarkably high regioselectivity and stereoselectivity. It should be noted that low diastereoselectivity was only observed in 1,3-dipolar cycloaddition reactions between nitrile oxides and chiral α,β-unsaturated γ-sultams, for example, **97** (268).



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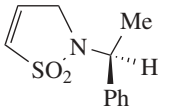
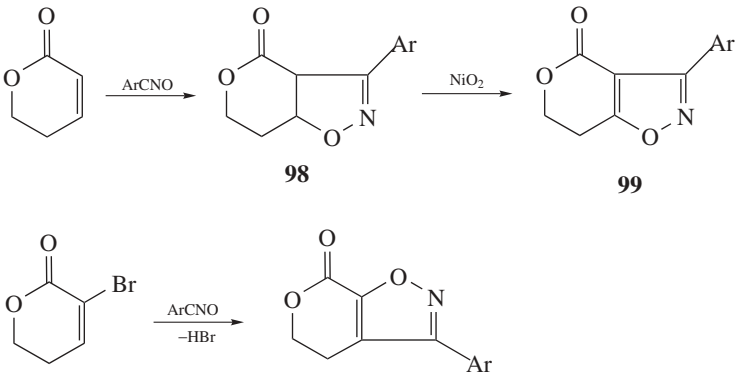


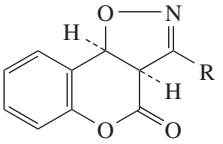
97

Cycloaddition of 5,6-dihydropyran-2-one with aromatic nitrile oxides leads to 3-aryl-3a,6,7,7a-tetrahydropyrano[3,4-*d*]isoxazol-4(4*H*)-ones **98**. The latter react with nickel peroxide to give the corresponding dihydropyranoisoxazolones **99**. Similar to 2-bromocyclohex-2-enone, 3-bromo-5,6-dihydropyran-2-one undergoes nitrile oxide cycloaddition, followed by dehydrobromination, to form regioisomeric 3-aryl-5,7-dihydropyrano[4,3-*d*]isoxazol-7(4*H*)-ones **100** (Scheme 1.24) (242).

Coumarin reacts with 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide affording a single regioisomer **101** ($R = 3,5\text{-}Cl_2C_6Me_3$) in high yield (269).

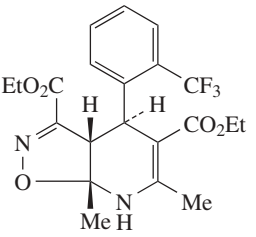


Scheme 1.24



101 (R = 3,5-$Cl_2C_6Me_3$)

Cycloaddition reactions of nitrile oxides with 5-unsubstituted 1,4-dihydropyridine derivatives produced isoxazolo[5,4-*b*]pyridines in moderate to good yield. In each case examined, the reaction produced only a single isomer, the structure of which was assigned by NMR spectra and confirmed by X-ray diffraction analysis of **102** (270). A study of the cycloaddition behavior of substituted pyridazin-3-ones with aromatic nitrile oxides was carried out (271). Nitrile oxides undergo position and regioselective 1,3-dipolar cycloaddition to the 4,5-double bond of pyridazinone to afford 3a,7a-dihydroisoxazolo[4,5-*d*]pyridazin-4-ones, for example, **103**.



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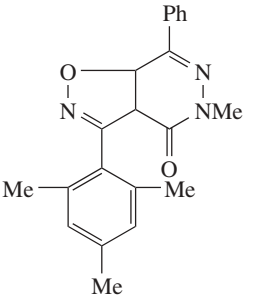
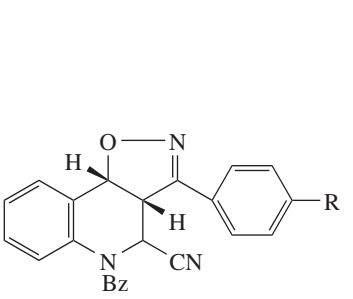


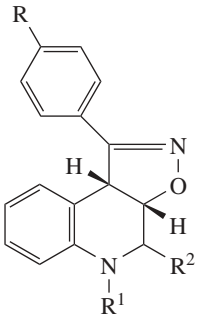
103

Reactions of benzonitrile oxide and its 4-substituted derivatives with 1-benzoyl-2-cyanodihydroquinoline gave mixtures of regioisomers **104** and **105** ($R^1 = Bz$, $R^2 = CN$). In contrast, the reaction with dihydroquinoline, bearing the phenyl substituent in the position 2 and the benzyl group in the position 1, gave only one regioisomer **105** ($R^1 = PhCH_2$, $R^2 = Ph$) (272). The 1,3-dipolar cycloaddition of aromatic nitrile oxides (generated *in situ* from aromatic aldoxime precursors in a two-phase $CHCl_3$/NaOCl system) to 1,2-dihydroisoquinoline derivatives proceeds regioselectively and results in 3-aryl-3a,8,9,9a-tetrahydroisoxazolo[5,4-*c*]isoquinolines (273). The latter undergo ring cleavage, under the action of silica gel or refluxing in ethanol in the presence of an acid, to give aryl 1,2-dihydro-4-isoquinolyl ketone oximes.

There are a few communications concerning cycloadditions of nitrile oxides to unsaturated oxa and aza cage systems. Benzo- and mesitonitrile oxides RCNO give, with five substituted 7-oxanorbornenes **106**, mixtures of the corresponding *exo*-adducts **107** and **108** in nearly quantitative yields. No traces of compounds resulting from the *endo*-face attack was detected (274). Substituents at positions 5 and 6 of **106** render the process highly regioselective.



104



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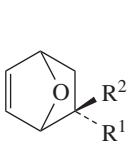
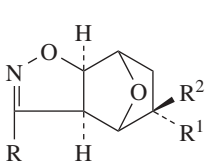
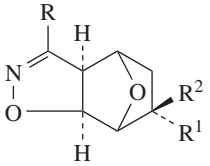


106



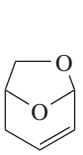
107



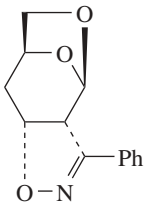
108

R = Ph, 2,4,6-$Me_3C_6H_2$; R^1 = OAc, R^2 = CN; R^1R^2 = O, OCH_2CH_2O

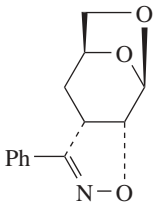
Benzonitrile oxide, generated by dehydrochlorination of benzohydroximoyl chloride, undergoes regio- and face-selective cycloadditions to 6,8-dioxabicyclo [3.2.1]oct-3-ene **108a** yielding a 4:1 mixture of 4,5-dihydroisoxazoles **109** and **110**. Both products have *exo*-stereochemistry, resulting from the approach of the nitrile oxide from the face opposite to the the methyleneoxy bridge. Structures of the adducts were determined by ^{1}H NMR spectroscopy and, in the case of compound **109**, by X-ray diffraction analysis (275).



108a

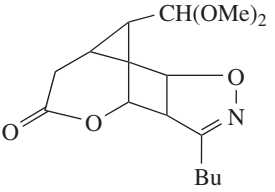


109



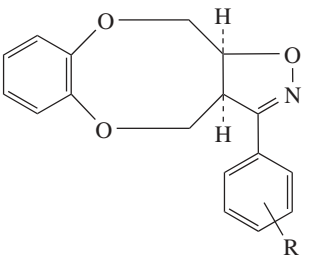
110

Pentanenitrile oxide, BuCNO, formed *in situ* from 1-nitropentane, PhNCO and Et_3N in benzene, added stereo- and regioselectively to 8-*syn*-(dimethoxymethyl)-3-oxo-2-oxabicyclo[3.2.1]oct-6-ene to give 75% of the tricyclic lactone **111** (276). Introduction of a methoxycarbonyl group into the plane asymmetrical double bond of 2,3-dioxa- and 2,3-oxazabicyclo[2.2.2]oct-5-enes, brought about a clear-cut increase in syn selectivity of their reactions with 1,3-dipoles (277).



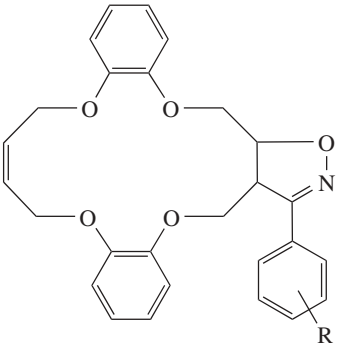
111

Isoxazolobenzodioxocines **112** were prepared in 29% to 65% yields by the 1,3-dipolar cycloaddition. of the corresponding benzenenitrile oxides to 2,5-dihydro-1,6-benzodioxocine. Similarly, monoadducts **113** were obtained from the 16-membered tetraether as the dipolarophile (278).



112

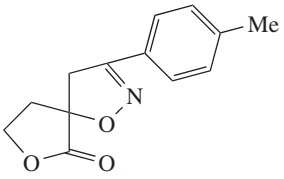
R = H, 4-OMe, 4-Me, 4-Cl, 4-NO_2, 4-Br, 4-F, 3-Cl



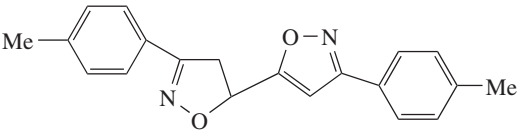
113

R = H, 4-Cl, 4-NO_2, 3-Cl

Alkylidene-substituted heterocycles readily enter 1,3-cycloaddition reactions with nitrile oxides to give the corresponding spiroadducts. Thus, reaction of methylene-γ-butyrolactones with aromatic nitrile oxides proceeds at room temperature producing spiroheterocycles, for example **114** (279). However, cycloaddition with 5-methylene-5*H*-furan-2-one, carried out in refluxing toluene gives the unexpected product **115** (279). Some 4-substituted benzonitrile oxides undergo 1,3-dipolar cycloadditions with 3-methylenephthalide affording expected spiroisoxazolines. These spiroadducts can be converted to the corresponding 2-(3-arylisoxazol-5-yl)benzoic acids by various methods, including thermal and acidic treatments, as well as electrooxidation (280).

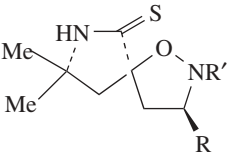


114



115

5,5-Dimethyl-3-methylenepyrrolidine-2-thione, which reacts with nitrones regio- and stereoselectively at its exocyclic C=C bond to give only spirocycloadducts **116**, behaves more complicatedly with nitrile oxides. The latter undergo 1,3-dipolar cycloaddition both to the exocyclic C=C and C=S double bonds with subsequent cycloreversion and formation of spiro-lactams **117** (281).



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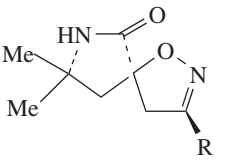
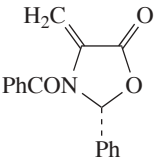


117

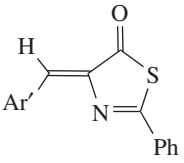
R = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-$O_2NC_6H_4$

The 1,3-dipolar cycloaddition reactions of the chiral 3-benzoyl-4-methylene-2-phenyloxazolidin-5-one **118** and nitrile oxides RCNO (R = Ph, Me) had the expected stereochemistry, addition of the 1,3-dipole having occurred from the less hindered π-face of the exocyclic methylene of **118** (282).

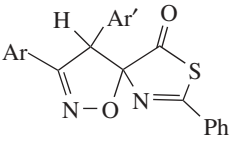


118

Stable mesito- and 2,6-dichlorobenzonitrile oxides, ArCNO, add to the C=C bond of 4-arylidene-2-phenyl-5(4*H*)-thiazolones **119** (Ar′ = Ph, *p*-MeC_6H_4) affording spiroisoxazolines **120**. The cycloaddition reactions are regioselective and only one of the two possible regioisomers has been isolated (283).



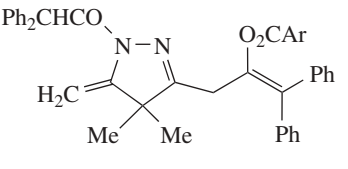
119



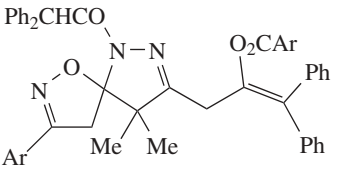
120

Ar = 2,4,6-$Me_2C_6H_2$, 2,6-$Cl_2C_6H_3$; Ar′ = Ph, *p*-MeC_6H_4

Substituted 3-alkenyl-5-methylene-4,5-dihydro-1*H*-pyrazole **121** reacts with 4-MeC_6H_4CNO to give the spiro compound **122** (Ar = 4-C_6H_4Me) (284).

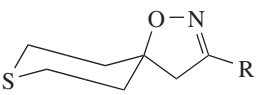


121



122

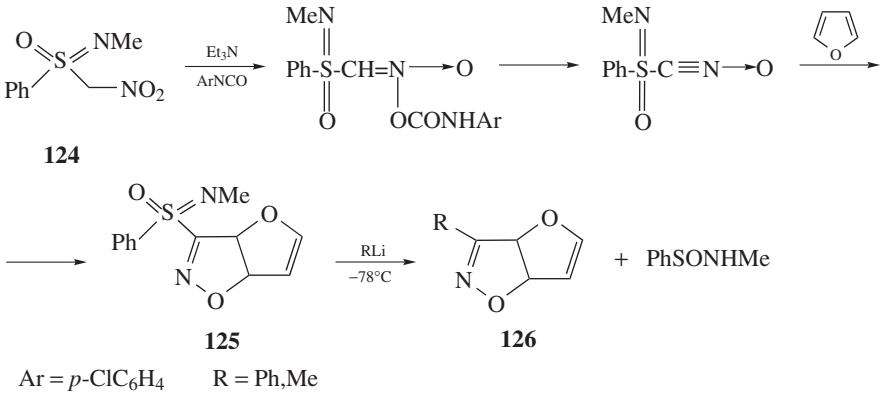
The cycloaddition of nitrile oxides to 4-methylenetetrahydrothiopyran proceeds regioselectively with the formation of spiro-substituted isoxazolines **123** (R = H, Cl, NO_2). Semiempirical calculations (AM1) were used to analyze the electronic structure of reactants, energies of products, and activation barriers leading to these products, in order to rationalize this exclusive regioselectivity. It was shown that the main factor responsible for the high stereoselectivity of this reaction is not frontier orbital control, but mainly electrostatic and steric interactions. Spiro compounds **123** were cleaved by hydrogenolysis to γ-amino alcohols which were recyclized to spiro-oxazines (285). Cycloadditions of nitrile oxides to 4-methylene-1-methylpiperidine gave spiro-substituted isoxazoline derivatives. NMR studies confirmed that only one regioisomer was formed selectively. X-ray structure analysis, carried out for one of these products, showed the occurrence of only one stereoisomer, explicable by comparing AM1-calculated ΔH_f values of all possible cycloadducts (286).



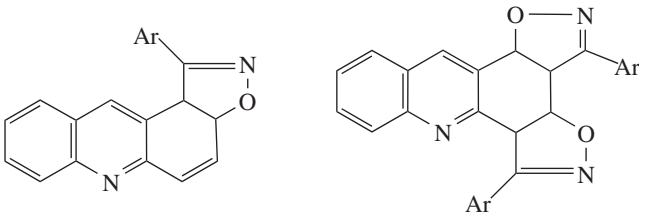
123

Among heteroaromatic compounds able to react with nitrile oxides as dipolarophiles, furan, probably, is the best known. Recently, a novel nitrile oxide was generated from a sulfoximine and converted *in situ* to a cycloadduct with furan (Scheme 1.25) (287). The starting racemic N-methyl-S-nitromethyl-S-phenylsulfoximine **124** was prepared in 87% yield via nitration of N,S-dimethyl-S-phenylsulfoximine. Reaction of **124** with *p*-chlorophenyl isocyanate and a catalytic quantity of triethylamine, in the presence of furan, afforded dihydrofuroisoxazole **125**, the product of nitrile oxide cycloaddition, in 42% yield (65:35 diastereomer ratio). The reaction of **125** with phenyllithium and methyllithium afforded compounds **126**, which are products formed by replacement of the sulfoximine group by Ph and Me, respectively.

Mesitonitrile oxide and acridine (1:2 ratio) react site- and regioselectively to give mono-cycloadduct **127**. The reaction of the same reagents in a 10:1 ratio afforded the mono-cycloadduct **127**, and the bis-cycloadduct **128** with the opposite regiochemistry to that of the mono-cycloadduct (288).

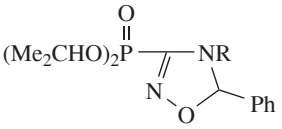


Scheme 1.25



1.3.4.2. Intermolecular Cycloaddition at C=X or X=Y Bonds Cycloaddition reactions of nitrile oxides to double bonds containing heteroatoms are well documented. In particular, there are several reviews concerning problems both of general (289) and individual aspects. They cover reactions of nitrile oxides with cumulene structures (290), stereo- and regiocontrol of 1,3-dipolar cycloadditions of imines and nitrile oxides by metal ions (291), cycloaddition reactions of *o*-benzoquinones (292, 293) and aromatic seleno aldehydes as dipolarophiles in reactions with nitrile oxides (294).

1.3.4.2.1. Aldimines, Ketimines, and Related Compounds as Dipolarophiles Reactions of aldimines with nitrile oxides proceed readily to give 1,2,4-oxadiazolines independently of the nature of substituents both in dipole and dipolarophile molecules. 1,2,4-Oxadiazolines were prepared by the regiospecific 1,3-dipolar cycloaddition of nitrile oxides with fluoro-substituted aldimines (295). Phosphorylnitrile oxides gave with azomethines, PhCH:NR, phosphorylated 1,2,4-oxadiazolines **129** (296). Expected 1,2,4-oxadiazolines were also obtained from azomethines, derived from 4-formylcoumarine (179) and 1,3-diphenylpyrazole-4-carbaldehyde (297).

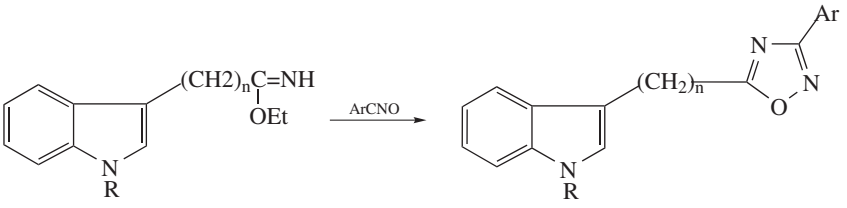


129 (R ≅ Ph, C_6H_4Br-4, Bu)

1,3-Dipolar cycloaddition of nitrile oxide at the C=N bond of indole imino esters **130**, followed by elimination of the alcohol moity gives oxadiazole derivatives **131** (Scheme 1.26) (298). Reaction of N-arylbenzamidines with arenenitrile N-oxides (generated *in situ* from oximoyl chlorides) produce unstable 5-amino-4,5-dihydro-1,2,4-oxadiazoles which, on aqueous acidic treatment hydrolyze to open-chain N-benzoyloxy-N′-arylareneamidines (299).

Poly(ethylene glycol) supported liquid-phase syntheses by both the reaction of (polyethylene glycol (PEG))-supported imines with nitrile oxides, generated *in situ* from aldoximes, (300) and 1,3-dipolar cycloadditions of nitrile oxide, generated *in situ* on soluble polymers with a variety of imines (301, 302) have been described. The solid-phase synthesis of 1,2,4-oxadiazolines via cycloaddition of nitrile oxide generated *in situ* on solid support with imines has also been elaborated (303). These syntheses of 1,2,4-oxadiazolines provide a library of 1,2,4-oxadiazolines in good yields and purity.

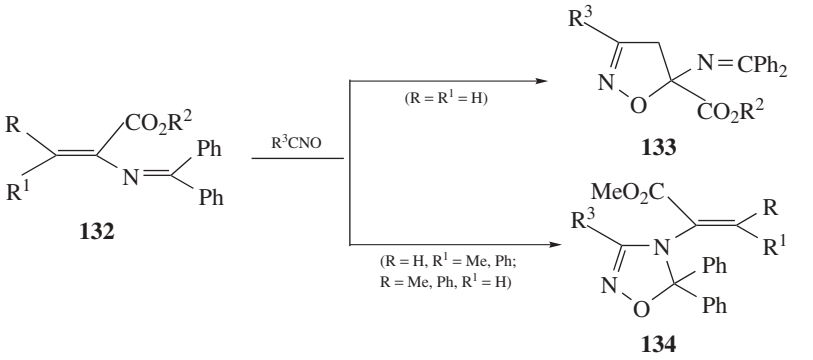
Cycloaddition reactions of ketimines have interesting features, especially with N-substituted imines. Results of 1,3-dipolar cycloaddition reactions of 1,1-diphenyl-2-aza-1,3-butadiene derivatives **132** with nitrile oxides depend on the type and on the stereochemistry of the β-substituents (304, 305). With the unsubstituted compounds **132** ($R = R^1 = H$, $R^2 = Me$, Et) the reaction occurs at the C=C double bond, providing a good method for the synthesis of 4,5-dihydroisoxazole derivatives **133** ($R^2 = Me$, Et, $R^3 = Ph$; $R^2 = Me$, $R^3 = CMe_3$). The β-substituted compounds **132** undergo reactions at the N=C double bond, thus giving, with R^3CNO ($R^3 = Ph$, 4-ClC_6H_4), the 4,5-dihydro-1,2,4-oxadiazole derivatives **134** (Scheme 1.27). All the reactions occur with high site- and regioselectivity. The crystal structure of **134** ($R = Me$, $R^1 = H$, $R^3 = 4\text{-}ClC_6H_4$) has been determined (304).



130 **131**

R = H, n = 0, 1; R = Me, n = 0. Ar = Ph, 4-$O_2NC_6H_4$, 4-ClC_6H_4, 3-MeC_6H_4, 5-nitro-2-furyl

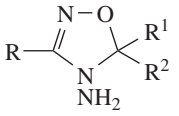
Scheme 1.26



R, R^1 = H, Me, Ph; R^2 = Me, Et; R^3 = Ph, 4-ClC_6H_4, Me_3C

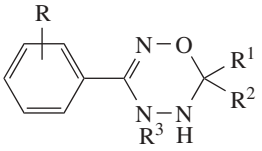
Scheme 1.27

Some data reporting reactions of nitrile oxides with hydrazones seem to be contradictory to each other. It was communicated that 1,3-dipolar cycloaddition of aromatic nitrile oxides RCNO (R = Ph, substituted Ph), generated *in situ* from respective hydroxymoyl chlorides, with ketone hydrazones $R^1R^2C{=}NNH_2$ proceed in a quite "normal" fashion to give 4-amino-4,5-dihydro-1,2,4-oxadiazolines **135** (306). However, products of reactions of similar nitrile oxides with other hydrazones, mainly N-substituted, $R^1R^2C{=}NNHR^3$, were described by the same investigator as 5,6-dihydro-4*H*-1,2,4,5-oxatriazines **136** (307).



135

$R^1R^2 = (CH_2)_n, (CH_2)_2CHMe(CH_2)_2$; R^1 = Me; R^2 = Et; $R^1 = R^2$ = Et, Me; n = 4–7

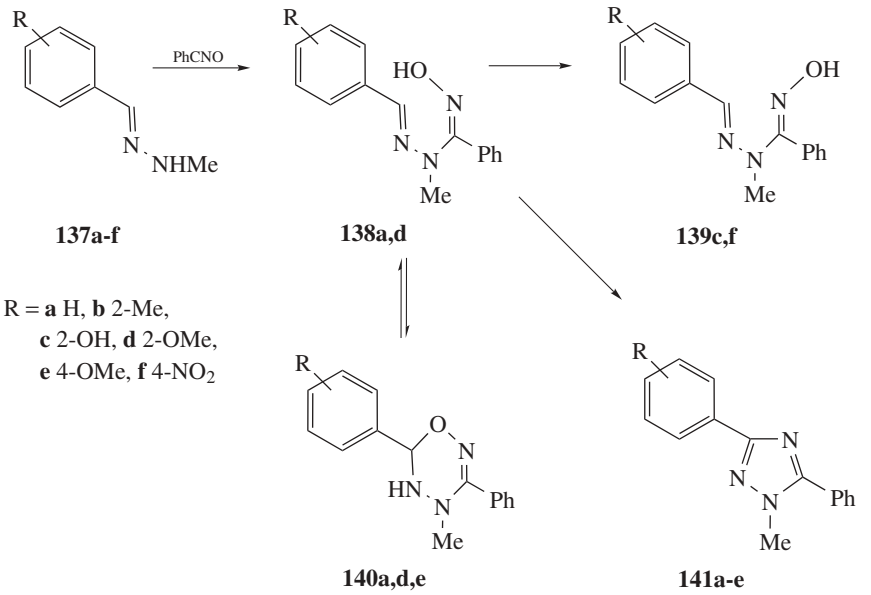


136

R^1 = 4-$MeOC_6H_4$, 2-HOC_6H_4, 2-$MeOC_6H_4$, Me_2CH, Ph; R^2 = H, Ph; $R^1R^2 = (CH_2)_5$; R^3 = H, Me

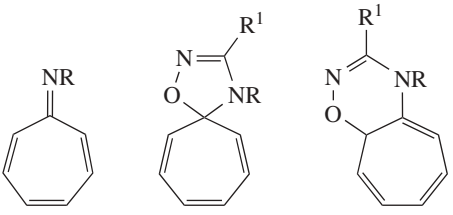
Later it was shown in reactions of aromatic aldehyde methylhydrazones **137a–f** with benzonitrile oxide that the initially formed *Z*-adduct **138**, depending on the reaction procedure and the substituents, undergoes either isomerization to the thermodynamically stable *E*-adduct **139**, tautomerization to an oxatriazine **140** or irreversible cyclization to a triazole **141** (Scheme 1.28). The structure of 4-methyl-3,6-diphenyl-5,6-dihydro-4*H*-1,2,4,5-oxatriazines**140a** was confirmed by an X-ray study (308).

Some features are characteristic of reactions of nitrile oxides with 2,4,6-cycloheptatrien-1-imines (8-azaheptafulvenes). 1,3-Dipolar cycloaddition to the C=N double bond of N-aryl-2,4,6-cycloheptatrien-1-imines **142** (R = Ar), affording



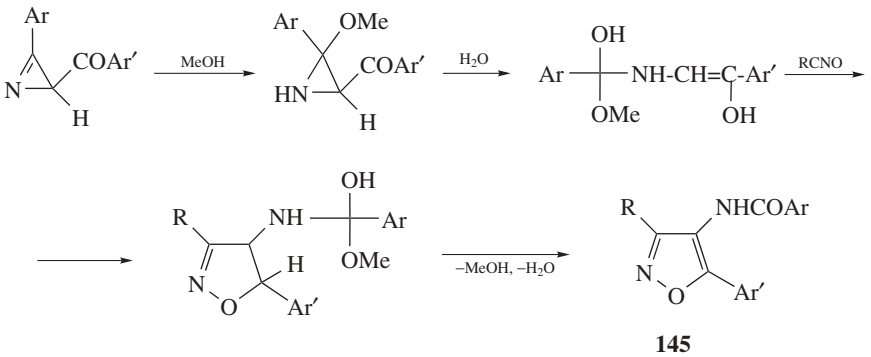
Scheme 1.28

1,2,4-oxadiazaspiro[4.6]undeca-6,8,10-trienes **143**, is described for *p*-substituted benzonitrile oxides (309, 310). The study of a more extended series of azaheptafulvenes **142** (R = Me, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4) and nitrile oxides R^1CNO (R^1 = alkyl, Ph, substituted Ph, MeCO, Bz, CO_2Et) show that the above-mentioned reactions give, as a rule, only adducts derived from a reaction involving the C=N moiety of **142**. However, the adducts consist of a mixture of rapidly equilibrating spiro and fused isomers, that is, **143** and **144**, whose ratio is found to be dependent on substituents, temperature, and solvent (311). It is interesting to note that only products arising from the spiro isomer **143** are obtained in high yields in the catalytic hydrogenation of **143/144** (310, 311).



142 **143** **144**

In the reaction of *o,o'*-disubstituted benzonitrile oxides with 8-(*p*-tolyl)-8-azaheptafulvene (**142**, R = 4-MeC_6H_4) in cyclohexane, there is a competition between attack by the nitrile oxides on the C=N moiety (to give a mixture of



145

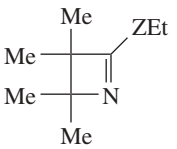
R = Ph, 4-MeC_6H_4, 4-ClC_6H_4; Ar = Ph, 4-MeC_6H_4; Ar′ = Ph, 4-MeC_6H_4

Scheme 1.29

equilibrating fused and spiro adducts) and on the $C_{(2)}=C_{(3)}$ double bond of **142**. Site selectivity is highly enhanced by carrying out the reaction in polar solvents, only the attack at the C=N moiety has been observed in methanol (312). The relative stabilities of rapidly equilibrating mixtures of fused (**144**) and spiro (**143**) isomers have been well reproduced by B3LYP/6−31G* calculations (313).

1.3.4.2.2. Nonaromatic Unsaturated Heterocycles Reactions of aromatic nitrile oxides with 1-azirines are followed by the ring opening of the latter to give 4-benzamidoisoxazoles **145** (314). The structure of **145** (R = 4-ClC_6H_4, Ar = Ar′ = Ph) was established by single-crystal X-ray analysis. A mechanism for the formation of **145** has been proposed, (see Scheme 1.29).

1,3-Dipolar cycloadditions of 2-ethoxy- and 2-ethylthio-1-azetines **146** (Z = O, S) with nitrile oxides give 4,5,6,6a-tetrahydroazeto[1,2-*d*]oxadiazoles, for example **147** (315, 316).



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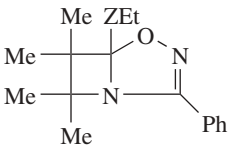
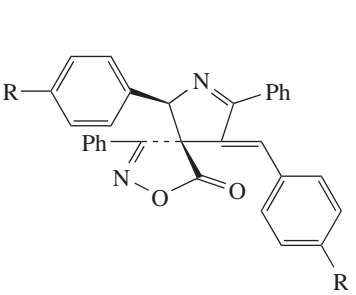
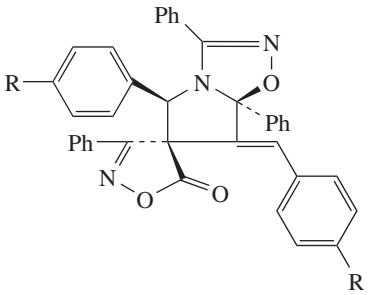


147

Cyclic imidate esters, 2-ethoxypyrrolin-5-one and 2-ethoxy-1*H*-indol-3-one, undergo 1,3-dipolar cycloaddition reactions with nitrile oxides, the reaction site being at the pyrroline C=N bond (317). Rigid and sterically congested pyrroline spiro compounds **148** demonstrate complete diastereofacial selection in site and regiospecific cycloaddition reactions with nitrile oxides to give products **149** (318).



148



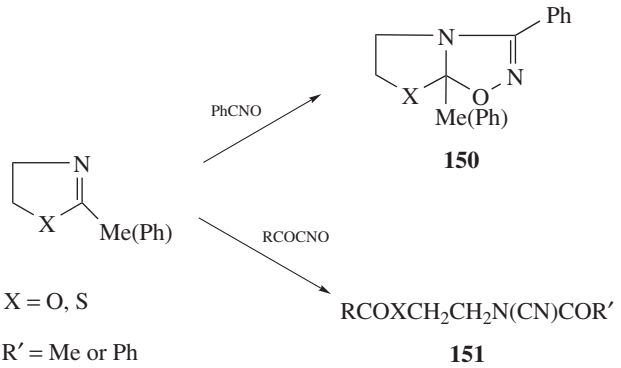
149

R = H, Me, OMe, Cl

2-Methyl-4,5-dihydrooxazole (319), 2-phenyl-4,5-dihydrooxazole (320), and 2,4,4-trimethyl-4,5-dihydrooxazole (319), which are examples of cyclic imidate esters, undergo 1,3-dipolar cycloaddition reactions with benzonitrile N-oxide to give the 7a-substituted 3-phenyl-5,6-dihydro-7a*H*-oxazolo[3,2-*d*]-1,2,4-oxadiazoles **150**. 2-Methyl-4,5-dihydrothiazole gives the thia analog of **150** (319). Alkanoyl- and aroylformonitrile oxides (RCOCNO), 2-methyl- 4,5-dihydrooxazole, 2-methyl-4,5-dihydrothiazole (319) as well as 2-phenyl-4,5-dihydrooxazole (320) give the open-chain compounds **151** (X = O and S, respectively) (Scheme 1.30).

Among six-membered unsaturated nitrogen heterocycles, cycloaddition reactions of nitrile oxides at the C=N bond have been described for individual 3,4-dihydroisoquinolines, such as the reactions of 6,7-dimethoxy-3,4-dihydroisoquinoline and its 1-methyl- and 1-cyanomethyl-substituted derivatives with acylcarbonitrile oxides (321). They have also been described for 1,3,4-oxadiazin-6-ones (322), and for fused dihydro-1,3-oxazine derivatives (323, 324).

Reactions of 2,5-diaryl-1,3,4-oxadiazin-6-ones **152** (R = H, Me, MeO, Cl, NO_2) with stable nitrile oxides R^1CNO (R^1 = 2,4,6-$Me_3C_6H_2$, 2,6-$Cl_2C_4H_3$)

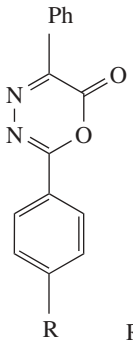


150

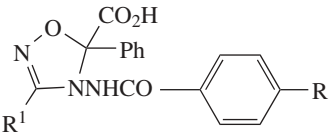
151

Scheme 1.30

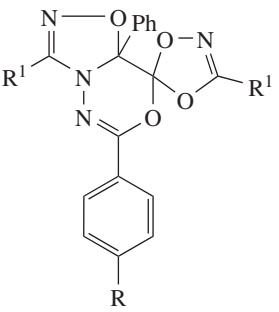
gave 1,2,4-oxadiazoles **153**. When mesitonitrile oxide was used, bis-adducts **154** (at C=N and C=O bonds) were also formed. The cycloadditions showed a remarkable site selectivity toward one of two carbon–nitrogen double bonds. The structures of both adducts were confirmed by X-ray analysis (322).



152

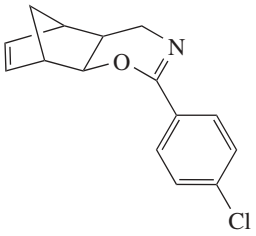


153



154

Cycloaddition of benzonitrile oxide to di-*exo*- and di-*endo*-norbornane and norbornene-fused dihydro-1,3-oxazine structural isomers gave tetracyclic 1,3-oxazino-1,2,4-oxadiazolines. With norbornene dipolarophiles, which contain C=N and C=C bonds, the cycloaddition with PhCNO takes place at the olefinic bond. The di-*exo* compound yields one tetracyclic isoxazoline, regioselectively, whereas the di-*endo*-isomer gives an isomeric mixture of isoxazolines. The di-*exo*-norbornene derivative **155** and PhCNO, however, gave a bis-adduct (323). *cis*-5,6-Tetramethylene-1*H*-1,3-dihydrooxazines **156** ($Z = CH_2CH_2$, $R = 4\text{-}ClC_6H_4$, $4\text{-}MeC_6H_4$), and analogs unsaturated in the carbocyclic ring **156** (Z = CH:CH) gave adducts at the hetero-double bond with benzonitrile oxide, furnishing 1,3-oxazino-1,2,4-oxadiazolines **157** ($Z = CH_2CH_2$, CH:CH; X = O, $R = 4\text{-}MeC_6H_4$). The site selectivity of the cycloaddition differs from that of the above-mentioned norbornene-fused dihydrooxazines, where the nitrile oxide dipole attacks first the C:C rather than the C:N bond (324).



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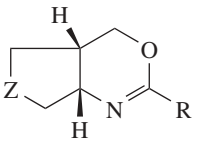

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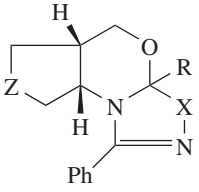
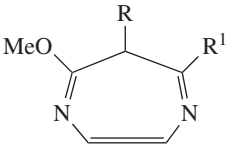


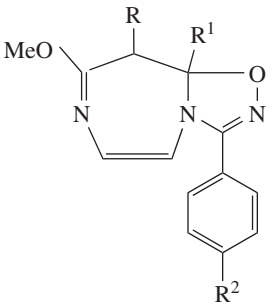
157

Methoxymethyldiazepines **158** ($R = Me$, $R^1 = H$; $R = H$, $R^1 = Me$) undergo regioselective 1,3-cycloaddition with benzonitrile oxide and its 4-substituted

derivatives 4-$R^2C_6H_4CNO$ ($R^2 = Me$, Cl) to give good yields of dihydrooxadiazolodiazepines **159** (R = Me, $R^1 = H$, $R^2 = H$, Me, Cl; $R = R^2 = H$, $R^1 = Me$). The crystal structure of **159** (R = Me, $R^1 = H$, $R^2 = Cl$) has also been reported (325).



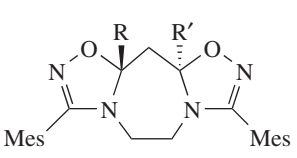
158



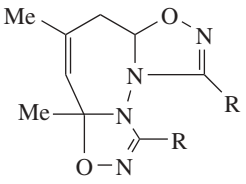
159

Reactions of 2,3-dihydro-1*H*-1,4-diazepines with mesitonitrile oxide proceed with site- and regiospecific 1,3-dipolar cycloaddition leading to bis[1,2,4]oxadiazolo[1,4]diazepine derivatives **160** (326). Of the three compounds **160** only the one with $R = R' = Ph$ is formed with *trans* arranged substituents. The two other products ($R = R' = Me$ and R = Me, R′ = Ph) are mixtures of diastereoisomers. The heterotricyclic 6,10a,11,11a-tetrahydro-5*H*-bis[1,2,4]oxadiazolo[4,5-*d*:5′,4′-*g*][1,4]diazepine structure **160** of the obtained bis-adducts indicates that the hetero double bonds are much more reactive than the olefinic ones. No evidence for the formation of monoadducts was obtained.

Bis[1,2,4]oxadiazolino[4,5-*b*;5′,4′-*g*][1,2]diazepines **161** (R = mesityl, CF_3) were prepared by a one-step cycloaddition of mesitonitrile and trifluoroacetonitrile oxides, with 5,7-dimethyl-4*H*-(or 2*H*)-1,2-diazepines (327).

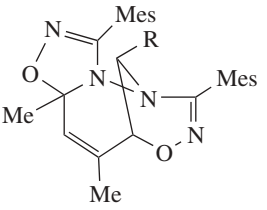


160



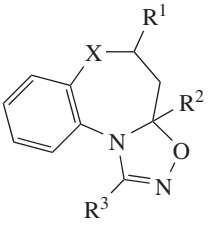
161

Reactions of 1,2-diazepines with nitrile oxides are sometimes difficult to elucidate because they give mixtures (328) or unexpected products. Thus, reactions of 3-methyl- and 3,7-dimethyl-1,2-diazepines with mesitonitrile oxide leads to 5,10-dioxa-1,2,4,11-tetrazatricyclo[7,3,1,$0^{2,6}$]trideca-3,7,11-triene derivatives **162** (R = H, Me, respectively) (329). Such structures were determined by X-ray diffraction studies (330).



162

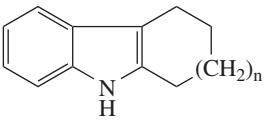
The 1,3-dipolar cycloaddition of 1,5-benzodiazepine to a nitrile oxide occurs at the N=C double bond at the 1 and 2 positions of the benzodiazepine system (331, 332). A second nitrile oxide molecule adds at the $C_{(4)}=N_{(5)}$ bond (333). Behavior of 1,5-benzothiazepines is similar to that of 1,5-benzodiazepines. 3a,4,5,11-Tetrahydro-1,2,4-oxadiazolo[4,5-*d*][1,5]benzothiazepines **163** (X = S, R^1 = Ph, 2-, 3-, 4-ClC_6H_4, 4-$MeOC_6H_4$, Me, R^2 = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-FC_6H_4, R^3 = Ph, 3-BrC_6H_4, CO_2Et) and 3a,4,5,11-tetrahydro-6H-1,2,4-oxadiazolo[4,5-*d*] [1,5]benzodiazepines **163** (X = NH) were obtained by 1,3-dipolar cycloaddition reactions of 2,3-dihydro-1,5-benzothiazepines and 2,3-dihydro-1H-1,5-benzodiazepine with benzonitrile oxides, respectively (332, 334).



163

1.3.4.2.3. Nitrogen-containing Hetarenes Reactions of RCNO (R = 2,6-$Cl_2C_6H_3$, 2,4,6-$Me_3C_6H_2$) with cycloalkano[*b*]indoles **164** (n = 1, 2, 3) gave mainly the oxadiazolo[4,5-*a*]indoline adducts **165**. The structure elucidation of the adducts was based on their spectral data, chemical behavior and in the case of **165** (R = 2,6-$Cl_2C_6H_3$, n = 1) by X-ray analysis (335). The suggested mechanism takes into account the ability of 2,3-disubstituted indoles, especially, of 1,2,3,4-tetrahydrocarbazoles, to autooxidation and proposes the intermediate formation of compounds **166** which react with nitrile oxides to give the final products **165** (335).

Mesitonitrile oxide, but not benzonitrile oxide, adds to aza-analogs of phenanthrene, *viz*., benzo[*h*]quinoline, 1,10-, 1,7-, and 4,7-phenanthrolines to give low yields of mono-cycloadducts at the $C_{(5)}=C_{(6)}$ bond. Only 4,7-phenanthroline gave minor products, of which one the bisadduct **167** was isolated in approximately 7% yield. Phenanthridine reacts with two nitrile oxides but affords phenanthridin-6-one rather than a cyclo-adduct (336).



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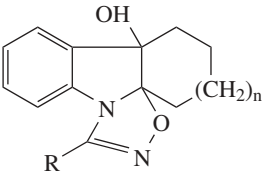

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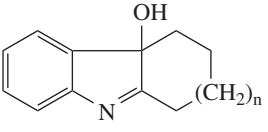
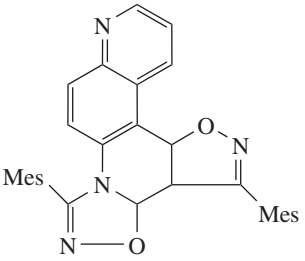
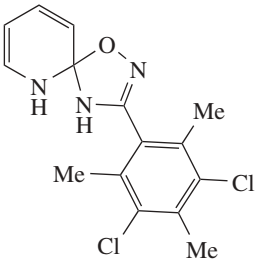


166



167

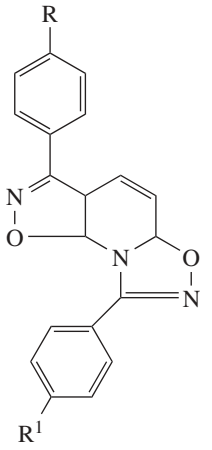
Stable 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide reacts with 2- and 4-aminopyridines in their imino forms, if acids are present to promote the formation of imine, to give cycloadducts such as **168** (337).



168

Bis-cycloadducts **169** and **170** (R = R^1 = MeO, Me, Cl) obtained from reactions of respective 4-substituted benzonitrile oxides and pyridine have been described. Crossed adducts, such as **169** (R = H, R^1 = MeO; R = MeO, R^1 = H), were also formed on treating pyridine with mixtures of various nitrile oxides (338). Addition of pyridine to benzoylcarbonitrile oxide affords an unstable

adduct, which slowly reverts to the addends, leading to BzNCO and products deriving from it. A moderately stable cycloadduct **171** has been obtained in the reaction with isoquinoline (339).



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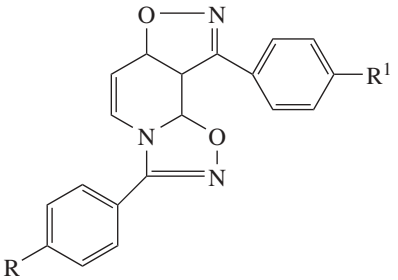
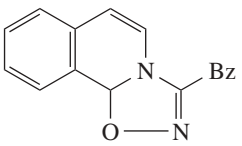
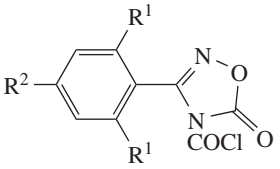


170

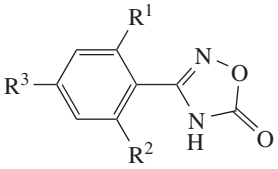


171

1.3.4.2.4. Heterocumulenes The 1,3-dipolar cycloaddition of substituted benzonitrile oxides to the C=N group of chlorocarbonyl isocyanate ClC(O)N=C=O gives 3-aryl-4-chlorocarbonyl-5-oxo-4,5-dihydro-1,2,4-oxadiazoles **172** in 75%–80% yield (340). A similar reaction with chlorosulfonyl isocyanate, $ClSO_2N{=}C{=}O$, affords 4-unsubstituted oxadiazolinones **173** (341).



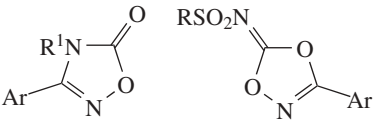
172



173

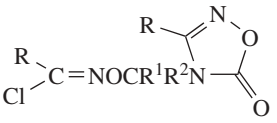
R = R^1 = Me, OMe; R = Cl, R^1 = H R^l = Cl, OMe, Me; R^2 = Cl, OMe, Me; R^3 = H, OMe, Me

The study of the above reaction by different authors (342) showed that besides oxadiazolones **172**, open-chain products from the 1,3-addition of chlorocarbonyl isocyanate to the fulminic group, $RCCl{=}N\text{-}O_2CN{=}C{=}O$ (R = mesityl, duryl), were formed (342). Reactions of aromatic nitrile oxides with various sulfonyl isocyanates RSO_2NCO (R = Pr, Cl, substituted Ph) gave oxadiazoles **174** ($R^1 = RSO_2$) and dioxazoles **175**, the latter being formed on cycloaddition at the C=O bond (343). The hydrolysis of **174** ($R^1 = RSO_2$) gave **174** (R^1 = H).



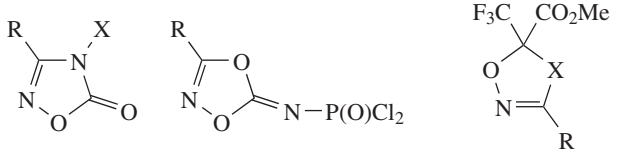
174 **175**

Reactions of stable mesito- and duronitrile oxides with 1-chloroalkyl isocyanates $R^1R^2CClNCO$ ($R^1 = CF_3$, $R^2 = Ph$, 4-MeC_6H_4; $R^1 = CCl_3$, $R^2 = H$) gave oxadiazolones **176**. The double adducts are formed by the cycloaddition of one nitrile oxide molecule at the isocyanate C=N bond and the nucleophilic addition of the chloroalkyl moiety to a second nitrile oxide molecule (344).



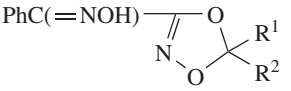
176

Cycloaddition of aromatic nitrile oxides, RCNO (R = 2,4,6-$Me_3C_6H_2$, 2,3,5,6-Me_4C_6H, 3,5-Cl_2-2,4,6-Me_3C_6) to isocyanatophosphoric dichloride occurs at both the C=N and C=O bond of the isocyanato group to afford an inseparable mixture of heterocyclic products, consisting of 3-aryl-4-dichlorophosphinoyl-4,5-dihydro-1,2,4-oxadiazol-5-ones **177** ($X = P(O)Cl_2$) and 5-aryl-2-dichlorophosphinoylimino-2*H*-1,3,4-dioxazoles **178**. The structure of these compounds was confirmed by spectral data and chemical transformations, in particular, by hydrolysis of **177** (R = 2,4,6-$Me_3C_6H_2$, $X = P(O)Cl_2$) to give **177** (X = H) (345). Reactions of methyl trifluoropyruvate and its (methoxycarbonyl)imine $CF_3C(:X)CO_2Me$ (I; X = O, NCO_2Me) with aromatic nitrile oxides RCNO (R = mesityl, duryl) gave dioxazoles and oxadiazoles **179** (346).



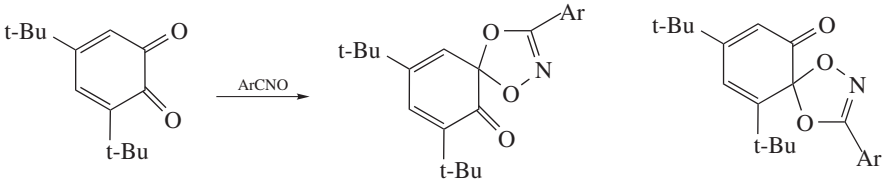
177 **178** **179** (X = O, NCO_2Et)

1.3.4.2.5. Carbonyl and Thiocarbonyl Compounds α-(Hydroxyimino)phenylacetonitrile oxide (generated *in situ* at room temperature from PhC(:NOH)C(:NOH)Cl in the presence of $NaHCO_3$ or Et_3N) reacts with simple aldehydes and ketones R^1R^2CO to give 1,4,2-dioxazoles **180** (347). Related dioxazoles, formed by cycloaddition of benzonitrile oxide to aromatic aldehydes, upon treatment with *t*-BuOK, undergo cyclo-reversion, allowing direct conversion to substituted benzoic acids or their esters (348).



180

$R^1 = H, R^2 = H, Me; R^1 = Me, R^2 = Me, Et; R^1R^2 = (CH_2)_6$



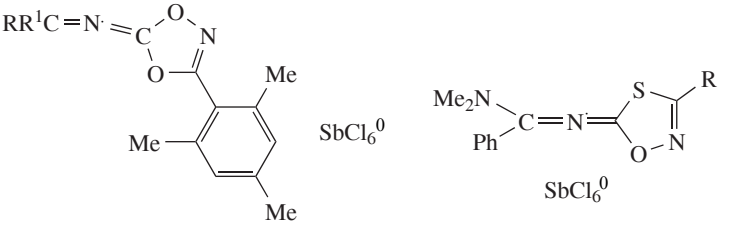
181 **182**

Ar	Ph	4-$MeOC_6H_4$	3,4-$(MeO)_2C_6H_3$	4-ClC_6H_4	3-ClC_6H_4	4-MeC_6H_4
181/182	1 : 1	1 : 1	1 : 1	1.6 : 1	2 : 1	3 : 1

Scheme 1.31

A synthesis of novel spirodioxazole systems by the 1,3-dipolar cycloaddition reactions of 3,5-di-*tert*-butyl-1,2-benzoquinone with aromatic nitrile oxides has been described (Scheme 1.31). Though yields are high (80%–100%), the regioselectivity is low, the regioisomer ratio **181**:**182** being dependent on the Ar nature (349).

Mesitonitrile oxide undergoes a reversible cycloaddition to the carbonyl group of the 1-oxo-3-azoniabutatriene salts $RR^1C{=}N^+{=}C{=}O\ SbCl_6^-$ to give the 2-azoniaallene salts **183**. X-ray structural analysis of **183** (R = NMePh, R^1 = H) confirmed the proposed structure (350). 1-Thia-3-azoniabutatriene salts, $RR^1C{=}N^+{=}C{=}S\ SbCl_6^-$ (R,R^1 = H, Me_2N; Ph, Me_2N) react with nitrile oxides at the C=S double bond to yield 2-azoniaallene salts **184** (351).

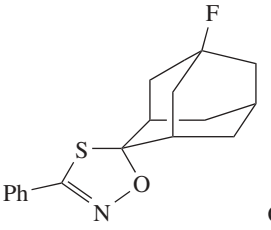


183 **184**

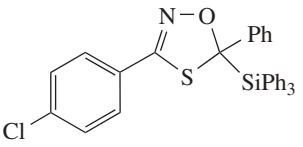
$R \cong Me_2N$, MePhN; $R^1 \cong$ H, Ph R ≅ mesityl, 2,4,6–$(MeO)_3C_6H_2$

Face selectivity in the 1,3-dipolar cycloaddition reactions of benzonitrile oxide and its *p*-substituted derivatives with 5-substituted adamantane-2-thiones,

N-benzyladamantyl-2-imines, and 2-methyleneadamantanes were studied (352, 353). In particular, X-ray single-crystal analysis confirmed the configuration of the oxathiazoline **185**, resulting from the favored attack of nitrile oxide on the 5-fluoroadamantane-2-thione. 2-Silyl-substituted oxathiazole **186** was synthesized by the 1,3-dipolar cycloaddition reaction of phenyl triphenylsilyl thioketone with 4-chlorobenzonitrile oxide (354).

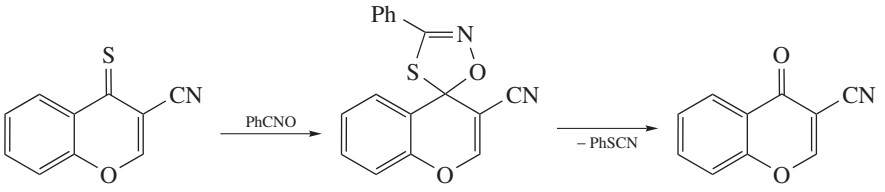


185



186

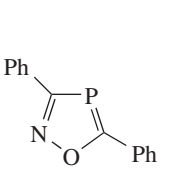
1,3-Dipolar cycloaddition of 3-cyano-4*H*-1-benzopyran-4-thione **187** with benzonitrile oxide proceeded regioselectively to give cycloadduct **188** (involving the thione function). The unstable cycloadduct fragmented to yield 3-cyanochromone **189** and phenyl isothiocyanate (Scheme 1.32) (355).



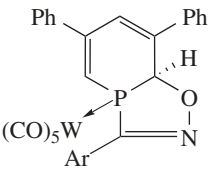
187 **188** **189**

Scheme 1.32

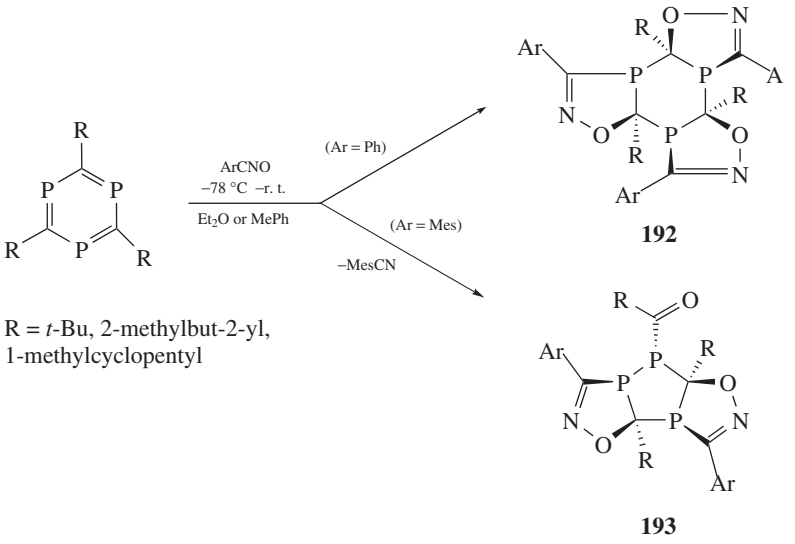
1.3.4.2.6. Compounds with Unusual Double Bonds 1,3-Dipolar cycloaddition of 1-chloro-2-phenyl-2-trimethylsilyl-1-phosphaethene with nitrile oxides, followed by elimination of Me_3SiCl, results in 3,5-diphenyl-1,4,2-oxaphosphazole **190** (356). Chromium, molybdenum, and tungsten pentacarbonyls of 3,5-diphenyl-λ^3-phosphinins react with nitrile oxides to give the corresponding 1,3-dipolar cycloadducts, at the P = C bond, see **191** (Ar = Ph, Mes) (357).



190



191

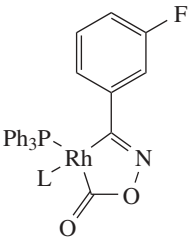


Scheme 1.33

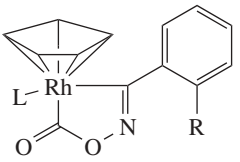
Benzonitrile oxide and mesitonitrile oxide undergo 1,3-dipolar cycloaddition reactions with 1,3,5-triphosphinines under mild conditions to afford fused heterocyclic compounds (Scheme 1.33), for example, **192** and **193**. Oxaphosphazoles and oxadiphospholes have become accessible by thermal fragmentation reactions of such fused heterocyclic compounds (358).

Low-valence metal carbonyl complexes give in good yield (50%–85%), five-membered metalacycles by 1,3-dipolar cycloaddition of aromatic nitrile oxides to a M–CO bond. Synthesis of metalacycles from metalacarborane carbonyl anions [*closo*-3-PPh_3-3-(CO)-3,1,2-$MC_2B_9H_{11}$]$^-$ (M = Ir, Rh) and [*closo*-2-PPh_3-2-(CO)-2,1,7-$RhC_2B_9H_{11}$]$^-$, from a number of pentamethylcyclopentadienyl and cyclopentadienyl complexes of Co, Rh, and Ir of the type (η^5-C_5R_5)ML(CO) (R = H, Me; L = PPh_3, PMe_3, CO) and from the metal carbonyl anions $M(CO)_5^-$ (M = Mn, Re) have been described (359). Single-crystal X-ray diffraction studies of the rhodaisoxazolinone metalacycles, for example, **194** (L is carborane ligand) have also been reported. The reaction of rhodium complex $C_5H_5Rh(CO)(L)$ [L = $P(CHMe_2)_3$], which is prepared from C_5H_5 $Rh(CO)_2$ and neat triisopropylphosphine, with benzonitrile oxide and 2-chlorobenzonitrile oxide affords metalaheterocycles **195** in 90% to 95% yield. The X-ray structural analysis of **195** (R = H) reveals the presence of an almost planar RhCONC heterocycle in which the two Rh–C distances differ by 0.045 Å (360).

Kinetically stabilized germanothiones Tbt(Tip)Ge = S, Tbt(Dis)Ge = S and germanoselones Tbt(Tip)Ge = Se, Tbt(Dis)Ge = Se [Dis = bis(trimethylsilyl) methyl, Tbt = 2,4,6-trisbis(trimethylsilyl)methylphenyl, Tip = 2,4,6-tris(isopropyl)phenyl], have been synthesized and have shown to enter 1,3-dipolar cycloaddition reactions with mesitonitrile oxide (361).

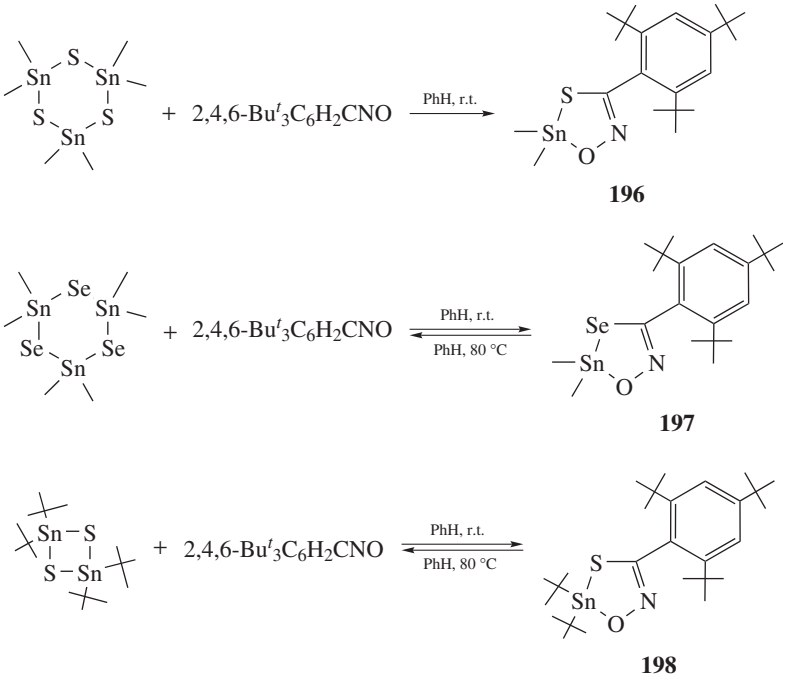


194



195

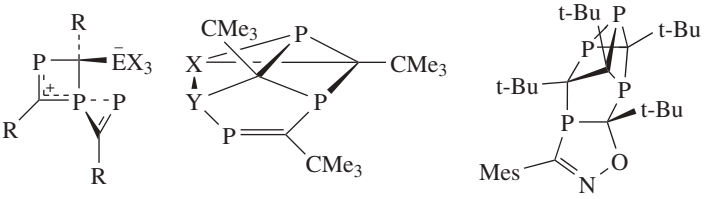
Reactions of 2,2,4,4,6,6-hexamethyl-1,3,5-trithia- and -1,3,5-triselena-2,4,6-tristannins with 2,4,6-tri-*t*-butylbenzonitrile oxide, at room temperature, gave 2,2-dimethyl-1,3,5,2-oxathiazastannole **196** and 2,2-dimethyl-1,3,5,2-oxaselenazastannole **197**, respectively. The reaction of 2,2,4,4-tetra-*t*-butyl-1,3,2,4-dithiadistannetane with 2,4,6-tri-*t*-butylbenzonitrile oxide gave 2,2-di-*t*-butyl-1,3,5,2-oxathiazastannole **198**, which was characterized by X-ray crystallography (362). The reactions yielding oxachalcogenazastannoles **197** and **198**, are reversible; the equilibrium is shifted to the addends at 80°C (Scheme 1.34). In these reactions, trichalcogenatristannines and dithiadistannetane can be regarded as cyclic forms of unstable stannanethiones and stannaneselones.



Scheme 1.34

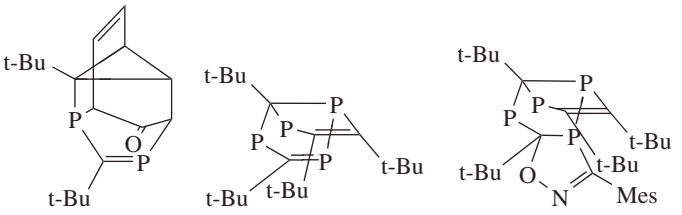
The reaction of a highly crowded 2,4,6-tris[bis(trimethylsilyl)methyl]phenyldihydrostilbine ($TbtSbH_2$) with elemental sulfur, in the presence of nitrile oxides, results in the formation of [2 + 3] cycloaddition reaction products of a thioxostilbine TbtSb = S and a dithioxostiborane TbtSb(S) = S (363).

Some interesting transformations of cage organophosphorus compounds, including their 1,3-cycloaddition reactions with nitrile oxides at the C=P bond have been described. In the presence of aluminum halides and gallium chloride, phosphaalkynes undergo spiro-cyclotrimerization, with incorporation of the corresponding Lewis acid, to form the betaines **199** (R = CMe_3, CMe_2Et, 1-adamantyl, $EX_3 = AlCl_3$; R = CMe_3, $EX_3 = AlBr_3$, AlI_3, $GaCl_3$). The reaction of **199** (R = CMe_3, $EX_3 = AlCl_3$) with DMSO allows the selective generation of two isomeric triphospha Dewar benzene derivatives. Both are trapped efficiently, by further reaction with the phosphaalkyne, to the phosphaalkyne cyclotetramers **200** (X = $CCMe_3$, Y = P; X = P, Y = $CCMe_3$). In the case of **200** (X = P, Y = $CCMe_3$), further functionalization of the phosphaalkene unit is possible by [3 + 2] cycloaddition with mesitonitrile oxide, to give annulated isoxazoline **201** (364).



199 **200** **201**

On heating at 95°, in the presence of tropone, *tert*-butylphosphaacetylene, P≡C–Bu formed along with the tetracyclic adduct **202** gave 5% of tetraphosphasemibullvalene **203**. The latter reacted with mesitonitrile oxide to give oxaphosphazole **204**, which was characterized by X-ray crystallography (365).



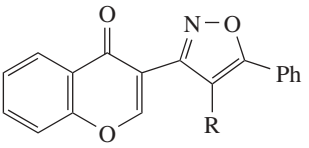
202 **203** **204**

1.3.4.3. Intermolecular Cycloaddition at C≡C, C≡N, and C≡P Bonds

1.3.4.3.1. Cycloaddition at C≡C Bonds Cycloaddition of nitrile oxides to triple carbon–carbon bonds is a rather trivial reaction. Therefore, most attention is to new types of dipoles and dipolarophiles as well as to unusual reaction routes

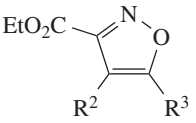
and modern preparative procedures. In particular, reagents and approaches in nitrile oxide chemistry become closer to those of organometallic and coordination chemistry.

Chromone-3-carbonitrile oxide undergoes cycloaddition reactions with phenyl- and diphenylacetylenes to give isoxazoles **205** (R = H, Ph). The nitrile oxide is obtained from 3-formylchromone oxime by bromination and subsequent dehydrobromination (175).



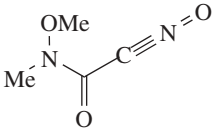
205

The reaction of ethoxycarbonylformohydroximinoyl chloride EtO_2CCl:NOH with acetylene derivatives gave isoxazoles **206** (R^2 = H, CO_2Et, CO_2Me, $COC_6H_4NO_2$-4; R^3 = CO_2Et, CO_2Me, Ph, COPh) (366).

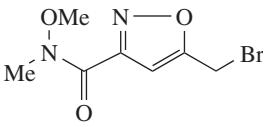


206

The cycloaddition of Weinreb amide functionalized nitrile oxide with a range of dipolarophiles has been studied. N-Methoxy-N-methylcarbonocyanidic amide, nitrile oxide **207** (i.e., a nitrile oxide of Weinreb amide type derivative) was generated from 2-chloro-2-(hydroxyimino)-N-methoxy-N-methylacetamide as intermediate and used *in situ*. Thus, addition of 3-bromo-1-propyne as dipolarophile to this precursor of **207**, followed by quenching with triethylamine, gave 5-(bromomethyl)-N-(methoxy)-N-methyl-3-isoxazolecarboxamide **208** in 55% to 60% yield (367).



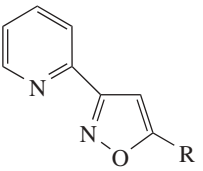
207



208

Iodoacetylene (prepared *in situ* from ethynylmagnesium bromide or tributyl (ethynyl)tin with iodine) was used as a dipolarophile in the 1,3-dipolar cycloaddition reactions with nitrile oxides to produce 2-(5-iodoisoxazol-3-yl)pyridine and 3-(4-fluorophenyl)-5-iodoisoxazole in good yield (70%–90%). Subsequently,

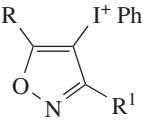
several 5-substituted 3-(pyridin-2-yl)isoxazole derivatives **209** (R = C≡CSiMe$_3$, Ph, 2-thienyl, CH=CH$_2$) were obtained by Pd-catalyzed coupling reactions. The crystal structure of 2-(5-iodoisoxazol-3-yl)pyridine has been determined (368).



R = C≡C-SiMe$_3$, Ph, 2-thienyl, vinyl

209

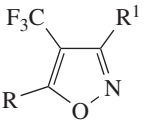
Arylethynyl(phenyl)iodonium salts, RC≡CI$^+$Ph 4-MeC$_6$H$_4$SO$_3^-$, react as 1,3-dipolarophiles with nitrile oxides R^{1}CNO to afford phenyl(substituted isoxazolyl)iodonium salts **210**, which give iodoisoxazoles on reaction with nucleophiles. The crystal structure of **210** (R = Ph, R^1 = mesityl) has been determined (369).



R = Ph, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$; R^1 = mesityl, 2,6-Cl$_2$C$_6$H$_3$

210

Syntheses of 1-aryl-3,3,3-trifluoro-1-propynes and their reactions with nitrile oxides to give 3,5-diaryl-4-trifluoromethylisoxazoles have been carried out. In particular, 1-(4-chlorophenyl)-3,3,3-trifluoro-1-propyne, on reaction with 4-chlorobenzohydroximoyl chloride in the presence of Et$_3$N in PhMe, give a 45% mixture of **211** (R = R^1 = 4-ClC$_6$H$_4$) and the regioisomer **212** in the ratio of 97:3, respectively (370).



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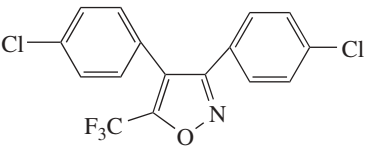
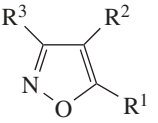


212

The triethylamine-induced reaction of benzohydroximinoyl chlorides, precursors of nitrile oxides, with β-trifluoromethyl-substituted acetylenic esters gives rise to three products: 5-trifluoromethyl-4-isoxazolecarboxylates, **213** (R^1 = CF$_3$,

$R^2 = MeO_2C$, $R^3 = 4\text{-}F_3CC_6H_4$), regioisomeric 4-trifluoromethyl-5-isoxazolecarboxylates, **213** ($R^1 = MeO_2C$, $R^2 = CF_3$, $R^3 = 4\text{-}F_3CC_6H_4$) and unexpectedly oximinoyl chloride **214**, resulted by 1,4-addition. Product distribution is rationalized in terms of two competing reactions, either 1,4-addition of the oximate anion to the acetylenic ester or formation of the nitrile oxide followed by 1,3-dipolar cycloaddition. Anionic 1,4-addition of the oximinoyl chloride to the acetylenic ester is favoured at low temperatures, while nitrile oxide formation, followed by cycloaddition, occur at temperatures above 0 ° (371).



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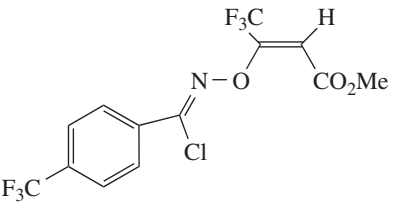
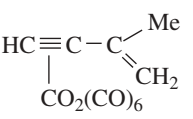


214

A characteristic feature of contemporary investigations in the field under consideration, is the interest in cycloaddition reactions of nitrile oxides with acetylenes in which properties of the C≡C bond are modified by complex formation or by an adjacent metal or metalloid atom. The use of such compounds offers promising synthetic results. In particular, unlike the frequently unselective reactions of 1,3-enynes with 1,3-dipoles, nitrile oxides add chemo-, regio- and stereoselectively to the free double bond of (1,3-enyne)$Co_2(CO)_6$ complexes to provide 5-alkynyl-2-oxazoline derivatives in moderate to excellent yield. For example, enyne **215** reacts with *in situ* generated PhCNO to give 80% yield of isoxazoline **216** (372).



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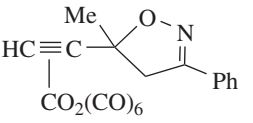
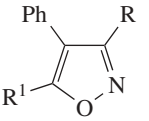
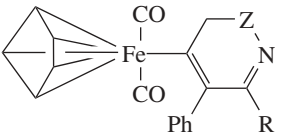


216

η^1-Ethynyl complexes $Cp(CO)_nLMC{\equiv}CPh$, (Cp = η-cyclopentadienyl; n = 1, 2; L = CO, PPh_3; M = Fe, Mo) react with nitrile oxides RCNO (R = Ph, CO_2Et) to give the σ-isoxazolyl transition metal derivatives **217** [same R, R^1 = $Cp(OC)_nLM$]. An X-ray diffraction study of **217** [R = Ph, $R^1 = Cp(OC)(Ph_3P)Fe$] has been performed (373). Treatment of iron complex (η^5-C_5H_5)$Fe(CO)_2$ $CH_2C{\equiv}CPh$ with nitrile oxides yields six-membered σ-heterocyclic iron complexes, **218** (R = Ph, CO_2Et, Z = O), arising from cycloaddition and subsequent 1,2-migration of the (η^5-C_5H_5)$_2Fe(CO)$ group (374).



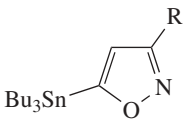
217



218

2-Alkynyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolanes participate in 1,3-dipolar cycloaddition reactions with mesito-, benzonitrile oxide or *tert*-butylformonitrile oxide to provide isoxazoleboronic esters in good yield and with excellent levels of regiocontrol. In addition, these potentially valuable synthetic intermediates have been shown to participate efficiently in Suzuki coupling reactions (375). The [3 + 2] cycloaddition reaction of nitrile oxides and alkynylboronates provide direct access to a wide variety of isoxazole boronic esters with high levels of regiocontrol. For example, mesitonitrile oxide reacts with 2-(1-hexynyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, in refluxing diethyl ether, giving 5-butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(2,4,6-trimethylphenyl)isoxazole in 73% yield. The application of this methodology in the synthesis of non-steroidal anti-inflammatory agents has also been described (376).

3-Substituted 5-(tributylstannyl)isoxazoles have been synthesized in good yields by the 1,3-dipolar cycloaddition reaction of ethynyltributylstannane with nitrile oxides, generated *in situ*. $Bu_3SnC{\equiv}CH$ and RCNO (R = Me, Ph, CO_2Et) give isoxazoles **219** in 85% to 100% yield. 3-Methyl-5-(tributylstannyl)isoxazole is easily converted to the corresponding 5-benzoyl- and 5-arylisoxazoles by a Pd-catalyzed reaction (377). Ynamines, such as, $PhNMeC{\equiv}CH$, react with nitrile oxides to give the 5-aminoisoxazoles **220** ($R = Me_3C$, Ph, substituted Ph). The stannyl-substituted ynamine $PhNMeC{\equiv}CSnBu_3$ also furnishes the compounds, **220** on reaction with hydroximoyl chlorides (378).



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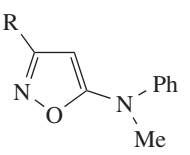
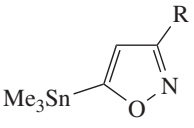


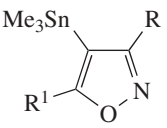
220

1,3-Dipolar cycloaddition reaction of trimethylstannylacetylene with nitrile oxides yielded 3-substituted 5-(trimethylstannyl)isoxazoles **221**. Similar reactions of (trimethylstannyl)phenylacetylene, 1-(trimethylstannyl)-1-hexyne, and bis (trimethylsilyl)acetylene give the corresponding 3,5-disubstituted 4-(trimethylstannyl)isoxazoles **222**, almost regioselectively (379). The 1,3-dipolar cycloaddition reaction of bis(tributylstannyl)acetylene with acetonitrile oxide, followed by treatment with aqueous ammonia in ethanol in a sealed tube, gives 3-methyl-4-(tributylstannyl)isoxazole **223**. The palladium catalyzed cross coupling reaction of

223 with 2-iodonitrobenzene, followed by reductive cyclization give 3-acetylindole (380). 1,3-Dipolar cycloaddition reactions between nitrile oxides and stannylalkynes proceed in a regiospecific manner to afford 4-stannylisoxazoles in good yields. No reaction has been observed with vinyl- or allylstannanes (381).



221



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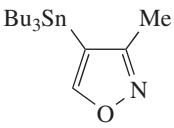
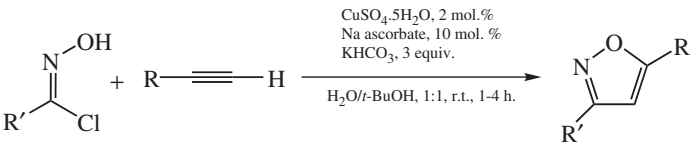


223

R = Me, Ph, CO_2Et; R^1 = Bu or Ph, Me_3Si, Me_3Sn

Exciting results have been obtained by using copper(I)-catalyzed 1,3-cycloaddition reactions with 1-alkynes (382). The process is apparently mediated by species like R-C≡C-Cu, formed *in situ* by reduction of copper(II) sulfate with sodium ascorbate, and proceeds at room temperature to give products, in high yield and with high regioselectivity (Scheme 1.35). For example, thermal cycloaddition of 4-methoxybenzonitrile oxide to phenylacetylene results, after 8h at 60°C, in a 4:1 mixture of 3,5- and 4,5-isomers in 62% yield, whereas only a single regioisomer has been obtained in 92% yield after 1h at ambient temperature, using Cu(I) as a catalyst. Different alkynes have been employed in the Cu(I)-catalyzed cycloadditions. In particular, a steroidal isoxazole has been obtained from 17-ethynylestradiol and 4-methoxybenzonitrile oxide in 98% yield.

A number of publications have appeared concerning polymer-supported syntheses of isoxazoles via 1,3-dipolar cycloadditions. In particular, soluble polymer-supported alkynes react with nitrile oxides, generated *in situ*, to give isoxazoles in good yield (383). A library of isoxazoles and 5-isoxazol-4-yl-[1,2,4]oxadiazoles has been prepared by combined solution- and solid-phase syntheses (384). Acetylenic sulfones attached to solid supports by means of ester linkers [polymer-supported 4-(alkynylsulfonyl)benzenemethanol benzoate derivatives] have been employed in cycloaddition reactions with mesitonitrile oxide, followed by cleavage of the products from the resin by ester hydrolysis or reductive desulfonylation (385). Solid-phase synthesis of 3-hydroxymethylisoxazoles, by cycloaddition of alkynes to resin-bound nitrile oxides, give the products in moderate yields and fair to good purity, depending on the alkyne substituents (386).



Scheme 1.35

Different aspects of 1,3-dipolar cycloaddition reactions of nitrile oxides at the C≡C bond have been studied using quantum chemical methods. Quantitative predictions of substituent and solvent effects on the regioselectivities of nitrile oxide cycloadditions to electron-deficient alkynes have been made, using hybrid DFT calculations, with the B3LYP/6−31G* method, to calculate the activation barriers of nitrile oxide cycloadditions to the unsymmetrical alkynes, cyanoacetylene and Me propiolate. Both, inherent electronic effects and solvent polarity have been shown to influence regioselectivity (387). 1,3-Dipolar cycloaddition reactions of substituted nitrile oxides RCNO, (R = F, NO_2, OMe, OH, CO_2Me, CHO, $CONH_2$, H, Me) with propyne were studied, using the DFT at the 6−311 + + G** level. The reaction rates have been calculated at different temperatures from 200 to 400 K. The conclusions are that formation of 5-methyl-substituted isoxazoles is dominant at low temperatures, while 4-methyl-substituted isoxazoles are favored at relatively high temperatures (388).

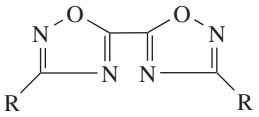
The mechanism for the 1,3-dipolar cycloaddition of benzonitrile oxide to ethynyl- and propynylboronate has been studied by DFT at the B3LYP/6−31G* level. These reactions are concerted [3 + 2] processes. The presence of the two oxygens on the boronic ester precludes the participation of the B atom in the [3 + 3] processes. The two pathways leading to the formation of the regioisomeric isoxazoles, bearing the boronic ester unit on the 4- or 5- positions, have been characterized. The activation parameters are in acceptable agreement with experiments, allowing the explanation of the factors controlling these regioselective cycloadditions (389).

It is of interest to mention that DFT study performed, prior to experimental observations, revealed for Cu(I)-catalyzed cycloaddition of nitrile oxides to 1-alkynes, a stepwise mechanism involving unprecedented metalacycle intermediates, which appear to be common for a variety of dipoles (382).

1.3.4.3.2. Cycloaddition at C≡N and C≡P Bonds Important information concerning cycloadditions of nitrile oxides to C≡N and C≡P bonds is collected in review (289). Here, recent data and those concerning individual unconventional types of nitriles and phosphaacetylenes are presented.

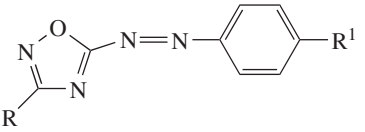
Reactions of hydroximinoyl chlorides, RCCl:NOH, with cyanogen and diazocyanides, 4-$R^1C_6H_4N$ = NCN gave bi[1,2,4]oxadiazoles **224** or arylazooxadiazoles **225** (390). The reaction of dialkylcyanamides with EtO_2CCl:NOH gave (dialkylamino)oxadiazolecarboxylates **226**; the reaction of arylcarbohydroximinoyl, chloridesRCCl:NOH, with N-cyanomorpholine gave 3-aryl-5-morpholino-1,2,4-oxadiazoles **226** (366).

The carbon-nitrogen triple bond of aryl thiocyanates acts as a dipolarophile in 1,3-dipolar cycloadditions. Reactions with nitrile oxides yield 5-arylthio-1,2,4-oxadiazoles **227** (X = O; Y = S). Aryl selenocyanates behave similarly forming 5-arylseleno-1,2,4-oxadiazoles **227** (X = O; Y = Se). Reactions of 5-aryl-1,2,4-oxadiazoles with secondary amines, such as piperidine, yield 5-piperidino-1,2,4-oxadiazoles **227** (X = O; YR^1 = piperidino) (391).



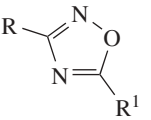
224

R = Ph, 3-FC_6H_4, 4-FC_6H_4, 4-$O_2NC_6H_4$, 2-$O_2NC_6H_4$;
R^1 = Cl, Br, NO_2



225

R = EtO_2C;
R^1 = NMe_2, morpholino, piperidino
R = 4-$O_2NC_6H_4$, 3-FC_6H_4, 2-FC_6H_4;
R^1 = morpholino



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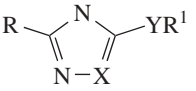
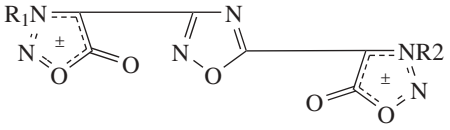


227

R = Ph, 3-MeC_6H_4, 4-$O_2NC_6H_4$; R^1 = 4-$O_2NC_6H_4$, 1-naphthyl

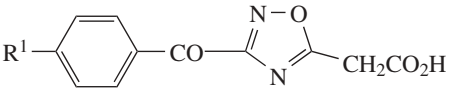
3-Arylsydnone-4-carbonitrile oxides, which are generated *in situ* by thermal dehydrochlorination of the corresponding hydroximic acid chlorides, undergo 1,3-dipolar cycloadditions with sydnone-4-carbonitriles to give 3-aryl-4-[5-(3-arylsydnonyl)-1,2,4-oxadiazol-3- yl]sydnones **228** (392).



228

R^1 = *p*-$EtOC_6H_4$, Ph, *p*-tolyl; R^2 = *p*-anisyl, *p*-tolyl, *p*-$EtOC_6H_4$, Ph, cyclohexyl

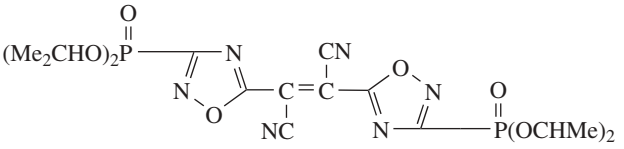
Aroylglyoxylonitrile oxides 4-$R^1C_6H_4COCNO$, undergo a cycloaddition reaction with $CH_2(CN)_2$. The 3-aroyl-1,2,4-oxadiazole-5-acetonitrile obtained are converted to the corresponding (3-aroyl-1,2,4-oxadiazol-5-yl)acetic acids **229** (393).



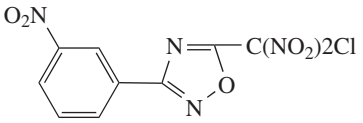
229

R^1 = H, Me, OMe, Cl, F

A phosphorylnitrile oxide $(Me_2CHO)_2P(O)CNO$ reacts with tetracyanoethylene to give the bisadduct **330** (296). Reaction of cyanodinitrochloromethane with 3-nitrobenzonitrile oxide gives 5-chlorodinitromethyl-3-(3-nitrophenyl)-1,2,4-oxadiazole **331** (394).



330



331

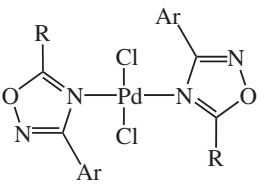
A significant acceleration of 1,3-dipolar cycloaddition of nitriles with nitrile oxides is shown, in the absence of solvent, at microwave irradiation (395). The reactions are finished within 2 to 10 min, to give 1,2,4-oxadiazoles in good yields.

A new route to 1,2,4-oxadiazoles and their complexes via Pt- and Pd-mediated 1,3-dipolar cycloaddition of nitrile oxides to organonitriles, has been reported. The sequence of the metal-mediated [2 + 3] cycloaddition offers an alternative route for the preparation of oxadiazoles.

Significant activation of the CN group in organonitriles upon their coordination to a Pt(IV) center has been found in the reaction of $[PtCl_4(RCN)_2]$ (R = Me, Et, CH_2Ph) with stable aromatic nitrile oxides, ArCNO (Ar = 2,4,6-$R'_3C_6H_2$; R′ = Me, OMe), to give the (1,2,4-oxadiazole)platinum(IV) complexes, $PtCl_4$.HetH (HetH = 3-Ar-5-R-1,2,4-oxadiazole; Ar and R see above). The [2 + 3] cycloaddition has been performed under mild conditions even starting from complexed acetonitrile and propionitrile, which exhibit low reactivity in the free state. The reaction between complexes $PtCl_4$.HetH and one equivalent of $Ph_3P{:}CHCO_2Me$ in CH_2Cl_2 leads to the appropriate Pt(II) complexes $PtCl_2$.HetH; the reduction fails only in the case of $PtCl_4$.HetH (Ar = mesityl, R = Me) because it is insoluble in most common organic solvents. The oxadiazoles formed in the metal-mediated reaction are liberated, almost quantitatively, from their Pt(IV) complexes by reaction of the latter with an excess of pyridine in $CHCl_3$, giving free 1,2,4-oxadiazoles and *trans*-$[PtCl_4(pyridine)_2]$ (396).

The reactions between stable 2,4,6-trisubstituted benzonitrile oxides ArCNO and *trans*-$[PdCl_2(RCN)_2]$ complexes, or RCN (R = Me, Et, CH_2CN, NMe_2, Ph), in the presence of $PdCl_2$, proceed under mild conditions and give the 1,2,4-oxadiazole *trans*-complexes of the type **332** in 40% to 85% yields. In CH_2Cl_2, the reaction between the nitrile oxides and $[PdCl_2(MeCN)_2]$ furnishes

complexes $[PdCl_2(ONCAr)_2]$, which are the first representatives of metal compounds in which nitrile oxides act as ligands. The liberation of the heterocyclic species from **332** is successfully performed by substitution reactions either with 1,2-bis(diphenylphosphino)ethane or with an excess amount of $Na_2S.7H_2O$ in MeOH (397).



332

Ar = 2,4,6-$Me_3C_6H_2$, 2,4,6-$(MeO)_3C_6H_2$
R = Me, Et, CH_2CN, NMe_2, Ph

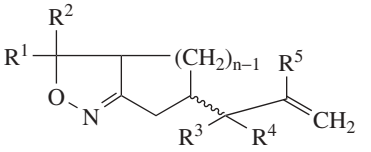
The cycloaddition of nitrile oxides to nitriles, and its Pt(II) and Pt(IV) complexes, *trans*-$[PtCl_2(NCMe)_2]$ and *trans*-$[PtCl_4(NCMe)_2]$, was investigated by quantum chemical methods at different levels of theory, using quasi-relativistic pseudopotentials for the platinum atom. The activation of the nitriles ligated to Pt(IV) can be interpreted in terms of both kinetic (activation parameters) and thermodynamic (reaction energies) viewpoints. The higher reactivity of the Pt(IV) complex, when compared with that of the Pt(II) complex, is kinetically controlled. The calculations predict that the Pt(II) complex should be less reactive than free acetonitrile, and that the relative reactivity of the Pt(II) complex is governed mainly by the entropic factor. The cycloaddition of nitrile oxide to nitriles is mainly controlled by the $HOMO_{nitrile\ oxide}$-$LUMO_{nitrile}$ type of interaction and occurs via a concerted asynchronous mechanism for both free and bound nitriles rather than via a stepwise mechanism (398).

Mesitylphosphaacetylene 2,4,6-$Me_3C_6H_2C{\equiv}P$, (synthesized by $AlCl_3$-initiated elimination of $(Me_3Si)_2O$ from $Me_3SiP=C(OSiMe_3)C_6H_2$-2,4,6-Me_3), undergoes [3 + 2] cycloaddition reactions with nitrile oxides to yield oxaazaphosphole derivatives (399).

1.3.4.4. Intramolecular Cycloaddition Intramolecular nitrile oxide cycloaddition (INOC) is widely used in the synthesis of various compounds, particularly, natural products. This field is reviewed in detail in Chapter 6 of the monograph/Reference 5 and also in Reference 400 limited to nitrile oxides generated from nitroalkenes. Some features of INOC are illustrated in this subsection by new data and those omitted in Reference 5.

Reactions with participation of the C=C bond are the most studied of INOCs. Normal products of such reactions are annulated isoxazolines. A synthesis of bicyclic isoxazolines via sequential Michael and intramolecular 1,3-dipolar additions (403) are mentioned as an example. Michael addition of 1-nitroalkadiene, $R^1R^2C{=}CH(CH_2)_nCH{=}CHNO_2$ to allylic stannane $R^3R^4C{=}C(R^5)CH_2SnR^6{}_3$

($R^6 = Me, Ph$) was induced by $TiCl_4$ at -78° in CH_2Cl_2. A nitrile oxide, generated by subsequent addition of Et_3N in THF, underwent intramolecular addition to give 8% to 92% of compounds **333** as diastereoisomeric mixtures.



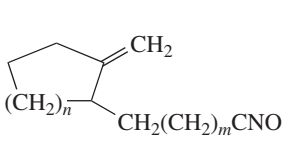
333

R^1 = H, Me, Ph, $CH{:}CH_2$; R^2 = H, Me; n = 2, 3;

R^3 = H, Me, Ph; R^4, R^5 = H, Me

A study of Lewis acid-promoted reactions of 1-nitroalka-1,5-(or 1,6-)dienes with allylic stannanes shows that, in the presence of $TiCl_4$, 1-nitrohexa-1,5-diene reacts smoothly with allyltrimethylstannane to give a diastereoisomeric mixture of 6-allyl-3a,4,5,6-tetrahydro-3*H*-cyclopent[*c*]isoxazoles, while the reaction, using $AlCl_3$ as catalyst, leads to allylated cyclohexanone oxime derivatives in good yield. A similar reaction of 1-nitrohepta-1,6-diene, however, gives a bicyclic isoxazoline, irrespective of the Lewis acids employed. In the latter case, nitrile oxides derived from 1-nitroalka-1,6-dienes undergo a stepwise cycloaddition, as shown by the lack of stereospecificity in the reactions of (1*E*,6*Z*)-1-nitro-7-phenylhepta-1,6-diene and (1*E*,6*Z*)-1-nitroocta-1,6-diene (402).

Certain specific steric effects are operative on intramolecular nitrile oxide—olefin cycloadditions. These effects are governed by both ring size and character of substituents. Thus, cycloadditions to the exomethylene group are successful with substituted methylenecyclohexanones **334** ($m = 1, 2$; $n = 2$) and gave tricyclic **335** ($m = 1, 2$), but do not occur with methylenecyclopentanones **334** ($m = 1, 2, 3$; $n = 1$). Activation energies calculated by molecular mechanics are consistent with these results. Cleavage of **335** ($m = 2$) by Raney Ni gives *cis*-decalone **336** (403).



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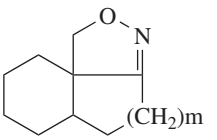

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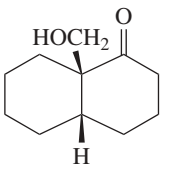
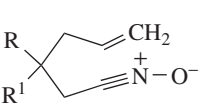


336

Substituent effects on intramolecular dipolar cycloadditions can be illustrated by the *gem*-dicarboalkoxy effect (404). This effect (rel. rate > 20) has been

measured for the reaction **337** → **338** (R = R′ = CO_2Me) and good diastereoselectivity (ca 9:1) has been observed in reactions **337** → **338** (R = Me, Ph; R′ = H) for the intramolecular dipolar cycloaddition of three substituted 5-hexene nitrile oxides.



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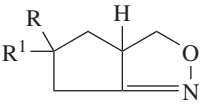
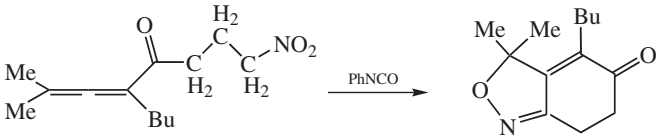


338

The study of the intramolecular nitrile oxide—allene cycloaddition shows, in particular, that dehydration of nitroallene **339** by PhNCO, generates a nitrile oxide *in situ*, which gives isoxazoline **340** (Scheme 1.36). Thus, the reaction of the more remote double bond with the formation of six-membered ring prevails (405).

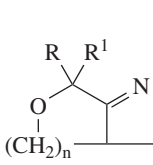


339 **340**

Scheme 1.36

Many investigations are devoted to INOCs leading to fused biheterocyclic systems.

The reaction of O-trimethylsilyl α-bromoaldoximes, $RR^1CBrCH{=}NOSiMe_3$ (R = R^1 = Me; R = Ph, Me, R^1 = H) with unsaturated alcohols produces oximino ethers $RR^1C(CH{=}NOH)O(CH_2)_nCH{=}CH_2$ (n = 1, 2), which can be readily oxidized with sodium hypochlorite. The intermediate nitrile oxide formed, undergoes cyclization affording fused isoxazolines **341** (406). O-Allylsalicylaldoxime, o-$CH_2{=}CHCH_2OC_6H_4CH{=}NOH$ gives isoxazoline **342** on treatment with iodobenzene dichloride (57). Intramolecular nitrile oxide—olefin cycloaddition of 2-(2-nitro-1-phenylethoxy)-1,5-hexadiene **343** proceeds with high regioselectivity to form a [5,5] ring system (407).



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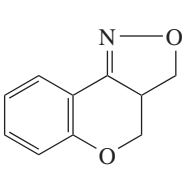
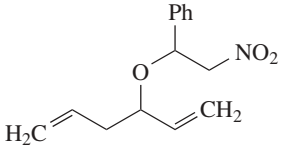
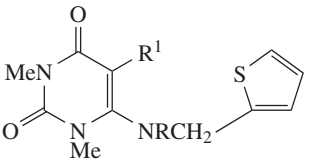


342



343

INOCs in biheterocyclic systems, where the CNO group is bonded to one heterocycle and the C=C bond belongs to the second heterocycle, open an elegant route to polyheterocyclic systems. Thus, nitrile oxides **344** (R = 4-BrC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, etc., R^1 = CNO), generated from the corresponding oximes **344** (R^1 = CH=NOH) on treatment with Et_3N–NaOCl in H_2O-CH_2Cl_2 undergo intramolecular cycloaddition to give 75% to 80% heterocycles **345** (408).



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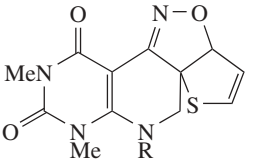
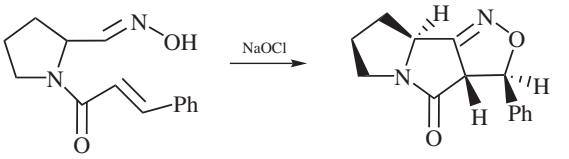


345

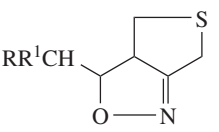
Functionalized, enantiomerically pure 3,4-dihydropyrrolidin-2-one and 1,2-dihydropyrrolizidin-3-one systems, have been prepared by INOC, starting from enamido-oximes **346** (Scheme 1.37) and by subsequent reduction of the obtained cycloadducts, **347** (409). Substituted hexahydroisoxazolo[3,4-*a*]pyrrolizinone **347** has been obtained by an *in situ* INOC procedure in 60% yield, as a mixture (4:1) with its minor diastereoisomer, and purified by semipreparative HPLC.



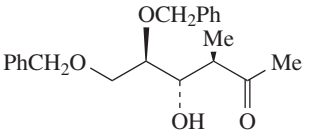
346 **347**

Scheme 1.37

The INOC reaction of chiral olefins with a sulfur atom in the carbon chain, connecting dipole and dipolarophile, occurs with poor to excellent *anti*-stereoselectivity, which is mainly affected by the substituents at the allylic stereocenter. Thus, treating chiral (*E*)- and (*Z*)-$RR^1CHCH{=}CHCH_2S(CH_2)_2NO_2$ with 4-ClC_6H_4NCO and Et_3N leads to isoxazolines **348** as diastereomeric mixtures. Catalytic hydrogenation of **348** (R = CH_2OCH_2Ph, R^1 = OCH_2Ph), using Raney nickel, affords β-ketol **349** quantitatively (410).

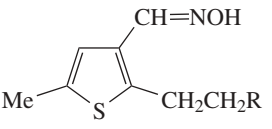


348



349

Oxidation of (alkenylthio)thiophenecarboxaldehyde oxime **350** (R = allyl) by NaOCl gives the nitrile oxide, which cyclizes to thieno[2,3-*b*]thiocino[4,5-*c*] isoxazole **351**. However, isomeric **350** (R = isopropenyl), under the same conditions, is converted to the unusual product, thieno[2,3-*b*]thiocin **352**. In both reactions, cyclodimerization products of nitrile oxides are also obtained. Structures of compounds **350** (R = isopropenyl) and **352** have been studied by X-ray diffraction analysis (411).



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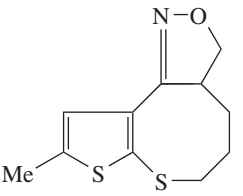

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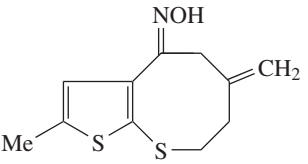
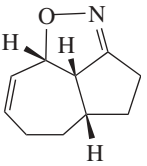


352

Intramolecular 1,3-dipolar cycloaddition of cyclo-1,3-diene- and -1,3,5-triene-tethered nitrile oxides give tricyclic isoxazolines, for example, **353**, as a single stereoisomer.

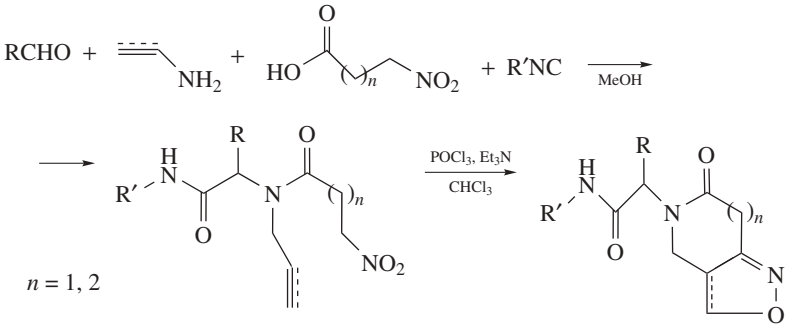


353

The relative stereochemistry of tricycle-fused isoxazolines resulting from 1,3-dipolar cycloaddition of cyclo-1,3-diene-tethered nitrile oxides is *cis-cis*, whereas from cyclohepta-1,3,5-triene-tethered nitrile oxides the cis-trans isomer predominates (412).

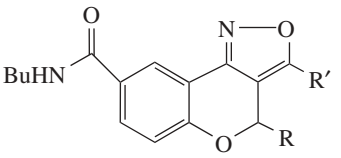
A promising combination of sequential multicomponent Ugi reaction and INOC has been carried out for the preparation of fused isoxazoles and isoxazolines (413). The coupling of these two reactions (Scheme 1.38) provide access to the heterocyclic ring systems in two steps, from easily available starting materials (e.g., R = Ph, R′ = $PhCH_2$), in moderate to good overall yields (the yields of Ugi reaction products **354** were 50%–70%, those of the INOC products **355** were 27%–64%).

A solid-phase synthesis of substituted benzopyranoisoxazoles **356** (I; R = H, Me, Et, Pr, Ph, $CHMe_2$; R^1 = H, Me, decyl, Ph) has been described (414). The six-step synthesis includes a method of generating nitrile oxides on a polymer support, followed by an intramolecular 1,3-dipolar cycloaddition with a tethered alkyne, for assembly of the benzopyranoisoxazole scaffold.



354 **355**

Scheme 1.38

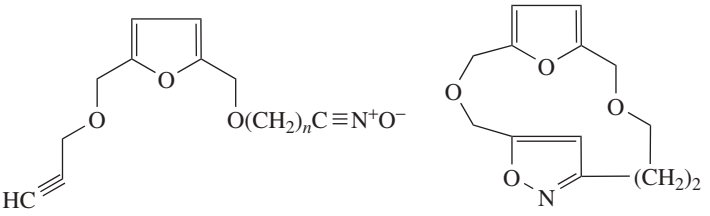


356

R = H, Me, Et, Pr, Ph, $CHMe_2$

R′ = H, Me, decyl, Ph

The intramolecular cycloaddition reactions of the nitrile oxides **357** ($n = 1$, 2, 3, 9), obtained *in situ* from the 2,5-difunctional furan hydroximoyl chlorides or nitro compounds (415) has specific features because of the 2,5-arrangement of two open chains bearing acetylenic and fulminic moieties. Only with **357** ($n = 3$) is the expected furanoisoxazolophane **358** formed, in acceptable yield. Compound **357** ($n = 9$) gives a complex product mixture whereas **357** ($n = 1$, 2) gives rise to the exclusive reaction of the dipole with a double bond of the furan system.



357 **358**

1.3.5. Miscelaneous

Reactions other than those discussed in subsections 1.3.1. to 1.3.4. are presented here. Transformations of nitrile oxides by the action of reductive agents and

electrophiles as well as processes involving oxidation steps and some unconventional cycloadditions are considered in this subsection.

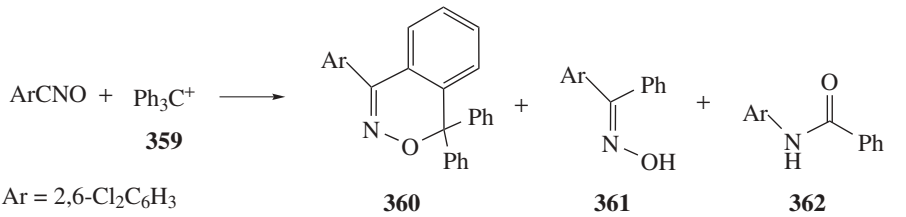
Electrochemical behavior of a series of stable aromatic nitrile oxides as well as benzonitrile oxide and 1-adamantylformonitrile oxide have been studied (416). Radical anions were detected by electron spin resonance (ESR) in the first stage of electrochemical reduction of *p*- and *m*-NO_2-substituted benzonitrile oxides. Analysis of the splitting constant reveal that the unpaired electron is localized mainly on the nitro group and the aromatic ring. The suggested mechanism of electrochemical reduction of nitrile oxides includes successive stages of radical anion formation, recombination of the latter to dioxime dianion and, finally, the protonation of the dianion to dioxime monoanion RC(=NO^-)C(=NOH)R, furoxan formation being excluded.

Reactions between nitrile oxides ArCNO and benzylic carbocations **359** produce addition products, such as benzoxazines **360**, oximes **361**, and amides **362** (Scheme 1.39) (417).

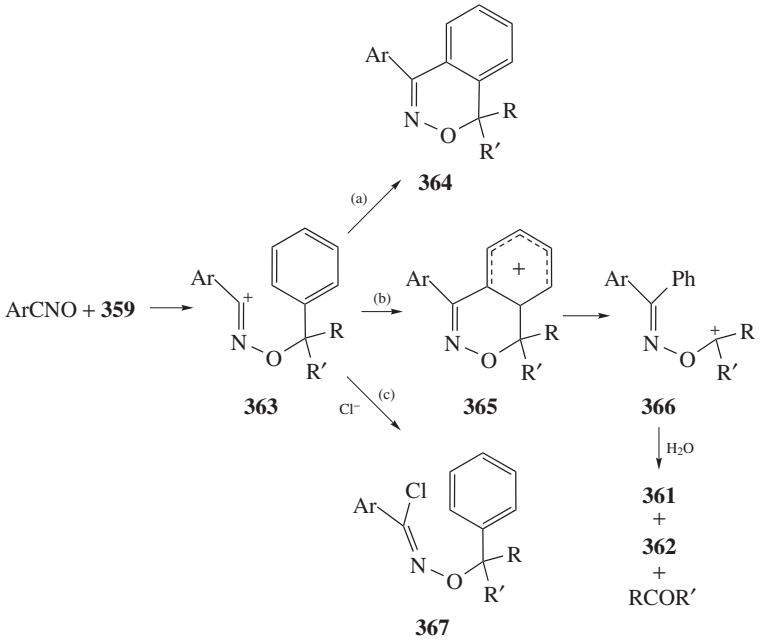
Different results have been obtained when the carbocations are generated from the corresponding chlorides with various Lewis acids. Primary, secondary, and tertiary carbocations showed different reactivities. The product ratios depend strongly on the substituents on the aromatic ring of the benzylic carbocations. The proposed mechanism (417) is illustrated by Scheme 1.40. The key cationic intermediate **363**, formed from ArCNO and **359**, undergoes further transformations. Route (a) leads to benzoxazines **364**, which are isolated for tertiary, for example, **360**, and secondary carbocations, **364** (R = H, R′ = 3-$MeOC_6H_4$). Route (b) gives successively cations **365** and **366**. Hydrolysis of the latter affords oximes of the type **361**, amides of the type **362**, and ketones (aldehydes) RCOR′. Finally, route (c) giving O-substituted chlorooximes **367** is confirmed by the isolation of compounds with R = 4- $MeOC_6H_4$.

In the case of primary carbocation, reaction with nitrile oxide gives a mixture of two regioisomeric oximes (Scheme 1.41). Probably, this is a result of the attack of the nitrile oxide – BF_3 complex on neutral 3-chloromethylanisole.

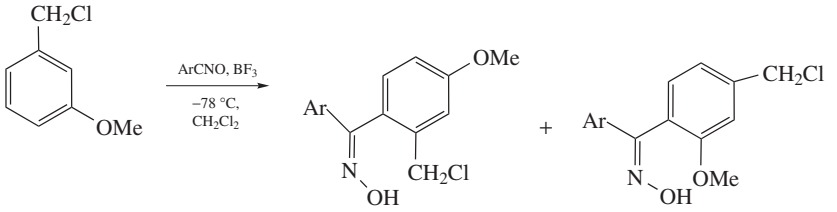
Treatment of γ-nitrothioamides **368** with phenyl isocyanate and triethylamine (nitrile oxide generation conditions) leads to α,β-unsaturated nitriles **369**. The mechanism proposed for this reaction is shown in Scheme 1.42, which includes the dehydration stage of the nitrile oxide formed (418).



Scheme 1.39

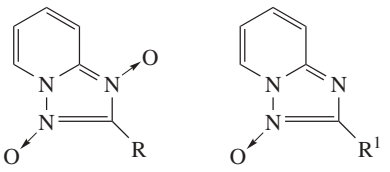


Scheme 1.40



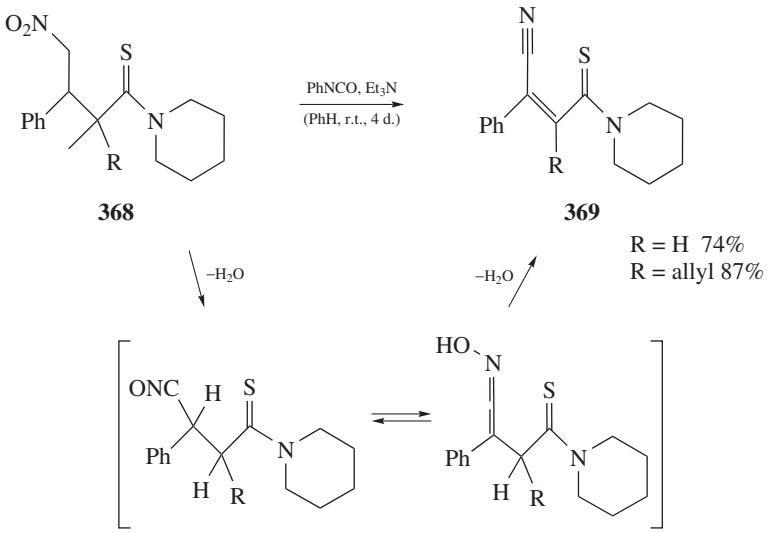
Scheme 1.41

Reactions of 2-nitrosopyridine with nitrile oxides afford, depending on structure of the latter, either 1,2,4-triazolo[1,5-*a*]pyridine 1,3-di-N-oxides (**370**) or the corresponding 1,2,4-triazolo[1,5-*a*]pyridine 3-oxides (**371**) (419).



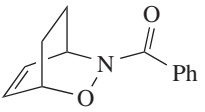
370 **371**

R = 2,6-$Cl_2C_6H_3$, 4-$O_2NC_6H_4$; R^1 = 2,4,6,-$Me_3C_6H_2$, Ph, 4-MeC_6H_4, 4-ClC_6H_4



Scheme 1.42

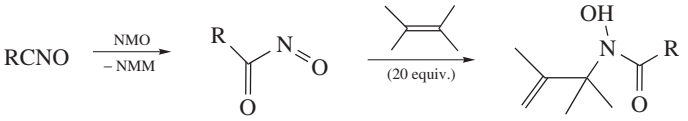
Nitrile oxides are oxidized by tertiary amine N-oxides, for example, N-methylmorpholine N-oxide, in various solvents at room temperature to unstable nitrosocarbonyl compounds. In the presence of dienes, such as 1,3-cyclohexadiene, they afford Diels–Alder adducts, e.g., **372** from PhCNO, in fair yields. The mild conditions used in oxidizing a variety of nitrile oxides promise a wide application of this method in synthetic processes (420).



372

Nitrosocarbonyl intermediates **373**, generated under mild conditions, (r.t., 12h) by the mild oxidation of nitrile oxides RCNO with N-methylmorpholine N-oxide, undergo ene reactions with tetramethylethylene and cyclohexene to give N-hydroxy-substituted amides **374** in 95% to 99% yield (Scheme 1.43). Other nitrile oxides RCNO (R = 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, Me, Pr, Hex, $PhCH_2$, PhCH=CH and PhCO), also react *in situ*, to give products of ene reactions in high yield. With less substituted ethylenes (1,1-dimethyl-, 1,2-dimethylethylenes and α-methylstyrene), the ene pathway is still active but the oxidation step of the nitrile oxides competes with the cycloaddition to the olefins. The nitrosocarbonyl intermediates, such as **373**, are claimed as "super-enophiles", allowing mild carbon-nitrogen bond formations (421).

The synthesis of 1,2,4-oxadiazole-4-oxides with a polystyrene solid phase attached at position 3 of the heterocycle has been performed in cycloadditions



373 **374**

R = Ph, 4-ClC_6H_4, Mes

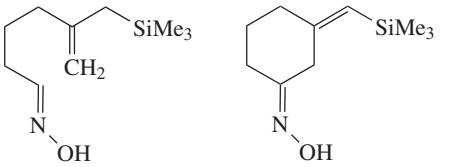
NMO is N-methylmorpholine N-oxide

NMM is N-methylmorpholine

Scheme 1.43

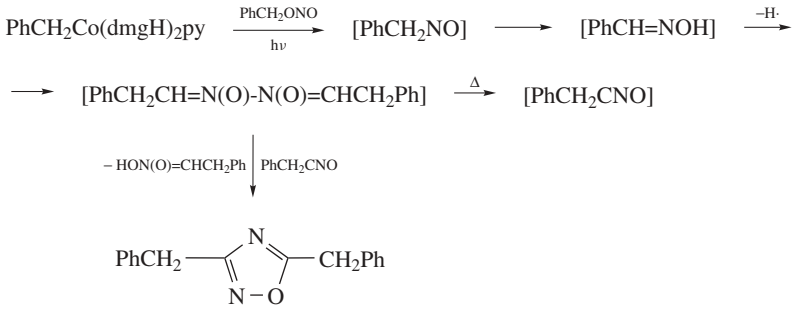
of stable supported nitrile oxides to amidoximes. The photochemical cycloreversion of these heterocycles affords free nitrosocarbonyl intermediates, which are trapped by suitable dienes or enes. The method is considered a clean and environmental friendly approach to the fleeting nitrosocarbonyl intermediates, which afford valuable adducts in various synthetic applications. The isomeric heterocycles, adhered at position 5 of the ring, are also obtained by cycloaddition of nitrile oxides to supported amidoximes. Their photolysis affords resin-bound nitroso carbonyls that are trapped with dienes, affording valuable supported adducts suitable for further elaboration in solid-phase chemistry (422).

Rather than the expected [3 + 2] cycloaddition, a novel ene-like cycloisomerization occurs on deprotonation of allyltrimethylsilyl-oxime compounds, when the β-sp^2 carbon atom of the allyltrimethylsilyl moiety is tethered to the oxime unit. The resulting nitrile oxide group serves as an enophile, and the final cyclized product still has two functional groups suitable for further manipulations. Thus, ene-like cycloisomerization of allyltrimethylsilyl-oxime **375** with NaOCl in CH_2Cl_2 gives 82% of cyclized product **376** (423). See also Reference 424.



375 **376**

DFT studies of the intramolecular ene-like (or the so-called 1,3-dipolar ene) reaction between nitrile oxides and alkenes show that this reaction is a three-step process involving a stepwise carbenoid addition of nitrile oxide to form a bicyclic nitroso compound, followed by a retro-ene reaction of the nitrosocyclopropane intermediate. The competitive reactions, either the intramolecular [3 + 2] cycloaddition between nitrile oxides and alkenes or the intermolecular dimerization of nitrile oxides to form furoxans, can overwhelm the intramolecular 1,3-dipolar ene reaction if the tether joining the nitrile oxide and alkene is elongated, or if substituents such as trimethylsilyl are absent (425).



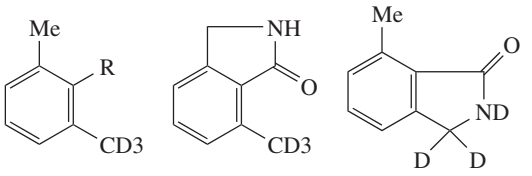
Scheme 1.44

The benzyl ligand of benzylbis(dimethylglyoximato)pyridine cobalt complex has been selectively converted to 3,5-dibenzyl-1,2,4-oxadiazole by a reaction with alkyl nitrite in the presence of light (426). The reaction proceeds by the *in situ* formation of an oxime and a nitrile oxide (Scheme 1.44).

Ion-molecule reactions of ionized nitrile oxide, R-C≡N^+-O, with several neutral nitriles, R′CN, were studied, using both tandem mass spectrometric techniques and *ab initio* MO calculations (427). Ionized oxygen atom transfer and formal substitution of nitric oxide by the neutral reagent in the radical cation are the main processes. Whereas the former reaction yields the corresponding ionized nitrile oxide, R′-C≡N^+-O, the second process gives an electron species tentatively ascribed, following high-kinetic energy collisional activation experiments, to an aromatic azirinium cation. All the experimental data point to a two-step reaction sequence where the primarily formed intermediate ions competitively dissociate by the loss of nitrile or of nitric oxide, respectively, giving nitrile oxide ions and azirinium ions.

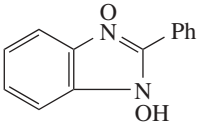
The mechanism of the simplest reaction $HCNO^+ + HCN \rightarrow$ *cyclo*-$HCCHN^+$ + NO has been explored at the MP2/6–31G(d) level of theory. The most favorable reaction profile involves the formation of a C—N bond between the positively charged carbon atom of $HCNO^+$ and the nitrogen atom of hydrocyanic acid giving an $HCNO^+$/HCN intermediate which isomerizes into an ionized nitrosoazirine before losing NO.

Photolysis of nitrile oxide **377** (R = CNO) gives acylnitrene **377** (R = CON), which undergoes intramolecular insertion reactions to give products **378** and **379** (428).



377 **378** **379**

Benzonitrile oxide reacts with nitrosobenzene to give α-nitrosonitrone $PhN(O)=CPhNO$, which cyclizes to hydroxyphenylbenzimidazole oxide **380** and/or benzoxadiazine **381** (R = Ph). Similar reactions of PhNO with *p*-MeC_6H_4CNO and EtO_2CCNO give **381** (R = *p*-tolyl and CO_2Et). Nitrosomesitylene 2,4,6-$Me_3C_6H_2NO$ reacts with PhCNO and *p*-MeC_6H_4CNO to give α-nitrosonitrones 2,4,6-$Me_3C_6H_2N(O)=CRNO$ (R = Ph, *p*-tolyl), which do not undergo cyclization reactions (429).



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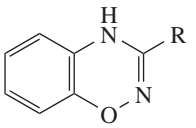
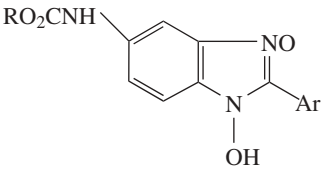


381

Arenecarbonitrile oxides react with alkyl (*p*-nitrophenyl)carbamates at the nitro group, the nitrogen atom of the latter being the nucleophilic center. Tautomeric N-hydroxybenzimidazole N-oxides **382** and **383** form as the final products (430).



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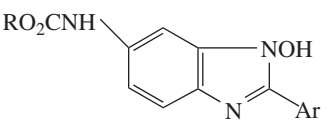
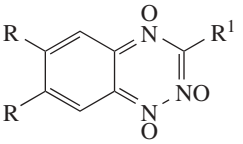


383

Benzo-*as*-triazine tri-N-oxides **384** (R = H, Me; R^1 = mesityl, 2,6-ClC_6H_3) are formed from the reaction of nitrile oxides R^1CNO with benzofuroxans **385**. The structure of **384** (R = Me, R^1 = mesityl) has been confirmed by X-ray crystal structure analysis (431).



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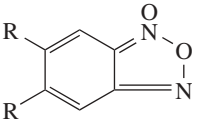
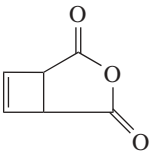


385

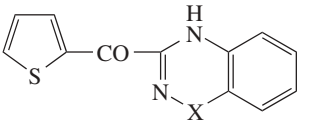
The efficiency and limitations of 3-oxabicyclo[3.2.0]hept-6-ene-2,4-dione **386** (cyclobut-3-ene-1,2-dicarboxylic anhydride) as an acetylene equivalent in 1,3-dipolar cycloadditions has been reported. It reacted readily with a variety of reagents, including nitrile oxides. In all cases, the sterically favored anti-isomers

are formed exclusively. When subjected to flash-vacuum pyrolysis, the adducts undergo thermal fragmentation, either by a retro-cleavage, or by loss of maleic anhydride, to form products that are similar to those from reactions of acetylene in the cycloaddition step. A concerted pathway is proposed for the pyrolytic conversion into the "formal acetylene cycloadduct" rather than a stepwise radical mechanism (432).



386

2-Thenoylcarbohydroxamoyl chloride, as precursor of 2-thienylglyoxylonitrile oxide undergoes nucleophilic 1,3-addition with *o*-phenylenediamine, *o*-aminothiophenol and methyl anthranilate to afford benzotriazine **387** (X = NH), benzothiadiazine **387** (X = S), and quinazoline **388**, respectively. With acrylonitrile and diethyl acetylenedicaboxylate, 1,3-dipolar cycloaddition proceeds to give 5-cyano-3-thenoylisoxazoline **389** and diethyl 3-thenoylisoxazole-4,5-dicarboxylate **390**, respectively. However, nitroso derivatives of imidazo[1,2-*a*]pyridines **391** (X = X^1 = CH; R = H, 8-Me, 6-Cl), imidazo[1,2-*a*]pyrimidine **391** (X = N, X^1 = CH, R = H), and imidazo[1,2-*a*]pyrazine **391** (X = CH, X^1 = N) have been obtained in good yields by the action of 2-thenoylhydroxamoyl chloride to 2-aminopyridines, 2-aminopyrimidines and 2-aminopyrazines, respectively (433).



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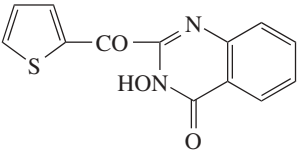

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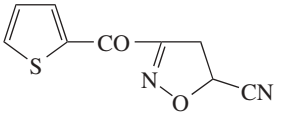

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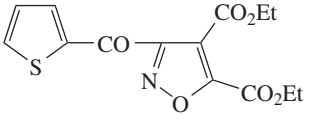

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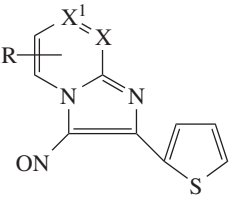


391

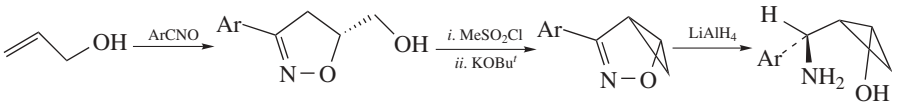
β-(2-Aminophenyl)-α,β-ynones react with nitrile oxides by domino [3 + 2] cycloaddition/annulation reactions, giving rise to isoxazolo[4,5-*c*]quinolines in satisfactory yields (434). Nitrile oxides undergo addition to allylzinc bromide to generate 5-butenylisoxazolines in good yields. The domino reaction combines 1,3-cycloaddition with Wurtz coupling (435).

1.4. APPLICATIONS OF NITRILE OXIDES

1.4.1. Nitrile Oxides in Organic Synthesis

Versatile uses of nitrile oxides in organic synthesis up to year 2000 are well reviewed by Jaeger and Colinas (5). Therefore, this subsection is limited to data published after 2000 with the exclusion of those cited in Reference 5. The contents of the subsection are organized by taking into account the chemical structure (Sections 1.4.1.1 and 1.4.1.2), natural origin of parental compounds (Section 1.4.1.3), and biological activity of synthesized compounds (Section 1.4.1.4).

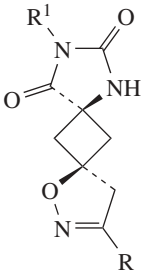
1.4.1.1. Syntheses of Carbocyclic Compounds (1*S*,2*S*)-2[(*S*)-Amino(4-methoxyphenyl)methyl]cyclopropan-1-ol **392** (Scheme 1.45) has been prepared by a stepwise procedure involving a 1,3-dipolar nitrile oxide cycloaddition to allyl alcohol followed by a construction of the cyclopropa[*d*]isoxazole system, and reduction of the bicycle (436).



Ar - 4-MeOC$_6$H$_4$ **392**

Scheme 1.45

Achiral hydantoin- and isoxazoline-substituted dispirocyclobutanoids **394** have been prepared by solid-phase synthesis (437). The facial and selective Boc-NH-mediated H-bond delivery of nitrile oxides afford dispirocyclobutanoids **394** (R = Bz, Et; R^1 = Ph, PhCH$_2$, Bu) as major compounds.



394

On treatment with a base such as NaOMe or even $LiAlH_4$, mono-cycloadducts of mesitonitrile oxide and polycyclic aromatic hydrocarbons have been cleaved to yield the corresponding oximes, which are oxidized to ketones by the Dess–Martin method. The same ketones have been obtained by reductive ring opening of the mono-cycloadducts with Raney Ni (438).

Anthracene groups have been linked to [60]fullerene by the [3 + 2] cycloaddition of the corresponding nitrile oxides. The anthryl groups of the fullerene derivatives react readily with singlet oxygen to form the 9,10-epidioxides on photo-oxidation (439). The adduct of fullerene C_{60} with ferrocenylformonitrile oxide (generated from the corresponding oxime) has been prepared. The ferrocene derivative is bound to C_{60} at the 6–6 bond of the isoxazoline ring. The reaction may lead either to a mono- or diadduct (440).

The addition of nitrile oxides to [60]fullerene, leading to fullerenoisoxazolines, can be reversed, using reducing agents such as $Mo(CO)_6$ or DIBALH. The liberated nitrile oxide is reduced to the corresponding nitrile. This reaction can be used, in principle, for protection/deprotection of [60]fullerene or for solubilization purposes. The isoxazoline moiety can be removed using $Mo(CO)_6$ from the bis-adduct, carrying isoxazoline and pyrrolidine fragments, giving a fullerenopyrrolidine derivative (441).

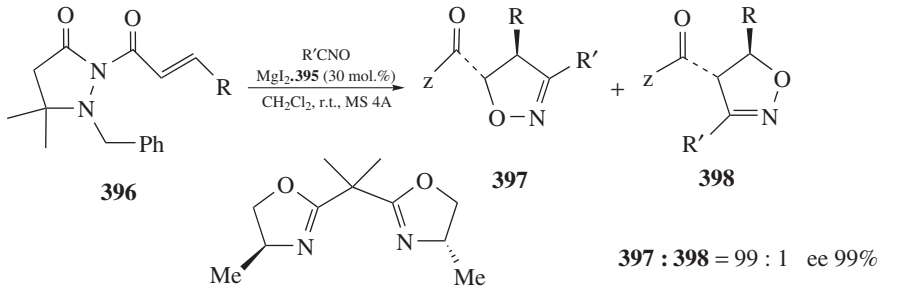
1.4.1.2. Heterocyclic Compounds It is useful to begin this paragraph with recent syntheses of rather simple heterocyclic derivatives, important as intermediates for the preparation of more complicated products. These syntheses can also be used as models for elaboration of new syntheses, first of all, those of stereoselective syntheses.

Formyl C-glycosides, prepared in three steps via the thiazole-based formylation of sugar lactones are readily condensed with hydroxylamine to give the corresponding oximes. The latter are the precursors of glycosyl nitrile oxides via the N-bromosuccinimide method (41).

A highly regio- and enantioselective nitrile oxide cycloaddition to alkenes, using sub-stoichiometric amounts of a chiral Lewis acid like MgI_2**.395** complex, has been reported (442). Pyrazolidinones **396**, prove to be effective achiral templates in the cycloadditions, providing C-adducts, **397**, in high selectivity (compared to isomers **398**) and enantiomeric excess (Scheme 1.46). To avoid potential problems, involving coordination of the Lewis acid by amine bases, a method for the generation of unstable nitrile oxides from hydroximinoyl chlorides, using Amberlyst 21 as the base, has been developed.

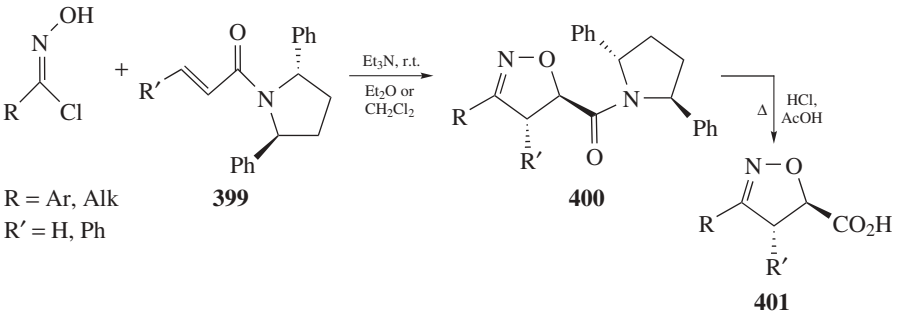
The 1,3-dipolar cycloaddition of a variety of aromatic and aliphatic nitrile oxides to 2,5-*trans*-2,5-diphenylpyrrolidine-derived acrylamide and cinnamamide **399**, efficiently affords the corresponding 4,5-dihydroisoxazole-5-carboxamides **400** in highly regio- and stereoselectivity (Scheme 1.47). Acid hydrolysis of these products affords enantiopure 4,5-dihydroisoxazole-5-carboxylic acids **401** (443).

The cycloaddition of aliphatic nitrile oxides to the analogous methacrylamide also proceeds smoothly to afford the expected cycloadducts in moderate yields



R = Me, Et, Ph, CO_2Et
R′ = Mes, Ph, 2-ClC_6H_4, 4-ClC_6H_4, *t*-Bu, *i*-Bu
z is achiral template

Scheme 1.46



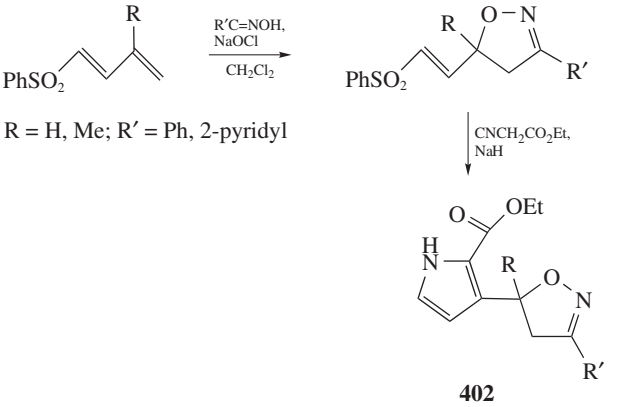
R = Ar, Alk
R′ = H, Ph

Scheme 1.47

and very high regio- and stereoselectivity. In sharp contrast, aromatic nitrile oxides react with the same amide to afford 5-methyl-4,5-dihydroisoxazole-5-carboxamides in higher yields but with a nearly 1:1 mixture of diastereoisomers (443).

5-(3-Pyrrolyl)-4,5-dihydroisoxazole derivatives **402** have been synthesized (Scheme 1.48) in good yields (66%–78%) by regioselective 1,3-dipolar cycloaddition of nitrile oxides to 1-phenylsulfonyl-1,3-dienes, followed by Barton–Zard pyrrole annulation using ethyl isocyanoacetate anion (444).

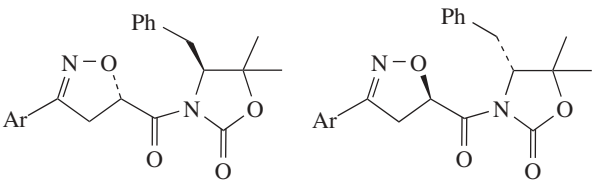
Optically active 3-arylisoxazoline-5-carboxylic acid derivatives **403** or **404** have been, prepared by the reaction of (*S*)- or (*R*)-3-acryloyl-4-benzyl-5,5-dimethyloxazolidin-2-one (**405** or **406**) with nitrile oxides, obtained from benzohydroximoyl chloride and its substituted derivatives in the presence of a catalytic amount of metal salt, for example, $Yb(OTf)_3$ (445). This procedure improves the diastereoselectivity of compounds **403** or **404**, which are industrially useful as intermediates for various drugs and agrochemicals. It also enables the amount



402

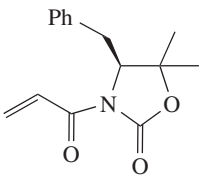
Scheme 1.48

of metal salts to be reduced and thereby makes the reaction industrially applicable. In particular, a mixture (86:14) of diastereomers **403** and **404** (Ar = Ph) was prepared in 71% yield.



403

404



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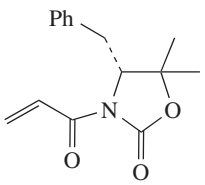
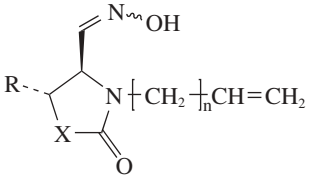


406

Regioselective dipolar cycloadditions of 4-nitro-, 5-nitro-, and 2-methyl-5-nitro-1-vinylimidazoles with nitrile oxides afford the corresponding 5-(imidazol-1-yl)isoxazolines, which are potential intermediates in the synthesis of aminoimidazole analogs of purine nucleosides (446). Isoxazole, isoxazoline and isoxazolidine analogs of C-nucleosides, related to pseudo-uridine, have been synthesized by 1,3-dipolar cycloaddition reactions of nitrile oxides and nitrones, derived from mono- and disubstituted uracil-5-carbaldehydes and 2,4-dimethoxypyrimidine-5-carbaldehyde. The dimethoxy derivatives have been easily deprotected to the corresponding uracil, bearing the heterocyclic ring instead of a sugar moiety (447).

Intramolecular nitrile oxide—olefin cycloaddition of oxazolidine and thiazolidine oximes **407** (R = H, Me; R^1 = H, Me; X = O, S; n = 1,2) proceed stereoselectively, yielding tricyclic fused pyrrolidines and piperidines. Thus, **407** (n = 2; R = H; R^1 = Me; X = S) has been oxidized to the nitrile oxides with sodium hypochlorite, in the presence of triethylamine in methylene chloride, to give the isoxazolothiazolopyridine **408** in 68% yield. Reduction of **408** with lithium aluminum hydride affords mercaptomethylmethylpiperidine **409** in 24% yield (448).



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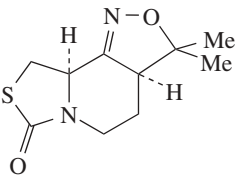

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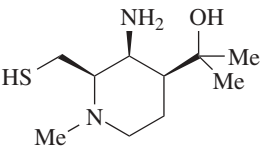
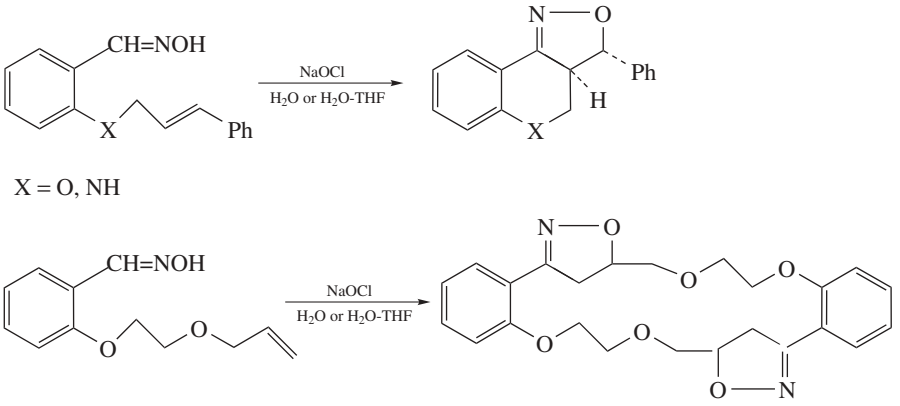


409

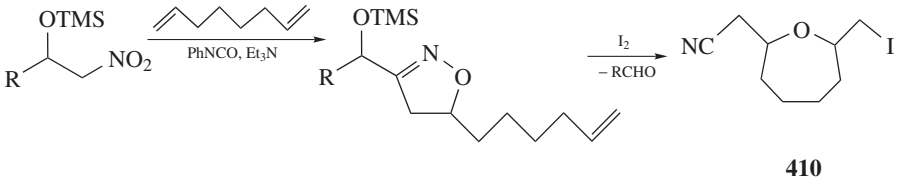
Examples of one-pot 1,3-dipolar cycloaddition in water have been described, affording novel benzopyran, quinoline, and cyclophane isoxazolines (Scheme 1.49) (38).

A variety of cyclic ethers, **410**, have been obtained via both, solution-phase and polymer-supported methods in the [3 + 2] cycloadditions of nitrile oxides to alkenes and dienes to give isoxazolines (Scheme 1.50). Both simple and substituted dienes have been found suitable for polymer-supported formation of cyclic ethers of ring sizes five through seven (449).

Chiral 10 to 12-membered nitrogen and oxygen heterocycles, fused to isoxazoline rings have been prepared with high regio- and stereoselectivity by INOCs of tethered N- and O-allyl carbohydrate derivatives. The use of a -Y-Ar-CH_2 tether, containing a 1,2-disubstituted aromatic ring between the heteroatom attached to

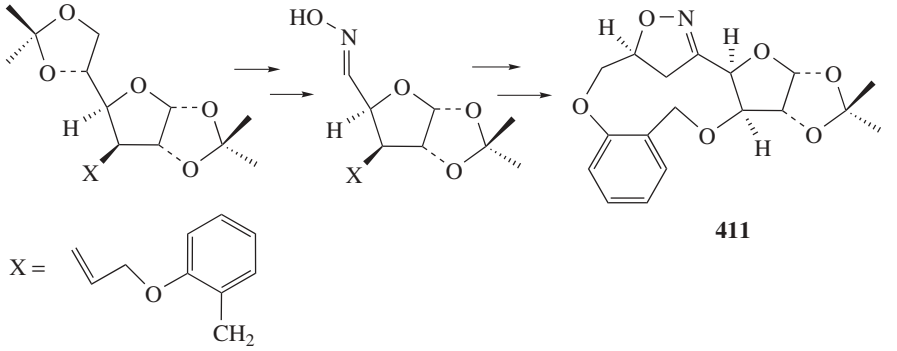


Scheme 1.49



410

Scheme 1.50

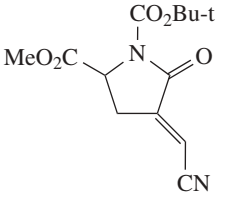


411

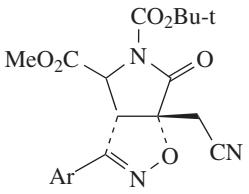
Scheme 1.51

a nitrile oxide-bearing carbohydrate scaffold, and the allyl group, facilitates the formation of medium-sized rings. The cycloaddition affords bridged isoxazolines, **411**, with O-tethered allyl carbohydrate derivatives (Scheme 1.51). But a fused isoxazoline was obtained when a N(Ts)-tethered allyl derivative was used (450).

Reactions of (2*S*,4*E*)-4-(cyanomethylidene)-5-oxo-1,2-pyrrolidinedicarboxylate **412** with 2,4,6-trimethoxybenzene nitrile oxide, performed in the presence of a base, afford racemic isoxazolo fused 2-pyrrolidinone **413** in 82% to 86% diastereomeric excess (451).



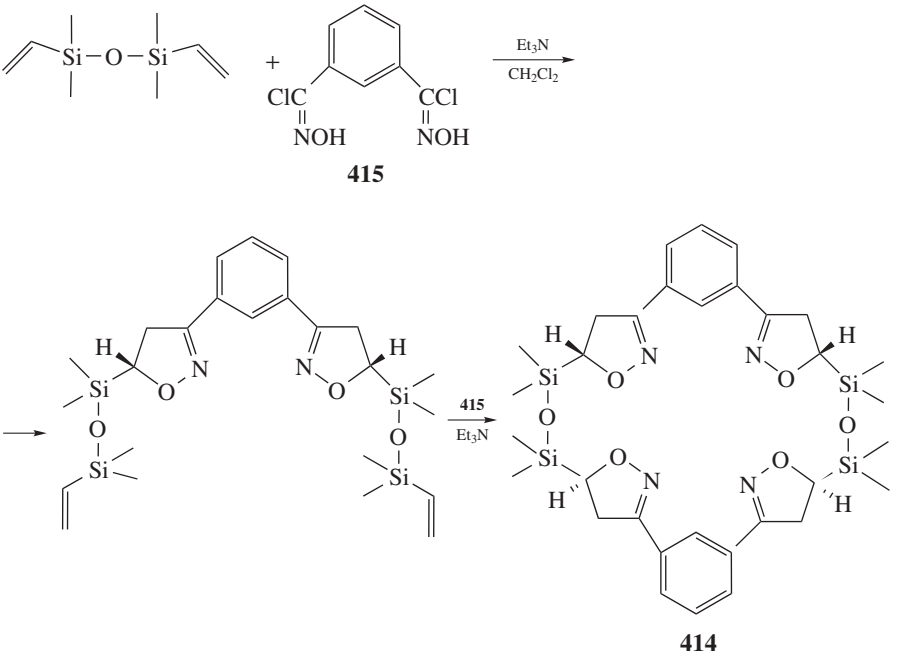
412



413

Ar = 2,4,6-$(MeO)_3C_6H_2$

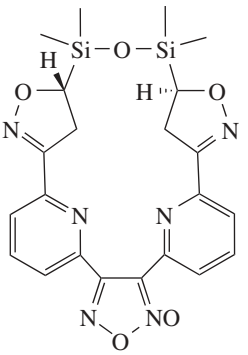
Silacyclophanes **414**, were synthesized (Scheme 1.52) by using quadruple macrocyclization of bis(vinyldimethyl)disiloxane with an aromatic bis(nitrile oxide) formed from bis(hydroxymoyl chloride) **415** (452).



414

Scheme 1.52

The yields of the first and the second stages were 53% and 48%, respectively. The yields of the *para*-analog of **414** were similar (55% and 35%, respectively). A one-pot reaction with pyridine-2,6-biscarbohydroximinoyl dichloride gives a pyridine analog of **414** as a minor product (8%). The main product **416** (25% yield) arises from an intramolecular nitrile oxide dimerization. The macrocyclic cycloadducts have been characterized spectroscopically and by X-ray crystallography (452).



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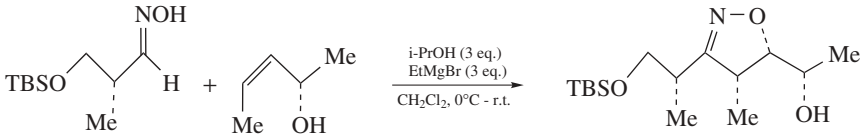


417

TBS = *t*-$BuMe_2Si$

Scheme 1.53

Macrocycles containing isoxazoline or isoxazole ring systems, potential receptors in host–guest chemistry, have been prepared by multiple (double, triple or quadruple) 1,3-dipolar cycloadditions of nitrile oxides, (prepared *in situ* from hydroxamoyl chlorides) to bifunctional calixarenes, ethylene glycols, or silanes containing unsaturated ester or alkene moieties (453). This one-pot synthetic method has been readily extended to the preparation of different types of macrocycles such as cyclophanes, bis-calix[4]arenes and sila-macrocycles. The ring size of macrocycles can be controlled by appropriate choices of the nitrile oxide precursors and the bifunctional dipolarophiles. Multiple cycloadditive macrocyclization is a potentially useful method for the synthesis of macrocycles.

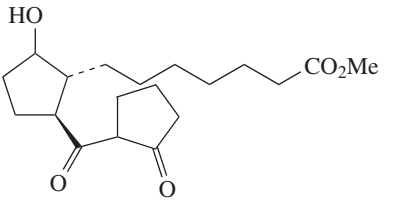
Enantiomerically pure isoxazolines **417** have been prepared (Scheme 1.53) via the stereo- and regioselective cycloaddition of chiral nitrile oxides and allylic alcohols (454). By ring opening with Et_3SiCl followed by imine hydrolysis with Raney nickel/$B(OH)_3$, isoxazolines **417** were converted with stereo integrity to the respective hydroxy ketones, the latter being used as polyketide building blocks. This method has been used to prepare an isoxazoline analog of erythronolide A seco acid. A new procedure for the selective reduction of conjugated Δ^2-isoxazolines to unsaturated β-hydroxy ketones has been described. The use of SmI_2 as the reducing agent and $B(OH)_3$ to hydrolyze the resulting imine results in a mild, convenient, and chemoselective protocol for this otherwise difficult transformation. It complements the existing methodology for the preparation of β-hydroxy ketones via nitrile oxides (455).

Intramolecular cycloaddition of nitrile oxides, prepared from 1,2-isopropylidene-protected ether-linked oligo-pentoses leads to the diastereoselective formation of chiral isoxazolines fused to 10–16-membered oxa-cycles (456).

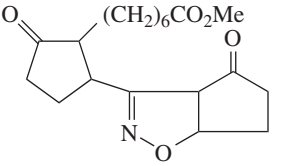
A rapid access to carbocyclic nucleosides, containing a fused isoxazoline ring has been proposed, starting from cyclopentadiene. The route involves a hetero Diels–Alder cycloaddition reaction of nitrosocarbonylbenzene followed by a 1,3-dipolar cycloaddition of nitrile oxides, cleavage of the N–O tether and transformation of the heterocyclic aminols into nucleosides via construction of purine and pyrimidine heterocycles (457).

1.4.1.3. Syntheses of Natural Products and Related Compounds 1,3-Dipolar cycloaddition reactions of nitrile oxides in the synthesis of natural products and their analogs has been the subject of a recent review (458).

The synthesis of new 11-deoxyprostaglandin analogs with a cyclopentane fragment in the ω-chain, prostanoid **418**, has been accomplished by a reaction sequence involving nitrile oxide generation from the nitromethyl derivative of 2-(ω-carbomethoxyhexyl)-2-cyclopenten-1-one, its 1,3-cycloaddition to cyclopenten-1-one and reductive transformations of these cycloadducts (459). Diastereoisomers of a new prostanoid precursor **419** with a 4,5,6,6a-tetrahydro-3a*H*-cyclopent[*d*]isoxazole fragment in the ω-chain have been synthesized. Reduction of **419** gives novel 11-deoxyprostanoids with modified α- and ω-chains (460).



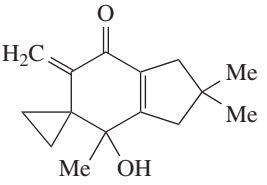
418



419

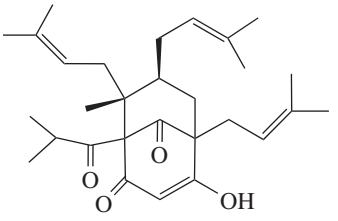
The 1,3-dipolar addition to terminal alkenes of nitrile oxides, generated from nitromethylene derivatives of bicycloheptane, provides 9,11-ethano-13,15-isoxazolinoprostanoids, PGH analogs, with alkyl, phenyl, or additional heterocyclic fragment in the ω-chain (461). Chemical transformations of 9,11-ethano-13,15-isoxazolinoprostanoids furnish prostanoids with bifunctional fragments of β-hydroxyketone and α-aminoalcohol in the ω-chain. The reaction of β-hydroxyketones with methanesulfonyl chloride gives rise to prostanoids with an enone component in the ω-chain. 9,11-Ethano-16-thiaprostanoids have been prepared, for the first time, by nucleophilic addition of thiols to the polarized double bond in the ω-chain. The 1,3-dipolar addition to terminal alkenes of nitrile oxides, generated from nitromethylene derivatives of bicycloheptane provides 9,11-ethano-13,15-isoxazolinoprostanoids with an alkyl, phenyl, or additional heterocyclic fragment in the ω-chain (462).

A total synthesis of the sesquiterpene (±)-illudin C **420** has been described. The tricyclic ring system of the natural product is readily quickly assembled from cyclopropane and cyclopentene precursors via a novel oxime dianion coupling reaction and a subsequent intramolecular nitrile oxide—olefin cycloaddition (463).



420

A synthetic approach to hyperevolutin A **421**, prenylated bicyclo[3.3.1] nonanone derivative, with an acylated phloroglucinol-type fragment, has been described (464). Intramolecular allene–nitrile oxide cycloaddition of **422** has been used to construct the bicyclic framework and the vicinal quaternary centers in cycloadduct **423**.



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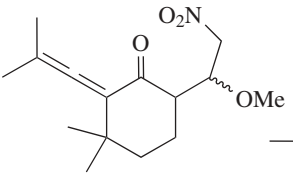

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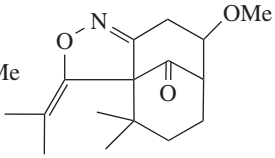
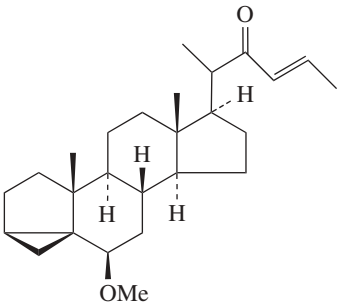


423

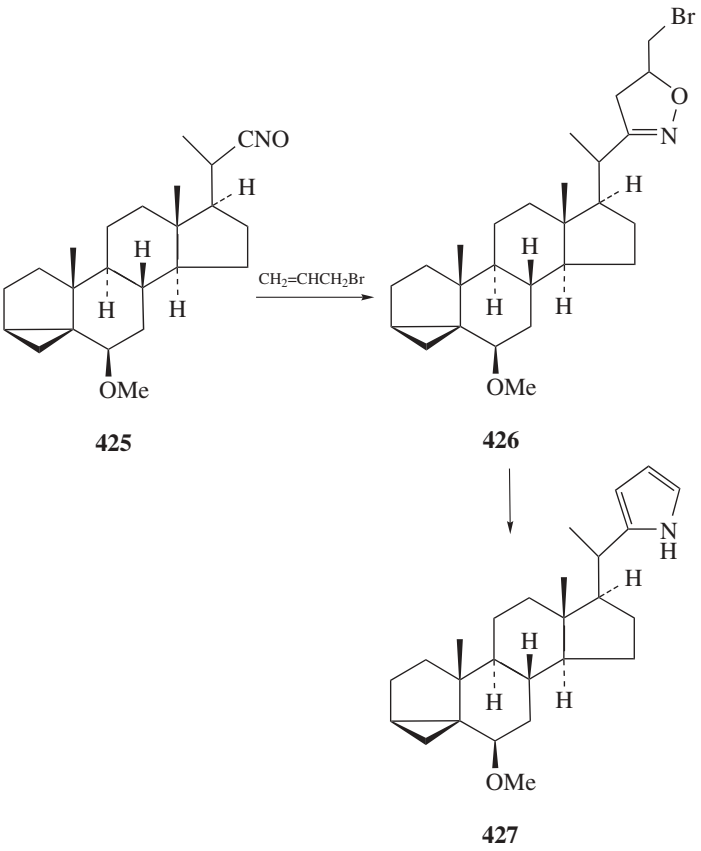
Δ^{23}-22-Oxo steroids **424** have been synthesized via 1,3-dipolar cycloaddition of steroidal nitrile oxides to low-molecular dipolarophiles. Cycloaddition of 2-propynyl bromide to 20-carbonitrile oxide, followed by hydrogenation of the isoxazole derivative, gives 22-enamino-24-keto steroid. The latter has then been converted into the target enones in several steps (465).



424

1,3-Dipolar cycloaddition of nitrile oxide **425** with allyl bromide followed by hydrogenation of dihydroisoxazole derivative **426** (Scheme 1.54) gives a pyrrol-substituted steroid derivative **427** (466).

A total synthesis of functionalized 8,14-seco steroids with five- and six-membered D rings has been developed (467). The synthesis is based on the transformation of (S)-carvone into a steroidal AB ring moiety with a side chain at $C_{(9)}$, which allows the creation of a nitrile oxide at this position. The nitrile oxides are coupled with cyclic enones or enol derivatives of 1,3-diketones, and reductive cleavage of the obtained cycloadducts give the desired products. The formation of a twelve-membered ring compound has been reported in the cycloaddition of one of the nitrile oxides with cyclopentenone and as the result of an intramolecular ene reaction, followed by retro-aldol reaction.



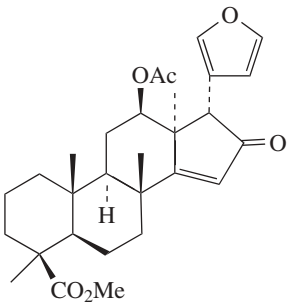
425 **426** **427**

Scheme 1.54

Starting from quinic acid, a highly substituted, *cis*-α,β unsaturated nitrile oxide has been synthesized and used in a 1,3-dipolar cycloaddition, to afford a precursor of the *cis*-decalin system of branimycin (468).

The stereoselective synthesis of the 12-acetoxy enone **428**, related to the limonoid azadiradione, has been achieved in 12 steps (16% overall yield), starting from tricyclic diester **429**. The key steps involve an intramolecular 1,3-dipolar cycloaddition of a nitrile oxide and a Stille coupling reaction of vinyl iodide with stannylfuran (469).

9-Anthracenecarbonitrile oxide, prepared directly from 9-anthracenecarbaldoxime and N-chlorosuccinimide, reacts with dimethyl acetylenedicarboxylate to afford dimethyl 3-(9′-anthracenyl)isoxazole-4,5-dicarboxylate in good yield. Double activation reactions between this diester and hydrogenated lexitropsin **430**, in a 1:2 molar ratio, produce a novel intercalating isoxazolyl bis-lexitropsin conjugate **431** as the major product (43).



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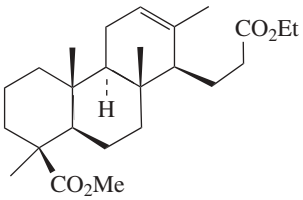

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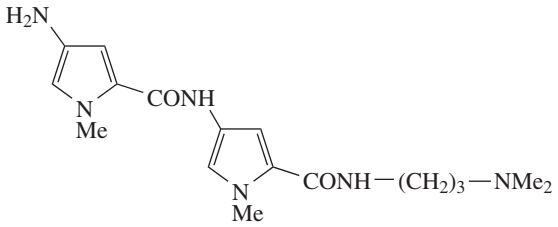

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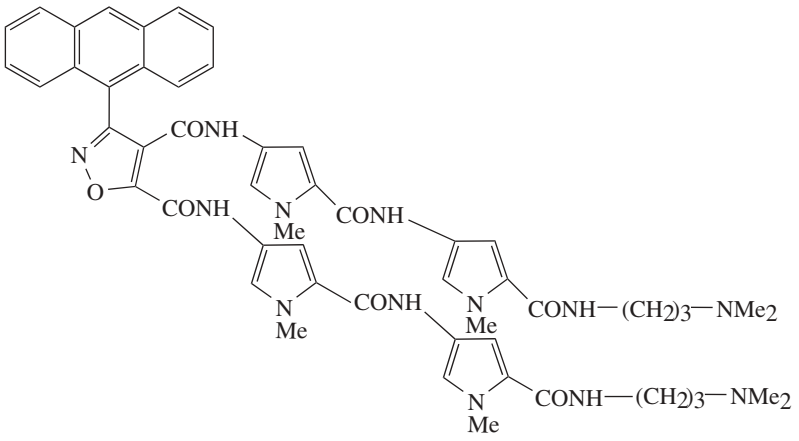
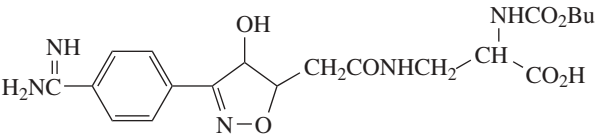


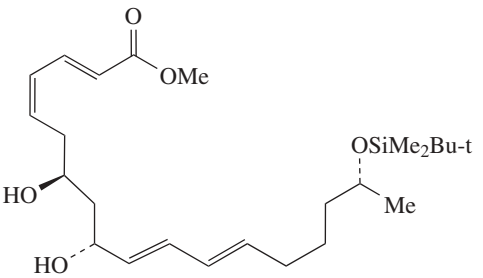
431

Four diastereoisomers of isoxazolinol **432** have been prepared via [3 + 2] dipolar cycloadditions of nitrile oxides. The ring 4*S*,5*S* isomer shows the configuration of an isolated metabolite of roxifiban, a platelet glycoprotein receptor antagonist (470).

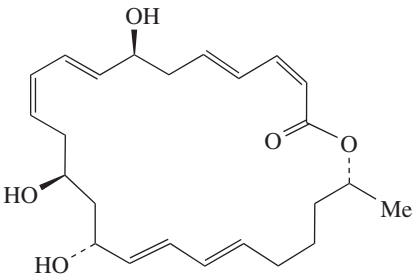


432

Diastereoselective intermolecular nitrile oxide—olefin cycloaddition has been used in an enantioselective synthesis of the $C_{(7)}$-$C_{(24)}$ segment **433** of the 24-membered natural lactone, macrolactin A **434** (471, 472). Two (carbonyl)iron moieties are instrumental for the stereoselective preparation of the $C_{(8)}$-$C_{(11)}$ E,Z-diene and the $C_{(15)}$ and $C_{(24)}$ sp^3 stereocenters. Also it is important to note that the (carbonyl)iron complexation serves to protect the $C_{(8)}$-$C_{(11)}$ and $C_{(16)}$-$C_{(19)}$ diene groups during the reductive hydrolysis of an isoxazoline ring.

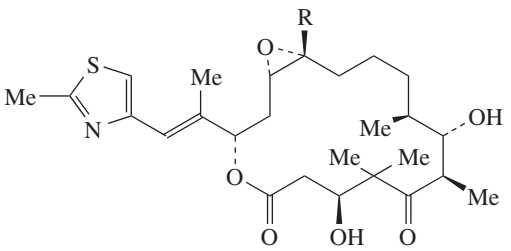


433



434

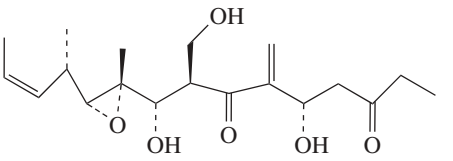
An expedient and fully stereocontrolled synthesis of epothilones A (**435**, R = H) and B (**435**, R = Me) has been realized (473, 474). The routes described, involve an extensive study of nitrile oxide cycloadditions, as substitutes for aldol addition reactions, leading to the realization of a highly convergent synthesis, based on the Kanemasa hydroxyl-directed nitrile oxide cycloaddition.



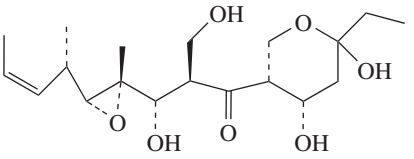
435

Two stereoselective aldol reactions, followed by a nitrile oxide cycloaddition and a stereoselective late-stage epoxidation are the key steps in the total synthesis of myriaporones 1, 3, and 4 (**436**, **437**, and **438**). The synthesis allows

the unambiguous assignment of stereogenic centers, not previously assigned for these compounds (475, 476).



436



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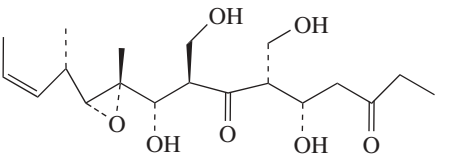
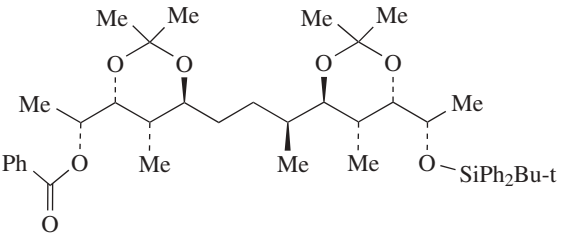


438

Carbohydrate derivatives with a spiroisoxazoline moiety, present in psammaplysins and ceratinamides (metabolites isolated from marine sponges) have been prepared in good yields and excellent regio- and diastereoselectivity by a route involving Wittig olefination and 1,3-dipolar cycloaddition as key steps (477).

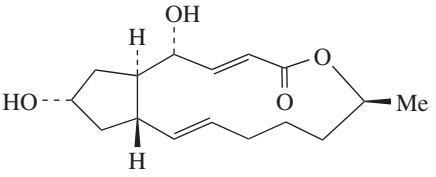
3,4-Di(2,3,4,6-tetra-O-acetyl-b-D-mannopyranosyl)-1,2,5-oxadiazole 2-oxide has been synthesized from D-mannose by a route, involving as the key step, dimerization of mannopyranosyl nitrile oxide. Three methods have been used for the generation of the nitrile oxide: isocyanate-mediated dehydration of nitromethylmannose derivative, treatment of aldoxime with aqueous hypochlorite and base-induced dehydrochlorination of hydroximoyl chloride. D-gluco, D-galacto, D-xylo and L-fucopyranosyl analogs has been prepared similarly. The structure of D-mannose-derived 1,2,5-oxadiazole 2-oxide has been established by X-ray crystallography (478).

A strategy based on the diastereoselective dipolar cycloaddition reaction of nitrile oxides and allylic alcoholates, has been applied to the synthesis of bis-(isoxazolines) that are precursors to polyketide fragments. These intermediates can be elaborated into protected polyols, for example, **439**, by sequential chemoselective reductive opening of each isoxazoline or, alternatively, by simultaneously, providing access to all stereoisomers of this carbon skeleton (479).



439

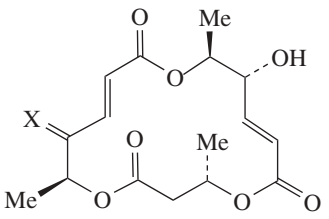
Three novel stereo- and regioselective schemes for the total synthesis of (+)-brefeldin A **440** have been accomplished. Each of them exploit intermolecular nitrile oxide cycloaddition for constructing the open chain and introducing substituents, but differ in subsequent stages. The first (480) and the second (481) use intramolecular cycloaddition for the macrocycle closure. However, in the second scheme INOC is followed by C=C bond *cis-trans*-isomerization. In the third scheme (481) intermolecular cycloaddition is followed by ring closing metathesis as the key step.



440

A stereoselective total synthesis of erythronolide A, using two Mg^{II}-mediated cycloadditions of nitrile oxides has been described. Of broader significance, the strategy not only facilitates the synthesis of specific polyketide targets (i.e., natural products) but also opens up new possibilities for the preparation of nonnatural analogs (482).

The unified highly convergent total and formal syntheses of (+)-macrosphelides B (**441**; X = O) and A (**441**; X = α-OH, β-H), respectively, have been described (483). Key features of the syntheses include the concise synthesis of the optically active δ-hydroxy-γ-keto α,β-unsaturated acid fragment **442** via the direct addition of a *trans*-vinylogous ester anion equivalent to a readily available Weinreb amide, and the facile construction of the 16-membered macrolide core of the macrosphelide series via an INOC.



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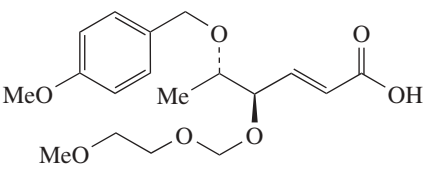
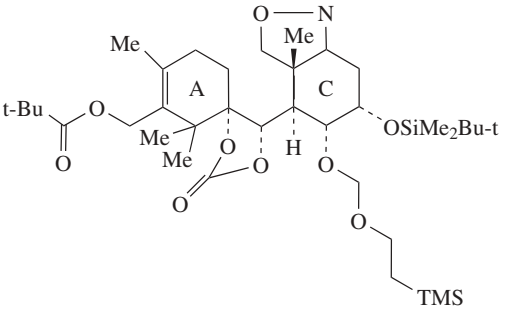


442

The stereoselective formation of the C ring of paclitaxel **443** has been accomplished by the nitrile oxide [3 + 2] cycloaddition of intermediate **444** to the preformed A ring (484).



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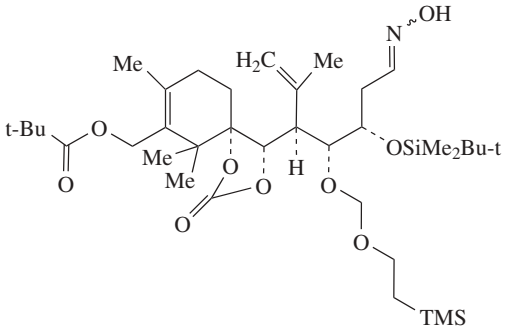
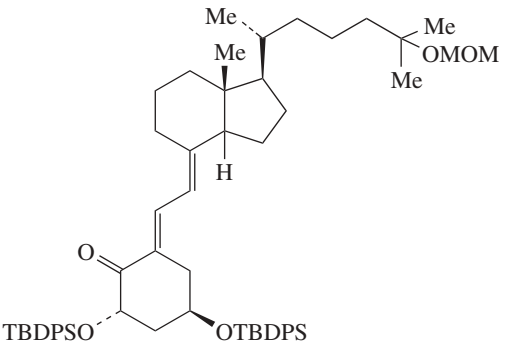


444

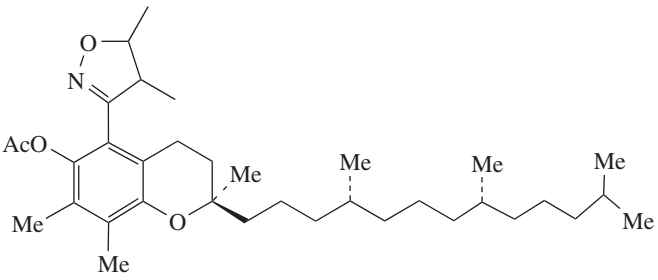
Starting from the Ni *meso*-formyloctaethylporphyrin oxime complex, the *meso*-cyanooctaethylporphyrin N-oxide complex has been synthesized for the first time. The double addition of the nitrile oxide to 2,5-norbornadiene afford a porphyrin dimer, whose structure has been established by X-ray diffraction analysis (485). The 1,3-dipolar cycloaddition reaction of *meso*-tetraarylporphyrins with 2,6-dichlorobenzonitrile oxide yields isoxazoline-fused chlorins and stereoisometric bacteriochlorins. The crystal structure of one of bacteriochlorins has been characterized by X-ray diffraction (486, 487).

An efficient synthetic route to (10*Z*)- and (10*E*)-19-fluoro-1α,25-dihydroxy vitamin D_3 has been developed (488). The key feature of this pathway is the introduction of a 19-fluoromethylene group to a (5*E*)-19-nor-10-oxo-vitamin D derivative. The 10-oxo compound **445** has been obtained via a 1,3-dipolar cycloaddition reaction of (5*E*)-1α,25-dihydroxyvitamin D with *in situ* generated nitrile oxide, followed by ring cleavage of the formed isoxazoline moiety with molybdenum hexacarbonyl. Conversion of the keto group of (5*E*)-19-nor-10-oxo-vitamin D to the *E* and *Z* fluoromethylene group has been achieved via a two-step sequence, involving a reaction of lithiofluoromethyl phenyl sulfone, followed by the reductive de-sulfonylation of the α-fluoro-β-hydroxysulfone. The dye-sensitized photoisomerization of the (5*E*)-19-fluorovitamin D affords the desired (5*Z*)-19-fluorovitamin D derivatives, (10*Z*)- and (10*E*)-19-fluoro-1α,25-dihydroxy-vitamin D_3.



445

New isoxazoline derivatives of α-tocopherol, the main component of vitamin E, have been synthesized in a facile, two-step sequence consisting of nitration followed by 1,3-dipolar cycloaddition. 5-Nitromethyl-α-tocopheryl acetate, obtained from α-tocopheryl acetate by direct nitration in one step, act as the nitrile oxide precursor in the reaction with various alkenes. The facile conversion proceeds in the presence of equimolar amounts of PhNCO and catalytic amounts of triethylamine to give isoxazolines, **446** (489).



446

A novel class of activators for chloride conductance in the cystic fibrosis transmembrane conductance regulator protein has been identified. These 3-(2-benzyloxyphenyl)isoxazoles and 3-(2-benzyloxyphenyl)isoxazolines have been synthesized employing the 1,3-dipolar cycloaddition of nitrile oxides with various alkene and alkyne dipolarophiles (490).

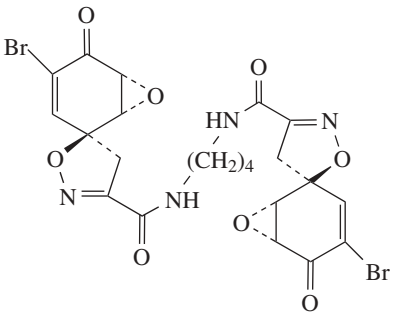
3,4-Diarylisoxazole analogs of valdecoxib [4-(5-methyl-3-phenylisoxazol-4-yl) benzensulfonamide], a selective cyclooxygenase-2 (COX-2) inhibitor, have been synthesized by the 1,3-dipolar cycloaddition of arencarbonitrile oxides to the enolate ion of phenylacetone, regioselectively prepared *in situ* with lithium diisopropylamide at 0° (491). The corresponding 3-aryl-5-methyl-4-phenylisoxazoles are easily generated by a dehydration/aromatization reaction, under basic conditions, of 3-aryl-5-hydroxy-5-methyl-4-phenyl-2-isoxazolines and are further transformed into their benzenesulfonamide derivatives. The biochemical COX-1/

COX-2 selectivity was evaluated *in vitro* by using the human whole blood assays of COX isoenzyme activity. Three compounds, not bearing the sulfonamide group present in valdecoxib, have been found to be selective COX-1 inhibitors.

A total synthesis of (+)-vinblastine widely used in cancer chemotherapy, has been reported. It includes the synthesis of (−)-vindoline. 1,3-Dipolar cycloaddition of a nitrile oxide has played an important role in the preparation of the indoloazacycloundecane moiety, whose coupling with (−)-vindoline occurs with the desired stereochemistry, leading to an intermediate readily transformed to the target (+)-vinblastine (492).

The synthesis of multivalent neoglycoconjugates by 1,3-dipolar cycloaddition of nitrile oxides and alkynes has been reported (493). The nitrile oxides have been generated *in situ* in the presence of alkynyl derivatives, allowing the access to homo and hetero multivalent systems containig O- and C-linked glycosides and isoxazole bridges.

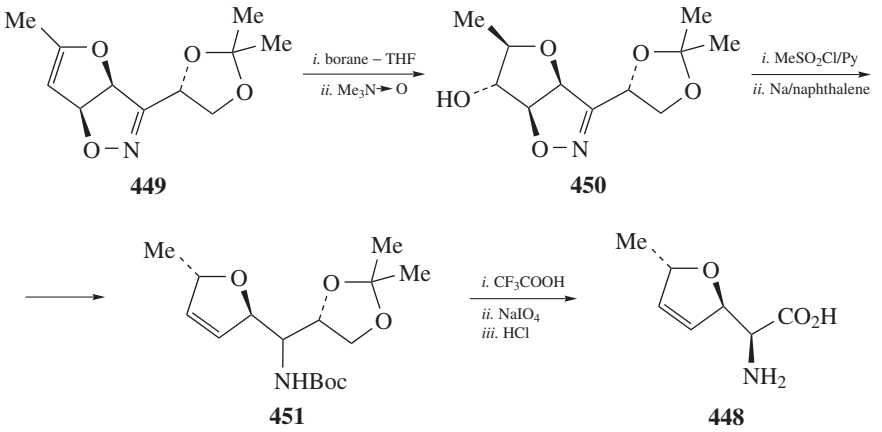
The synthesis of the spiroisoxazoline natural product (+)-calafianin **447** has been reported, using asymmetric nucleophilic epoxidation and nitrile oxide cycloaddition as key steps. Syntheses and spectral analyses of all calafianin stereoisomers lead to unambiguous assignments of relative and absolute stereochemistry (494).



447

The 1,3-dipolar cycloaddition of nitrile oxides and 2-methylfuran provides suitable precursors for α-amino acids such as L-furanomycin **448** that contains a dihydrofuran ring (495). By using a chiral nitrile oxide derived from mannitol bis(acetonide), the enantiomerically pure furoisoxazoline **449** has been obtained. Hydroboration–oxidation of the latter leads to the hydroxy-substituted annulated THF derivative **450**, which is converted via dihydrofuran **451** to furanomycin **448** in enantiomerically pure form (Scheme 1.55).

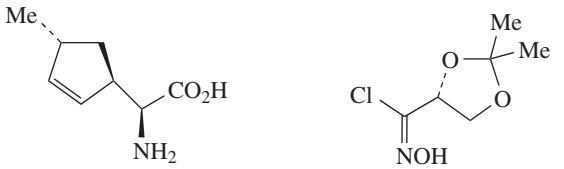
A concise and efficient asymmetric synthesis of L-(+)-carbafuranomycin **452**, a novel analog of L-(+)-furanomycin, which is an unusual antibiotic amino acid of great interest, due to its activity as an isoleucine antagonist, has been reported (496). The synthesis starts with the 1,3-dipolar cycloaddition of a chiral nitrile oxide (obtained *in situ* from hydroximinoyl chloride **453** via slow addition of NEt_3) with cyclopentadiene. Then methylation of cyclopentenyl acetate **454**,



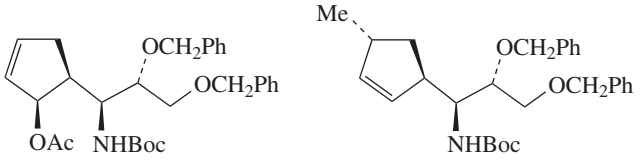
449 **450** **451** **448**

Scheme 1.55

using MeMgBr with CuCN in Et_2O, affords stereo- and regioselective addition of the Me group to the cyclopentene ring of cyclopentenyl(dibenzyloxy)propylamine **455**, a precursor to **452**.



452 **453**

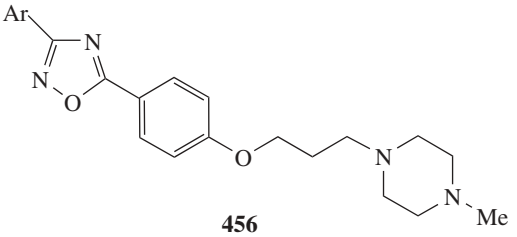


454 **455**

1.4.1.4. Synthetic Biologically Active Compounds Silyl- and carbonyl-substituted isoxazoles have been prepared and screened for their cytotoxic activity (497). Some exhibited moderate cytotoxicity toward the HT-1080 and MG-22A cell lines. The highest activity level has been displayed by 3-methyl-5-diphenyl-methylsilylisoxazole.

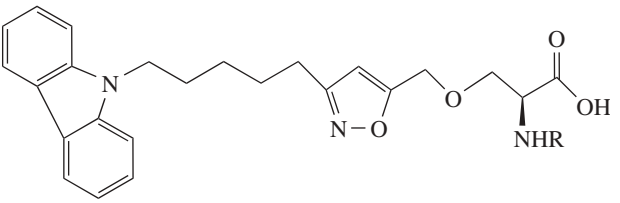
A series of 3,5-diarylisoxazole and 3,5-diaryl-1,2,4-oxadiazole derivatives, novel classes of small molecule interleukin-8 (IL-8) receptor antagonists, **456** (Ar = 4-FC_6H_4), have been identified as IL-8 inhibitors. These compounds exhibit activity in an IL-8 binding assay as well as in a functional assay of IL-8 induced

elastase release from neutrophils. In addition, one of the compounds exhibited oral activity in a rat adjuvant arthritis test (498).



456

Peroxisome proliferator-activated receptors (PPARs), important molecular targets for developing drugs for the treatment of human metabolic diseases, inflammation, and cancer, are known to be activated by a variety of structurally diverse compounds. Using a structure-based drug design approach, a series of novel isoxazolyl-serine-based PPAR ligands **457** [R = Boc, Cbz, *o*-Cl-Cbz, H, $Ph(CH_2)_3$, $CO(CH_2)_4Me$], possessing moderate binding affinities to the three PPAR subtypes, has been synthesized (499). Some of the new PPAR ligands stimulate cardiomyocyte differentiation from murine embryonic stem (ES) cells. Ligand **457** (R = Boc) is the most active one tested at concentrations between 1.25 to 20 μM between 2 and 6d. This is the period when mesodermal cells become cardiomyocytes.



457

1.4.2. Nitrile Oxides in Polymer Chemistry and Technology

The ability of nitrile oxides to undergo addition and cycloaddition reactions makes it possible to use them in polymer chemistry and technology. Major trends might be synthesis, modification, cross-linking of polymers, addition of nucleophiles, and 1,3-dipolar cycloaddition of nitrile oxides. Taking into account the scarcity of reviews devoted to this topic, not only recent but also previous references will be cited in this subsection.

1.4.2.1. Synthesis and Modification of Polymers Unstable bis(nitrile oxide), generated by dichloroglyoxime dehydrochlorination, polymerizes in solution to give poly(furoxan) or (in the presence of 1,3-dienes) gives rise to their being cross-linked (500). Polymerization of terephthalonitrile dioxide and its

co-polymerization with bis-unsaturated compounds, for example, *p*-diethynylbenzene, is also described (501). Interaction of bis(nitrile oxides) with ketene dimer leads to polymers (502).

Efficient generation of aliphatic bis(nitrile oxides) has been investigated for preparing novel polymers with a polymethylene backbone. Conventional methods, using α,ω-dinitroalkanes and phenylisocyanate, give the corresponding bisisoxazoline compounds in poor yields, presumably because of the intramolecular reaction of terminal groups. The reaction of aliphatic dialdehydes with N-chlorosuccinimide, followed by thermal and/or base catalyzed reactions gives fair yields. Polycycloaddition reactions of bis(nitrile oxides) with diene compounds have also been studied (503).

Important for both the synthesis and modification of polymers is also the elongation of polymer chains. Bisnitrile oxides have been claimed as reagents for chain elongation of polyimides containing terminal groups with C=C, C≡C, C≡N, C=O, and C=N bonds (504).

Modification of *cis*-poly(butadiene) and *cis*-poly(isoprene) has been attained on heating in boiling toluene, in the presence of mononitrile oxides: 35%–55% of C=C bonds have been replaced by isoxazoline fragments. The process also demands the presence of a base because the nitrile oxides have been generated from hydroximoyl chlorides (505).

Unsaturations of hydroxy-containing compounds are reduced on reaction with nitrile oxides such as tetramethyl terephthalonitrile N,N'-dioxide (506) or 1,3,5-triethylbenzene-2,6-dicarbonitrile oxide (507). The reaction of a nitrile oxide with terminal unsaturation, associated with the preparation of a poly-ol from propylene oxide, reduces the mono-ol content of the poly-ol composition. Thus, stirring a solution of an ethylene oxide–propylene oxide copolymer with an OH content of 2.39% and vinyl unsaturation of 3.58% in THF with 1,3,5-triethylbenzene-2,6-dicarbonitrile oxide for 1 min results in an effective removal of the terminal unsaturation.

1.4.2.2. Cross-linking of Polymers Among applications of nitrile oxides, cross-linking of polymers is of main importance. Both nucleophilic addition and 1,3-dipolar cycloaddition are the pertinent reactions.

Cross-linking of mercapto group-containing polymers using thiol nucleophilic addition to nitrile oxide has been reported (508). Several aromatic bis(nitrile oxides) have been prepared as potential curing agents for elastomeric sealants, produced from thiol-terminated liquid polysulfides (509). All have been obtained by dehydrohalogenation of α-halo oximes, and the requisite aldehydes have been synthesized from the dimethyl derivatives or the chloromethylated hydrocarbons. The direct chloromethylation of naphthalene, which offers a convenient route to the naphthalene-1,4- and -1,5-bis(carbonitrile oxides), is used. Naphthalene-2,6-bis(carbonitrile oxide), anthracene-9,10-bis(carbonitrile oxide), and 4,4′-sulfonylbisbenzonitrile dioxide have also been prepared.

Efficient addition between various nitrile oxides and both, short (C_2) and long-chain (C_{16}) alkyl thiols, aliphatic dithiols and aryl thiols occurs rapidly at

ambient temperature with the formation of thiohydroximic acid derivatives (510). Competitive experiments with bis(nitrile oxides) shows that for terephthalonitrile oxide the second addition proceeds more readily than the first, whereas with anthracene-9,10-bis(carbonitrile oxide) elevated temperatures are needed to obtain the diadduct. The reaction between prop-2-ene-1-thiol and *p*-nitrobenzonitrile oxide affords products resulting from both cycloaddition and 1,3-addition with the latter predominating. The polysulfide prepolymer LP-2 has been vulcanized effectively at ambient temperatures by both, terephthalonitrile oxide and 4,4′-sulfonylbisbenzonitrile dioxide, at CNO to SH ratios of 1.5 and higher. Unreinforced sealants produced in this manner are firm elastomers. The naphthalenebis(carbonitrile oxides) afford softer products, while anthracene-9,10-bis (carbonitrile oxide) is ineffective. Formulations involving *in situ* generation of nitrile oxide from hydroximoyl chlorides and $Ba(OH)_2$ (formed by action of water vapor on BaO) have been also carried out.

Sealants obtained by curing polysulfide liquid polymers with aryl bis(nitrile oxides) possess structural feature of thiohydroximic acid ester. These materials exhibit poor thermal stability; when heated at 60°C they soften within days and liquefy in 3 weeks. Products obtained with excess nitrile oxide degrade faster than those produced with equimolar amounts of reagents. Spectroscopic studies demonstrate that, after an initial rapid addition between nitrile oxide and thiol, a second slower reaction occurs which consumes additional nitrile oxide. Thiohydroximic acid derivatives have been shown to react with nitrile oxides at ambient temperature to form 1,2,4-oxadiazole 4-oxides and alkyl thiol. In the case of a polysulfide sealant, the rupture of a C–S bond to form the thiol involves cleavage of the polymer backbone. Continuation of the process leads to degradation of the sealant. These observations have been supported by thermal analysis studies on the polysulfide sealants and model polymers (511).

It is evident that reactions of unsaturated polymers with bisnitrile oxides lead to cross-linking. Such a procedure has been patented for curing poly(butadiene), butadiene–styrene copolymer, as well as some unsaturated polyethers and polyesters (512–514). Bisnitrile oxides are usually generated in the presence of unsaturated polymers by dehydrochlorination of hydroximoyl chlorides. Cross-linking of ethylene–propylene–diene co-polymers with stable bisnitrile oxides has been studied (515, 516). The rate of the process has been shown to reduce in record with the sequence 2-chloroterephthalonitrile oxide > terephthalonitrile oxide > 2,5-dimethylterephthalonitrile oxide > 2,3,5,6-tetramethylterephthalonitrile oxide > anthracene-9,10-dicarbonitrile oxide (515).

Bis(nitrile oxides) obtained from dialkylbenzenes have been claimed as low-temperature rubber vulcanization agents (517). Curing of poly(butadiene-co-acrylonitrile) with 2,4,6-trimethylisophthalodinitrile N-oxide produces rubbery material of good quality, however, curing of (polybutadiene) was unsuccessful (518). The solubility of dinitrile oxides and stability of their ketone solutions has been studied for their application as vulcanizing agents in the production of rubberized materials (519).

Anthracene-9,10-dicarbonitrile oxide has been used for cross-linking of cyano group-containing poly(arylene sulfides) (520). Acrylic polymers containing nitrile groups do not possess typical curing sites such as double bonds. Addition of stable bis(nitrile oxide) to the acrylic polymer, causes cross-linking at a low-temperature. Heat-resistant thermoplastic vulcanizates with high resistance to solvents and increased compression resistance are formed (521).

Nitrile oxides have been used as reagents for heat activated cross-linking of polymers having appropriate functionality, such as alkenes, alkynes, nitriles, and isocyanates. The use of nitrile oxide compounds are in filled or unfilled applications such as pressure sensitive adhesives, reactive hot melts, polyurethane dispersions, thermosetting adhesives, thermoplastic adhesives and coatings (522, 523). Formulations containing stable nitrile oxide reagents have been developed for coatings, composites, and moldings (524).

Aqueous polynitrile oxide curing compositions, with good storage stability, have been patented (525). The compositions comprise aqueous dispersions containing nitrile oxides and are useful for coating systems that are cured at room temperature without the release of byproducts. Latexes are cured by mixing a polymer latex with a stable polynitrile oxide, for example, 2,4,6-triethylbenzene-1,3-dicarbonitrile oxide, and removing water from the mixture.

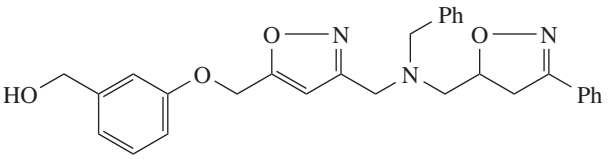
Foam compositions, including a latex and a polynitrile oxide such as 2,4,6-triethylbenzene-1,3-dicarbonitrile oxide, or a latex and an epoxy silane, or a latex and a mixture of the two crosslinkers have been prepared (526). The compositions may also contain additional components, including fillers, surfactants, cell detackifiers, froth stabilizers, froth boosters, viscosity reducers, and compounds to improve resilience, and antioxidants. The compositions are particularly useful in the manufacture of flooring, wall covering, shoe lining and nonwoven materials.

Nitrile oxide precursors have been prepared by the reaction of an isocyanate and an alkyl nitroacetate. These precursors release alkanol and carbon dioxide when heated, to liberate the highly reactive nitrile oxide species. An improved synthetic procedure has been developed to afford novel cross-linking agents based on difunctional, trifunctional and aliphatic precursors. Application of these agents to polymer cross-linking has been demonstrated (527).

Although bisnitrile oxides are generated *in situ* in the presence of a polymer, the use of stable bisnitrile oxides prepared beforehand is more attractive owing to the absence of byproducts. Therefore, special attention has been paid to the development of syntheses of stable bisnitrile oxides (29–32, 102, 509, 517, 518, 522, 528).

1.4.3. Other Applications of Nitrile Oxides

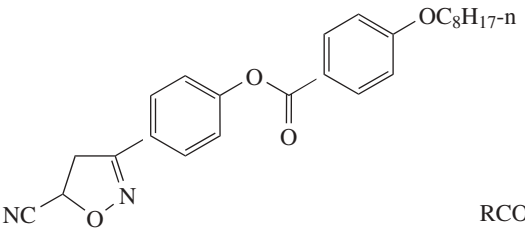
Using nitrile oxides, various compounds and materials possessing valuable properties have been prepared. Among them are thin-film resistors useful for a thermal head and comprising a nitrile oxide, ruthenium and oxygen, a method for manufacturing the resistor by coating or deposition (529), isoxazole and/or isoxazoline polyheterocyclic systems like **458**, which are useful for development of a new class of ionophores (530).



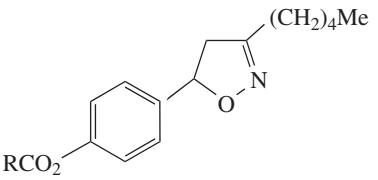
458

Transformations of nitrile oxides are very useful in the synthesis of isoxazole, isoxazoline, and oxadiazole compounds, possessing interesting optical properties. Thus, 1,3-dipolar cycloaddition of nitrile oxides, derived from corresponding oximes with phenylpropargyl aldehyde, give aldehydes **459**, subsequent Wittig–Horner reactions with $PhCH_2P(O)(OEt)_2$ or Knoevenagel condensation with malononitrile afford isoxazoles **460** and **461** (Scheme 1.56). These compounds have both high electron acceptability and electron-transfer character, and are useful for organic light emitting diode (OLED) in a plane panel display (531).

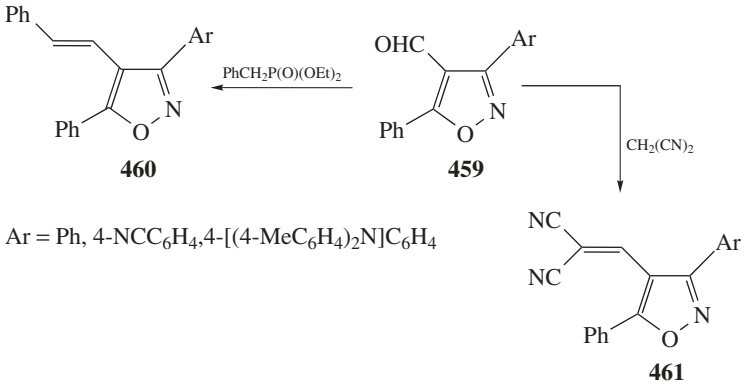
3-Aryl-5-cyano-2-isoxazolines, possessing liquid crystal properties (smectic phases A or E) have been synthesized, 1,3-dipolar cycloaddition of nitrile oxides to acrylonitrile being the key step (532). For example, nitrile **462** has been obtained in 66% yield from substituted benzaldoxime and acrylonitrile *via in situ* generated nitrile oxides.



462



463



460

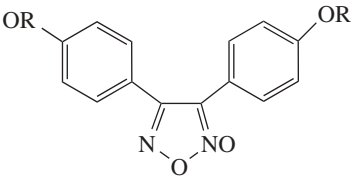
459

461

Scheme 1.56

Several 4-(3-alkyl-2-isoxazolin-5-yl)phenol derivatives that possess liquid crystal properties have also been obtained (533–535). In particular, target compounds such as **463** (R = pentyl, nonyl) have been prepared by the reaction of 4-acetoxystyrene with the nitrile oxide derived from hexanal oxime, followed by alkaline hydrolysis of the acetate and esterification (535). A homologous series of 3-[4-alkyloxyphenyl]-5-[3,4-methylenedioxybenzyl]-2-isoxazolines, having chiral properties has been synthesized by the reaction of nitrile oxides, from the dehydrogenation of 4-alkyloxybenzaldoximes. These compounds exhibit cholesteric phase or chiral nematic phase (N*), smectic A (S_A), and chiral smectic phases (S_C*), some at or just above room temperature (536).

Liquid-crystalline 3,4-disubstituted furoxans such as **464** (R = 4-alkoxybenzoyl, Ph) have been prepared by cyclodimerization of 4-$AcOC_6H_4CNO$, followed by hydrolysis to **464** (R = H) and acylation. The products form a nematic mesophase (537).



464

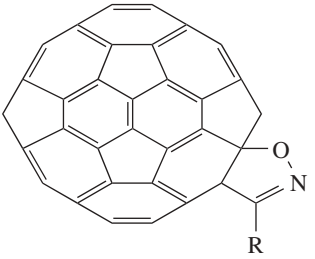
Many papers and patents are devoted to the use of nitrile oxides for the preparation of fullerene derivatives with practically attractive properties.

Electroactive 3-(N-phenylpyrazolyl)fullereno[1,2-*d*]isoxazolines have been synthesized by using 1,3-dipolar cycloaddition of pyrazole nitrile oxides, generated *in situ*, to C_{60} at elevated temperature or microwave irradiation. The cyclic voltammetry measurements show a strong donor pyrazole ring, and a better acceptor ability of the fullerene moiety than the parent C_{60} (538). Treating fullerene C_{60} with mesitonitrile oxide in toluene gives fullerene–nitrile oxide adduct, which is supposed to be useful for electrical and optical components (539).

The methodology required for the construction of fullerene-based nanostructures including fullerenes and rigid spacers has been investigated. Such assemblies require the ability to control the regiochemistry of multiple addition of fullerenes. The kinetic and thermodynamic isomer distribution of nitrile oxide dipolar additions to C_{60}, as well as the separation and characterization of the major species have been reported (540, 541). The structures of such fullerene isoxazolines, as nano-scale connectors, have been optimized by using the semiempirical PM3 calculations. Also the regiochemistry of the second addition of a nitrile oxide to a fullerene isoxazoline has been considered. The results indicate that fullerene isoxazoline derivatives are useful nano-scale connectors with the possibility of attaching spacer units in a specific angular arrangement (542, 543).

Novel C_{60} and C_{70} adducts have been synthesized by [2 + 3] cycloadditions of the appropriate nitrile oxides. Variations in the distance and geometry of the donor

and acceptor substituents have been shown to have an influence on the redox behavior of the fullerene adducts in cyclic voltammetry experiments (544). Thus, 3-R-substituted fullereno[1,2-d]isoxazolines **465** (R = 2,4,6-trimethoxyphenyl, 2,4,6-trimethoxystyryl, 2-(2-thienyl)phenyl) shows shifts of about 30mV or 40mV to more negative values as compared with the reference compound (R = H). Strong acceptor properties have been detected in the compounds with $R = CH{=}C(CO_2Me)_2$, which show a positive shift of 30mV relative to R = H.



465

The data demonstrate that the electron-transfer rate in donor-substituted fullerenes can be controlled by the electron-releasing property of the substituent as well as by the electronic structure and/or length of the spacer used.

The synthesis of C_{60}-based dyads in which the C_{60} core is covalently attached to a strong electron acceptor moiety, has been carried out by 1,3-dipolar cycloaddition of *in situ* generated nitrile oxides with C_{60}. As expected, the obtained adducts show reduction waves of the fullerene core that are anodically shifted in comparison with the parent C_{60}. This indicates that they are remarkably stronger acceptors than C_{60}.The electron acceptor organic addend also undergoes an anodic shift due to the electronic interaction with the C_{60} moiety (545).

Properties of FeC_{60} solid samples have been studied by X-ray diffraction, ^{57}Fe Mossbauer spectroscopy and magnetic measurements to stimulate the interaction of Fe with fullerene. FeC_{60} samples have been prepared by decomposition of the 1,3-dipolar cycloadduct of the fullerene and ferrocene nitrile oxide. The components exhibit super paramagnetic properties originating from an interaction between FeC_{60} complexes within the nano-particles. Each nano-particle consists of hundreds to thousands complexes (546).

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2 Nitrones: Novel Strategies in Synthesis

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2.1. INTRODUCTION

For the last 50 years many scientists have drawn special attention to nitrones due to their successful application as building blocks in the synthesis of various natural and biologically active compounds, of stable nitroxyl radicals, and of other important products for special purposes such as spin traps for the study of radical processes including those that take place in biological systems, and they also found use as both, modifiers and regulators of molecular weight in radical polymerization.

Nowadays, a great deal of literature (1–4) is devoted to certain aspects of nitrone chemistry and its application, or to specific classes of nitrones (5). However, at the present time, the reviews dealing with all or practically all aspects of nitrone chemistry, except those which are well-known and widely covered in the literature (6), are still lacking.

The main aim of this work is to make an attempt to analyze all the aspects of nitrone chemistry and its application which have been developed over the last 15 years. The early works will also be considered to make comparisons, or if these works were not covered in previous reviews; but if, as we see it, without mentioning these works, the representation of the diverse chemistry of nitrones seems incomplete.

To illustrate the multifaceted chemistry of nitrones and their application in synthesis, let us consider the synthetic scheme of bicyclic and tricyclic chiral ligands (Scheme 2.1) (7) as well as diastereo- and enantiostereoselective syntheses of alkaloids (Scheme 2.2) (8).

Many successful chemical transformations based on the rich and multifaceted chemistry of nitrones underlie various synthetic strategies.

Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis: Novel Strategies in Synthesis, Second Edition, By Henry Feuer
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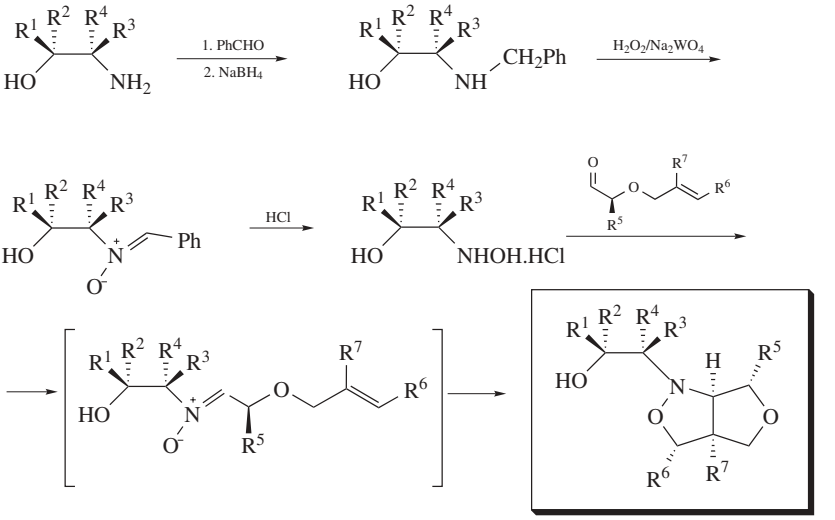
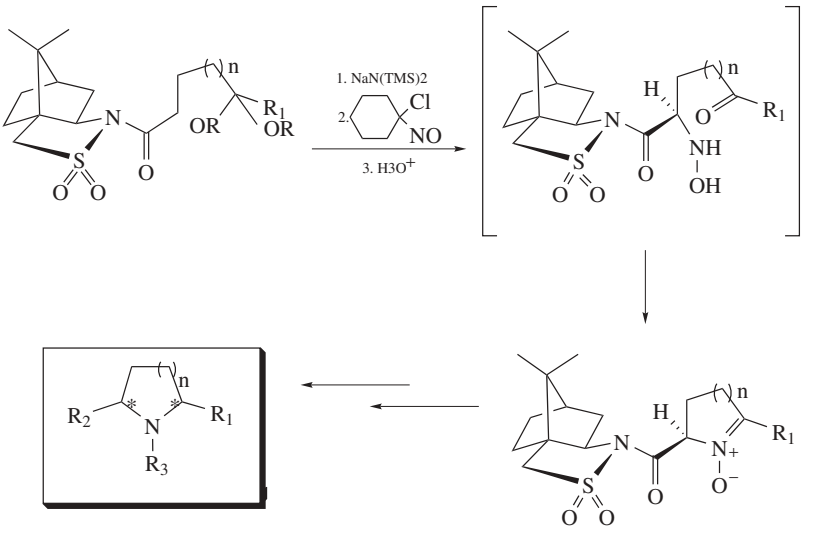


Scheme 2.1



Scheme 2.2

2.2. SYNTHESIS OF NITRONES

2.2.1. Oxidative Methods

2.2.1.1. Oxidation of Imines Oxidation of imines with peracids leads to oxaziridines, with the possibility of their successive rearrangement into nitrones, depending on their structure and the employed oxidant.

Treated with *m*-CPBA as an oxidant, spontaneous rearrangement of oxaziridines derived from 2*H*-imidazole -1-oxide (9), pyrroline (10), and *N*-adamantylphenylimine (11) into nitrones is observed, either upon heating or treatment with acids. Substituted *N*-benzylidene-*tert*-butylamines are oxidized by *m*-CPBA into oxaziridines, which can easily be isomerized into nitrones, with electron-donor substituents facilitating this process (12–14). Peracid oxidation of the corresponding imines gives *N*-arylbenzoquinonimine-*N*-oxides (15). Oxidation of imines (**2**) and (**4**) resulting from the interaction between amino acid (**1**) and its tripeptide (**3**), upon treatment with benzaldehyde and *m*-CPBA, gives the corresponding oxaziridines (**5**) and (**7**), which can be isomerized into stable nitrones (**6**) and (**8**) (Scheme 2.3) (16).

It is noteworthy that quick and effective formation of diaryl nitrones can be achieved through oxidation of diaryl imines with Oxone (potassium peroxymonosulfate) in such media as aqueous solution of $NaHCO_3$ in acetonitrile or acetone. When oxidized under such conditions, dialkyl or monoaryl imines give oxaziridines (17). Oxidation of 3,4-dihydroisoquinoline (**9**) with Oxone initially leads to the formation of oxaziridine (**10**) which is easily transformed into the corresponding 3,4-dihydroisoquinoline *N*-oxide (**11**) upon treatment with catalytic amounts of *p*-toluenesulfonic acid (Scheme 2.4) (18).

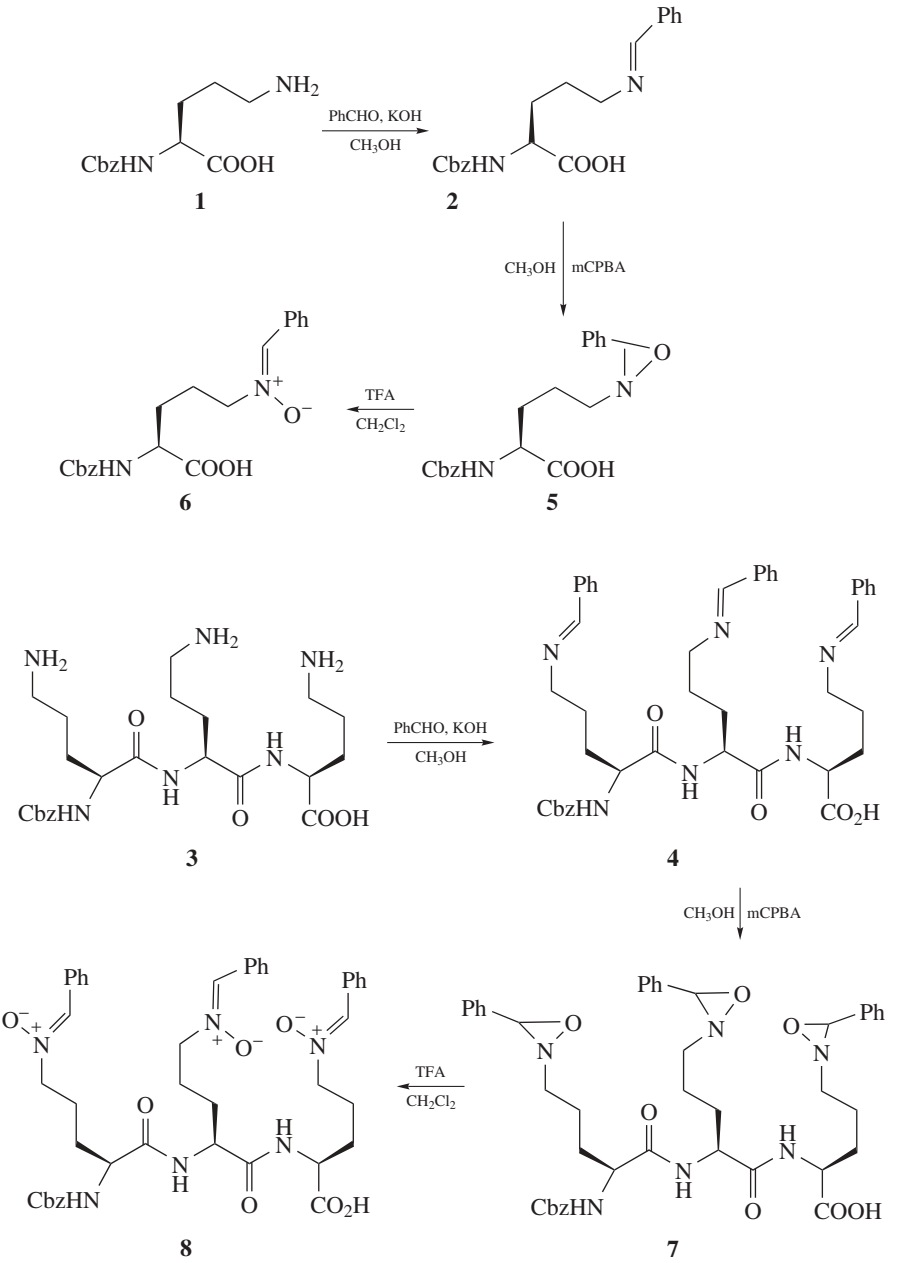
Oxidation of *N*-alkyl imines with dimethyldioxirane (DMD) in a solution of dichloromethane-acetone gives nitrones without the apparent formation of oxaziridines (13). Under the conditions of phase transfer, imines can be oxidized into nitrones upon treatment with permanganate ion MnO_4^- (19).

Also, nitrones can be formed by photochemical oxidation ($\lambda 350$ *nm*) of aldimines in acetonitrile, in the presence of O_2 over a TiO_2 suspension (20, 21). Air oxidation of imines into oxaziridines with their subsequent transformation into nitrones, using cobalt catalysts, provides good yields. Utilization of molecular oxygen in the oxidation process seems highly promising due to its cost-effectiveness, availability, and the possibility of industrial application (22).

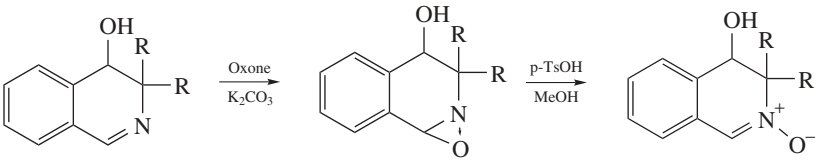
Efficient oxidation of imines into nitrones can be achieved by using methyl (trifluoromethyl)dioxirane as an oxidant. This method provides enantiopure nitrones derived from 2*H*-pyrrole 1-oxide (23, 24).

Diaryl diselenides and benzisoselenazole-3(2*H*)-ones are used as efficient catalysts in the process of imine oxidation with hydrogen peroxide and *tert*-butylhydroperoxide (25).

2.2.1.2. Oxidation of Amines Oxidation of primary amines is often viewed as a particularly convenient way to prepare hydroxylamines. However, their direct oxidation usually leads to complex mixtures containing nitroso and nitro compounds and oximes. However, oxidation to nitrones can be performed after their conversion into secondary amines or imines. Sometimes, oxidation of secondary amines rather than direct imine oxidation seems to provide a more useful and convenient way of producing nitrones. In many cases, imines are first reduced to secondary amines which are then treated with oxidants (26). This approach is used as a basis for a one-pot synthesis of asymmetrical acyclic nitrones starting from aromatic aldehydes (Scheme 2.5) (27a) and 3,4-dihydroisoquinoline-2-oxides (27b).

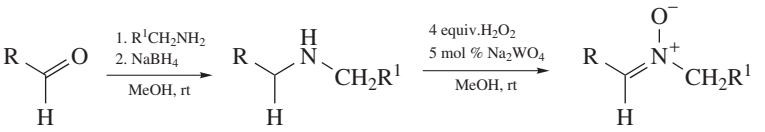

NH2
CbzHN
COOH
1
PhCHO, KOH
CH3OH
Ph
N
2
CH3OH
mCPBA
Ph
O
N
5
TFA
CH2Cl2
N+
O−
6
NH2
O
H
N
CO2H
3
4
CH3OH
mCPBA
7
8

Scheme 2.3



9 **10** **11**

Scheme 2.4



R = Ph, 2-$NO_2C_6H_4$, 3,4-*and*-2,3-$(MeO)_2C_6H_3$;
R^1 = H, Ph, 2,3-$(MeO)_2C_6H_3$;

Scheme 2.5

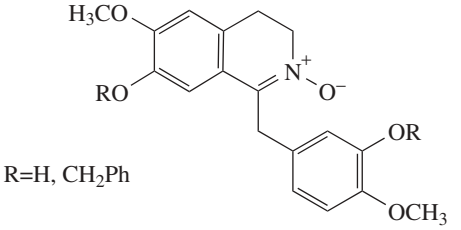
Oxidation of secondary amines into nitrones has been extensively studied and a variety of well-known efficient oxidants and catalysts which can be employed in this process are available. Catalytic oxidation by hydrogen peroxide at room temperature is carried out by using sodium tungstate (Fig. 2.1) (28–47).

Under suitable conditions, oxidation of *N*-alkyl-α-amino acids, accompanied by decarboxylation, has made it possible to carry out regioselective syntheses of nitrones which were utilized in the synthesis of 1-azabicyclic alkaloids (Scheme 2.6) (48, 49).

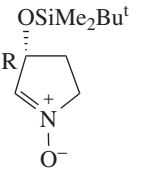
Recently, based on such an oxidative system, the synthesis of nitrone (**12**) an inhibitor of 5α-reductase has been carried out (Scheme 2.7) (50). Oxidation of amines with H_2O_2 can be catalyzed with peroxotungstophosphate (PCWP) (51), SeO_2 (52–54), and titanium silicalite molecular sieves TS-1 and TS-2 (55, 56).

Quantitative oxidation of secondary amines occurs upon treatment with Mo(VI) and W(VI) polyperoxo complexes (PPC) of general formula $[C_5H_5N^+(CH_2)_{14}CH_3]_3PO_4[MO(O_2)_2]_4^{3-}$ (57–60). When studying this reaction by UV- and electron spin resonance (ESR)-spectroscopy, intermediate formation of nitroxyl radicals was revealed (61). Secondary amines are oxidized in high yields by using a methyltrioxorhenium (MTO)/H_2O_2 system (62–64). Moreover, application of MTO makes it possible to oxidize secondary amines to nitrones upon treatment with molecular oxygen (65).

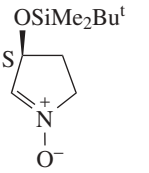
In recent years, the use of heterogeneous catalysts Mg-Al LDH (66, 67) and Mg-Al-O -^{t}Bu hydrotalcite (HT-O-^{t}Bu), in the oxidation of secondary amines with hydrogen peroxide, has been reported (68). The reaction appears to proceed quickly at room temperature, affording high yields. Similarly, it has been found



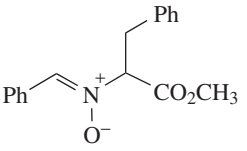
Ref.[28]



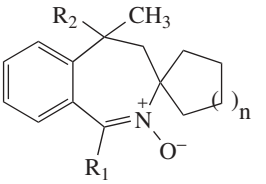
Ref.[30]



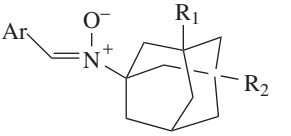
Ref.[30]



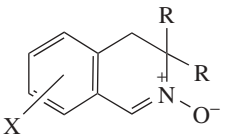
Ref.[31]



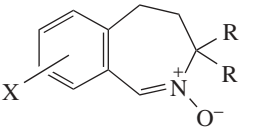
Ref.[32]



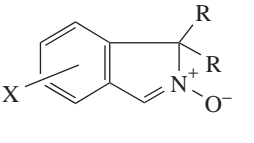
Ref.[34-37]



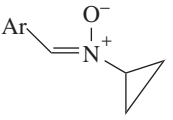
Ref.[38-41]



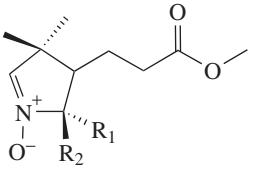
Ref.[38-40]



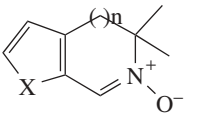
Ref.[41]



Ref.[43]

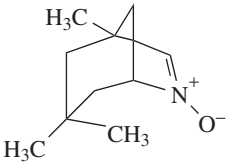


Ref.[44]

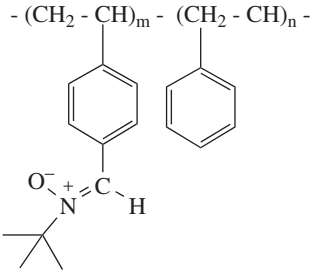


X = 0, X = S
n = 0,1,2

Ref.[45]

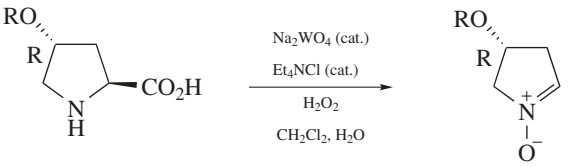


Ref.[46]

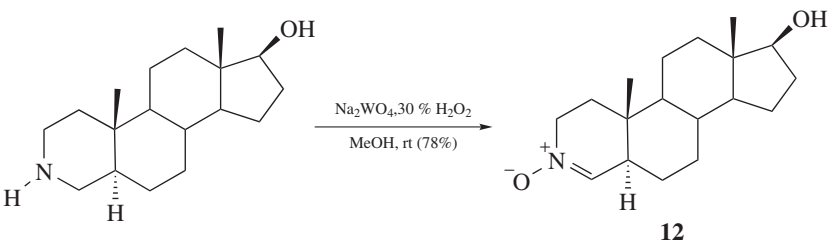


Ref.[47]

Fig. 2.1



Scheme 2.6



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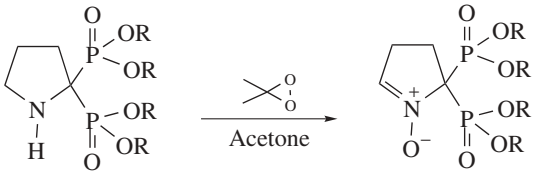
Scheme 2.7



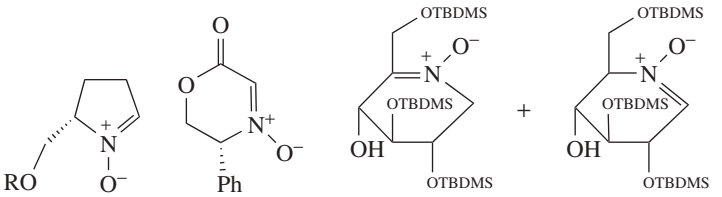
13 **14**

Scheme 2.8

that oxidation of secondary amines with alkyl hydroperoxides proceeds very efficiently by using polymeric catalytic Ti(IV)-based membranes, which can be recycled up to five runs with no loss of activity. Reactions proceeded very quickly, selectively, and in high yields (69, 70).

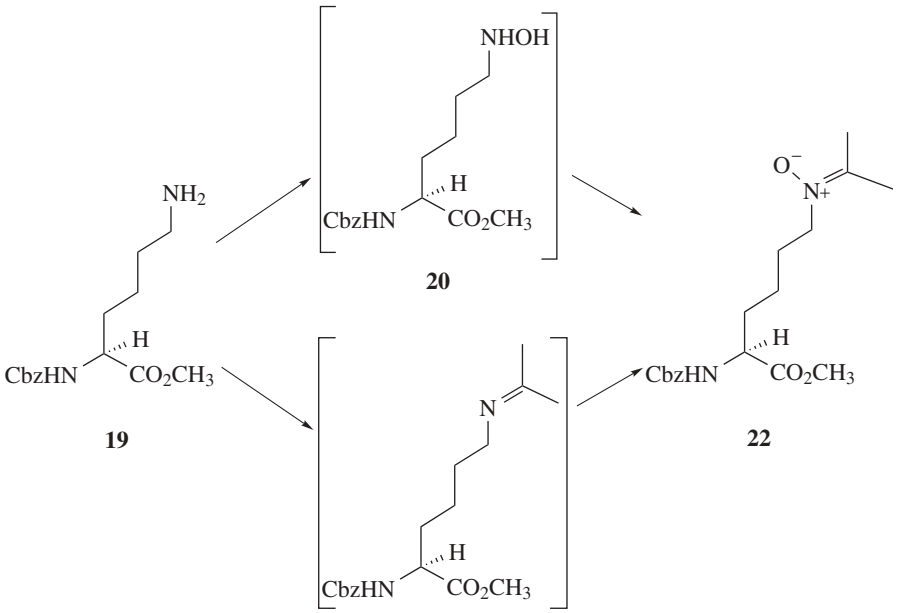
Nitrones can also be obtained in high yields by treating secondary amines with DMD (Scheme 2.8) (71). Oxidation of pyrrolidine (**13**) at 0°C with DMD (produced *in situ* from oxone and acetone "Brik procedure") leads to *gem*-bisphosphorylated nitrone (**14**) (Scheme 2.8) (72).

Mild reaction conditions make it possible for DMD to be used in the formation of optically active nitrones such as (S)-5- hydroxymethyl -1-pyrroline *N*-oxide (**15**) (73), (5 R)-3,4,5,6- tetrahydro -5- phenyl -2*H*-1,4 oxazine-2-one-*N*-oxide (**16**) (74), and homochiral cyclic nitrones derived from 1-1-deoxynojirimycin (**17**) and (**18**) (Fig. 2.2) (75).



15 **16** **17** **18**

Fig. 2.2

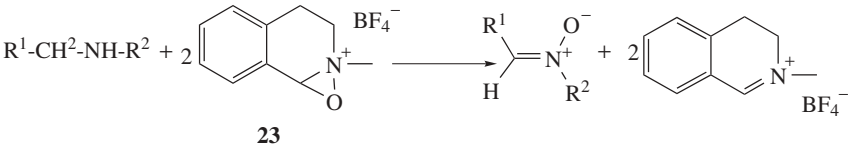


Scheme 2.9

Oxidation of primary amines with DMD or other oxidants leads to the formation of a complex mixture of nitroso, oximes, and nitro compounds (76). Utilization of DMD in acetone affords dimethyl nitrone (**22**). This is likely to be a result of the initial oxidation of primary amine (**19**) to hydroxylamine (**20**) with the subsequent condensation of acetone and oxidation of imine (**21**) (Scheme 2.9) (77).

DMD was employed to oxidize *N* α-carbobenzyloxy (Cbz)-L-lysine *tert*-butyl ester to the corresponding lysine-based dimethyl nitrone, an important synthetic intermediate of the mycobactins (78).

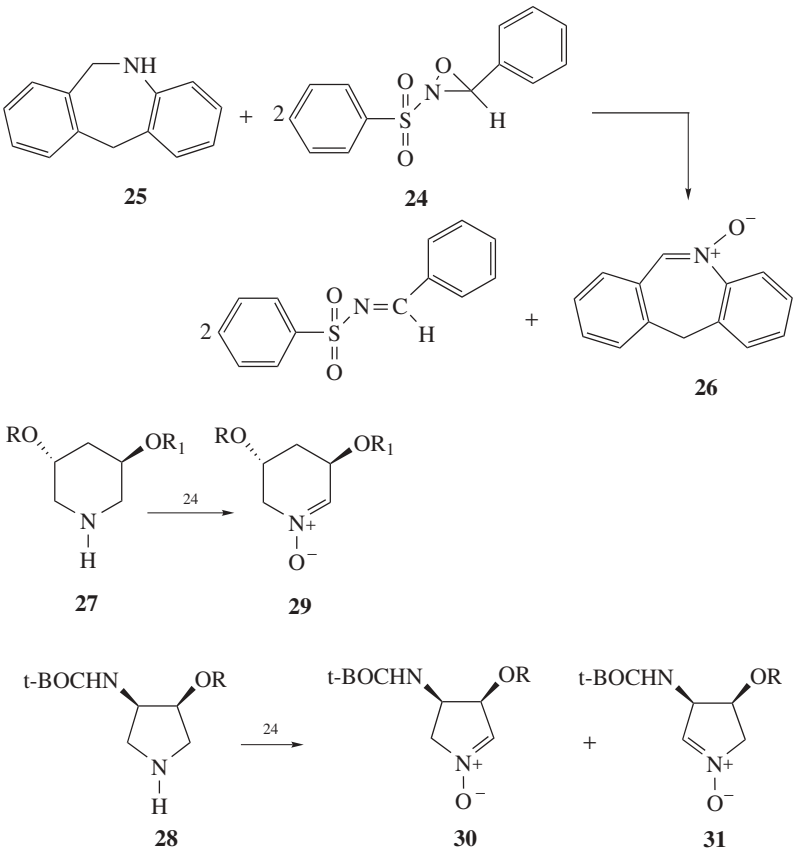
Nitrones can be formed upon treatment of secondary amines with an oxaziridine salt (**23**) generated from dihydroisoquinoline (Scheme 2.10) (79).



23

R^1 = Ph, R^2 = Bn; R^1 = ^{i}Pr, R^2 = ^{t}Bu; $R^1 + R^2$ = -$(CH_2)_2O(CH_2)_2$-

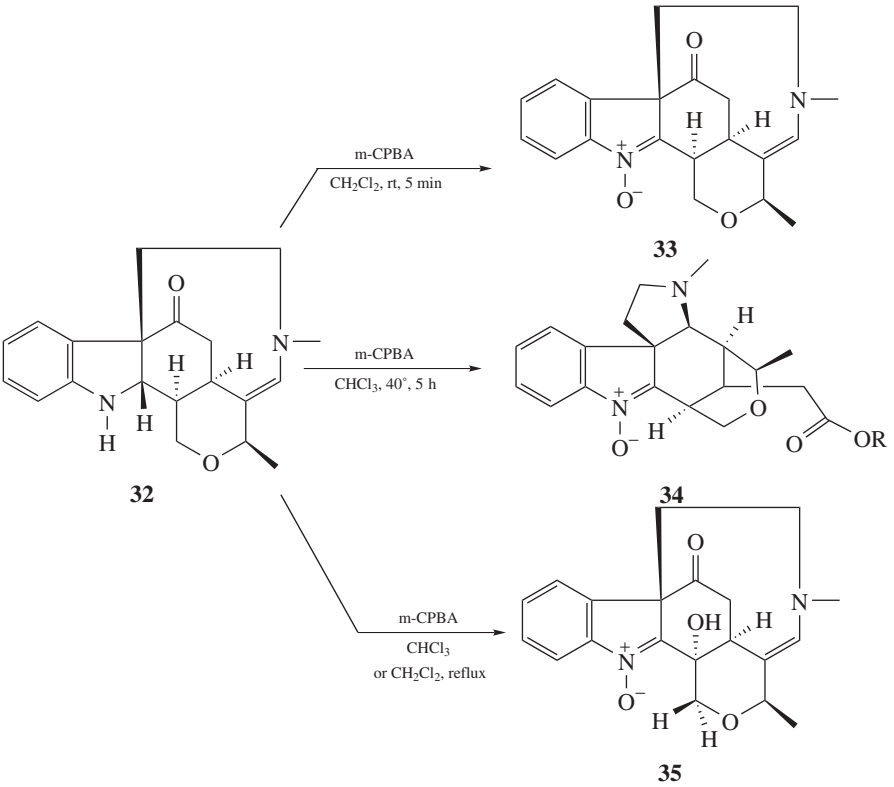
Scheme 2.10



25 **24** **26** **27** **29** **28** **30** **31**

Scheme 2.11

C- Phenyl -*N*-phenylsulfonyloxaziridine (**24**) (Davis reagent) is also used as an oxaziridine type oxidant. The use of this reagent in oxidations of diazepine derivatives (**25**), piperidine (**27:** R and R^1 = Bz or TBDMS), and pyrrolidine (**28:** R = Bz or TBDMS) gives the corresponding nitrones (**26**), (**29**), (**30**), and (**31**) in quantitative yields (Scheme 2.11) (80–82).



Scheme 2.12

Urea complex with hydrogen peroxide (UHP) seems to be a very useful and convenient oxidation system in nonaqueous medium. The UHP reaction proceeds in methanol and is catalyzed by Mo (VI), W (VI) salts, or SeO_2 (83). Catalytic oxidation in a water-free medium can be carried out with alkylhydroxyperoxides, the catalysts being titanium alkoxides (84) or selenium compounds (85). The reaction appears to proceed quickly and with good selectivity.

The most effective and frequently used oxidant of secondary amines in organic solvents (CH_2Cl_2, CH_3CN, MeOH) is *m*-chloroperbenzoic acid (*m*-CPBA). Oxydation with *m*-CPBA of *seco*-curane type indoline alkaloids of strychnobrasiline (**32**), in deacetylated form, gives the corresponding nitrones (**33**), (**34**), and (**35**) (Scheme 2.12) (86).

The synthesis of camphor-derived nitrones (87), of spin traps containing alkylphenylphosphoryl (**36a,b**) (88) and diethoxyphosphoryl substituents (**37–39**) requires *m*-CPBA as an oxidant (Fig. 2.3) (89, 90).

m-CPBA oxidation of cyanomethylamines (**41**) into nitrones (**42**) proceeds regioselectively, which is obviously determined by the inductive effect of the cyano group (91). A three-stage protocol has been proposed for converting

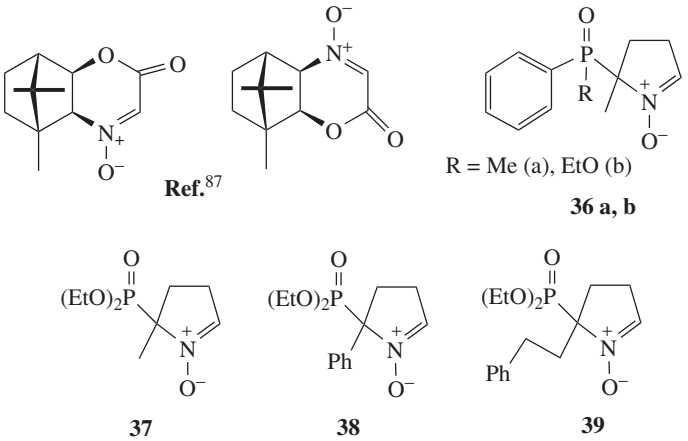
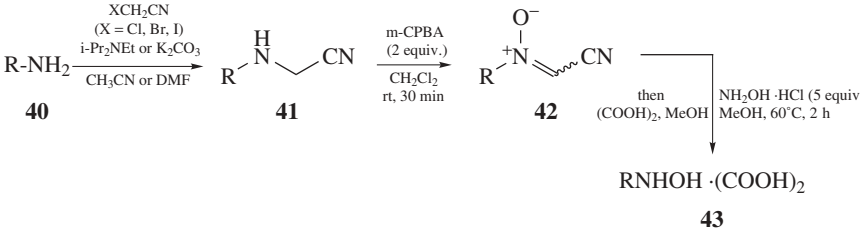


Fig. 2.3



Scheme 2.13

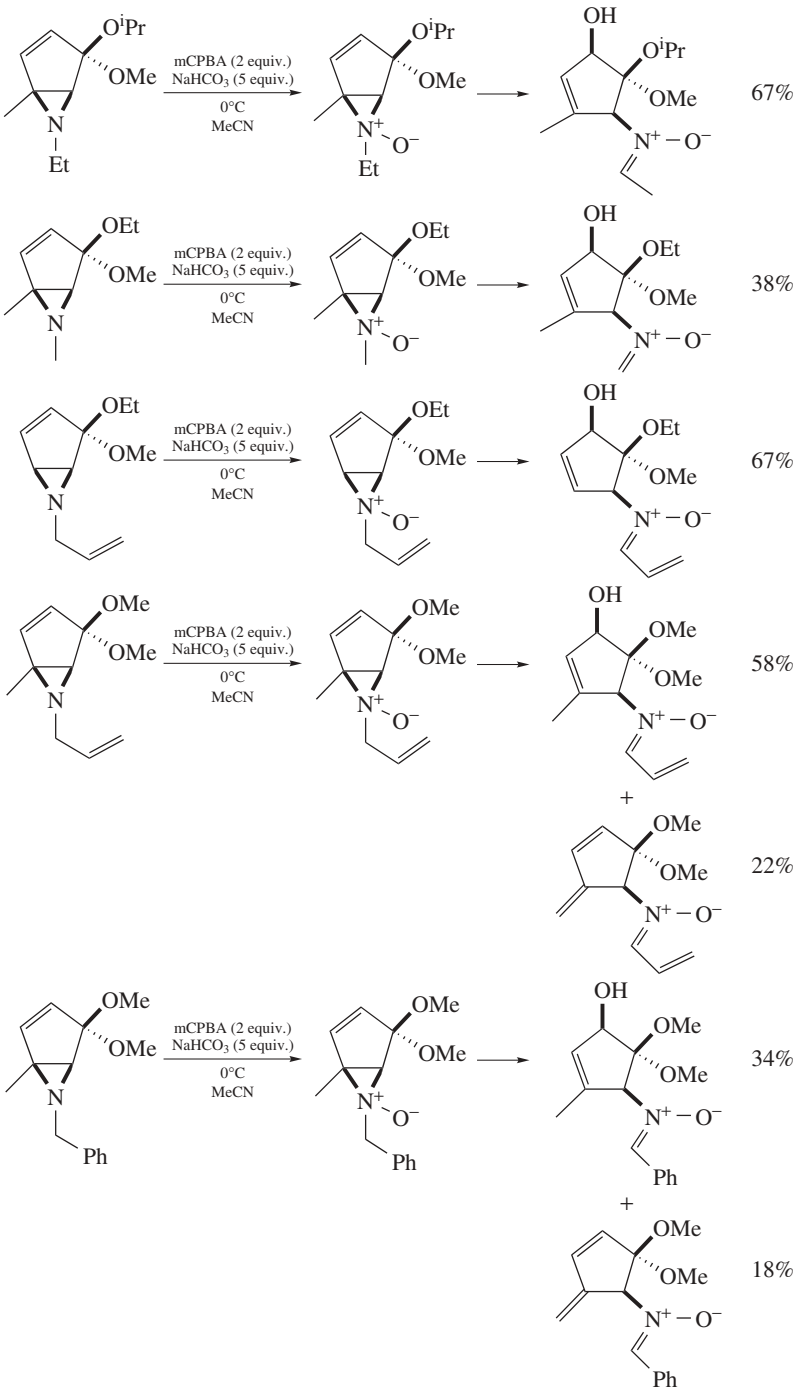
primary amines (**40**) into the corresponding hydroxylamine oxalates (**43**). This method can be applied to a wide variety of primary amines (Scheme 2.13).

In order to optimize oxidation conditions of diethyl(2-methylpyrrolidine-2-yl) phosphonate into the corresponding nitrone, a comparative analysis of the action of various oxidants such as H_2O_2, *m*-CPBA, Oxone, 2-phenylsulfonyl-3-phenyl-oxaziridine (PSPO), DMD, and *N*-methylmorpholine *N*-oxide in the presence of a catalytic quantity of tetrapropylammonium perruthenate (NMO/TPAP) has been made (92).

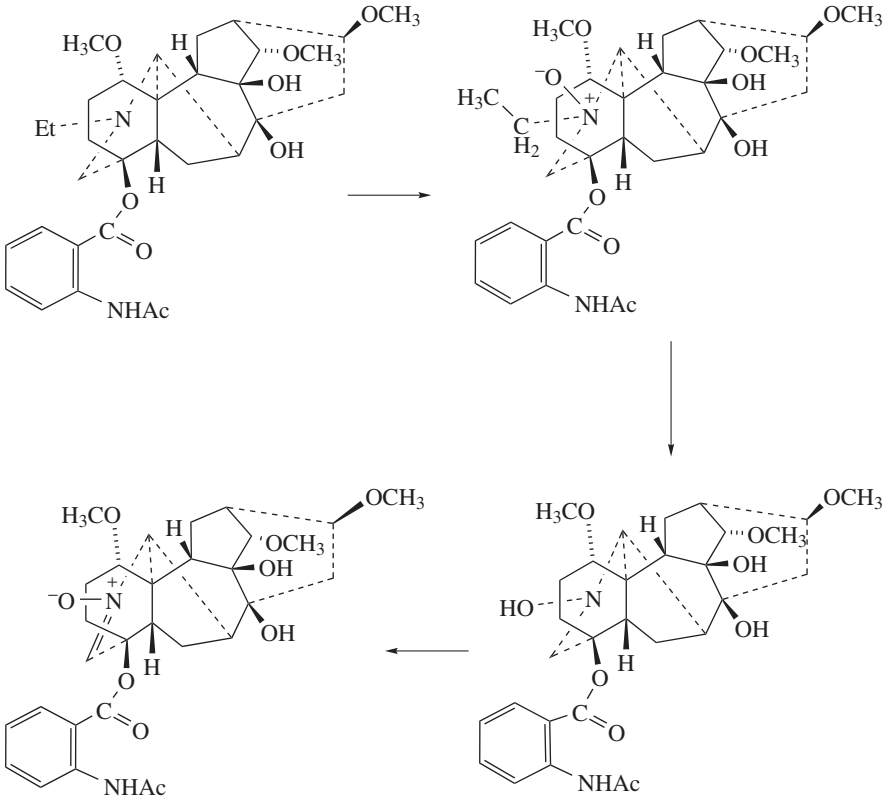
The use of *m*-CPBA allows the formation of nitrones in the oxidation of tertiary amines. The resulting amines *N*-oxides are subject to either Cope or Meisenheimer rearrangements, providing formation of nitrones. Thus, the generated corresponding nitrones in the oxidation of bicyclic aziridines give nitrones as a result of a Meisenheimer rearrangement (Scheme 2.14) (93).

Oxidation of lappaconitine and elatine alkaloids leads to de-ethylation by a Cope reaction, with the formation of nitrones (Scheme 2.15) (94).

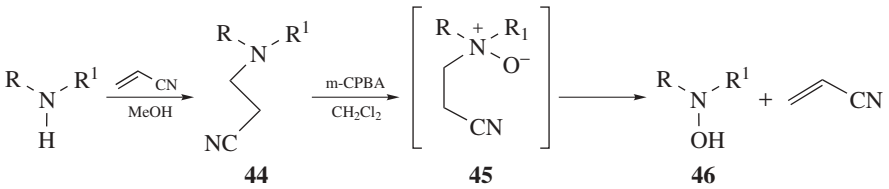
Similarly, oxidation with DMD and $KMnO_4$ of diterpene alkaloids eldeline, talatizamine, aconitine, and zongorine has been carried out. (95).


O^iPr
OMe
N
Et
mCPBA (2 equiv.)
NaHCO3 (5 equiv.)
0°C
MeCN
N+ O−
OH
67%
OEt
38%
67%
OMe
58%
+
22%
Ph
34%
18%

Scheme 2.14



Scheme 2.15

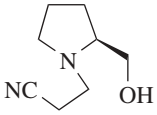
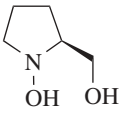
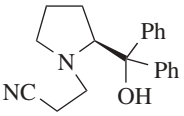
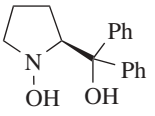
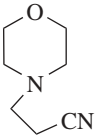
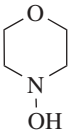
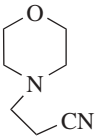
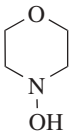
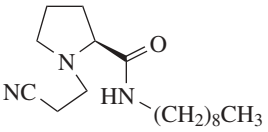
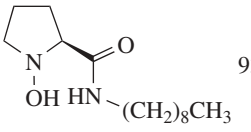
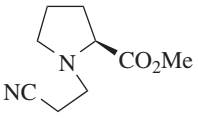
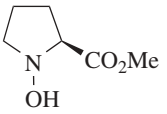
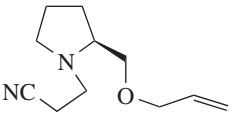
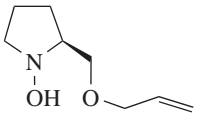
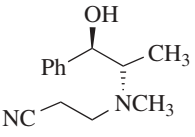
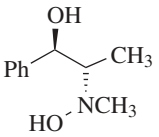


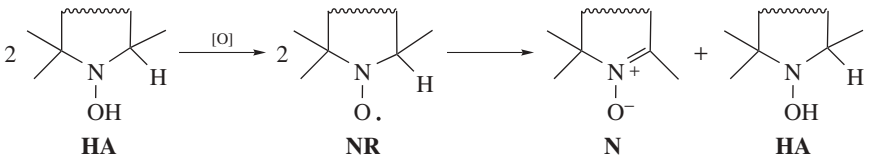
Scheme 2.16

Oxidations of a range of β-cyanoethyl tertiary amines (**44**) with *m*-CPBA in CH_2Cl_2 give the corresponding *N*-oxides (**45**), which can be isolated or undergo Cope elimination affording hydroxylamines (**46**) in high yields (Scheme 2.16) (Table 2.1) (96). Hydroxylamines (**46**) can be easily oxidated into nitrones (see Section 2.2.1.3).

Recently, an oxidative biotransformation of secondary amines into nitrones applying cyclohexanone monooxygenase, an enzyme isolated from *Acinetobacter*

Table 2.1 Synthesis of secondary hydroxylamines via Cope elimination of β-cyanoethylamines

Entry	Substrate	(%) Yield cyano ethylamine **45**	Product	(%) Yield hydro xylamine **46**
1		90		68
2		100		96
3		100		93
4		94		72
5		97		93
6		93		96
7		90		90
8		89		95



Scheme 2.17

calcoaceticus NCIMB 9871 (CHMO) (EC 1.14.13.22) has been reported (97, 98). The reaction is of limited synthetic value; however, it has become a subject of considerable mechanistic interest.

2.2.1.3. Oxidation of Hydroxylamines The mildest oxidation method of nitrone formation seems to be via oxidation of the corresponding hydroxylamines (**HA**) containing one or more protons at α-C. In this reaction, air, H_2O_2, *m*-CPBA, oxides of different metals (MnO_2, PbO_2, HgO, Ni_2O_3, etc.) can be used as oxidants. The resulting nitroxyl radicals (**NR**) undergo a disproportionation reaction (Scheme 2.17), and with an excess of the oxidant, give nitrones (**N**) as the final reaction products (99, 100).

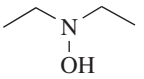
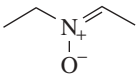
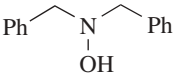
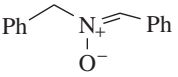
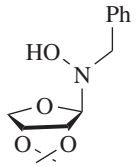
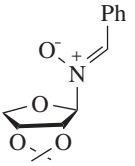
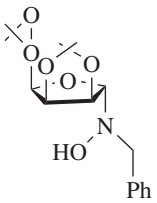
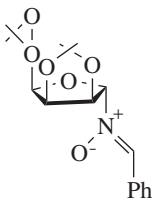
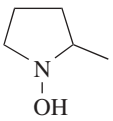
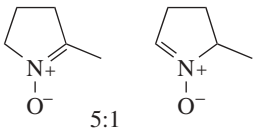
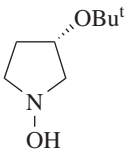
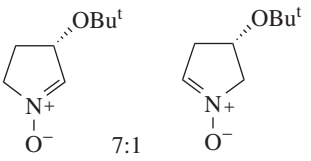
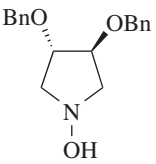
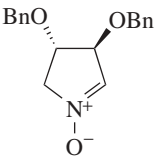
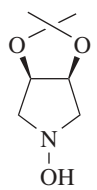
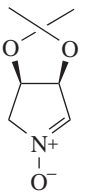
In electrochemical oxidation of 1-hydroxy-3-imidazoline-3-oxides containing one to four H atoms at α-C, one observes in ESR-spectra not only triplet splitting of the nucleus ^{14}N of the nitroxyl group (a_N 15-16 G) but also splitting of the neighboring protons (a_H 18-20 G), with multiplets corresponding to their number (from doublet to quintet) (101). Unlike spatially hindered hydroxylamines which show reversibility in electrochemical oxidation, hydroxylamines with H at α-C are oxidized irreversibly. Oxidation of hydroxylamines with nitroxyl radical proceeds easily and with quantitative yields (102). In the oxidation of asymmetric polyfluorinated hydroxylamines with MnO_2, isomeric polyfluorinated nitrones have been obtained (103).

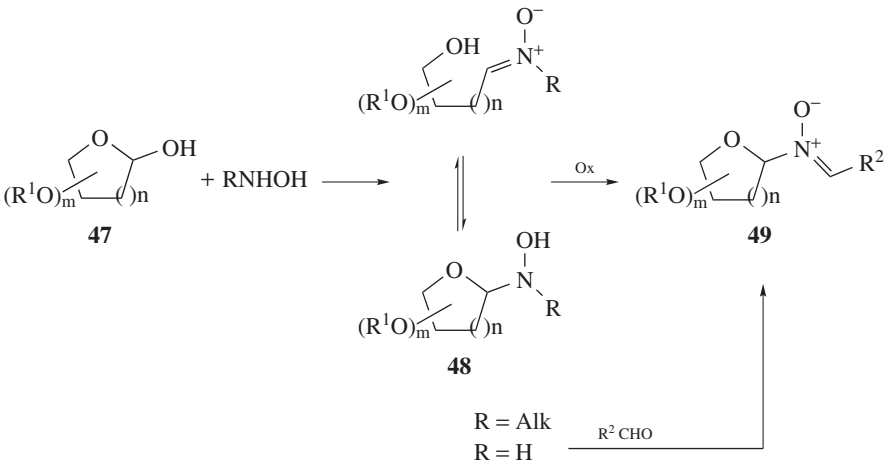
Study of the kinetics of the oxidation of asymmetric secondary hydroxylamines to nitrones with H_2O_2, catalyzed by methylrhenium trioxide, has led to the elucidation of the mechanism of the reaction (104). Full transformation of *N,N*-disubstituted hydroxylamines into nitrones upon treatment with H_2O_2 occurs on using polymeric heterogeneous catalysts such as polymer-supported methylrhenium trioxide systems (105).

In the mechanism study of *N*-benzyl-*N*-alkyl hydroxylamines, regarding oxidation with HgO and *p*-benzoquinone, it has been proposed on the basis of intra- and intermolecular kinetic isotope effects that, initially, there takes place a one-electron transfer from a nitrogen atom to the oxidant, with a subsequent proton abstraction (106–108).

Oxidation of cyclic and acyclic hydroxylamines with yellow mercuric oxide appears to proceed with high regioselectivity (109–115). Regioselectivity is determined by the electronic nature of the substituents (116). The oxidative regioselectivity of MnO_2 is comparable to that of HgO, but due to its lower toxicity, it has been proposed to use MnO_2 rather than HgO (Table 2.2) (117).

Table 2.2 Oxidations of hydroxylamines with MnO_2

Hydroxylamines	Reaction time (h)	Nitrones	Yield (%)
	2		90
	2		93
	12		96
	12		96
	2	 5:1	92
	2	 7:1	85
	2		95
	2		91



Scheme 2.18

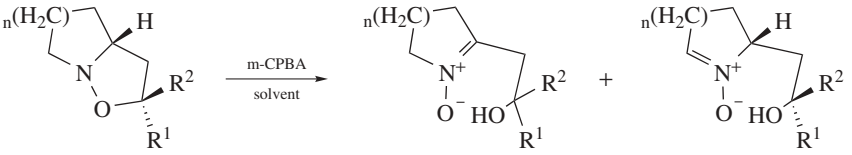
Oxidation with MnO_2 of N-glycosylhydroxylamines (**48**), obtained in the reaction of sugars (**47**), with *N*-methyl- and *N*-benzylhydroxylamines, leads selectively to the corresponding *C*-unsubstituted and *C*-phenyl-*N*-glycosyl nitrones (**49**) (Scheme 2.18) (118, 119).

The use of sodium hypochlorite (bleach) as an oxidant was suggested due to its efficiency and environmental safety (120). This method can be easily applied in a large scale production. To catalyze enantioselective oxidation of hydroxylamines with hydrogen peroxide, sodium hypochlorite, *m*-CPBA, UHP and PhIO, Jacobsen's catalyst (Salen)Mn(III)Complex (Salen ligand: *N,N'*-bis(salicylidene) ethylenediamine) was used (121). Using the system, *N*-*tert*-butylbenzenesulfineimidoyl chloride/diazabicycloundecene (DBU) in CH_2Cl_2, under mild conditions (-78° C), both cyclic and acyclic nitrones have been isolated in high yields (122). Tetra-*n*-propylammonium perruthenate (TPAP) is used as a catalyst in the oxidation of secondary hydroxylamines with NMO (123). In the oxidation of hydroxylamines into nitrones, polymer supported perruthenate (PSP) was utilized (124).

Oxidative ring opening of isoxazolidines leads to nitrones. Thus, bicyclic isoxazolidines (**50**) and (**51**), treated with *m*-CPBA, afford nitrones (**52**), (**53**), (**54**), and (**55**) (Scheme 2.19). Conformational analysis has confirmed the key role of the nitrogen lone pair with respect to regioselectivity of the reaction and of the intramolecular kinetic deprotonation of the intermediate oxoammonium derivative (125).

Similar oxidative ring opening occurs in other bi- and tricyclic isoxazolidines upon treatment with *m*-CPBA (126, 127).

Oxidation with *m*-CPBA of monocyclic isoxazolidines (**56**) without H at α-C gives a tautomeric mixture of acyclic nitrones (**57**) and six-membered cyclic hydroxylamines (**58**), with their proportion depending on the substituents



$n = 1$ **50** **52** **53**

$n = 2$ **51** **54** **55**

(52 a) : (53 a) 0 : 100 in CH_2Cl_2 (52 b) : (53 b) 0 : 100 in CH_2Cl_2

(52 a) : (53 a) 100 : 0 in CH_3CO_2H (54 b) : (55 b) 85 : 15 in CH_2Cl_2

a, $R_1 = H$, $R_2 = Ph$ b, $R_1 = CO_2CH_3$, $R_2 = CH_3$

Scheme 2.19

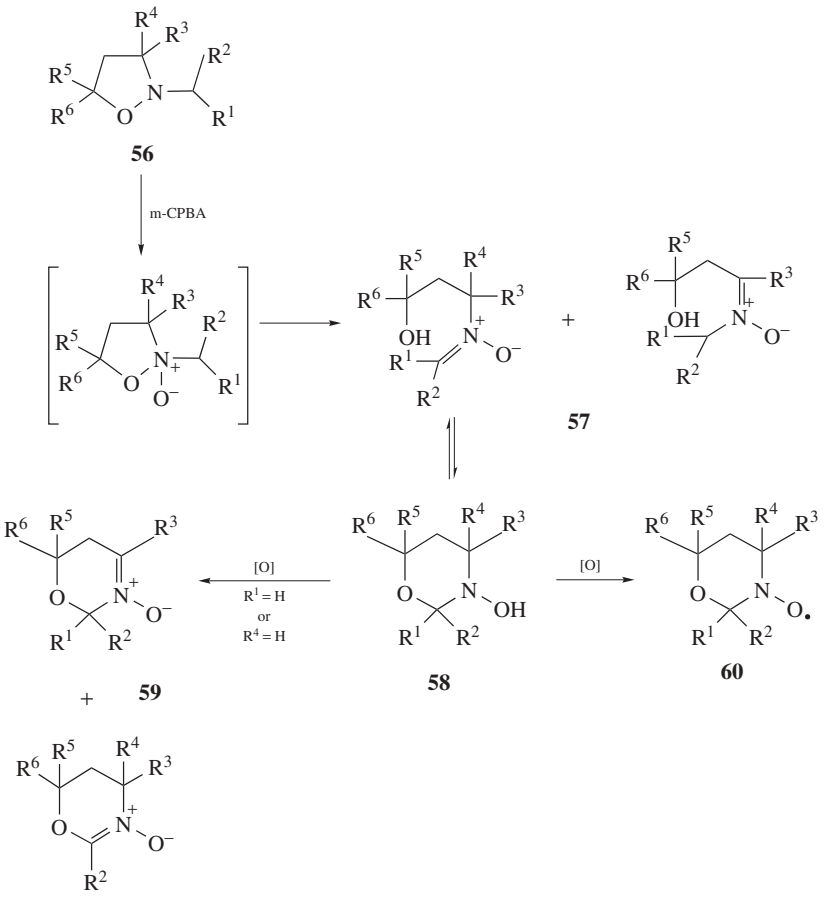
(different combinations of $R^1-R^6 = H$, Me, Et, Ph, CH_2OH, CH_2CH_2OH, $CH_2Si^tBuMe_2$, CO_2Me) (128). Tautomeric cyclic hydroxylamines have been converted to six-membered heterocyclic nitrones (**59**) by oxidation with HgO or *p*-benzoquinone. The cyclic hydroxylamines lacking hydrogen at the α-carbons have been oxidized to nitroxyl radicals (**60**) (Scheme 2.20).

To undertake oxidation of both cyclic and acyclic hydroxylamines to nitrones, an electrochemical oxidative system has been developed, where WO_4^{2-}/WO_5^{2-} are used as cathodic redox mediators and Br^-/Br_2 or I^-/I_2 as anodic redox mediators (129–131).

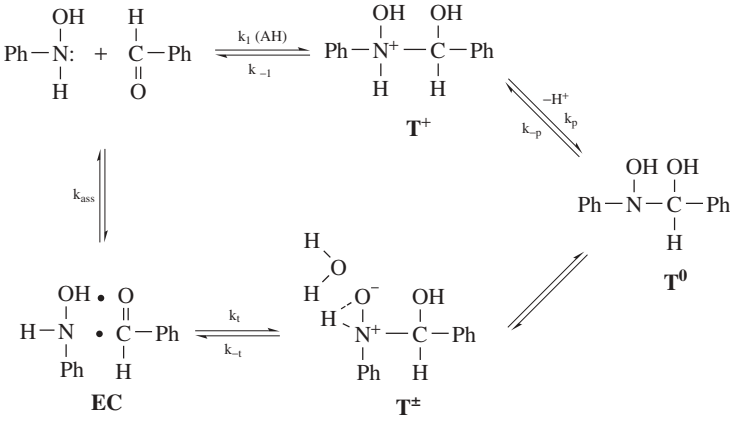
2.2.2. Nonoxidative Methods

2.2.2.1. Condensation of N-Monosubstituted Hydroxylamines with Carbonyl Compounds Condensation of *N*-monosubstituted hydroxylamines with carbonyl compounds is used as a direct synthesis of many acyclic nitrones. The synthesis of hydroxylamines is being carried out *in situ* via reduction of nitro compounds with zinc powder in the presence of weak acids (NH_4Cl or AcOH) (14, 18, 132). The reaction kinetics of benzaldehyde with phenylhydroxylamine and the subsequent reaction sequence are shown in Scheme 2.21 (133).

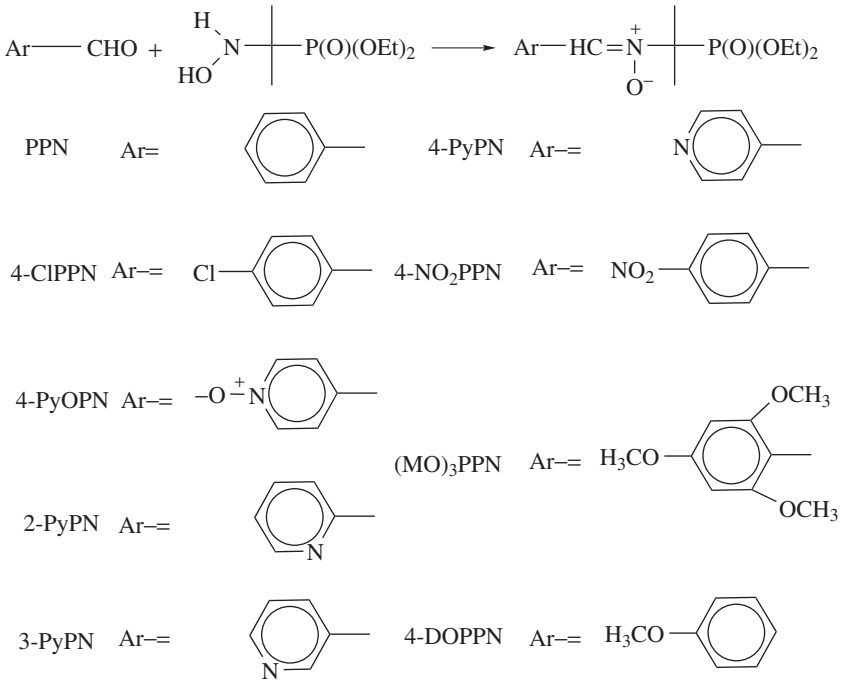
The condensation is carried out under mild conditions; this allows the synthesis of various nitrones to proceed without affecting functional groups. Thus, condensation of various aromatic, heteroaromatic, and aliphatic aldehydes with alkylhydroxylamines makes it possible to synthesize a variety of *N*-alkylnitrones (134–141), such as β-phosphorylated phenyl-*N*-*tert*-butylnitrone (PBN) derivatives (142), photochromic spin traps derived from spiro [indoline-naphthoxazine] (143), [3*H*]- naphtho[2,1-b]pyran (144), glycosylated *N*-*tert*-butyl nitrones (145), glycolipidic amphiphilic nitrones (146), nitrone containing a fragment of lipoic acid (147), poly(β-phosphorylated) nitrones (148), α-^{14}C-labelled nitrones (149), and a polymer bearing *C*-phenyl-*N*-*tert*-butylnitrone fragments (150). The reaction of 4-acetyl- and 4- formyl- [2.2]paracyclophane with *N*-methylhydroxylamine



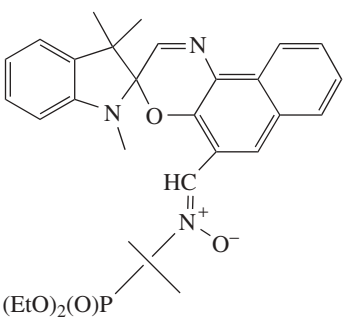
Scheme 2.20



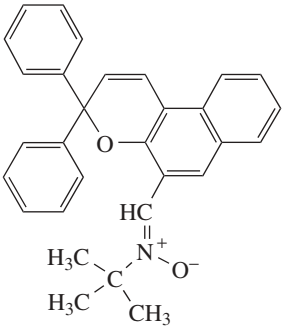
Scheme 2.21



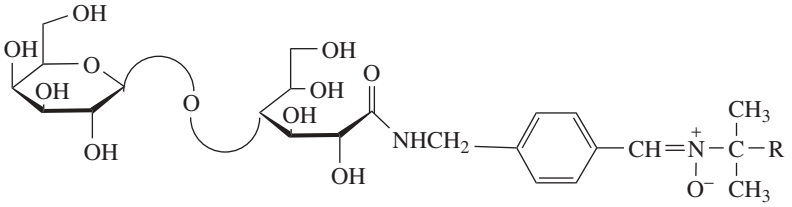
Ref. [142]



Ref. [143]

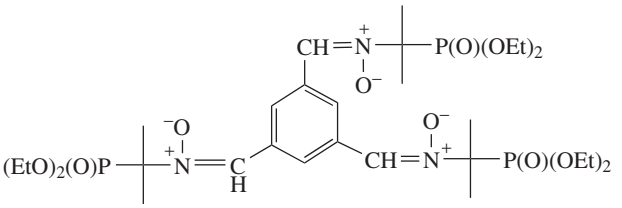


Ref. [144]

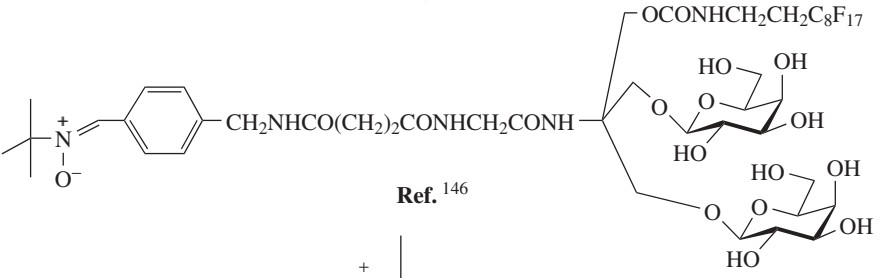


Ref. [145]

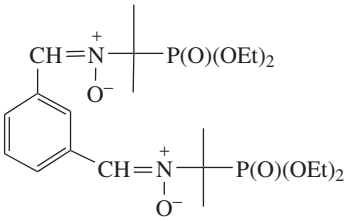
Fig. 2.4



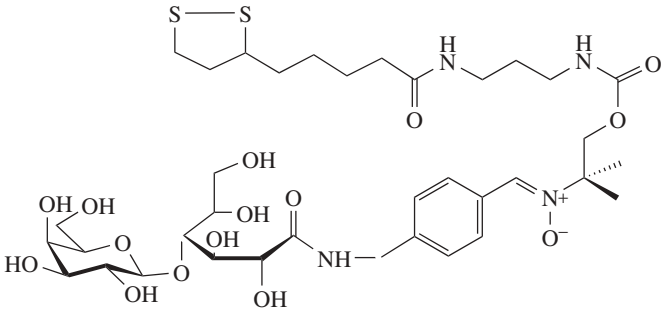
TN 1, Ref. [148a]



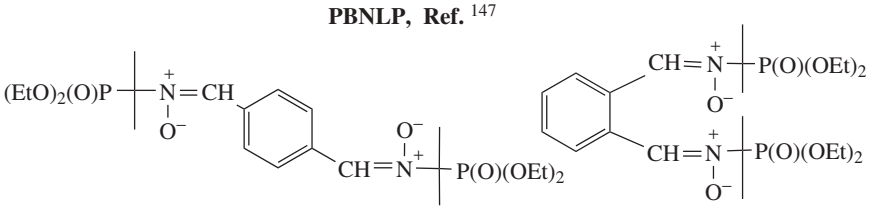
Ref. [146]



MDN 2, Ref. [148a]



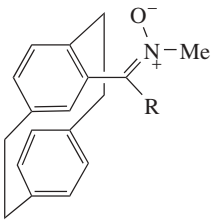
PBNLP, Ref. [147]



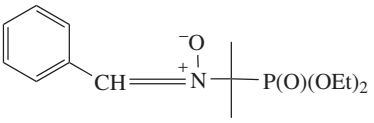
PDN 3, Ref. [148a]

ODN 4, Ref. [148a]

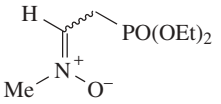
Fig. 2.4 (*continued*)



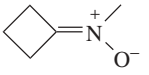
Ref. R = H (a)[151]**,**
R = CH_3 (b)[152]



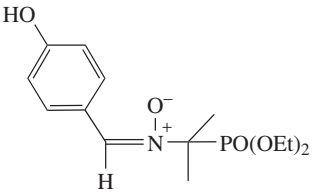
PPN 5, Ref. [148a]



Ref.[152]



Ref. [153]



4-HOPPN, Ref. [148b]

Fig. 2.4 (*continued*)

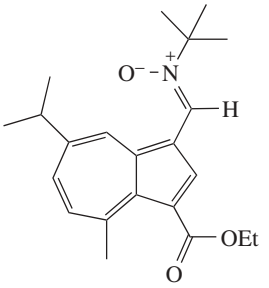
hydrochloride gave α-(4'-[2.2]paracyclophanyl) nitrones (151). From diethylphosphonoacetaldehyde was obtained diethylphosphonomethylnitrone (152). The reaction of cyclobutanone with *N*-methylhydroxylamine leads to *N*-methylcyclobutylideneamine-*N*-oxide, which undergoes spontaneous dimerization. Therefore, *N*-methylcyclobutylideneamine-*N*-oxide was used *in situ* in a 1,3-cycloaddition reaction with active dipolarophiles (153) (Fig. 2.4).

For the synthesis of α-aryl-*N*-methylnitrones a silica gel-NaOH catalytic system has been used. The reaction proceeds without solvents and in good yields, irrespective of the electron-donor or electron-acceptor nature of the substituents in benzaldehyde. Under similar reaction conditions ketones do not undergo the reaction; therefore, it makes it possible to carry out selective syntheses in cases where the system contains both aldehyde and ketone groups (154).

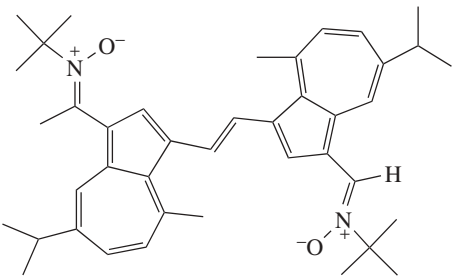
Z- Configuration is typical of the majority of α-aryl(hetaryl)-*N*-alkylaldonitrones. The isolation of *E*-isomers in the condensation of aromatic aldehydes with *N*-β-phenylethylhydroxylamine has been described (155). The synthesis of α, *N*-diarylnitrones gives best results if acidic catalysis is employed (156), or when clay is used as a catalyst (157). Significant reduction of reaction time and increase in the yields of nitrones can be achieved if microwave irradiation is used (158, 159). On the basis of polymeric arylaldehydes, the synthesis of polymeric α,*N*-diarylnitrones has been described (160).

Condensation of *N*-substituted hydroxylamines with aldehydes and ketones is widely used in the synthesis of various spin traps and biologically active nitrones (Fig. 2.5) (161–186).

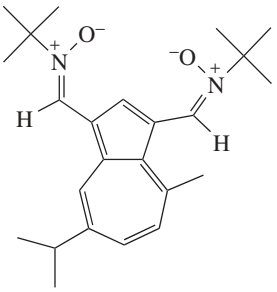
Molecular sieves are often used in condensation reactions. Thus, using 3Å molecular sieves at room temperature, the condensation of alkylaldehydes with



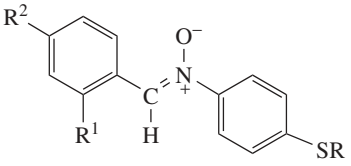
AZN[166, 167]



STAZN[168, 169]

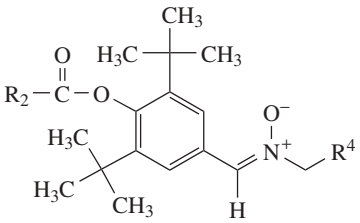


WAZN[170]

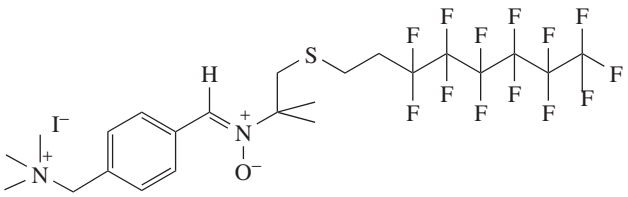


a; $R^1 = R^2 = H$
b; $R^1 = H$, $R^2 = Me$
c; $R^1 = H$, $R^2 = OMe$
d; $R^1 = H$, $R^2 = Cl$
e; $R^1 = H$, $R^2 = NMe_2$
f; $R^1 = H$, $R^2 = SMe$
g; $R^1 = H$, $R^2 = SO_2Me$
h; $R^1 = H$, $R^2 = NO_2$
i; $R^1 = H$, $R^2 = SPh$
j; $R^1 = H$, $R^2 = S$ p-tolyl
k; $R^1 = OH$, $R^2 = H$
l; $R^1 = OMe$, $R^2 = H$
m; $R^1 = Cl$, $R^2 = H$
n; $R^1 = NO_2$, $R^2 = H$
o; $R^1 = SPh$, $R^2 = H$

Ref. R = Ph[171]**, Me** [172]

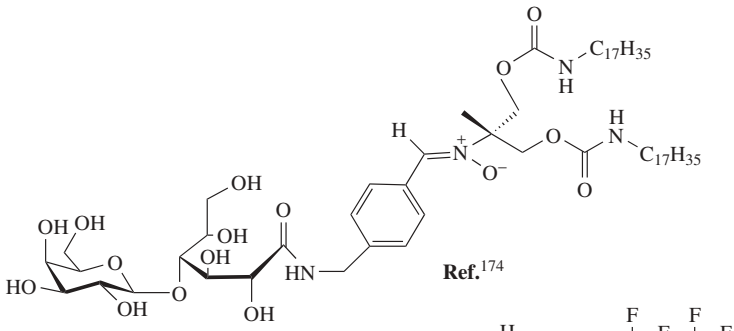


Ref.[173]

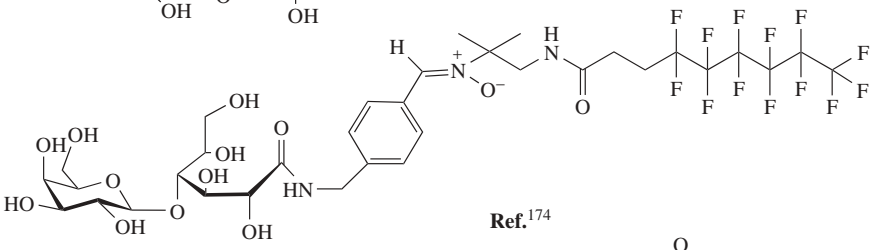


Ref.[174]

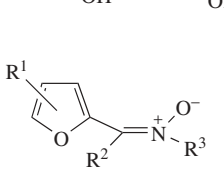
Fig. 2.5



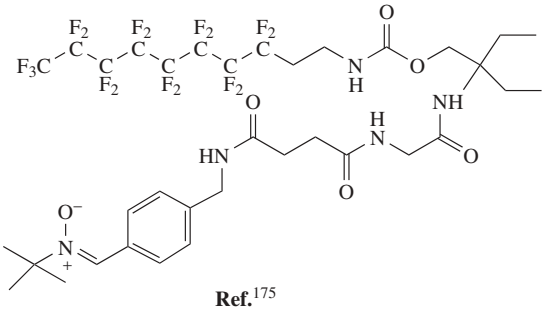
Ref.[174]



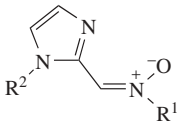
Ref.[174]



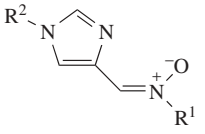
Ref.[177]



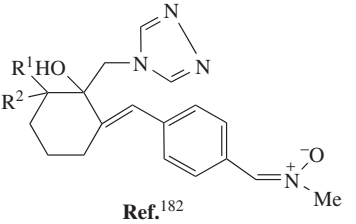
Ref.[175]



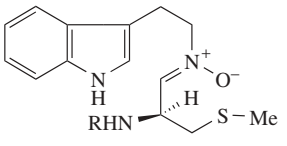
Ref.[181]



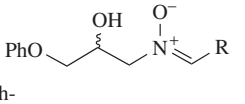
Ref.[181]



Ref.[182]



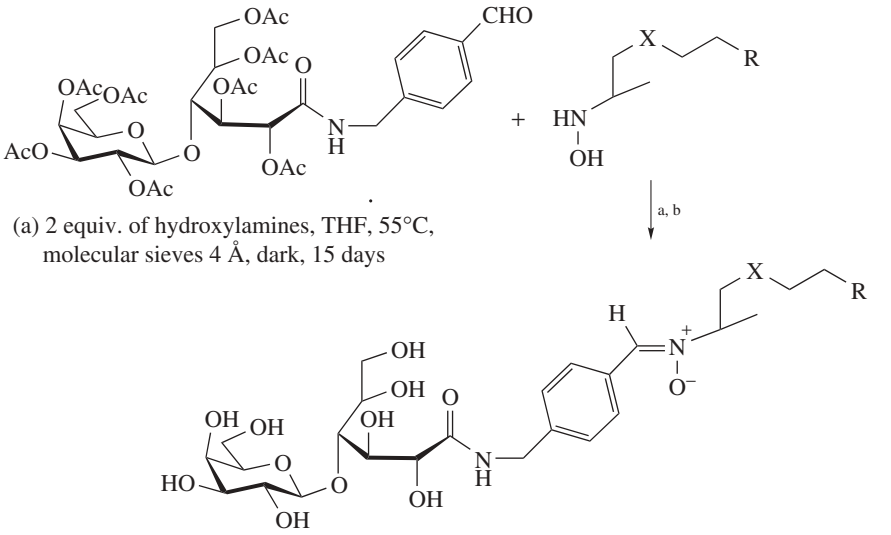
Ref.[185]



R = Ph-
R = 4-NO_2-C_6H_4-
R = $(CH_3)_3C$-
R = CH_3-

Ref.[186]

Fig. 2.5 (*continued*)



(a) 2 equiv. of hydroxylamines, THF, 55°C, molecular sieves 4 Å, dark, 15 days

(b) MeONa, MeOH, 1 h, quantitative yields

X-CH_2-CH_2-R	Yield %[a]
O-CO-NH-C_6H_{13}	65
S-C_8H_{17}	68
S-CH_2-CH_2-C_6F_{13}	56
NH-CO-C_7H_{15}	63
NH-CO-CH_2-CH_2-C_6F_{13}	44 (70)[b]

[a] Coupling reaction yields, measured after purification on silica gel and on Sephadex resin.

[b] Calculated with the residual starting benzaldehyde.

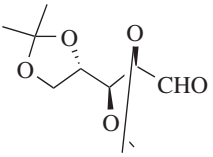
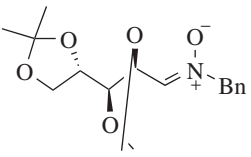
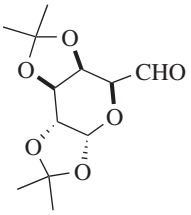
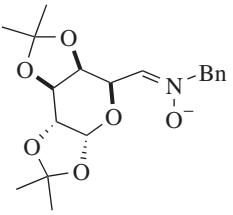
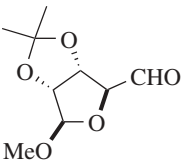
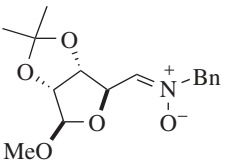
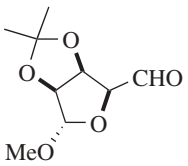
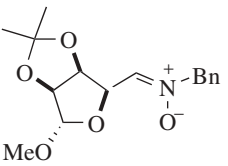
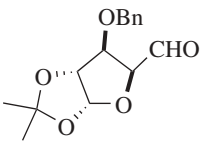
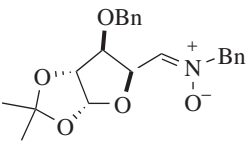
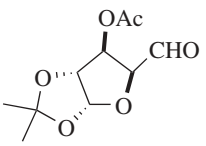
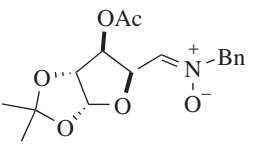
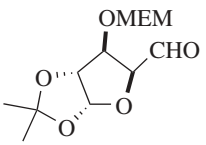
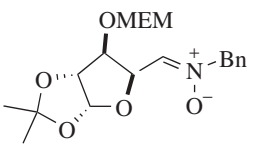
Scheme 2.22

N-hydroxyglycine ethyl ester affords nitrones in good yields (187). Several α-aryl-*N*-methylnitrones have been produced in yields of 80% to 100% without solvents, in the presence of 3Å molecular sieves (188). Using 4Å molecular sieves, it was possible to carry out the synthesis of novel glycolipidic nitrones – potential antioxidant drugs for neurodegenerative disorders (Scheme 2.22) (189).

High yields of *N*-benzylketonitrones were obtained in the condensation reaction of *N*-benzylhydroxylamine with ketones in methylene chloride using $ZnCl_2$ (190).

Condensation of *N*-benzylhydroxylamine with various aldehydes and ketones in CH_2Cl_2 in the presence of anhydrous magnesium sulfate has made it possible to carry out successful syntheses of a great number of chiral and achiral sugar-containing *N*-benzylnitrones (partly presented in Table 2.3) (191–208).

Table 2.3 Physical properties of N-benzyl nitrones[192]

Aldehyde	Nitrone	Yield (%)	mp (°C)	$[\alpha]_D$ (c)
		73	90	+18.3 (1.1)
		80	106	−120.5 (1.0)
		76	54	−85.7 (0.9)
		78	74	−65.8 (0.8)
		86	96	−135.7 (0.4)
		80	138	−102.0 (0.9)
		71	52	−93.4 (0.6)

Similarly, chiral nitrones (**61a–c**) and (**62a–c**) were obtained from the corresponding α-amino aldehydes (209, 210), nitrones (**63a,b**) from β-amino-α-hydroxy aldehydes (211), and chiral nitrones (**64**) and (**65**) from *N*-fluorenylmethoxycarbonyl (*N*-Fmoc) amino acids and *N*-Fmoc-dipeptides (Fig. 2.6) (212).

Reactions of furanose and pyranose with *N*-benzylhydroxylamine at 110°C without solvent give *N*-benzyl-*N*-glycosylhydroxylamines (**66**), which are in equilibrium with the open nitrone form (**67**) (Scheme 2.23) (213–215).

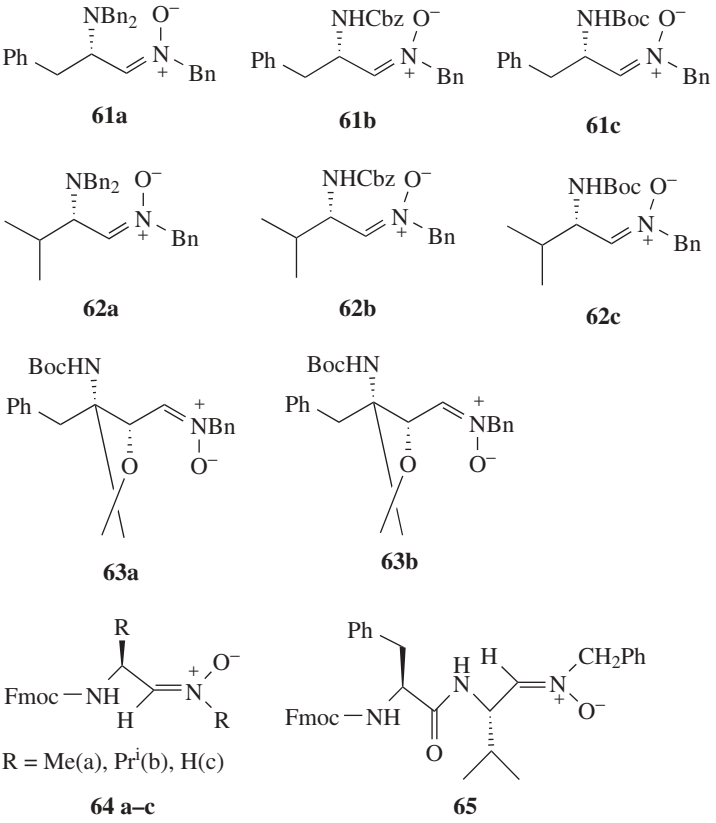
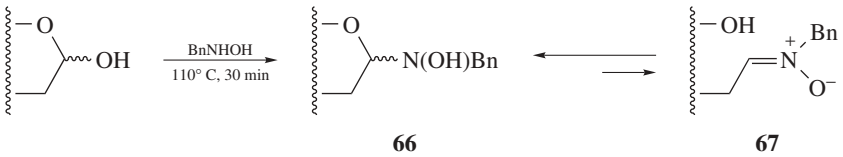
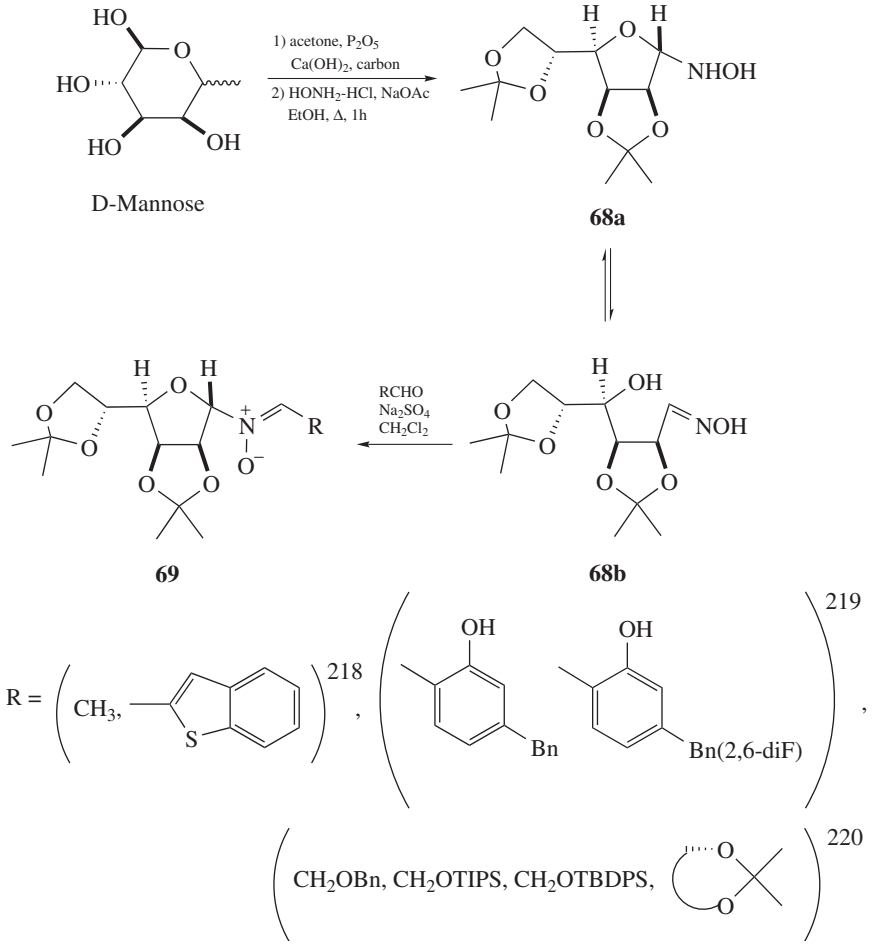


Fig. 2.6



Scheme 2.23

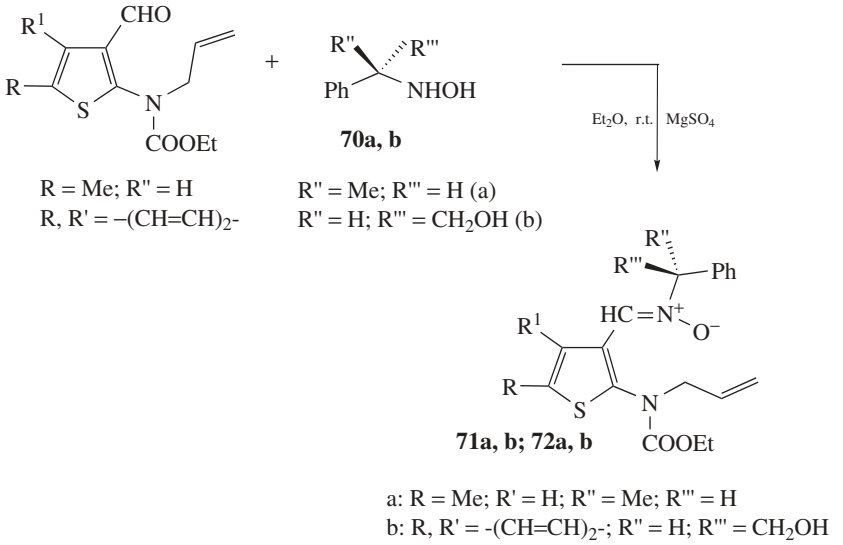


Scheme 2.24

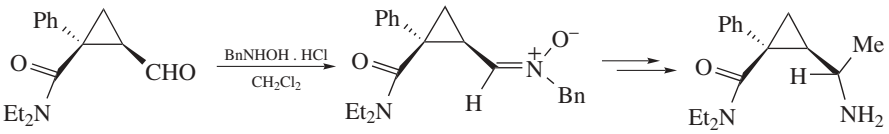
Another synthetic approach for generating sugar-containing nitrones is by initial treatment of sugars with unsubstituted hydroxylamine. The resulting cyclic hydroxylamine of the tautomeric mixture (**68a**) and of the open chain oxime (**68b**) react with aldehydes to give the corresponding nitrones (**69**) (Scheme 2.24) (216–220).

The chirality source in the synthesis of optically active nitrones (**71**) and (**72**) are known to be enantiopure chiral benzyl type hydroxylamines, (*R*)-α-methylbenzylhydroxylamine (**70a**) and (*R*)-α-(hydroxymethyl)-benzylhydroxylamine (**70b**) (Scheme 2.25) (221).

The main building block of PEDC (1-phenyl-2-[(S)-1-aminoethyl]-*N,N*-diethylcyclopropanecarboxamide), a potent NDMA (*N*-methyl-D-aspartic acid) receptor antagonist of a cyclopropane structure, *N*-benzyl-*C*-cyclopropyl nitrone



Scheme 2.25



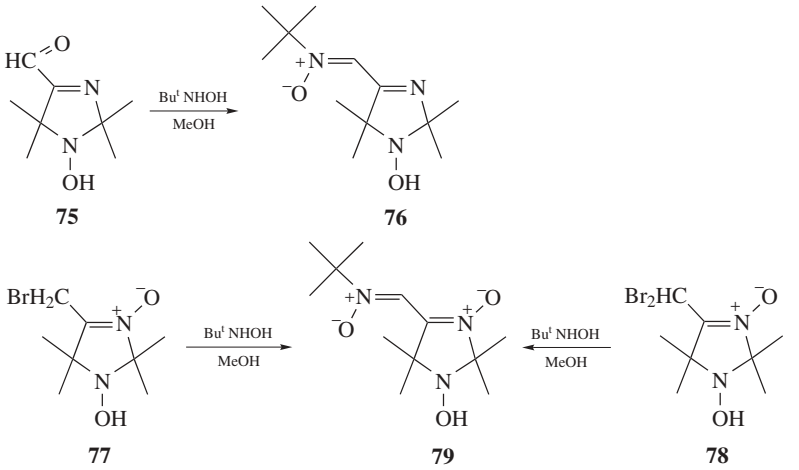
Scheme 2.26

(**74**) was generated in quantitative yield by condensation of asymmetric cyclopropylcarbaldehyde (**73**) with *N*-benzylhydroxylamine hydrochloride in CH_2Cl_2 (Scheme 2.26) (222, 223).

Condensation of 4-formyl-3-imidazoline (**75**) with *tert*-butylhydroxylamine in aqueous-alcoholic solvent gives conjugated nitrone-imine (**76**) (224), whereas the reaction of *N*-*tert*- butylhydroxylamine both with α-monobromomethyl nitrone (**77**), and α,α-dibromomethylnitrone (**78**) generated dinitrone (**79**) (Scheme 2.27) (225).

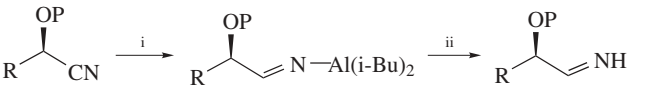
In order to study the mechanism of reverse Cope elimination reactions in the condensation of pentenal and hexenal with *N*-methylhydroxylamine, it seemed reasonable to synthesize unsaturated nitrones (226).

To generate chiral nitrones (**81**) and (**82**) the direct transformation of chiral *o*-substituted cyanohydrins was used. Both of the approaches described in Reference 227 allow the production of nitrones in high yields and high optical purity in a *one-pot* synthesis (Schemes 2.28 and 2.29).



75 **76** **77** **79** **78**

Scheme 2.27



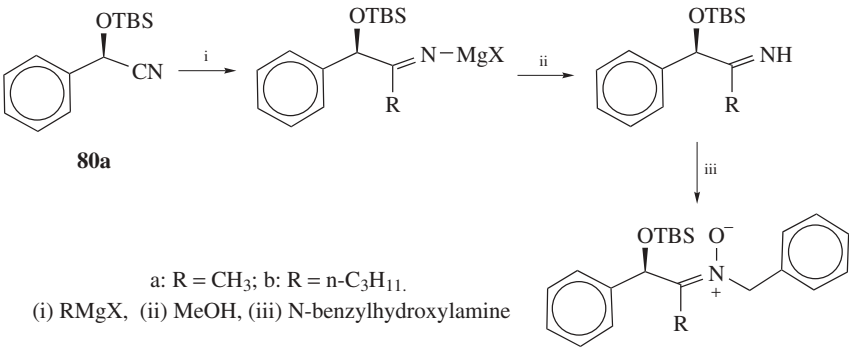
80a–g

a: R = C_6H_5, P = TBS;
b: R = C_6H_5, P = MIP;
c: R = 4-Cl-C_6H_4, P = MIP;
d: R = 4-MeO-C_6H_4, P = MIP;
e: R = 4-MeO-C_6H_4, P = TBS;
f: R = propenyl, P = TBS;
g: R = 5-Me-furanyl, P = TBS.

81a–g

(i) DIBAL; (ii) MeOH, (iii) N-benzylhydroxylamine

Scheme 2.28



80a

a: R = CH_3; b: R = n-C_3H_{11}.
(i) RMgX, (ii) MeOH, (iii) N-benzylhydroxylamine

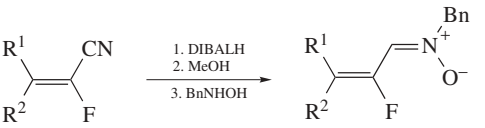
82a–b

Scheme 2.29

In a similar procedure, through diisobutylaluminium hydride (DIBALH)-reduction of nitrile into imine and condensation with *N*-benzylhydroxylamine, *C*-(1-fluorovinyl) nitrones were synthesized (Scheme 2.30, Table 2.4) (228).

To obtain materials with increased contrast range at light exposure with wavelength 300 to 450 *nm*, nitrones soluble in alkali have been prepared (229).

A number of α-aryl-*N*-alkyl nitrones and α,*N*-dialkyl nitrones were synthesized for studying contrast enhancement compositions, which can be used to make contrast enhancement layer photoresist composites (230, 231), and inhibitors of free radical polymerization of monomers in nonexposed regions of the photoresist layer at selective actinic radiation (232). Histidine was used as a catalyst in the synthesis of α,*N*-diaryl nitrones *in situ* (233). To study diphenylborate chelates with mono- and bidentate ligands, a series of hydroxyl-containing nitrones have been synthesized (Fig. 2.7) (234–237).

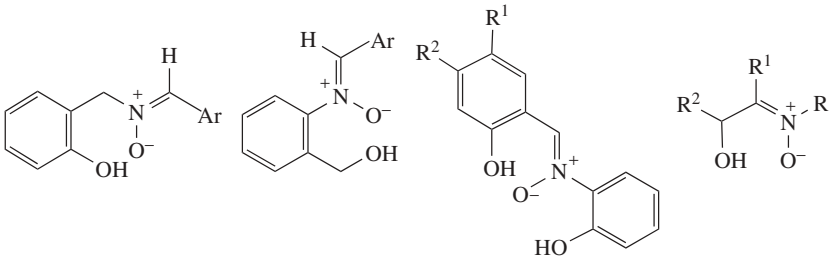


83a–f

Scheme 2.30

Table 2.4 Synthesis of C-(1-fluorovinyl)nitrones

Substrate($R^1R^2C{=}O$)	Yield(%)	(E)/(Z)(C=N)
a 3-Phenylpropanl	79	< 2:98
b Benzyloxyacetaldehyde	18	< 2:98
c *tert*-Butylcyclohexanone	81	10:90
d 1,4-Dioxaspiro[4,5]cyclodecan-8-one	93	10:90
e Cyclododecanone	98	< 5:95 (20:80)
f Adamantanone	67	2:98 (4:96)

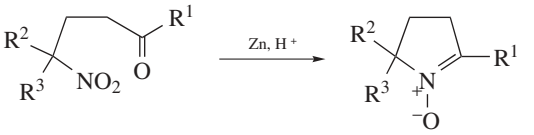


Ref. [234] **Ref.** [235] **Ref.** [236] **Ref.** [237]

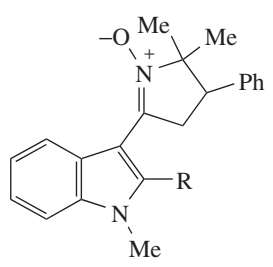
Fig. 2.7

Intramolecular variations of a series of bifunctional derivatives lead to the formation of cyclic nitrones. Many pyrroline *N*-oxide derivatives were obtained in the course of intramolecular interaction *in situ* between carbonyl and hydroxylamine groups, resulting from the reduction of a γ-nitro group (Scheme 2.31) (Fig. 2.8) (238–253).

The same approach was implemented in the synthesis of isoquinoline- (**a–f**) and isoindoline-(**g–i**) nitrones (Fig. 2.9) (254).

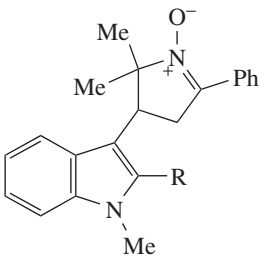


Scheme 2.31



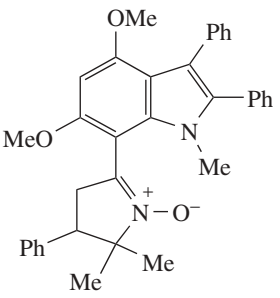
R = H, Ph

Ref.[238]

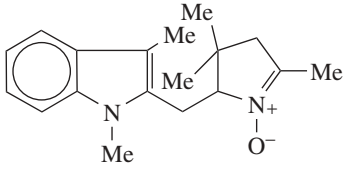


R = H, Ph

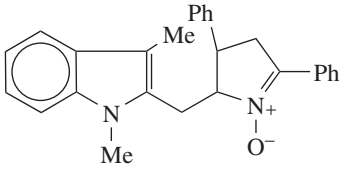
Ref.[238]



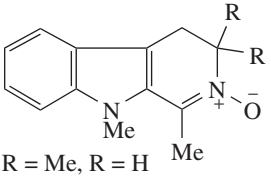
Ref. [239]



Ref. [240]

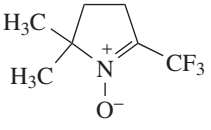


Ref. [240]

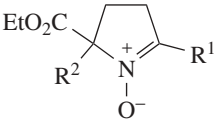


R = Me, R = H

Ref. [241]

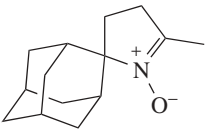


Ref. [242]



Ref. [243]

Fig. 2.8



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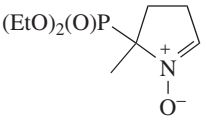

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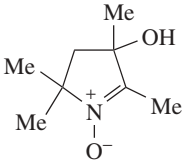

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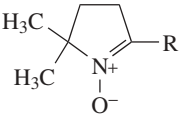
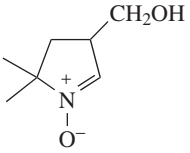


R = H (a), CH_3 (b), $C(CH_3)_3$ (c),
C_6H_5, d) C_6D_5 (e), C_6H_5(nitronyl-^{13}C) (f),
4-F-C_6H_4 (g), 4-ClC_6H_4 (h), 4-Bu^t C_6H_4 (i),
4-$CH_3C_6H_4$ (j), 2-$CH_3C_6H_4$ (k).

Ref. [247]



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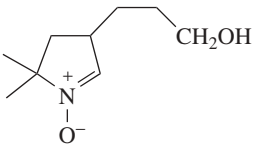
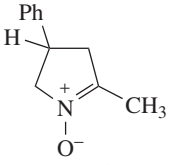


Ref. [249]



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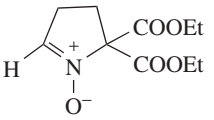

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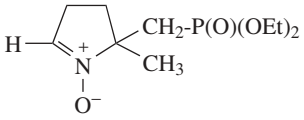


Ref. [253]

Fig. 2.8 (*continued*)

Condensation of 1,2-bishydroxylamines (**84**) with 1,2-dicarbonyl compounds leads to derivatives of 2,3-dihydropyrazine-1,4-dioxides (**85**) (255), whereas the reaction with ninhydrin gives [1,2-b] pyrazine *N,N'*-dioxides (**86**) (Scheme 2.32) (256).

Chiral imidazoline nitrone (**88**) was synthesized by condensation of hydrochloride α-amino oxime (**87**) with triethyl orthoformate according to Scheme 2.33 (257).

N-Methylnitrones (**90**) were obtained from the reaction of aldehydes and ketones with *N*-methyl-*N,O-bis*-(trimethylsilyl)hydroxylamine (**89**) (Scheme 2.34) (258).

Treatment of 3-(α-hydroxybenzyl-*N*-hydroxylamine)-1,3-diarylpropen-1-ol (**91**) with hydroxylamine hydrochloride and sodium acetate in acetone gave

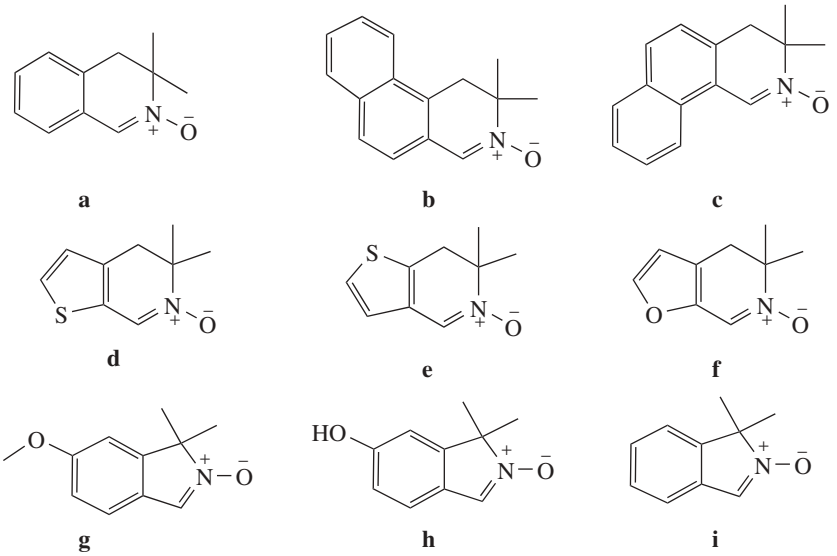
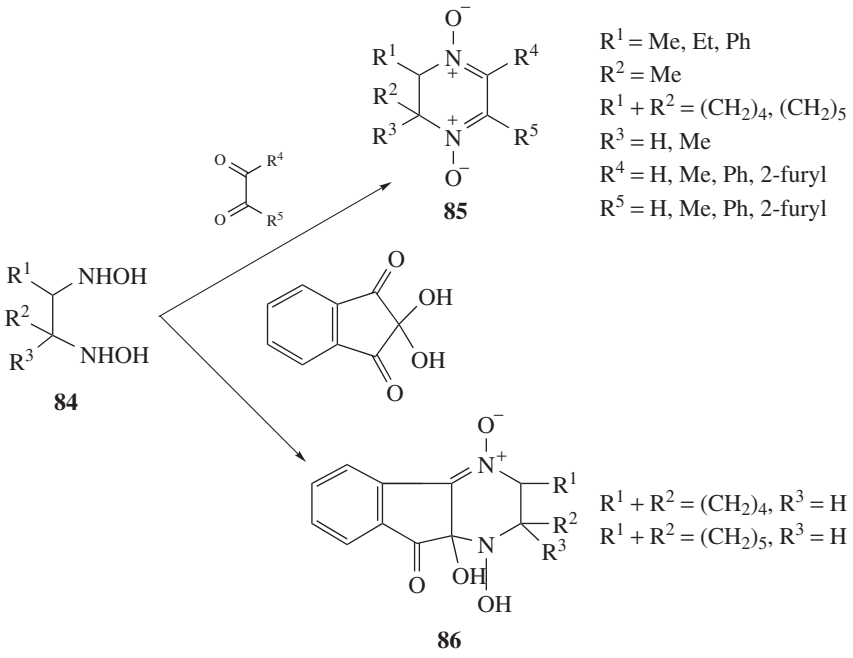
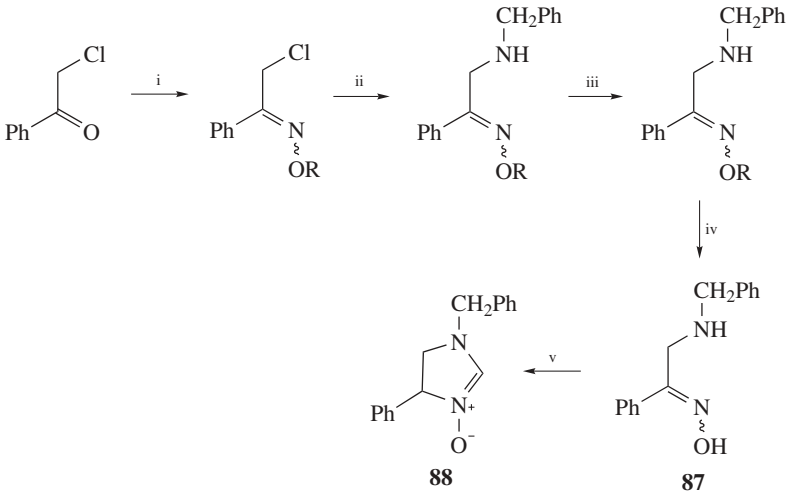


Fig. 2.9



Scheme 2.32

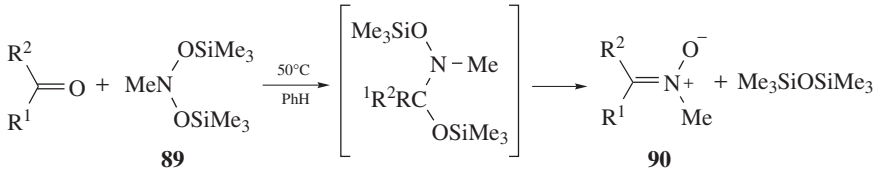


(i) $^{t}BuONH_2$•HCl, NaOAc, MeOH, 20°C
(ii) $PhCH_2NH_2$, DMF, 20°C
(iii) BH_3•THF, 0 - 20°C; then 6M HCl
(iv) conc. H_2SO_4, MeOH; then HCl (g), Et_2O
(v) $HC(OEt)_3$, PhMe, 60°C

a: R = Bu^t
b: R = CH_2Ph
c: R = H

a: R = Bu^t
b: R = CH_2Ph

Scheme 2.33



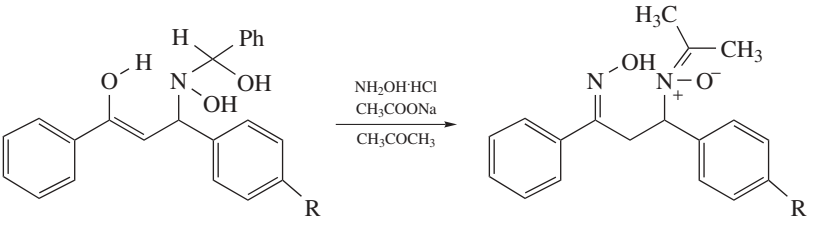
R^1 = Ph, p(Me_2N)C_6H_4, p-(O_2N)C_6H_4, 2-furyl, -$(CH_2)_3$ $CH{=}CH_2$, Pr^i, Bu^t, or Me
R^2 = H or Me
$R^1 + R^2$ = -$(CH_2)_3$-

Scheme 2.34

a series of 1,3-diphenyl-3-hydroxyimino-*N*-(1'-methylidene)-1-propylamine *N*-oxides (**92**) (Scheme 2.35) (259).

Nitrones resulting from the condensation of aldehydes and ketones with *N*-monosubstituted hydroxylamines were used in a four component Ugi reaction in a *one-pot* synthesis of α-acyloxyamino-amides (260).

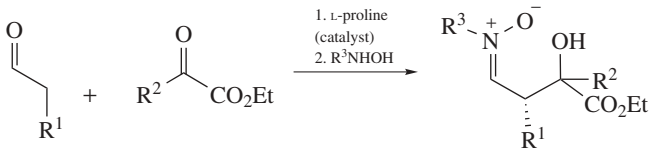
The synthesis of optically active nitrones (**95**) was carried out by an aldol reaction of aldehydes (**93**), catalyzed by L- proline, with carbonyl activated compounds (**94**) and by an *in situ* reaction with *N*-alkylhydroxylamines (Scheme 2.36, Table 2.5) (261).



91a–e **92a–e**

a: R = H; b: R = CH_3; c: R = OCH_3; d: R = NO_2; e: R = Cl

Scheme 2.35



93 **94** **95**

Scheme 2.36

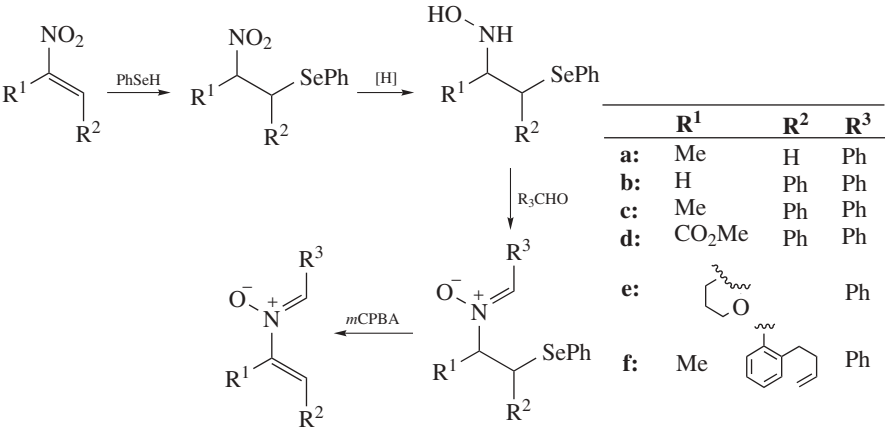
Table 2.5 Formation of optically active functionalized β-hydroxy-nitrones 95 by reaction of aldehydes 93 with activated carbonyl compounds 94 and substituted *N*-alkyl hydroxylamine hydrochloride in the presence of L-proline as the catalyst

R^1	R^2	R^3	Yield(%)	ee (%)
Me	CO_2Et	Bu^t	95a-87	77
Et	CO_2Et	Bu^t	95b-73	92
Me	CO_2Et	Bn	95c-83	83
Et	CO_2Et	Bn	95d-95	92
i-Pr	CO_2Et	Bn	95e-82	96
Allyl	CO_2Et	Bu^t	95f-66	86
Me	CF_3	Bu^t	95g-66[a]	68/91

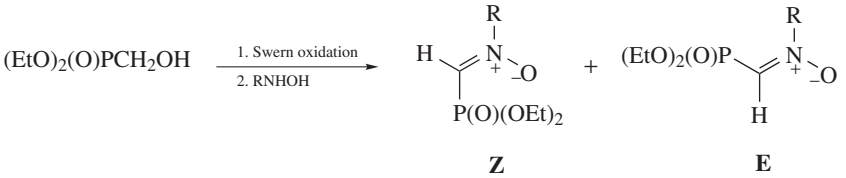
[a]The product is obtained as diastereomers (dr 1.1:1)

Recently (262), a new general synthetic method of producing heterodienes - *N*-vinyl nitrones has been reported. This method begins with the benzeneselenol addition to nitroalkenes which, in their turn, are generated in a Henry reaction from aldehydes and nitroalkanes, leading to selenonitroalkanes. These are reduced with aluminum amalgam to the corresponding hydroxylamines which, after condensation with aldehydes, give *N*-vinylnitrones (Scheme 2.37).

As shown in Scheme 2.38, it was possible to obtain *E*- and *Z*-isomers of *N*-substituted (R = Bn or Me) C-diethoxyphosphorylated nitrones (263).



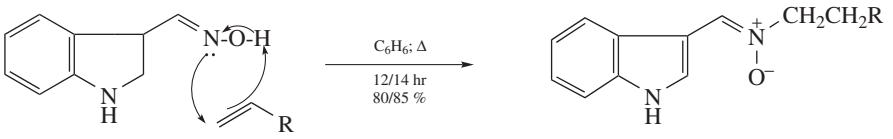
Scheme 2.37



Scheme 2.38

2.2.2.2. Synthesis from Oximes Alkylation of oximes at the nitrogen atom with various reagents seems to be one of the easiest and convenient methods for synthesizing nitrones. The significant advantage of this method is that there is no need to use oxidants, as is shown in Section 2.2.2.1. Electron poor alkenes, resulting from the activation of electron-accepting groups and action of electrophiles or metal ions as catalysts, are used as the most available alkylation agents. The reaction known as Grigg's nitrone formation, involving formal Michael addition is widely used (141, 262–285). In most cases, the resulting nitrones quickly enter into a specific 1,3-cycloaddition reaction. Similar transformations are observed in the reactions of oximes with alkynes (286, 287). Therefore, Grigg's reaction, which seems very effective in using the sequence of oxime-nitrone-products and 1,3-dipolar cycloaddition, can hardly be considered as an overall synthetic approach to nitrones. However, under certain conditions, the resulting nitrones can be isolated. Thus, the reaction of indol-oxime (**96**) with methyl acrylate, methyl vinyl ketone, acrylonitrile, and acrylamide gives indol-nitrones (**97**) (Scheme 2.39) (288, 289).

Cyclization of oximes containing γ-,δ-, or ω-alkenyl substituents, upon treatment with *N*-bromosuccinimide (NBS) or iodine leads in good yields to the corresponding cyclic nitrones or their dimeric H- bonded hydriodide salts (290).



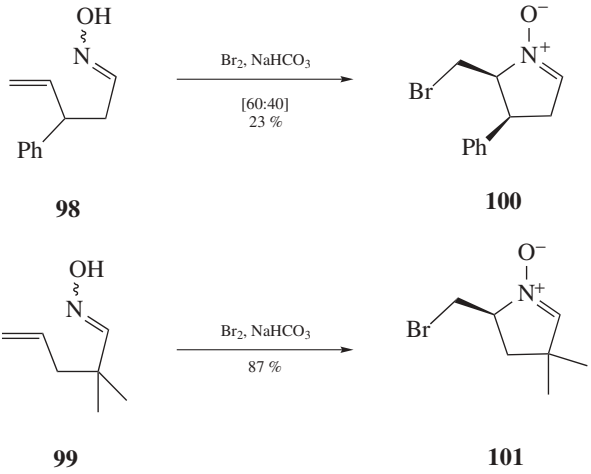
96a–d **97a–d**

R = $COOCH_3$ (a), $COCH_3$ (b), CN (c), $CONH_2$ (d)

Scheme 2.39

Bromocyclization of γ,δ-unsaturated oximes (**98**) and (**99**) affords the corresponding bromomethylpyrroline-*N*-oxides (**100**) and (**101**). Depending on the structural characteristics, the yields vary from 23% to 87% (Scheme 2.40).

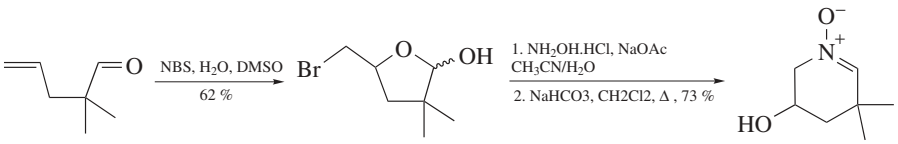
Reversal of steps, that is addition of Br/OH to the C=C bond of the unsaturated aldehyde (**102**) first, followed by oximation, opens access to six-membered nitrones (**103**) (Scheme 2.41) (290).



98 **100**

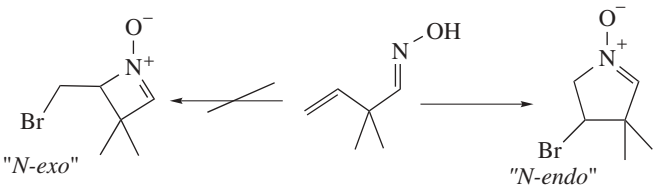
99 **101**

Scheme 2.40



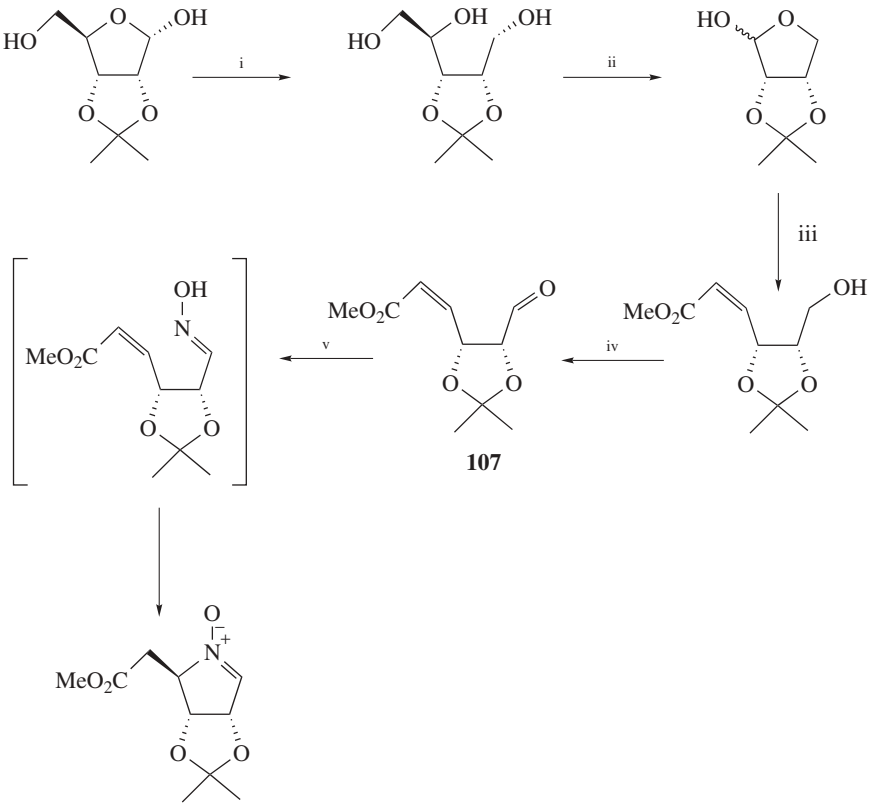
102 **103**

Scheme 2.41



105 **104** **106**

Scheme 2.42



107

108

(i) $NaBH_4$,MeOH, 0°C, 1h; (ii) $NaIO_4$, Bu^t OH, H_2O, 25°C; (iii) $Ph_3P{=}CHCO_2Me$, PhCOOH (cat.), CH_2Cl_2, reflux, 18 h; (iv) PDC, molecular sieves 3 Å (powder), dry AcOH, CH_2Cl_2, 25°C, 30 min; (v) $NH_2OH{\bullet}HCl$, $NaHCO_3$, MeOH, 25°C, 12 h.

Scheme 2.43

In the case of β,γ-enoximes (**104**) an unusual *N-endo*-cyclization occurs. This results in the formation of bromomethylpyrroline-*N*-oxide (**106**) rather than in the expected four-membered nitrone (**105**) (Scheme 2.42) (291).

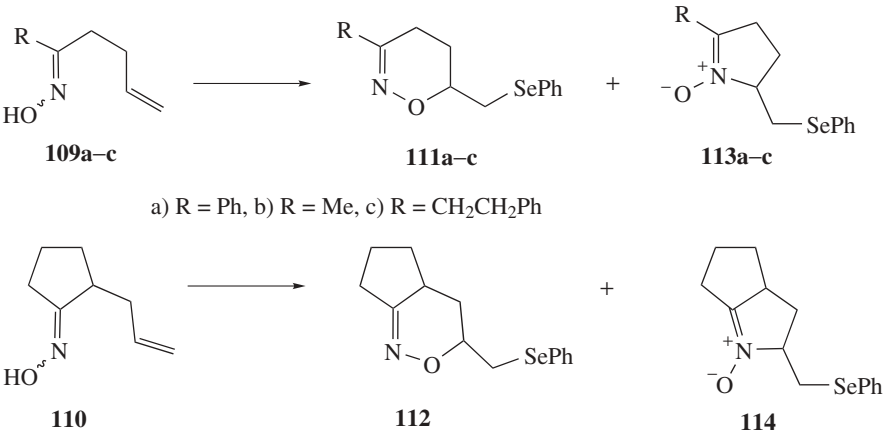
A convenient synthetic route to enantiomerically pure hydroxylated pyrroline-*N*-oxides (**108**) has been reported (292). A key step is the formation of ω-oxo-enoates from D-ribose (**107**) and the subsequent 1,3-azaprotio cyclo-transfer reaction of the resulting oximino alkenoate derivatives (Scheme 2.43).

Cyclization of γ-alkenyloximes (**109**) and (**110**) proceeds with strong electrophilic phenyl- selenating agents (293–295). This regioselective reaction provides the formation of (phenylseleno)methylsubstituted 1,2-oxazines (**111**) and (**112**), of cyclic nitrones (**113**) and (**114**). Basically, the ratio of the two reaction products should depend on the E/Z ratio of the starting oximes, but this does not appear to be the case. The formation of five-membered cyclic nitrones (**113**) and (**114**) is favored over the six-membered 1,2-oxazines (**111**) and (**112**) (Scheme 2.44) (296).

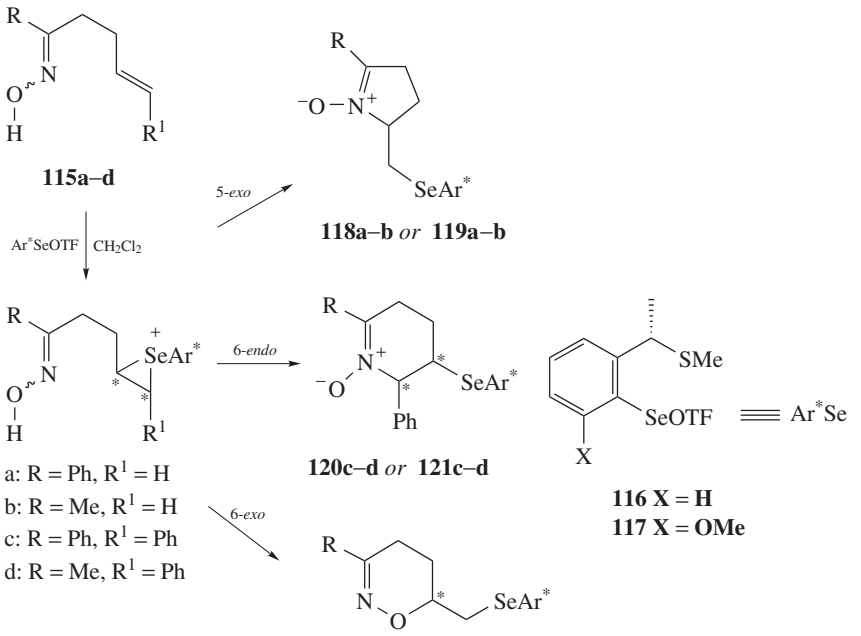
In the asymmetrical selenium-induced cyclization of γ-alkenyloximes (**115 a,b**) and δ-phenyl-γ-alkenyloximes (**115 c,d**), selenated triflates (**116**) and (**117**) were used as electrophilic reagents (297). These reactions proceed in good yields, with full regioselectivity and good diastereoselectivity, and therefore are viewed as very convenient methods for asymmetrical syntheses of cyclic nitrones (**118**), (**119**), (**120**), (**121**), and 1,2-oxazines (**122**) and (**123**) (Scheme 2.45).

As a result of Ag (I) catalyzed cyclization of allenic oximes (**124**) and (**125**), stable five- (**126**) and six-membered (**127**) cyclic nitrones were obtained (Scheme 2.46) (298a). Recently, a novel method of pyrroline-type nitrone formation via β-allenyl-oxime cyclization has been described (298b).

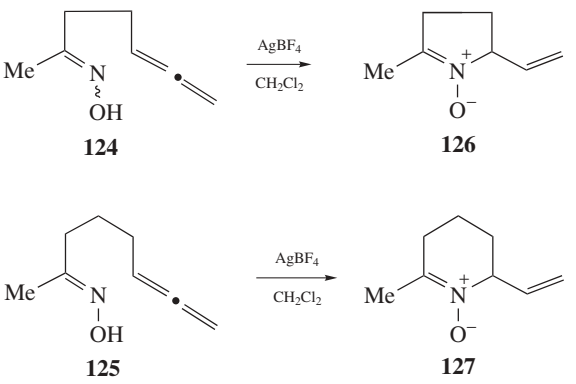
In the presence of Lewis acids (ZnI_2 and $BF_3{\cdot}OEt_2$), aldoximes react with α,β-unsaturated carbonyl compounds (**129**) at room temperature affording good yields of *N*-alkyl nitrones (**130**) (Scheme 2.47) (299).



Scheme 2.44

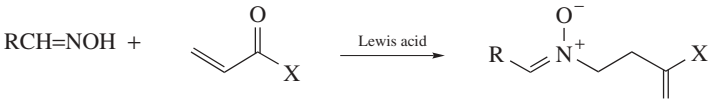


Scheme 2.45



Scheme 2.46

Bicyclic nitrones (**132**) were formed from the reaction of alkenyl carbonyl compounds (**131**) with hydroxylamine. The reaction requires the presence of the terminal olefinic electron withdrawing ester group CO_2Et. Also, the product(s) of reaction are shown to depend on the space filling capacity of substituents $R^1 - R^4$

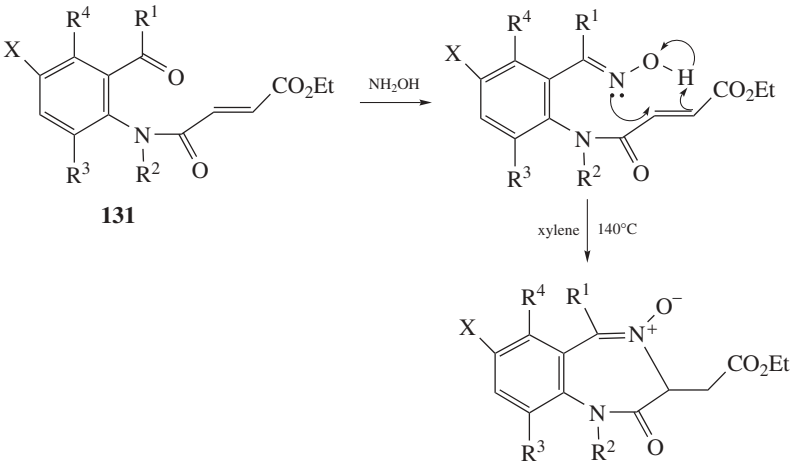


128a–i **129a–d** **130**

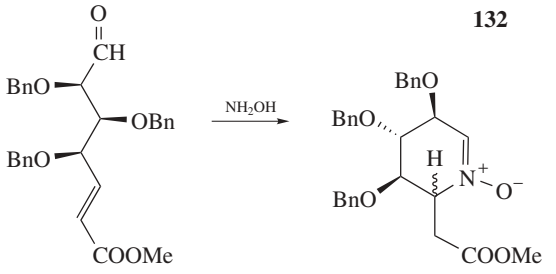
a: Ph
b: p-$MeOC_6H_4$
c: p- MeC_6H_4
d: 2-Thienyl
e: 2-Furyl
f: (E)- PhCH=CH-
g: (E)-MeCH=CH-
h: n-C_7H_{15}
i: Bu^t

a: X = Me
b: X = OMe
c: X = H
d: X = 2-Oxo-3-oxazolidinyl

Scheme 2.47



131 **132**



133

Scheme 2.48

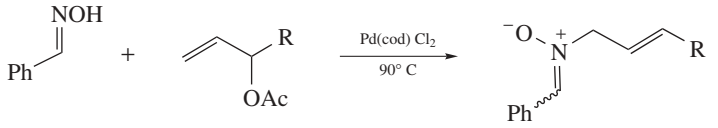
(where R^1, R^2, R^3,R^4 = H, Me, Ph; X = H,Cl, NO_2) (300, 301). Cyclic nitrone (**133**) results from the intramolecular addition of the oxime group to the olefinic bond (302)(Scheme 2.48).

Selective formation of nitrones can be achieved using Pd (II) [Pd(cod)Cl_2] as a catalyst, in the reaction of oximes with allylic acetate (Scheme 2.49) (303).

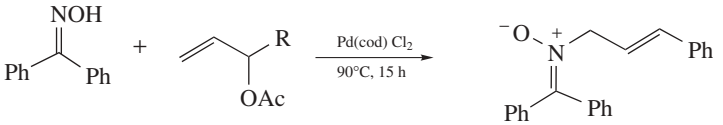
The reaction of *Z*-2-furaldoximes (**134**) with oxirane affords in good yield *N*-(2- hydroxyethyl)-α-2-furylnitrone (**135**) the product of *N*-alkylation. *E*-benzaldoxime, predominantly gives the O-alkylation product (**136**), whereas its *Z*-isomer leads to a mixture with an insignificant amount of *N*-alkylation product (**138**) (Scheme 2.50) (304).

A mixture of nitrones (**142**) and dioxazines (**143**) forms from a mixture of *Z*- and *E*-isomers of oximes (**141**), obtained from acetonide of erythrulose (**140**). The reaction is carried out in a mixture of acetone and 2,2-dimethoxypropane, in the presence of catalytic quantities of TsOH (Scheme 2.51) (305).

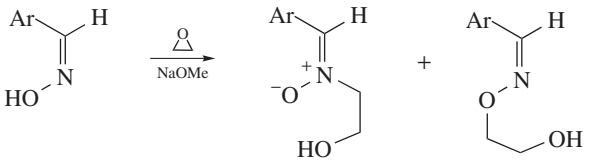
Alkylation of *Z*-aldoximes (**144**) and (**145**) with bromo esters (**146**) and (**147**) provides good yields of high purity **DEEPN** and **EPPyON** nitrones (Scheme 2.52) (306).



R = 4-F_3C-C_6H_4, 1-Naph, 4-Cl-C_6H_4, 4-Me-C_6H_4, cyclohexyl



Scheme 2.49

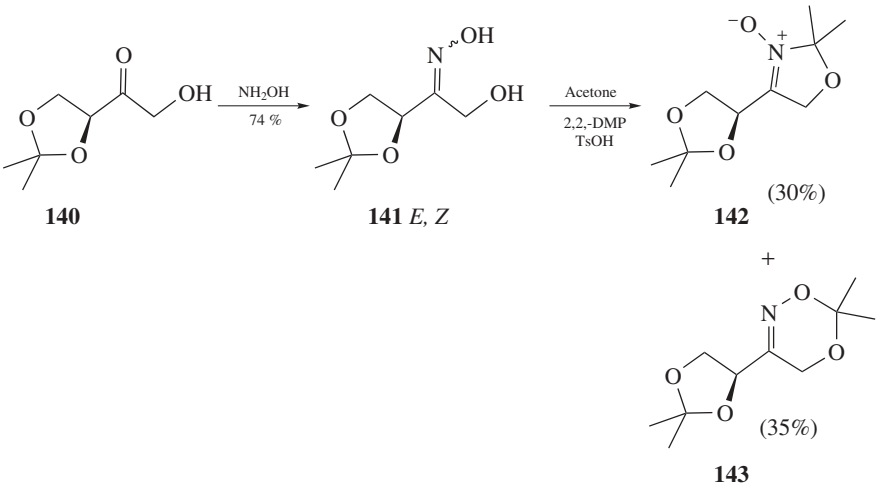


134 **135** **136**

137 **138** **139**

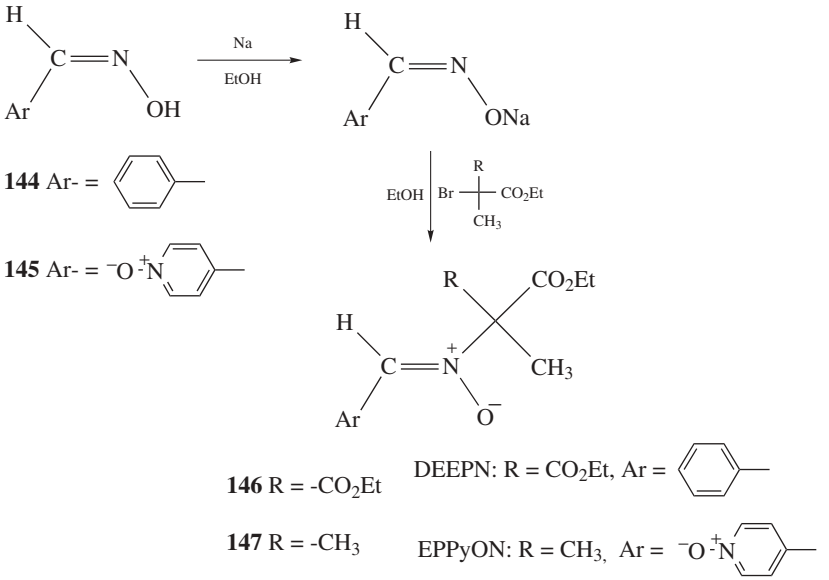
Ar = 2-Furyl (**134, 135, 136**)
Ph (**137, 138, 139**)

Scheme 2.50



140 **141** *E, Z* **142** **143**

Scheme 2.51



144 Ar- =

145 Ar- =

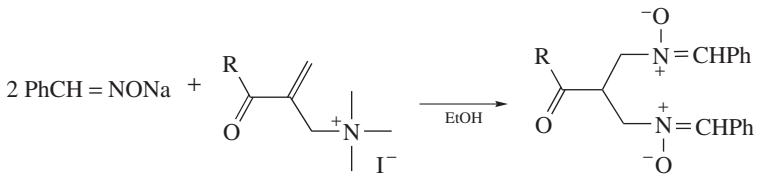
146 R = -CO_2Et

147 R = -CH_3

Scheme 2.52

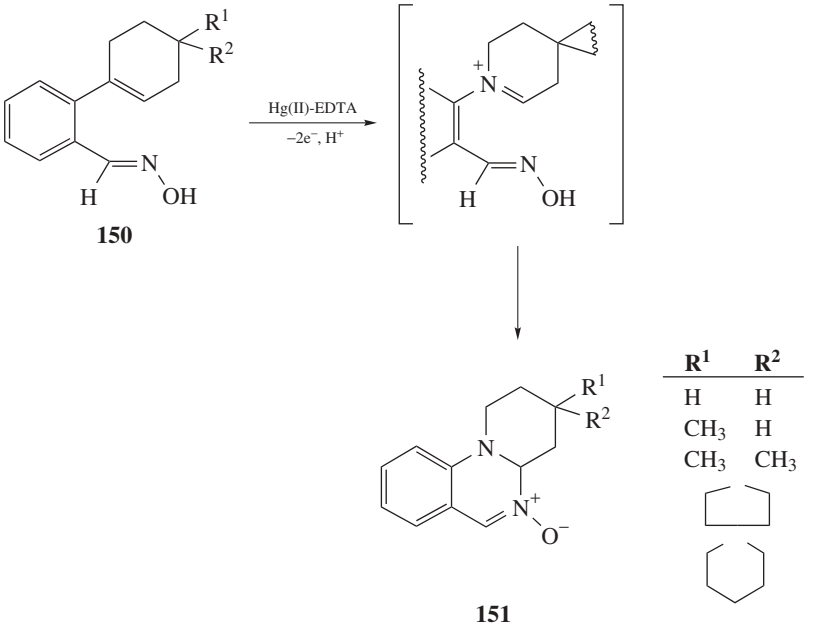
Interaction of Mannich base methyliodides (**148**, R = Ph, 2-Thenyl) with *anti*-benzaldoxime gives dinitrones (**149**) (Scheme 2.53) (307).

Formation of heterocyclic nitrones (**151**) from the corresponding amino oximes (**150**) has been observed upon treatment with Hg(II)-ethylenediaminetetraacetic acid (EDTA) (Scheme 2.54) (308, 309).



148 **149**

Scheme 2.53



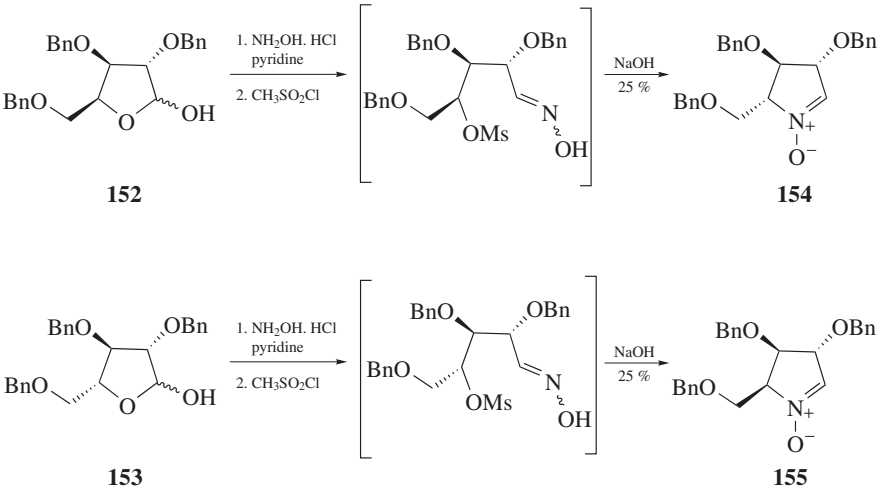
150

151

Scheme 2.54

Enantio-pure five-membered cyclic nitrones (**154**) and (**155**) were formed in a *one-pot* synthesis from the corresponding lactols (**152**) and (**153**) as the result of their reactions with unsubstituted hydroxylamine and by (a) subsequent treatment with MsCl and NaOH (Scheme 2.55) (310a) or by (b) subsequent treatment with TBDMSCl, I_2, TPP, imidazole, and tetrabutylammonium fluoride (TBAF) (310b).

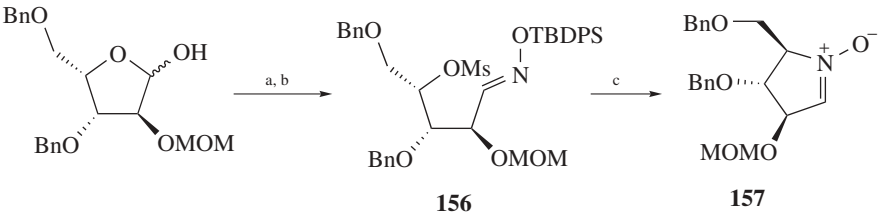
Several chiral cyclic nitrones have been synthesized by cyclization of ω-mesyloxy-*O*-*tert*-butyldiphenylsilyloximes (**156**) which is formed in the successive treatment with sugars of *O*-*tert*-butyldiphenylsilylhydroxylamine and MsCl. Cyclization (**156**) when performed with tetrabutylammonium triphenyldifluorosiliconate (TBAT) gives sugar-containing cyclic nitrones (**157**) in good yields (Scheme 2.56) (311, 312).



152 **154**

153 **155**

Scheme 2.55



156 **157**

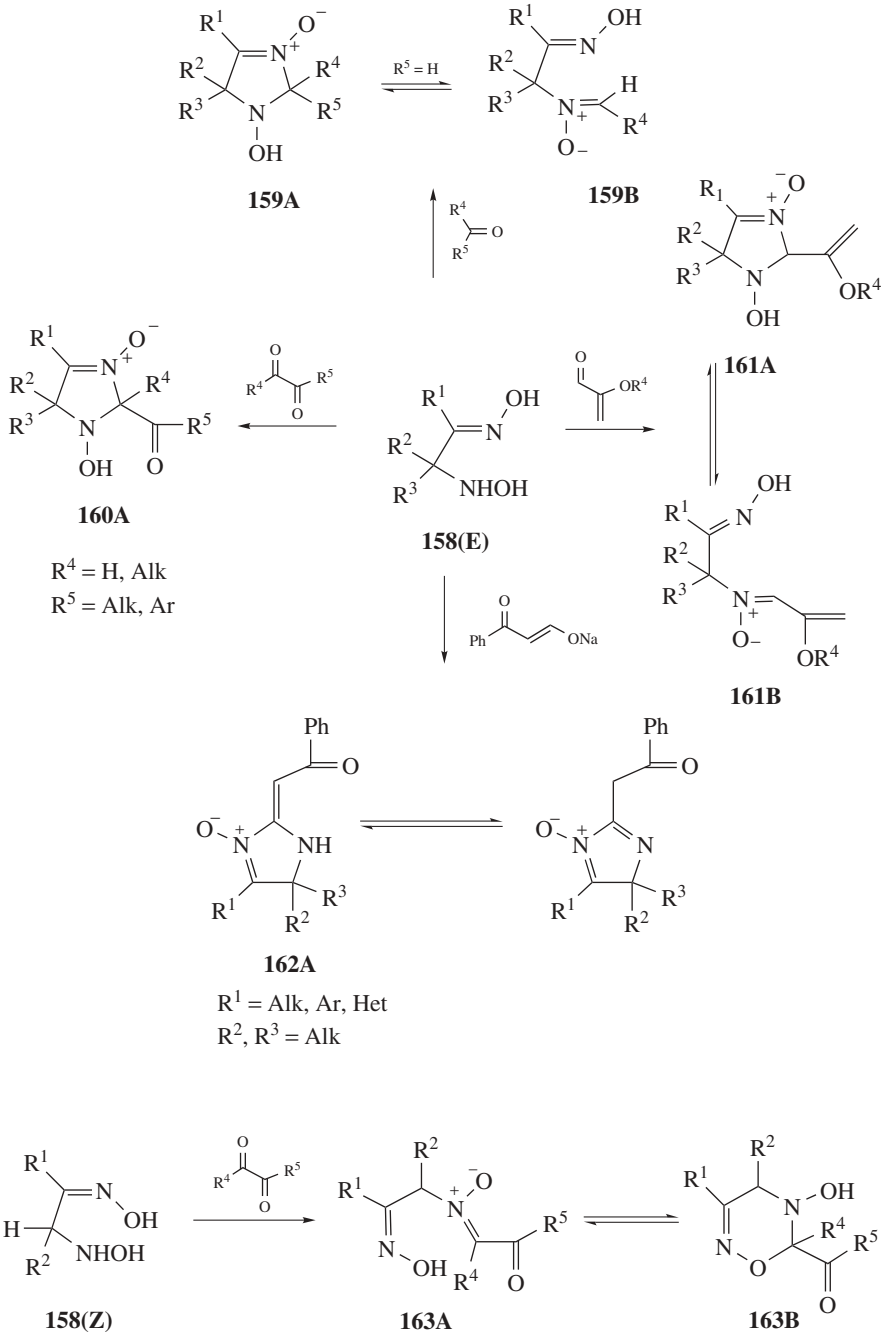
a: $NH_2OTBDPS$, cat. PPTS, $MgSO_4$, benzene, reflux
b: MsCl, Et_3N, toluene, 0°C, 98%
c: TBAT (1.05 equiv), MS 4Å, THF, reflux, 15 min, 72%

Scheme 2.56

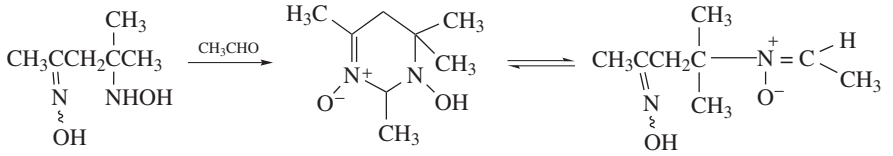
The synthesis of another large group of cyclic nitrones is based on the reaction of α-hydroxylamino-oximes (**158**) with aldehydes, ketones, diketones, and keto acids. Depending on the structure of (**158**) and the carbonyl components, the reaction can lead to imidazoline-3-oxide derivatives (**159A–162A**), acyclic nitrones (**159B, 161B**), or to their tautomeric mixtures. In the case of *Z*-isomers, oxadiazines (**163A**) are formed (Scheme 2.57) (313–320).

Six-membered cyclic nitrones of the tetrahydropyrimidine series (**165A**) were obtained from the condensation of β-hydroxylamino-oxime (**164**) with acetaldehyde (Scheme 2.58) (321).

These reactions are catalyzed by ammonium acetate, the function of which is to generate protonated imines (322). Under mild reaction conditions, condensation of α- hydroxyamino-oximes with acetone dialkylketals takes place. The procedure can be successfully applied in cases where direct condensation with acetone

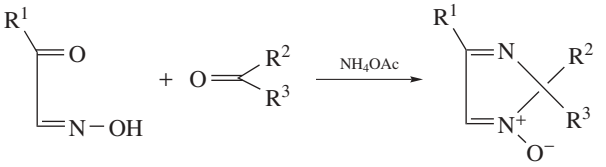

159A
159B
161A
161B
160A
158(E)
R^4 = H, Alk
R^5 = Alk, Ar
162A
R^1 = Alk, Ar, Het
R^2, R^3 = Alk
158(Z)
163A
163B

Scheme 2.57



164 **165A** **165B**

Scheme 2.58



166 **167**

R^1 = Ph, m-$O_2NC_6H_4$, p-$O_2NC_6H_4$, Me, CH=NOH
R^2 = Me, $CH_3(CH_2)_7$, Pr, $CH_3(CH_2)_{12}$
R^3 = Me, $CH_3(CH_2)_7$, $CH_3(CH_2)_8$, CH_2Cl, $EtOCOCH_2$, $HOCOCH_2CH_2$, Pr, $CH_3OCO(CH_2)_4$
R^2, R^3 = $(CH_2)_5$

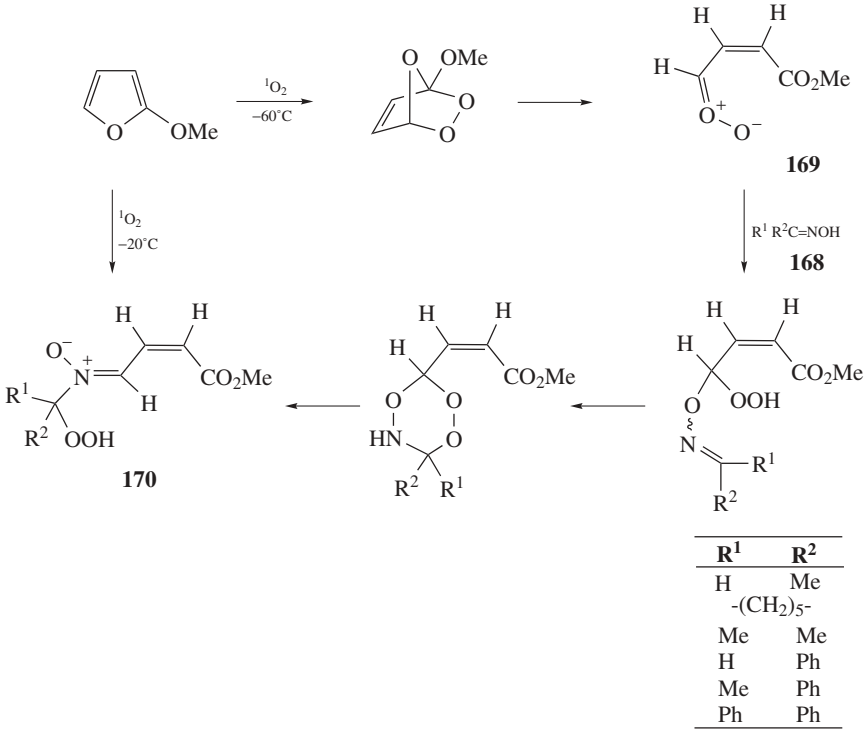
Scheme 2.59

does not occur (323). It is noteworthy that such reactions also form secondary hydroxylamine groups which can be oxidized to nitrones or nitroxyl groups (313).

Condensation of hydroxyamino-ketones (**166**) with ketones and ammonium acetate leads to the formation of 2*H*-imidazole-1-oxides (**167**) (Scheme 2.59) (324).

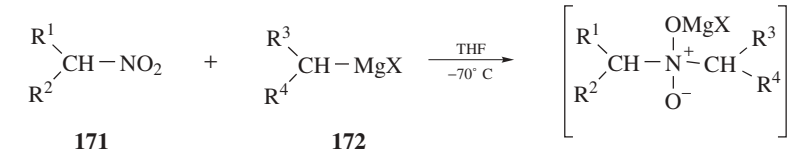
Addition of carbonyl oxide (**169**) to oximes (**168**) results in the formation of (*E*)-*N*-(hydroperoxyalkyl) keto nitrones (**170**); the reaction involves a *one-pot* step synthesis (Scheme 2.60) (325, 326).

2.2.2.3. Synthesis from Nitro Compounds Nitrones can be obtained in good yields from the addition of benzyl and allyl Grignard reagents to aryl- and alkyl-nitro compounds. This reaction proceeds chemoselectively; carbonyl groups and other reactive electrophilic groups are not affected by the reaction conditions. Double bond stereochemistry is determined by the nature of the employed Grignard reagent. Benzylmagnesium halides give exclusively *Z*-isomers of nitrones (**173**) and (**174**), whereas 2-butenylmagnesium chloride gives nonconjugated *Z*-nitrones with the predominance of *E*-isomers in the conjugated nitrone (**174**) (Scheme 2.61) (327–329). Ce(III) chloride facilitates the addition of Grignard reagents to nitroalkanes. (330)



R^1	R^2
H	Me
-$(CH_2)_5$-	
Me	Me
H	Ph
Me	Ph
Ph	Ph

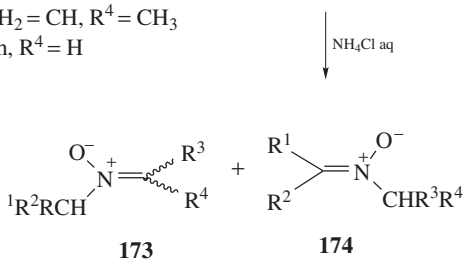
Scheme 2.60



171 **172**

b: $R^1 = R^2 = H$
c: $R^1 = CH_3$, $R^2 = H$
d: $R^1 = n\text{-}C_3H_7$, $R^2 = H$
e: $R^1 = n\text{-}C_5H_{11}$, $R^2 = H$
f: $R^1 = R^2 = CH_3$
g: $R^1 = CH_3COCH_2$, $R^2 = H$
h: R^1 = 2-FurylCH$_2$, $R^2 = H$
i: $R^1 = CH_3CH(Cl)CH_2$, $R^2 = H$
j: $R^1 = CH_3COCH_2CH_2$, $R^2 = CH_3$
k: $R^1 = (CH_3)_2CH$, $R^2 = H$
m: $R^1 = C_6H_5$, $R^2 = H$

a: $R^3 = CH_2 = CH$, $R^4 = CH_3$
b: $R^3 = Ph$, $R^4 = H$



173 **174**

Scheme 2.61

Light irradiation of styrenes in the presence of aromatic and heteroaromatic compounds leads to the formation of α,*N*-diarylnitrones in good yields (331, 332).

2.2.2.4. Synthesis from Nitroso Compounds Aryl nitroso compounds (**175**) react easily with dimethyl bromomalonate in the presence of alkali to give the corresponding *N*-aryl-*C,C*-dimethoxycarbonyl-nitrones (**177**) (Scheme 2.62) (333).

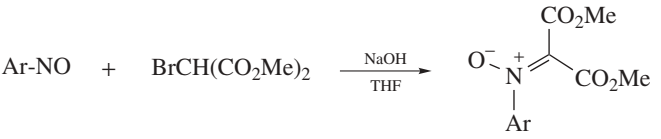
A general method for nitrone formation is based on the interaction of nitro compounds with carbanions. Interaction between nitroso compounds (**175**) and anions of aliphatic nitro compounds (**178**) leads to nitrones (**179**). The source of anions are metal salts of nitro compounds, triethylamines, and trimethylsilylnitronates (Scheme 2.63) (334, 335).

Formation of nitrones can be achieved in the first stage of a Kröhnke type reaction in which *p*-nitrosodimethylaniline reacts with 2-ω-bromoacetylphenoxathiin in alkaline medium (336). The synthesis of a series of cyclic nitrones of structure (**182**) has been achieved by regioselective, and by an unusual [3 + 2] cycloaddition of α-nitrosostyrenes (**181**) to 1,3-diazabuta-1,3-dienes (**180**) (Scheme 2.64) (337a). Theoretical studies of the substitution effect at the imine nitrogen on the competitive [3 + 2] and [4 + 2] mechanisms of cycloaddition of simple acyclic imines with nitrosoalkenes have been reported (337b).

Chiral cyclic nitrones (**185**) were synthesized in the reaction of isonitroso-derivatives of Meldrum's acid (**183**) with ketones in boiling toluene (338–344). The reaction is likely to proceed, as in the case of the cycloaddition of α-nitrosostyrenes, by [3 + 2] cycloaddition of ketones to nitrosoketone (**184**), resulting from thermolysis of (**183**) (Scheme 2.65) (345).

The reaction of [3 + 2] cycloaddition of nitrosoalkenes (**181**) to the imino group of bicyclic 1,2-oxazines (**186**) gives tricyclic nitrones (**187**) (Scheme 2.66) (346).

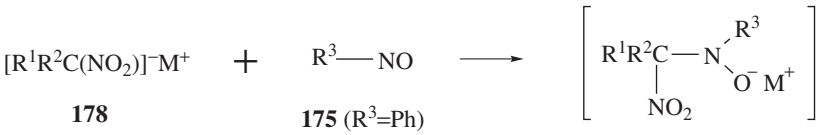
A theoretical analysis of the reactions of acyclic imines with nitrosoalkenes has been presented (347).



175 **176** **177**

Ar	R^1	R^2
1-naphthyl	a: CO_2Me	CO_2Me
2-naphthyl	b: Me	CO_2Me
Ph	c: Ph	CO_2Et

Scheme 2.62



178

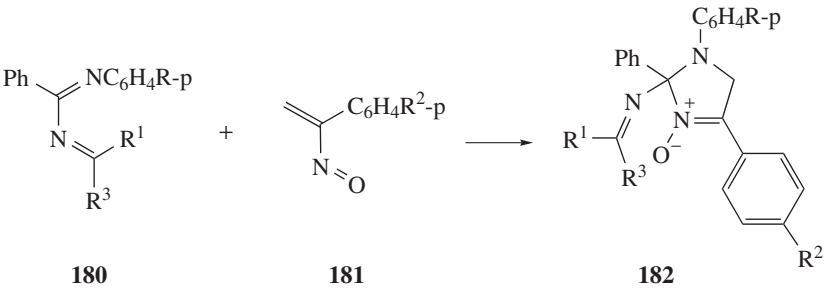
175 (R^3=Ph)
175 (R^3=Bu)

179

R^1	R^2	M
a: H	Me	Na
b: Me	Me	Na
c: H	$C(O)NMe_2$	K
d: H	C(O)NHMe	K
e: H	CO_2Me	K

R^1	R^2	R^3
a: H	Me	Ph
b: Me	Me	Ph
c: H	$C(O)NMe_2$	Ph
d: H	C(O)NHMe	Ph
e: H	CO_2Me	Bu^t
f: H	C(O)NMe	Bu^t
g: H	C(O)NHMe	Bu^t

Scheme 2.63

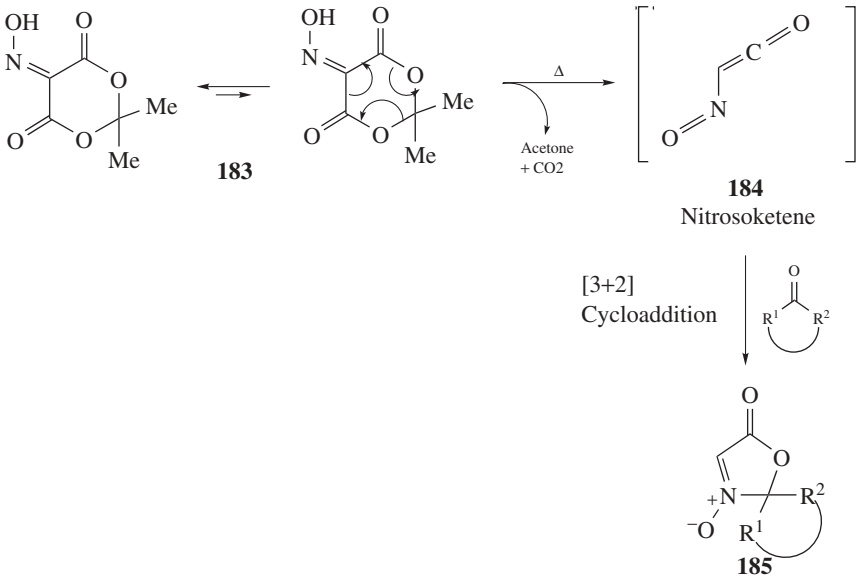


180 **181** **182**

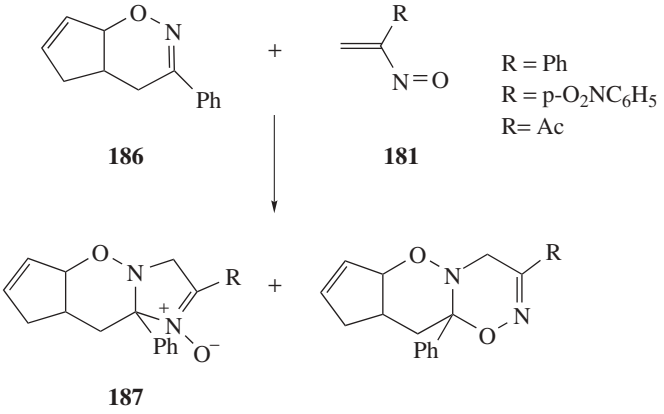
R = H, Me R^1 = H, Me R^2 = H, Me $R^3 = NMe_2$
$R^3 = NMe_2$

a: R = R^1 = R^2 = H; b: R = Me, R^1 = R^2 = H; c: R = Cl, R^1 = R^2 = H
d: R = Br, R^1 = R^2 = H; e: R = R^1 = H, R^2 = Me; f: R = R^2 = Me, R^1 = H
g: R = Cl, R^1 = H, R^2 = Me; h: R = Br, R^1 = H, R^2 = Me; i: R = R^1 = Me, R^2 = H
j: R = R^1 = R^2 = Me

Scheme 2.64



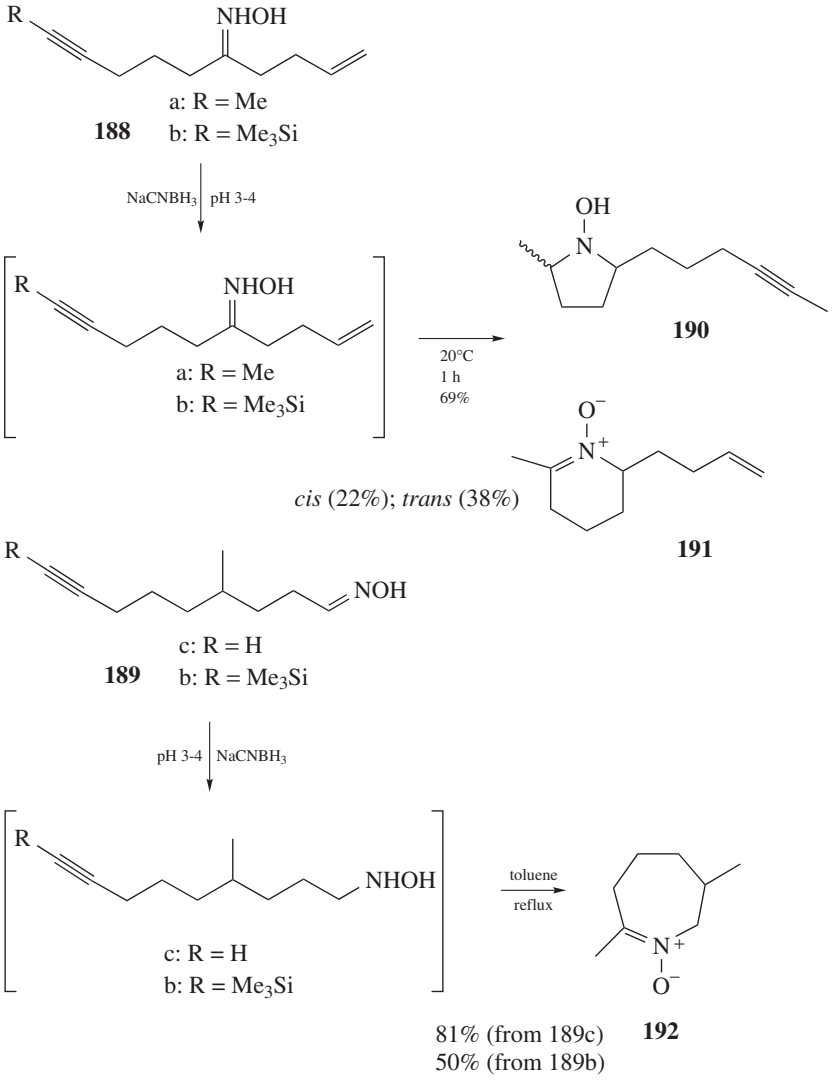
Scheme 2.65



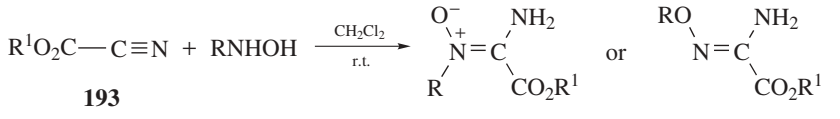
Scheme 2.66

2.2.2.5. Other Methods of Synthesis Intramolecular cyclic hydroxyaminoalkynes (**188**) and (**189**), depending on the relative position between the hydroxylamino group and acetylenic fragment, leads to five-(**190**), six-(**191**), and seven-(**192**) membered cyclic nitrones (Scheme 2.67) (348–350).

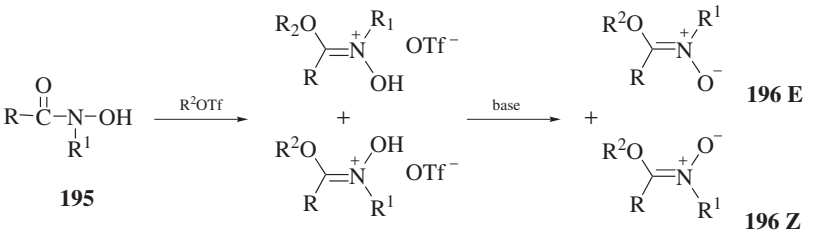
The reaction of *N*-alkyl- and *N*-arylhydroxylamines with ethyl cyanoformate (**193**) leads to carbethoxyamino nitrones (**194**) (Scheme 2.68), which appear to be excellent starting materials for the synthesis of various nitrogen-bearing



Scheme 2.67



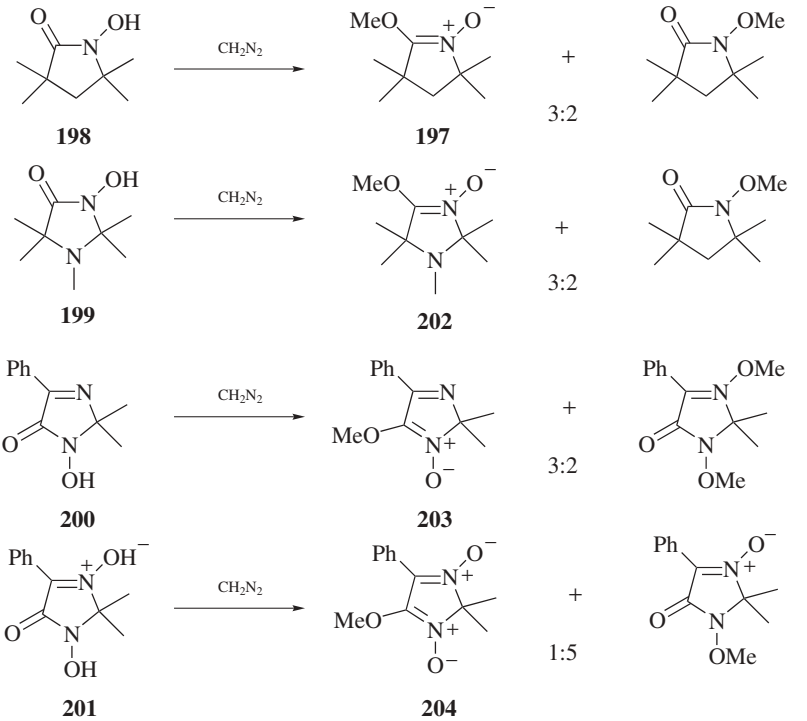
Scheme 2.68



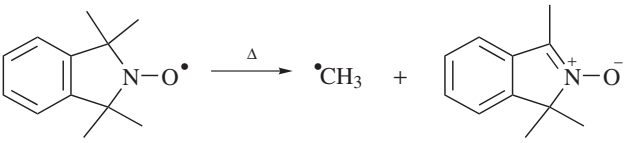
195 a: R = Ph; R^1 = Bu^t
b: R = *p*-$MeOC_6H_4$; R^1 = Bu^t
c: R = *p*-$NO_2C_6H_4$; R^1 = Bu^t
d: R = Me; R^1 = Bu^t
e: R = H; R^1 = Bu^t
f: R = Ph; R^1 = Me

196 a: R = Ph; R^1 = Bu^t; R^2 = Me
b: R = *p*- $MeOC_6H_4$; R^1 = Bu^t; R^2 = Me
c: R = *P*-$NO_2C_6H_4$; R^1 = Bu^t; R^2 = Me
d: R = CH_3; R^1 = Bu^t; R^2 = Me
e: R = H; R^1 = Bu^t; R^2 = Me
f: R = Ph; R^1 = Me; R^2 = Me
g: R = Ph; R^1 = Bu^t; R^2 = Et
h: R = Ph; R^1 = Me; R^2 = Et

Scheme 2.69



Scheme 2.70



TMIO **TMINO**

Scheme 2.71

compounds, such as imidazoles, benzimidazoles, benzimidazolones, oxazolones, *N*-arylamidines, and quinoxalones (351).

A general synthetic method for acyclic α-alkoxynitrones (**196**) involves the alkylation with triflates of hydroxamic acids (**195**) in neutral conditions (Scheme 2.69) (352). Similarly, the synthesis of cyclic methoxynitrone of pyrrolines (**197**) has been carried out (353).

The presence in the heterocycle of additional basic centers or those open to alkylation can lead to a change in reaction directions. It essentially limits the application of this method in the formation of α-methoxy nitrones. In such cases, it is reasonable to use diazomethane and, depending on the structure of hydroxamic acid (**198–201**) the yields of α-methoxy nitrones (**197**), (**202–204**) can rise from 17% up to 62% (Scheme 2.70) (353).

Recently, the use of flash vacuum pyrolysis, at 420°C and at pressure less than 0.5 mm Hg has been described for the synthesis of isoindolyl nitrone 1,1,3-trimethylisoindole *N*-oxide (**TMINO**) from isoindoline nitroxide 1,1,3,3-tetramethylisoindolin-2-yloxy (**TMIO**), with yields up to 73% (Scheme 2.71) (354).

2.3. STRUCTURE AND SPECTRA OF NITRONES

2.3.1. Electronic Structure of Nitrones

The electronic structure of the nitrone group, except for the main **A** structure, includes four canonical **B–E** structures. In the case of aromatic derivatives, it is necessary to consider the conjugation with the benzene ring (structures **F** and **G**) (Fig. 2.10) (355, 356).

Relative contribution of each of these structures differs significantly and is determined by internal structural characteristics of the nitrones and by the influence of external factors, such as changes in polarity of solvent, formation of a hydrogen bond, and complexation and protonation. Changes in the electronic structure of nitrones, effected by any of these factors, which are manifested in the changes of physicochemical properties and spectral characteristics, can be explained, qualitatively, by analyzing the relative contribution of **A–G** structures. On the basis of a vector analysis of dipole moments of two series of nitrones (355), a quantum-chemical computation of *ab initio* molecular orbitals of the model nitrone CH_2=N(H)O and its tautomers, and methyl derivatives (356), it has been established that the bond in nitrones between C and N atoms is almost

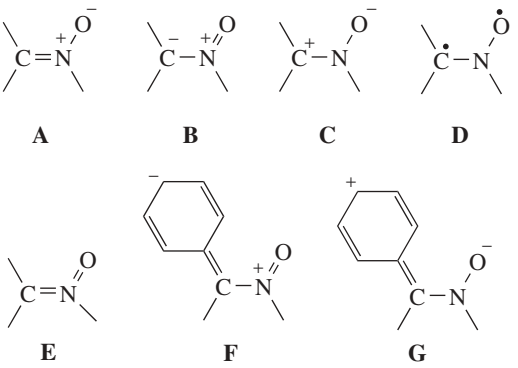


Fig. 2.10

of a pure double bond nature, and that between N and O atoms is of a partial double bond nature. This is established not only by zwitterionic **A** and **B** structures but also by the hypervalent **E** structure. However, neither experimental evidence, nor computational data have been reported for **C** and **D** structures, which are characterized by the single nature of all bonds.

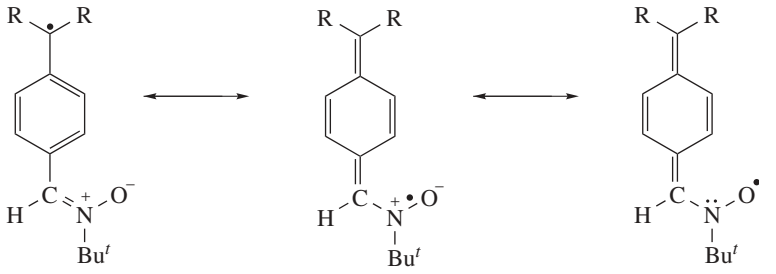
For the first time, the primary nitrone (formaldonitrone) generation and the comparative quantum chemical analysis of its relative stability by comparison with isomers (formaldoxime, nitrosomethane and oxaziridine) has been described (357). Both, experimental and theoretical data clearly show that the formaldonitrones, formed in the course of collision by electronic transfer, can hardly be molecularly isomerized into other [C,H_3,N,O] molecules. Methods of quantum chemistry and molecular dynamics have made it possible to study the reactions of nitrone rearrangement into amides through the formation of oxaziridines (358).

On the basis of photoelectron spectra and quantum-chemical computations, the effect of variation of substituents at N − 1 atoms in derivatives of 1-*R*-3-imidazoline-3-oxide has been studied. It has been found that the increase in ionization energy π−C=NO-MO occurs in the series $CH_3 \leq H \leq OH \leq O^{\cdot} \leq NO$ (359, 360).

Recently (361), on studying the full charge distribution in (*Z*)-*N*-methyl-*C*-phenylnitrone by high resolution X-ray diffraction and by comparing theoretical high level computational data, it was concluded, surprisingly, that in the N^+-O^- group both atoms carry a negative charge.

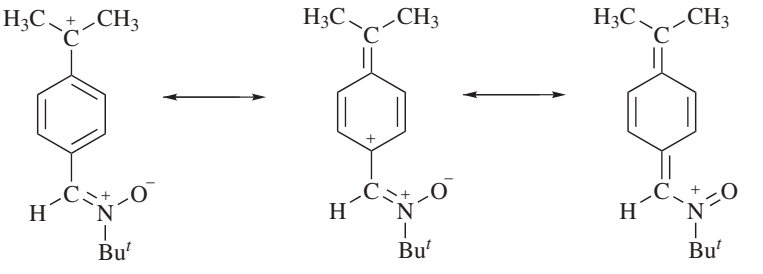
The study of the stabilizing effect of the nitrone group in cumyl radical (**205**) (Scheme 2.72) (362) and cumyl cation (**206**) (Scheme 2.73) (363) has shown that the nitrone group appears to be a "super radical stabilizer" and, at the same time, a "weak cation stabilizer."

Analysis of the conformational and structural stability of *N*-vinylnitrone CH_2=CH−N(O)=CH_2 and *N*-(2,2-dichlorovinyl)nitrone CCl_2=CH-N(O)=CH_2 with DFT-B3LYP and MP2 methods revealed that they have a planar structure resulting from the apparent conjugation between C=C and N=C bonds.



205

Scheme 2.72



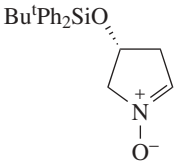
206

Scheme 2.73

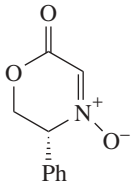
N-Vinylnitrones occur in a *s-trans*-conformation, whereas dichlorovinylnitrones occur in a mixture of *gauche* and *trans*-conformations (364).

2.3.2. X-Ray Data

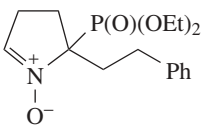
A considerable number of X-ray data of various types of acyclic and cyclic nitrones have been reported (Fig. 2.11, 148b) (49, 73, 90, 127, 148, 151, 152, 160, 234–236, 240, 252, 259, 262, 290, 319, 325, 341, 346, 351, 365–382). According to these data, all acyclic aldonitrones have *Z*-configuration (Fig. 2.11), whereas *E*-configuration is typical of acyclic aldonitrones. Configuration of keto-nitrones depends on the character of substituents at α-C. Thus, *N*,α-dimethyl-α-(4'-[2.2] paracyclopropanyl) nitrone (**107b**) (151) and nitrones (**207**) (365), unlike all α-aryl aldonitrones, exist in the *E*-configuration. In (*E*)-*N*-(α-cyanobenzylidene) methylamine *N*-oxide (**208**) the phenyl group retains *cis*-position toward the *N*-oxide (366). In almost all cases the α-aryl nitrone part has a plain or close to a plain structure, while the length of C=N and N^+-O^- bonds for α-arylnitrones are close in value and change slightly in the region $1.300 + 0.002$ Å. In α,α-dihalo-alkylnitrones (**209**) and (**210**) the corresponding length of bonds depends on the



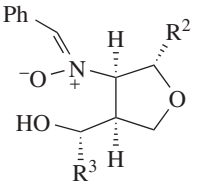
Ref.[49]



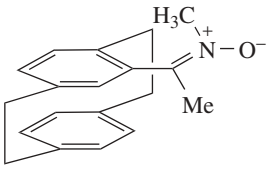
Ref.[73]



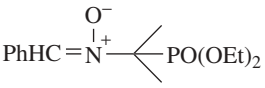
Ref.[90]



Ref.[127]



Ref.[151]



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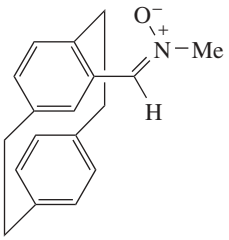

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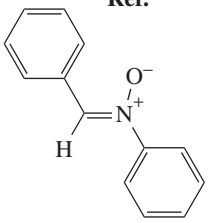

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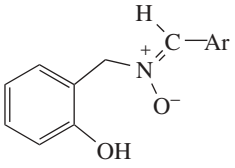

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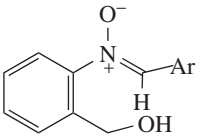

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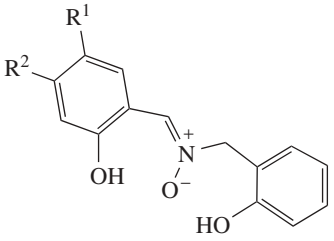
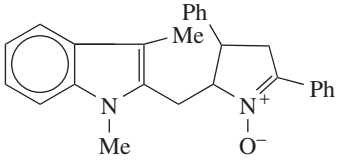


Ref.[236]



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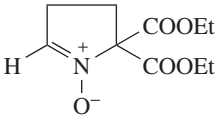

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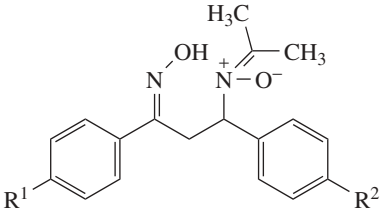
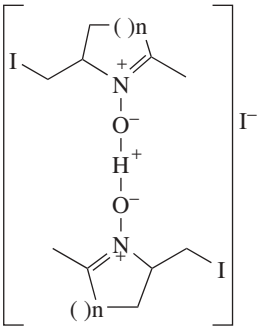


Ref.[259]

Fig. 2.11



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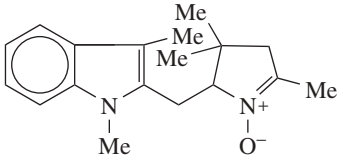

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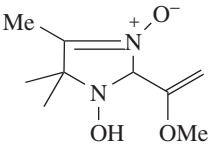

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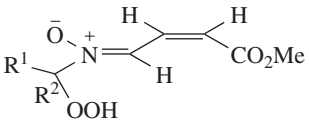

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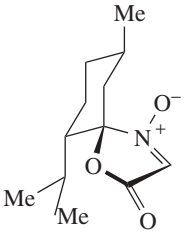

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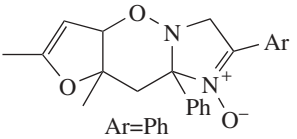

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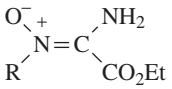

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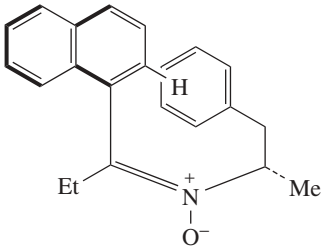
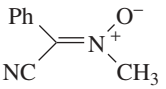
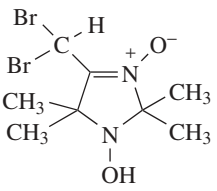


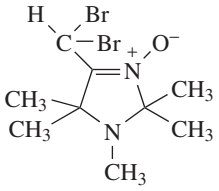
207 [365]



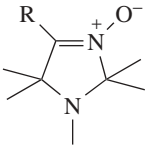
208 [366]



209[367]



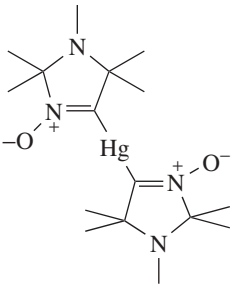
210[367]



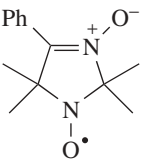
211[368]

R = $Si(CH_3)_3$
R = $Ge(C_2H_5)_3$
R = $Sn(n\text{-}C_4H_9)_3$
R = HgCl
R = $P(O)Ph_2$
R = PPh_2
R = SPh
R = SePh
R = $SO2C_6H_4$-(*p*-CH_3)
R = Cl

Fig. 2.11 (*continued*)



212[368]



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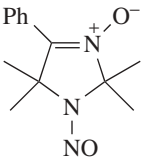

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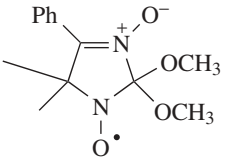

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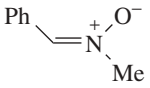
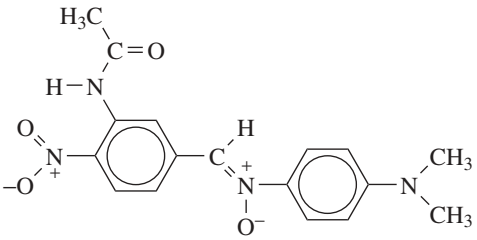
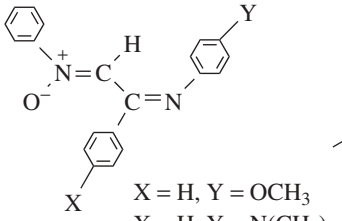


Ref.[372]



Ref.[373]



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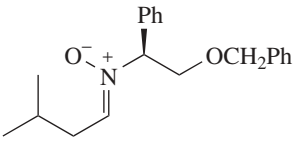
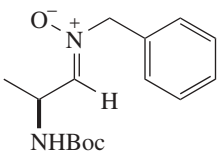


Ref.[376]



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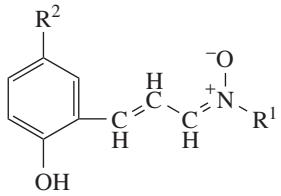
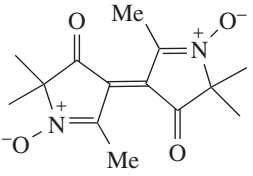
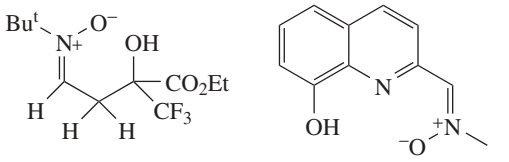


Ref.[378, 379]

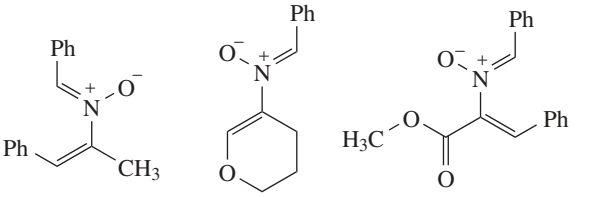


Ref.[380]

Fig. 2.11 (*continued*)



Ref.[381] **Ref.**[382]



Ref.[262]

Fig. 2.11 (*continued*)

conformation of the dihalomethyl nitrone group. In the *anti*-conformation of a halogen atom to the nitrone group, the C=N bond length increases approximately by 0,06 Å as compared to the C=N bond length in the conformation of the hydrogen atom in the *anti*-position (367). X-ray analyses of several new α-heteroatom substituted nitrones (**211**) and (**212**) have been reported (368–374, 376–382).

2.3.3. Vibration Spectra

For the nitrone group, one would expect the emergence of bands in the vibration spectrum typical of stretching vibrations $\nu_{C=N}$ and $\nu_{N^+\text{-}O^-}$. However, while identification of band $\nu_{C=N}$, appearing in a specific region 1610 to 1530 cm^{-1}, does not seem problematic, the assignment of band $\nu_{N^+\text{-}O^-}$ is frequently unjustified and erroneous. Labeling with ^{15}N of the nitrone group in the 3-imidazoline-3-oxides and analysis of the band shifts in their IR spectra, upon formation of the intermolecular hydrogen bond with a protic solvent revealed a band of varied intensity at 1340 to 1270 cm^{-1}, which corresponds to vibrations involving the $N^+\text{-}O^-$ bond (383, 384). Computational data of vibration spectra with isotopic ^{15}N substitution has been used in the identification of $N^+\text{-}O^-$ vibrations in α,*N*-diphenyl nitrones and in the study of the effect of fluoro substitution in benzene rings (385–387). Also, a comparative analysis of the effect of heteroatom substitutions at α-C on C=N and $N^+\text{-}O^-$ stretching vibrations in α-methoxy, α- amino, α-cyano, and α-mercapto nitrones has been made (388).

In the IR-spectra of 4-haloalkyl-3-imidazoline-3-oxides there are two bands $\nu_{C=N}$ due to the two conformers **A** and **B** (Fig. 2.12) (367, 389). Conformation **B** corresponds to the form with the lower frequency band $\nu_{C=N}$ ($\Delta\nu_{C=N}$ 30 cm^{-1}), where the halogen atom is located in the plain of the $C{=}N^+\text{-}O^-$ group in *anti*-position to the double bond. Conformation **A** corresponds to the

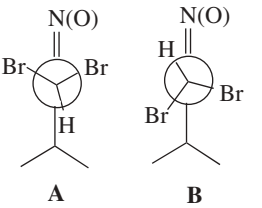


Fig. 2.12

form with a higher frequency band $\nu_{C=N}$ – with the *anti*-position of the proton. Thus, in contrast to α-haloalkyl ketones (390), eclipsed conformation is not observed in α-haloalkyl nitrones. A noticeable increase of the C=N bond length in conformer **B**, as compared with that in conformer **A**, testifies to the decrease of bond order and, resulting in the frequency decrease of the C=N vibration in conformation **B** (367).

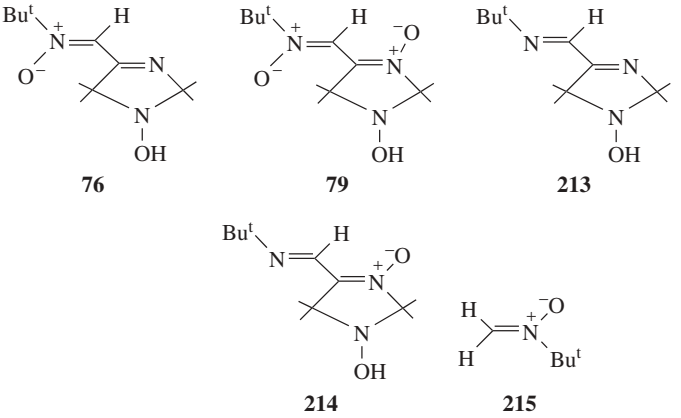
The stretching vibration band of the aldo-nitrone proton $\nu_{=C-H}$ is observed at 3140 cm^{-1}, being 200 to 250 cm^{-1} higher than in the structurally similar imines. The stretching frequency decrease in $\nu_{=C-H}$, due to the unbonded interaction of the unshared nitrogen pair with the C–H bond has been determined (391). The presence in the IR-spectra of a strong band ν_{CH} near 3100 cm^{-1} is a characteristic feature of cyclic aldo-nitrones (392).

The analysis of relations between intensities in the region of double bond stretching vibrations $\nu_{C=N}$ in the Raman spectra, allows one to arrive at a conclusion about *s-cis*- or *s-trans*-conformation of multiple bonds. The ratio between intensities of the high-frequency band to the low-frequency one for *s-trans*-conformers appears usually to be more than 0.5, whereas for *s-cis*-conformers it is less than 0.25 (393, 394).

2.3.4. Nuclear Magnetic Resonance (NMR) Spectra

2.3.4.1. ^1H NMR Spectra Owing to a significant anisotropic effect of the *N*-oxide group in ^1H NMR spectra it is used as a good indicator for determining the structure. There is a well-known considerable low field shift of *ortho*-protons in α-aryl nitrones, as compared to that in nitroaryl substituents (~0.6 ppm) (6 d, 395).Actually, a similar deshielding influence can be observed in the series of conjugated imines and nitrones (**76**), (**79**), (**213**), and (**214**), which illustrates their *s-trans*-configuration (Fig. 2.13) (224).

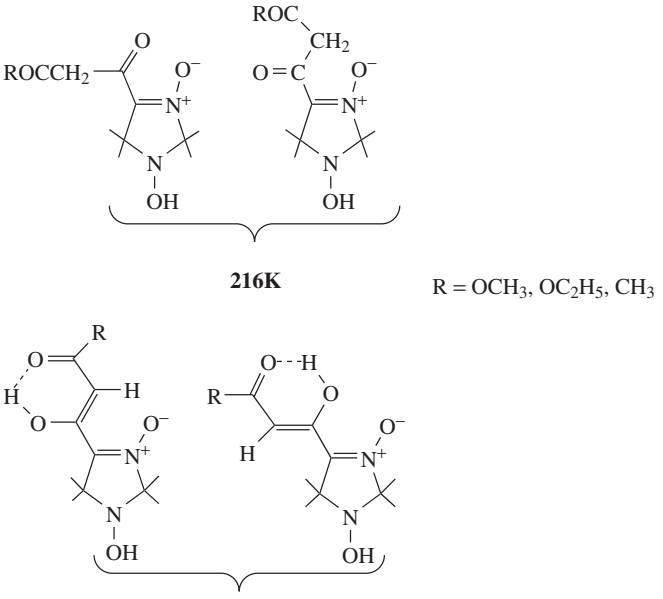
A shielding effect of the *N*-oxide group can be observed by the proton in the *trans*-position [compare the pairs (**76**) and (**213**), and (**79**) and (**214**) (224), and by the *cis*- and *trans*-protons in methylene-nitrone (**215**)] (135). The presence of strong deshielding (1,4 ppm) of olefinic protons in (**216E**) and its absence in (**216K**) allows one to draw conclusions about the preference of the *s-cis-s-cis*-conformation of the enolic form of *E* and *s-cis*-conformation of the keto-form **K** (Fig. 2.14) (396).



76 **79** **213**

214 **215**

Fig. 2.13



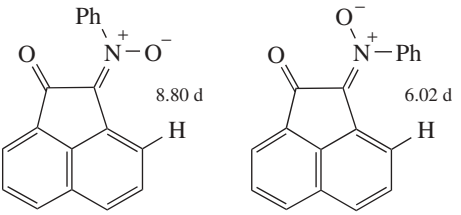
216K R = OCH_3, OC_2H_5, CH_3

216E

Fig. 2.14

A strong deshielding effect of the *N*-oxide group becomes apparent in the *E*-isomer of 2-(phenylimino)acenaphthenone *N*-oxide (**217**) (Fig. 2.15) (397).

Reference 135 gives a comparative analysis of 6 cyclic and 14 acyclic aldonitrones that in the solvents exist preferentially in *Z*-configuration, which agrees



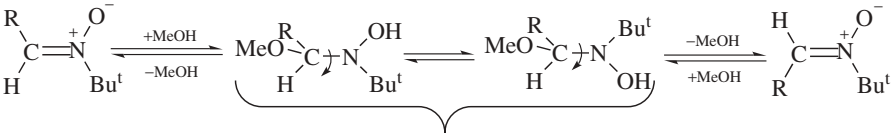
E-217 **Z-217**

Fig. 2.15

with the data of other authors (398, 399).Determination of the nitrone group configuration is based on the significant difference between the vicinal constants of *cis*- and *trans*-^{3}Jc,H; in cyclic *E*-isomers this is noticeably two to three times larger than in *Z*-isomers. In methylene-nitrone (**215**) J_{trans} equals 6.5 Hz, while J_{cis} equals 1.5 Hz.

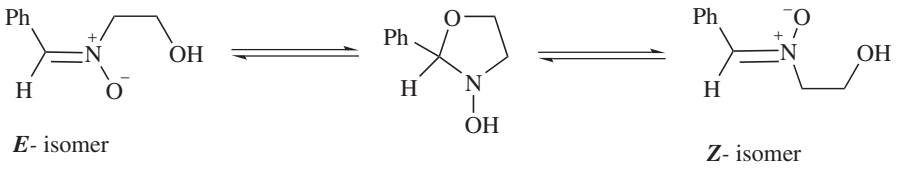
Using a variety of NMR 2-D techniques, such as H–H COSY, C–H COSY, DEPT, HMBC, and NOESY, an accurate assignment of the signals of 18 α-(5-substituted-2-hydroxyaryl)-*N*-aryl nitrones has been made (159).

Convincing evidence was found that the majority of acyclic aldo-nitrones exist in the *Z*-form, by investigating the ASIS-effect (aromatic solvent induced shift effect) (399). However, in some cases, specified by structural factors and solvent, the presence of both isomers has been revealed. Thus, in *C*-acyl-nitrones the existence of *Z*-and *E*-isomers was detected. Their ratio appears to be heavily dependant on the solvent; polar solvents stabilize *Z*-isomers and nonpolar, *E*-isomers (399). A similar situation was observed in α- methoxy-*N*-*tert*-butylnitrones. In acetone, the more polar *Z*-isomer was observed, whereas in chloroform, the less polar *E*-isomer prevailed. The isomer assignments were made on the basis of the Nuclear Overhauser Effect (NOE) (398). *E/Z*-Isomerization of acylnitrones can occur upon treatment with Lewis acids, such as, $MgBr_2$ (397). Another reason for isomerization is free rotation with respect to the C–N bond in adduct (**218**) resulting from the reversible addition of MeOH to the C=N bond (Scheme 2.74). The increase of the electron acceptor character of the substituent contributes to the process (135).



218

Scheme 2.74



E- isomer

Z- isomer

Scheme 2.75

Also, an intramolecular version of *E-Z* isomerization seems possible (Scheme 2.75) (304).

An NMR determination of the configuration exchange constant of methylene-nitrone (**215**) in 1,2-dichlorobenzene at 133°C gave $k = 88.6\ c^{-1}$. The estimated energy of isomerization activation was $\Delta G = 20.3$ kcal/mol (135).

A low field shift of proton signals of the OH-group in *N*-(salicylidene)phenyl-amine-*N*-oxides (~12,7–13,6 ppm) indicates the presence of an intramolecular hydrogen bond. The value of this shift depends on the pK_a value of the parent phenol (400). While studying solvation effects of ^1H NMR spectra in α-(2-hydroxy-1-phenyl)-*N*-(4-substituted-phenyl)nitrones, a Koppel-Palm three-parameter correlation was detected (401).

Recently, ^1H NMR spectroscopy has been used to study the effect of substituents in structural PBN (402) and 5,5-dimethylpyrroline *N*-oxide (DMPO) (403) analogs on their complexing ability with natural β-cyclodextrin (402, 403).

From a comparative analysis of ^1H NMR spectra of structurally similar pairs of nitroxyl radicals of 3-imidazoline and 3-imidazoline-3-oxide, it was concluded that the nitrone group contributes to a more efficient long-range spin density delocalization in the conjugated π-system of functional groups bonded with atom C-4 (404).

2.3.4.2. ^{13}C NMR Spectra A systematic study of the effect of various structural factors and solutions on the chemical shifts of carbon ^{13}C in the nitrone group and their correlation with the changes in electronic density has been made (405–407). Introduction of the *N*-oxide oxygen atom into the imino group leads to a shift in the high field of 30 to 33 ppm of the α-carbon signal as compared to the corresponding imines; this agrees with an increase of electron density (405). Similar results and conclusions were made from the study of the spectra of a great number of (*Z*)-α-aryl *N-tert*-butylnitrones (395), pyrroline-1-oxides, and 2*H*- pyrrole -1-oxides (408, 409). The chemical shift of the carbon atom in the nitrone group is located in the range of 117 to 152 ppm depending on the electronic influence of a substituent in positions 1, 2, 4, and 5 of a heterocycle. Increasing electrophilicity of the substituent in position 2 leads to a low field α-*C* shift due to the decrease of electronic density (405). The converse influence can be observed for substituents in positions 1, 4, and 5 (406). In solutions, in which hydrogen bonds are formed with the *N*-oxide group, one observes α-*C* signal shift in the low field at 1.5 to 2.5 ppm for solution in chloroform and at 5 to 9 ppm for solution in methanol. The shift value depends on the substituent in position

1 and decreases with the increase of its electrophilic character (407). Similar effects are observed in the formation of an intramolecular hydrogen bond with the oxygen atom of the nitrone group (400, 407). The value of the low field α-C shift in ^{13}C NMR spectra of α-(5-substituted-2-hydroxyaryl)-*N*-arylnitrones, due to the formation of an intramolecular hydrogen bond with the *N*-oxide oxygen, is approximately 12 ppm (159). A comparative analysis of the deutero-isotope effect on the chemical shifts of some α-(2-hydroxyaryl)-*N*-phenylnitrones and the corresponding Schiff's bases has been reported. It has been found that a weakening of the intramolecular hydrogen bond and conformational changes in deutero-substitution leads to a more significant isotope effect in nitrones than in imines (410). On protonation of the nitrone group, the value of the low field α-*C* signal shift is 30 to 40 ppm (407, 411, 412).

The same conclusions about the effect of substituents and protonation on chemical α-*C* shift have been made from the spectra of α-substituted *N-tert*-butylnitrones (388).

A noticeable low field shift (3.5–8.5 ppm) of the α-*C* signal was observed in the complex formed of the N^+-O^- group with Li^+ ion (135).

A strictly defined region of chemical shifts of C_2, C_4, and C_5 atoms in *N*-oxides of 4*H*-imidazoles allows to define clearly the position of the *N*-oxide oxygen atom (102). Chemical shifts of the α-C nitrone group in α-N-, O-, and S-substituted nitrones are located in the region of 137 to 150 ppm (388, 413). On the basis of ^{13}C NMR analysis of 3-imidazoline-3-oxide derivatives, the position of tautomeric equilibria in amino-, hydroxy-, and mercapto- nitrones has been estimated. It is shown that tautomeric equilibria in OH- and SH-derivatives are shifted toward the oxo and thioxo forms (approximately 95%), while amino derivatives remain as amino nitrones (413). In the compounds with an intracyclic amino group, an aminonitrone (**A**) - *N*-hydroxyaminoimino (**B**) tautomeric equilibrium was observed (Scheme 2.76), depending on both, the nature of the solvent and the character of the substituent in position 2 of the heterocycle (414).

From a comparative analysis of ^{13}C NMR spectra (415) of structurally similar pairs of nitroxyl radicals of 3-imidazoline and 3-imidazoline-3-oxide, the effectiveness of the nitrone group contribution to a long-range spin density delocalization was established. Analogous results were obtained from ^1H NMR spectra.

A **B**

Scheme 2.76

2.3.4.3. ^{14}N and ^{17}O NMR Spectra NMR spectra of ^{14}N and ^{17}O nucleus are quite limited and mostly concern conjugated *C,N*-diaryl-nitrones (416–419). Recently (420), for derivatives of 3-imidazoline-3-oxide, using ^{14}N and ^{17}O NMR, the influence of substituents and hydrogen bonds on chemical shifts and the range of chemical shift changes of nitrogen and oxygen of the nitrone group has been determined. Both in ^{17}O NMR spectra, and ^{14} N NMR spectra in the series of the derivatives examined, highest field signals of N^+-O^- group are those of amino derivatives, while the low field ones are those of cyano derivatives. Depending on the substituent (from amino- to cyano group), ^{17}O chemical shifts tend to change in the range of 155 ppm, with the interval of such changes in ^{14}N chemical shifts for the same substituents being 110 ppm. The range of ^{17}O chemical shifts in α,*N*-diaryl nitrones is 350 to 409 ppm (421).

The result of a study of ^{15}N NMR spectra of cyclic nitrones of 3-imidazoline-3-oxide and of the corresponding nitroxyl radicals has been reported (422).

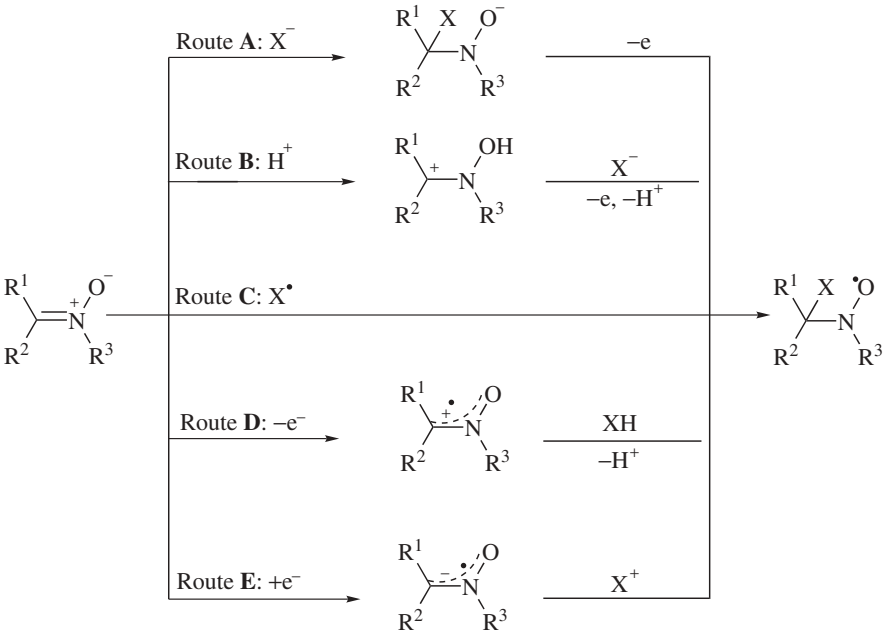
The hyperfine interaction (HFI) ^1J ($^{15}N^{13}C$) constants, both in *E* and *Z*-isomers, have a negative sign and are close in absolute value (−21.5 and −21.2 Hz respectively). Heminal constants ^2J (^{15}NH) in aldonitrones have close absolute values, but differ in sign; in *E*-isomers the sign is positive (+2.1 Hz), in *Z*-isomers it is negative (∼−2.3 Hz). Vicinal constants in keto nitrones $^3J(^{15}NH)$ in both isomers have a negative sign and a value close to ∼−3.3 Hz (423).

2.4. ELECTROCHEMICAL PROPERTIES AND ELECTRON PARAMAGNETIC RESONANCE (EPR)-SPECTRA OF NITRONE RADICAL IONS

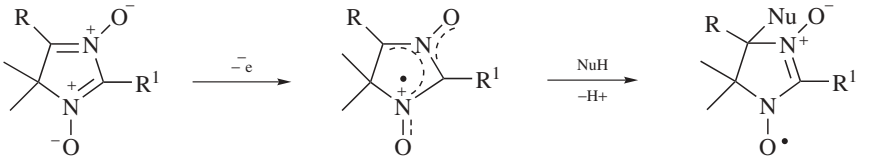
EPR study of electrochemical properties of nitrones and registration of resulting radical cation (RC) or radical anion (RA), such as, in the nitrone transformation into nitroxyl radicals, allows us to get direct answers to the questions concerning mechanisms of nitrone group reactions. The following schemes **A–E** can be realized depending on conditions as below (Scheme 2.77):

- **A:** nucleophilic addition of strong nucleophiles with further oxidation (Forrester-Hapburn mechanism);
- **B:** acid-catalyzed nucleophilic addition;
- **C:** radical addition (spin trapping);
- **D:** nitrone oxidation to RC with the subsequent addition of weak nucleophiles (reversed spin trapping);
- **E:** nitrone reduction to RA and addition of electrophiles.

To study mechanisms **C–E**, it seems reasonable to employ both, electrochemical approaches and EPR-spectroscopy. It is important to be aware of the electrochemical properties of nitrones if used as spin traps; for production of spin adducts (SA) is possible not only via homolytic process (**C**) but also via ionic processes shown in Scheme 2.77. In the case of (**B**), protonation can protect the



Scheme 2.77



219 **220** **NNR**

Scheme 2.78

obtained hydroxylamine from oxidation, but as a result of the subsequent work up (neutralization), it is likely to be oxidized to the corresponding SA.

On studying electrochemical properties of 1-hydroxy-3-imidazoline-3-oxides and their conversion into nitronyl nitroxyl radicals (**NNR**), the intermediate production of a nonaromatic radical cation (**220**) of 4*H*-imidazole-1,3- dioxides (**219**) (Scheme 2.78) (101) was suggested.

In the course of electrochemical oxidation (EO) of 4*H*-imidazole-1,3- dioxides (**219**) (Table 2.6) in dry CH_2Cl_2 at -80° to -40°C, RCs (**220**) were first detected (424, 425). Cyclic voltammograms (CVA) correspond to a one-electron reversible oxidation (**219c**) to RC (**220c**) (Fig. 2.16, curve A).

Table 2.6 Oxidation potentials of 4H-imidazole N-oxides 219,223,224

Compound	R^1	R^2	$E_{p/2}$, V
219 a	C_6H_5	H	1.38
219 b	C_6H_5	CH_3	1.33
219 c	C_6H_5	C_6H_5	1.41
219 d	C_6H_5	2-FC_6H_4	1.31
219 e	C_6H_5	3-$NO_2C_6H_4$	1.48
219 f	C_6H_5	4-$(CH_3)_{2NC6}H_4$	0.79
219 g	C_6H_5	2-Thienyl	1.31
219 h	2-Thienyl	C_6H_5	1.20
219 i	2-Furyl	C_6H_5	1.16
219 j	2-(5-Methyl)furyl	CH_3	1.02
219 k	2-(5-Methyl)furyl	C_6H_5	1.05
219 I	2-(5-Methyl)furyl	3-$NO_2C_6H_4$	1.12
223 a	C_6H_5	H	1.29
223 b	C_6H_5	CH_3	1.18
223 c	C_6H_5	C_6H_5	1.28
223 d	2-Furyl	C_6H_5	1.16
223 e	C_6H_5	$C_5H_{10}N$	0.49
224 a	C_6H_5	CH_3	1.52
224 b	C_6H_5	C_6H_5	1.56

[a] conc. 10^{-3} mol l^{-1} in MeCN

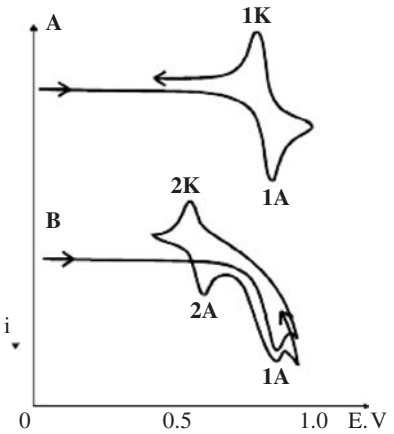


Fig. 2.16

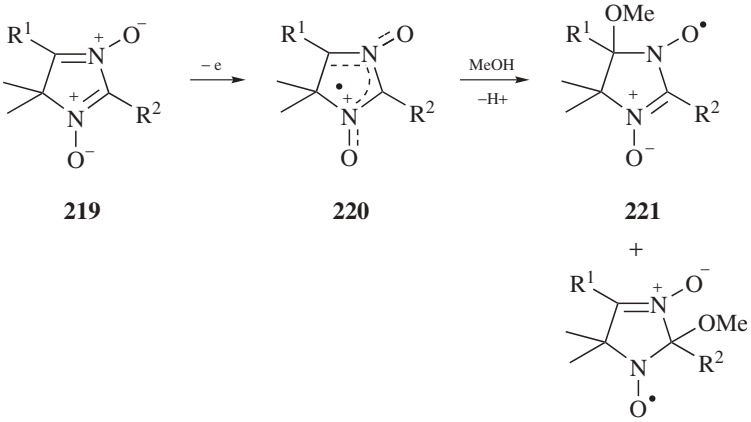
Formation of RCs (**220**) is proved by EPR-spectra registration in the same temperature range in an electrochemical cell placed in the EPR-spectrometer cavity resonator. The HFI of the observed EPR-spectra RCs (**220**) is determined by the interaction of unpaired electron with two nuclei ^{14}N: (**220c**) −6.76 and

4.72 G; (**220 d**) −6.97 and 4.39 G; (**220e**) −7.74 and 6.02 G; (**220 h**) −5.33 and 5.33 G. The hyperfine coupling constant was established on the basis of EPR-spectral analysis of RC (**220c***), labeled by ^{15}N isotope in position 1 of the heterocycle, and by quantum-chemical calculation (425). Direct experimental evidence of the reaction **D** as described in Scheme 2.77 has been obtained on the basis of electrochemical oxidation analysis of (**219c**) in the presence of nucleophile MeOH (425, 426). It has been shown that in the electrochemical oxidation of (**219c**) RC (**220c**) is initially formed (Fig. 2.16, curve B, peak 1A). It subsequently reacts with methanol yielding **NNR** (**221c**) (Fig. 2.16, curve B, peaks 2K and 2A: EO reversible) and 3-imidazoline-3-oxide **NR** (**222c**) (Fig. 2.16, curve B, peak 1A: EO irreversible), as a result of the nucleophilic attack of MeOH at carbon atoms C_2 or C_5 of oxidized dinitrone grouping of (**RC**) (**220c**), respectively. It is important to mention that the yields and ratios of the two products (**221**) and (**222**), obtained in the electrochemical oxidative methoxylation are similar to those observed when PbO_2 or MnO_2 is used as an oxidant. This is certainly a direct indication of the radical cation route (**D**) (Scheme 2.79) (425, 426).

The 4*H*-imidazole-3-oxides (**223**) have electrochemical potentials similar to 4H-imidazole-1,3-dioxides (**219**); 4*H*-imidazole-1-oxides (**224**) are more difficult to oxidize (Fig. 2.17) (Table 2.6) (425).

The 2*H*-imidazole *N*-oxides (**225**) have significantly higher oxidation potentials than their 4*H*-imidazole isomers (**223**) and (**224**); but oxidation potentials of 2*H*-imidazole *N,N*-dioxides (**226**) are similar to oxidation potentials of 4*H*-imidazole *N,N*-oxides (**219**) (Fig. 2.18) (Table 2.7) (427).

EPR-spectra RC (**227c**), obtained from the oxidation of 4,5- diphenyl-2*H*-imidazole-1,3-dioxide (**226c**), is a quintet with the HFI constant $a_N = 1.65$ G.

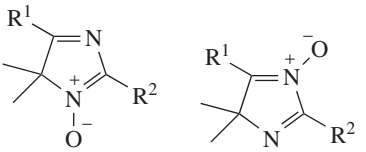


219 **220** **221**

+

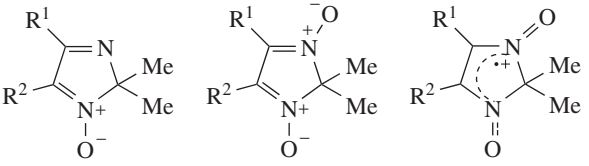
222

Scheme 2.79



223 **224**

Fig. 2.17



225 **226** **227**

Fig. 2.18

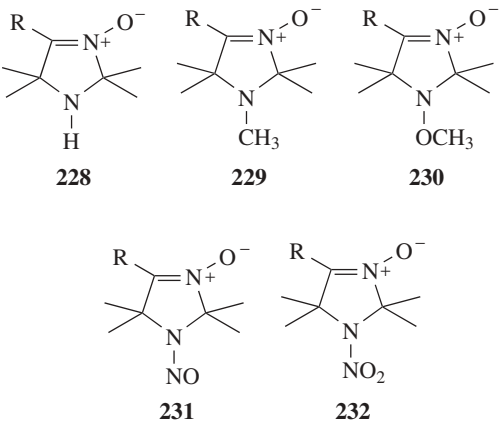
Table 2.7 Oxidation potentials of 2H-imidazole N-oxides 225 and 226

Compound	R^1	R^2	$E_{p/2}$, V
225a	Me	H	1.79
225b	Me	Ph	1.64
225c	Me	*o*-$NO_2C_6H_4$	1.91
225d	Me	*p*-$NO_2C_6H_4$	1.91
225e	Ph	H	1.87
225f	Ph	OMe	1.36
225g	*p*-$NO_2C_6H_4$	H	1.96
225h	CB_rMe_2	H	1.94
225i	CNO_2Me_2	H	2.02
225j	CH=NOH	H	1.92
225k	CN	H	2.25
226a	Ph	H	1.34
226b	Ph	Me	1.22
226c	Ph	Ph	1.29
226d	Me	Me	1.11

[a]conc. 10^{-3} mol 1^{-1} in MeCN

Such an insignificant value of a_N testifies to high localization of spin density in RC (**227c**) at the oxygen atoms (427).

Unlike the 4*H*- imidazoles (**219**), (**223**), (**224**) electrochemical oxidation of the nitrone group in 4-R-3-imidazoline-3-oxides (**228**), (**230–232**), as in α-PBN and DMPO is of irreversible nature. Therefore, the formation of radical cations



228 **229** **230**

231 **232**

Fig. 2.19

has not been detected (428). In this paper, electrochemical oxidation potentials are reported of 31 cyclic nitrones, derived from 4-R-3-imidazoline-3-oxide (**228**), (**230–232**) (Fig. 2.19), in which $E_{p/2}$ undergoes wide-range changes from 1.36 to 2.58 V (ca $E_{p/2}$ DMPO 1.57 V, PBN 1.41 V) depending on substituents R (Table 2.8). The effect of substituents R on $E_{p/2}$ can be described by two-parameter correlation Equations 2.1 and 2.2 for N-NO (**231**) and N-NO_2 (**232**) derivatives, respectively. In the 1-methyl-3-imidazoline-3-oxides (**229**) the *tert*-amino group, in position 1, oxidizes rather than the nitrone group (428).

$$E_{p/2} = 1{,}944 + 0{,}251\,\sigma_I + 1{,}404\,\sigma_R$$

$$E_{p/2} = 2{,}009 + 0{,}829\,\sigma_I + 0{,}768\,\sigma_R$$

In the series of α-substituted nitrones, the α-methoxy nitrones are the most easily oxidized nitrone derivatives. The study of electrochemical behavior of acyclic α-methoxy-, α-amino-, α-cyano- and α-mercapto-nitrones has shown an irreversible one-electron oxidation of the nitrone group (429).

Determination of electrochemical oxidation potentials and electrochemical reduction of 13 β-phosphorylated acyclic nitrones shows that phosphorylated compounds have a clear anodic shift of potentials of both, oxidation (E_p 1.40 to 2.00 V versus SCE in CH_3CN) and reduction (E_p −0.94 to −2.06 V). This is caused by a strong electron-acceptor influence of the diethoxyphosphoryl group (430). In contrast, a reversible one-electron oxidation of azulene nitrones (**233**) (Scheme 2.80) occurs 0.6 V below the E_p potential of PBN, that is at the value one observes the oxidation of 4*H*-imidazole-1,3-dioxides (**219**) (428, 429). In other words, the corresponding RC (**234**) is 14 kcal more stable than the RC of PBN. Although the EPR spectrum of RC (**234**) was not recorded, RC (**236**) from dinitrone (**235**) turned out to be rather stable and gave an EPR spectrum (170).

Table 2.8 Oxidation potentials of 4-R-3-imidazoline-3-oxides (228), (230-232)

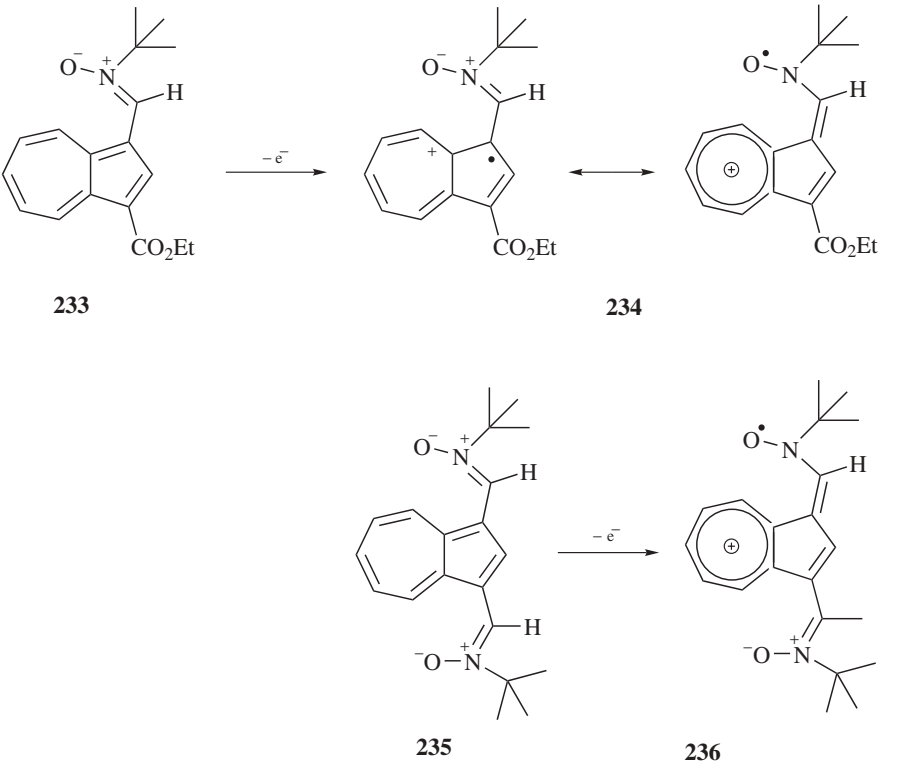
Compound	R	σ_1	σ_R	$E_{p/2}$, V
228 a	H			1.52
228 b	CH_3			1.43
228 c	C_2H_5			1.49
228 d	C_6H_5			1.36
230 a	H			1.42
230 b	CH_3			1.40
230 c	C_2H_5			1.42
230 d	C_6H_5			1.46
230 e	$CHBr_2$			1.58
230 f	$CHCl_2$			1.57
230 k	$CONH_2$			1.50
230 I	CN			1.94
231 a	H			1.94
231 b	CH_3	−0.08	−0.15	1.75
231 c	C_2H_5	−0.03	−0.14	1.80
231 d	C_6H_5	0.08	−0.09	1.83
231 e	$CHBr_2$	0.30	0.02	2.19
231 g	CHO	0.25	0.27	2.22
231 h	$COOCH_3$	0.11	0.19	2.20
231 i	COOH	0.21	0.17	2.28
231 k	$CONH_2$	0.12	0.13	2.15
231 I	CN	0.48	0.22	2.42
231 n	OCH_3	0.25	−0.43	1.33
231 o	SCH_3	0.13	−0.46	1.30
232 a	H			1.98
232 b	CH_3	−0.08	−0.15	1.81
232 c	C_2H_5	−0.03	−0.14	1.92
232 e	$CHBr_2$	0.30	0.02	2.25
232 g	CHO	0.25	0.27	2.41
232 h	$COOCH_3$	0.11	0.19	2.27
232 I	CN	0.48	0.22	2.58

[a] conc. 10^{-3} mol l^{-1} in MeCN

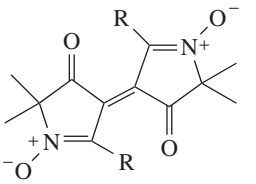
The CVA method shows that electrochemical reduction of 3,3'-bis(2-R-5,5-dimethyl -4-oxopyrrolidinylidene)-1,1'-dioxides (**237**) (Fig. 2.20), which *per se* are dinitrones conjugated with a C=C double bond, is an EE process that produces stable radical anions and dianions. Oxidation is an EEC- or EE-process that gives stable RC and dications (431, 432).

Also, the CVA method was used to study EO of some metal containing nitrone complexes (433, 434).

Radical cations of the most popular spin traps PBN and DMPO have been generated by the methods of ionizing radiolysis and laser flash-photolysis in solid matrices (435–437). As a polar solvent with high solvating ability for



Scheme 2.80



237a–d

R = CF_3 (a), Me (b), Bu^t (c), Ph (d

Fig. 2.20

nucleophiles and especially anions, 1,1,1,3,3,3-hexafluoropropan-2-ol (HFP) is used (438). The HFP solvent is convenient when it is necessary to achieve stabilization effect of RC, or when the participation of anions is undesirable.

The method of optically detected EPR (OD EPR) has been successfully employed to detect short-lived radical anions of cyclic nitrones DMPO and 1,2,2,5,5-pentamethyl-3-imidazoline-3-oxide (PMIO) (**229**, R = H), generated by

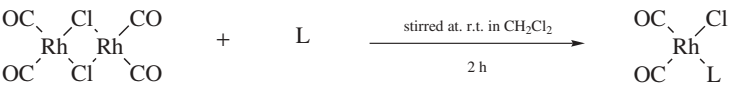
radiolysis in squalane (439, 440). Analysis of HFI constants and quantum-chemical calculations indicate that the RA of a five-member cyclic nitrone has a non-planar geometry with a pyramidal N^{+}-O^{-} group and that the spin density in the RA is localized in the $C{=}N^{+}$-O^{-} fragment.

Other experiments suggest that nitrone deoxygenation proceeds through intermediate formation of nitrone RC, rather than the product of its isomerization, a oxaziridine (441).

2.5. NITRONE COMPLEXES

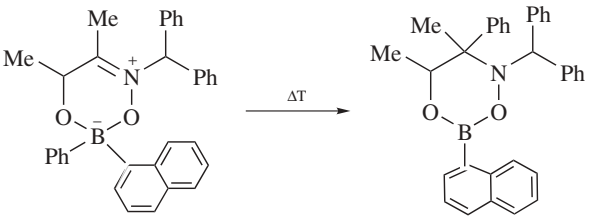
The electron-donor *N*-oxide oxygen atom of a nitrone makes it suitable for complexation and protonation. Such properties of nitrones have been widely used to influence their reactivity, using Lewis acids and protonation in nucleophilic addition reactions (see Section 2.6.6). In this chapter, the chemistry of nitrones with various metal ions [Zn (II), Cu(II), Mn (II), Ni (II), Fe (II), Fe (III), Ru (II), Os (II), Rh (I), UO_2^{2-}] (375, 382, 442–445), and diarylboron chelates is described (234–237, 446). Accurate descriptions of the structures of all complexes have been established by X-ray analysis.

DMPO has been used in the synthesis of the first metalloporphyrin nitrone complex (443). On the basis of nitrone ligands (**L**) (Scheme 2.81) the synthesis of rhodium (I) carbonyl complexes of the type $[Rh(CO)_2ClL]$ was carried out. These complexes are used as effective catalysts of methanol carbonylation into acetic acid and its ester (444).



L = α, N-diphenylnitrone (a); α-styryl-N-phenylnitrone (b); N,N'-diphenyldinitrone (c); α-(2-furyl)-N-phenylnitrone (d)

Scheme 2.81



238 **239**

Scheme 2.82

Diarylboron chelates C-(1-hydroxyalkyl)nitrones (**238**) on boiling in toluene tend to undergo 1,4-aryl migration and form heterocyclic arylboronates (**239**) (Scheme 2.82) (446).

2.6. NITRONE REACTIONS

2.6.1. Rearrangements of Nitrones

Rearrangements of nitrones due to migration of the *N*-oxide oxygen can be induced both, photochemically and by various reagents, but in specific conditions it can proceed spontaneously. On one hand, such transformations are caused by the O-nucleophilic character of nitrones able to react easily with acid anhydrides, their halo anhydrides, sulfonyl chloride and other agents; on the other hand, by a significant CH-acidity of α-alkyl groups.

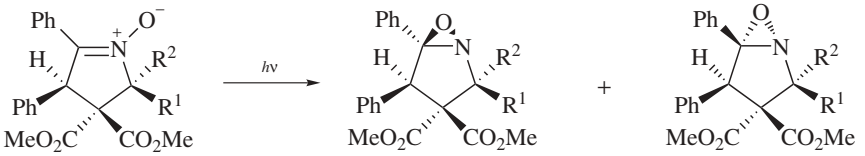
2.6.1.1. Photochemical Rearrangement Isomerization of nitrones to oxaziridines is a general reaction of various cyclic and acyclic nitrones (447–449). When this reaction is reversible, many transformations of nitrone to oxaziridine and back to nitrone can be carried out without decomposition. This reaction is of special interest in view of light energy accumulation (450, 451).

Photoisomerization of nonconjugated nitrones, in particular derivatives of 3-imidazoline-3-oxide and pyrroline-*N*-oxide, appears to be irreversible (Scheme 2.83) (10, 452).

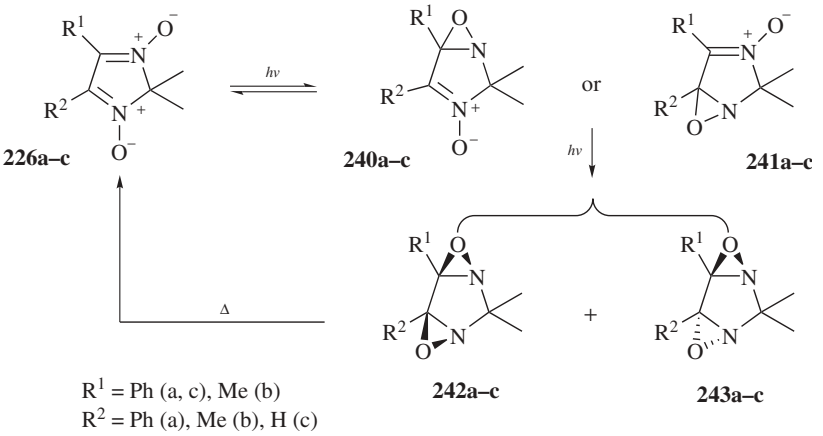
Stability of the products resulting from isomerization of conjugated nitrones seems to be highly dependent on the nature of conjugation and the solvent. Thus, as a result of 2*H*-imidazole 1,3-dioxides (**226a–c**) photolysis in nonpolar solvents, isomerization products of one of the nitrone group (**240**) or (**241**) were isolated, with their successive isomerization to the starting compounds (453). Significantly more stable are the products of isomerization of both nitrone groups in (**242**) and (**243**), where only the highly strained *cis*-isomer can be isomerized to the starting dinitrone on continuous heating in acetic acid (Scheme 2.84).

Similarly, oxaziridines (**244**) are not likely to undergo reverse isomerization to the initial nitrones (**225**) (Scheme 2.85) (453).

Oxaziridines, 6-oxa-1,4-diazabicyclo[3.1.0]hex-3-enes (**245**) and their 4-oxides (**246**), obtained in the photolysis of 4*H*-imidazole-3-oxides (**223**) and 1,3-dioxides (**219**), underwent a quick thermal isomerization to the starting nitrones. Further

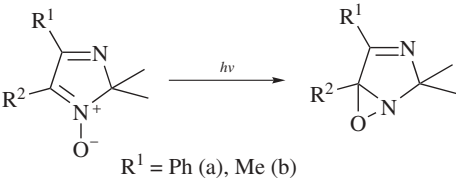


Scheme 2.83



226a–c **240a–c** **241a–c** **242a–c** **243a–c**

Scheme 2.84



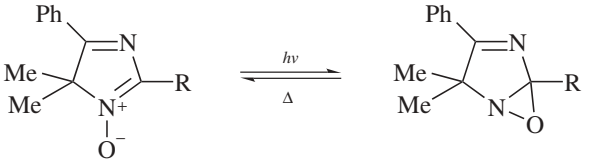
225a, b **244a, b**

Scheme 2.85

photolysis affords a mixture of *cis*- and *trans*-3,7-dioxa-1,4-diazatricyclo[4.1.0.0 2,4]heptanes, and similarly to (**242**), only *cis*-isomers are able to thermally isomerize to the starting 4*H*-imidazole -1,3-oxides (**219**) (Scheme 2.86) (454).

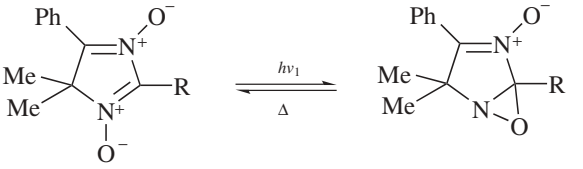
Stereoselective isomerization of oxaziridines into the corresponding nitrones can be carried out in a photosensitive electron transfer (PET) reaction (455). Upon studying photophysical and photochemical properties of a series of α,*N*-diarylnitrones in polar and proton solutions, the electronic influence of substituents at α-C and N atom, on the possible routes of cyclic oxaziridine transformation, was revealed (a) with homolytic C–O bond opening and (b) with N–O bond opening (Scheme 2.87) (456). The presence of electron donor groups at carbon and/or nitrogen atoms facilitates the reaction (according to path A) leading to nitrones, whereas electron-withdrawing group on the nitrogen atom stabilize the biradical structure as a result of delocalization of three electrons at the nitrogen atom (path B) (456).

Oxaziridines, the products of photochemical isomerization of polymeric nitrones, are characterized by high stability. The formation of an intramolecular hydrogen bond stabilizes the nitrone group with respect to UV-irradiation



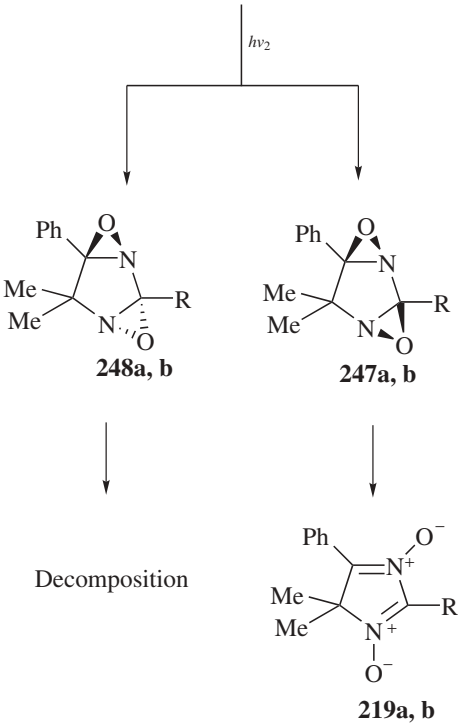
R = *n*-$Me_2NC_6H_4$ (a), *n*-$MeOC_6H_4$ (b), Ph (c), 3-Py (d), H (e), Me (f).

223a–f **245a–f**

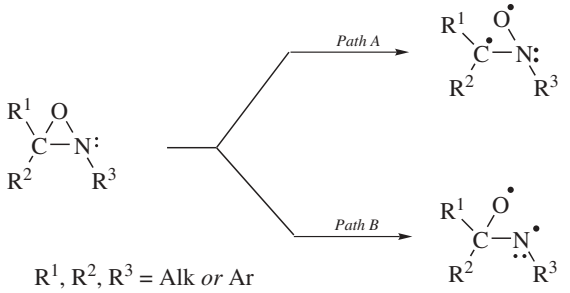


R = Me (a), Ph (b)

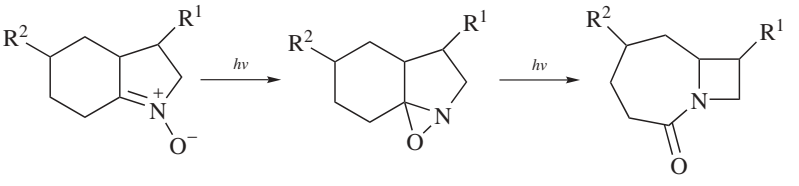
219a, b **246a, b**



Scheme 2.86



Scheme 2.87



Scheme 2.88

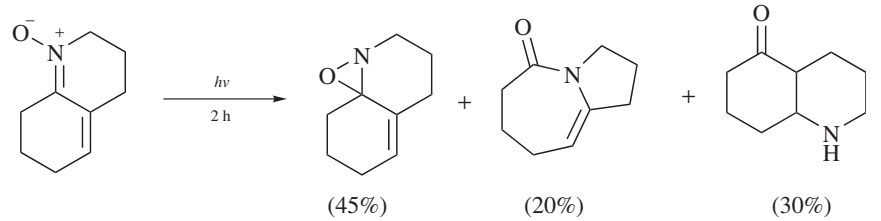
(457). Photochemical isomerization of nitrones to oxaziridines can occur in the crystal phase (458).

To illustrate the synthetic use of photochemical rearrangement, the photolysis of nitrones (**249**) leading to the formation of bicyclic lactams (**250**) is an example (Scheme 2.88) (459).

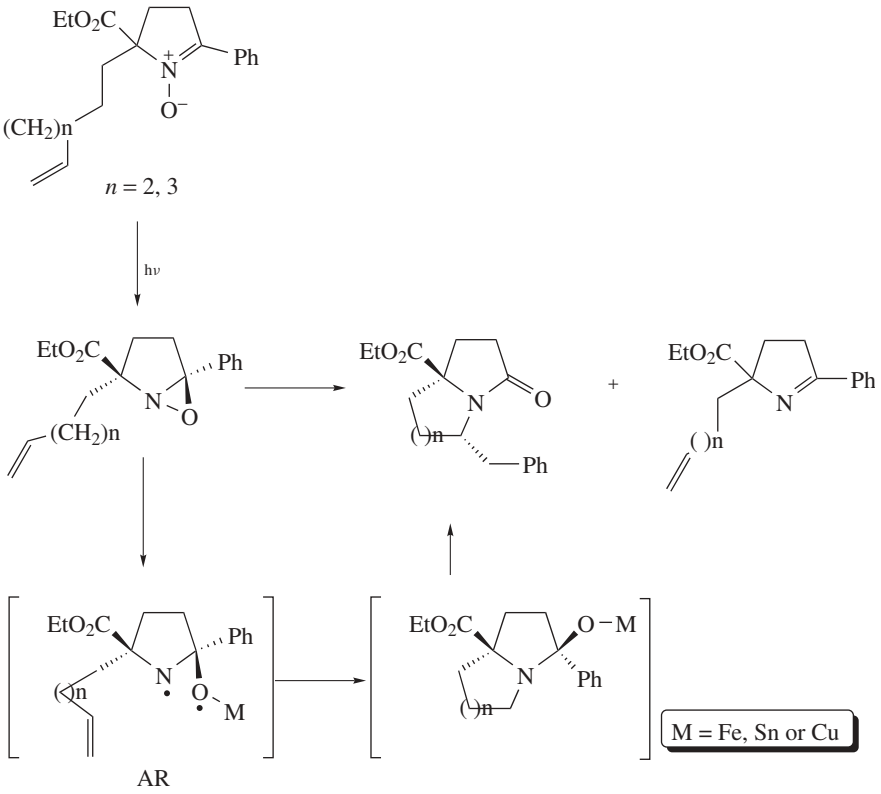
An alternative method in the synthesis of alkaloids, photochemical rearrangement of endocyclic nitrones into bicyclic lactams has drawn special attention. Analyses of photochemical rearrangement and application of modified conditions of the Barton reaction testify to the comparability of results obtained in these approaches (Scheme 2.89) (460).

Other examples of photochemical transformations of nitrones into alkaloids have been described (461). According to the view of the authors, some *trans*-oxaziridines give products derived from the trapping of aminyl radicals (**AR**) by the pendant alkenes (Scheme 2.90).

A detailed analysis of photoisomerization of the nitrone group in the nitroxyl radical 4-phenyl-2,2,5,5-tetramethyl-3-imidazoline-3-oxide-1-oxyl, based on double electron-nuclear resonance methods, has shown that in the absence of oxygen the photochemical reaction occurs without affecting the radical center. The



Scheme 2.89

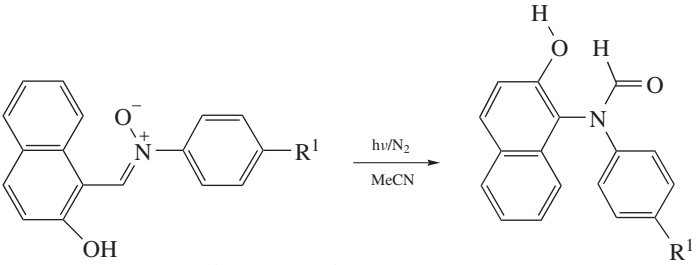


Scheme 2.90

observed destruction in the presence of oxygen is very likely due to photo-oxidation (462).

Experimental evidence of the formation of intermediate peroxide moieties in photo-oxidation of nitrones has been provided (463). Oxidation with singlet oxygen was observed in the photoirradiation of DMPO (464).

Specific regularities of nitrone rearrangements have been studied under photo-irradiation at various conditions (in solvent, in polymeric matrixes, and in films



a: R^1 = Me, b: R^1 = H

Scheme 2.91

produced by thermal vacuum evaporation) (465). Analysis of the effects of substituents and solvents has revealed an important role of intramolecular hydrogen bonding to the nitrogen of the oxaziridine ring in a novel photochemical transformation of hydroxyl substituted aromatic nitrones to *N,N*-diarylformamide (Scheme 2.91) (466).

Explanation of the observed de-oxygenation with the formation of the corresponding imines in the photochemical reaction of α-aryl-*N*-methylaldonitrones, confirms the intermediate formation of radical cations resulting from PET (441, 467).

Photo transformations in films of copolymers of α-(2-hydroxy-4-methacryloyloxyphenyl)—(2,6-dimethylphenyl)nitrone (HMDN) with methyl methacrylate (MMA) showed that, on radiation at 366 nm, an increase of the steric effect in the *N*-aryl group leads to a decrease of the refractive index (468, 469).

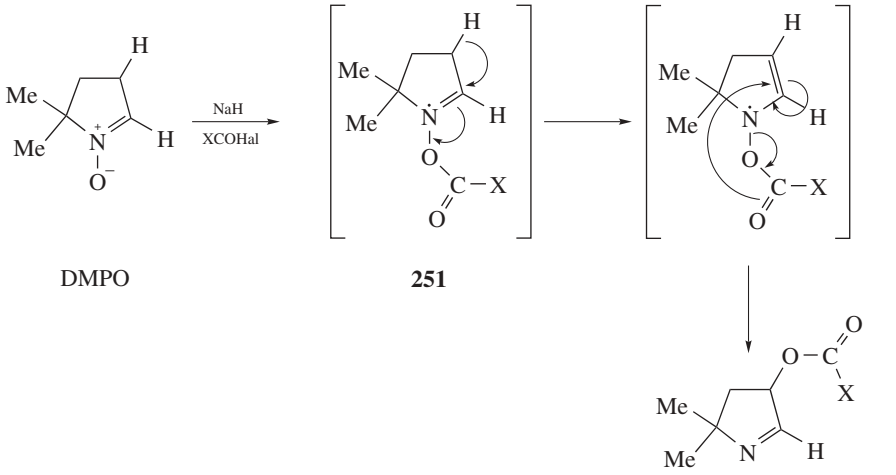
2.6.1.2. Oxygen Migration The reaction of pyrroline *N*-oxides (DMPO) with acid halides and acid anhydrides gives *N*-acyloxyimines (**251**), which undergo a hetero-Cope rearrangement to β-acyloxyimines (**252**) (Scheme 2.92) (470, 471).

Mesylation of α-amino nitrones (**253**) in dichloromethane gave amidines (**254**) via a 3,3-sigmatropic rearrangement (Scheme 2.93) (351).

On boiling in benzene, C-(4-oxo-4*H*[1]benzopyran-3-yl)-*N*-phenylnitrone (**255**) rearranges to 2-(*N*-phenylamino)-4-oxo-4*H*[1]-benzopyran-3-carboxaldehyde (**256**) (70%) and 3-(phenyliminomethylene)-chroman-2,4-dione (**257**) (25%) (Scheme 2.94) (472).

2.6.1.3. Rearrangement of Nitrones Into Amides The most common nitrone rearrangement caused by the migration of the oxygen atom is the conversion to amides (Beckman rearrangement). It occurs under the influence of electrophilic agents such as acid anhydrides, acid halides, and sulfonyl chlorides, as well as with nucleophilic agents such as alcoholate anions (6d).

Pyrroline-*N*-oxide (**258**) is isomerized into γ-lactam (**259**) in the presence of lithium diisopropylamine (LDA) (470) and sodium trityl (471). In these reactions, deprotonation at C_3 occurs, leading to carbanion (**260**). Then oxygen migration from N_1 to C_2 takes place via intermediate formation of oxaziridine



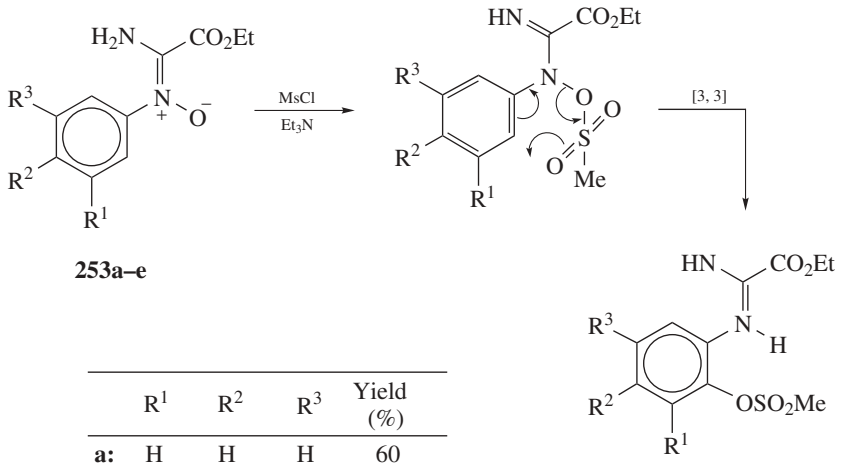
DMPO

251

X = OEt, Ph, CMe_3, $C(Me)_2Br$

252

Scheme 2.92

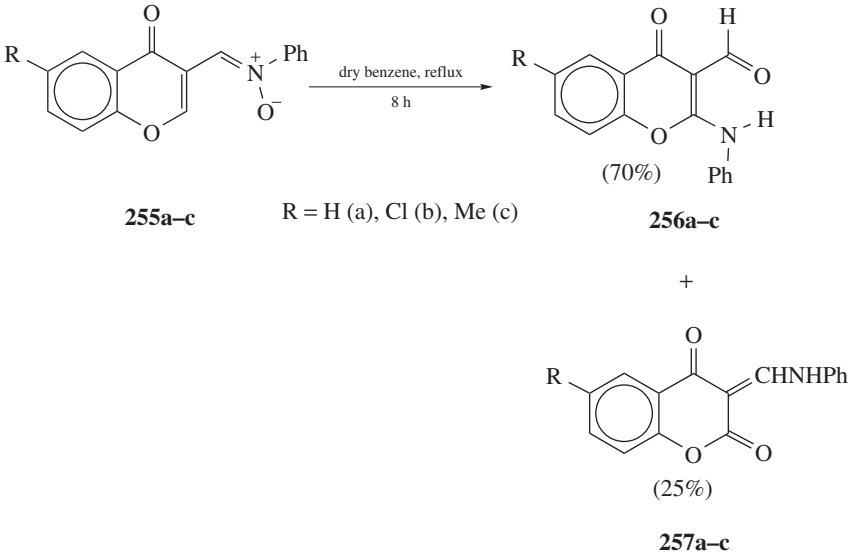


253a–e

254a–e

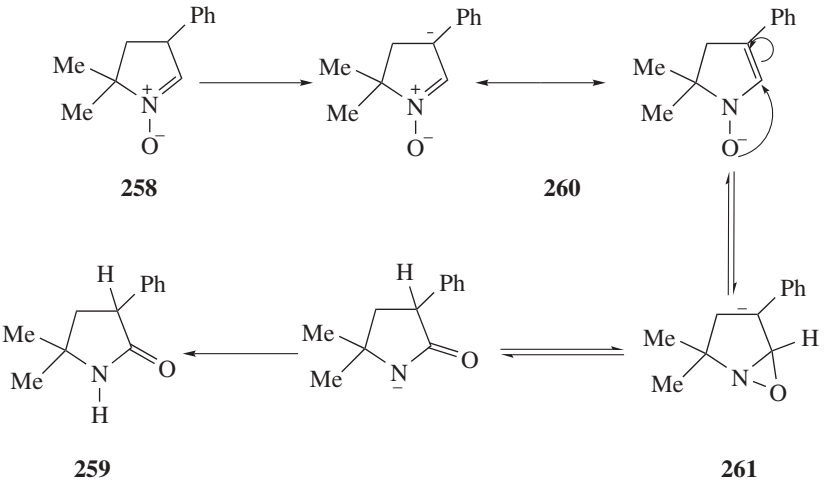
	R^1	R^2	R^3	Yield (%)
a:	H	H	H	60
b:	H	Me	H	56
c:	H	H	Me	50
d:	Me	H	H	15
e:	H	Br	H	40

Scheme 2.93



255a–c R = H (a), Cl (b), Me (c) **256a–c** + **257a–c**

Scheme 2.94

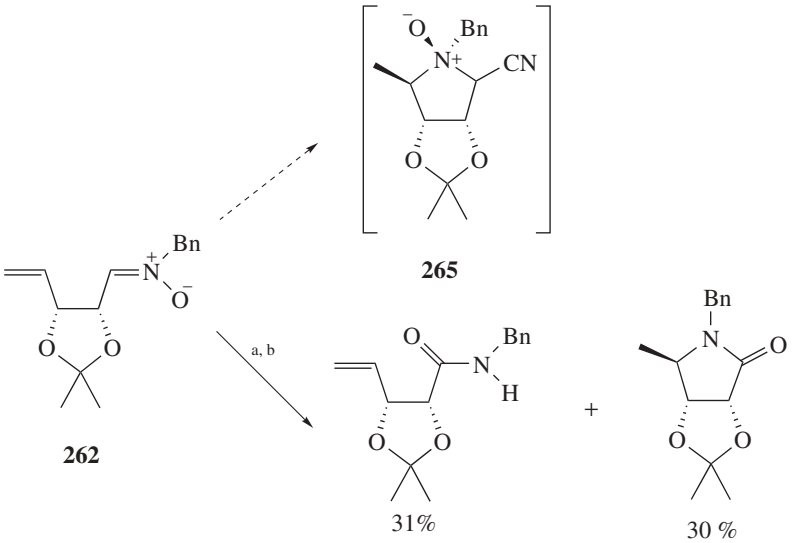


258 **260** **259** **261**

Scheme 2.95

(**261**) (Scheme 2.95). Usually these reactions afford dimerization products. Their absence is likely a consequence of the steric effect of the phenyl group.

Beckman rearrangement of nitrone (**262**) into amide (**263**) occurs in the reaction with lithium cyanide. However, this reaction gives lactam (**264**) instead of the expected 2-cyanopyrrolidine 1-oxide (**265**) (Scheme 2.96) (473).

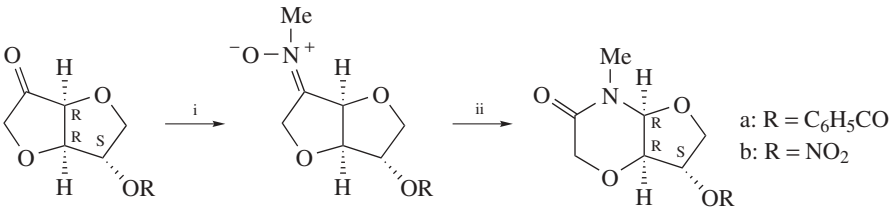


a: LiCN, CH_2Cl_2, –20°C, 5 h
b: $CHCl_3$, room temp., 5 d

263 **264**

Scheme 2.96

Rearrangement of α-aryl-*N*-(β-phenylethyl) nitrones into the corresponding amides under mild conditions and with good yields appears to proceed in the presence of chlorinating agents, such as SO_2Cl_2-Et_3N and NCS-NaOMe (474). Rearrangement of benz-2-azepine *N*-oxide into benz-2-azepine-1-one in boiling acetic anhydride affords quantitative yields (475, 476). Stereoisomeric bicyclic δ-lactams (**267 a,b**) were obtained on Beckman rearrangement of the corresponding *exo*-cyclic nitrones (**266 a,b**) (Scheme 2.97) (477).



i: MeNHOH·HCl, NaOAc, EtOH (78% for a and 81% for b);
ii: TsCl, Py, H_2O, 0° C, (52% for a and 63% for b).

266a, b **267a, b**

Scheme 2.97

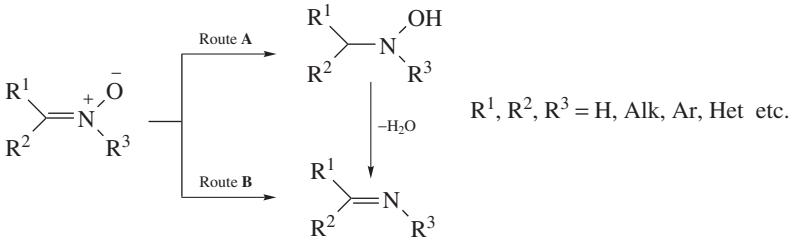
2.6.2. Reduction of Nitrones

Nitrones can be reduced to hydroxylamines (route A), or deoxygenated to the corresponding imines (route B) (Scheme 2.98).

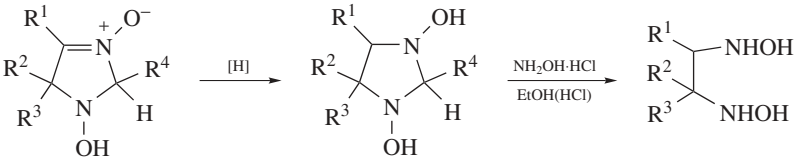
Reduction of nitrone groups to hydroxylamines occurs readily with sodium borohydride (201). In particular, the action of $NaBH_4$ on 1-hydroxy-3-imidazoline-3-oxides (**268**) leads to 1,3-dihydroxyimidazolidines (**269**), which on subsequent treatment with hydroxylamine hydrochloride afford 1,2-bishydroxylamines (**270**) (Scheme 2.99) (478).

Similarly, nitrones have been reduced to pyrrolines (479).

Asymmetric hydrogenation of nitrones in an iridium catalyst system, prepared from $[IrCl(cod)]_2$, (S)-BINAP, $NBu^n_4\ BH_4$, gives with high enantioselectivity the corresponding *N*-hydroxylamines which are important biologically active compounds and precursors of amines (480). Further reduction of hydroxylamines to secondary amines or imines can be realized upon treatment with Fe/AcOH (479), or anhydrous titanium trichloride in tetrahydrofuran (THF) at room temperature (481).



Scheme 2.98



268a–g **269a–g** **270a–f**

a: R^1 = Ph, $R^2 = R^3 = R^4$ = Me
b: $R^1 = R^2 = R^3$ = Me, R^4 = Ph
c: R^1 = Et, $R^2 = R^3$ = Me, R^4 = Ph
d: $R^1 + R^2 = (CH_2)_4$, R^3 = Me, R^4 = H
e: $R^1 + R^2 = (CH_2)_4$, $R^3 = R^4$ = H
f: $R^1 + R^2 = (CH_2)_5$, $R^3 = R^4$ = H
g: R^1 = Ph, $R^2 = R^3$ = Me, R^4 = H

Scheme 2.99

Enantioselective hydroxylation of the double bond in C=N nitrones with diphenylsilane, using Ru_2Cl_4-[(S)-(−)-*p*-tolbinap]$_2$(NEt_3) [p-tolbinap = 2, 2'-bis(di-*p*-tolylphosphino)-1,1'-binaphthyl] as a catalyst at 0°C, gives the corresponding optically active *N,N*-disubstituted hydroxylamines (482).

Deoxygenation of nitrones seems to be a useful transformation in organic synthesis. It can be carried out in many ways, for example, with low valency titanium (483), phosphorus- (484), sulfur- (485), and tellurium-derivatives (486), tin tributyl hydride (487) and Pd/C (488). Many of the methods are limited by side reactions, lack of chemoselectivity, low yields, or tedious procedures. Deoxygenation of nitrones with triphenylphosphine, catalyzed by dichlorodioxomolybdenum (VI), is achieved chemoselectively and under mild conditions (489). The use of benzyltriethylammonium tetrathiomolybdate ($PhCH_2NEt_3$)MoS_4 in CH_3CN at 25°C affords the corresponding imines in high yields (490). Deoxygenation of nitrones with $Mo(CO)_6$ proceeds under mild conditions and with good yields (491).

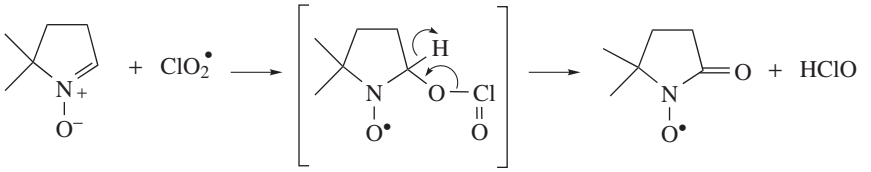
Deoxygenation of nitrones occurs in photocatalyzed reduction with TiO_2 in acetonitrile, in a nitrogen atmosphere.[20] Selective nitrone deoxygenation is also achieved with Zn-$AlCl_3.6H_2O$ in THF (492), $Zn(OTf)_2$, and $Cu(OTf)_2$. (493) On treatment with trimethylsilyl lithium, nitrones are converted into the corresponding imines in high yields (494). A simple way to deoxygenate nitrones is to treat their acetonitrile solutions with $InCl_3$ (495). Upon treatment with indium in alcohol, in the presence of ammonium chloride, and depending on the reaction conditions, one observes either formation of the corresponding imines or reductive coupling with formation of vicinal diamines (496). An efficient and easy method of nitrone deoxygenation seems to be treatment with $RuCl_3xH_2O$ (497). For nitrone reduction, the use of a $NiCl_2xH_2O$-Li-arene catalytic reduction system has been reported. Depending on reaction conditions it leads to de-oxygenation products in high yield or secondary amines (498, 499). AlI_3/MeCN (500) and $AlCl_3$ x $6H_2O$/KI/CH_3CN/H_2O (501) are effective deoxygenation systems. Deoxygenation of nitrones proceeds mildly and selectively in a $(CF_3CO)_2O$/NaI system (502).

Except for special cases, neither hydrazine, nor amines reduce the nitrone group. Even on reducing α-nitroaryl nitrones with hydrazine hydrate and Ni Raney, only the nitro group is reduced (503). Deoxygenation of the nitrone group with hydrazine is observed in paramagnetic 3-imidazoline-3-oxide derivatives (504). Reduction of the nitrone group with hydrazine groups and with secondary and tertiary amino groups takes place only intramolecularly in α-hydrazinoalkyl and α-aminoalkyl nitrones (see Section 2.6.6.2).

2-Phenyl-3-phenylimino-3-*H*-indole *N*-oxide (an indolic nitrone) reacts with triethyl and triisopropyl phosphite in refluxing xylene and *tert*-butylbenzene to give 2-phenylimino-3*H*-indole (indolenine) in very good yield (505).

2.6.3. Nitrone Oxidation

2.6.3.1. Nitrone Oxidation in Non-Nucleophilic Medium Treatment of nitrones with strong oxidants such as PbO_2, MnO_2 (506) and ClO_2 (507), in



Scheme 2.100

the absence of nucleophiles leads to the corresponding hydroxamic acids. During oxidation, the formation of acyl nitroxyl radicals was observed (Scheme 2.100).

The use of lead tetraacetate as an oxidant gives O-acetyl derivatives of the corresponding hydroxamic acids (475, 476, 506).

2.6.3.2. Oxidative Alkoxylation of Nitrones to α-Alkoxy Nitrones and α-Alkoxy Substituted Nitroxyl Radicals The first direct experimental evidence of the possibility to carry out radical cation nucleophilic addition to nitrones with the formation of nitroxyl radicals has been cited in Section 2.4. Further, such a reaction route was referred to as "inverted spin trapping"; this route is an alternative to a "conventional spin trapping" (508–512). Realization of either mechanism depends on the reaction conditions; namely, on the strength of both nucleophile and oxidant. The use of strong oxidants in weak nucleophilic media tends to favour the radical cation mechanism.

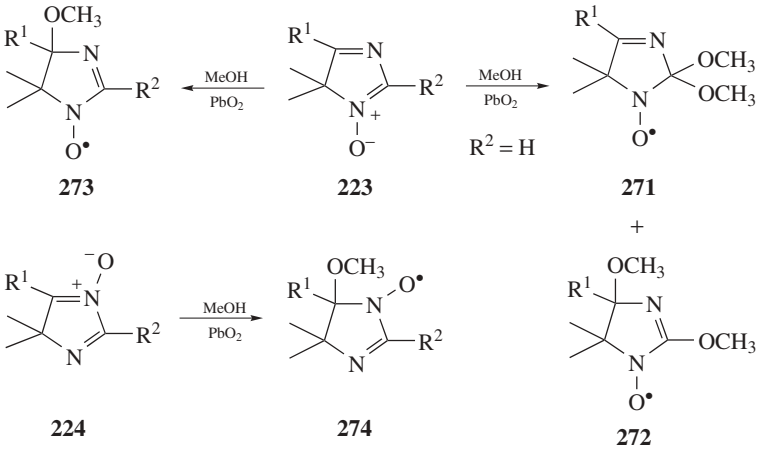
For the first time, the possibility of carrying out preparative inverted spin trapping was demonstrated by the oxidative methoxylation of heterocyclic nitrones derived from 4*H*-imidazole-1,3-dioxide (**219**) (Scheme 2.79) (513, 514).

Owing to the existence of two centers for nucleophilic attack (at C_2 and C_5) in radical cations (**220**) obtained from the oxidation of 4-*H*-imidazole-1,3-dioxides (**219**), the formation of two products of methoxy group addition was observed, namely NNR (**221**) and NR of 3-imidazoline-3-oxide (**222**). The ratio of the products depends on the electronic nature of substitutes R^1 and R^2. Both, the donor character of R^1 and acceptor character of R^2 facilitate the formation of nitroxyl radicals (**222**) with the yield of (**221**) increasing with the inverted effect of the substituents. As was mentioned in Section 2.4, the results of preparative electrochemical oxidative methoxylation of 4*H*-imidazole-1,3-dioxides are similar to the results of chemical oxidation.

Oxidation of mono-*N*-oxides 4*H*-imidazole (**223**) and (**224**) with PbO_2 in methanol leads to the formation of stable α,α-dimethoxy-substituted nitroxyl radicals (**271**) and methoxy substituted imino nitroxyl radicals (INR) (**272**)–(**274**) (Scheme 2.101) (514).

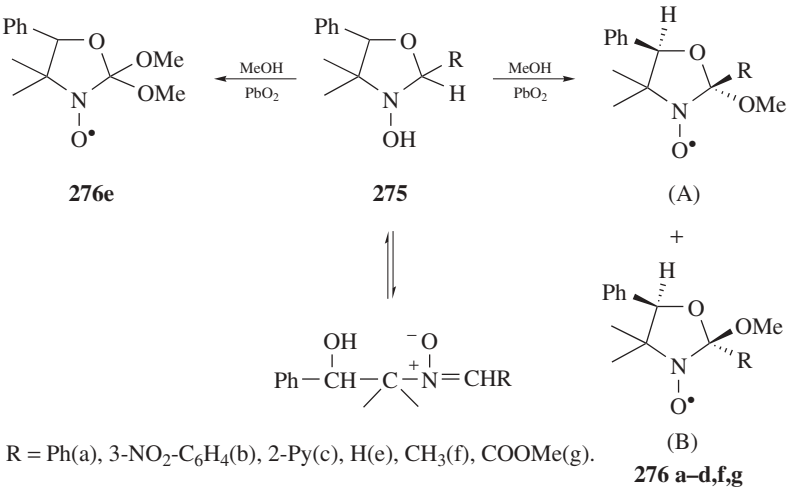
Oxidation of oxazolidine derivatives (**275**) gives isomeric pairs (A) and (B) of α-methoxy-substituted oxazolidine nitroxyl radicals (**276a–d, f, g**) and α,α-dimethoxy-substituted nitroxyl radical (**276e**) (Scheme 2.102) (515).

In addition to the oxidative alkoxylation of 4*H*-imidazole and oxazolidine derivatives, the reaction was also used with other cyclic aldo-nitrones such as DMPO, derivatives of 3-imidazoline-3-oxide (**228–232**) (506), and derivatives



273 **223** **271** + **224** **274** **272**

Scheme 2.101

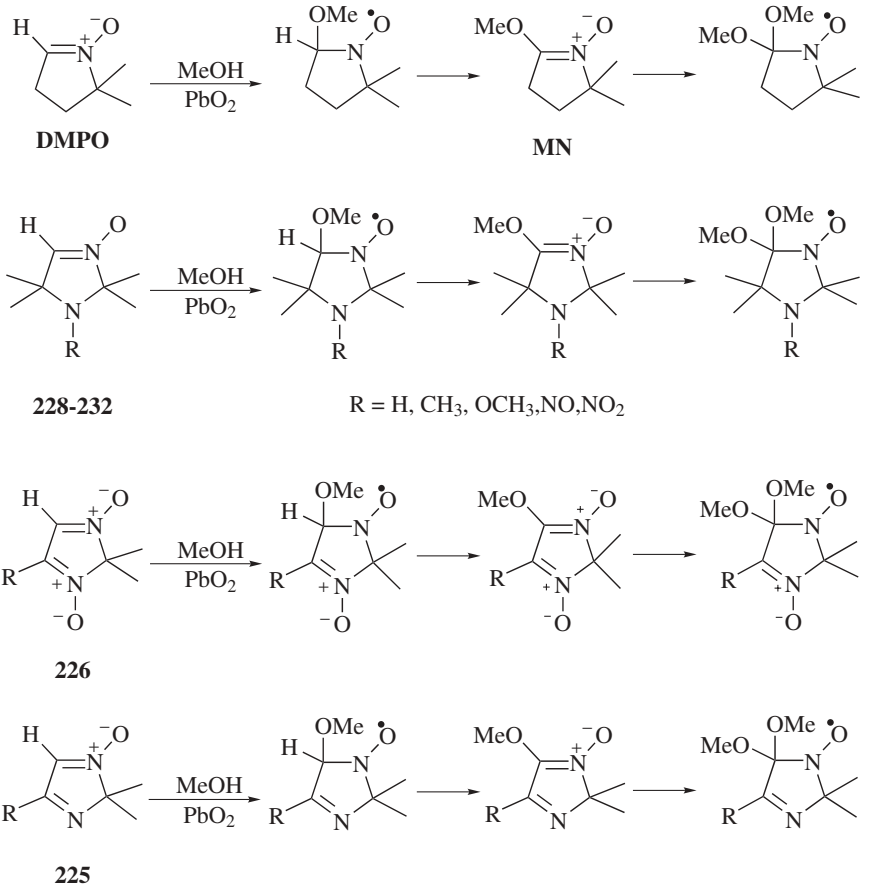


276e **275** (A) + (B)

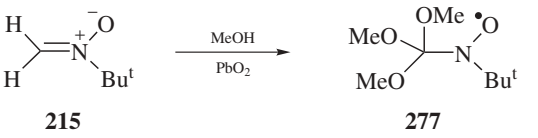
276 a–d,f,g

Scheme 2.102

of 2*H*-imidazole (**225**) (324) and (**226**) (516). In these reactions, the formation of stable nitroxyl radicals containing two alkoxy groups at the α-carbon atom of the nitroxyl group was observed. In some cases, α-methoxy nitrone intermediates have also been detected (Scheme 2.103) (506).



Scheme 2.103

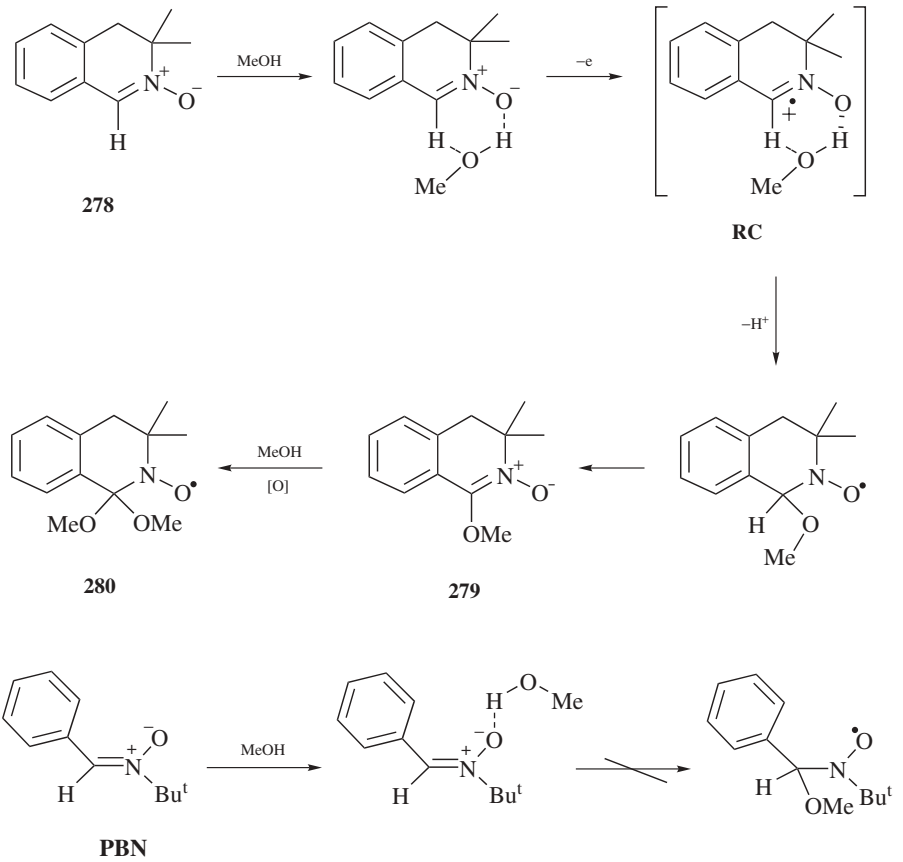


Scheme 2.104

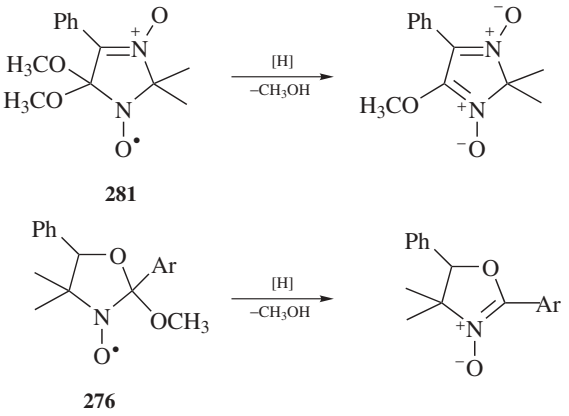
It is relevant to note that only cyclic aldo-nitrones tend to react in oxidative alkoxylations to give α,α-dialkoxy-substituted nitroxyl radicals. However, the only exception is methylene nitrone (**215**), which on oxidative methoxylation gives the α,α,α-trimethoxy-substituted nitroxyl radical (**277**). This is due to the proton in methylene nitrone (**215**), which, as in the case of cyclic nitrones, exists in the *cis*-position to the *N*-oxide oxygen (Scheme 2.104) (517).

Moreover, one should mention that in spite of similar electronic structures, PBN and the isoquinoline nitrone (**278**) react in a different way. Under no circumstances does PBN give an oxidative methoxylation product, whereas nitrone (**278**) reacts readily to form α,α-dialkoxy-substituted nitroxyl radical (**280**) (517). Perhaps this difference might be due to the ability to form a complex with methanol in aldo-nitrones with *E*-configuration. This seems favorable for a fast nucleophilic addition of methanol to the radical cation (**RC**), formed in the oxidation step. The α-methoxy nitrone (**279**), obtained in the initial methoxylation, has a lower oxidation potential than the initial aldo-nitrone (see Section 2.4). Its oxidation to the radical cation and subsequent reaction with methanol results in the formation of the α,α-dimethoxy-substituted nitroxyl radical (**280**) (Scheme 2.105).

In contrast, the reaction of acid-catalyzed nucleophilic addition of alcohols to derivatives of 4*H*-imidazol-1-oxide (**219**) and (**224**) leads only to nitronyl nitroxyl (**221**) and imino nitroxyl (**274**) radicals (518).



Scheme 2.105



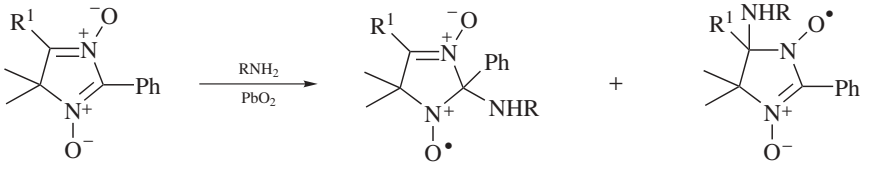
Scheme 2.106

In some cases, α-alkoxy-substituted nitroxyl radicals (**276**) and (**281**) turn out to be convenient starting compounds in the synthesis of α-alkoxynitrones. On reduction, they eliminate methanol affording α-alkoxy nitrones (Scheme 2.106). This method, leading to α-alkoxy nitrones makes it possible to generate these compounds when other methods are unsuccessful (514, 519).

2.6.3.3. Oxidative Amination of Nitrones to α-Amino-Substituted Nitroxyl Radicals Similar to the oxidative methoxylation reaction, oxidative amination of 4*H*-imidazole *N*-oxides, in amine saturated alcohol solutions, give stable nitroxyl (**282**), nitronyl nitroxyl (**283**), imino nitroxyl (**284**) and (**285**) radicals with the amino group at the α-carbon atom of the nitroxyl group (Scheme 2.107) (520, 521). The observed influence of substituents on the ratio of amination products at C_2 and C_5 atom is close to the ratio observed in the previously mentioned oxidative methoxylation reaction. It allows us to draw conclusions about the preference of the radical cation reaction route.

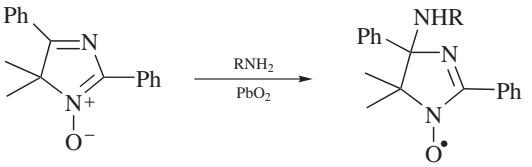
In contrast to this, it has been concluded that the formation of spin adducts on ultraviolet irradiation or mild oxidation of indole nitrones, in the presence of a *N*-heteroaromatic base, proceeds according to the Forrester-Hepburn mechanism (522).

2.6.3.4. Oxidative Fluorination of Nitrones to α-Fluorosubstituted Nitroxyl Radicals Formation of nitroxyl radicals by the radical cation route was observed in reactions of various nitrones with xenon difluoride in dry methylene chloride (520, 523). In this reaction, more than 40 nitrones, including 4*H*-imidazole *N,N*-dioxides (**219**), 4*H*-imidazole *N*-oxides (**223**) and (**224**), 2*H*-imidazole *N*-oxides (**225**), 2*H*-imidazole *N,N*-dioxides (**226**), 3,3,5,5-tetramethylpyrroline *N*-oxide (TMPO), derivatives of 3-imidazoline-3-oxides (**231**) and (**232**), have been examined. ESR spectra of nitroxyl radicals containing one or two fluorine atoms at α-C have been registered (Scheme 2.108) (523). In the case of



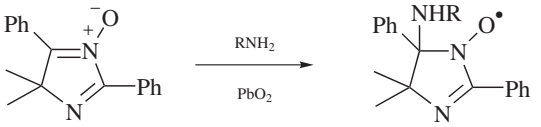
219 **282** **283**

R = H *or* CH_3; R^1 = Ph, 2-pyridyl, 2-thienyl, 2-furyl



223 **284**

R = H *or* CH_3



224 **285**

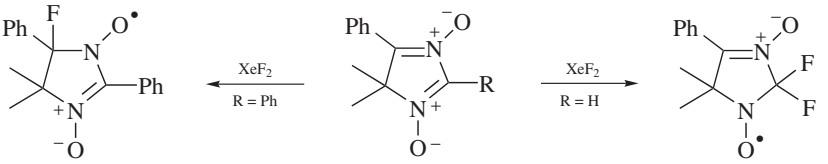
Scheme 2.107

the 4-phenyl-3-imidazoline-3-oxide derivative (**231 d**, $R = C_6H_5$) the first stable monofluoro substituted nitroxyl radical has been isolated. Nucleophilic substitution of fluorine anion by methoxy and amino groups has made it possible to prepare new functional derivatives of stable nitroxyl radicals (520).

Under similar reaction, the action of XeF_2 on PBN and DMPO led to similar spin adducts, proving the radical cation mechanism (524). Unlike this reaction, the formation of fluoro-containing spin adducts when using a weaker oxidant such as *N*-fluorodibenzsulfonamide [$(PhSO_2)_2$N-F] is believed to involve the Forrester-Hepburn mechanism (524).

2.6.4. Radical Reactions of Nitrones

The general trend of nitrones toward radical reactions can be explained by a variety of reasons: (a) their readiness to be transformed into stable nitroxyl radicals as a result of the so-called spin trapping; (b) one-electron oxidation into radical cations; and (c) one-electron reduction into radical anions (Scheme 2.77, routes **C,D** and **E**). Depending on the reaction conditions either route has been



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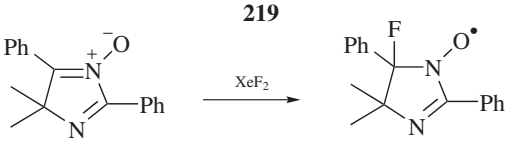

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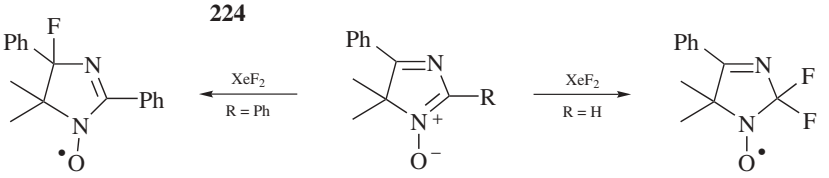

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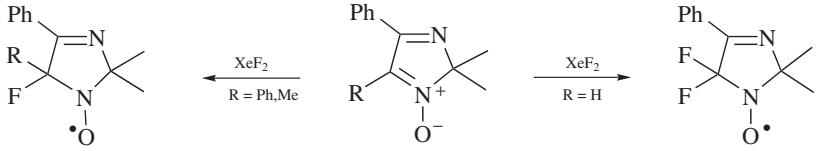

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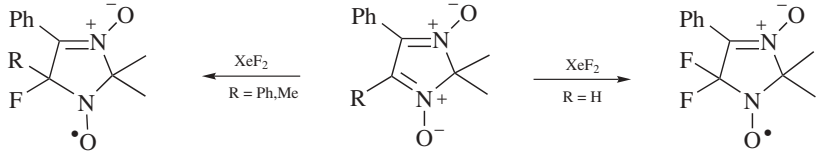
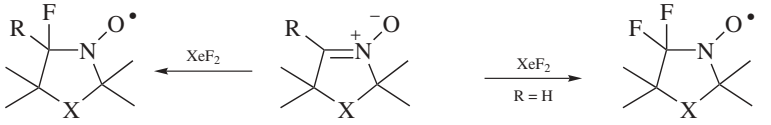


226



231, 232, TMPO

X = NNO (**231**), NNO_2 (**232**), CH_2 (**TMPO**)

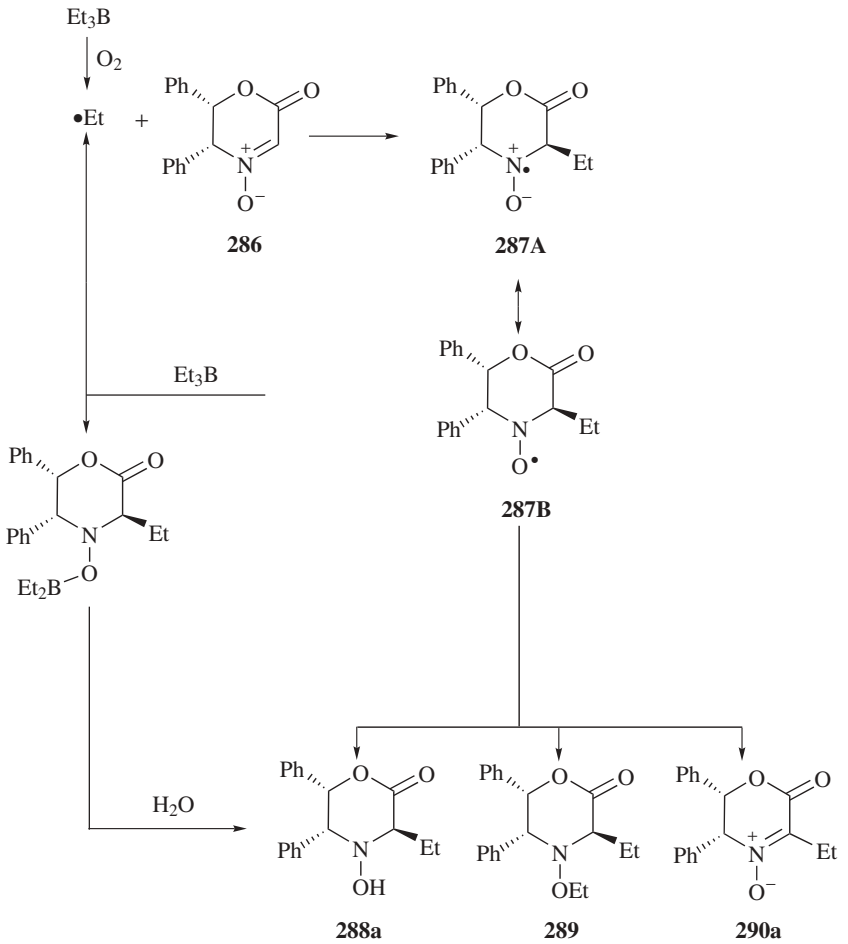
R = H, D, CH_3, CD_3, C_2H_5, CH_2Br, $CHBr_2$,
$CHCl_2$, $CHBrCH_3$, $CHClCH_3$, $CH(OCH_3)_2$, C_6H_5,
$CONH_2$, CHO, CH = NC_4H_9-*t*, $COOCH_3$, CN, OCH_3, SCH_3

Scheme 2.108

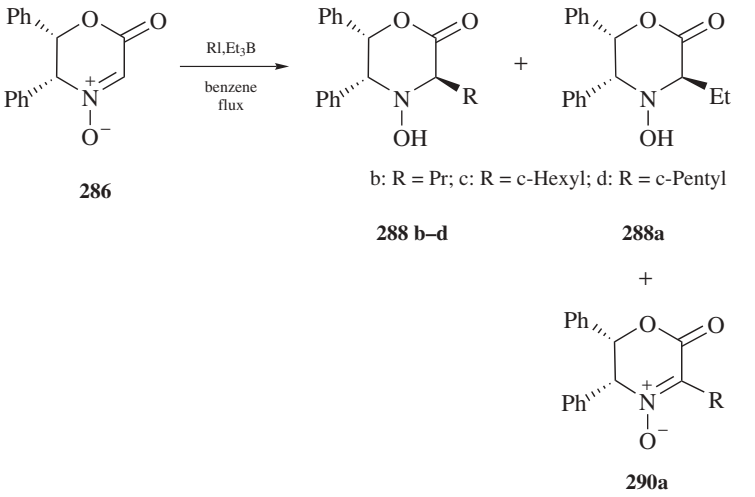
observed. "Spin trapping" has received wide application in the study of radical processes using spin traps (3). However, in some cases nitrone performance in radical reactions is of synthetic value.

2.6.4.1. Addition of C-Radicals to Nitrones Recently (525), the addition of alkyl radicals to chiral nitrones as a new method of asymmetrical synthesis of α-amino acids has been described. Addition of ethyl radicals to glycosyl nitrone (**286**) using Et_3B as a source of ethyl radicals appears to proceed with a high stereo-control rate.

Nitrone (**286**) reacts readily with nucleophilic ethyl radicals to give the expected ethyl product (**288**) in 50% yield as the only diastereomer, as well as a 32% yield of the *C,O*-diethyl product (**289**) and trace quantities of ethyl



Scheme 2.109



286

b: R = Pr; c: R = c-Hexyl; d: R = c-Pentyl

288 b–d **288a**

290a

Scheme 2.110

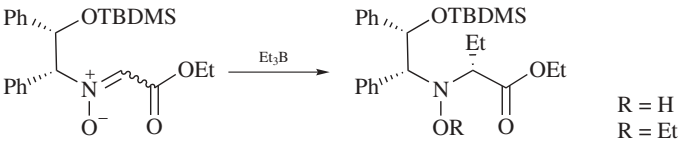
nitrone (**290a**). Nitrone (**290a**) results from a disproportionation reaction, involving the α-H, which is typical of nitroxyl radicals (**287**). Since Et_3B is not only a source of ethyl radicals in this reaction but also serves as a trap for radicals (**287**), an excess of Et_3B suppresses formation of nitrones (**290a**) (Scheme 2.109) (525).

The use of Et_3B as a radical initiator makes it possible to carry out the addition of other alkyl radicals to nitrone (**286**) using alkyl iodides. Good yields have been obtained of products (**288b–d**) when an excess of the appropriate alkyl iodide was used (Scheme 2.110). It has been established that the yield of alkyl by-products (**288a**) tends to decrease with the increase of the reaction temperature. The stereochemical features of this reaction are explained by the alkyl radical addition taking place predominantly from the less hindered *re*-face of (**286**) to avoid steric interaction with the phenyl group (525).

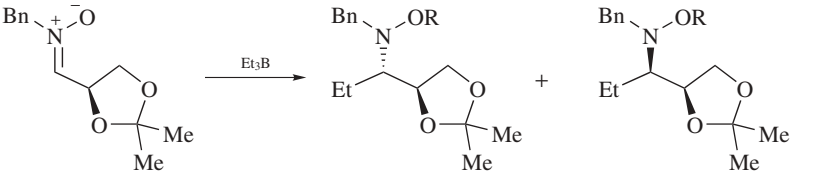
Excellent diastereoselectivity of alkyl radical addition was also observed in a number of other nitrones (**291–293**) (Scheme 2.111) (526).

2.6.4.2. Reductive Cross-Coupling of Nitrones Recently, reductive coupling of nitrones with various cyclic and acyclic ketones has been carried out electrochemically with a tin electrode in 2-propanol (527–529). The reaction mechanism is supposed to include the initial formation of a ketyl radical anion (**294**), resulting from a single electron transfer (SET) process, with its successive addition to the C=N nitrone bond (Scheme 2.112) (Table 2.9).

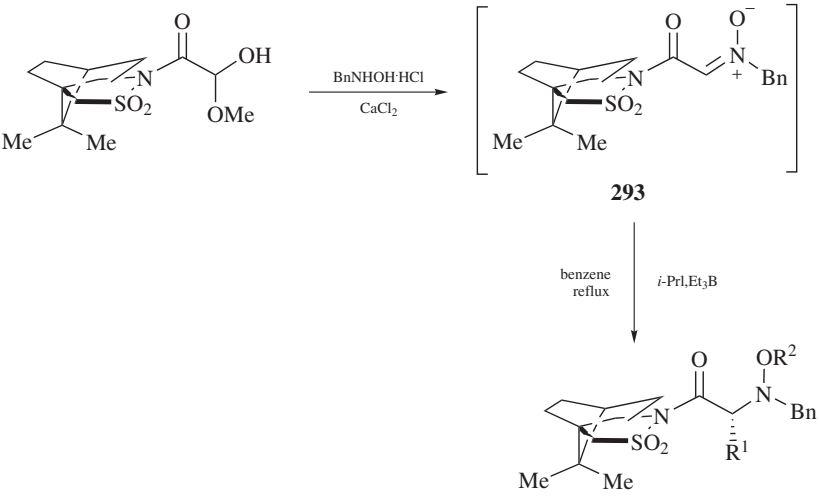
Cross-coupling reactions of nitrones with aldehydes and ketones make it possible to synthesize vicinal amino alcohols, which are common in natural products. These transformations have been performed by a new method of reduction



291



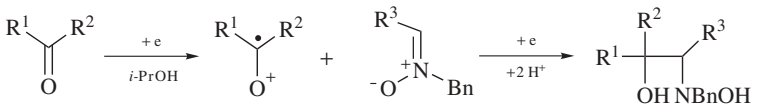
292a



293

a: $R^1 = {}^{i}Pr$, $R^2 = H$
b: $R^1 = R^2 = {}^{i}Pr$
c: $R^1 = Et$, $R^2 = H$

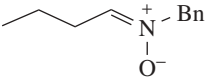
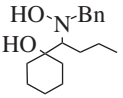
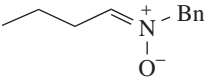
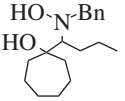
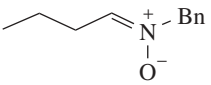
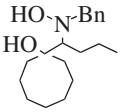
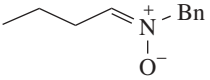
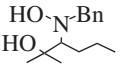
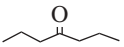
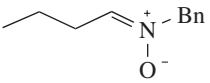
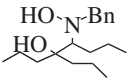
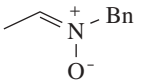
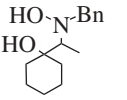
Scheme 2.111

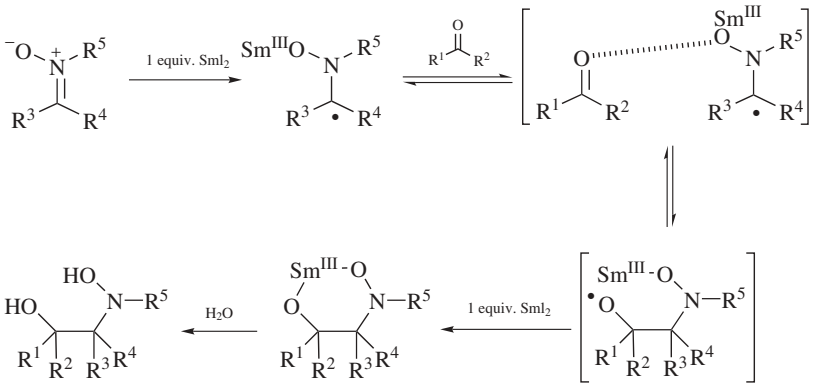


294

Scheme 2.112

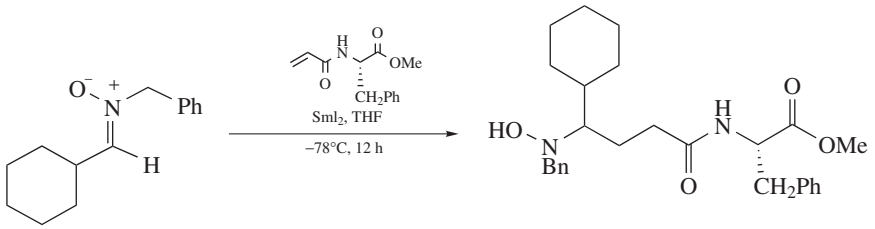
Table 2.9 Electroreductive coupling of ketones with nitrones

Ketone	Nitrone	Product	% Yield
			69
			56
			42
			
			49
			56



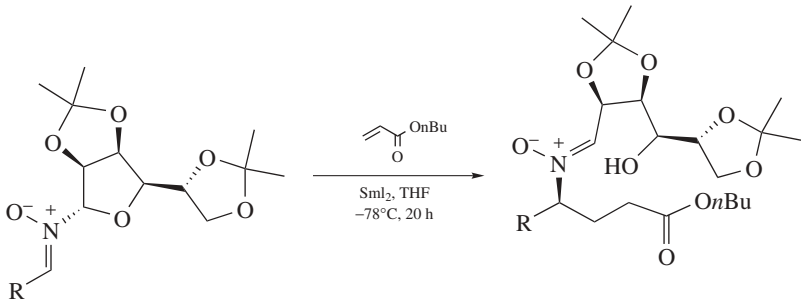
Scheme 2.113

cross-coupling, using SmI_2. This method enables the preparation of highly substituted asymmetrical vicinal *N*-hydroxylamino- and amino alcohols. The reaction mechanism includes a chemoselective SET step with SmI_2 at the nitrone group with the subsequent addition of the formed intermediate to the aldehyde or ketone (Scheme 2.113) (530).



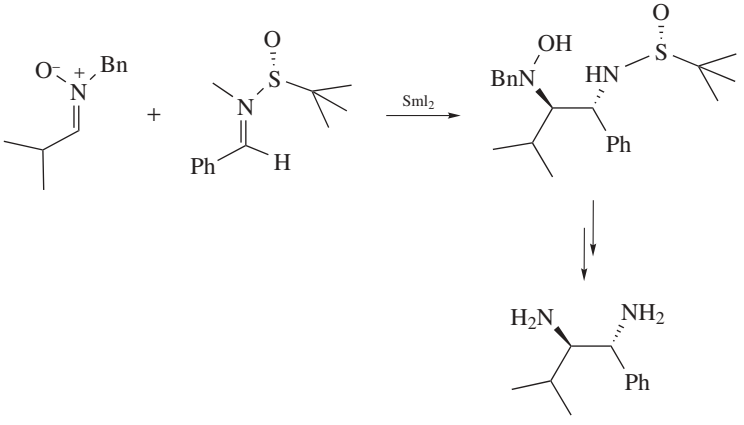
(53%, d.r. = 1.7:1)

Scheme 2.114



R = c-C_6H_{11}, ^{i}Pr, c-C_5H_9, 2-Et-Bn-, ^{i}Bn, $Ph(CH_2)_2$

Scheme 2.115



>99% ee

Scheme 2.116

This reaction is very important for the synthesis of natural products and for the design of diversely substituted ligands. The use of SmI_2 in radical additions of nitrones to α,β-unsaturated amides and esters, constitutes a convenient synthesis of various functionalized γ-amino acids with high enantiomeric excess (Schemes 2.114 and 2.115) (531–533).

Reductive coupling of the corresponding nitrones with alkyl acrylate is the key step in the short synthetic route of the selective and irreversible GABA inhibitor of amino transferase (S)-vigabatine (534) and of polyhydroxy pyrrolizidine alkaloid (+)-hyacinthacine A2 (535).

Using *N-tert*-butanesulfinilimines instead of carbonyl derivatives, constitutes an efficient synthetic route to optically pure asymmetric vicinal diamines that are widely used in asymmetric synthesis (Scheme 2.116) (536).

2.6.5. Electrophilic Reactions of Nitrones

2.6.5.1. Reactions of Electrophilic Substitution of α-Alkyl Nitrones

2.6.5.1.1. Reactions of Halogenation and Nitrosation Nitrones with protons in the α-alkyl group can occur in tautomeric nitrone–hydroxylamine equilibrium (Scheme 2.117) similar to keto-enol and imine-enamine tautomerisms.

Generation of the enhydroxyamine form takes place upon treatment with both bases and acids; the reaction with α-alkyl nitrones in D_2O shows a quick deutero exchange (537).

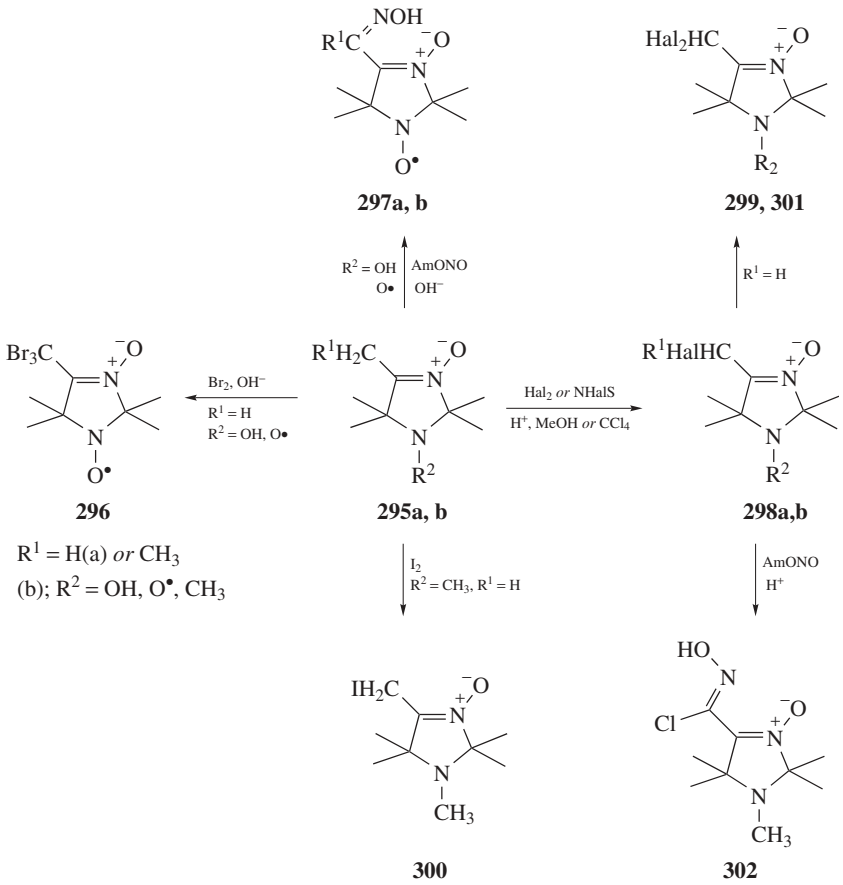
The reaction of nitrones of the 3-imidazoline series (**295**) with bromine and amyl nitrite, in the presence of base, gives α-tribromomethyl-(**296**) and α-hydroxyaminomethyl derivatives (**297**) (538). Bromination of nitrones (**295**) with *N*-bromosuccinimide (NBS) in CCl_4 or bromine in methanol leads to the formation of α-bromoalkyl (**298 a,b**, Hal = Br) and α-dibromomethyl (**299**) nitrones (539–541). The reaction with iodine in methanol gives the mono iodo derivative (**300**) (541). The reaction with *N*-chlorosuccinimide (NCS) in CCl_4 leads to α-chloroethyl nitrones (**298b**, Hal = Cl) and α,α-dichloromethyl nitrones (**301**) (Scheme 2.118) (225).

Nitrosation in acid medium of α-bromomethyl nitrone (**298a**) affords the chloro anhydride of hydroxymic acid (**302**), which is a precursor of nitrile *N*-oxide (541).

2.6.5.1.2. Reactions with Aldehydes and Ketones Crotone-type products have been obtained in reactions of nitrones (**295a**, $R^2 = OH$) with *p*-ethynyl-, *p*-bromo-, and *p*-iodobenzaldehydes (Scheme 2.119) (542, 543).

R = Alk, Ar, Het

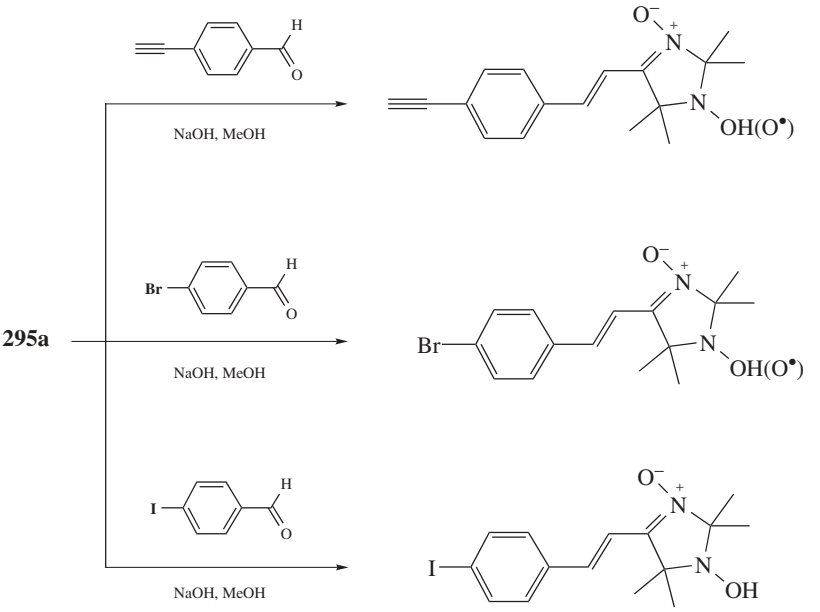
Scheme 2.117



Scheme 2.118

Aldol-type reactions of nitrones (**303**) occur with electron-deficient ketones, such as α-keto esters, α,β-diketones, and trifluoromethyl ketones. These reactions are catalyzed by secondary amines. The use of chiral cyclic amines **A1–A7** leads to α-(2-hydroxyalkyl)nitrones (**304**) in moderate yields and rather high optical purity (Scheme 2.120) (381). The mechanism of the nitrone-aldol reaction of *N*-methyl-*C*-ethyl nitrone with dimethyl ketomalonate in the absence and presence of L- proline has been studied by using density functional theory (DFT) (544).

2.6.5.1.3. Reactions with Carboxylic Acid Esters Alkyl nitrones can be metallized upon treatment with phenyl lithium in ether solution. The Li-derivatives react with carboxylic acid esters to give β-oxo nitrones (**305**)– the analogs of β-diketones and β-keto esters (545). With the help of the ^{13}C NMR method it has been found that β-oxo nitrones (**305**) exist as an equilibrium mixture



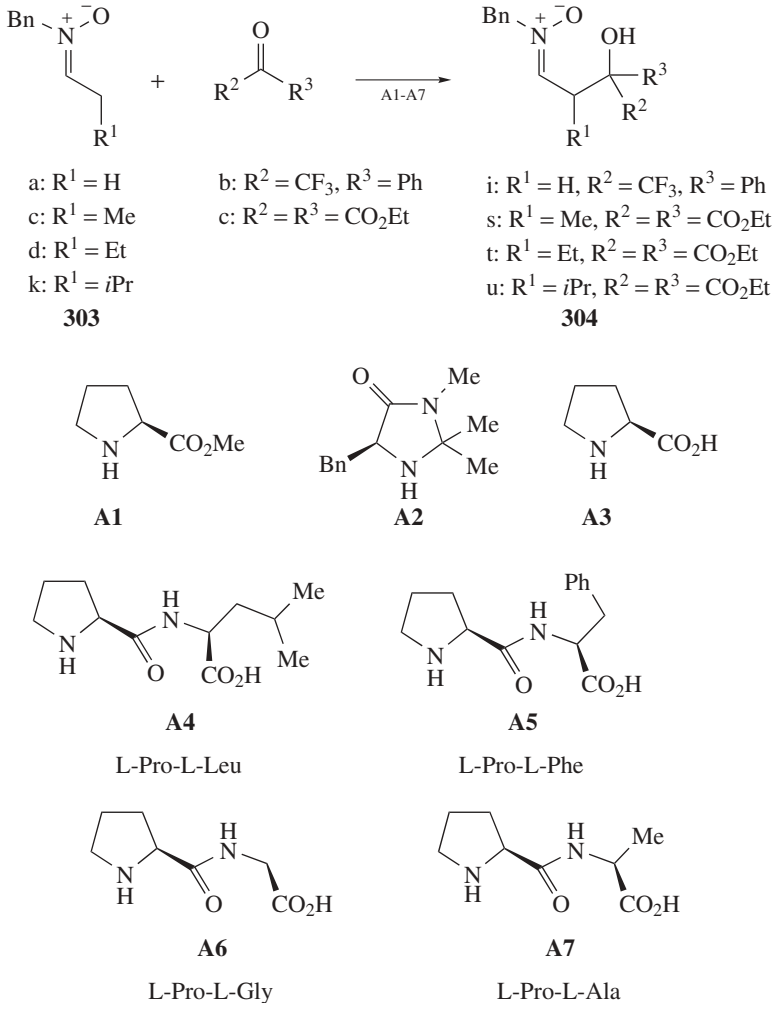
Scheme 2.119

of three tautomeric forms (**A–C**), with the prevalence of enol nitrone (**C**) and enhydroxyamino nitrone (**B**). The sulfur-containing analog in solutions of $CDCl_3$ and DMSO exists only in the enhydroxy-aminothioxo structure (**306B**) (Scheme 2.121) (546, 547).

2.6.5.2. Nitration of α-Aryl Nitrones The reactions of electrophilic substitution in α-aryl nitrones have not yet been studied in depth, and at present, the only reported reaction is the nitration of derivatives of 4-aryl-(**307a–c**) and 4-(2-hetaryl)-3-imidazoline-3-oxides (**308a,b**) (548, 549). Nitration takes place in concentrated sulphuric acid upon treatment with HNO_3. The nitrone group in 4-phenyl-3-imidazoline-3-oxides is known to be *ortho-para*-directing in the phenyl ring. The direction of α-aryl- and α-hetaryl nitrone nitrations, in more active aromatic systems, is determined by the orientation properties of the aromatic system *per se*. Thus, the *p*-tolyl group (**307b**) is nitrated in the *m*-position to the nitrone group, and the *p*-fluoroderivative (**307c**) is nitrated in the *o*-position. Hetaryl derivatives (**308a,b**) are nitrated only in the α-position of the hetero atom O or S (Scheme 2.122).

2.6.5.3. Electrophilic Substitution at α-Carbon Atom

2.6.5.3.1. Metalation of Nitrones Metalation of cyclic aldonitrones in the absence of an "external" electrophile gives dimeric compounds, the nonmetalated aldonitrone group being the electrophile. At the same time, depending on

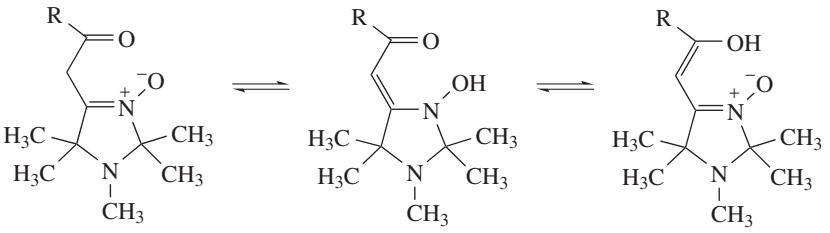


Scheme 2.120

the structure of the starting aldonitrone, the reaction can give either dimers with two conjugated nitrone groups (route **A**), or dimers with coupled nitrone and imine groups (route **B**) (Scheme 2.123) (550).

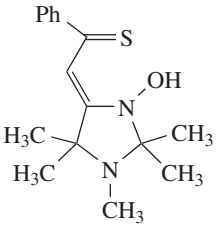
Metalated cyclic aldo-nitrones are characterized by high reactivity toward electrophilic reagents. Reactions with aldehydes and ketones afford satisfactory yields of α-hydroxymethyl substituted derivatives of nitrones (551). The reactions were also carried out with a number of aliphatic, aromatic, and hetero-aromatic aldehydes and ketones (Schemes 2.124 and 2.125).

With a terminal double bond to the nitrone group in the α-hydroxymethyl derivative (**309**), a typical 1,3-dipolar cycloaddition of nitrones gives compound



a: R = H; b: R = CH_3; c: R = C_6H_5; d: R = $(CH_3)_3C$; c: R = α–naphthyl;f: R = CF_3

305



306B

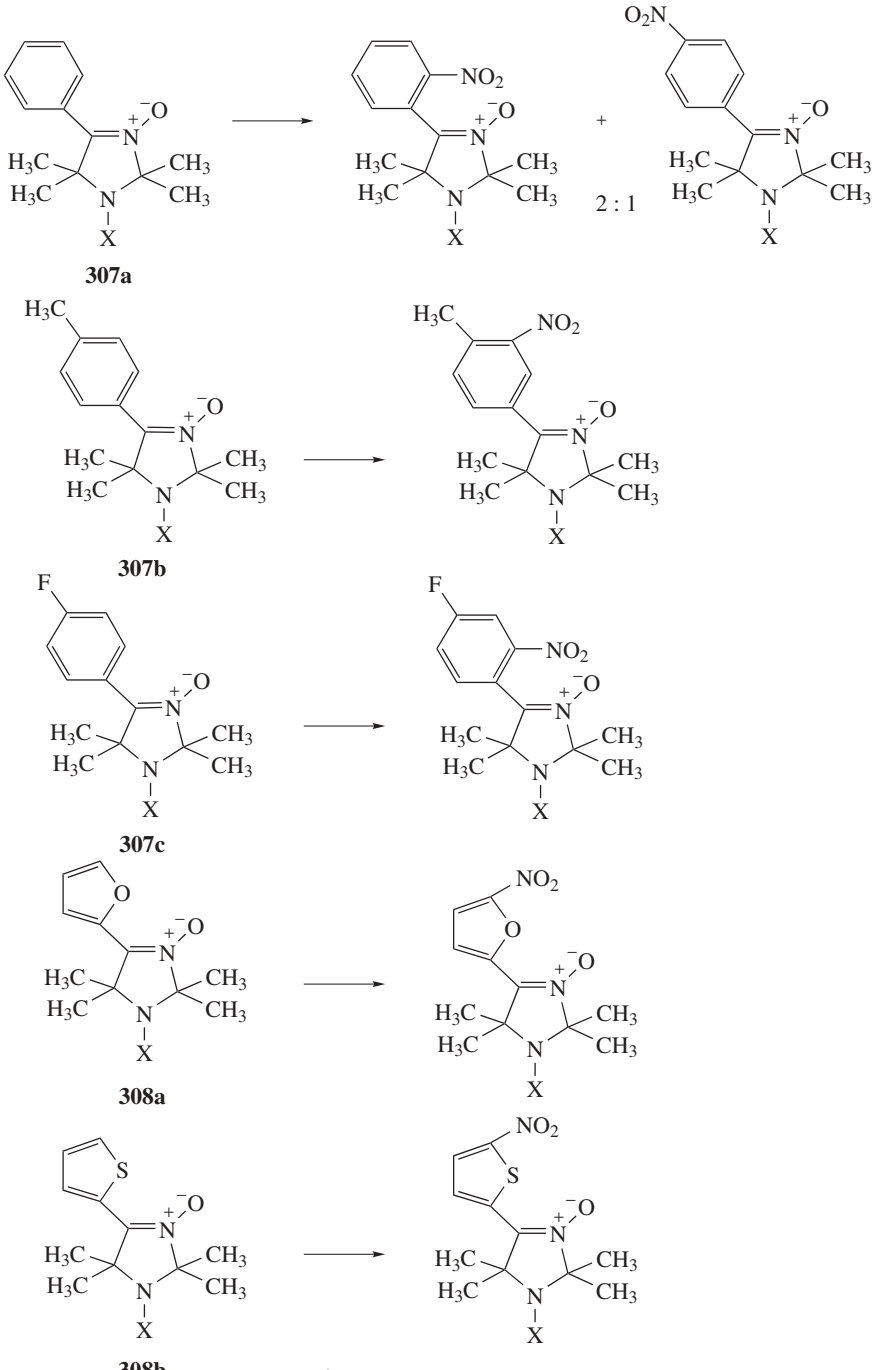
Scheme 2.121

(**310**). Its structure constitutes being a heterocyclic analog of naturally occurring tricyclic sesquiterpenes (Scheme 2.126).

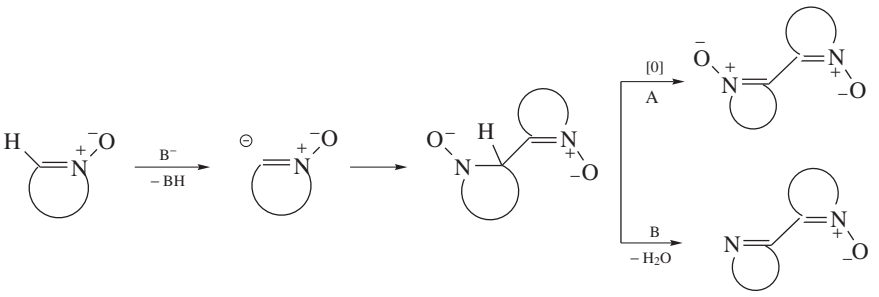
The reaction of metalated aldonitrones (**229**), performed with Me_3SiCl, $Ph_2P(O)Cl$, Ph_2PCl, PhSSPh, PhSeSePh, TsF, or TsCl generates nitrones with α-carbon-heteroatom bonds (**211a,e–h**). The reaction with TsCl gives α-chloro nitrone (**211j**), and with TsF, the corresponding sulfonyl derivative (**211i**). Using Et_3GeCl, *n*-Bu_3SnBr and $HgCl_2$ as electrophilic reagents, the synthesis of nitrones containing an α-carbon-metal bond (**211b–d**) and (**212k**) has been carried out for the first time (Scheme 2.127) (368, 552).

Thus, metalation of cyclic nitrones, followed by successive reactions with electrophilic reagents serves as a synthetic method toward α-heteroatom substituted nitrones, which are inaccessible by other methods. It is noteworthy that these reactions can take place only with cyclic nitrones with *E*-configuration of the aldonitrone group.

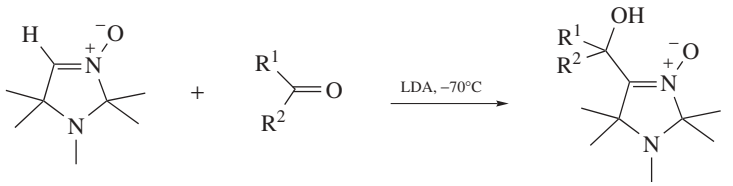
2.6.5.3.2. The Effect of Nitrone Group Configuration on H-D-Exchange of Hydrogen at α-C-Atom and Nitrone Metalation The readiness of aldonitrones toward metalation and H-D-exchange is determined by the configuration of the nitrone



Scheme 2.122

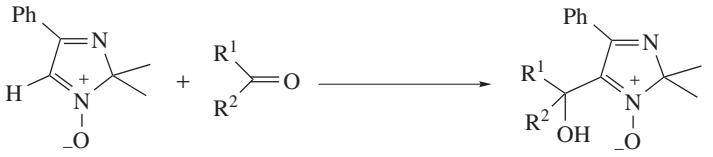


Scheme 2.123



R^1	R^2	Yield %	R^1	R^2	Yield %
H	Ph	70	CH_3	Ph	70
H	CH_3	55	CH_3	2-Thienyl	50
-$(CH_2)_5$-		47	CH_3	2-Pyridyl	65
-$(CH_2)_4$-		40	H	2-Pyrryl	55
-$(CH_2)_{11}$-		46	Ph	Ph	75
CH_3	CH_2=CH-	65	CH_3	Ferrocenyl	60
CH_3	CH_2=CH-CH_2-CH_2-	62	-CH_2-C$(CH_3)_2$-N-C$(CH_3)_2$-		65

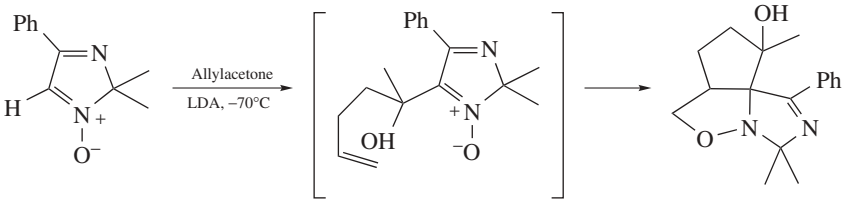
Scheme 2.124



225

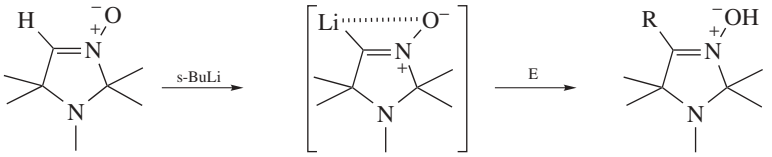
R^1	R^2	Yield %	R^1	R^2	Yield %
H	Ph	66	H	$(CH_3)_2$C=CH-$(CH_2)_2$-C(CH_3)=CH-	67
H	CH_3	58	CH_3	CH_2=CH-CH_2-CH_2	72

Scheme 2.125



225 **309** **310**

Scheme 2.126

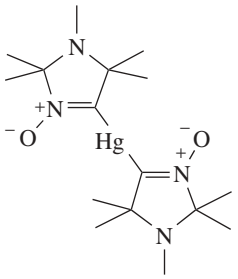


a: E = $(CH_3)_3SiCl$; R = $Si(CH_3)_3$
b: E = $(C_2H_5)_3GeCl$; R = $Ge(C_2H_5)_3$
c: E = $(n\text{-}C_4H_9)_3SnBr$; R = $Sn(n\text{-}C_4H_9)_3$
d: E = $HgCl_2$; R = HgCl
e: E = $Ph_2P(O)Cl$; R = $P(O)Ph_2$
f: E = Ph_2PCl; R = PPh_2

229

g: E = PhSSPh; R = SPh
h: E = PhSeSePh; R = SePh
i: E = TsF; R = $SO_2CH_6H_4$-(p-CH_3)
j: E =TsCl; R = Cl
k: E = $HgCl_2$; 0.5 equiv

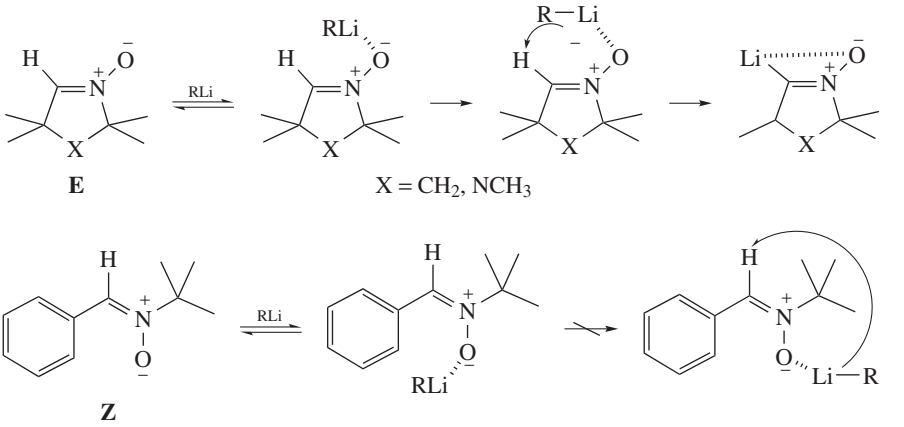
211a-j



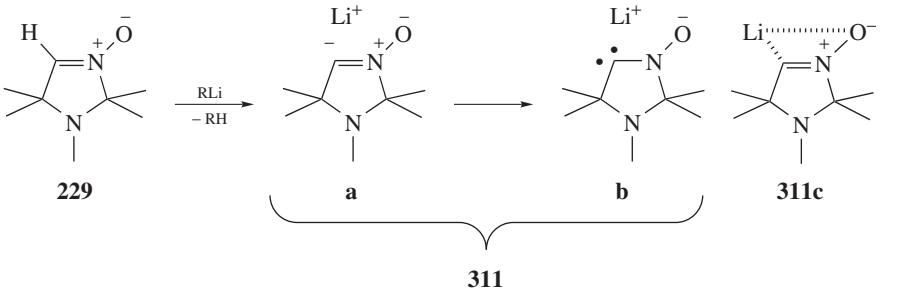
212k

Scheme 2.127

group (135). This spatial requirement is connected with the fact that deprotonation is carried out in the complex formed by the organolithium compound or alcoholate and the oxygen of the nitrone group at a stage immediately preceding the proton removal. The formation of this complex, kinetically facilitates proton removal from the *syn*-position to the *N*-oxide group. The participation of such a complex in deprotonation proves that metalation of aldonitrones is a Complex Induced Proximity Effect (CIPE)-controlled process(Scheme 2.128) (553).



Scheme 2.128

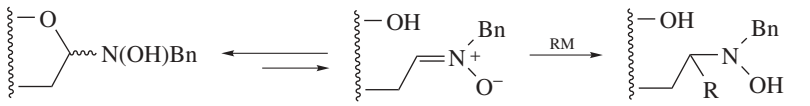


Scheme 2.129

2.6.5.3.3. ^{13}C, ^{14}N, and ^{7}Li NMR Spectra of Dipole-Stabilized Organolithium derivatives of cyclic nitrones Recently, NMR spectra of the compound resulting from metalation of the cyclic aldonitrone 1,2,2,5,5-pentamethyl-3-imidazoline-3-oxide (**229**) has been described (554). The chemical shift of the α-C atom is located in the region typical of both carbanion (**a**) and carbenoid (**b**) carbon atoms (213.14 ppm). The ^{14}N NMR spectrum of the metalated fragment and the calculated charge distribution data in a model compound show a considerable contribution of the carbenoid form (**b**) in structure (**311c**) in the ground state (Scheme 2.129).

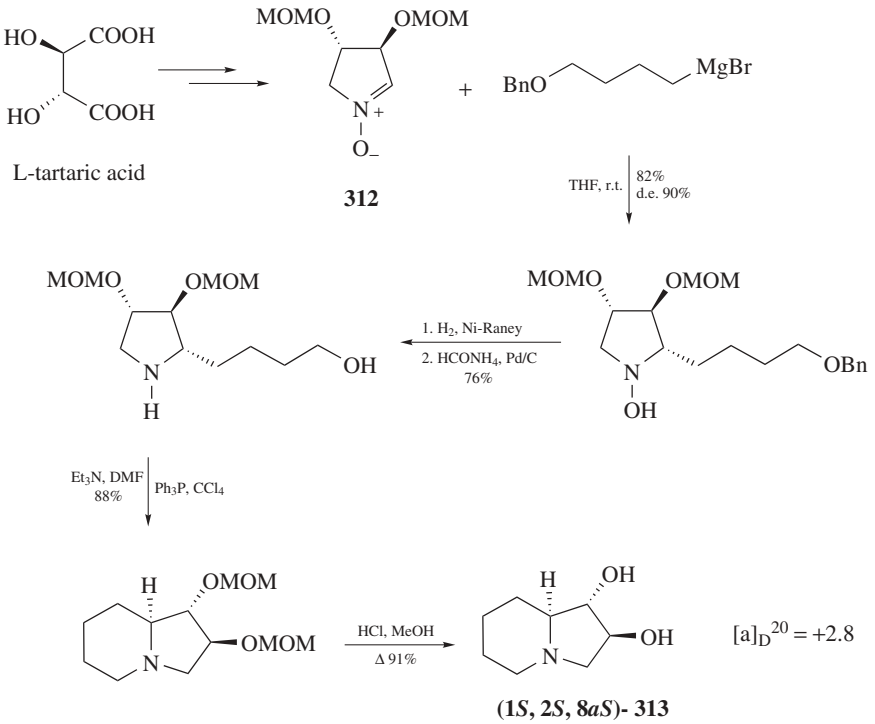
2.6.6. Nucleophilic Reactions of Nitrones

2.6.6.1. Reactions of Nucleophilic Addition The high tendency of nitrones toward nucleophilic attack at the α-carbon atom is determined by both, the electrophilic character of the nitrone group *per se* (Fig. 2.10, structure **C**) and by



Scheme 2.130

a high tendency toward complexation and protonation at the *N*-oxide group, leading to the increase of imino character, and consequently to increasing electrophilicity. Complexation can take place in the addition of organometalics and pre-complexation with Lewis acids. The protonation methods and preliminary complexation raises the possibility of employing a large number of various nucleophilic agents in nucleophilic additions to nitrones. This opens up a high synthetic potential for nitrones as building blocks in various synthetic strategies, and in the synthesis of biomolecules. The complexation potential of nitrone groups, both at the α-carbon atom and nitrogen atom, determines frequently the stereochemistry of addition reactions.



(1*S*, 2*S*, 8*aS*)- 313

Scheme 2.131

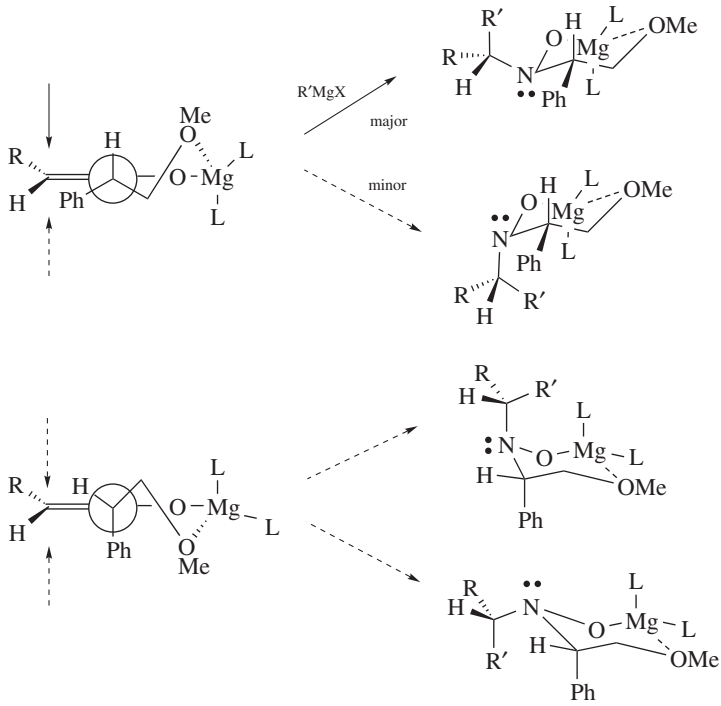
Nucleophilic addition of organometalic reagents occurs when the nitrone form is in equilibrium with the hydroxylamine form, for instance, in the case of *N*-benzyl-*N*-glycosyl hydroxylamines (Scheme 2.130) (213).

Addition of organometalic compounds to nitrones is known as an efficient method of enantioselective synthesis of primary amines that can be easily obtained by the reduction of hydroxylamines which are the products of nucleophilic addition.

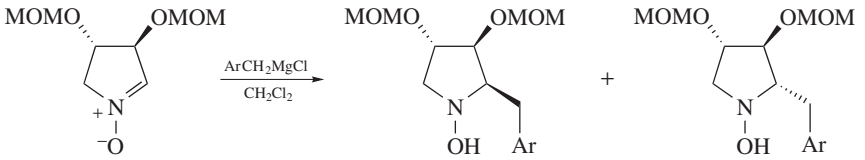
2.6.6.1.1. Addition of Alkyl and Aryl Derivatives To illustrate stereoselective syntheses in nucleophilic reactions of nitrones, the synthesis of (+)-lentiginosine (**313**) is presented in Scheme 2.131. One of the important steps is the addition of benzyloxybutylmagnesium bromide to pyrroline-*N*-oxide (**312**) (555).

Diastereoselective addition of a wide range of Grignard reagents to *C*-alkyl and *C*-aryl-*N*-[α-phenyl- or α-methyl-β-(benzyloxy)ethyl]nitrones is determined by the presence of a stereogenic *N*-substituent (136, 137). High diastereoselectivity in the addition of organometalic compounds to *N*-(β-methoxyalkyl) nitrones can be explained by a simple chelation model (Scheme 2.132) (136).

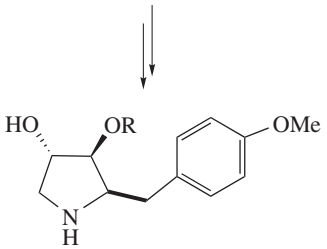
Addition of (4-methoxybenzyl)magnesium chloride to the pyrroline derivative (**312**) is a key step in the stereoselective synthesis of antibiotics (−)-anisomicine (**314**) (52) and (−)-deacetylanisomicine (**315**) (Scheme 2.133) (200).



Scheme 2.132



312 $ArCH_2^- = MeOC_6H_4CH_2^-$



314 R = COMe anisomycin
315 R = H deacetylanisomycin

Scheme 2.133

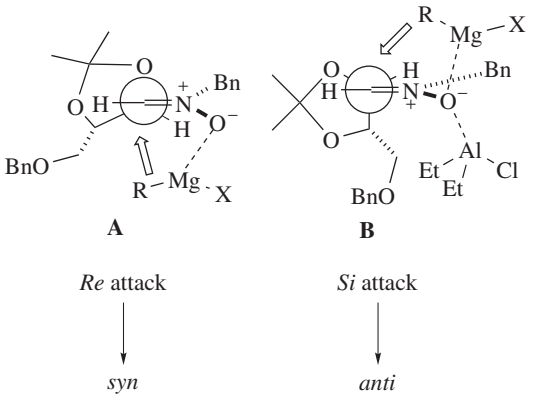
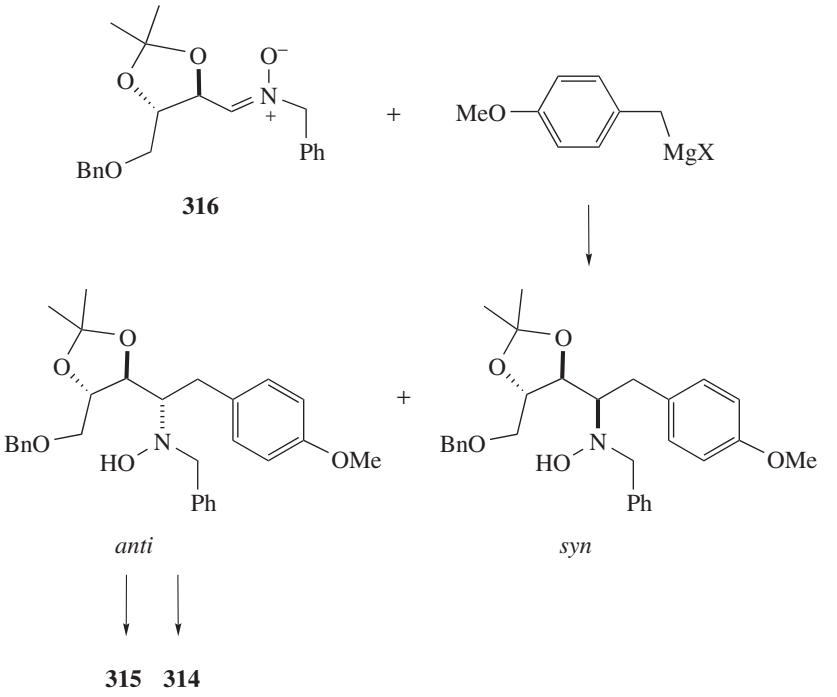


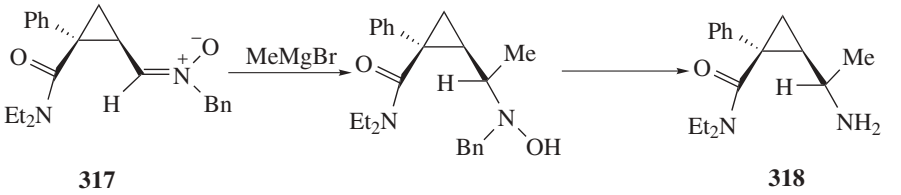
Fig. 2.21

The change in selectivity in the complexation of nitrone (**316**) with diethylaluminum chloride makes it possible to carry out a shortened synthesis of epimers at C_2 of both deacetylanisomicine (**315**) and anisomicine (**314**) (Scheme 2.134, Fig. 2.21) (200).

A seven step synthesis of (−)-codonopsinine (312) and a ten step synthesis of (−)-radicamine B (310b) also include nucleophilic addition of (4-methoxybenzyl) magnesium chloride and p-benzyloxyphenylmagnezium bromide derivatives to pyrroline-*N*-oxides as one of the key steps.



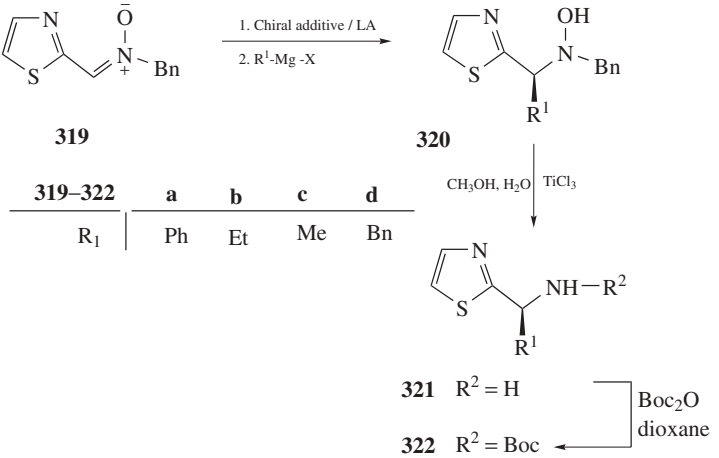
Scheme 2.134



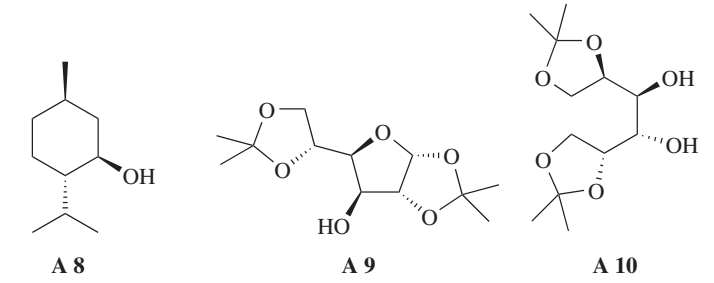
Scheme 2.135

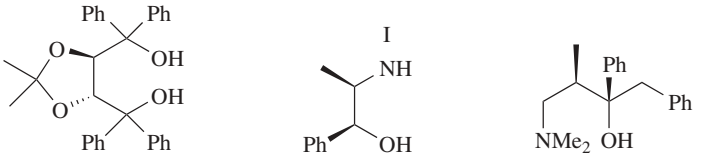
High selective addition of Grignard reagents to *C*-cyclopropyl nitrone (**317**) is the basis of the synthesis of PEDC (**318**), an efficient antagonist of NMDA (*N*-methyl-D-aspartic acid), a receptor with potential therapeutic properties for epilepsy and ischemia. X-ray and NOE analyses of (**318**) show that the bisected *s-trans* conformation appears to be more stable both in the solid state and in solution. Addition of the Grignard reagent to nitrone (**317**) proceeds stereoselectively, giving the *anti*-product with increasing selectivity in the presence of $MgBr_2$ used as an additive (Scheme 2.135) (222, 223, 556, 557).

To carry out enantioselective alkylation of 2-thiazolyl nitrone (**319**) (Scheme 2.136), chiral additives presented in Fig. 2.22 and Lewis acids ($MgBr_2$, Et_2AlCl,



Scheme 2.136





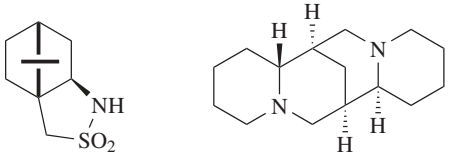
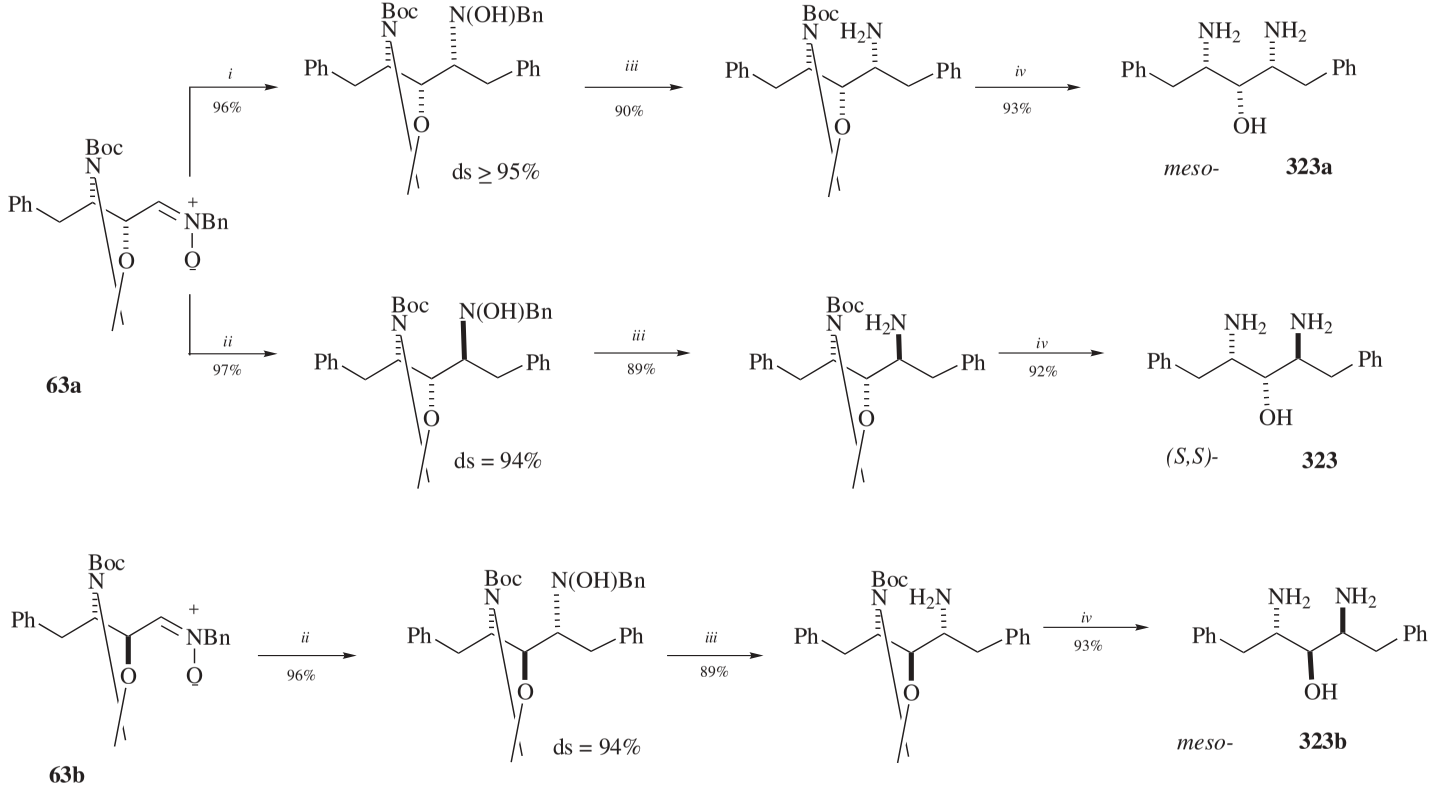
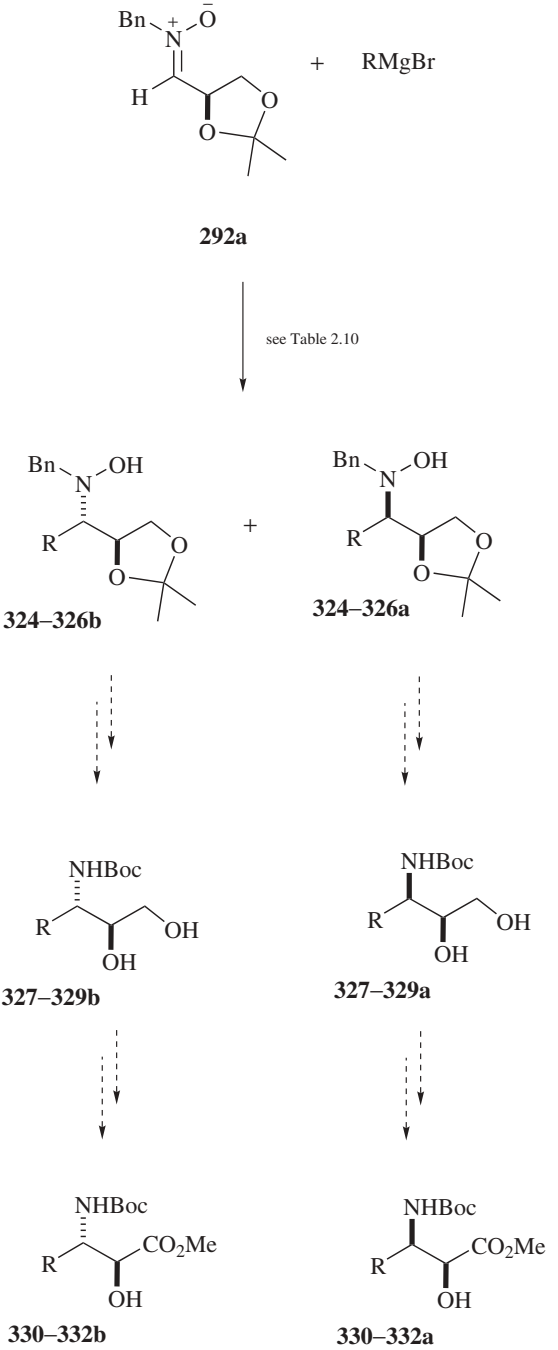


Fig. 2.22



***i*:** $PhCH_2MgCl$, Et_2O, −55°C, 3 h; ***ii*:** Et_2AlCl, Et_2O, rt, 30 min, then $PhCH_2MgCl$, −78°C, 3 h; ***iii*:** H_2 (1 atm), $Pd(OH)_2$, AcOH/EtOH (90%), 15 h; ***iv*:** HCl/dioxanc (4.8 M), 0°C then rt, 20 h.

Scheme 2.137


Bn
N
O
H
O
O
+
RMgBr
292a
see Table 2.10
Bn
N
OH
R
O
O
324–326b
+
Bn
N
OH
R
O
O
324–326a
NHBoc
R
OH
OH
327–329b
NHBoc
R
OH
OH
327–329a
NHBoc
R
CO2Me
OH
330–332b
NHBoc
R
CO2Me
OH
330–332a

Scheme 2.138

$EtAlCl_2$, $TiCl_4$, and $ZnBr_2$) were used. The highest optical purity of hydroxylamines (**320**) was obtained by using 0.5 equiv $ZnBr_2$ and D-glucose diacetonide (**A9**) (558).

Stereoselective synthesis of pseudo C_2-symmetrical 1,3-dibenzyldiamino alcohol (S,S) (**323**) a core unit of HIV protease inhibitors, and the two *meso*-stereoisomers (**323a**) and (**323b**) was achieved by stereocontrolled addition of benzylmagnesium chloride to nitrones (**63a**) and (**63b**) (Scheme 2.137). The yield of (S,S)-(**323**), based on *N*-*Boc*-L-phenylalaninal, accounts for 23% (Scheme 2.137) (211).

Sugar-derived nitrones are widely and effectively used as substrates in reactions with Grignard reagents and as starting materials in the synthesis of many biologically interesting compounds, including amino acids, amino alcohols, and nucleoside analogs (2). The reactions of nitrones derived from sugars with α-alkoxyalkyl (or β-alkoxy) groups, can be fully stereocontrolled by using appropriate Lewis acids as *pre*-complexing agents. Examples of these reactions are shown in Scheme 2.138, Table 2.10, and Fig. 2.23. They lead to β,γ-dialkoxyhydroxylamines (**324–326**) which can be further transformed into *syn*- and *anti*-3-amino-1,2-diols (**327–329**) and to α-hydroxy-β-amino acid esters (**330–332**). Stereocontrol of the nucleophilic additions requires $ZnBr_2$ or Et_2AlCl as *pre*-complexing agents (559–561).

A similar strategy was used in the synthesis of 1,4-diaminobutanediol derivatives (**335**) starting from dinitrone (**333**) (Scheme 2.139) (562, 563).

Stereoselectivity of nucleophilic addition of Grignard reagents can be improved by using trimethylsilyl triflate (207).

Table 2.10 Stereoselective additions of Grignard reagents to nitrone 292[a]

Entry	RMgBr[b]	Solvent	Lewis acid[c]	Hydroxylamine	syn/anti[d]	Yield (%)[e]	Isolated Yield (%)[f]
1	PhMgBr	THF	none	324	80:20	84	67 (*syn*)
2	PhMgBr	Et_2O	$ZnBr_2$	324	90:10	86	77 (*syn*)
3	PhMgBr	Et_2O	Et_2AlCl	324	5:95	72	68 (*anti*)
4	MeMgBr	THF	none	325	76:24	81	62 (*syn*)
5	MeMgBr	Et_2O	$ZnBr_2$	325	91:9	82	75 (*syn*)
6	EtMgBr	Et_2O	Et_2AlCl	325	18:82	77	63 (*anti*)
7	EtMgBr	THF	none	326	75:25	74	56 (*syn*)
8	EtMgBr	Et_2O	$ZnBr_2$	326	78:22	72	56 (*syn*)
9	EtMgBr	Et_2O	Et_2AlCl	326	30:70	81	57 (*anti*)

[a] All reactions were carried out at −60°C for 6 h.
[b] 1.5 equiv. were used.
[c] 1.0 equiv. were used.
[d] Measured from the intensities of ^1H NMR signals.
[e] Determined on isolated mixture of diastereomers.
[f] After purification by column chromatography.

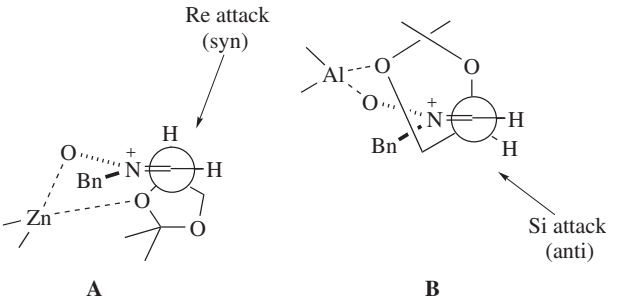
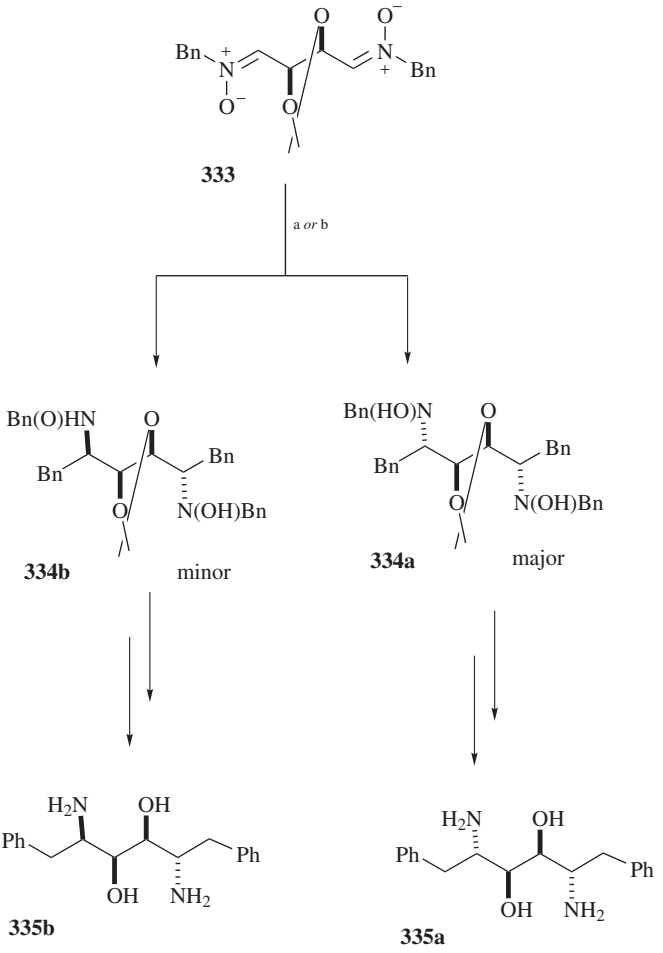


Fig. 2.23



a: BnMgCl, Et_2O, THF, −78°C; b: chelating agent, rt, then BnMgCl, Et_2O, THF, −78°C

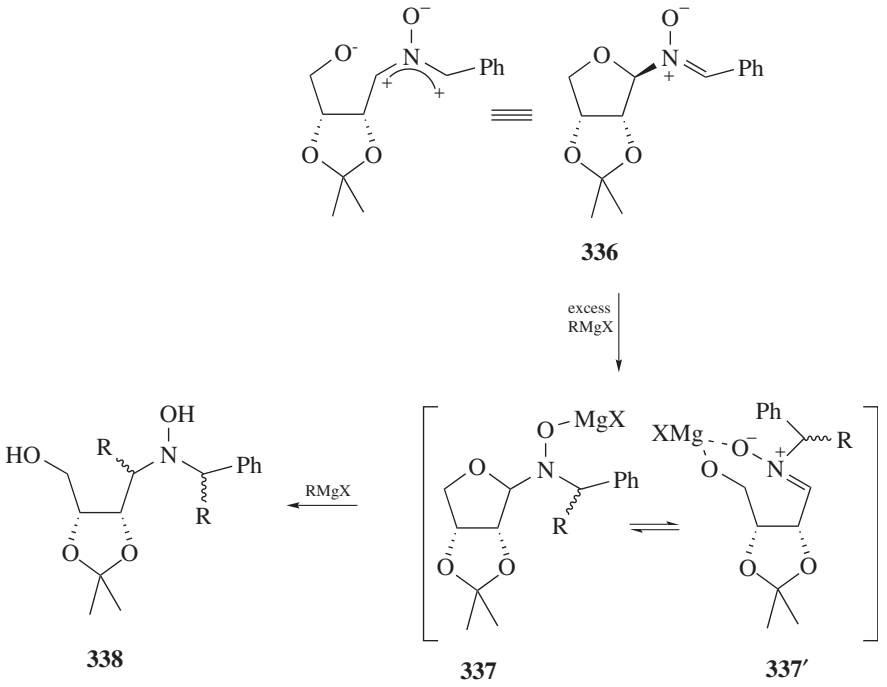
Scheme 2.139

Addition of various organometalic reagents to chiral nitrones, derived from L-erythrulose, proceeds with variable diastereoselectivity, depending on Lewis acids as additives. $ZnBr_2$ facilitates the attack at the *Si face* of the C=N bond, whereas Et_2AlCl makes the attack at the *Re face* more preferable. The obtained adducts can be transformed into derivatives of *N*-hydroxy-α,α-disubstituted-α-amino acids, with their further conversion into α,α-disubstituted α-amino acids (193, 202).

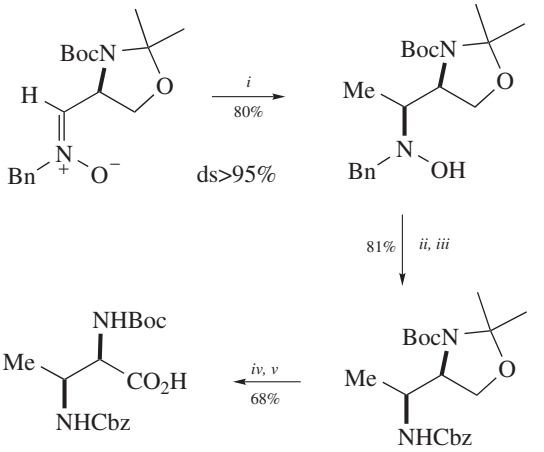
C-Phenyl-*N*-erythrosyl nitrone (**336**), as a C_1,C'_1-bis-electrophile, when subjected to the double addition of Grignard reagents (in a domino style), leads to acyclic hydroxylamine (**338**) via the formation of open-chain nitrone (**337′**). The reaction proceeds at 0°C with variable diastereoselectivity ranging from medium to good, depending on the organometalic reagent used (Scheme 2.140) (564).

As in all cases already mentioned, diastereoselective addition of Grignard reagents to β-amino nitrones (α-aminoalkyl nitrones) is a key step in the stereocontrolled syntheses of α,β-diamino acids (Scheme 2.141) (565, 566), of unsymmetrical α-amino hydroxylamines and 1,2-diamines (Scheme 2.142) (209, 567).

Recently, semiempirical PM3 computational analysis (568) and first *ab initio* study (569) of the nucleophilic addition to chiral nitrones of Grignard reagents have been carried out. The data revealed that all reactions are exothermic and proceed through *pre*-complexation of nitrones with the organometalic reagent.



Scheme 2.140



i: MeMgBr, THF, −50°C, 90 min; *ii*: H_2, $Pd(OH)_2$-C, MeOH, 70 psi, 3 days; *iii*: CbzCl, K_2CO_3, H_2O, 15 min, 0°C; *iv*: *p*-TosOH, MeOH, reflux, 1 h; *v*: RuO_2, $NaIO_4$, CH_3CN-CCl_4-H_2O, 5 min, r.t.

Scheme 2.141

The computational data prove the importance of chelation for the experimentally observed initial *Si attack*, leading to *syn*-adducts.

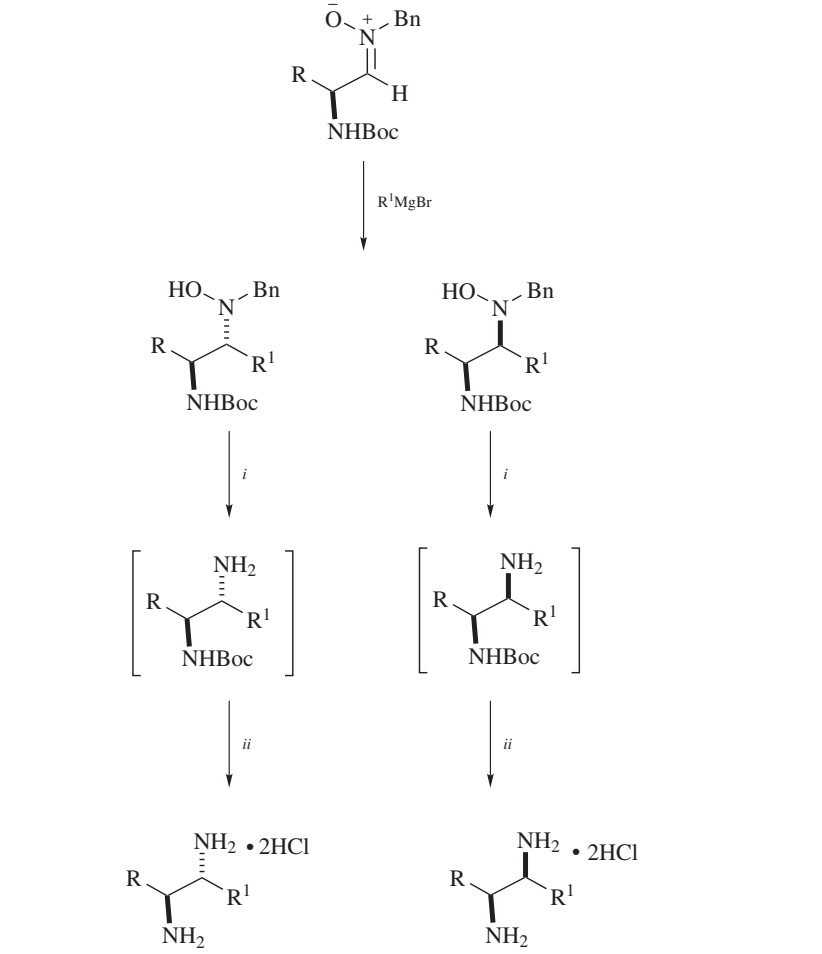
Stereocontrolled influence of precomplexing additives was used in the synthesis of (2 R,3 S)- and (2 S, 3 S)-2-amino-1,3,4-butanetrioles resulting from a stereo-divergent hydroxymethylation of D-glyceraldehyde nitrones (Fig. 2.24). The obtained *syn*- and *anti*-adducts were further converted into C-4 building blocks and to β-hydroxy-α-amino acids (570).

Addition of the Grignard reagent, prepared from 3-aryl-2-*iso*propyl-1-chloropropane (**340**) to nitrone (**339**) is a very important step toward the synthesis of compound (**342a**) which is used in preparing the antihypertensive agent SPP-100B and its epimer (**342b**) (Scheme 2.143) (197).

Recently, *tert*- butyl (phenylsulfonyl)alkyl-*N*-hydroxycarbamates (**343**), which are readily obtained from the reaction of aldehydes and *tert*-butyl-*N*-hydroxycarbamate in an aqueous methanol solution, were used as an equivalent of *N*−(*Boc*)protected nitrones in the nucleophilic addition of Grignard reagents (Scheme 2.144) (571).

The reaction of nitrones with 3-butenylmagnesium bromide was used in the diastereoselective synthesis of *cis*-2,5-disubstituted pyrrolidines, arising from a Cope retro-elimination (Scheme 2.145) (Table 2.11) (201, 572).

On the basis of the methylmagnesium bromide addition reaction to nitrones, an improved synthetic method of fluorinated *tert*-butyl amines was accomplished (Scheme 2.146) (573).



R = Me, ^{i}Pr, Bn; R^1 = Me, Ph

i: H_2, $Pd(OH)_2$-C, MeOH, r.t., 70 psi, 72 h
ii: 8% HCl - MeOH, 5°C, 30 min

Scheme 2.142

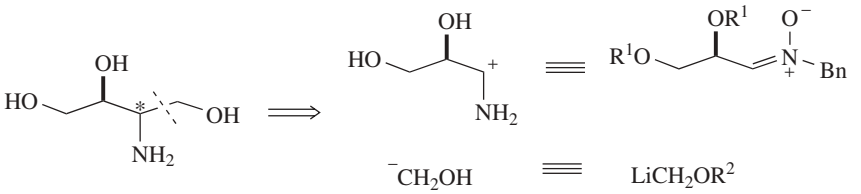
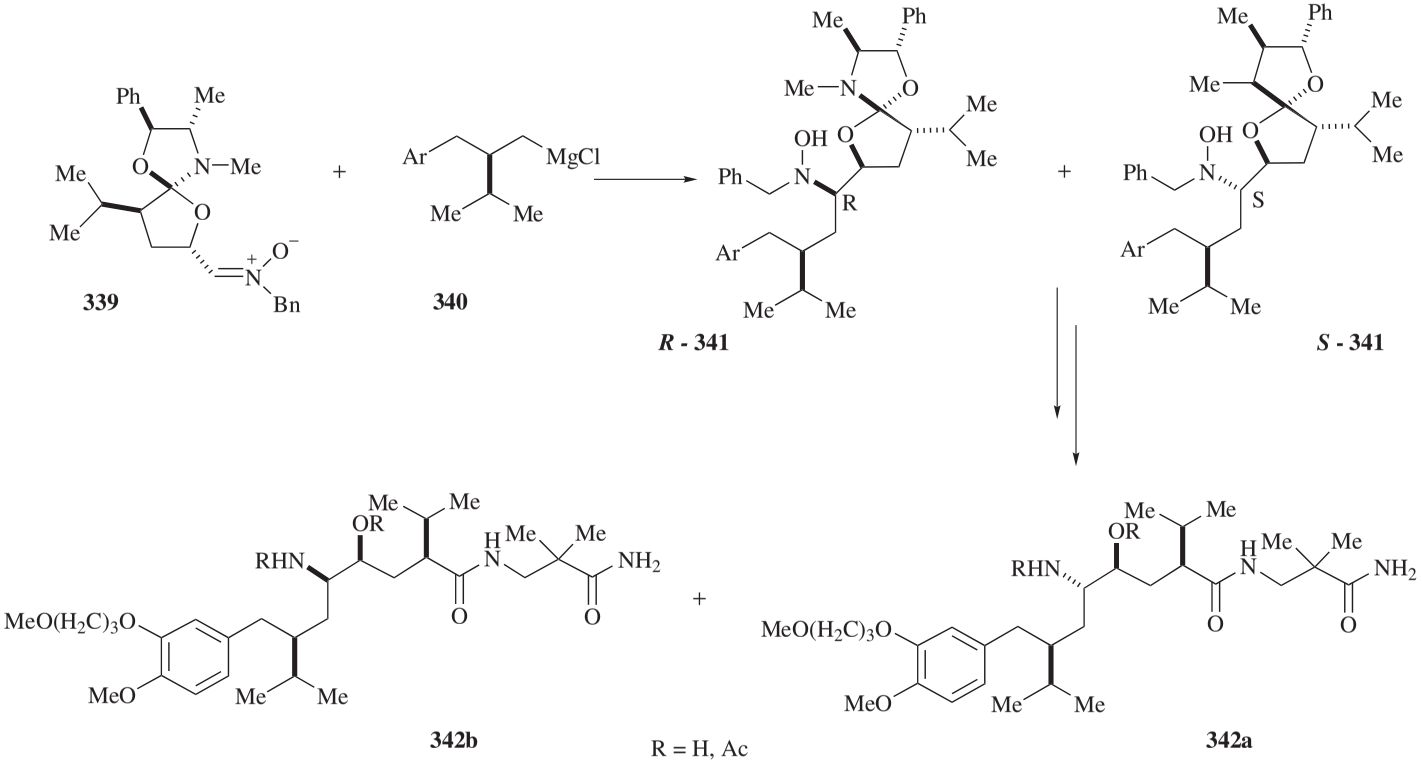
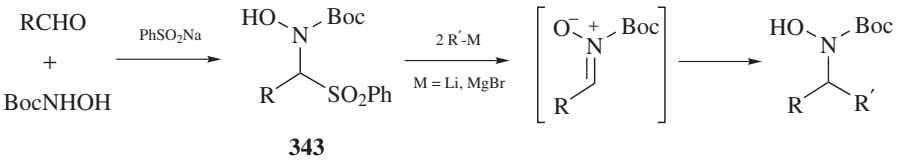


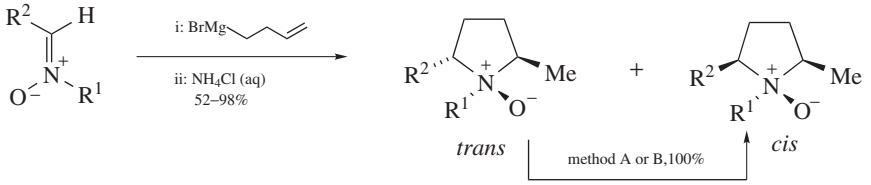
Fig. 2.24



Scheme 2.143



Scheme 2.144



Method A: $CHCl_3$,Δ ,1 day; method B: 95°C, 15–90 min

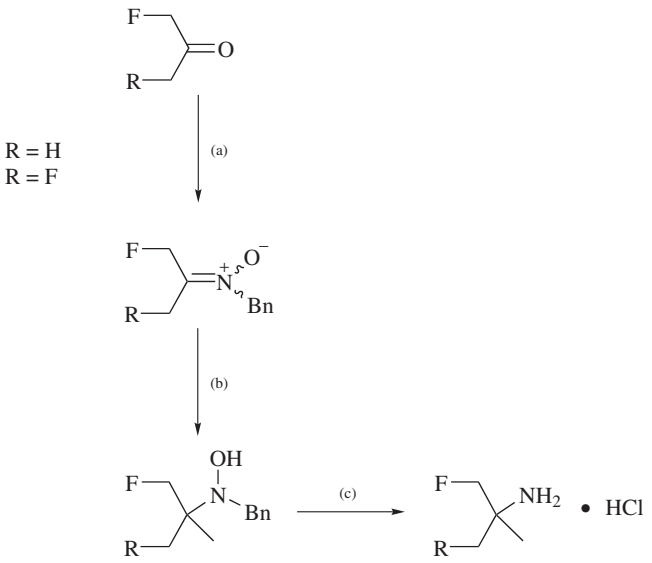
Scheme 2.145

Table 2.11 The isomerization of pyrrolidine *N*-oxides *trans* and *cis* at elevated temperatures.

R^1	R^2	d.r before heating[a]	Method A d.r.[a]	Method B d.r.[a]	Yield %
Me	Ph	40:60	57:43	98:2	96
Me	Me	58:42	83:17	96:4	52
Me	Et	50:50	94:6	94:6	94[d]
Me	i-Pr	67:33	[b]	96:4	62[e]
Me	t-Bu	94:6	[c]	96:4	73
Bn	Ph	75:25	[c]	83:17	95
Ph	Ph	93:7	[b]	95:5	98[d]
Cyclohexyl	Ph	> 98:2	[c]	> 98:2	71[e]

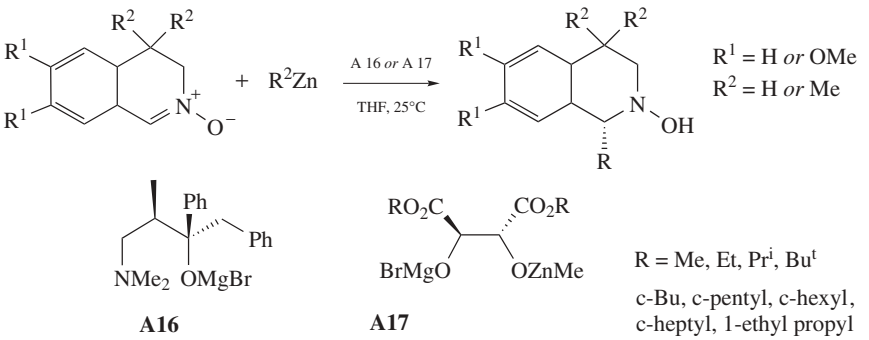
[a]Refers to the ratio of *cis / trans* -2,5-disubstituted products as determined by 400 MHz ^{1}H NMR assay (d.r.).
[b]Significant decomposition prevented calculation of d.r.
[c]No 2,5-disubstituted pyrrolidine *N*-oxides were detected.
[d]Some decomposition occured on heating.
[e]Heat was required to produce fully cyclised material.

Catalytic properties of external chiral additives such as (*2S,3R*)-4-dimethyl-amino-1,2-diphenyl-3- methyl-2-butoxide (**A16**) (574, 575) and 2-magnesium-3-zinc salts of dialkyl (*R,R*)-tartrate (**A17**) were employed in the highly stereoselective addition of organozinc reagents to derivatives of 3,4-dihydro-isoquinoline-*N*-oxide (Scheme 2.147) (576).



a: BnNHOH,anhydrous $MgSO_4$, benzene, r.t., 1 h
b: CH_3MgBr, ether, –40°C, 1 h
c: H_2, 40 psi, Pd/C (10%), CH_3OH, conc. HCl, 50°C, 20h

Scheme 2.146

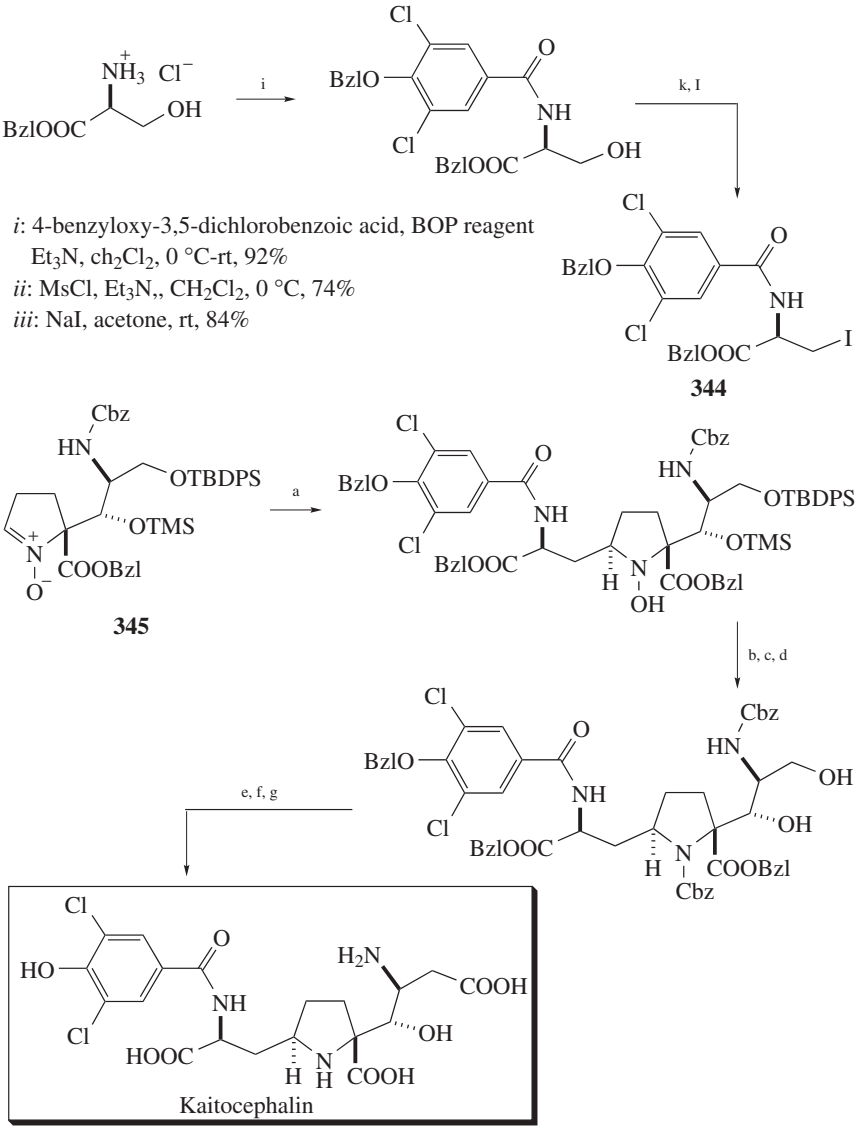


A16 **A17**

Scheme 2.147

A total synthesis of kaitocephalin, a glutamate receptor antagonist, was accomplished by employing a novel stereoselective C–C bond forming reaction between nitrone (**345**) and halide (**344**) as a key step (Scheme 2.148). The absolute configuration of kaitocephalin was confirmed to be 2 R,3 S,4 R,7 R,9 S (577).

Alkylation of nitrones and formation of α-alkylated hydroxylamines proceeds upon treatment with trialkylboranes (578).



i: 4-benzyloxy-3,5-dichlorobenzoic acid, BOP reagent
Et_3N, ch_2Cl_2, 0 °C-rt, 92%
ii: MsCl, Et_3N,, CH_2Cl_2, 0 °C, 74%
iii: NaI, acetone, rt, 84%

344

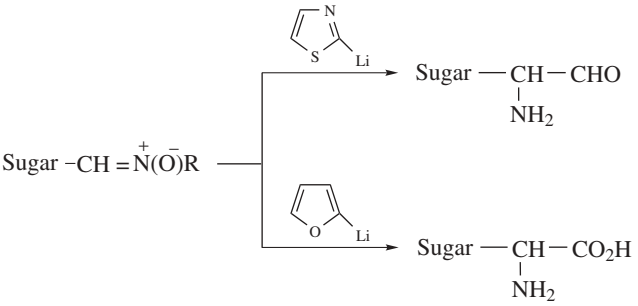
345

a: 344 - Zn (8 equiv.), CuI (3.6 equiv.), THF/H_2O (3.3:1), ultrasound, rt, 75%.
b: Zn, satd NH_4Cl, EtOH, 90%.
c: CbzCl, K_2CO_3, toluene/H_2O.
d: TMSCl, MeOH, rt, 45%.
e: 4-methoxy-TEMPO, KBr, satd $NaHCO_3$, NaClO, CH_2Cl_2, 0°C.
f: $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, Bu^tOH/H_2O (10:3), rt, 86%.
g: H_2, 20% $Pd(OH)_2$-C, EtOH/$CHCl_3$ (10:1), rt 27%, after preparative HPLC.

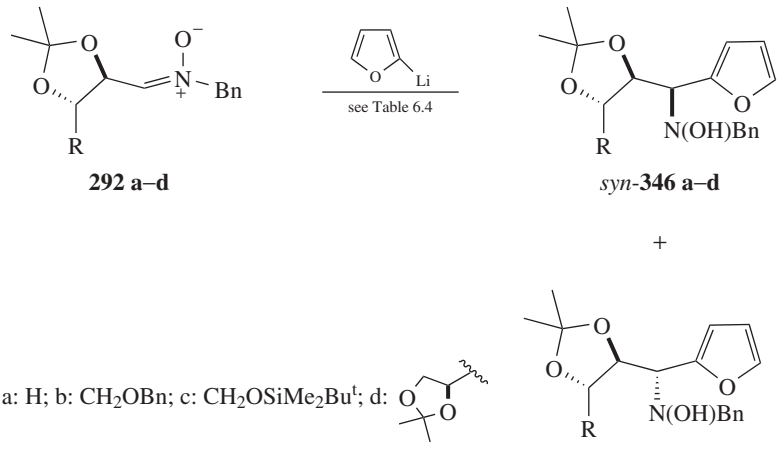
Scheme 2.148

2.6.6.1.2. Addition of Heterocyclic Compounds Stereocontrolled nucleophilic addition of heterocyclic compounds to chiral nitrones is of great synthetic importance in the synthesis of natural and biologically active compounds. In these reactions, the nitrone group serves as an amino group precursor and the heterocycle furnishes the formyl group (from thiazole) (192, 195, 214, 215, 579) or the carboxyl group (from furan) (194–196, 580–584) (Scheme 2.149).

In most cases, the stereochemical course of heterocyclic addition can be altered by *pre*-complexation of nitrones with Lewis acids. In the absence of complexation agents (Et_2AlCl, $TiCl_4$), addition of lithio-hetaryl derivatives to chiral β-alkoxy nitrones (**292a–d**) gives β-alkoxy-α-hydroxylamino-2-alkylhetaryls (**346a–d**) in good yields with *syn*-selectivity. In the presence of diethylaluminum chloride the reaction leads to the same adducts, but with *anti*-selectivity (Scheme 2.150) (Table 2.12) (581).



Scheme 2.149



Scheme 2.150

Table 2.12 Addition[a] of 2-lithiofuran to nitrones 292 a– d

Entry	Nitrone	Lewis acid[b]	*syn/anti*[c]	Hydroxylamine[d]	Yield (%)[e]
1	292 a	none	96:4	*syn*-346 a	98
2		Et_2AlCl	5:95	*anti*-346 a	94
3	292 b	none	92:8	*syn*-346 b	95
4		Et_2AlCl	10:90	*anti*-346 b	90
5	292 c	none	94:6	*syn*-346 c	72
6		Et_2AlCl	8:92	*anti*-346 c	70
7	292 d	none	73:27	*syn*-346 d	82
8		Et_2AlCl	46:54	*anti*-346 d	80

[a] All reactions were carried out using 3.0 equivalents of 2-lithiofuran at $-80^{\circ}C$ in THF as a solvent.
[b] Precomplexation was carried out using 1.0 equivalent Lewis acid in Et_2O as a solvent.
[c] Measured from the intensities of ^1H NMR signals.
[d] Major product.
[e] Determined on isolated mixtues of *syn*- and *anti*-**346**.

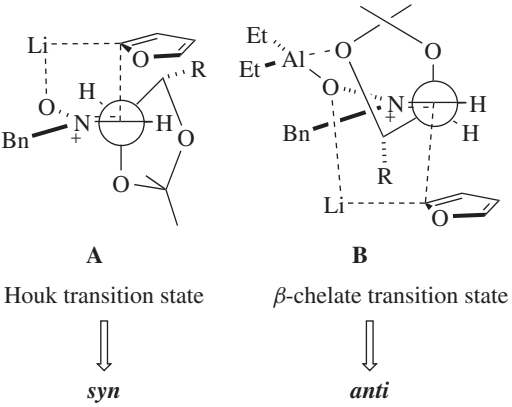
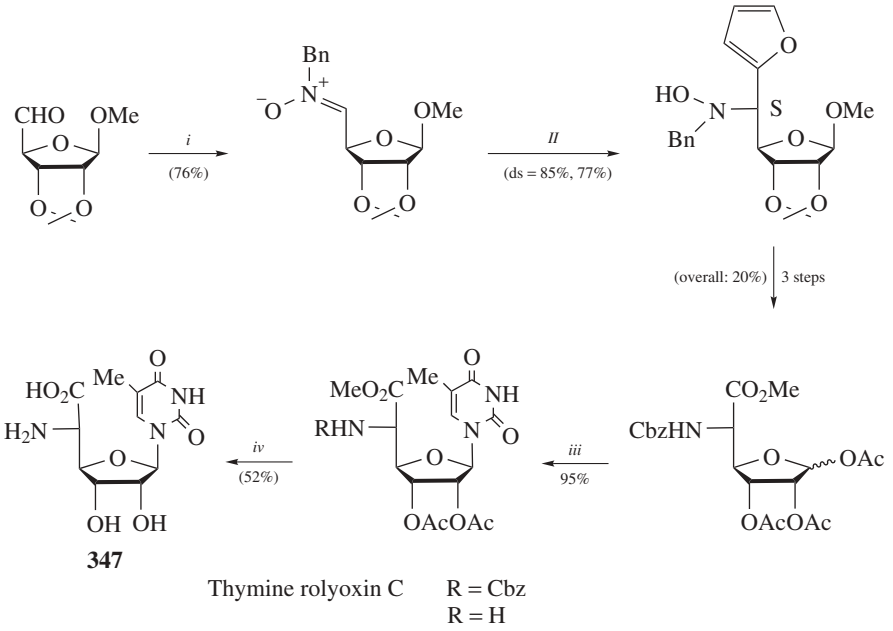


Fig. 2.25

The stereochemical outcomes of the above reactions can be explained by the proposed transition states **A** and **B** (Fig. 2.25). Model **A**, derived from the Houk model for nucleophilic addition to olefins, explains the formation of *syn*-adducts. Model **B**, involving a different nitrone conformation, due to the chelation of diethylaluminum chloride, accounts for the formation of *anti*-adducts (581).

Transformation of chiral nitrones into enantiomer enriched α-chiral *N*-hydroxylamines and their derivatives, has been successfully employed in the enantioselective synthesis of (+)-(R)- and (−)-(S)-zileuton (216). An expeditious synthesis of thymine polyoxin C (**347**), based on the stereocontrolled addition of 2-lithiofuran (a masked carboxylate group) to the *N*-benzyl nitrone derived from methyl 2,3-O-isopropylidene-dialdo-D-ribofuranoside, is described (Scheme 2.151) (194).



347

Thymine rolyoxin C R = Cbz
R = H

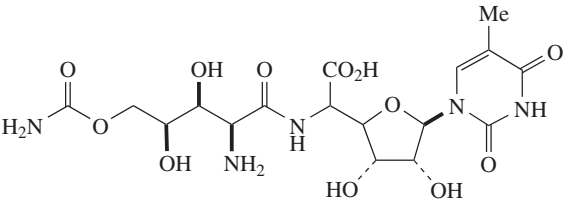
i: $PhCH_2NHOH$, CH_2Cl_2, $MgSO_4$.
ii: Et_2AlCl, Et_2O, r.t., 5 min; then 2-lithiofuran, THF, –80 °C, 1 h.
iii: 2,4,-bis(trimethylsiloxy)-5-methyl-pyrimidine, TMSOTf, CH_2Cl_2, reflux.
iv: LiOH, THF, 0 °C, 1h; then H_2, 10% Pd/C, MeOH, 1 atm., r.t., 4 h.

Scheme 2.151

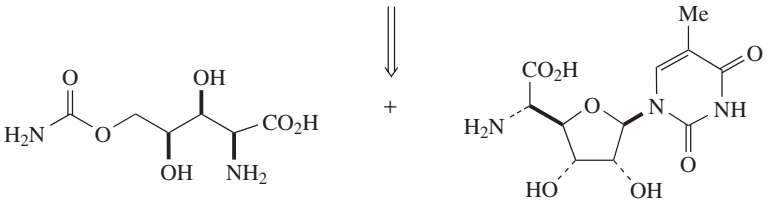
Antifungal antibiotic (+)-polyoxin J can be obtained in 46,4% yield by combining the derivative of 5-O-carbamoylpolyoxamic acid (**348**) with thymine polyoxin C (**347**) (Scheme 2.152) (196, 583)

Introduction of the furyl group was used as a key step in the stereoselective synthesis of a core building block for (2*S*,3*R*, 4*S*,5*S*,6*S*,11*E*)-3-amino-6-methyl-12-(4-methoxyphenyl)-2,4,5-trihydroxydodec-11-enoic acid (AMMTD) (584), and also in the synthesis of (2 S,3 R)-3-hydroxy-3- methylproline (**349**) and its (2 R)-epimer (Fig. 2.26) (585).

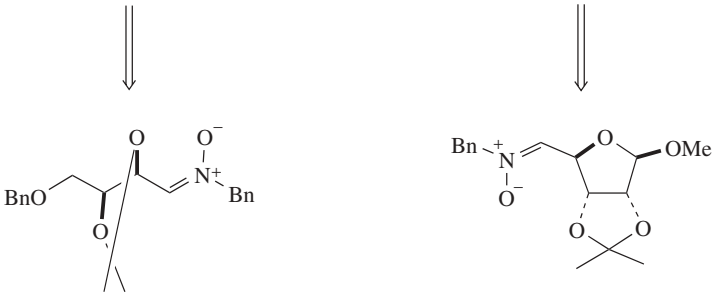
Transformation of the thiazole group into the formyl group has been used in the synthesis of pyrrolidine homo-azasugars. Thus, for example, (2*R*,5*S*)-bis (hydroxymethyl)-(3*R*,4*R*)- dihydroxypyrrolidine (**356**) (Scheme 2.154) was synthesized by adding 2-lithiothiazole to the nitrone derived from 2,3,5-*tri*-(O-benzyl)-D-arabinofuranose (**350**) which exists in equilibrium with the hydroxylamino form. Successive reduction of the hydroxylamino group in compound (**351**) to amino isomers (**352a,b**) was followed by conversion to benzylpyrrolidines (**353a,b**) (Scheme 2.153) (214).



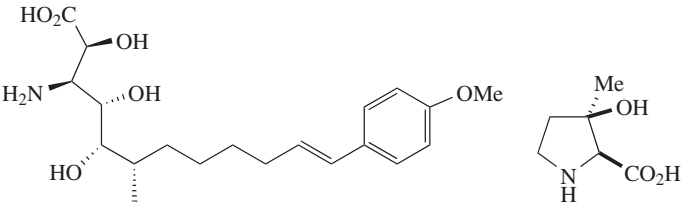
(Polyoxin J)



348 **347**



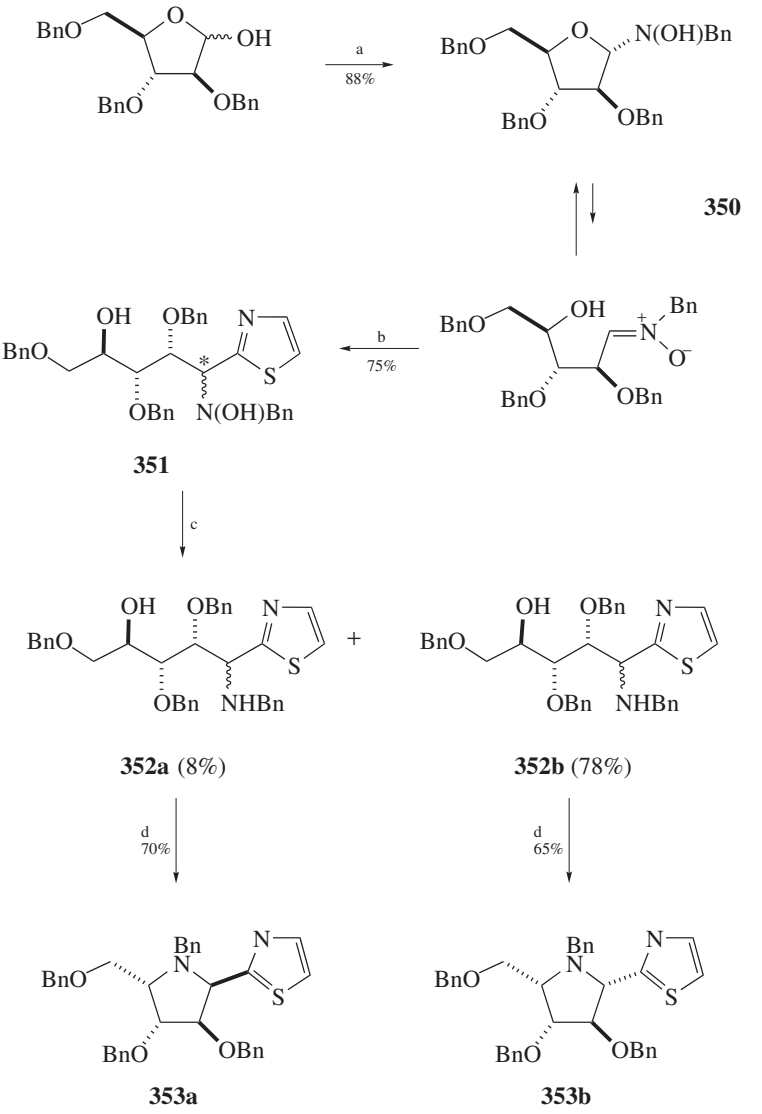
Scheme 2.152



AMMTD **349**

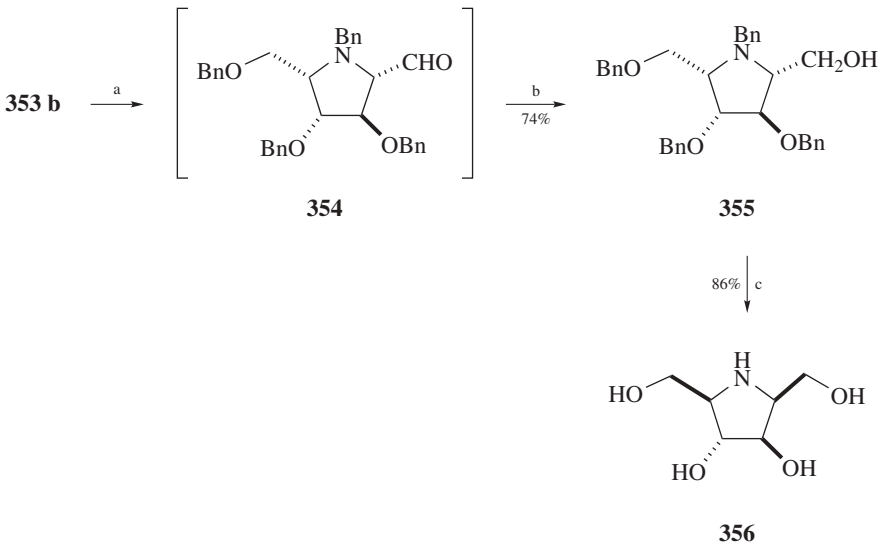
Fig. 2.26

Conversion of the thiazole group in (**353b**) into the formyl group leads to compound (**354**). Additional transformations gave compounds (**355**) and (**356**) (Scheme 2.154) (214, 215).



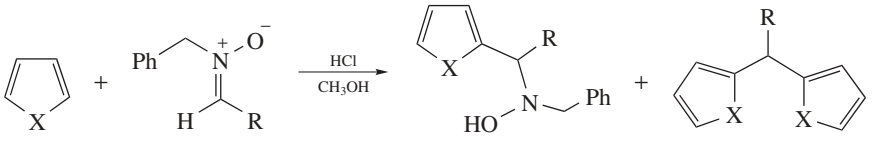
a: BnNHOH, $MgSO_4$, CH_2Cl_2, r.t., 48 h.
b: 2-lithiothiazole, Et_2O, −78 °C, 6 h.
c: $(AcO)_2Cu$, Zn, AcOH, H_2O, 70 °C, 1 h.
d: Tf_2O, pyridine, 40 °C, 30 min.

Scheme 2.153



a: TfOMe, MeCN, r.t.; then $NaBH_4$, MeOH, r.t.; then $HgCl_2$, MeCN-H_2O, r.t.
b: $NaBH_4$, r.t.
c: 20% $Pd(OH)_2$/C, H_2, AcOH, 1 atm., r.t. 18 h; then Dowex (OH^-)

Scheme 2.154

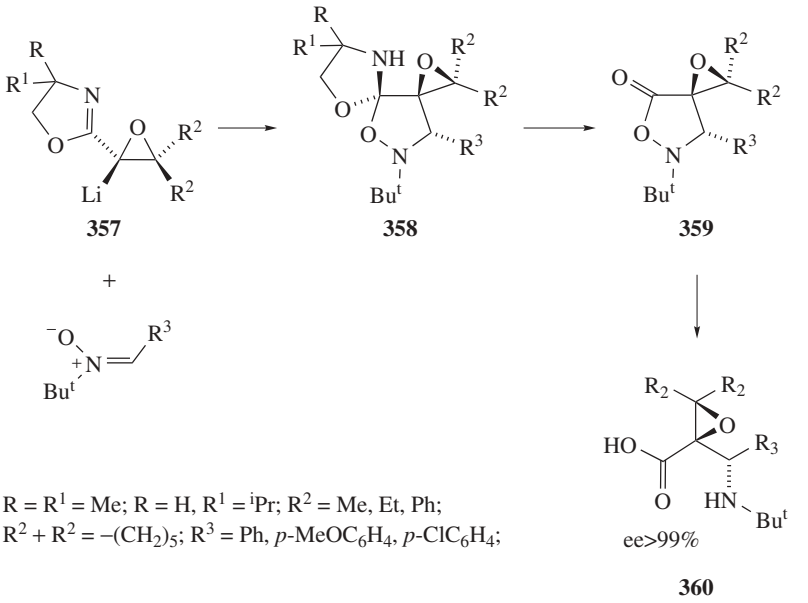


X = NH, O; R = Et, Ph

Scheme 2.155

Nucleophilic addition of furan to nitrone occurs upon treatment with trimethylsilyl triflate (TMSOTf) (586, 587). Catalyzed TMSOTf stereoselective addition of 2-[(trimethylsilyl)oxy]furan to chiral nitrones was carried out in a short synthesis of [1*S* (1α, 2β, 7β, 8α, 8aα)]-1,2-di(t-butyldiphenylsilyloxy)-indolizidine-7,8-diol (588). Addition to *N*-gulosyl-*C*-alkoxymethyl nitrones led to the synthesis of the core intermediate of polyoxin C (218).

The first example of a nitrone reaction with pyrroles and furan in the presence of HCl as an activating agent was recently reported (589). Depending on reaction conditions, these acid-catalyzed reactions make it possible to obtain both, 2-heteroaromatic *N*-benzylhydroxylamines and symmetric as well as asymmetric 2,2'-*bis* -(heteroaryl) alkanes (Scheme 2.155).



357 **358** **359** **360**

Scheme 2.156

Oxazolinyl-oxiranyllithiums (**357**) prepared from optically pure oxazolinyloxiranes react with nitrones diastereo and enantioselectively to give almost optically pure diazadispiroundecanes (**358**). These are appropriate candidates for the conversion to α-epoxy-β-amino acids (**360**) in view of the lability of the N–O bond of the isoxazolidinones (**359**) (Scheme 2.156) (590–596).

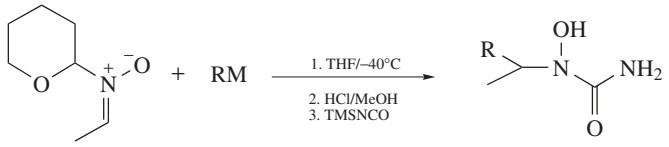
Nucleophilic addition of metallated heterocyclic derivatives to *N*-tetrahydropyranyl (THP) protected nitrones (**361**) makes it possible to synthesize α-branched hydroxylamines (**362**) (Table 2.13) (597).

2.6.6.1.3. Addition of 2-Alkyl-2-Oxazolines All of the above mentioned reactions of nucleophilic addition of nitrones give the corresponding hydroxylamines. In this chapter, the reactions of nitrones and nucleophiles and their conversions to compounds of other structures are considered.

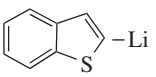
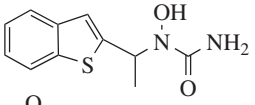
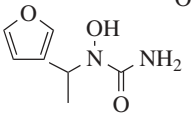
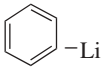
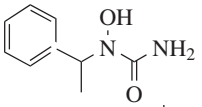
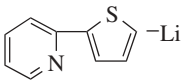
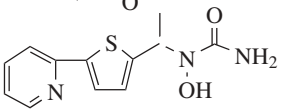
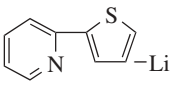
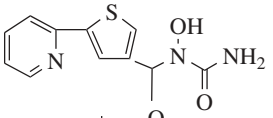
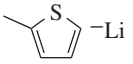
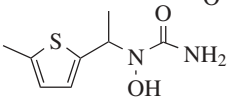
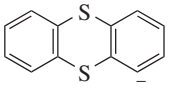
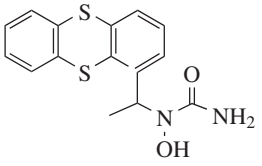
Lithiated 2-alkyl-4,5-dihydro-1,3-oxazoles (**363**) react with nitrones in high stereoselectivity to give initially 1,6-dioxa -2,9-diazaspiro [4.4] nonane (**364**). Upon further treatment with oxalic acid it is quantitatively converted to 4,4-dimethyl-2-(1-methyl-2-phenylvinyl)-4,5-dihydro-1,3-oxazole (**365**) (diastereomeric mixture: *E/Z* = 9:1) with elimination of *tert*-buthylhydroxylamine (Scheme 2.157) (598, 599).

Lithiated 2-(chloromethyl)- and 2-(1-chloroethyl)-4,5-dihydro-1,3-oxazoles (**366**) and (**367**) behave in a different way. The reaction of (**366**) with nitrones leads stereoselectively to 2-[(*Z*)-alkenyl]-4,5-dihydro-1,3-oxazoles (**368a**) and (**368b**) (Scheme 2.158), while the 2-(1-chloroethyl)-derivative (**367**) gives

Table 2.13 Addition of organolithium compounds to nitrone 361

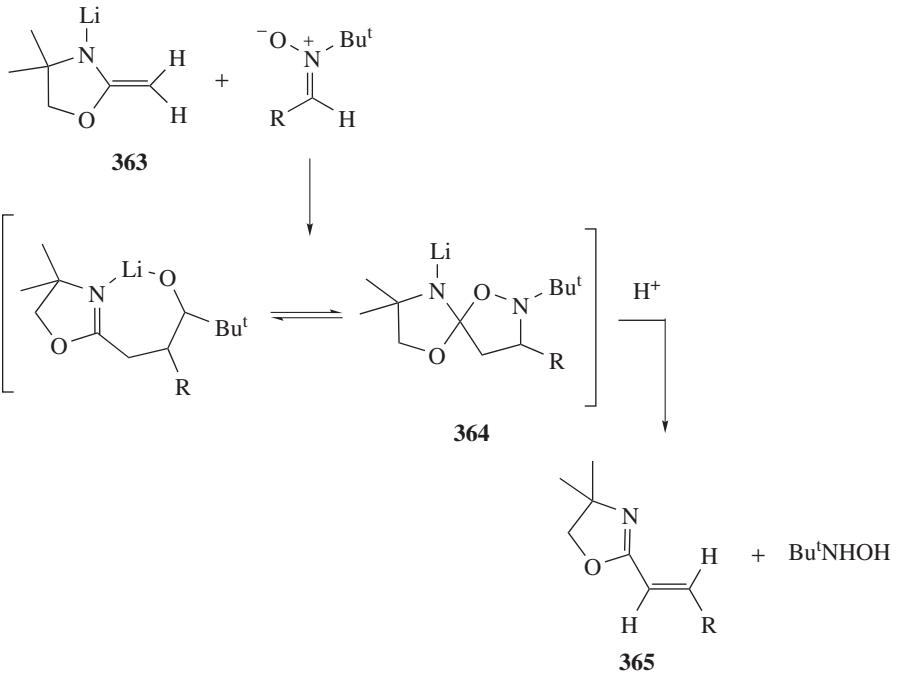


361 **362**

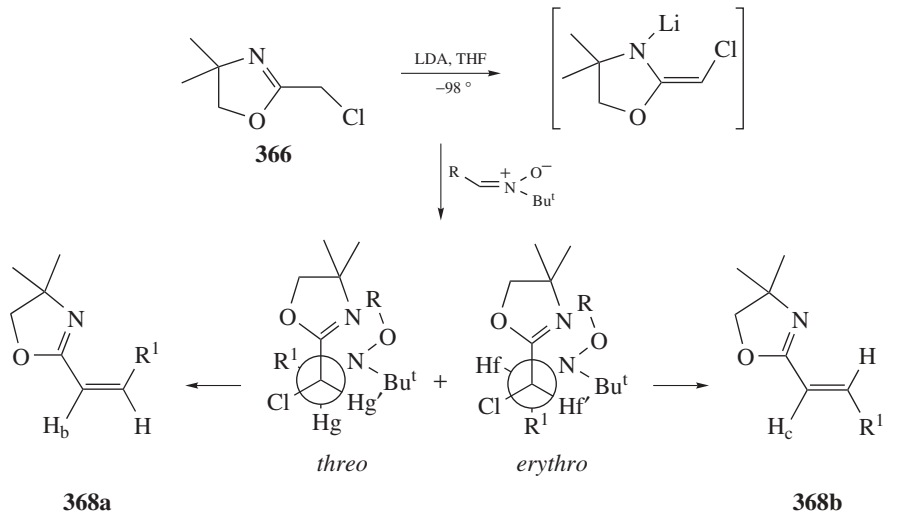
Entry	RM	Product	Yield (%)
1			36
2			25
3			28
4			30
5			34
6			24
7			25

1,6-dioxa-2,9-diazaspiro [4.4] nonanes (**369**) and (**370**). Compound (**369**) undergoes further transformation into oxazetidine (**371**) (Scheme 2.159) (599).

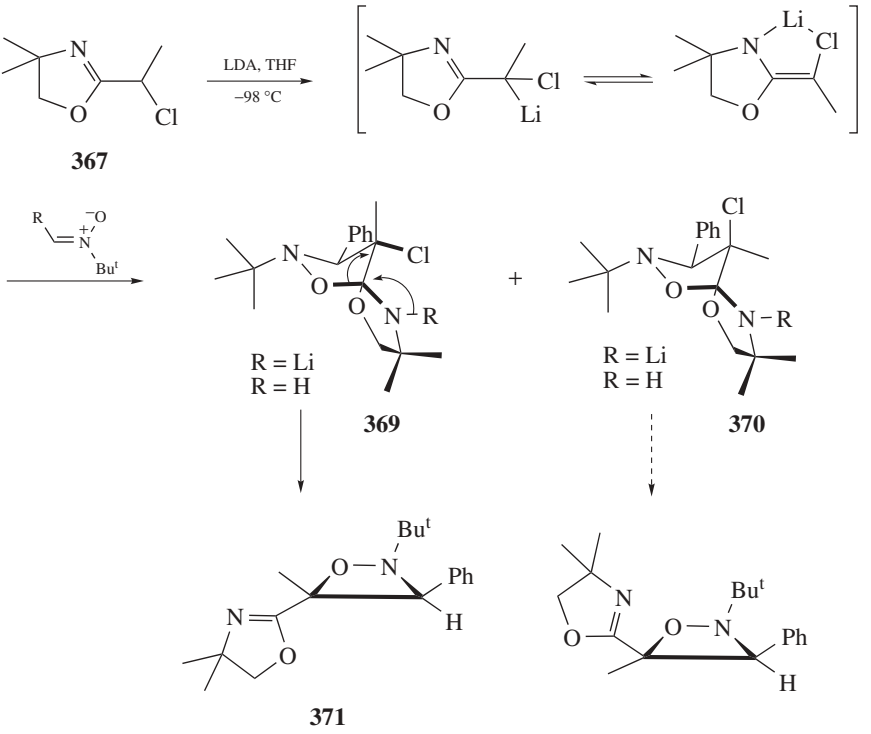
The reaction of lithiated 2-alkyl-2-oxazolines with nitrones enables stereoselective and enantioselective syntheses of 5-isoxazolidinones, which are used as precursors of β-amino acids. Highly enantiomerically enriched 5-izoxazolidonones and β-amino acids of inverse configuration can be generated by simply changing the chirality of the initial 2- *iso*propyl-2-oxazoline (600).



Scheme 2.157



Scheme 2.158



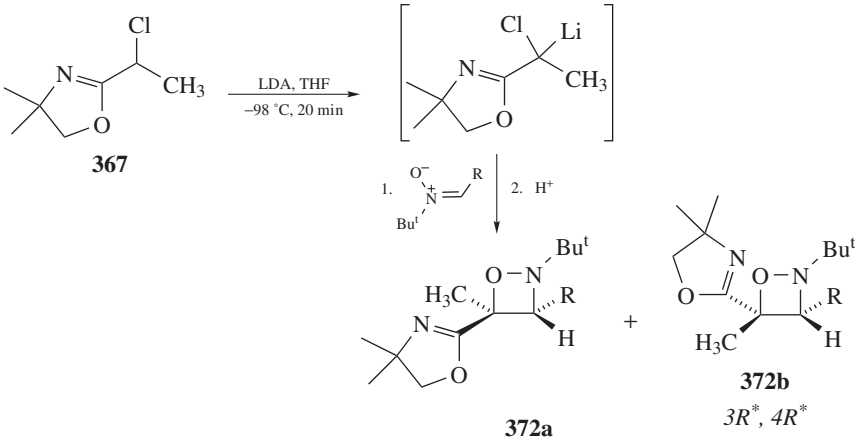
Scheme 2.159

The reaction of lithiated 2-(1-chloroethyl)-2-oxazolines (**367**) with nitrones led to the stereoselective synthesis of oxazolinyl-[1.2] oxazetidines (**372a,b**) which are important as precursors of α-hydroxy-β-amino acids (Scheme 2.160) (601).

2.6.6.1.4. Addition of Organometalic Compounds as an Efficient Synthetic Method of Stable Nitroxyl Radicals Nucleophilic additions of organometalic compounds have been successfully applied to the synthesis of stable nitroxyl radicals. Owing to structural and reactive variations of organometalic compounds, this reaction offers great possibilities for the synthesis of different types of nitroxyl radicals with wide variations of R^1-R^4 substituents. The resulting hydroxylamines can be readily oxidized to the corresponding nitroxyl radicals, at mild conditions (Scheme 2.161) (602).

A wide range of the nitroxyl radicals, presented in Fig. 2.27, have been obtained by this strategy (603–615).

It was found (616) that the course of the heterogeneous reaction of 1-hydroxy-5,5- dimethyl-2,4- diphenyl-3-imidazoline-3-oxide with PhLi depends on the crystalline phase of the starting compound, which can be obtained, predominantly, in cyclic or open chain tautomeric forms.



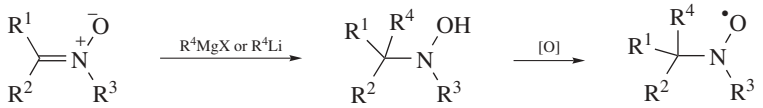
367

372a

372b

R = Ph, *p*-$CF_3C_6H_4$, *p*-$MeOC_6H_4$, *p*-ClC_6H_4 $3R^*, 4S^*$ $3R^*, 4R^*$

Scheme 2.160

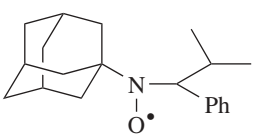


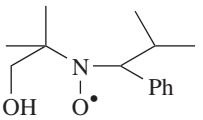
[O] = O_2 *and* Cu^+, AgO, MnO_2, PbO_2

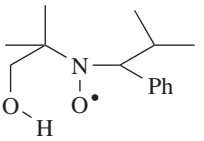
Scheme 2.161

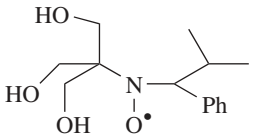
The reaction of organometalic compounds with nitrones can be applied not only to the synthesis of stable nitroxyl radicals but also to the preparation of optically active secondary amines (Scheme 2.162) (617, 618).

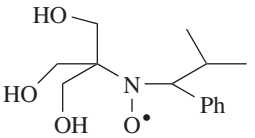
Stereochemistry of such transformations depends on reaction conditions, shown in Scheme 2.163 (619). The stereochemistry of the addition agrees with the model presented by Keana (model **A**). The organometallic reagent (R_{large}–M, where M is MgBr or Li) attacks the pyrrolidine nitrone from the less hindered site (602). When Et_2AlCl is absent, it is to be expected that PhLi attacks from the opposite direction of the phenyl group in the pyrrolidine ring because the phenyl group can be considered to be larger than the methoxymethyl group, as depicted in Scheme 2.163 (model **B**). When the Lewis acid coordinates to the oxygen atom of the methoxymethyl group, the upper side of the compound, see Scheme 2.163, becomes more crowded (model **D**). The chelating methoxymethyl group is considered to be larger than the phenyl group. The chelation model also rationalizes the lower *trans* addition of PhMgBr to nitrone (model **C**). As to the nitrone bearing ether functions, a similar chelation model has been proposed in which a molecule of the Grignard reagent coordinates to the oxygen atoms in the nitrone, and another molecule of the Grignard reagent attacks the nitrone from the less hindered side.

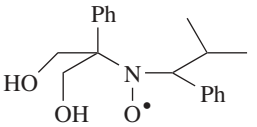


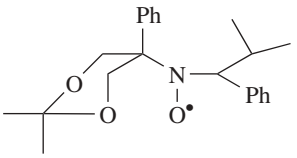


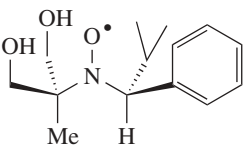


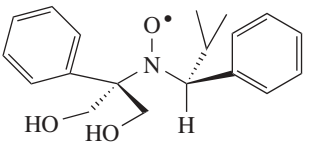




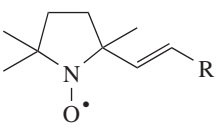








Ref.[11]



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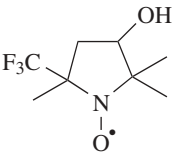

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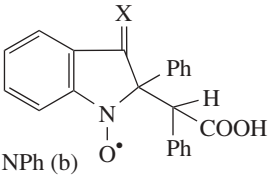
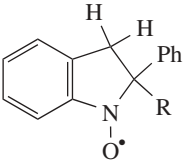
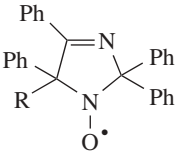


X = O (a), NPh (b)

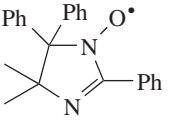
Ref.[603]



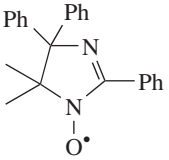
Ref.[605]



Ref.[606]

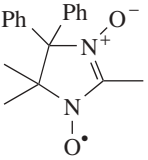


Ref.[606]



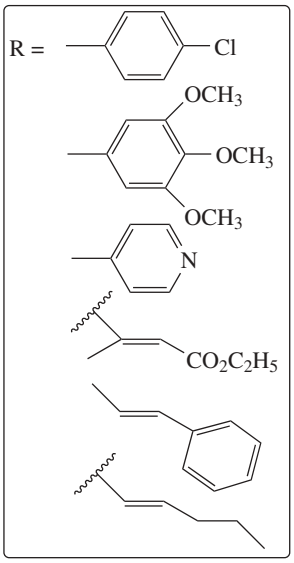
Ref.[606, 608]

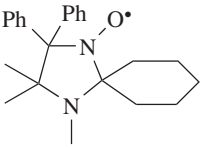
a: R = Me
b: R = Et
c: R = Pr
d: R = Bu^n
e: R = Bu^t
f: R = $Hexyl^n$
g: R = Cyclohexyl
h: R = Allyl
i: R = Benzyl
j: R = Ph



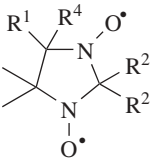
Ref.[606, 608, 609]

Fig. 2.27

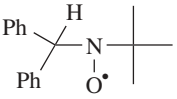




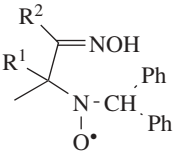
Ref.[606]



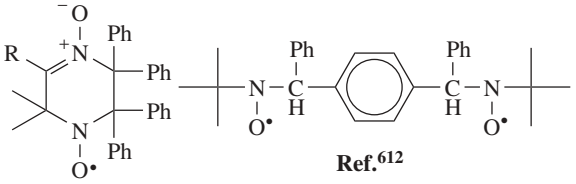
Ref.[606, 610]



Ref.[606, 611, 612]

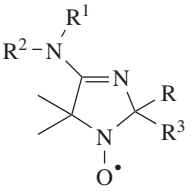


Ref.[606, 611, 612]

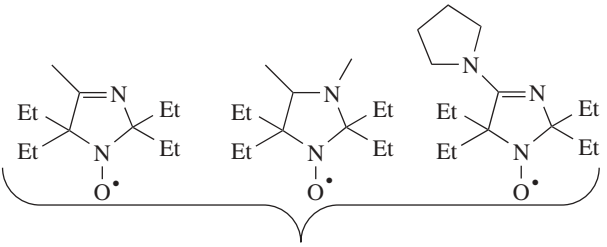


Ref.[612]

Ref.[606, 607]



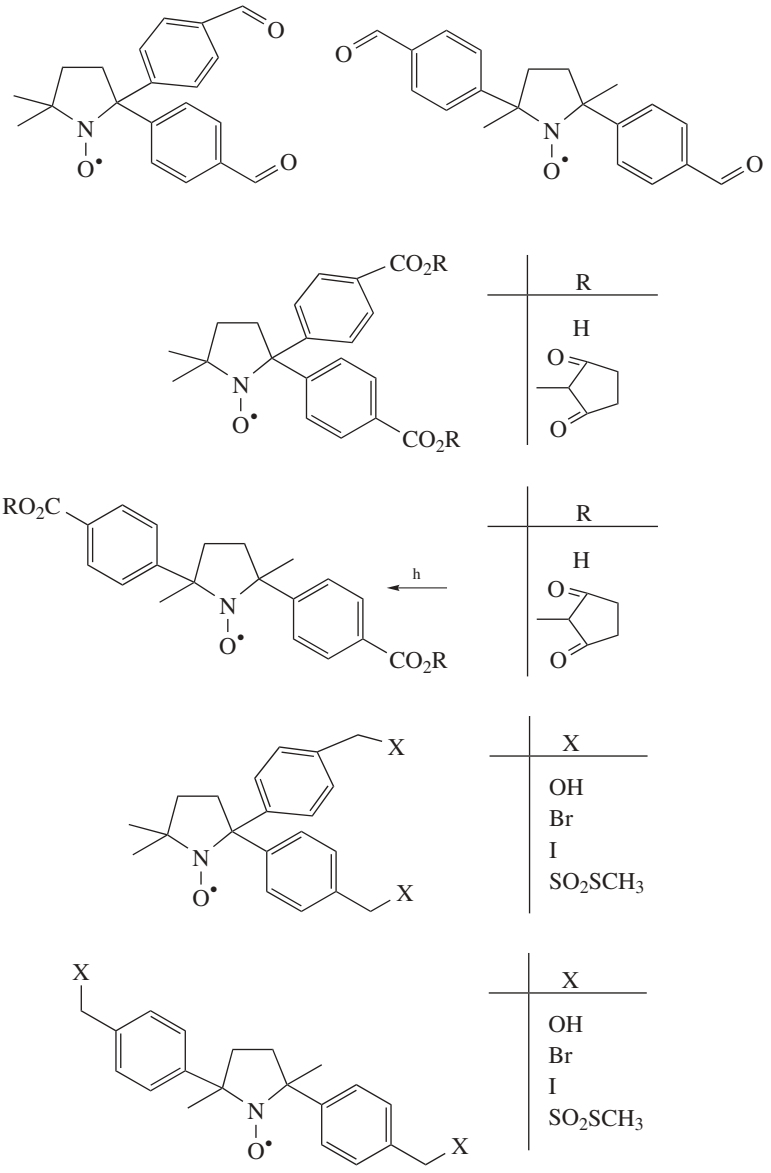
Ref.[613]



Ref.[614]

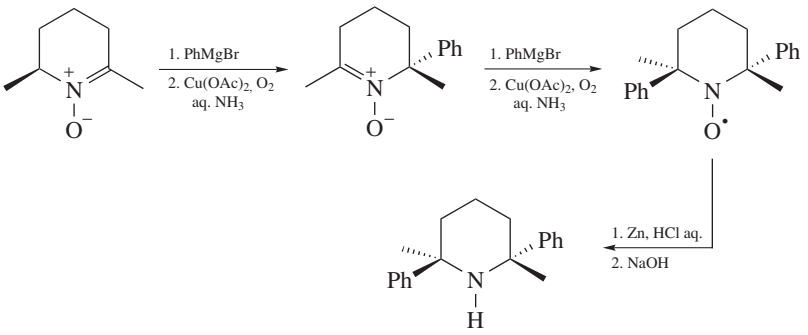
R	R^1	R^2	R^3
Ph	Me	Me	Et
Ph	$(CH_2)_5$		Me
Ph	$HO(CH_2)_2$	$HO(CH_2)_2$	Et
2-Py	H	Me	Et
Et			Et
Et	Me	Me	Et
m-$H_2NC_6H_4$	Me	Me	Et

Fig. 2.27 (*continued*)

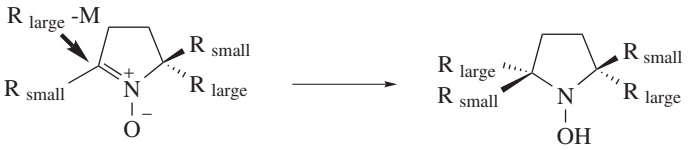


Ref.[615]

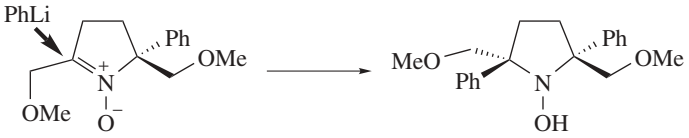
Fig. 2.27 (*continued*)



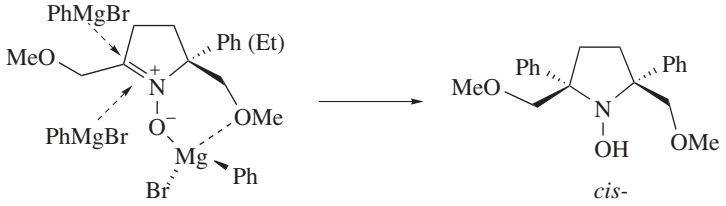
Scheme 2.162



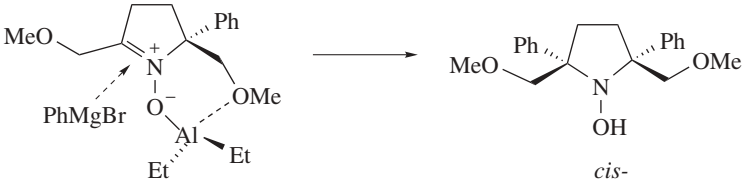
A Stereo-course proposed by Keana



B Stereo-course with PhLi *trans-*

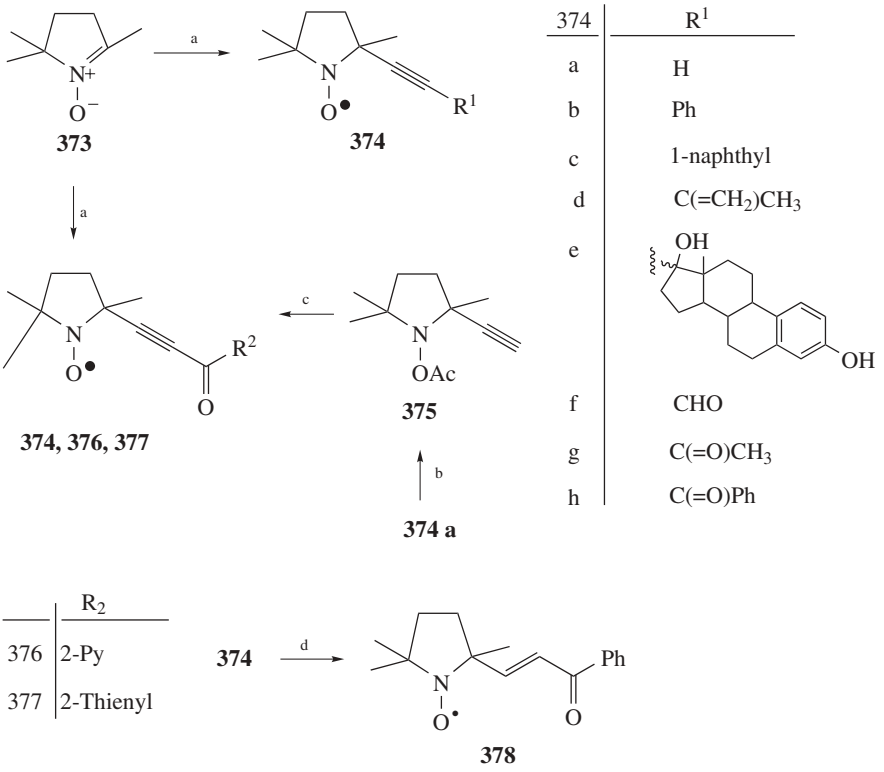


C Stereo-course with PhMgBr *cis-*



D Stereo-course with PhLi and Et_2AlCl *cis-*

Scheme 2.163



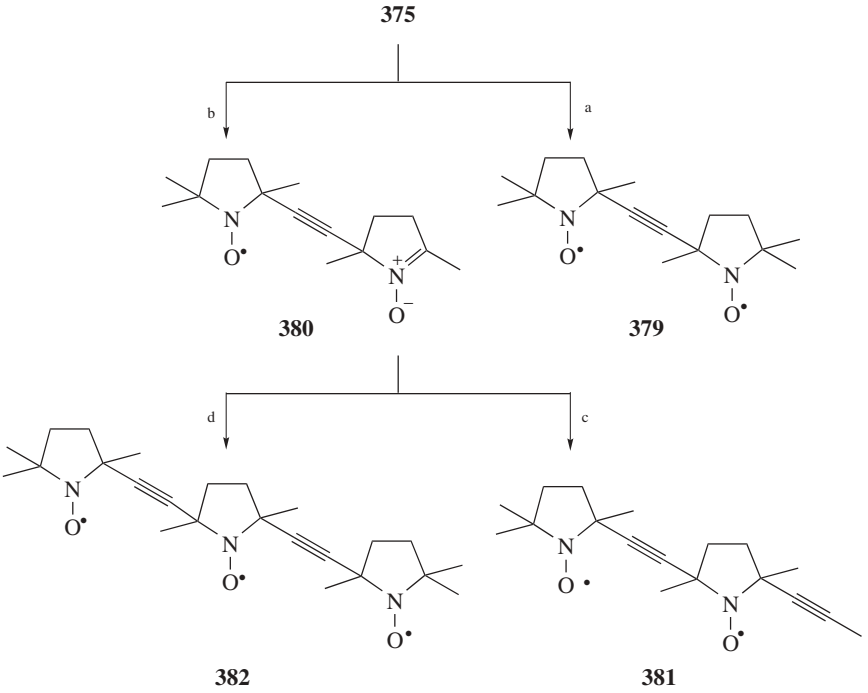
a: R-≡-MgBr/THF/**373**, −10 °C to r.t., 2 h, then $NH_4Cl/MnO_2/CHCl_3$, r.t. or reflux, 30 min (46–78%).
b: Ascorbic acid (5 equiv)/dioxane/H_2O (2:1), 40 °C, 15 min, then $CHCl_3$/ Et_3N/AcCl, 0 °C to r.t., 1 h (87%).
c: EtMgBr (2 equiv)/THF/**375**, 50 °C, 30 min, then aromatic aldehyde, −10 °C to r.t., 1 h, NH_4Cl, then $MnO_2/CHCl_3$, reflux, 15 min (52–71%).
d: SMEAH/THF, 5 h, r.t., then 10% NaOH then $MnO_2/CHCl_3$, reflux, 30 min (74%).

Scheme 2.164

Interaction of pyrroline-*N*-oxides (**373**) with alkynylmagnesium bromide gives alkyne substituted nitroxyl radicals (**374**), (**376**), and (**377**) (Scheme 2.164) (620).

Addition of the Grignard reagent, generated *in situ* from (**375**), to nitrone (**373**) or to 2,5-dimethyl-1-pyrroline-*N*-oxide, affords biradical (**379**) or nitrone containing monoradical (**380**). Furthermore, (**380**) can be transformed into biradical (**381**) and triradical (**382**) (Scheme 2.165) (620).

Nucleophilic addition of α-lithiated sulfoxides to α-PBN, followed by oxidation, gives β-sulfinyl nitroxyl radicals (**383**) (Scheme 2.166) (621).

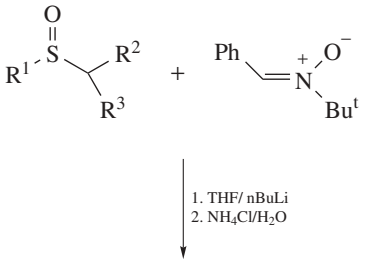


a: EtMgBr(2 equiv)/THF/**375**, 50 °C, 30 min, then **373**,
−10 °C to r.t., 2 h, then $NH_4Cl/MnO_2/CHCl_3$, r.t.,30 min (66%).
b: EtMgBr(2 equiv)/THF/**375**, 50 °C, 30 min, then 2,
5-dimethyl-1-pyrroline*N*-oxide, 2 h, then $NH_4Cl/MnO_2/CHCl_3$, r.t.,
30 min (58%).
c: HC=CMg-Br/THF/**380**, −10 °C to r.t., 2 h, then $NH_4Cl/MnO_2/CHCl_3$,
r.t.,30 min (62%).
d: EtMgBr(2 equiv)/THF/**375**, 50 °C, 30 min,
then **380**, −10 °C to r.t., 2 h, then $NH_4Cl/MnO_2/CHCl_3$, 30 min (39%).

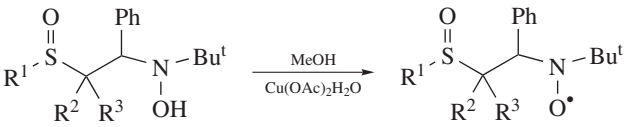
Scheme 2.165

2.6.6.1.5. Addition of Lithiated Sulfoxides and Sulfones Nucleophilic addition of lithiated methylaryl sulfoxides (**384**) to nitrones of various structures proceeds easily and in good yields (622). The reactions are applied to the synthesis of optically active α-substituted and α,α-disubstituted hydroxylamines, to secondary amines (623), and to enantioselective syntheses of alkaloids (624). The preferred approach to (+)-euphococcinine is based on the use of homochiral β-sulfinyl nitrones (**385**) (Scheme 2.167).

Nucleophilic addition of lithiated sulfones to nitrones made it possible to develop new stereoselective approaches to the synthesis of pyrrolidine-*N*-oxides based on a reverse-Cope-type elimination. One method is based on the reaction of lithiated sulfones with nitrones (**386**) (Scheme 2.168) (625).

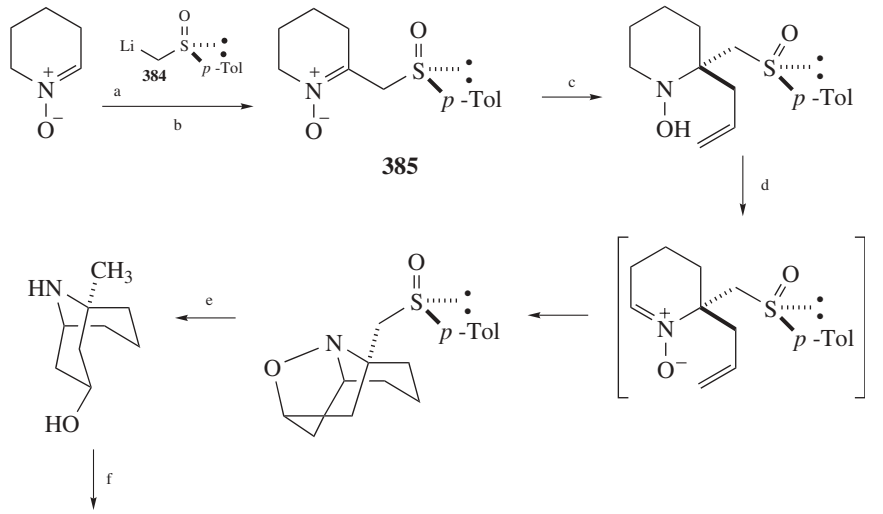


R^1	R^2	R^3
Ph	H	H
Me	H	H
Et	Me	H
Pr^i	Me	Me



383

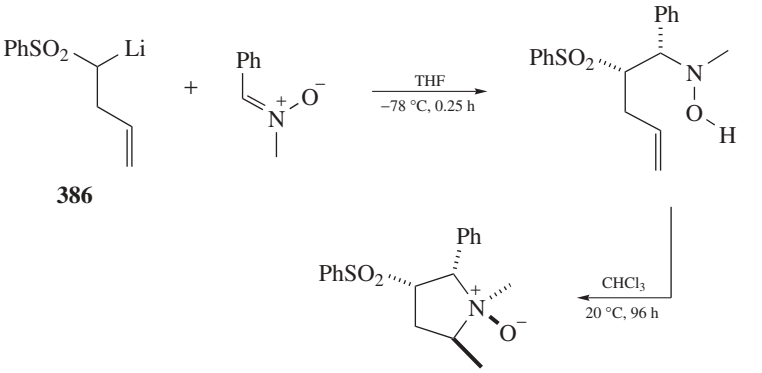
Scheme 2.166



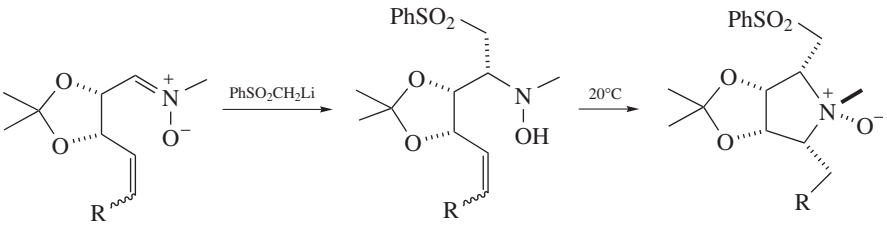
(+)– Euphococcinine

a: THF, –78 °C.
b: Ni_2O_3, $CHCl_3$, r.t.
c: $AlCl_3$, CH_2=$CHCH_2MgBr$,THF, –78 °C (54%).
d: Ni_2O_3, $CHCl_3$, r.t. (54%).
e: Raney Ni (W-2), H_2O, 30 °C, (95%).
f: PCC, CH_2Cl_2, r.t. (30%).

Scheme 2.167



Scheme 2.168

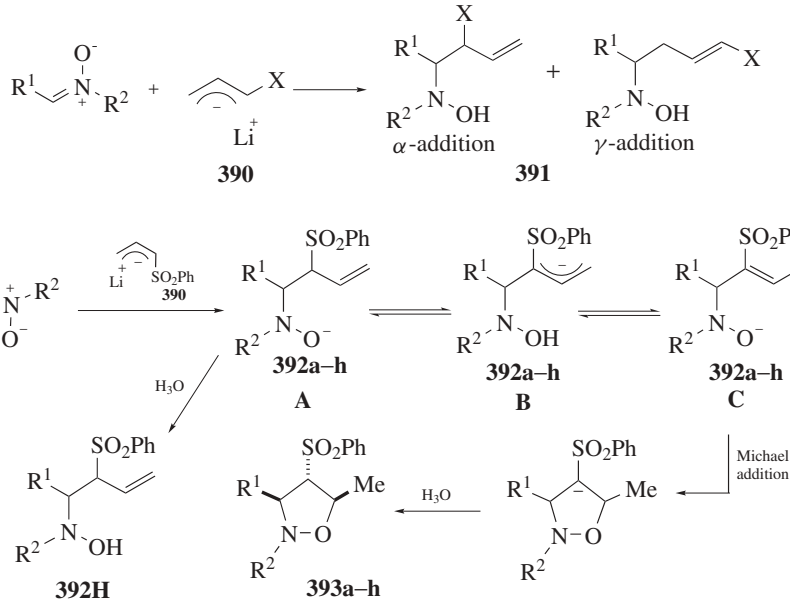


Scheme 2.169

Another approach is based on the condensation of lithiated sulfones to unsaturated nitrones (**387**). Good yields of single stereoisomers of unsaturated hydroxylamines (**388**) are obtained. They undergo a reverse-Cope elimination leading to a single enantiomer of pyrrolidine-*N*-oxide (**389**) (Scheme 2.169) (626).

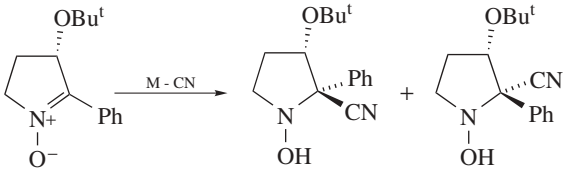
Nucleophilic addition of lithiated allylphenylsulfone (**390**) to nitrones at $-80^{\circ}C$ proceeds exclusively α to the phenylsulfonyl group (**391**, α-addition) affording *anti*-adducts (**392a–h**) in high yields, which at $0^{\circ}C$ give isoxazolidines (**393a–h**). The formation of these compounds involves isomerization of the allylsulfonyl moiety (**A-B-C**) to give a transient vinylsulfone (**392 C**), which then undergoes an intramolecular Michael addition (Scheme 2.170). The addition to several nitrones has been studied; the formation of γ-addition products (**391**) has never been observed. Theoretical calculations have been refined to explain accurately the selectivity of the allylation reaction (627).

2.6.6.1.6. Addition of CN^- Anion Stereoselective addition of the CN-group to nitrones has received considerable attention for the synthesis of optically active α-hydroxyamino nitriles which can be further transformed into α-hydroxyamino acids and α-amino acids. Me_3SiCN (TMSCN), Et_2AlCN, Bu_4NCN, and LiCN



392 / 393	a	b	c	d	e	f	g	h
R^1	Ph	Ph	Ph	Ph	2-Py	2-Furyl	Pr^i	
R^2	Ph	Bu^t	Bn	Me	Bn	Bn	Bn	Bn

Scheme 2.170

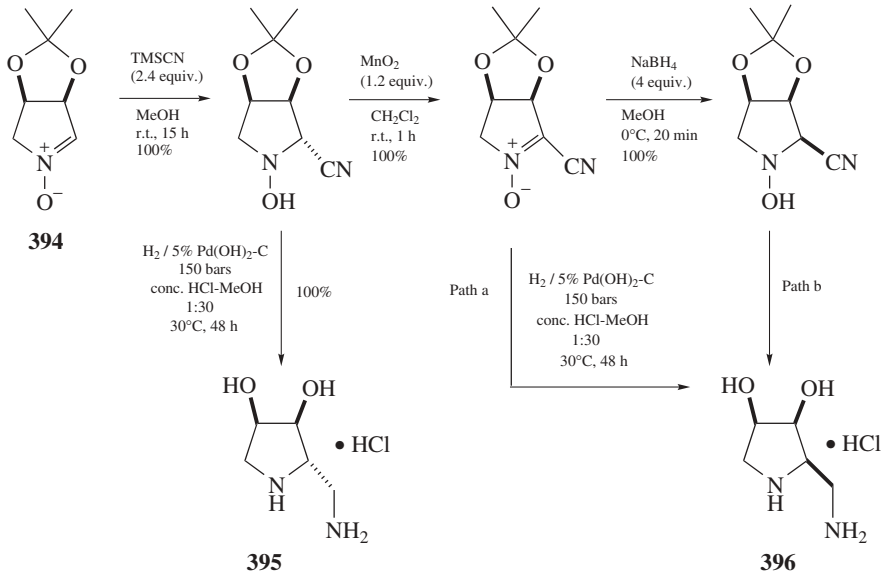


Scheme 2.171

are used as cyanating reagents. Addition of trimethylsilyl cyanide and diethylaluminium cyanide to chiral nitrones proceeds in good to excellent diastereoselectivity, and in high yield (in some cases quantitatively) (Scheme 2.171) (628–630).

The stereocontrolled addition of TMSCN to chiral 3,4-dihydro-2*H*- pyrroline *N*- oxides (**394**) is being used to prepare enantiopure 2-aminomethylpyrrolidines (**395**) and (**396**) (Scheme 2.172) (631).

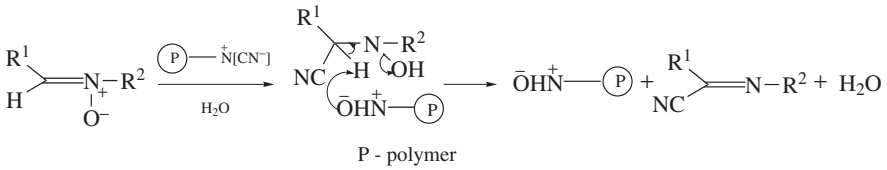
On the basis of theoretical data and experimental observations it was concluded that TMSCN reacts via a concerted transition state. Et_2AlCN initially forms a



Scheme 2.172

complex, which evolves to the final product via intramolecular carbon-carbon bond formation. On the basis of intrinsic reactivity data, there is no doubt that Et_2AlCN behaves as an intramolecular cyanating agent. A comparison of the results of the two cyanating reagents, employed under a variety of conditions, clearly shows that the stereoselectivity furnished by TMSCN is always considerably higher than that seen with Et_2AlCN. A study of the reaction profile by ^1H NMR and theoretical calculations allow to assign this difference to the switch from an intermolecular to an intramolecular mode of addition, on passing from TMSCN to Et_2AlCN (632). Reactions of nitrones with thiourea derivatives, containing electron accepting groups, substantially accelerates nucleophilic TMSCN addition (633).

When an anion exchange resin Amberlite IRA-400 [CN-] is used as a cyanating agent, the final products of the aldonitrone cyanating reaction are α-iminonitriles (Scheme 2.173) (Table 2.14) (634).



Scheme 2.173

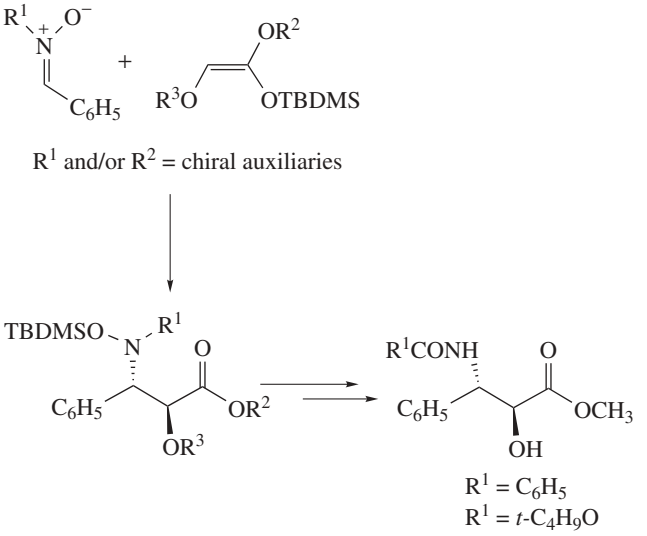
Table 2.14 Synthesis of α-iminonitriles using Amberlite IRA-400 [CN]

R^1	R^2	Yield %	Time/h
Ph	Ph	90	3
p-Cl-C_6H_4	Me	80	3.5
p-Me-C_6H_4	C_6H_{11}	75	4
o-Cl-C_6H_4	*p*-NO_2-C_6H_4	78	3.6
p-NO_2-C_6H_4	*m*-NO_2-C_6H_4	82	4
PhCH = CH	Ph	76	6
PhCH = CH	*p*-Br-C_6H_4	77	5
PhCH = CH	*p*-OMe-C_6H_4	81	5.5

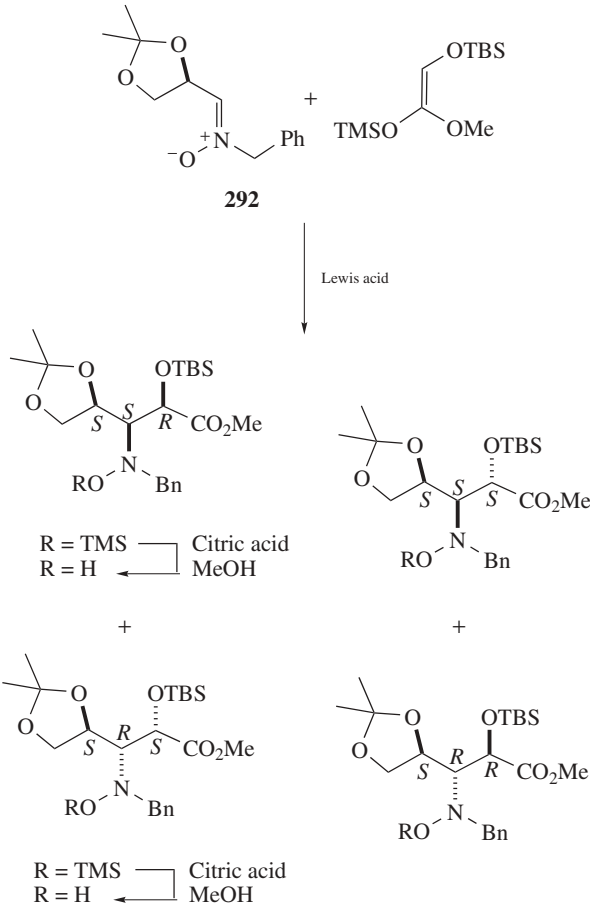
2.6.6.1.7. Addition of Ketene Acetals and Enoles In recent years, much attention has been given to the synthesis of optically active nitrogen-containing compounds, with the key step being the highly stereoselective nucleophilic addition of ketene silyl acetals to nitrones (Scheme 2.174). Similar to nitrone cyanations, in ketene silyl acetal reactions one observes an accelerating effect with thiourea derivatives (633).

Silyl ketene acetal addition to nitrone (**292**) is likely to generate four diastereomers. Depending on the employed Lewis acid, either O-silylhydroxylamines or free hydroxylamines (Scheme 2.175) are obtained (635).

The reaction of silyl ketene acetal addition to nitrones has been used for the synthesis of optically active (2*S*,3*S*)-benzoyl- and *N-boc*-phenylisoserine (636a) of isoxazolidine nucleoside–analog of thymine polyoxine C(636b) and of



Scheme 2.174

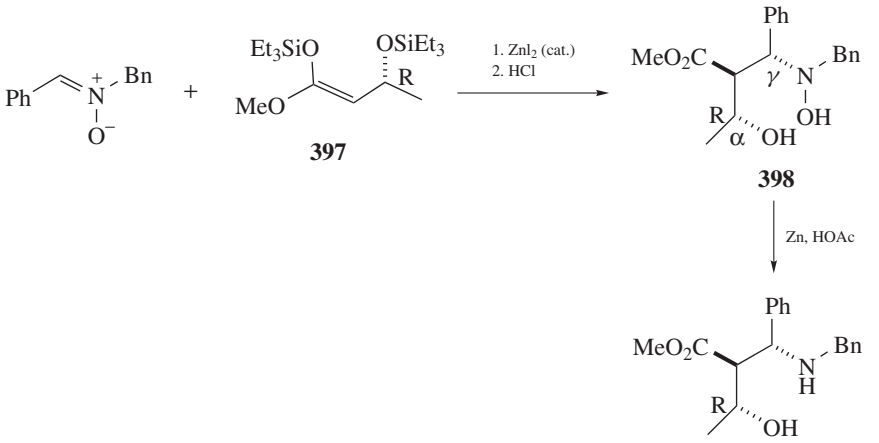


Scheme 2.175

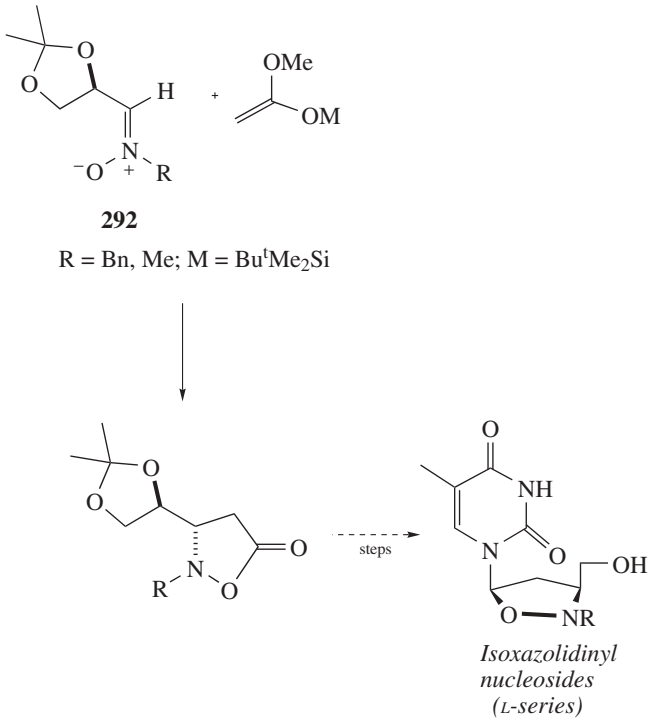
2-[(*N*-benzyl-*N*-hydroxylamine)phenylmethyl]-3-hydroxybutanoate (**398**) (637). The absolute configuration (**398**) was determined as (α*R*,β*S*,γ*R*); thus, diastereoselective addition of ketene silyl acetals (**397**) to nitrone proceeds as anti-α, β-anti-β, γ (Scheme 2.176).

The reaction of O-methyl-O-*tert*-butyldimethylsilyl ketene acetal with *N*-benzyl- and *N*-methyl-2,3-O-*iso*propylidene D-glyceraldehyde nitrones (**292**), in the presence of boron trifluoride etherate, affords the corresponding isoxazolidine-5-ones in high yields. These compounds were successfully applied as key intermediates in the synthesis of isoxazolidinyl nucleosides of the L-series (Scheme 2.177) (638).

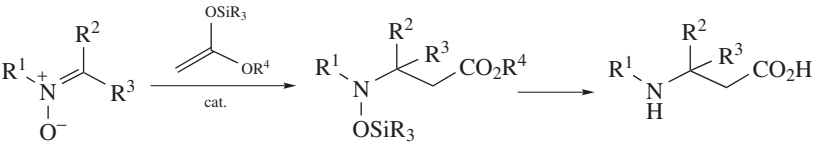
Addition of ketene silyl acetals to α,N-diarylnitrones, catalyzed by lanthanum trifloromethanesulfonate [lanthanide triflate, $La(OTf)_3$], affords addition



Scheme 2.176



Scheme 2.177



Cat.: Ti-(S) - BINOL - 2ArOH *or* $Ar(OH)_2$
R^1 = Ph, Bn, Bu^t; R^2 = H; R^3 = Ph, 2-Naphthyl
p-MeC_6H_4, 3-Pyridyl, 3,4-$(OCH_2O)C_6H_3$

Scheme 2.178

products in excellent yield. α-Aryl-*N*-*tert*-butylnitrone reacted with ethyl trimethylsilylacetate to yield the unexpected α,β-unsaturated ester $ArCH=CHCO_2Et$ in a 100% E-form (639). The use of a chiral titanium complex, prepared from $Ti(O^iPr)_4$, BINOL, and *tert*-butylcatechol, directs the addition reaction of silyl ketene acetals enantioselectively. Further transformations of adducts give optically active β-amino acids (Scheme 2.178) (640).

Theoretical calculations at DFT level agree that the reactions of nitrones with silyl ketene acetal proceeds via 1,3-dipolar cycloaddition followed by the transfer of the silyl group, yielding an open-chain product (641).

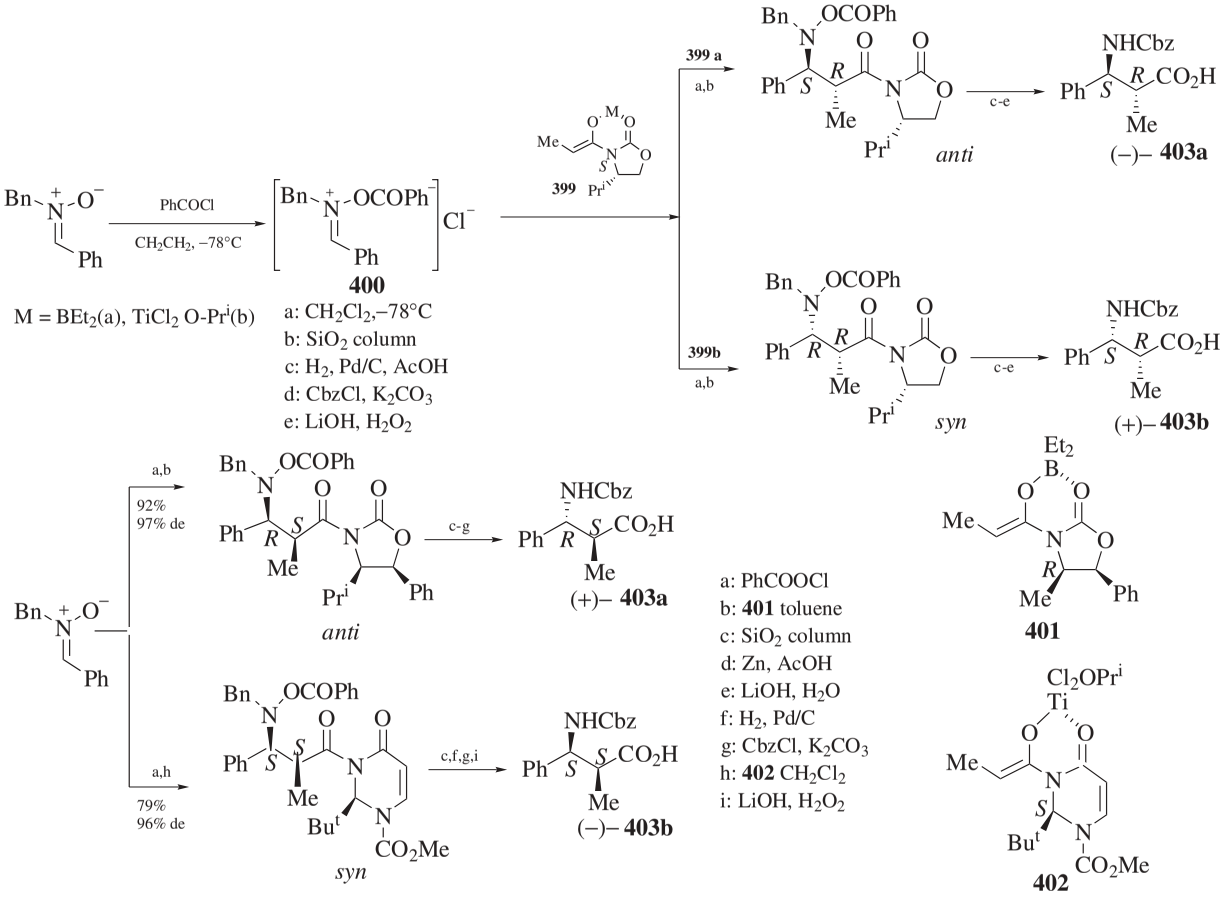
Asymmetric syntheses of β- amino acids result from the addition of chiral enolates (**399**) to nitrone (**400**) via *N*-acyloxyiminium ion formation (642, 643). Regioselective convergence is obtained in the reactions of chiral boron- and titanium- enolates (**399a,b**), (**401**), and (**402**). This methodology was used in preparing four stereoisomers of α-methyl-β-phenylalanine (**403**) in enantiomeric pure form (Scheme 2.179) (644).

The addition of lithium or magnesium ester enolates to nitrones in THF at 78°C or in Et_2O at −20°C, constitutes a direct synthesis of *N*-hydroxy-β-amino acid esters (Scheme 2.180) (645).

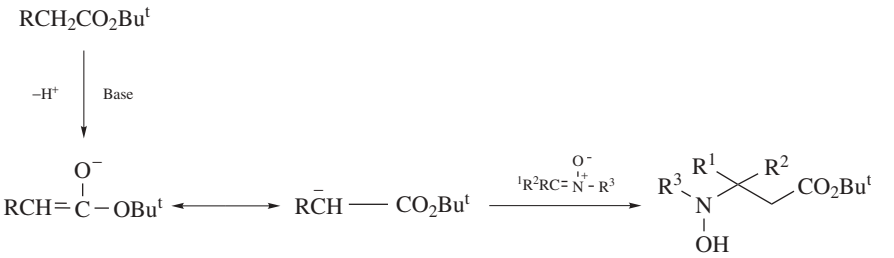
The *N*-hydroxylamino compounds (**404**) and (**405**), obtained from the reaction of *tert*-butyl acetate with 3,4-dihydroisoquinoline-*N*-oxide or 5,5-dimethylpyrroline-*N*-oxide, when boiled in methylene chloride in the presence of triphenylphosphine, carbon tetrachloride and triethylamine, are transformed to (1,2,3,4- tetrahydroisoquinolin-1-ilidene) acetate (**406**) or (pyrrolidin-2-ilidene) acetate (**407**) (Scheme 2.181) (645).

High diastereoselectivity occurs in the addition of lithiated methoxyallene to chiral cyclic nitrones. The hydroxylamines obtained can be easily transformed into derivatives of 1,2-oxazine hydroxylamine, which are products of a novel [3 + 3] cyclization reaction (Scheme 2.182) (646, 647).

2.6.6.1.8. Reactions of Vinylation and Ethynylation Vinylation and ethynylation of nitrones using vinyl (137, 202, 563, 564) and ethynyl (199, 213, 219) organometalic reagents is a convenient method for synthesizing various nitrogen-containing compounds such as α-amino aldehydes, α-amino acids, amino

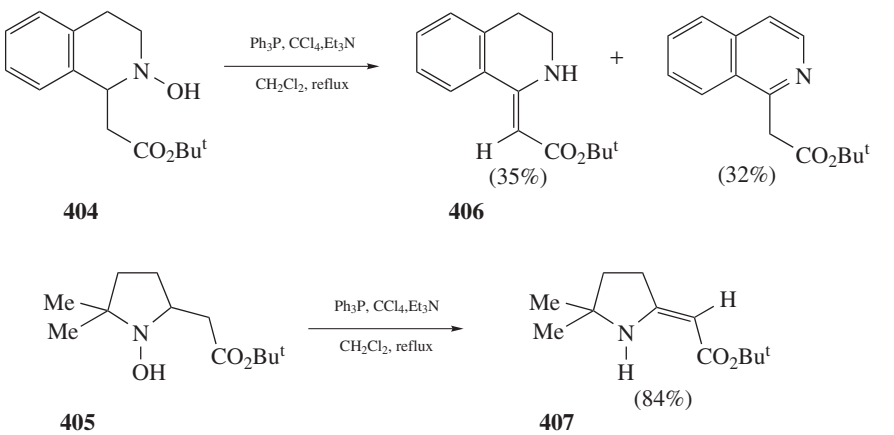

PhCOCl
CH2CH2, –78°C
400
M = BEt2(a), TiCl2 O-Pri(b)
a: CH2Cl2,–78°C
b: SiO2 column
c: H2, Pd/C, AcOH
d: CbzCl, K2CO3
e: LiOH, H2O2
399
399 a
399b
a,b
c-e
anti
syn
(–)– 403a
(+)– 403b
a,b
92%
97% de
a,h
79%
96% de
c-g
c,f,g,i
(+)– 403a
(–)– 403b
a: PhCOOCl
b: 401 toluene
c: SiO2 column
d: Zn, AcOH
e: LiOH, H2O
f: H2, Pd/C
g: CbzCl, K2CO3
h: 402 CH2Cl2
i: LiOH, H2O2
401
402

Scheme 2.179



Ester: R = Bu^t, Et;
Nitrone: **a:** $R^1 = R^3 = Ph$, $R^3 = H$;
b: $R^1 = Me$, $R^2 = H$, $R^3 = Et$;
c: $R^1 = R^2 = Me$, $R^3 = Pr^i$;
d) $R^1 - R^3 = (CH_2)_3$, $R^3 = H$;
e: $R^1 - R^3 = O\text{-}C_6H_4(CH_2)_2$, $R^2 = H$;
f: $R^1 - R^3 = (CH_2)_2CMe_2$, $R_2 = H$

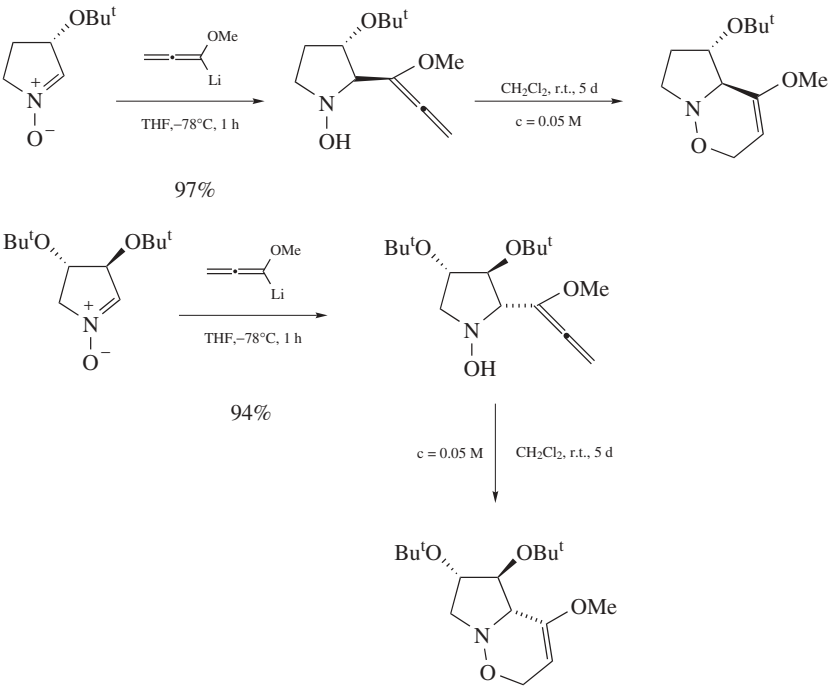
Scheme 2.180



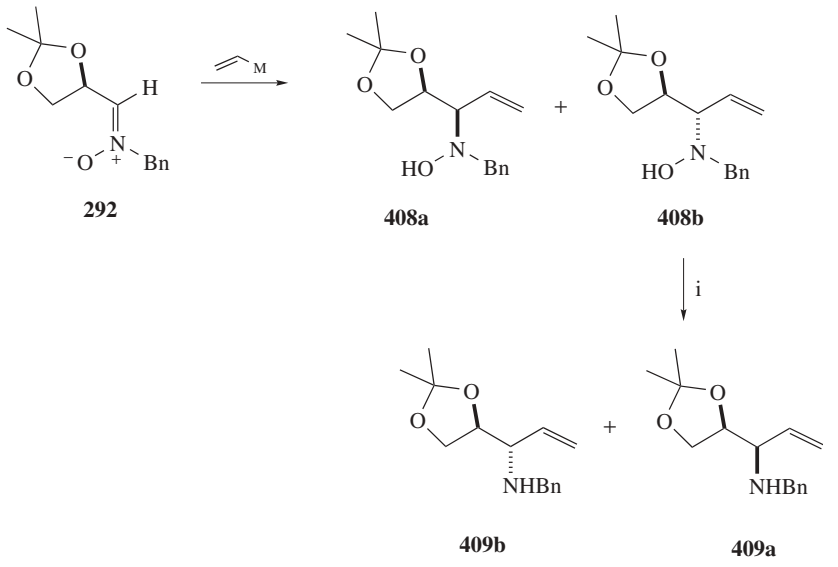
404 **406** **405** **407**

Scheme 2.181

sugars, and α-amino nitriles (193, 648, 649). Thus, the reaction of vinylmagnesium bromide with various nonchiral nitrones proceeds to the corresponding allyl amines in good yields (650). Addition of vinylmagnesium bromide to chiral nitrones takes place with high diastereoselectivity in good yields (651). To illustrate stereocontrolled addition of vinyl organometalic compounds (CH_2CHM, where M = MgBr, $CeCl_3$, $CuLi_{1/2}$, Li and $AlEt_2$) the synthesis of allylamines (**409a,b**) has been carried out. Hydroxylamines (**408a,b**), the products of nucleophilic addition of vinyl organometalics to *N*-benzyl-2,3-O-*iso*propylidene-D-glyceraldehyde nitrone (BIGN) (**292**) are then reduced to (**409a,b**) upon treatment with Zn(0)/Cu(II) (Scheme 2.183) (Table 2.15) (652).



Scheme 2.182



i: Zn, Cu(OAc),AcOH, 70˚C, 1 h

Scheme 2.183

Table 2.15 Diastereoselective addition of vinyl reagents to nitrone BIGN 292

Entry	M	(eq)	Lewis acid[a]	Solvent	(t^0)	Time	*syn/anti*[b]	Yield (%)[c]
1	MgBr	(1.2)	none	THF	(0°C)	1 h	76:24	86
2	MgBr	(1.2)	$ZnBr_2$	Et_2O	(0°C)	1 h	53:47	84
3	MgBr	(1.2)	$MgBr_2$	Et_2O	(0°C)	1 h	56:44	80
4	MgBr	(1.2)	Et_2AlCl	Et_2O	(0°C)	1 h	8:92	86
5	$CeCl_3$	(1.2)	none	THF	(−40°C)	2 h	58:42	74
6	$CeCl_3$	(1.2)	Et_2AlCl	THF	(−40°C)	2 h	30:70	78
7	$(CuLi)_{1/2}$	(1.0)	none	THF	(−80°C)	2 h	70:30	80
8	$(CuLi)_{1/2}$	(1.0)	Et_2AlCl	THF	(−80°C)	2 h	22:78	79
9	Li	(1.5)	none	THF	(−80°C)	15 min	35:65	90
10	Li	(1.5)	Et_2AlCl	Et_2O	(−80°C)	15 min	4:96	92
11	$AlEt_2$	(1.1)	none	Et_2O	(−40°C)	2 h	52:48	86
12	$AlEt_2$	(3.0)	none	Et_2O	(−40°C)	2 h	32:68	87

[a]Nitrone was precomplexed with 1.0 eq of the Lewis acid prior to the addition.
[b]Measured from the intensities of ^1H NMR signals.
[c]Determined on isolated mixtures of *syn* and *anti* adducts.

High stereoselective addition of vinylmagnesium bromide to L-tartaric acid-derived nitrone was used as a key step in the synthesis of (+)-lentiginosine and its structural analogs (653).

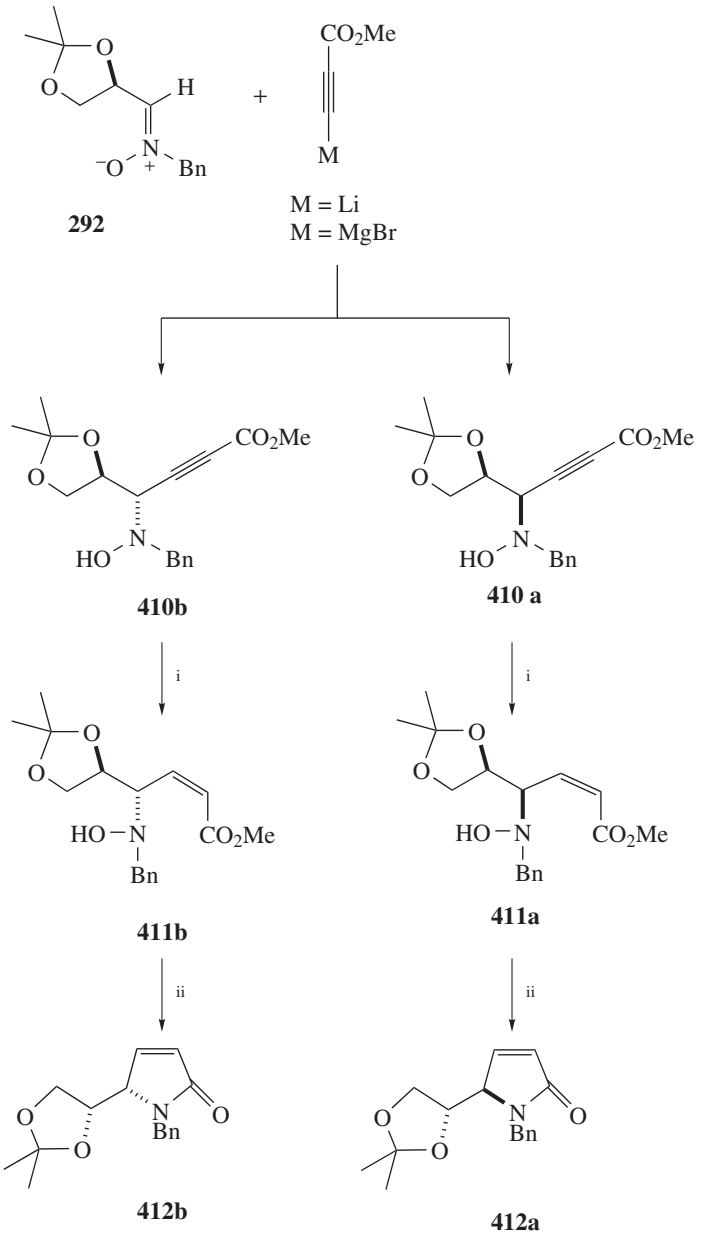
It was shown (654) that the sequence terminal alkyne hydrozirconation, Zr to Zn exchange and addition to nitrones, is a good method to the stereoselective synthesis of (E)-N-allylhydroxylamines, under mild conditions and in good yield.

Another useful method for generating various *N*-allylhydroxylamines is the reaction between vinyl boronic ester of pinacol and nitrone in the presence of dimethylzinc (655).

Addition of lithium derivatives of acetylenides (Li—C≡C–CO_2R) to chiral nitrones proceeds with high stereoselectivity, giving α-acetylene substituted hydroxylamines (**410a,b**) (656). This reaction has been successfully applied to the synthesis of γ-hydroxyamino-α,β-ethylene substituted acids (**411a,b**), formed in the reduction of (**410**) with Zn in the presence of acid (657, 658), and to chiral 5-substituted-3-pyrroline-2-ones (**412a,b**) (Scheme 2.184) (658).

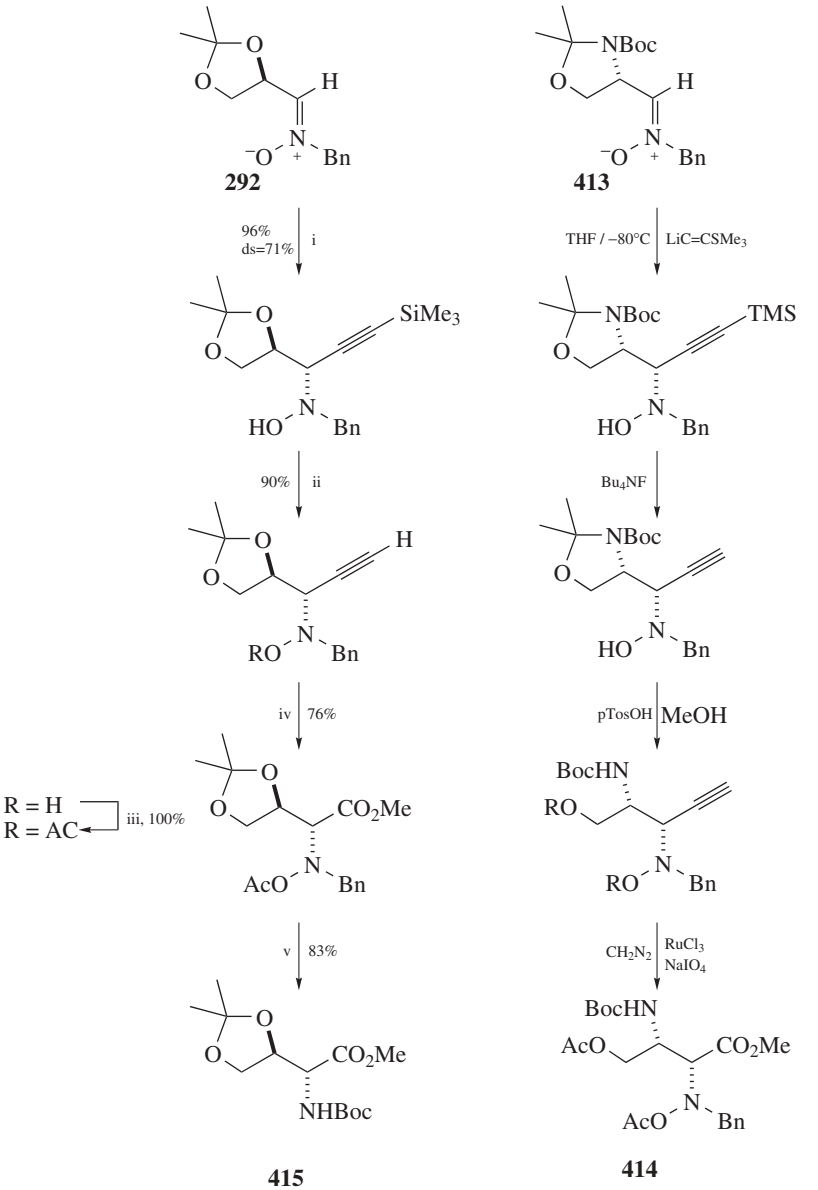
Similar addition reactions of alkyl 3-lithiopropiolates to nitrones with subsequent Raney Ni hydrogen reduction and amino group protection, led to the synthesis of (S) and (R)-vigabatrin (659).

Addition of (trimethylsilyl)acetylides to chiral α-aminoalkyl- (**413**) and α-alkoxyalkyl-(BIGN) (**292**) nitrones proceeds stereoselectively. Successive desilylation (Bu_4NF, THF) and transformation of the ethynyl group into carboxyl ($RuCl_3$-$NaIO_4$) led to the synthesis of diastereomerically pure *N*-hydroxy-α-amino acids (**414**) and α-amino acids (**415**) (Scheme 2.185) (199, 202, 652, 660).



i: Zn, AcOH / MeOH
ii: 20% aqueus solution of $TiCl_3$

Scheme 2.184



i: EtAlCl, R.T., 5 min, then LiC=CSiMe$_3$, THF, −80°C, 1 h
ii: Bu$_4$NF, r.t., 2 min
iii: Ac$_2$O, Py, r.t., 4 h
iv: RuCl$_3$, NaIO$_4$, CH$_3$CN-CCl$_4$-H$_2$O, r.t., 2 min, then CH$_2$N$_2$, Et$_2$O, 0°C, 15
v: H$_2$, Pd(OH)$_2$-C, Boc$_2$O, r.t., 80 psi, 6 days

Scheme 2.185

The reaction of nitrones with terminal alkynes proceeds in excellent yields and high purity, in the presence of stoichiometric quantities of diethylzinc and zinc triflate (219, 661–663). To optimize the process of diastereoselective addition of terminal alkynes to chiral nitrones, $ZnCl_2$ and NEt_3 in toluene were used. This reaction protocol is facile to perform, cost-effective and environmental friendly (664).

Asymmetrical addition of alkynylzinc reagents to nitrones has been achieved in the presence of L-tartaric acid ester as a chiral additive (665).

2.6.6.1.9. Reactions of Allylation and Propargylation Allylation of prochiral and chiral nitrones (**292**) with allylmagnesium chloride leads to homoallylic hydroxylamines (**416**), which via an iodo cyclization step are converted to 5-(iodomethyl)isoxazolidines (**417**) (Scheme 2.186) (202, 213, 666–668).

Double addition of Grignard reagents to *N*-glycosyl nitrones (**336**), in a domino fashion, affords hydroxylamines. Their usefulness has been shown with the synthesis of pyrroloazepine (**418**) via a ring closing metathesis key step (Scheme 2.187) (564).

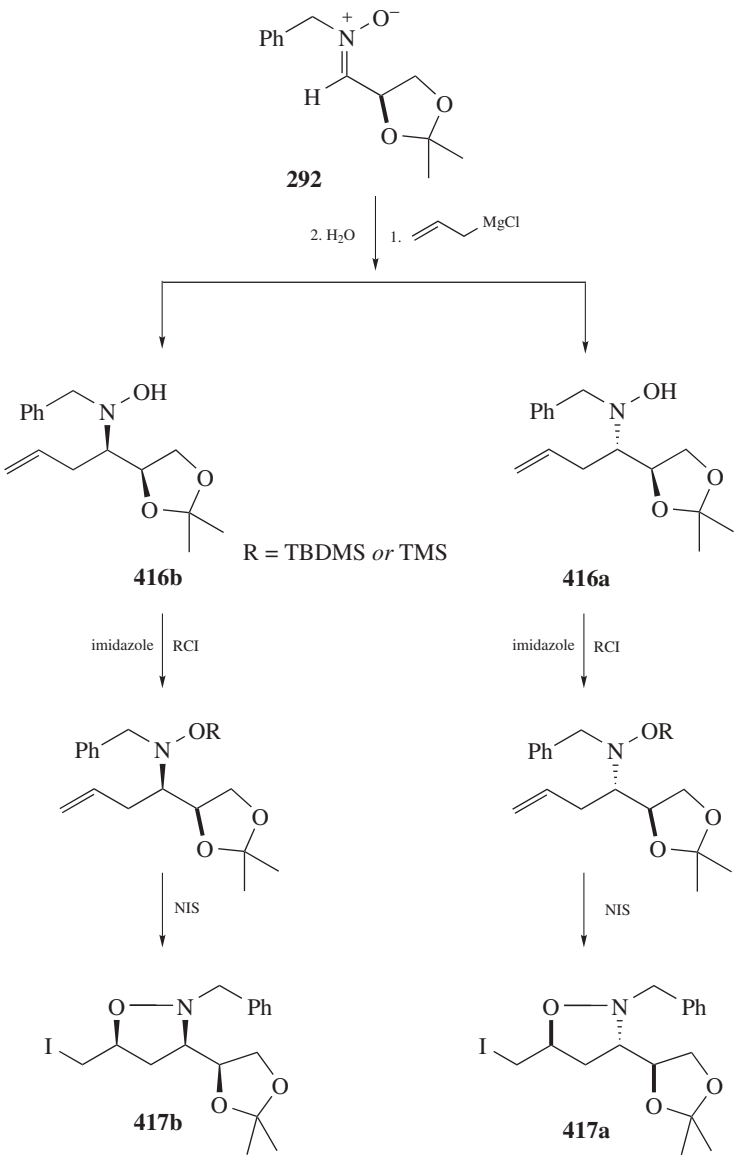
The stereocontrolled addition of allyllithium or allylmagnesium bromide to chiral nitrones (Fig. 2.28), promoted by the addition of Lewis acids ($ZnBr_2$, $TiCl_4$, Et_2AlCl, $BF_3{\cdot}Et_2O$, $Ti(^iPrO)_2Cl_2$, $Ti(^iPrO)_4$, TMSOTf and TMEDA) is described (669). Whereas for α-alkoxyalkyl nitrones, the stereocontrol depends on the Lewis acid, used as an activator, for α-aminoalkyl nitrones, the diastereofacial course of the reaction depends on the protection of the α-aminoalkyl group. The successful implementation of the methodology is represented by the enantiodivergent synthesis of *N*-Boc- L- (**L-AG**) and *N*-Boc-D-allylglycine (**D-AG**) (Scheme 2.188).

Addition of allylic zinc bromides to nitrones, generated *in situ* from allylbromides and zinc powder in THF (670), allyltributylstannane (671) and lithiated allyl *tert*-butyldimethylsilyl ether (672), proceeds regioselectively in good yields and is used to synthesize homoallyl hydroxylamines (Scheme 2.189). The latter were subjected to an iodo cyclization reaction (see Scheme 2.186).

Using trimethylsilyl triflate, a *one-pot* reaction of acetoxyallylation and O-silylation of nitrones, gave silylated hydroxylamines (673). Enantiomers of the naturally occurring alkaloid dihydropinidine, potential antifeedants against the pine weevil *Hylobius abietis*, were prepared by diastereoselective, dimethylzinc mediated addition of pinacolyl 2-propenylboronate to (*R*)- and to (*S*)-2-methyl tetrahydropyridine-*N*-oxide, obtained from D-alanine and L-alanine, respectively (Scheme 2.190) (674).

The use of allylindium reagent, generated *in situ*, makes it possible to introduce the allyl group into C-aromatic aldonitrones, in dimethylformamide DMF-H_2O at room temperature (675). Under similar conditions the indium-catalyzed reaction of propargyl bromide with nitrones leads to the corresponding homoalkynyl hydroxylamines (Scheme 2.191) (676).

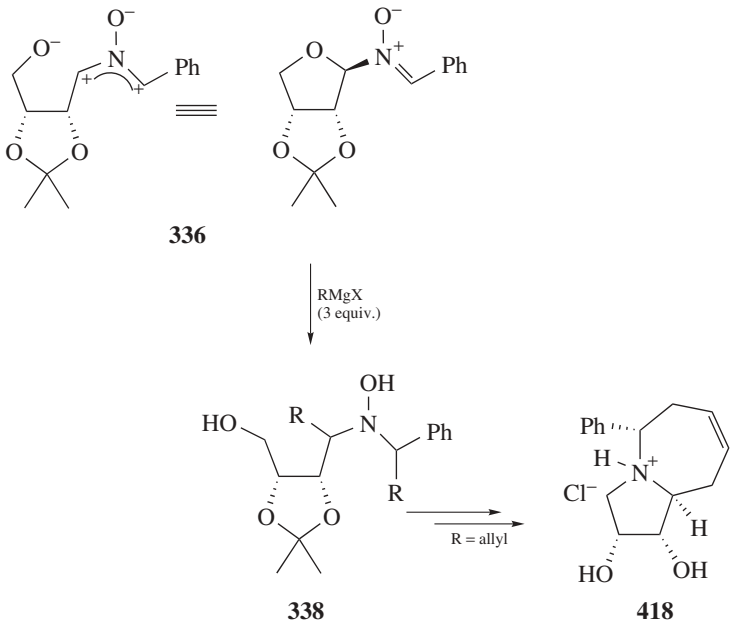
2.6.6.1.10. Addition of Indoles Pictet-Spengler intramolecular reaction of nitrones (**419**), synthesized from N_b-hydroxytryptamine with aldehydes, gave the



Scheme 2.186

corresponding 1-substituted-2-hydroxytetrahydro-β-carbolines (**420**) with optical purity up to 91%. This reaction is catalyzed by chiral binaphtol-derived Brønsted acid-assisted Lewis acids (BLA) (**421**) and (**422**) (Scheme 2.192) (677).

The Pictet-Spengler intramolecular reaction was used as one of the important steps in the total synthesis of (−)-eudistomins (184, 185).



336 **338** **418**

Scheme 2.187

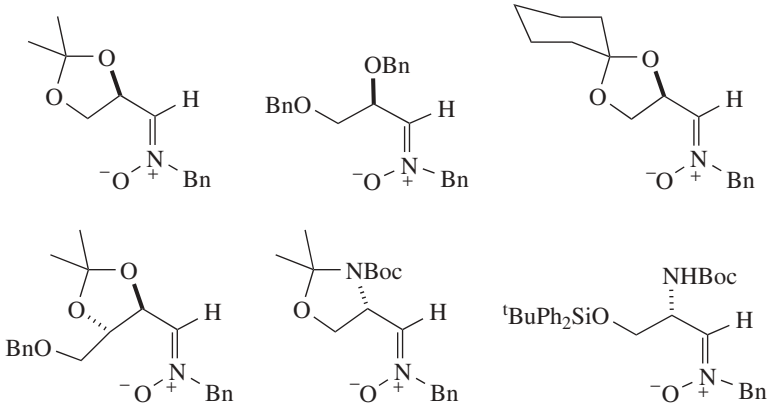
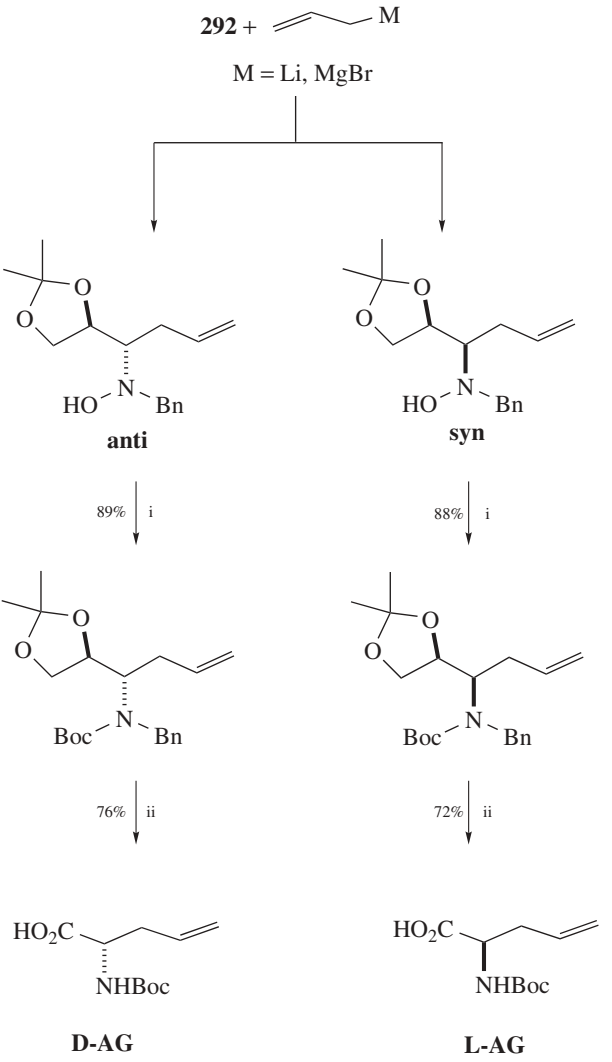


Fig. 2.28

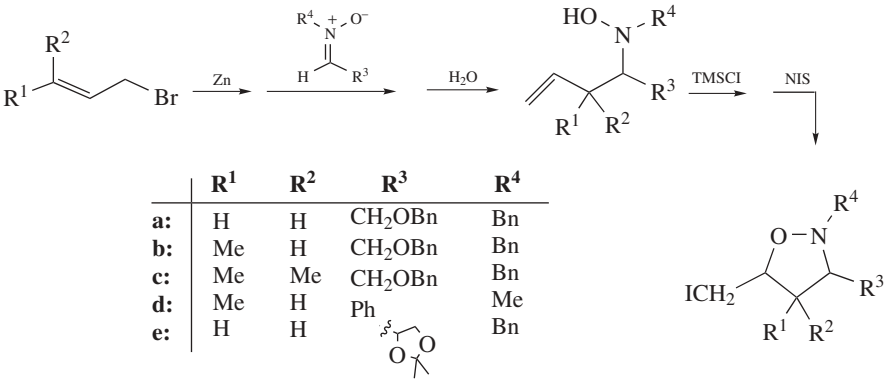
An efficient catalyst of the Pictet-Spengler reaction was found to be the $Yb(OTf)_3$-TMSCl system (678).

The reaction of nitrones with indoles in the presence of HCl gives indolyl *N*-hydroxylamines. In the presence of Me_3SiCl symmetrical diindolylalkanes are formed (Scheme 2.193) (679, 680).



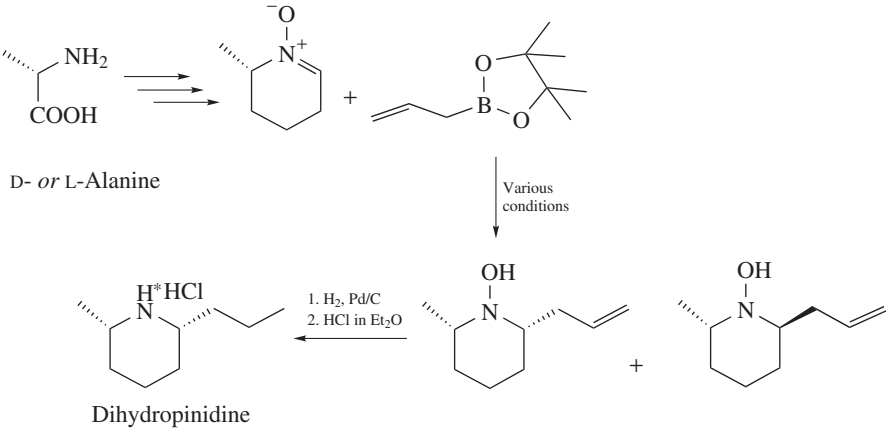
Reagents and conditions: **(i)** Zn, AcOH, 70°C; then Boc_2O, dioxane, rt; **(ii)** Li, NH_3 (liq); then *p*-TosOH, MeOH; then $NaIO_4$, SiO_2, CH_2Cl_2; then TEMPO, [bis(acetoxy)iodo]benzene, MeCN-H_2O;

Scheme 2.188

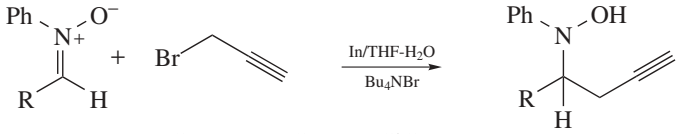


	R1	R2	R3	R4
a:	H	H	CH_2OBn	Bn
b:	Me	H	CH_2OBn	Bn
c:	Me	Me	CH_2OBn	Bn
d:	Me	H	Ph	Me
e:	H	H		Bn

Scheme 2.189

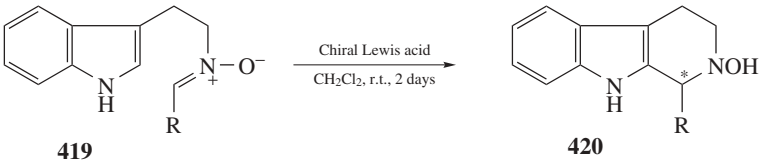


Scheme 2.190

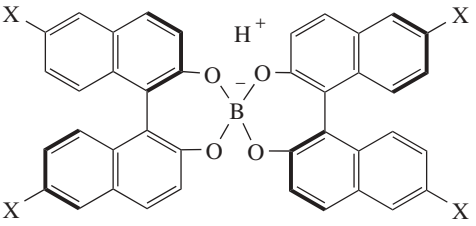


R = C_6H_5, *p*-MeC_6H_4, *p*-ClC_6H_4

Scheme 2.191



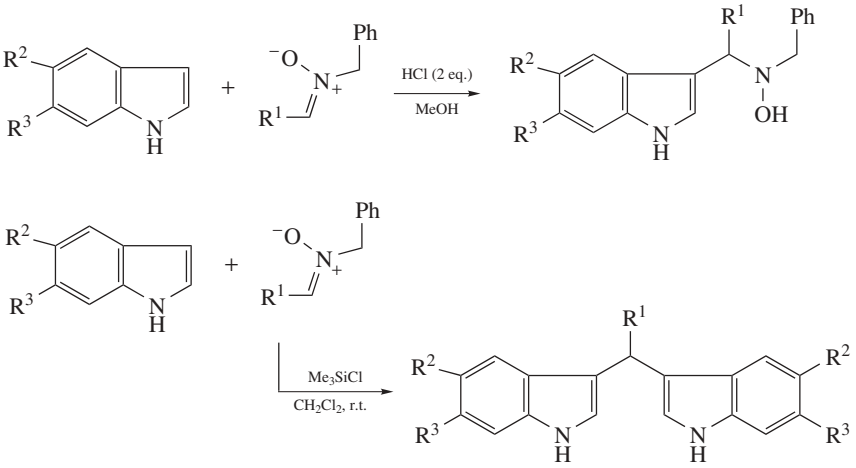
419 **420**



a: R = Ph
b: R = *p*-MeO-C_6H_4
c: R = *p*-NO_2-C_6H_4
d: R = 1-Naphthyl
e: R = Me
f: R = Bu^i

R - **421** X = H
R - **422** X = Br

Scheme 2.192

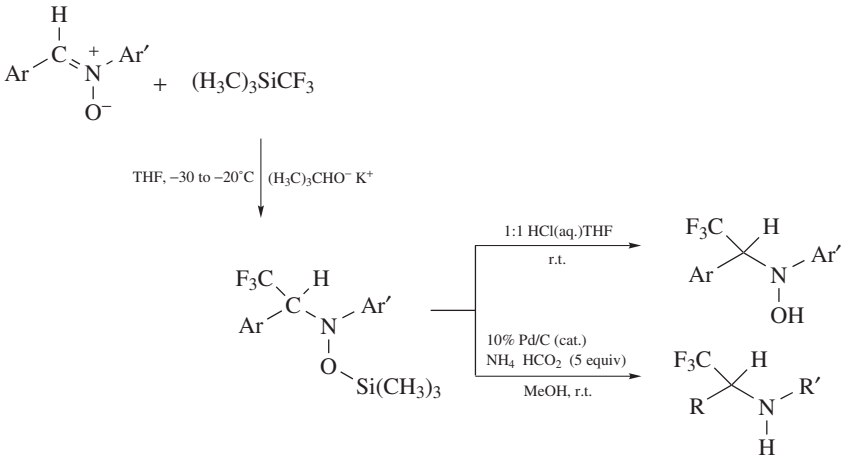


	a	b	c	d	e	f	g
R^1	Me	CH_2NHBoc	CH_2OCH_2Ph	Me	Et	CH_2NHBoc	Me
R^2	H	H	H	Br	Br	H	MeO
R^3	H	H	H	H	H	Br	H

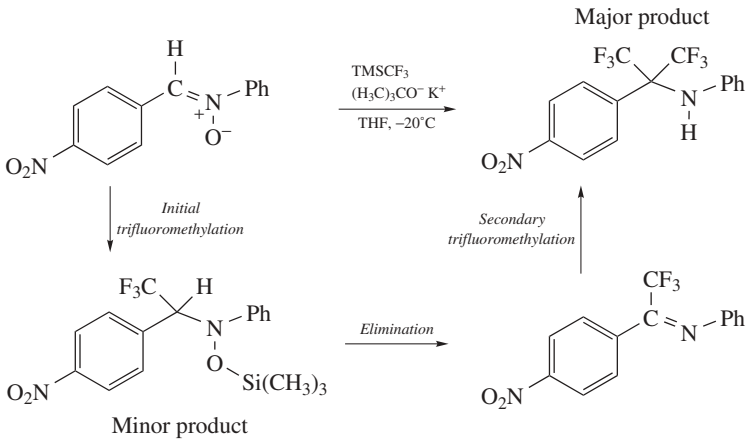
Scheme 2.193

2.6.6.1.11. Nucleophilic Perfluoroalkylation of Nitrones The reaction of α,*N*-diaryl nitrones with (trifluoromethyl)trimethylsilane ($TMSCF_3$) gives O-trimethylsilyl ethers of α-(trifluoromethyl)-hydroxylamines. This reaction is initiated by potassium *tert*-butoxide. Removal of the trimethylsilyl group on acid treatment leads to α-(trifluoromethyl)hydroxylamines, whereas catalytic hydrogenation gives α-(trifluoromethyl)amines (Scheme 2.194).

The adducts of nitrone/$TMSCF_3$ with strong electron-withdrawing groups in the α-aryl ring or in the α-heterocyclic groups, undergo an elimination/addition sequence, generating α-aryl-α,α-bis(trifluoromethyl) *N*-phenylamines (major product) (Scheme 2.195).



Scheme 2.194

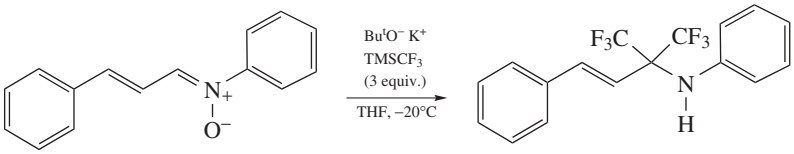


Scheme 2.195

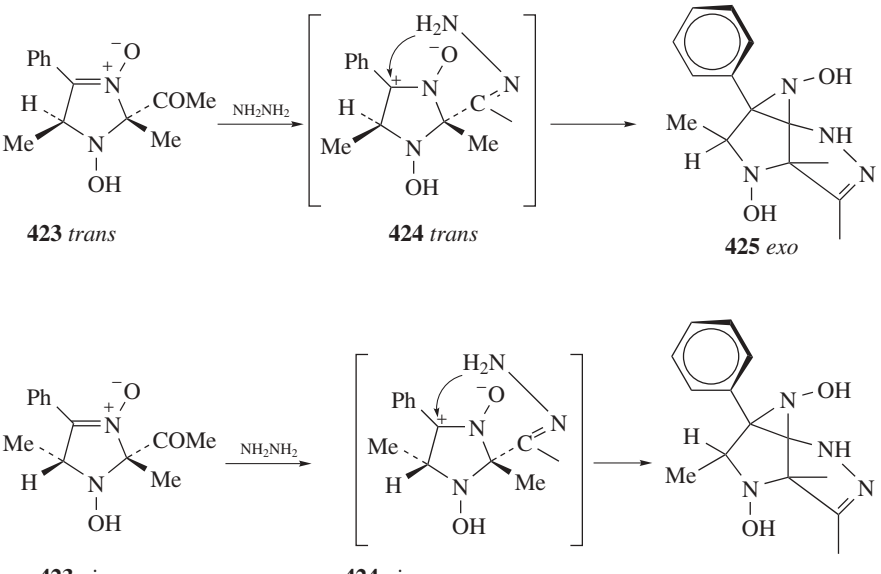
Nitrones with alkyl groups bound directly to the 1,3-dipolar moiety fail to react with $TMSCF_3$, but trifluoromethylation of β,γ-unsaturated nitrones such as α-styryl-*N*-phenyl nitrone gives the products of trifluoromethylation (Scheme 2.196) (681, 682).

2.6.6.1.12. Addition of N-, S- and P-Nucleophiles The reaction of nitrones with heteroatom centered nucleophiles has been little investigated and are mainly applied to the synthesis of new heterocyclic systems and stable nitroxyl radicals, containing a heteroatom at the α-carbon atom.

The formation of derivatives of 2,3,6,8-tetraazabicyclo-[3.2.1]3-octene (**425**) arises from an intramolecular nucleophilic addition to the nitrone group of hydrazone (**424**). Compound (**424**) was prepared by reaction of 2-acyl-3-imidazoline-3-oxides (**423**) with hydrazine. From the *cis*- and *trans*-derivatives (**424**), *exo*- and *endo*-isomers (**425**) were obtained (Scheme 2.197). The reaction of intramolecular cyclization does not occur in cases with monosubstituted hydrazones (316).



Scheme 2.196

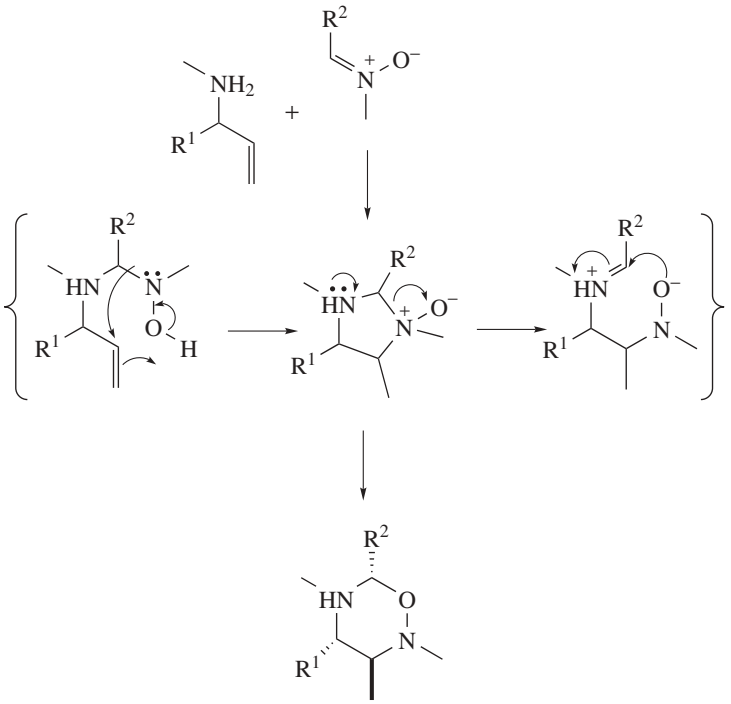


Scheme 2.197

Nucleophilic addition of primary α-R^1-allylamine to nitrone followed by a reverse Cope cyclization and Meisenheimer rearrangement gives the oxadiazinanes (**426a–h**) (Scheme 2.198). These reactions have found use for the preparation of oxadiazines, vicinal aminohydroxylamines, and diamines; the latter are of particular interest as chiral ligands (683, 684).

Similarly, nitrones react with α-R^1-allylthiols to give 1,3-thiazolidine-*N*-oxides (**427**). On heating, they are transformed into 1,5,2-oxathiazinanes (**428**) (Scheme 2.199) (685).

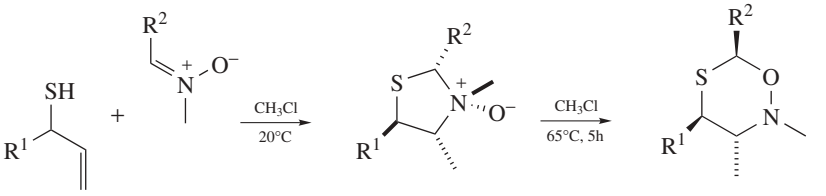
Nitrone reactions with lithiated dialkyl phosphite results in the formation of α-(hydroxyamino)phosphonate, which, depending on the character of the R substituent at α-C lead to α-phosphorylated nitrones (**429**) or β-phosphorylated nitroxyl radicals (**430**) after successive oxidations (Scheme 2.200) (686–689).



426 a-h

a: R^1 = H, R^2 = c-C_3H_5; **b:** R^1 = H, R^2 = n-hexyl; **c:** R^1 = R^3 = H; **d:** R^1 = H, R^2 = Ph; **e:** R^1 = Me, R^2 = c-C_3H_5; **f:** R^1 = Me, R^2 = n-hexyl; **g:** R^1 = Ph, R^2 = c-C_3H_5; **h:** R^1 = Ph, R^2 = n-hexyl;

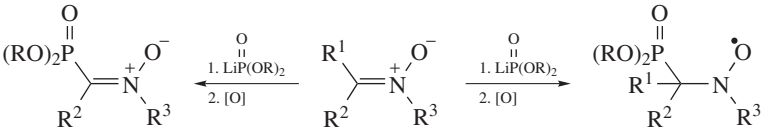
Scheme 2.198



427 a–e **428 a–e**

a: $R^1 = H$, $R^2 = Ph$; **b:** $R^1 = H$, $R^2 = c\text{-}C_3H_5$;
c: $R^1 = H$, $R^2 = n\text{-}C_5H_{11}$; **d:** $R^1 = Ph$, $R^2 = c\text{-}C_3H_5$;
e: $R^1 = Ph$, $R^2 = n\text{-}C_5H_{11}$

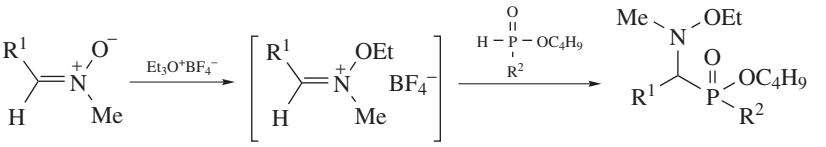
Scheme 2.199



429 **430**

R = Me, Et; R^1 = Alk, Ar; R^2 = H, Alk, Ar; R^3 = Alk, Ar; $R^2 + R^3 = -(CH_2)_n-$ ($n = 3,4$)

Scheme 2.200



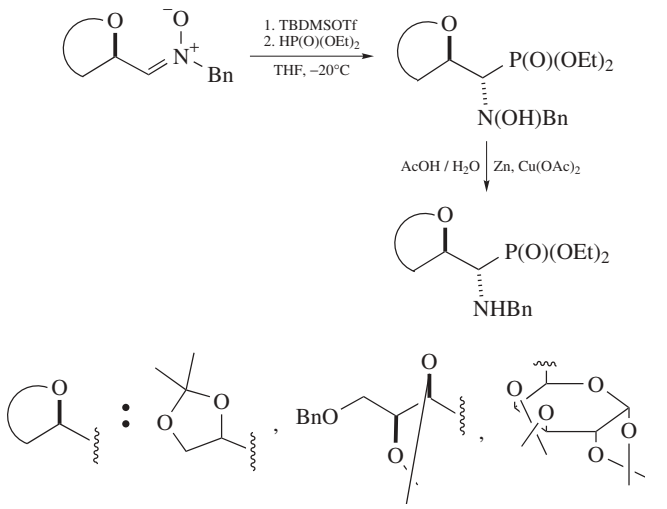
R^1 = Ph, *n*-ClC_6H_4; R^2 = Me, Ph

Scheme 2.201

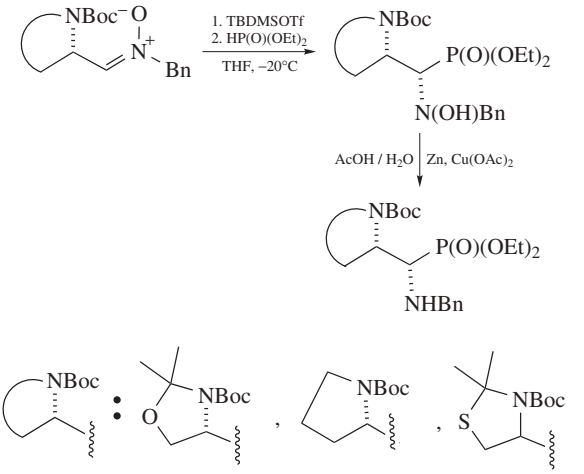
A convenient route to β-phosphorus nitroxides involves the 1,3-addition of trimethylsilyl phosphites (e.g., diethyl) or trimethylsilyl phosphines (e.g., diphenyl) to aldo nitrones (e.g., α-PBN, DMPO), or keto nitrones (e.g., 2-Et-DMPO or 2-Ph-DMPO), to form α-phosphityl- or α-phosphinyl-O-silylhydroxylamines. Acidic hydrolysis provides the corresponding hydroxylamines which are easily oxidized to β-phosphorus-nitroxides (690).

Nucleophilic addition of methyl- or phenylphosphite *n*-butyl- esters to oxoimine salts, generated by nitrone alkylation of triethyloxoniumtetrafluoro borate (Meerwein salt), leads to α-aminophosphinic acid esters (Scheme 2.201) (691).

Addition of diethyl phosphites to aldo nitrones derived from chiral α-alkoxy (Scheme 2.202) and *N*-Boc-α-amino (Scheme 2.203) aldehydes can be achieved



Scheme 2.202



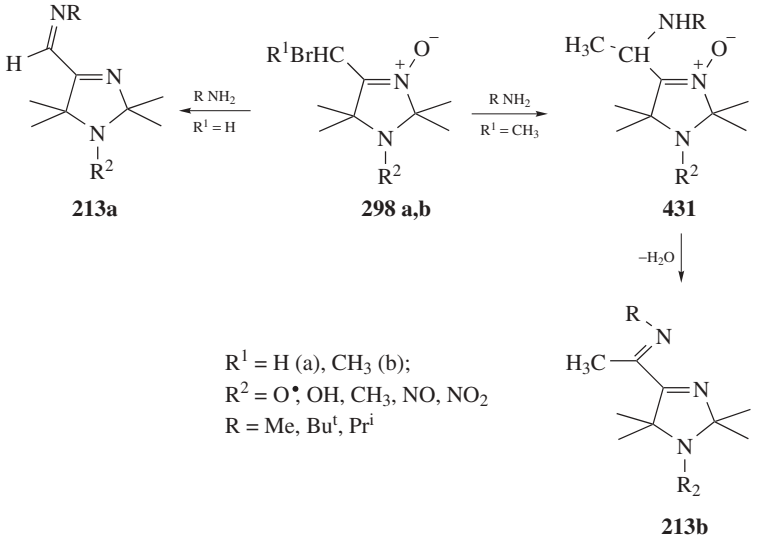
Scheme 2.203

by the addition of an equimolar quantity of *tert*-butyldimethylsilyl triflate (TBDMSOTf). This method makes it possible to use nitrones in the stereoselective synthesis of various α-aminophosphonates and their *N*-hydroxy derivatives (198, 692). They are of particular interest in biological researches (693, 694).

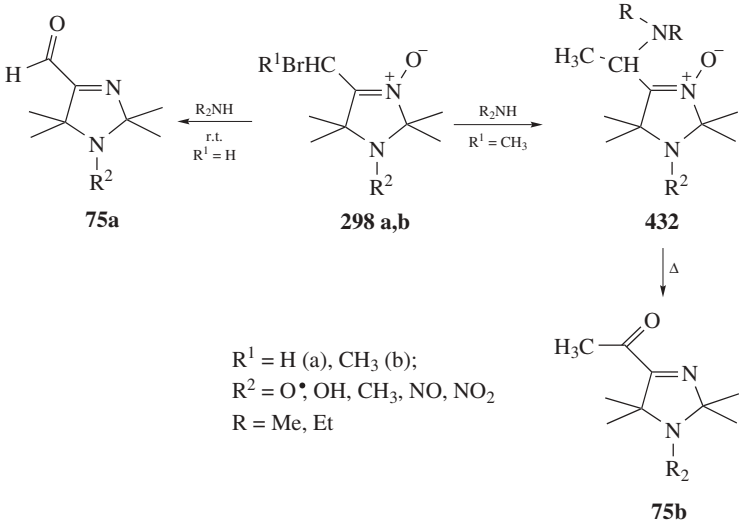
2.6.6.2. Nucleophilic Substitution in α-Haloalkylnitrones α-Monobromomethyl derivatives of nitrones (**298a**) react with primary amines or hydrazine, giving de-oxygenated products (**213a**). With α-bromoethyl derivatives (**298b**)

products of initial nucleophilic substitution (**431**) were obtained. They were readily transformed into compounds (**213b**) shown in Scheme 2.204 (539, 540).

The reactions of α-bromoalkyl nitrones (**298**) with secondary amines lead initially to α-dialkylamino derivatives (**432**), which on heating, give aldehydes and ketones (**75a,b**) in high yield (Scheme 2.205) (540).



Scheme 2.204



Scheme 2.205

2.7. NITRONE APPLICATION IN RADICAL POLYMERIZATION

The tendency of nitrones to react with radicals has been widely used in new synthetic routes to well-defined polymers with low polydispersity. The recent progress in controlled radical polymerization (CRP), mainly nitroxide-mediated polymerization (NMP) (695), is based on the direct transformation of nitrones to nitroxides and alkoxyamines in the polymerization medium (696, 697). In polymer chemistry, NMP has become popular as a method for preparing living polymers (698) under mild, chemoselective conditions with good control over both, the polydispersity and molecular weight.

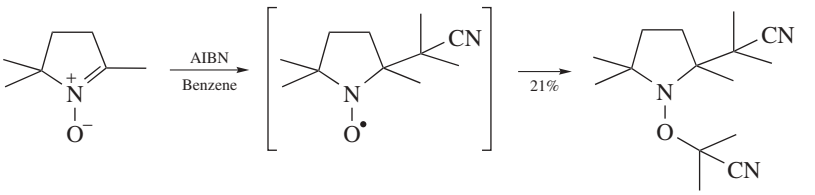
Significant improvement in controlled polymerizations of a variety monomers, including styrene, acrylates, acrylamide, acrylonitrile, 1,3-dienes, and maleic anhydride has been achieved when alkoxyamines have been used as initiators for living, free radical polymerization.(696c, 697) Alkoxyamines can be easily synthesized *in situ* by the double addition of free radicals, generated by thermal decomposition of an azo-initiator, such as 2,2'-azo-*bis*-*iso*-butyronitrile (AIBN), to nitrones (Scheme 2.206).

The effect of the nitrone structure on the kinetics of the styrene polymerization has been reported. Of all the nitrones tested, those of the C-PBN type (Fig. 2.29, family 4) are the most efficient regarding polymerization rate, control of molecular weight, and polydispersity. Electrophilic substitution of the phenyl group of PBN by either an electrodonor or an electroacceptor group has only a minor effect on the polymerization kinetics. The polymerization rate is not governed by the thermal polymerization of styrene but by the alkoxyamine formed *in situ* during the pre-reaction step. The initiation efficiency is, however, very low, consistent with a limited conversion of the nitrone into nitroxide or alkoxyamine.

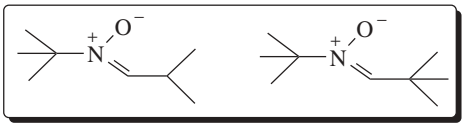
A study of the polymerization kinetics of methyl methacrylate, in the presence of PBN, and of molecular-mass properties of the obtained polymers shows that the systems react by the "pseudoliving" mechanism (699). In the first stages of the polymerization process, PBN reacts with oligomeric radicals, forming stable nitroxyl radical-spin adducts **A**·, see Scheme 2.207.

Nitroxyl spin adducts (**A**·) react with the growing radical chain leading to the formation of labile end groups (Scheme 2.208).

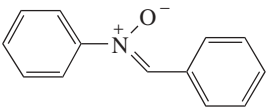
A labile bond at the end of the polymeric chain is capable of cleavage with regeneration of the active macroradical. The periods of "sleep" and "life" of polymer chain alternate, and the molecular weight of the polymer increases



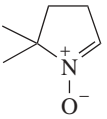
Scheme 2.206



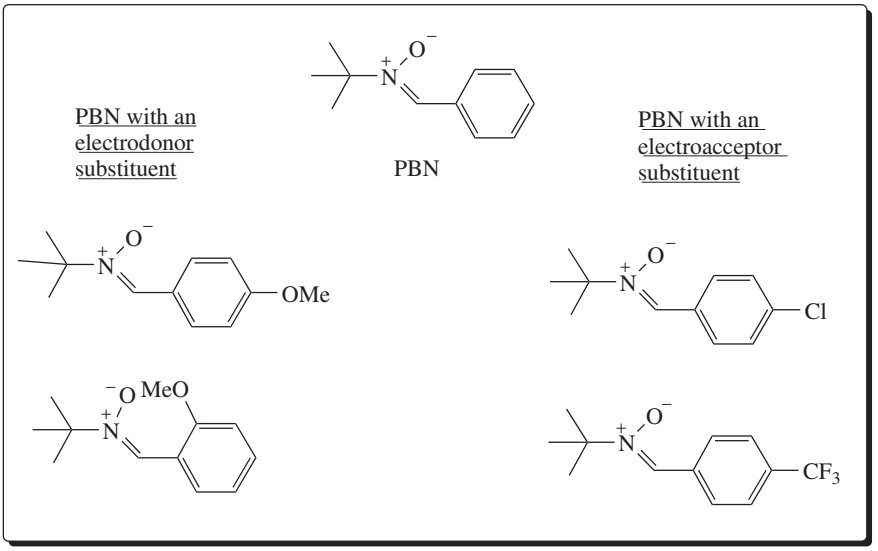
Family 1



Family 2

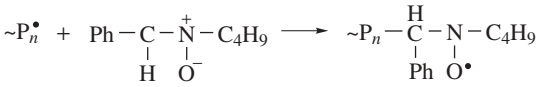


Family 3



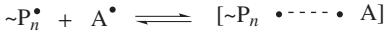
Family 4

Fig. 2.29

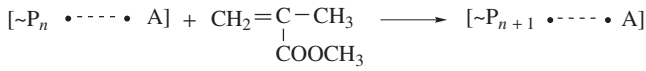


(A•)

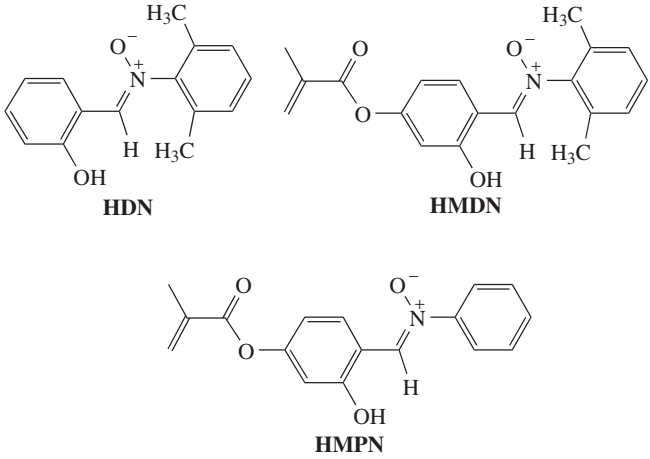
Scheme 2.207



Scheme 2.208



Scheme 2.209



HDN **HMDN** **HMPN**

Fig. 2.30

successively, due to the introduction of monomer at the labile bond [$\sim P_n \cdot\!-\!\cdot A$]. As a result, polymers with narrow molecular weight distribution (MWD) are formed (Scheme 2.209).

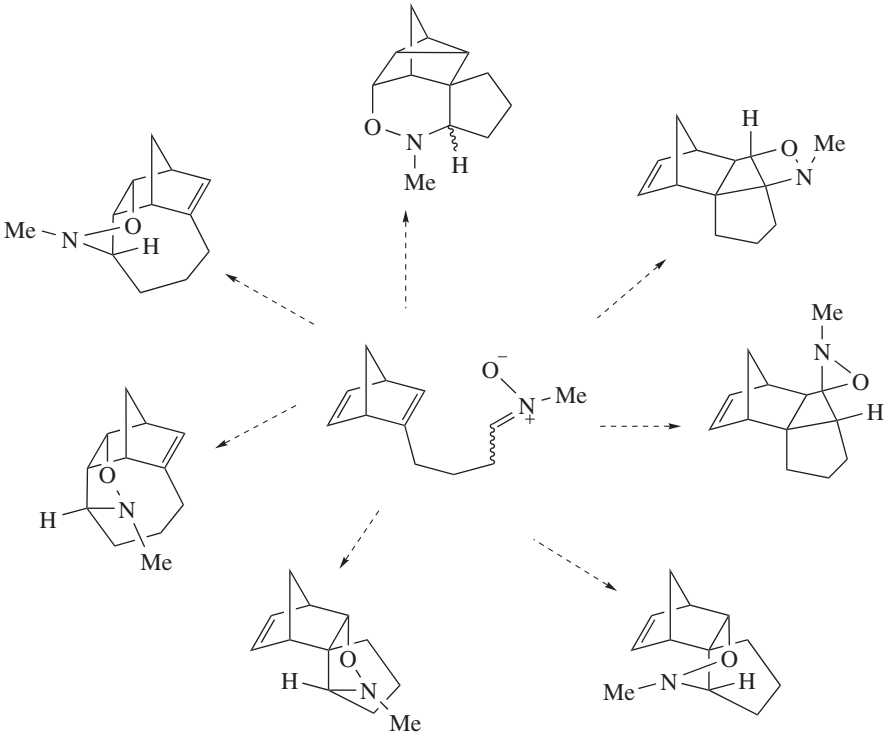
Therefore, nitrones, being potential sources of stable radicals are able to participate directly in the growth stage of the polymer chain. In the case of nitrones the "pseudoliving" mechanism is realized at lower temperatures (50–60° C) then in the case of nitroxides (> 100° C).

Radical copolymerization of diaryl nitrones, such as α-(2-hydroxyphenyl)-*N*-(2,6-dimethylphenyl) nitrone (**HDN**), α-(2-hydroxy-4-methacryloyloxyphenyl)-*N*-(2,6-dimethylphenyl) nitrone (**HMDN**), and α-(2-hydroxy-4-methacryloyloxyphenyl)-*N*-phenylnitrone (**HMPN**) (Fig. 2.30), with methyl methacrylate leads to copolymers in good yields with considerable quantities of hydroxy substituted diaryl nitrone pendants. The presence of photoactive nitrone pendants in these copolymers allows one to control photochemically the refractive index of polymethyl methacrylate films (468, 700, 701).

2.8. REACTIONS OF DIPOLAR 1,3-CYCLOADDITION ([3 + 2] CYCLOADDITION)

2.8.1. Cycloaddition of Alkenes

2.8.1.1. Intramolecular Reactions Intramolecular 1,3-cycloaddition with high regio- and stereo-control seems to be an important instrument for an effective



Scheme 2.210

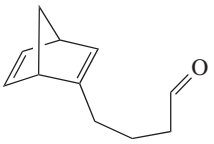
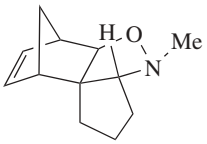
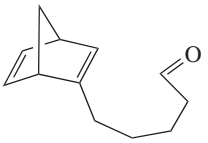
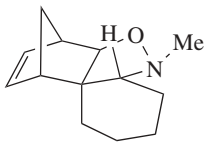
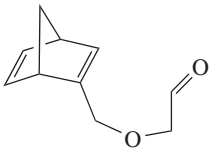
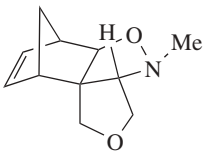
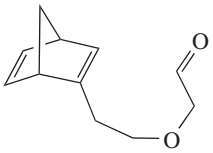
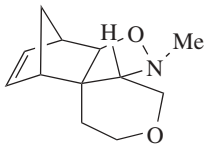
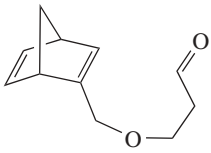
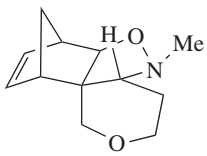
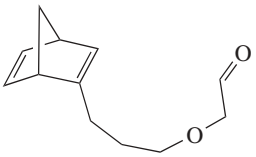
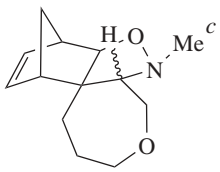
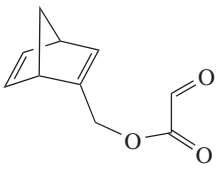
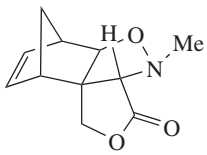
design of complex molecule structures, such as key building blocks of chiral ligands, alkaloids, antibiotics, and other biologically active compounds. Introduction of the olefinic component and nitrone fragment into a molecule can be realized in different ways and in various sequences. Depending on the distance between them, and conformational mobility of the connective fragments, various polycyclic structures can be obtained.

In Scheme 2.210, possible variants of intramolecular 1,3-dipole cycloaddition of norbornadiene derivatives with 2-substituted norbornadiene-tethered nitrones are presented.

These reactions give regio- and stereoisomers in satisfactory yields (Table 2.16) (702).

The most convenient and frequently used systems for carrying out intramolecular 1,3-cycloaddition reactions are systems (**a–f**) with various mutual arrangements of the nitrone group and olefinic fragment. In systems (**a–d**), the substituent with the olefinic fragment is situated at the α-*C*, while in (**e**) and (**f**) the substituent is attached at the *N* atom. Depending on the connecting chain length and the location of the X ($X = CH_2$, O, NR, S) group, intramolecular 1,3-cycloadditions give different polycyclic systems (Scheme 2.211).

Table 2.16 1,3-Dipolar cycloaddition of norbornadiene-tethered nitrones

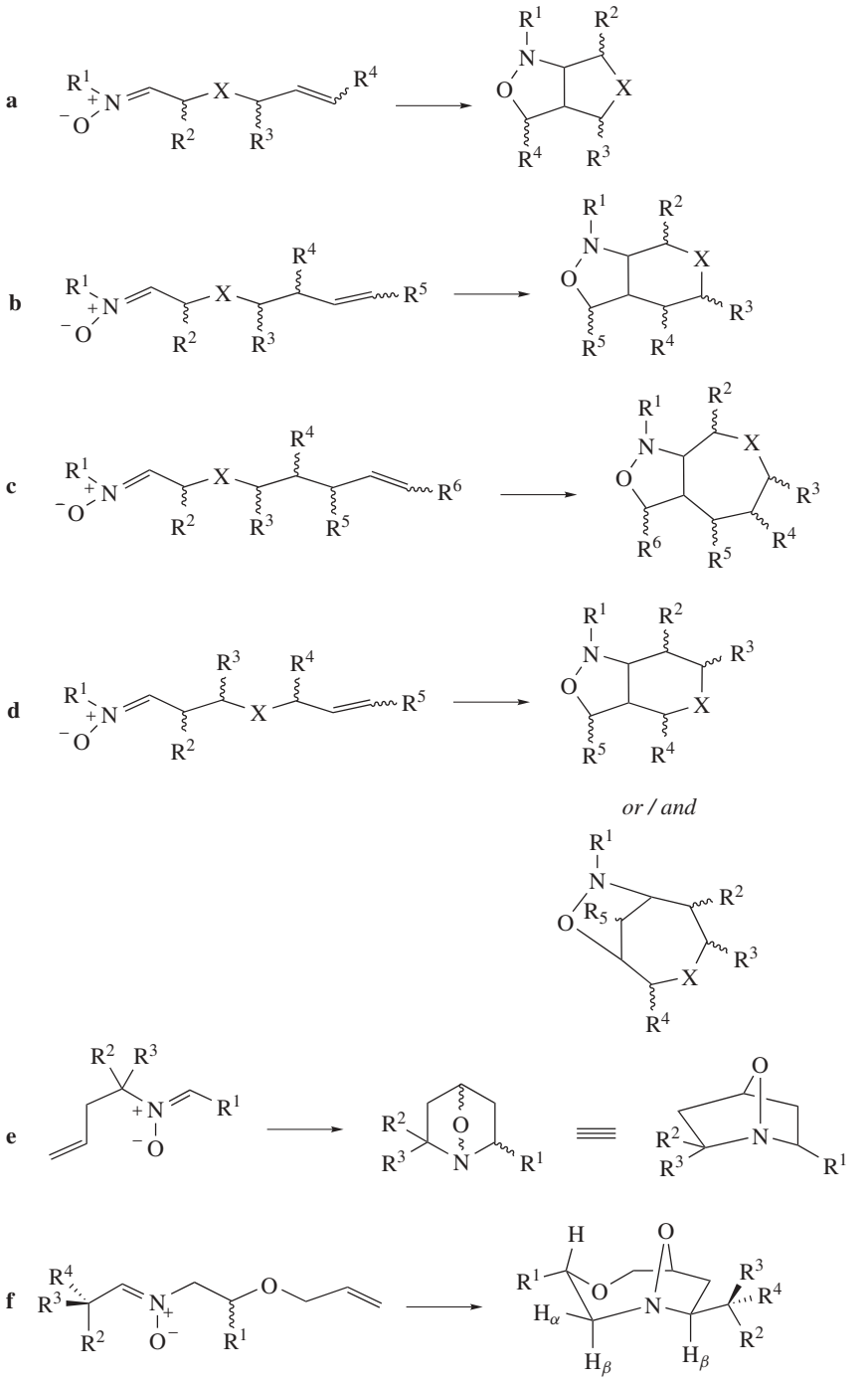
Entry	Starting aldehyde	Cycloadduct[a,b]	Yield[d] (%)
1			51
2			19
3			71
4			60
5			47
6			52
7			43

[a] *Reaction conditions*: MeNHOH HCl (1.2–2 eq.), pyridine (3–5 eq.), 4 Å molecular sieves, toluene, r.t., 12–24 h then 60°C to 90°C 12–24 h.

[b] Except in entry 6, the cycloadducts shown were the only *regio*- and *stereo*- isomers isolated in the cycloadditions.

[c] An inseparable mixture of three isomers was obtained.

[d] Isolated yields after column chromatography.



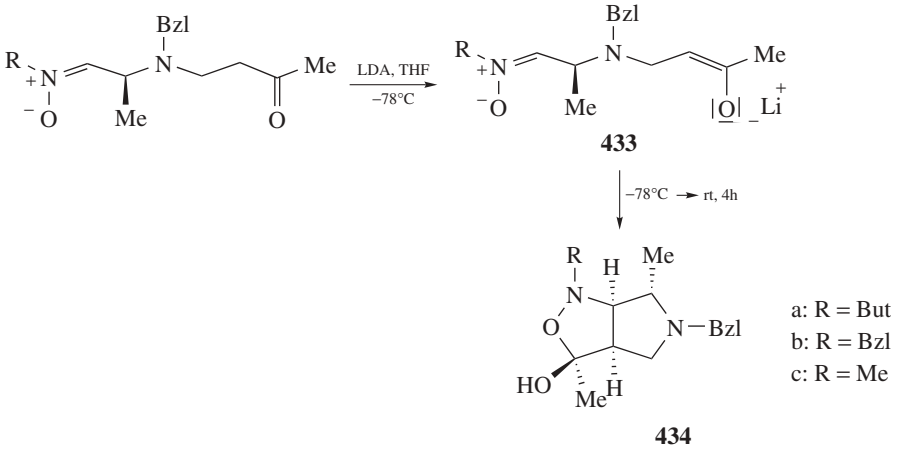
Scheme 2.211

According to general (or principal) Scheme 2.211a, the enolate group of nitrone (**433**), generated on treatment with LDA, acts as the dipolarophile on attacking the nitrone group. The bicyclic compound (**434**) is obtained from a spontaneous intramolecular cycloaddition (Scheme 2.212) (703).

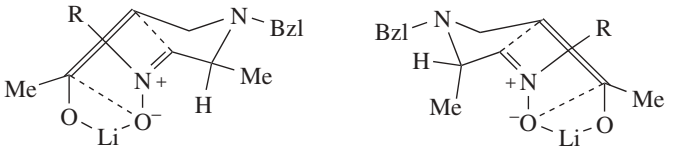
The stereochemistry of this reaction is determined by the preference of an *Re* side attack and chelation of the lithium ion to the oxygen atom of the nitrone group in the transition state (Fig. 2.31a) (703).

Similar to Scheme 2.211a, intramolecular cycloaddition with high stereoselectivity occurs with chiral nitrones (**435a,b**), leading to bicyclic compounds (**436a,b**) (Scheme 2.213a) (704), and with dinitrones (**437**), leading to tetracyclic compounds (**438**) (Scheme 2.213b) (705).

The formation of enantiopure tricyclic compounds takes place by intramolecular 1,3-dipolar cycloadditions of acyclic nitrones to cyclic olefinic fragments (Scheme 2.214a,b) (706, 707a), or of cyclic nitrones to acyclic olefins (Scheme 2.214c) (116). Recently (707),b intramolecular nitrone cycloaddition reactions (according to Scheme 2.211a) have been applied in the synthesis of

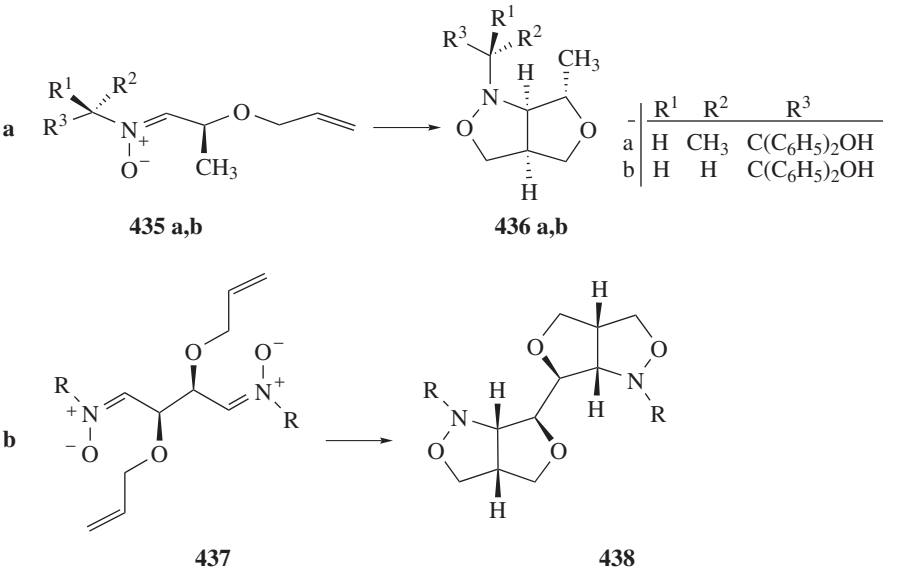


Scheme 2.212



Nitrone group is attacked (*a*) from the Re side (*b*) from the Si side

Fig. 2.31



Scheme 2.213

enantiomers of nucleoside 2-(6-chloropurin-9-yl)-3,5-bishydroxymethylcyclopentanol (Scheme 2.214 d,e).

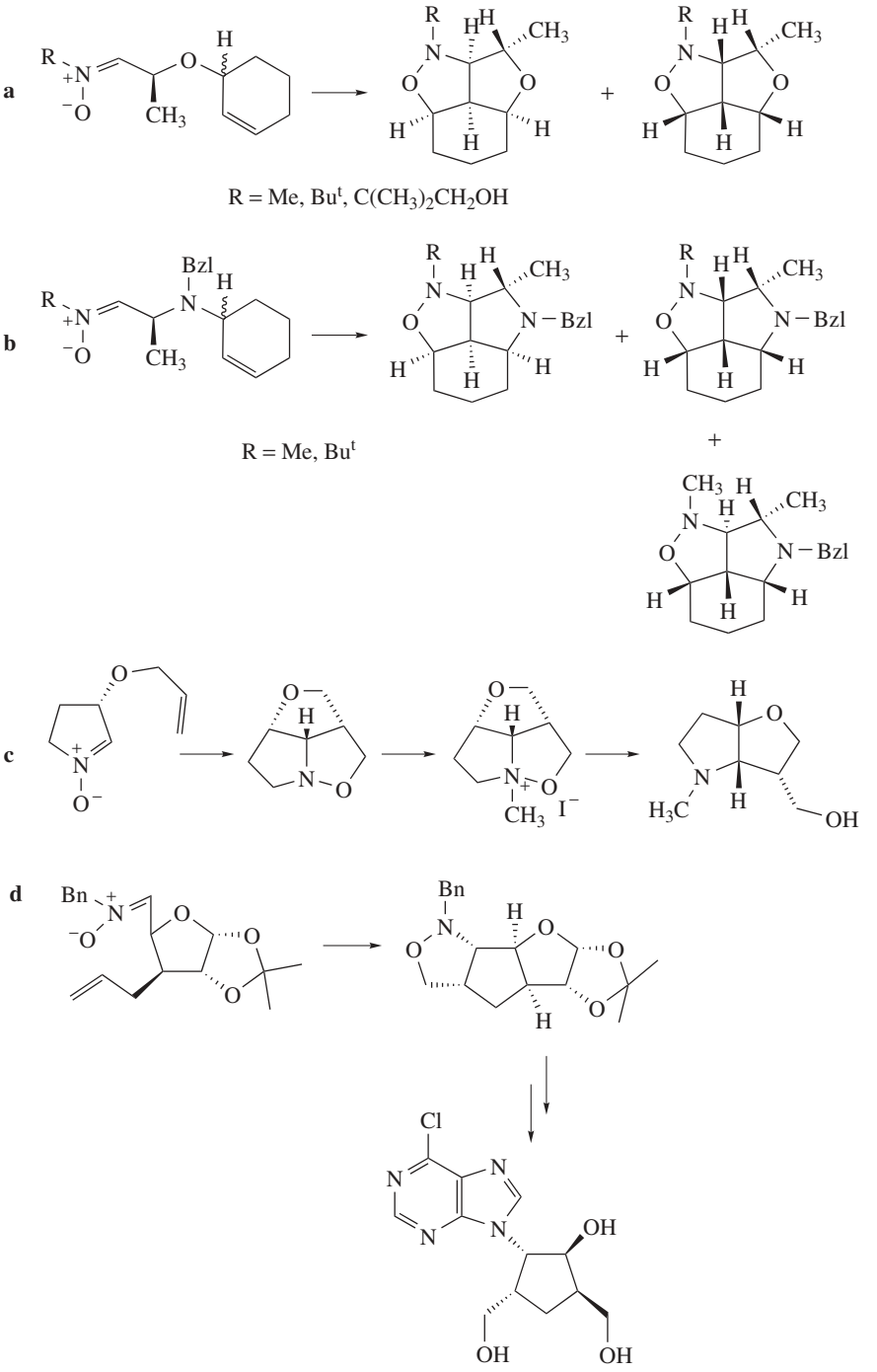
The tricyclic compound (**441**) is a key compound in the synthesis of enantiomerically pure indolizidine (**442**). It was obtained in an intramolecular 1,3-cycloaddition of nitrone (**440**), by retro-cycloaddition from isoxazolidine (**439**) (Scheme 2.215) (708).

By employing intramolecular 1,3-dipolar cycloadditions, syntheses of pyrrolo-, pyrido[1,2-a]indol (140),a pyrrolizidine and indolizidine (140b) derivatives have been reported (Scheme 2.216).

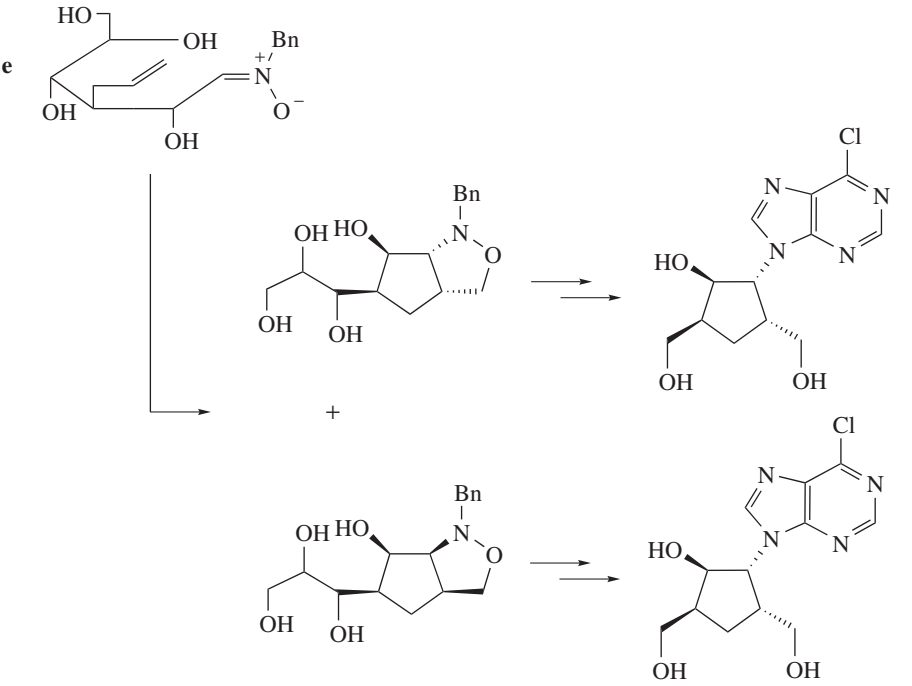
Regiospecific intramolecular cycloadditions of nitrones to sulfur-substituted dienes, with 3-sulfolene precursors, has been realized (Scheme 2.217). The stereochemical outcome of these reactions is affected by the structure of the substituent (sulfide or sulfone) in the diene and by the chain length connecting the diene and nitrone (**a**) and (**b**) (*see* Scheme 2.211). The bicyclic products obtained from these reactions have been converted to interesting heterocyclic compounds (709).

Diastereoselective intramolecular 1,3-dipolar cycloadditions of alkylidenecyclopropyl nitrones provide spirocyclopropylisoxazolidines. These compounds have been shown to undergo either thermally induced ring expansion to octahydro[1]pyrindin-4-ones or to acid induced ring contraction into β-lactams with concomitant loss of ethylene (Scheme 2.218) (710–716). Use of chiral auxiliaries, that is (L)-2-acetoxylactate can lead to enantiomerically enriched heterocycles (715).

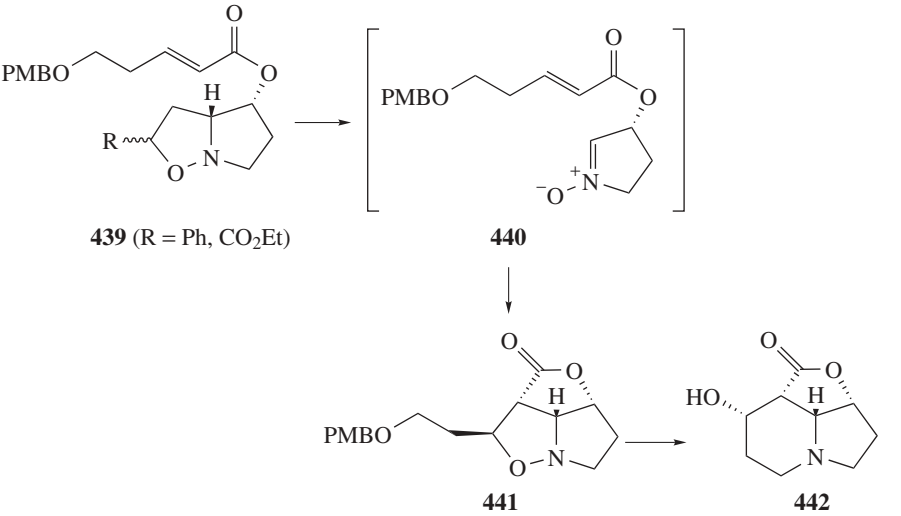
Bicyclopropylidenyl-substituted nitrones (**443**) and (**444**) undergo regio- and diastereoselective intramolecular cycloadditions to afford exclusively the



Scheme 2.214

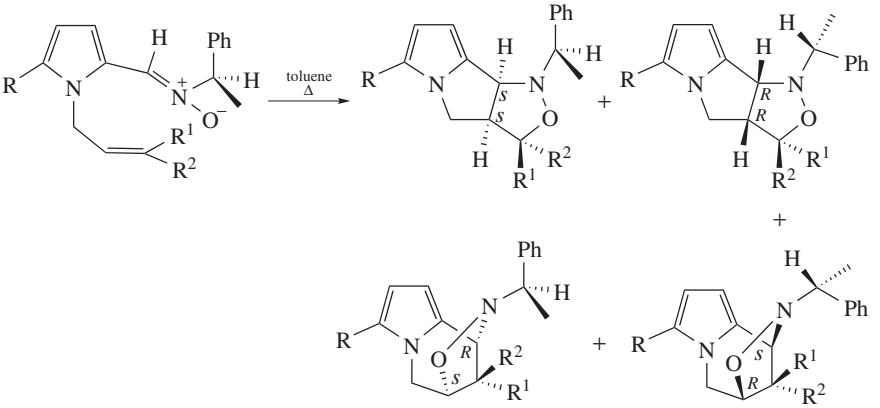


Scheme 2.214 (*continued*)



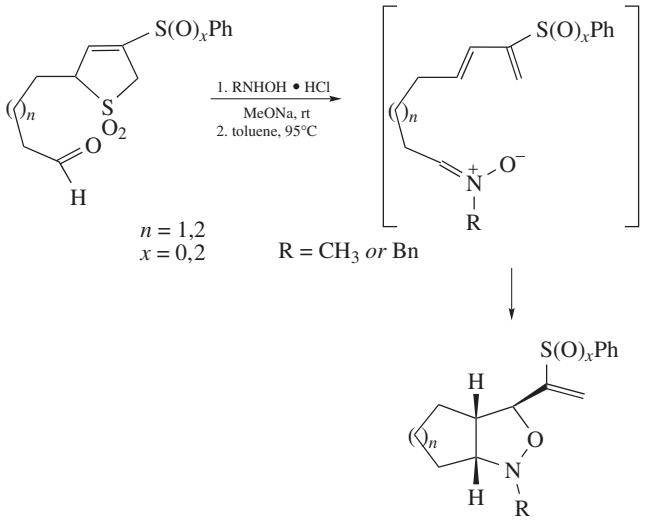
439 (R = Ph, CO_2Et) **440** **441** **442**

Scheme 2.215

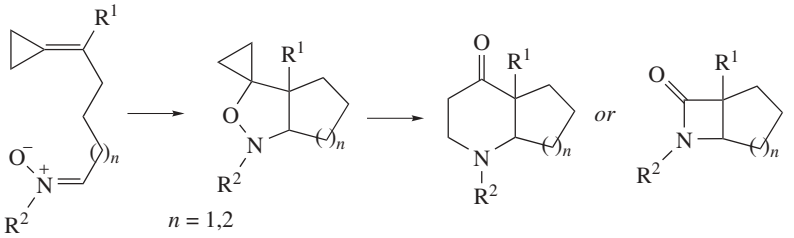


R = H or C_4H_9; R^1 = H or CH_3; R^2 = H, CH_3, C_3H_7 or Ph;

Scheme 2.216



Scheme 2.217

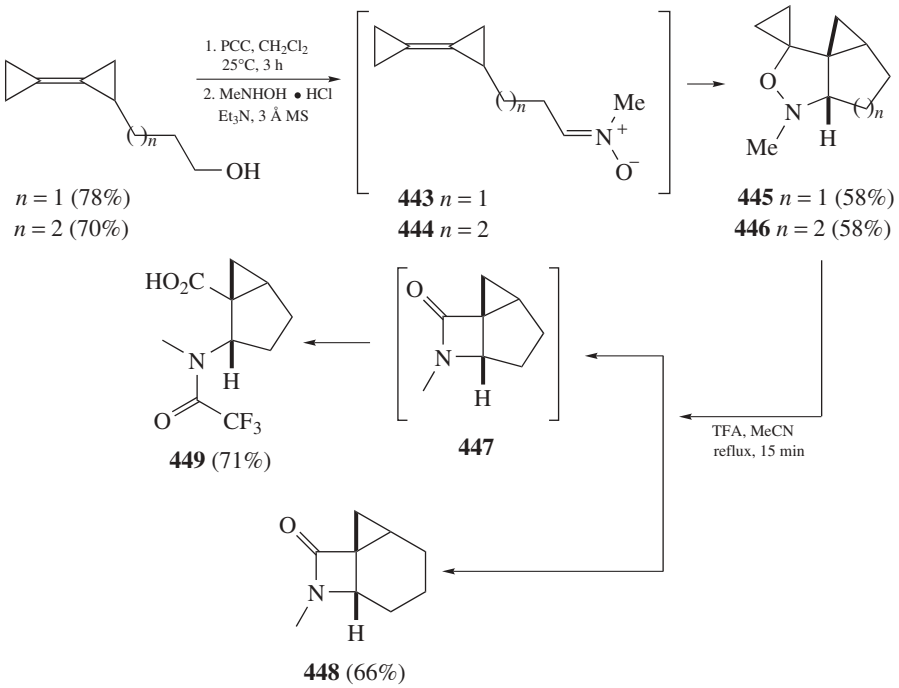


Scheme 2.218

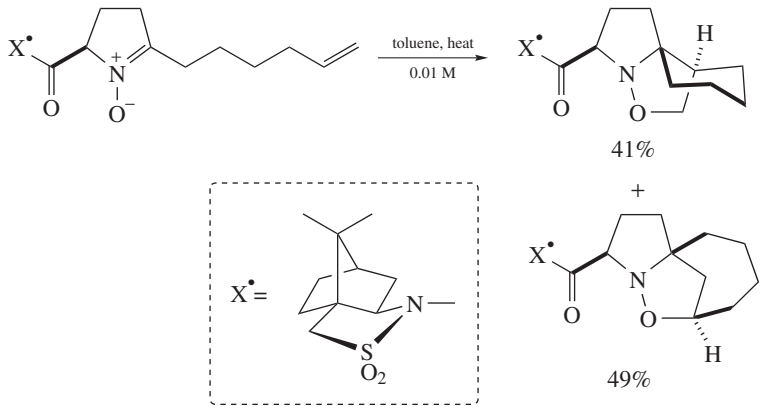
ring-fused polycyclic compounds (**445**) and (**446**). Thermal rearrangement of (**445**) and (**446**), at acidic conditions (trifluoroacetic acid [TFA]), leads to the tricyclic β-lactams (**447**) and (**448**). At the reaction conditions shown, (**447**) undergoes lactam-amide bond cleavage to yield the bicyclic *N*-trifluoroacetylated β-amino acid derivative (**449**) (Scheme 2.219) (717).

Stereochemical control of intramolecular 1,3-dipolar cycloadditions by route **b** (Scheme 2.211) was realized in the asymmetric synthesis of 1-azaspiro[4.5] decanes by using the chiral (2 R)-bornane-10,2-sultam (X*) auxiliary in the dipolarophilic fragment (Scheme 2.220) (718).

Stereoselectivity and regioselectivity have been experimentally and theoretically studied in the reactions of intramolecular nitrone-alkene cycloadditions (INAC) of 6-heptenoses derived from carbohydrates such as D-ribose (**450a,b**) (Scheme 2.221) and D-arabinose derivatives (**451a,b**) (Scheme 2.222) (719). It has been found that the stereoselective outcome in these INAC reactions is strongly affected by the 2,3-O-isopropylidene blocking group in D-ribose derivatives (**450a,b**) (Scheme 2.221) and by the 2,3-O-trans-diacetyl blocking group in D-arabinose derivatives (**451a,b**) (Scheme 2.222). It is also affected by the stereochemistry of the substituents. Stereochemical directions in these reactions have been explained by calculating transition state energies. Nitrones (**450a,b**) with a 2,3-O-isopropylidene cycle undergo INAC reactions to give



Scheme 2.219



Scheme 2.220

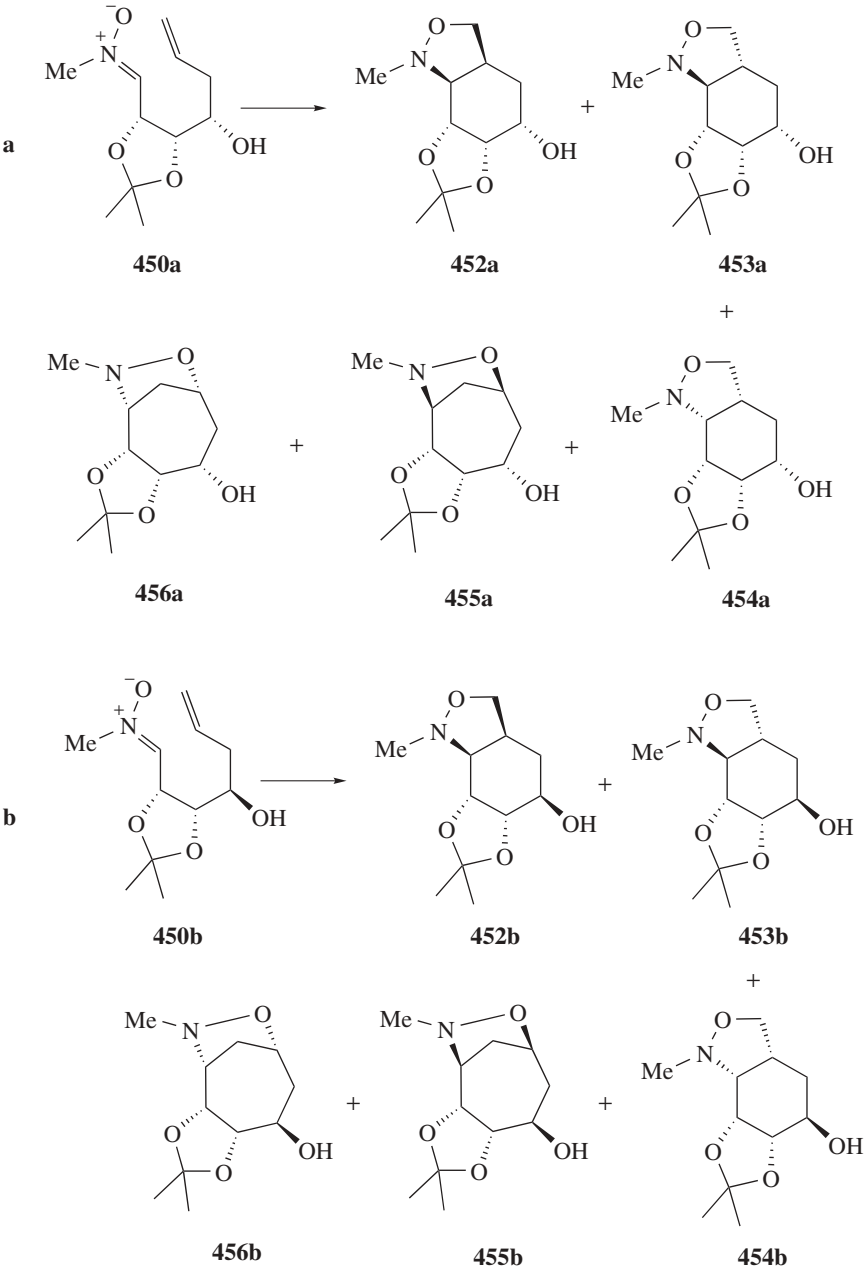
exclusively *cis*-fused isoxazolidines (cyclohexanols) (**452a,b**) (Scheme 2.221). Nitrones (**451a,b**) with 2,3-O-*trans*-diacetyl blocking groups give a mixture of *cis*-(**457a,b**), *trans*-(**458a,b**) and bridged bicyclo[4.2.1]isoxazolidines (cycloheptanols) (**459a,b**) and (**460a,b**) (Scheme 2.222). The bridged isoxazolidines (cycloheptanols) (**459a,b**) and (**460a,b**) were synthesized for the first time from unbranched sugar derivatives (**451a,b**). These INAC reactions showed insignificant temperature dependence, but important solvent dependence. In the case of nitrones (**451a,b**), the INAC in 2-propanol gave the highest yield of fused isoxazolidines (cyclohexanols) (**457**) and (**458**), whereas the INAC in dichloromethane afforded the highest yield of bridged isoxazolidines (cycloheptanols) (**459**) and (**460**) (719).

According to general (or principal) Scheme 2.211b, intramolecular 1,3-cycloadditions of nitrones derived from 3-oxa-6-heptenals (**461**) and (**462**) proceed stereoselectively, leading to cycloadducts (**463–465**) (Scheme 2.223) and (**466–468**) (Scheme 2.224) in good yields (720).

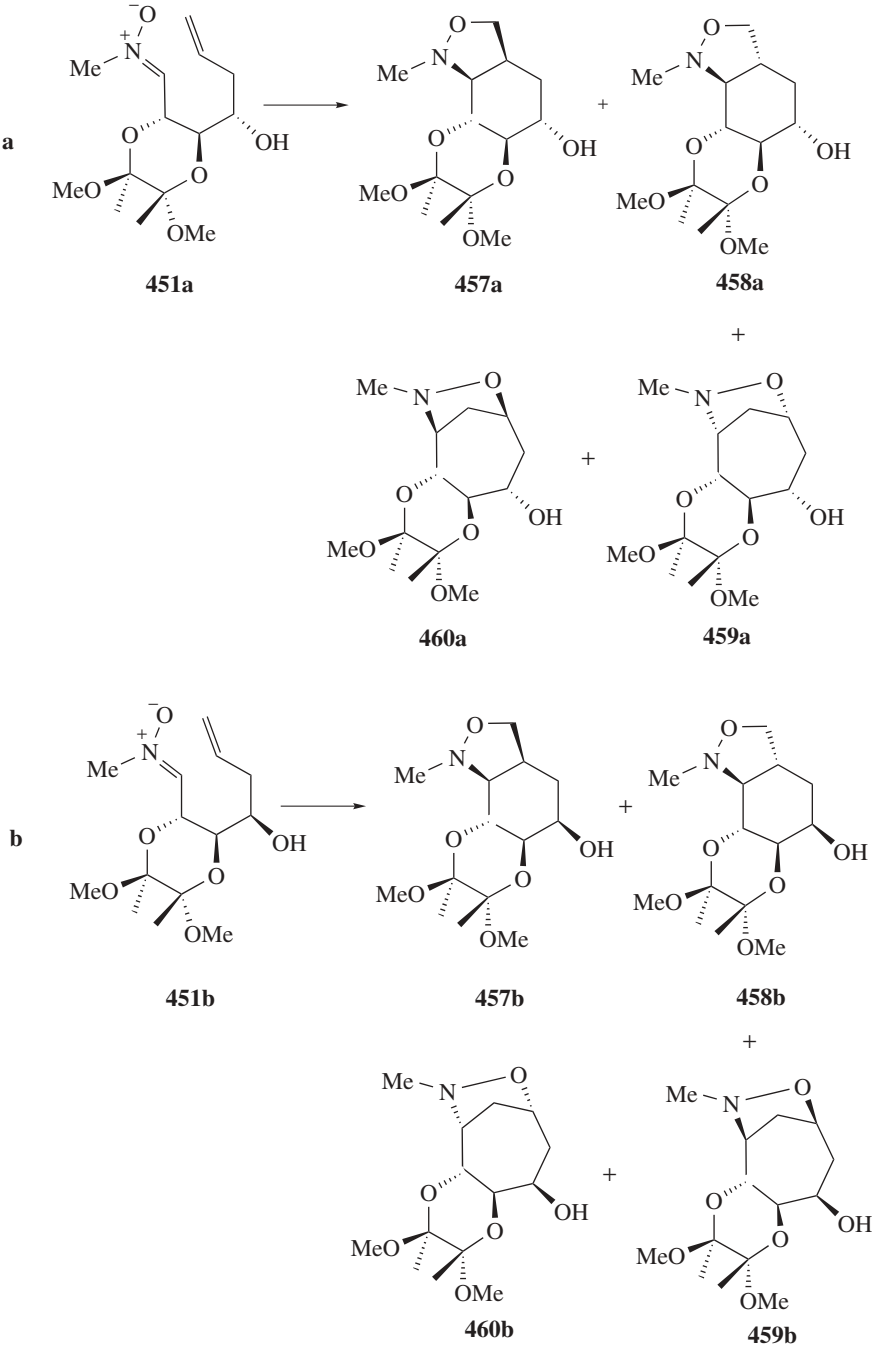
In agreement with Schemes 2.211b and 2.211c, intramolecular cycloadditions of nitrones to 5-allyl- (Scheme 2.225) or 5-homoallylproline (Scheme 2.226), are fully regio- and stereoselective. These reactions are the key steps in the synthesis of functionalized azaoxobicyclo[*X*.3.0] alkane amino acids, mimics of a homoSer-Pro dipeptide (721).

As shown in Scheme 2.211d, starting with *N*-allyl carbohydrate-nitrones (**469**), a series of chiral six- (**470**) and seven-membered(**471**) *N*-heterocycles were synthesized (Scheme 2.227). A very interesting and useful aspect of this cycloaddition is the control of regioselectivity by the substitution at the nitrogen atom. Therefore, it is possible to direct reactions towards the syntheses of preferred six- or seven-membered heterocycles from carbohydrate derivatives (722).

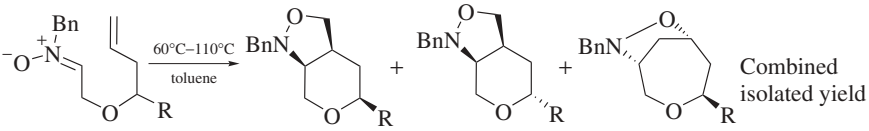
Similarly, according to Scheme 2.211 d, the INAC reaction of *N*-allyl-carbohydrate nitrone (**472**) gave the pyrrolo[1,2-*a*]azepine derivative (**473**) (Scheme 2.228) (723).


a
Me
N
O
OH
450a
452a
453a
456a
455a
454a
b
450b
452b
453b
456b
455b
454b

Scheme 2.221


a
Me
N
O
OH
MeO
OMe
451a
457a
458a
460a
459a
b
451b
457b
458b
460b
459b

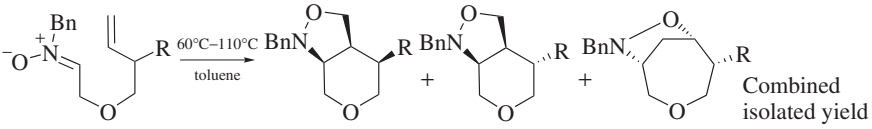
Scheme 2.222



461 **463** **464** **465**

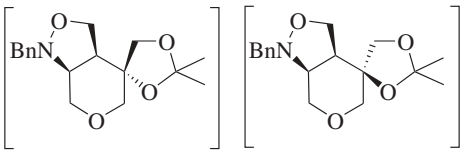
a: R = Me	70	19	11	72
b: R = Ph	50	33	17	83
c: R = CH_2OBn	72	trace	28	68

Scheme 2.223

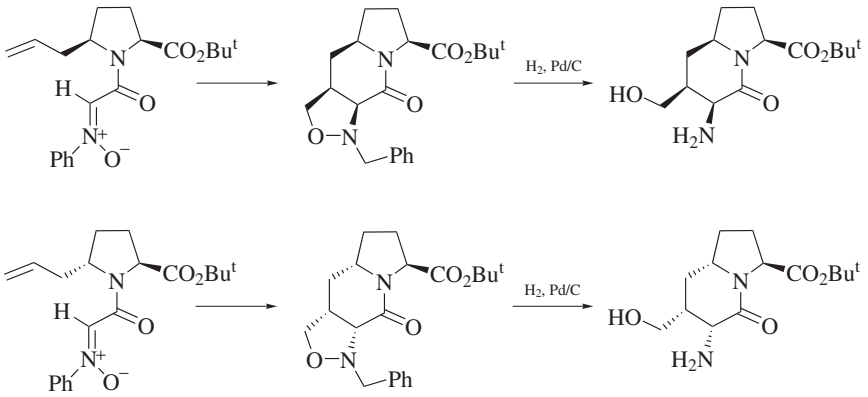


462 **466** **467** **468**

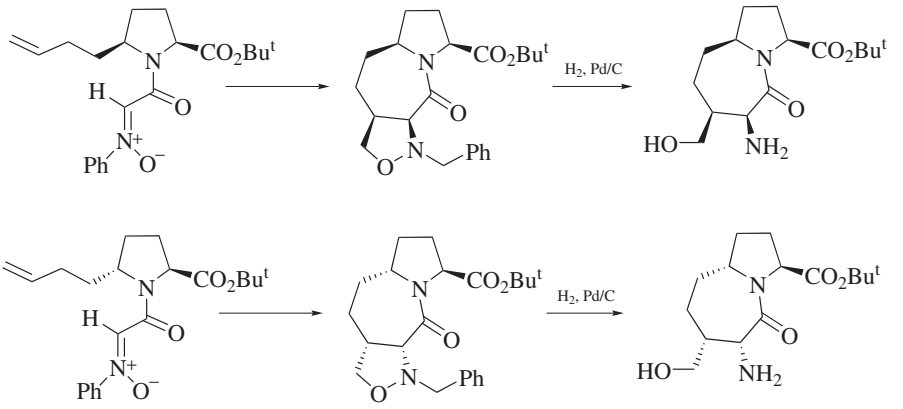
d: R = Me	16	67	17	57
e: R = Ph	<5	>95	trace	46
f: R = $CH_2OTBDMS$	<5	>95	0	63
g: R = OBn	30	70	0	53
h: R = 	34	60	6	57



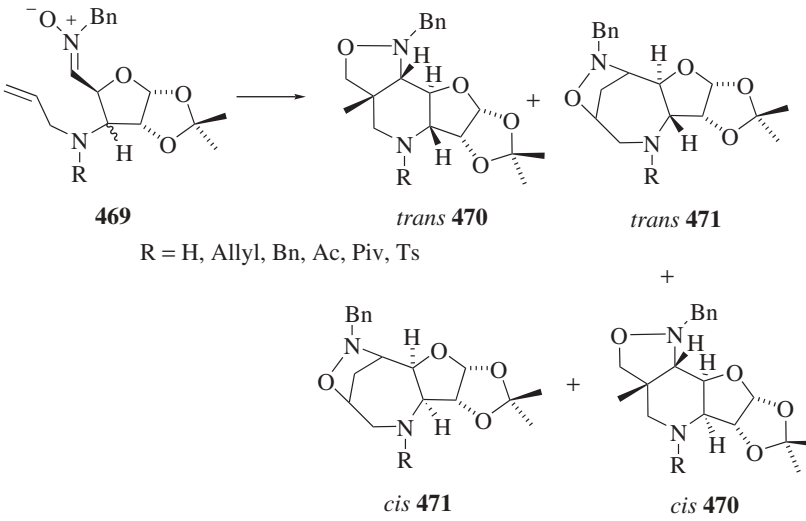
Scheme 2.224



Scheme 2.225



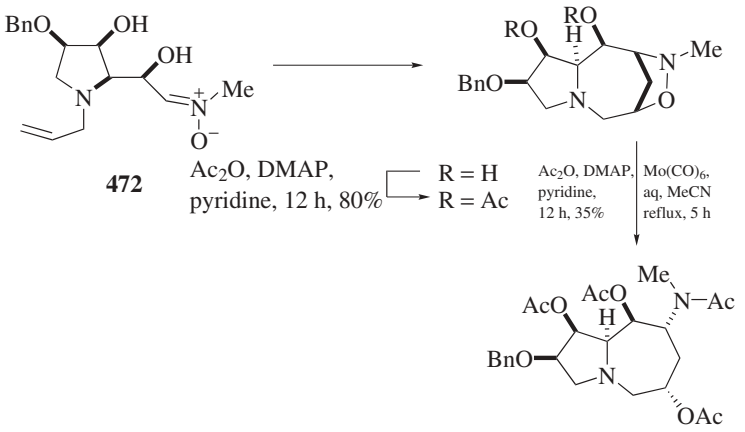
Scheme 2.226



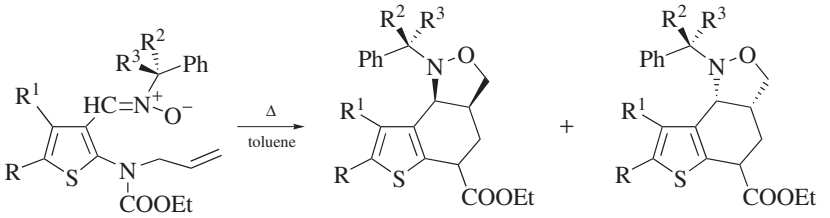
Scheme 2.227

INAC reactions have also led to enantioselective syntheses of key intermediates in the synthesis of antibiotic 1β-Methylcarbapenem (724), to optically pure derivatives of tetrahydropyrano[2,3]cyclohexane (725a) to novel terahydroisoxazolo-fused pyrano[2,3-*b*] quinolines (725b) and to a novel heterocyclic system, isoxazolo[3,4-d]thieno[2,3-b]pyridine (Scheme 2.229) (221).

Recently for the first time, a highly stereoselective surfactant-catalyzed INAC reaction in aqueous media, leading to the exclusive formation of a single isomer has been reported (726a). Either oxepane (mode A) or pyran (mode B) (Scheme 2.230) is formed from 3-O-allyl furanoside derivatives, which constitute



Scheme 2.228

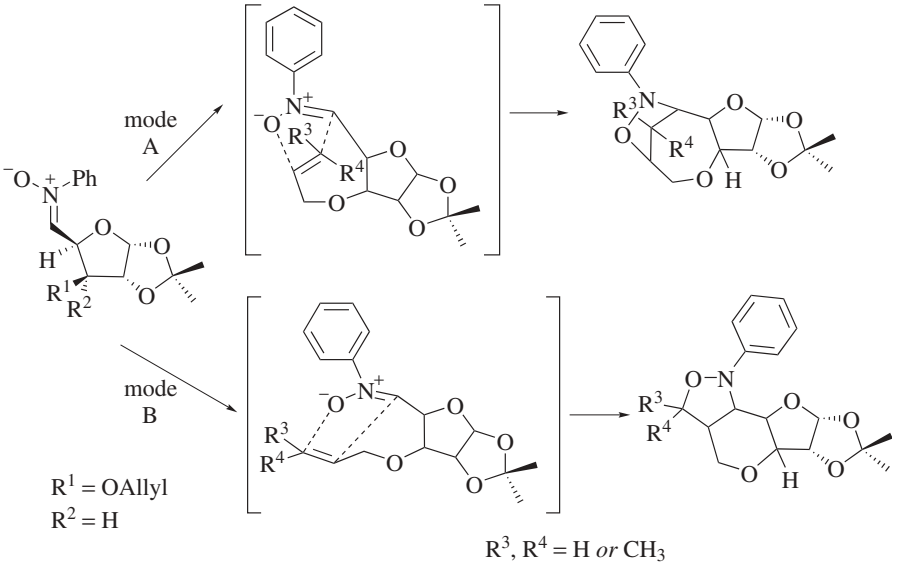


R	R^1	R^2	R^3				
Me	H	Me	H	(α *R*, 3a*S*, 8b*S*)	(42%)	(α *R*, 3a*R*, 8b*R*)	(31%)
–(CH=CH)$_2$–		Me	H	(α *R*, 3a*S*, 10c*S*)	(34%)	(α *R*, 3a*R*, 10c*R*)	(14%)
Me	H	H	CH_2OH	(α *R*, 3a*S*, 8b*S*)	(17%)	(α *R*, 3a*R*, 8b*R*)	(51%)
–(CH=CH)$_2$–		H	CH_2OH	(α *R*, 3a*S*, 10c*S*)	(25%)	(α *R*, 3a*R* 10c*R*)	(54%)

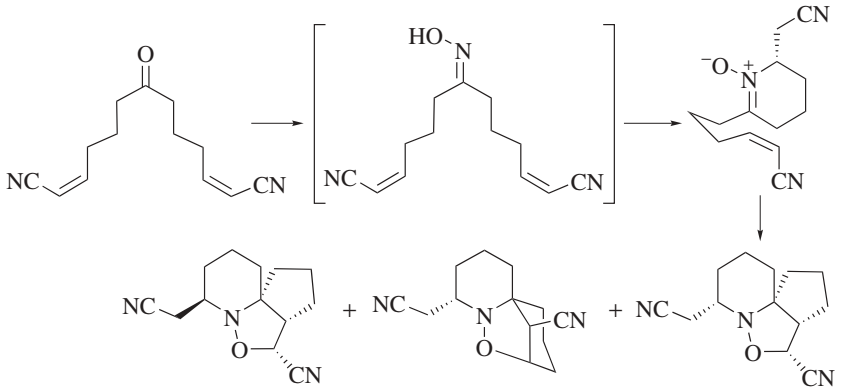
Scheme 2.229

the framework of a large number of biologically active compounds. It was demonstrated that an achiral nano-reactor is a useful and "green tool" for the stereoselective intramolecular 1,3-dipolar nitrone cycloaddition of chiral substrates. This reactor leads to the formation of chiral oxepanes and pyrans with a much greater stereoselectivity than that obtained in conventional organic solvents. Exclusive formation of single diastereomers of polyhydroxy-9-oxa-1-azabicyclo[4.2.1] nonanes from intramolecular 1,3-cycloaddition of ω-unsaturated nitrones have been obtained in chiral ionic liquids (726b, c).

The sequential intramolecular conjugate addition of the oxime followed by intramolecular dipolar cycloaddition of the intermediate nitrone affords a



Scheme 2.230

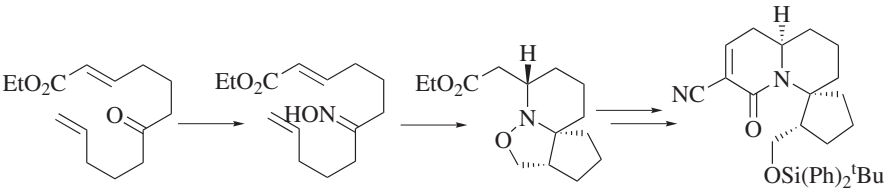


Scheme 2.231

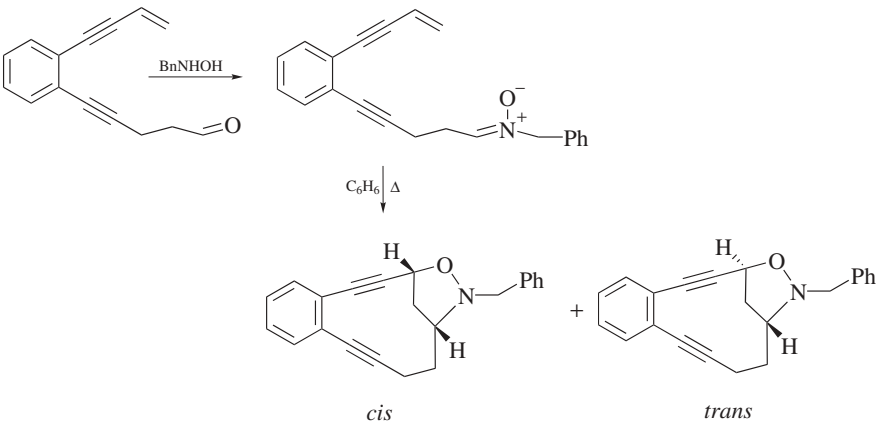
mixture of isoxazolidines (Scheme 2.231) (285, 727). This reaction was used in the synthesis of dendrobatid alkaloid precursors.

The tandem intramolecular Michael addition and 1,3-cycloaddition reactions of the corresponding alkenyl oxime have been used for the synthesis of the tricyclic core of the alkaloid halichlorine (Scheme 2.232) (728).

Similar INAC reactions of oximes with olefin moieties proceed in the presence of Lewis acids (729) and also under microwave irradiation of unsaturated oximes, placed on the surface of silica gel (730).



Scheme 2.232



Scheme 2.233

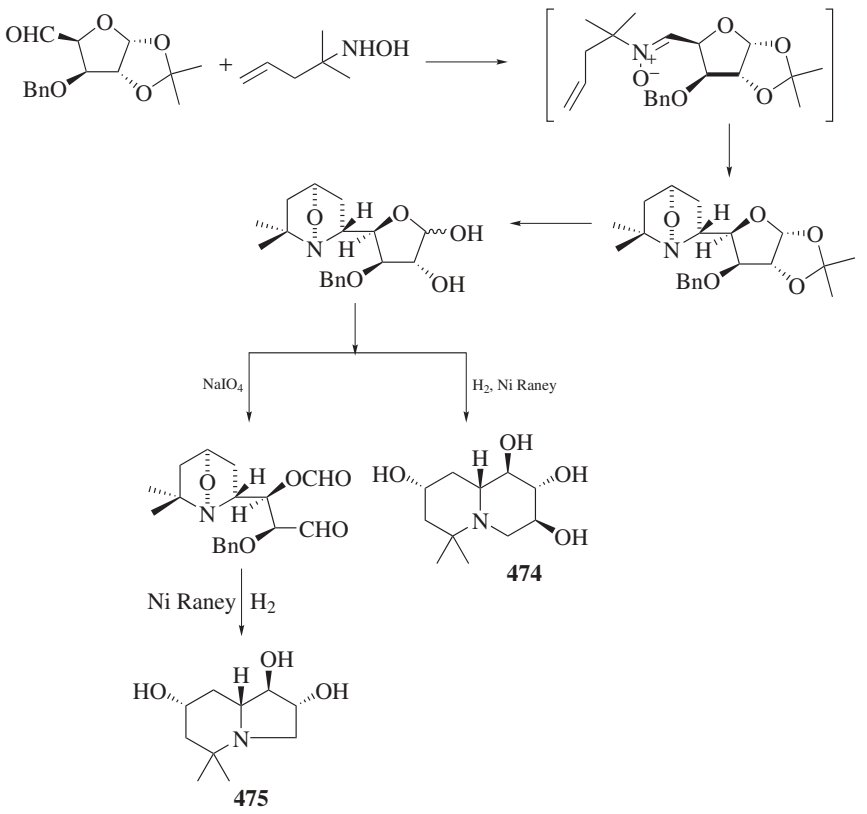
Bicyclic *cis*- and *trans*-isoxazolidinyldiynes have been prepared by intramolecular nitrone cycloaddition of the two side chains of an acyclic enediyne-nitrone precursor (Scheme 2.233) (731).

Intramolecular 1,3-dipolar cycloaddition reactions of *N*-(3-alkenyl)nitrones, as presented in Scheme 2.211e, led to the synthesis of polyhydroxy derivatives of quinolizidine (**474**) and indolizidine (**475**) (Scheme 2.234) (732).

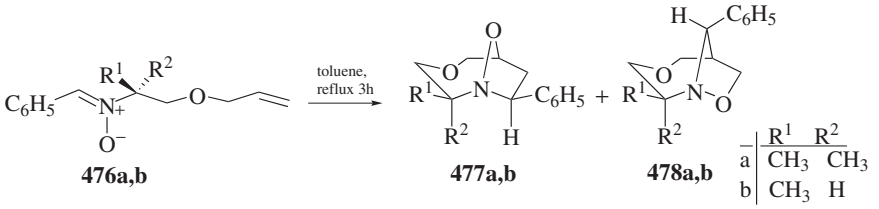
According to Scheme 2.211f, heating of nitrones (**476a,b**) in toluene gave bridged bicyclic compounds (**477a,b**), as the major reaction products (Scheme 2.235) (704).

2.8.1.2. Intermolecular Reactions Intermolecular 1,3-dipolar cycloaddition reactions of nitrones to olefins seem to be the most studied. They are widely used for the synthesis of different enantiomerically pure compounds, including biologically active ones. For example, two new glycosidase inhibitors have been obtained by the nitrone cycloaddition strategy (Fig. 2.32) (733).

The optically active isoxazolidines obtained in these cycloaddition reactions can be easily transformed into biologically active β-amino acids, into β-lactams and into important chiral building blocks such as γ-amino alcohols. The multitude of synthetic results in these reactions is of course expected by the wide variety



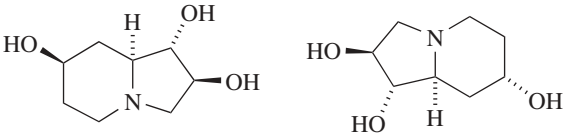
Scheme 2.234



Scheme 2.235

of nitrone structures and dipolarophiles. Examples of widely used dipolarophiles are shown in Fig. 2.33.

Dipolarophiles D1 and D2. In the study of steric and electronic factors on regioselectivity and stereoselectivity of 1,3-cycloaddition of nitrones to olefins, 1-decene (734) and styrene derivatives (735) have been used. By comparative analyses of the kinetic and thermodynamic parameters in the 1,3-cycloadditions



(1*S*,2*S*,7*R*,8a*S*) **(1*S*,2*S*,7*S*,8a*S*)**

Fig. 2.32 Structures of Trihydroxyoctahydroindolizine.

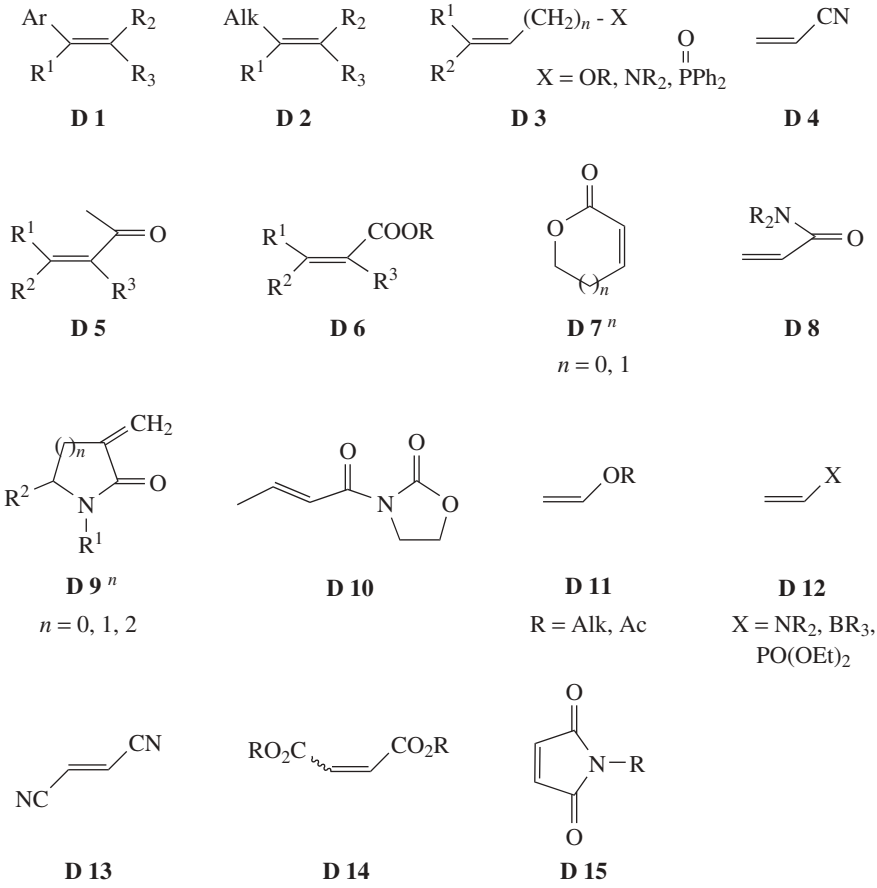
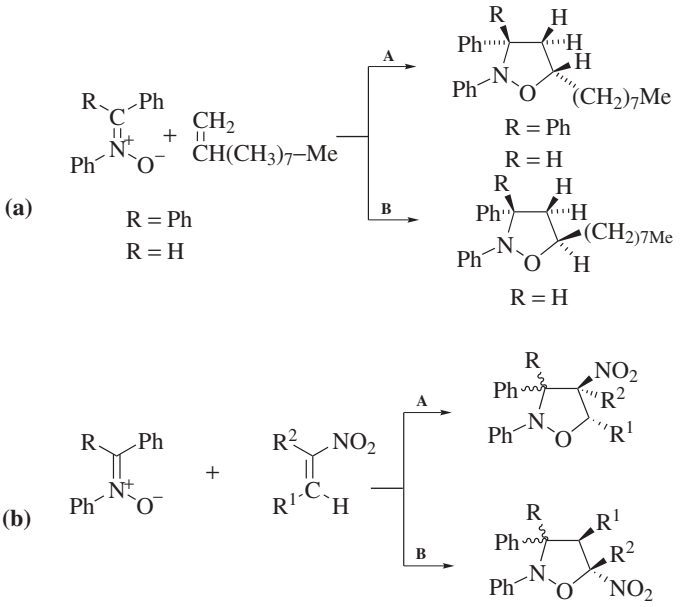


Fig. 2.33 Types of dipolarophiles.

of 1-decene to α,α,*N*-triphenyl and α,*N*-diphenyl nitrones, it was found that the steric factors have a significant effect on the dipolarophilic activity of the nitrones. It was shown, by spectroscopic methods, that the 1,3-cycloaddition of α,α,*N*-triphenyl nitrone to 1-decene is regiospecific and leads to 2,3,3-triphenyl-5-octylisoxazolidines as the only reaction product (Scheme 2.236a, route A).



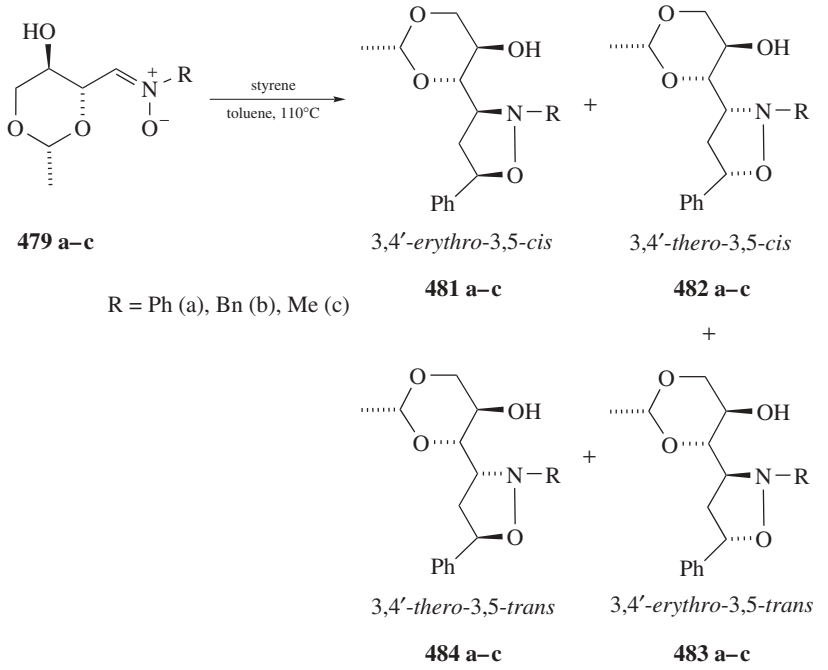
R = H, Ph; R^1,R^2 = H, Alk, Ph, *p*-XC_6H_4, thienyl, etc.

Scheme 2.236

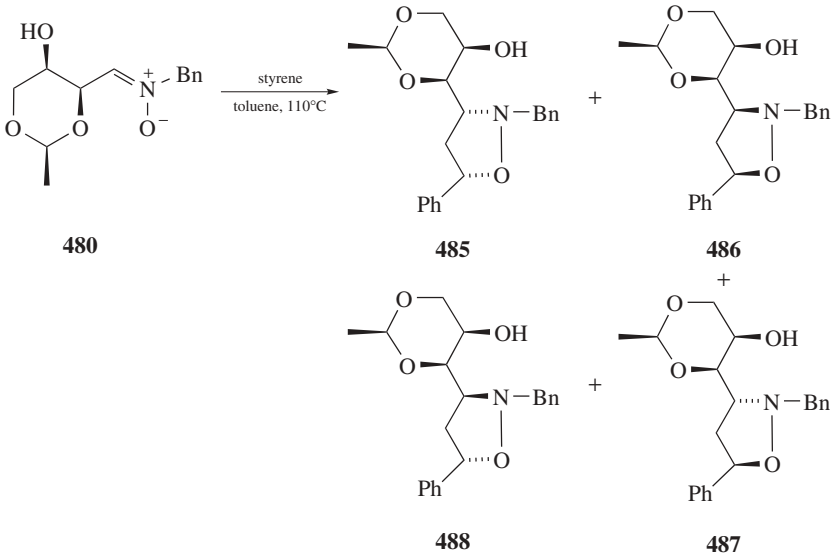
However, α,*N*-diphenyl nitrone with the same alkene forms a mixture of stereoisomeric 2,3-diphenyl-5-octylisoxazolidines (Scheme 2.236a, routes A and B) (734). Owing to the strong electronic influence of the nitro group, the nitro-olefines are of special interest. Analysis of frontier molecular orbital interaction in 1,3-cycloaddition reactions of α,α,*N*-triphenyl and α,*N*-diphenyl nitrones with α- and β-substituted nitroethylenes has been carried out. In all of the examples studied, orbital effects lead to the formation of the corresponding 4-nitroisoxazolidines (Scheme 2.236b, route A) (736). The 1,3-cycloaddition reactions of α,*N*-diphenyl nitrone with *trans*-1-nitro-1-propene and *trans*-3,3,3-trichloro-1-nitro-1-propene occur via a concerted mechanism despite the high π-deficient character of the dipolarophiles. This mechanism is indicated by the *cis*-stereospecificity of the cycloaddition, the obtained values of activation parameters and the weak solvent effect on the reaction kinetics (737).

To study asymmetric induction from the nitrone part in 1,3-dipolar cycloaddition to styrene, D-erythrose derived nitrones (**479 a–c**) have been used. Cycloaddition of nitrones (**479 a–c**) to styrene, in boiling toluene for 10 h, affords a mixture of four diastereomeric 3,5-disubstituted isoxazolidines (**481 a–c–484 a–c**) in high yields (82%–94%) (Scheme 2.237) (208).

Under similar reaction conditions the D-threose derived nitrone (**480**) is converted in high regioselectivity to diastereomeric cycloadducts (**485–488**) in an overall yield of 84% (Scheme 2.238).



Scheme 2.237



Scheme 2.238

Table 2.17 1,3-Dipolar cycloaddition of C-α-alkoxyalkyl-substituted nitrones to styrene

Entry	Nitrone	Yield (%)	*erythro-cis*	*threo-cis*	*erythro-trans*	*threo-trans*	*erythro*:*threo*	*cis*:*trans*
1	**479 a**	94	82	9	5	4	87:13	91:9
2	**479 b**	82	81	12	7	—	88:12	93:7
3	**479 c**	85	69	17	10	4	79:21	86:14
4	**480**	84	90	5	3	2	93:7	95:5

The stereoselectivity of these cycloaddition reactions is influenced by the steric hindrance of both, the *N*- and *C*-substituent of the nitrone, that is, the selectivity increases as the nitrogen substituent of the nitrone becomes bulkier. As shown in Table 2.17, the highest diastereoselectivity in these reactions was observed with *N*-benzyl nitrones (**479b**) and (**480**).

The major products (**481**) and (**485**) were found to have the *erythro*-configuration at C-3/C-4′ and *cis*-substitution at C-3/C-5. The high diastereoselectivity found in reactions of (**479b**) with styrene can be ascribed to the more favored approach of the dipole (**479b**) to styrene, to give *erythro-cis* (**481b**) and *threo-cis* (**482b**), as depicted in Fig. 2.34. It is likely reasonable that attack of *Z*-(**479b**) proceeds via the less hindered *endo* transition state, in an antiperiplanar manner in regard to the largest group of the heterocyclic acetal to give the major product, (**481b**), with C-3/C-4′ *erythro* and C-3/C-5 *cis*-configuration. The more pronounced steric hindrance, present in the approach to *the threo-cis*-diastereomer (**482b**), might explain the observed ratio *erythro/threo* 88:12 (Table 2.17).

Chiral oxazinone-derived nitrone (**16**), being of particular interest as a prototype for the synthesis of γ-oxygenated α-amino acids, reacts with alkenes (**D2**) efficiently and with high stereoselectivity, to give cycloadducts (**489**) (Scheme 2.239) (73).

Cycloaddition of homochiral imidazolone-derived nitrone (**490**) to various alkenes (**D1,D2**) (Scheme 2.239) (Table 2.18) affords good yields of cycloadducts (**491 a–c**) with high stereoselectivity (738).

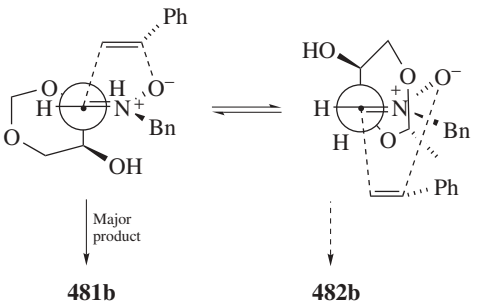
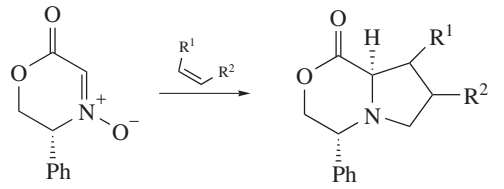
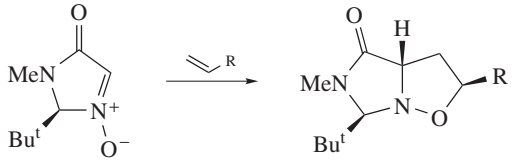


Fig. 2.34



16 **489 a-c**

$R^1 = R^2 = H$ (a);
$R^1 + R^2 = (CH_2)_3$ (b);
$R^1 = H$, $R^2 = C_6H_{13}$(c);

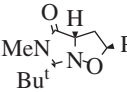
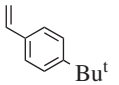
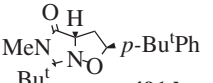
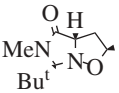


490 **491 a-c**

R = Ph (a); *p*-Bu^{t}C$_6$H$_4$ (b); C$_6$H$_{11}$ (c);

Scheme 2.239

Table 2.18 Isoxazolidine derivatives 491 a–c obtained from the 1,3-dipolar cycloaddition of 490 to alkenes

	Alkene	Cycloadduct[a]	Yield[b]; *exo/endo*[c]
D1		 **491 a**	89%;[d] 10:1
D1		 **491 b**	95% (91%); >20:1
D2		 **491 c**	86% (76%); 10:1

[a]Reactions were performed with 2–10 equiv alkene in $ClCH_2CH_2Cl$ at reflux for 5–52 h. The structure of the major isomer is shown.
[b]Total yield of *exo* and *endo* isomers (purified major isomer).
[c]*Exo* refers to 5-alkyl or aryl substituent; determined by integration of ^{1}H NMR spectra of unpurified reaction mixture.
[d]Major isomer not isolated in pure form.

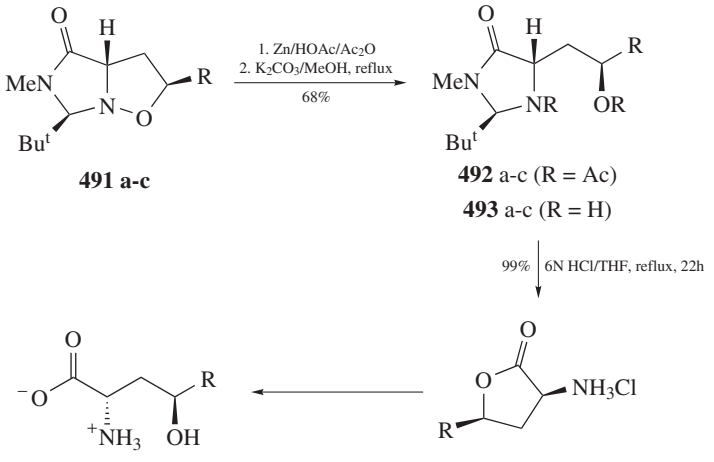
Isoxazolidine cycloadducts (**491**) undergo easy transformation into α-amino-γ-lactones (**494**), which can be readily converted into γ- hydroxy-α-amino acids (**495**) (Scheme 2.240) (Table 2.19).

Cycloaddition of *N*-substituted *C*-phosphorylated nitrones (**496**) to terminal alkenes leads to C-5 substituted isoxazolidines (**497**) and (**498**) with moderate (20%) to high (up to 90%) *trans* to *cis* diastereoselectivities (Scheme 2.241) (Table 2.20). In $ZnCl_2$-catalyzed cycloadditions, mixtures enriched in *cis* diastereomers were produced (263).

Improvements in 1,3-dipolar cycloaddition were achieved at high pressures (15 kbar) (74), and by solvent-free microwave activation (739).

Brandi et al. performed 1,3-dipolar cycloadditions of nitrones (**499**) to methylenecyclopropane (**500**). The resulting isoxazolidines (**501**), on subsequent heating, were transformed to piperidones (**502**). Addition of nitrone (**499**) to bicyclopropylidene (**503**) yielded isoxazolidines (**504**), which upon heating, gave piperidones (**505**) with annulated spirocyclopropane groups (Scheme 2.242) (740, 741). Compounds arising from 1,3-dipolar cycloadditions of appropriately substituted cyclic nitrones, for instance DMPO, lead to aza analogs (**507**), having the structure and major functionalities of the cytotoxic illudines and ptaquilosides (741).

Dipolarophiles D3. 1,3-Dipolar cycloadditions of suitably functionalized cyclic nitrones with terminal alkenes, which have potential leaving groups X at the end of the alkane chain -$(CH_2)_n$- (**D3**), were successfully used for the synthesis of pyrrolozidine, indolizidine and quinolizidine alkaloids, such as (+)- and (−)-lentiginosine, a potent amyloglucosidase inhibitor (Scheme 2.243) (742). Reductive cleavage of the N−O bond in the cycloadduct is important for the subsequent cyclization to pyrrolozidines, indolizidines, and quinolizidines.



491 a-c

492 a-c (R = Ac)

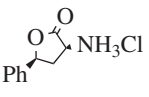
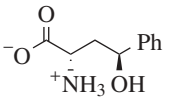
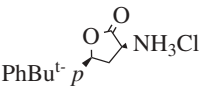
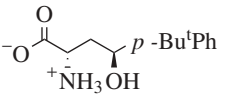
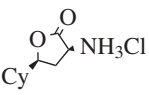
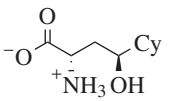
493 a-c (R = H)

494 a-c

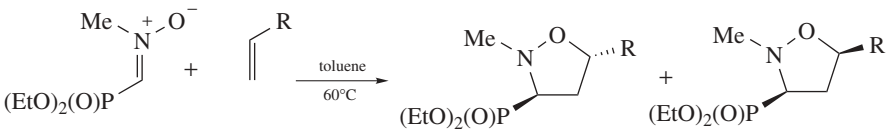
495 a-c

Scheme 2.240

Table 2.19 γ-Hydroxy-α-amino acids and lactones derived from cycloadducts 491 a–c

Cycloadduct	Lactone (method;[a] yields[b])	α-amino acid (yield[c])
491a		
	494 a (A; 68%, 99%)	**495 a** (75%)
491b		
	494 b (A; 83%, 99%)	**495 b** (50%)
491c		
	494 c (B; 87%, 99%)	**495 c** (62%)

[a]*Method A:* (1) Zn/HOAc/AC_2O; (2) K_2CO_3/MeOH; (3) 6N HCl, reflux.
Method B: (1) Pd/C, ammonium formate/MeOH; (2) 6N HCl, reflux.
[b]amino alcohol, lactone.
[c]After basic hydrolysis, neutralization, ion exchange chromatography, and lyophilization.



496 **497** **498**

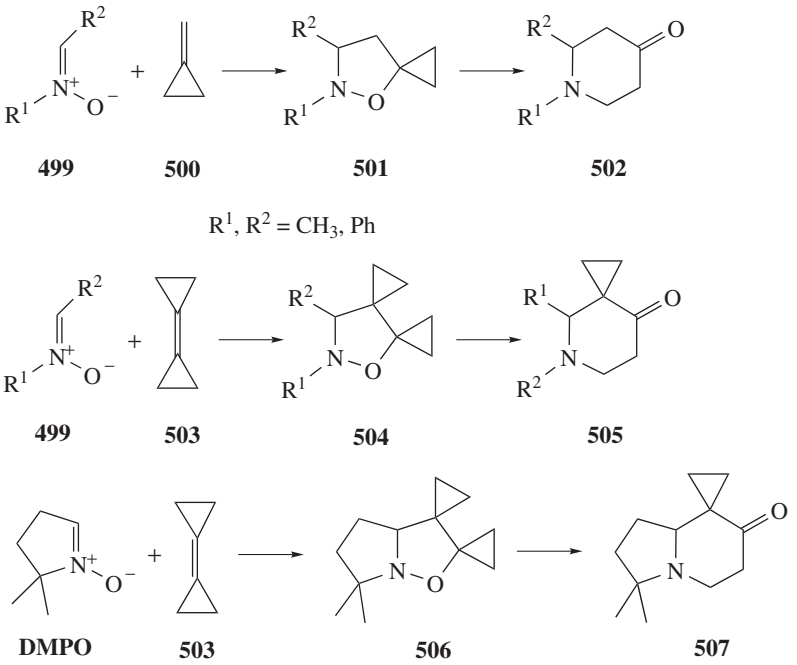
Scheme 2.241

Cycloaddition of nitrone (**508**) to allyl alcohol at ambient temperature gave a mixture of four cycloadducts in a 23:5:4:1 ratio (Scheme 2.244). All of the adducts (**509**) are derived from the regiochemical approach opposite to the intramolecular pathway (Fig. 2.35). Formation of the cycloadduct in the intramolecular cycloaddition reaction is ascribed to a high preference for an *endo-syn* transition state, due to the constraint imposed by the short, three atom connecting chain (116). The major product in the intermolecular cycloaddition reaction was the *exo-anti* –(**509**) adduct (Scheme 2.244 and Fig. 2.35).

Table 2.20 Isoxazolidines 497 and 498 produced via Scheme 2.241

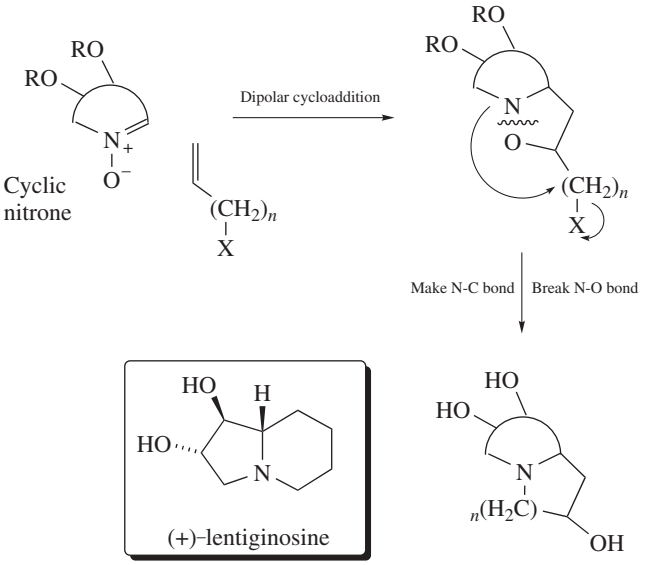
Entry	R	Reaction time (h)	Trans/cis ratio (497:498)	Yield[a]
a	CH_2OH	48	62:38	497a, 38% 497a, 20%
b	CH_2NHBoc	48	72:28	Inseparable
c	CH_2Br	40	65:35	Inseparable
d	CH_2SiMe_3	40	95:5	497d, 64%
e	$CH_2P(O)(OEt)_2$	50	74:26	497e, 23% 498e, 4%

[a] Yield of pure materials obtained after silica gel chromatography.

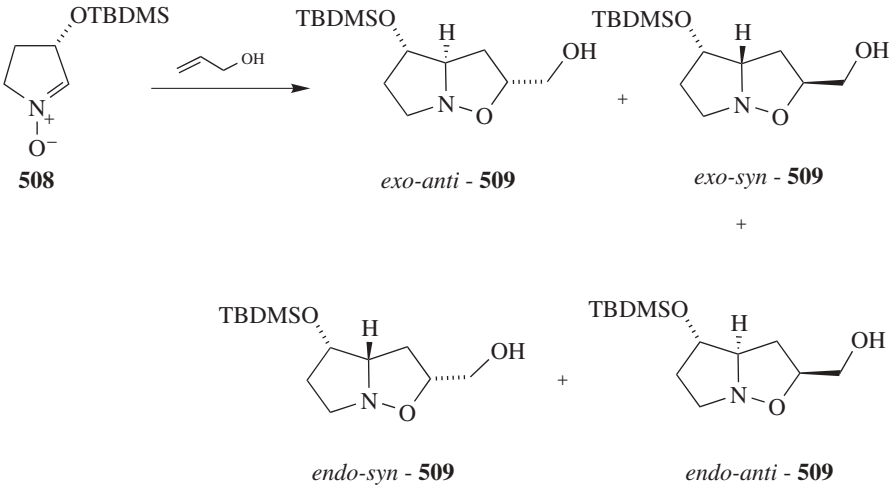


Scheme 2.242

Cycloaddition of allyl alcohol to the D-glucose-derived nitrone (**510**) is the key step in the synthesis of polyhydroxy indolizidine alkaloids, namely, 2-hydroxy-1-deoxycastanospermine (**513a,b**) and 2-hydroxy-1-deoxy-8a-*epi*-castanospermine (**513c,d**). The intermolecular 1,3-cycloaddition of allyl alcohol to nitrone (**510**), followed by tosylation afforded the four diastereomeric sugar-substituted isoxazolidines (**511a–d**) with the desired regioselectivity. The one-pot conversion of (**511a–d**) to pyrrolidines (**512a–d**) by hydrogenolysis, followed by removal of



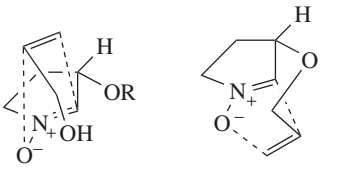
Scheme 2.243



Scheme 2.244

the 1,2-acetonoid functionality and hydrogenation, afforded the target compounds (**513a–d**) (Scheme 2.245) (743).

The asymmetric 1,3-dipolar cycloaddition of nitrones (**515**), possessing an electron-withdrawing group, to allylic alcohols was achieved by using diisopropyl (*R,R*)-tartrate [(*R,R*-DIPT)] as a chiral auxiliary. The isoxazolidines (**516**) and



Intermolecular
exo-anti
major

Intramolecular
endo-syn
exclusive

Fig. 2.35 Preferred transition states for the inter- and intramolecular cycloadditions to 3-OR-substituted nitrones.

(**517**) were obtained with high regio-, diastereo-, and enantioselectivity (Scheme 2.246). 1,3-Dipolar cycloaddition of nitrones, possessing electron-withdrawing cyano or *tert*-butoxycarbonyl groups, to 2-propen-1-ol gave 3,5-*trans*-isoxazolidines with high enantioselectivity. In contrast, nitrones with an amide moiety, afforded the corresponding 3,5-*cis*-isoxazolidines with completely opposite diastereoselectivity. Catalytic asymmetric 1,3-dipolar cycloaddition of nitrones, possessing a *N,N*-diisopropylamide moiety, to allylic alcohols gave di- and trisubstituted isoxazolidines with excellent enantioselectivity of up to 99% ee. Asymmetric 1,3-dipolar cycloadditions were also used for preparing (2*S*,4*R*)-4-hydroxyornithine derivatives. The ready availability of both, (*R,R*)- and (*S,S*)-tartaric acid esters allows the application of these methods to the preparation of either enantiomer of the desired compounds (744).

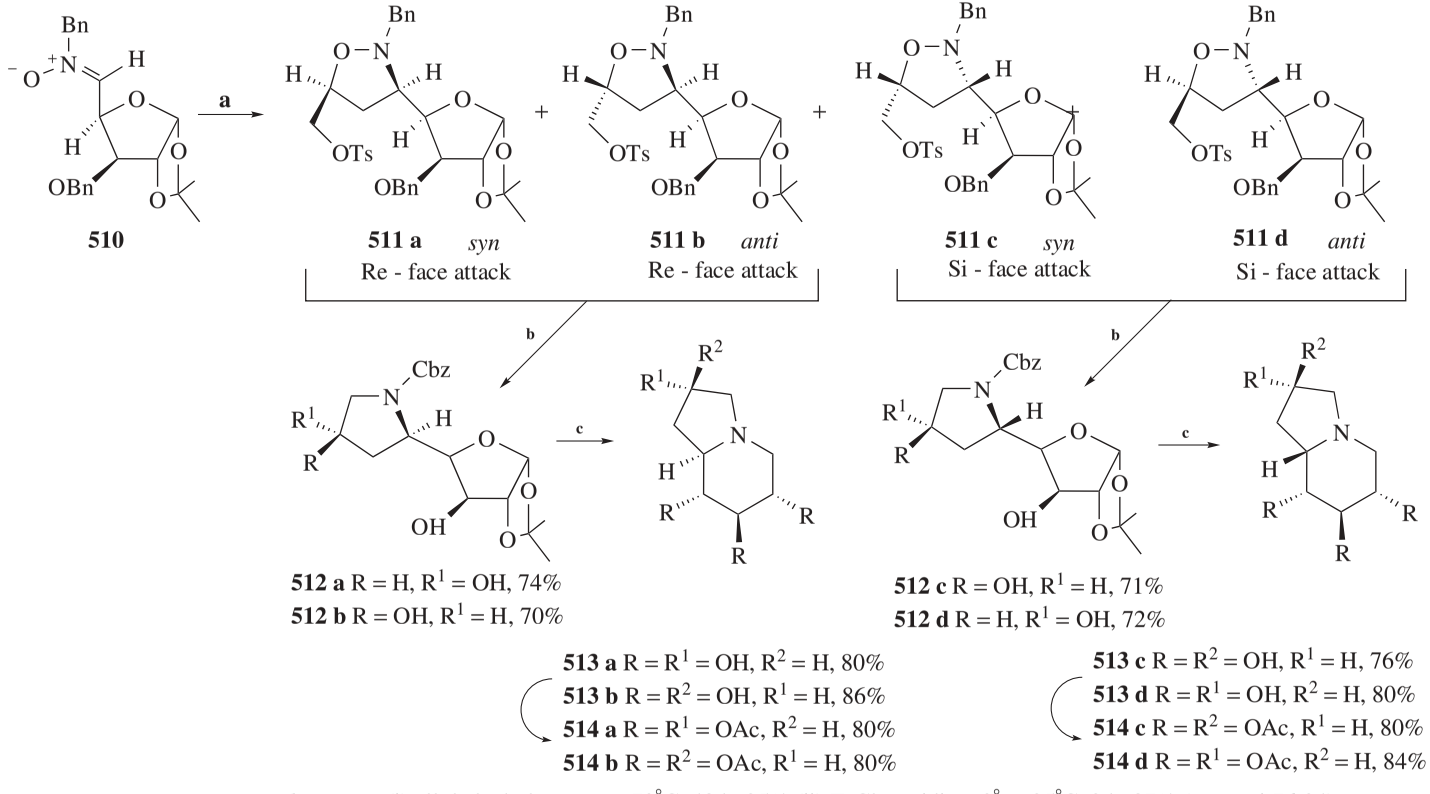
Isoxazolidinyl polycyclic aromatic hydrocarbons (**518a–f**) and (**519a–f**) have been synthesized in good yields by the 1,3-dipolar cycloaddition methodology using microwave irradiation (Scheme 2.247) (Table 2.21). Compounds (**518c**) and (**518e**) show high levels of cytotoxicity on MOLT-3 leukemia cells. Compound (**518e**) exerts a remarkable enhancing activity on apoptosis, caused by anti-fas antibody addition. Furthermore, compounds (**518b**) and (**519b**) scheme specific antiviral effects against the Punta Toro virus (745).

Synthesis of (−)-monatin (**524**), a high-intensity sweetening agent, was achieved by chelation-controlled cycloaddition of chiral oxazinone-derived nitrone (**16***) to allyl alcohol (**520**) in the presence of $MgBr_2{\cdot}OEt_2$ (Scheme 2.248) (746).

The reaction of 1,3-dipolar cycloaddition of enantiopure cyclic nitrones to protected allyl alcohol, is the basis of stereoselective syntheses of bicyclic *N,O-iso*-homonucleoside analogs (747), of isoxazolidine, to analogs of *C*-nucleosides related to pseudouridine (748) and to homocarbocyclic-2'-oxo-3'-azanucleosides (749) (Fig. 2.36).

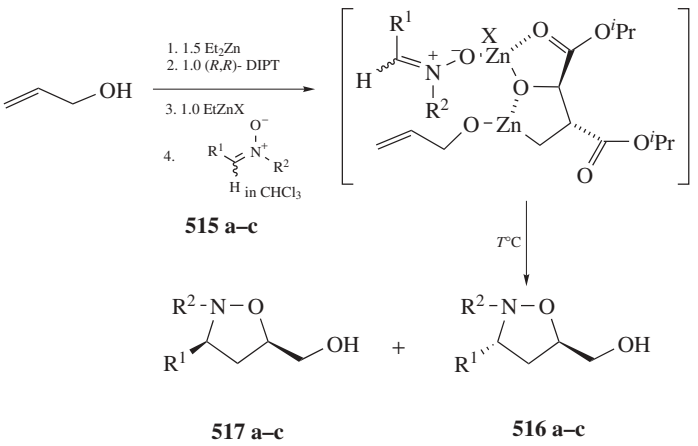
Cycloadditions of pyrroline-derived nitrones (**525**) to 3-buten-1-ol (**526**) afford bicyclic isoxazolidines (**527**) which were transformed into indolizidines (**528**) (Scheme 2.249) (82, 111, 116, 750).

The reaction of *C*-arylcarbamoyl-*N*-phenylnitrones (**529**) with ricinolic acid derivatives (**530**) leads to the formation of a mixture of diastereomeric



Reaction conditions: **a:** (i) allyl alcohol, acetone, 70°C, 48 h, 95% (ii) TsCl, pyridine, 0° to 25°C, 2 h, 87% (syn:anti 76:24); **b:** (i) $HCOONH_4$, Pd/C, MeOH, 80°C, 1 h; (ii) CbzCl, $NaHCO_3$, MeOH, 0 to 25°C, 2 h; **c:** (i) TFA-H_2O (3:2), 25°C, 2 h; (ii) H_2, Pd/C, MeOH, 80 psi, 25°C, 12 h; **d:** Ac_2O, pyridine, DMAP, 0° to 25°C, 12 h.

Scheme 2.245

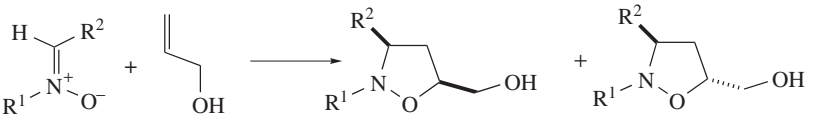


515 a–c

517 a–c **516 a–c**

R^1 = CN, R^2 = Ph (a); R^1 - CO_2Bu^t, R^2 = Me (b); R^1 = $CONBn_2$, R^2 = PH (c);

Scheme 2.246



499 a–f **518 a–f** **519 a–f**

Scheme 2.247

Table 2.21 Reaction of nitrones 499 with allyl alcohol

Entry	Nitrone	R^1	R^2	Microwave conditions time (min)[a]	isolated yield[b] (%)	Classical heating[c] (% yield)	518/519 ratio
1	**499 a**	Me	9-anthryl	80	53	1	1.1:1.0
2	**499 b**	Me	9-phenanthryl	20	83	30	1.3:1.0
3	**499 c**	Me	1-pyrenyl	20	75	20	1.5:1.0
4	**499 d**	Bn	1-pyrenyl	20	85	30	1.6:1.0
5	**499 e**	Bn	9-phenanthryl	20	39	NR[d]	1.5:1.0
6	**499 f**	Bn	9-anthryl	80	NR[e]	NR	

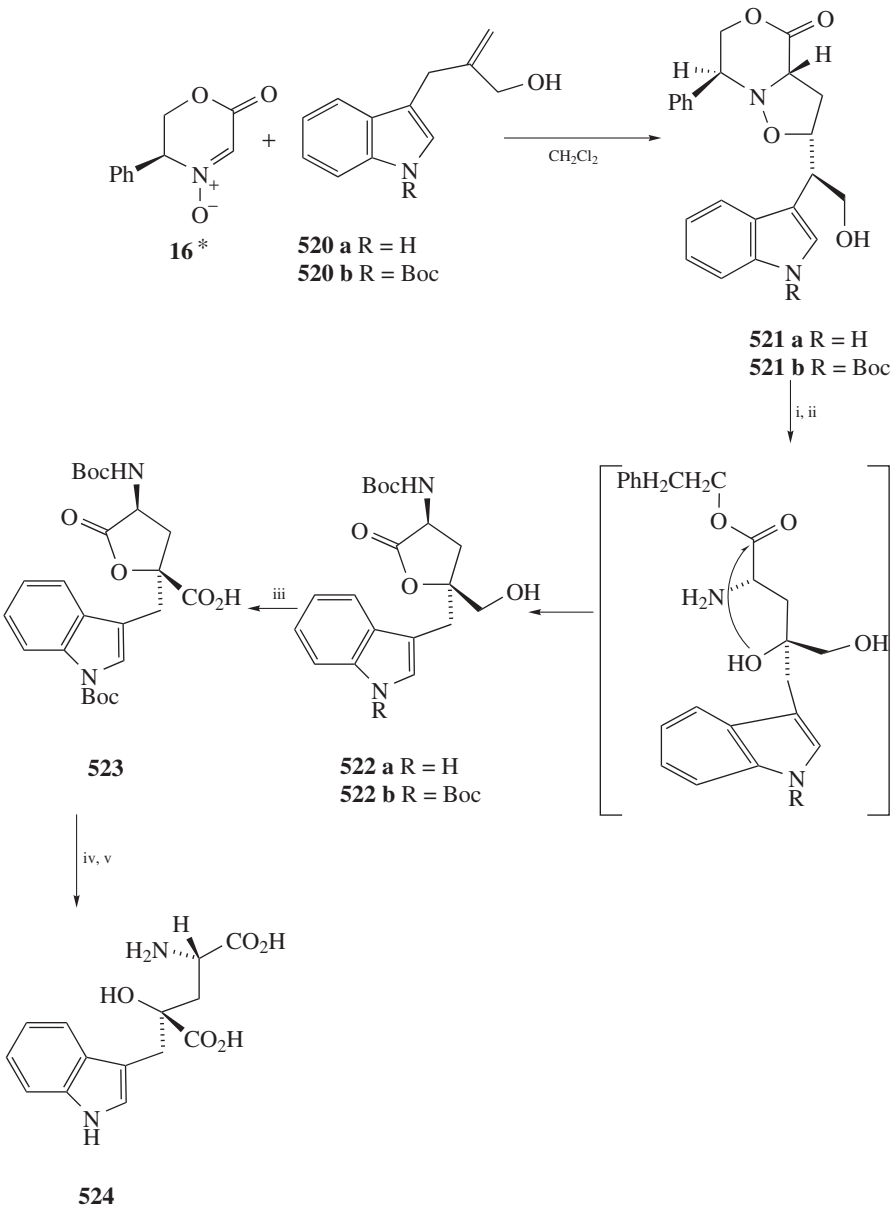
[a]Irradiation at 90 W; the temperatures reached by the reaction mixture are in the range from 150 to 160°C.

[b]Reaction performed in a pressure tube equipped with stir bar, in the absence of solvent, using a 1:200 relative ratio of dipole/dipolarophile.

[c]Reaction performed in sealed tube in absence of solvent, using a 1:200 relative ratio of dipole/dipolarophile at 130°C for 48 h.

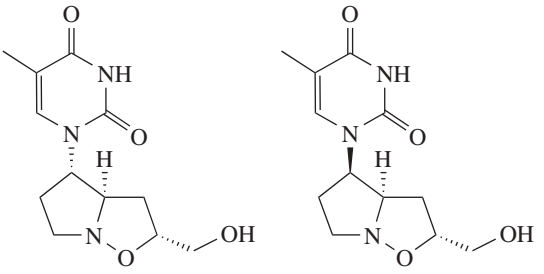
[d]No reaction.

[e]When irradiated at 120 W (200–210°C), only decomposition products are observed.

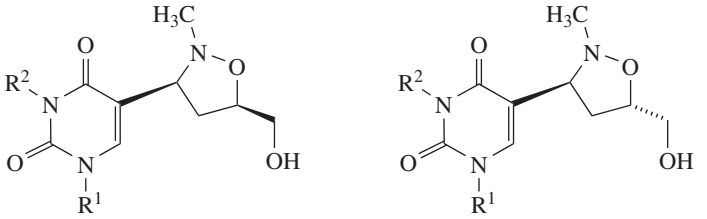


Reagents and conditions: (i) H_2, $Pd(OH)_2/C$, MeOH; (ii) Boc_2O, CH_3CN, 16-68% for **522a** from **521a**, 81% for **522b** from **521b**; (iii) PDC, DMF, 69% from **522b**; (iv) HCl, HCO_2H; (v) NaOH, MeOH then Amberlite IR-120-H^+ form, aq. NH_3, 92%

Scheme 2.248

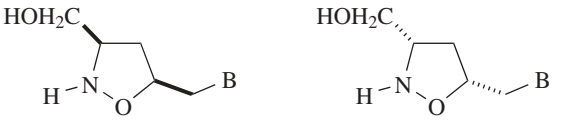


Ref.[751]

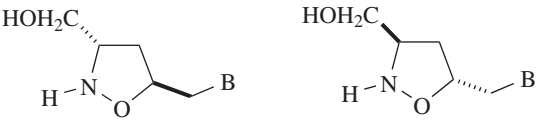


(*a*) $R^1 = CH_3(CH_2)_6CH_2$; $R^2 = H$; (*b*) $R^1 = R^2 = CH_3(CH_2)_6CH_2$;

Ref.[752]



B = Thymine (*a*)



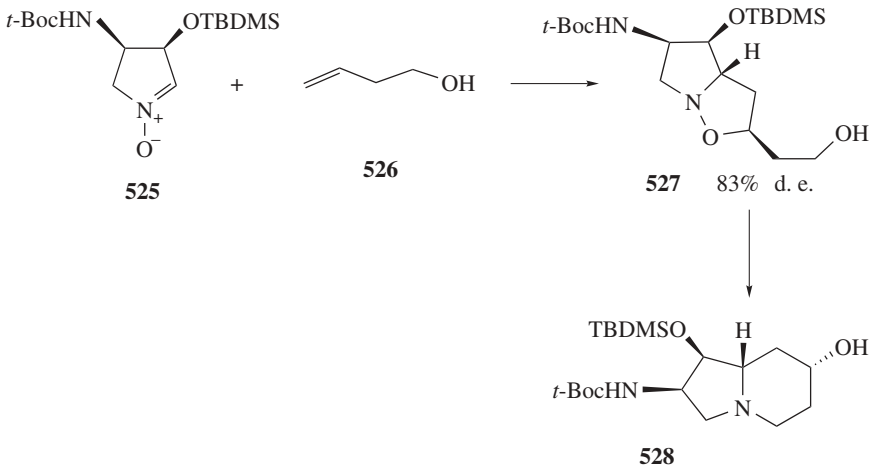
5-Fluorouracil (*b*)

Ref.[753]

Fig. 2.36

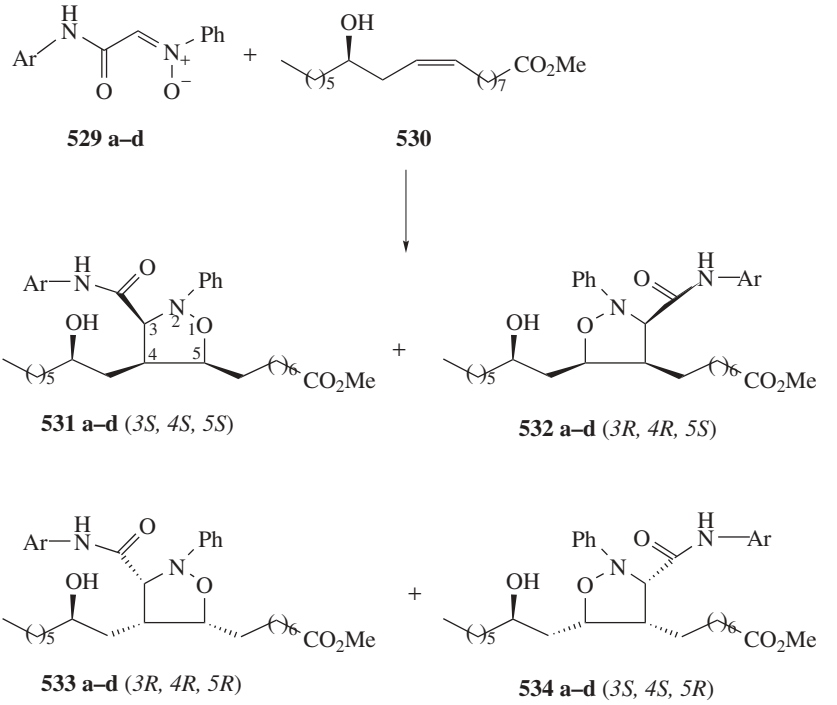
regioisomers of isoxazolidines (**531**)-(**534**). Their compositions and yields depend on the structure of the starting reagents with substituents at C3, C4, and C5 in the *cis*-position (Scheme 2.250) (751).

Cycloadditions of cyclic (**a**) and acyclic (**b**) nitrones to achiral (**535a**) and chiral α-diphenylphosphinyl alkenes (**535b,c**) have been reported (752). In each case, addition to allyldiphenylphosphine oxide (**535a**) gave a single isoxazolidine



525 **526** **527** 83% d. e. **528**

Scheme 2.249



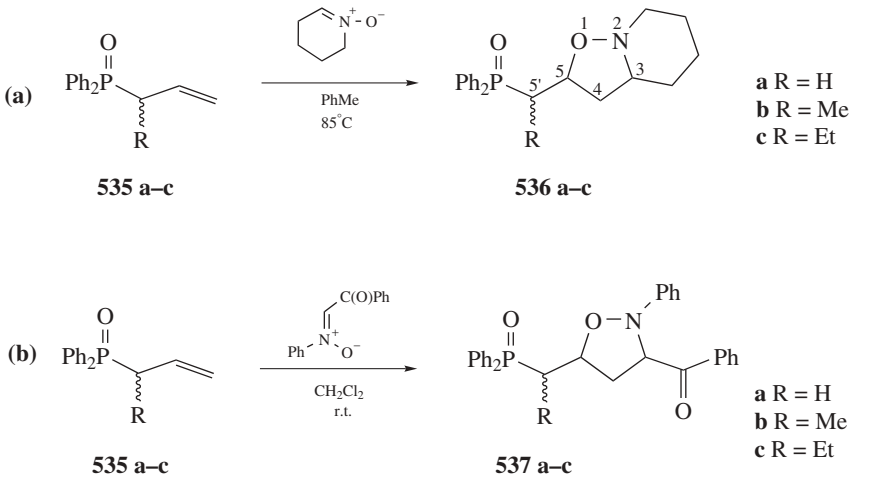
529 a–d **530**

531 a–d (*3S, 4S, 5S*) **532 a–d** (*3R, 4R, 5S*)

533 a–d (*3R, 4R, 5R*) **534 a–d** (*3S, 4S, 5R*)

R = Ph (a), 2-MeC_6H_4 (b), 3-MeC_6H_4 (c), 2-ClC_6H_4 (d)

Scheme 2.250



Scheme 2.251

product: (**536a**), in reactions (**a**) and (**537a**) in those of (**b**) (Scheme 2.251). With α-chiral alkenes (**535 b,c**), the reactions are still believed to involve *exo* transition states. Two diastereoisomeric products are formed, of which the major exerts *anti* stereochemistry across the 5,5'chiral centers.

Cycloaddition of nitrone (**26**) to allylamine (**538**) leads to the synthesis of chiral tetracyclic isoxazolidine (**539**) which is used in the preparation of compound R107500. This compound has been found to be active as an antiolytic and antidepressant. It also has the potential to inhibit drug abuse (Scheme 2.252) (80).

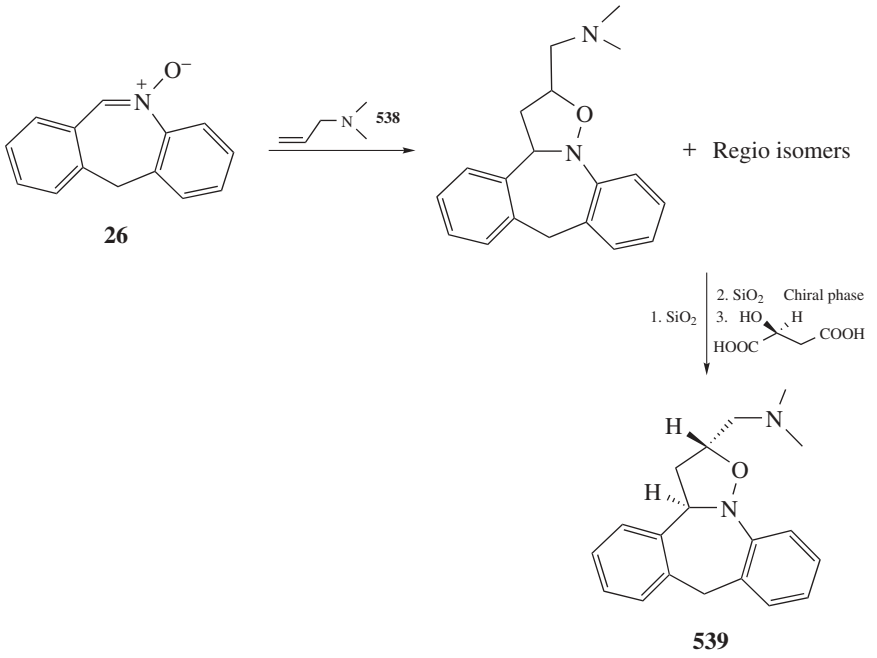
Dipolarophiles D4. 1,3-Dipolar cycloaddition between acrylonitrile (**D4**) and chiral nonracemic nitrones is a key step in an efficient synthetic route to isoxazolidinyl analogs of thiazofurin (**540**) (Scheme 2.253). Opposite diastereofacial induction was observed when the chiral group was placed at either the carbon or the nitrogen atom of the nitrone function (753).

The 2-isoxazolidine nitriles (**540b**) and (**540a**) obtained, were further converted into the enantiomeric target compounds (**541**) and (**542**) by producing the thiazole ring via condensation with L-cysteine (Scheme 2.254) and (Scheme 2.255) (753).

Dipolarophiles D5. Electron-deficient alkenes based on acrolein and its analogs are widely used as dipolarophiles. To carry out asymmetrical 1,3-dipolar cycloadditions between various nitrones and acrolein, the bis-titanium catalyst (**543**) (Fig. 2.37) was used as the chiral Lewis acid (Table 2.22) (754a).

In enantioselective, 1,3-dipolar cycloadditions of nitrones to methacrolein the catalysts used were (η^5-C_5Me_5)MR-Prophoscontaining complexes (M = Rh, Ir and (*R*)-Prophos = 1,2-bis(diphenylphosphino)propane) (754b).

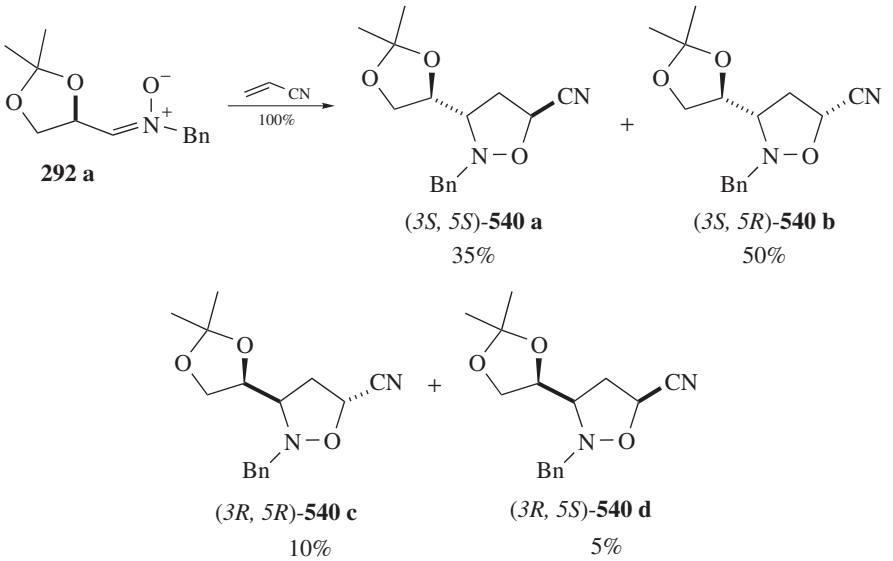
Cationic 3-oxobutylidenaminatocobalt complexes (**544a**), with hexafluoroantimonate as a counter anion, activate α,β-unsaturated aldehydes in 1,3-dipolar



26

539

Scheme 2.252



292 a

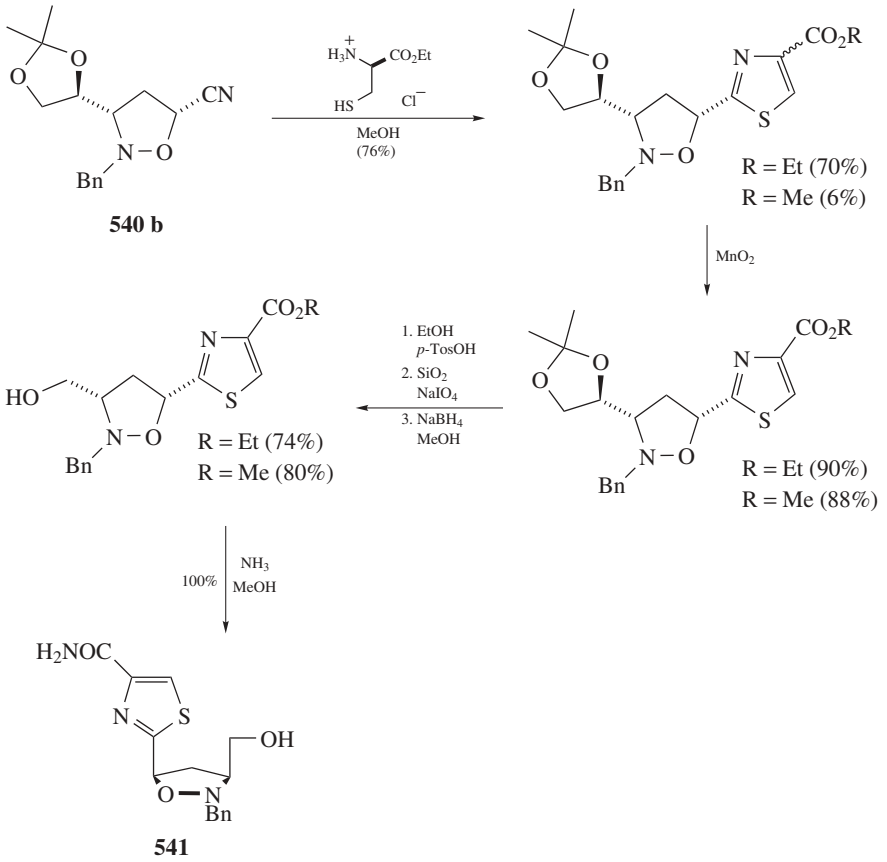
(*3S, 5S*)-**540 a**
35%

(*3S, 5R*)-**540 b**
50%

(*3R, 5R*)-**540 c**
10%

(*3R, 5S*)-**540 d**
5%

Scheme 2.253



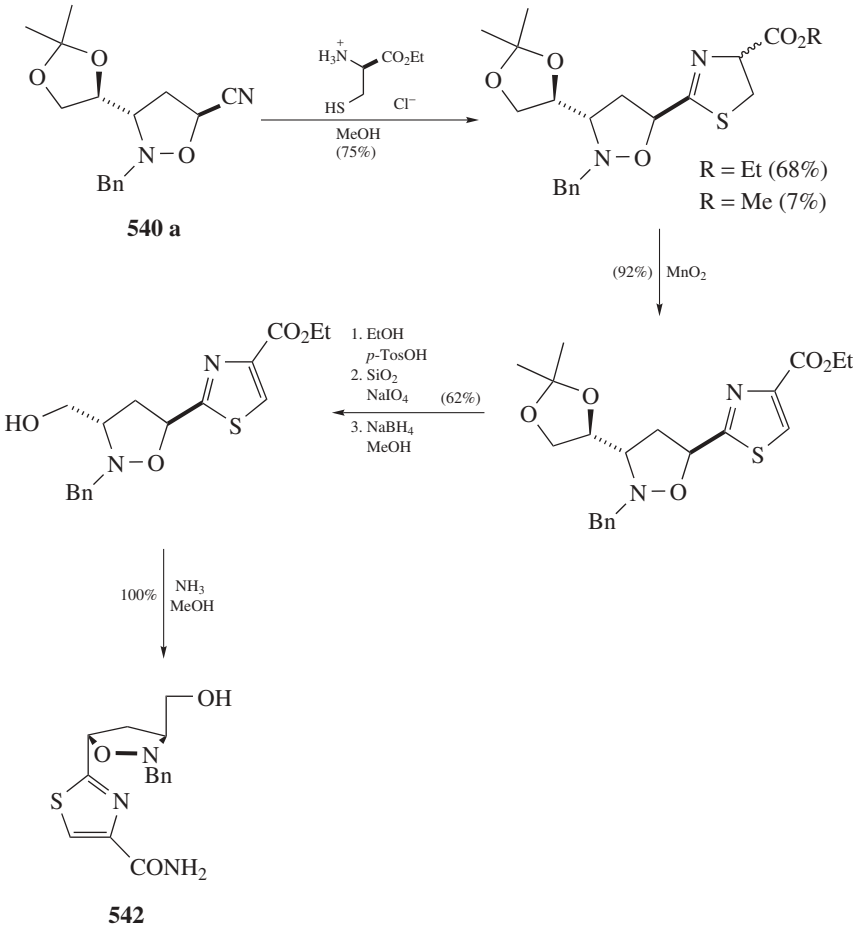
Scheme 2.254

cycloaddition reactions. Using (**544a**) the isoxazolidines were obtained in high yield and with high regio-, endo-, and enantioselectivities (Table 2.23) (755–758).

A variety of imidazolidinium and pyrrolidinium salts (Fig. 2.38) have been found to catalyze the reaction between nitrones and cyclic α,β-unsaturated aldehydes, affording bicyclic adducts with high diastereoselectivity and enantioselectivity (Scheme 2.256) (759).

1,3-Cycloaddition of α-aryl-*N*-phenylnitrones to the C16-C17 π-bond in 16-dehydropregnenolone-3β-acetate (**545**) involves only the minor rotamer (*E*-form) of the nitrones. It proceeds regio-, stereo- and π-facial-selectively to give steroido[16,17-d]isoxazolidines (**546**) in high yield (Scheme 2.257), (Table 2.24) (760). Similarly the cycloaddition of α,*N*-diphenylnitrones proceeds with five-membered heterocyclic enones (761).

Regio- and stereospecific 1,3-cycloaddition of di-*tert*-butylated acyl nitrone (**548**), generated *in situ* from (**547**), with *Z*-2-cyclodecanone and subsequent aromatization is the key step in the synthesis of biomimetic pyridomacrolidin



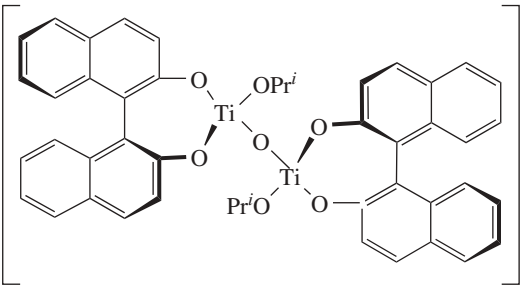
540 a

542

Scheme 2.255

(**549**) (Scheme 2.258) (762–765). The biological activity of (**549**) has been shown to inhibit the protein tyrosine kinase (PTK) activity at concentrations of 100μg/mL (766, 767).

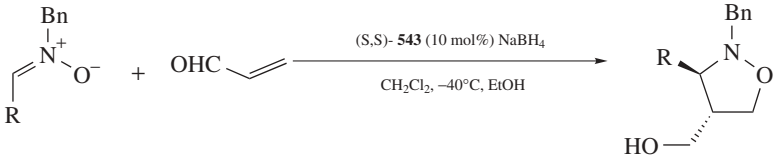
1,3-Dipolar cycloadditions of cyclic nitrones (**551**) and (**552**) to achiral and chiral *p*-benzoquinone mono-ketals (**550a–d**), give cycloadducts (**553–558**). These reactions have shown poor chemo- and stereoselectivity. To overcome these problems, a highly efficient strategy has been used, based on the temporary conjugate addition of thiophenol to the dipolarophile. The phenylthio derivative (**559**), available in both enantiopure forms, has been shown to be effective as a masked chiral synthetic equivalent of *p*-benzoquinone in the cycloaddition reaction with cyclic nitrones (**551**) and (**552**). In these reactions a very high degree of both, regio- and stereoselective formation of cycloadducts (**560**) to (**563**) occurred (Scheme 2.259) (768).



(*S*,*S*)-**543**

Fig. 2.37

Table 2.22 Asymmetric 1,3-dipolar cycloadditions of nitrones with acrolein[a]



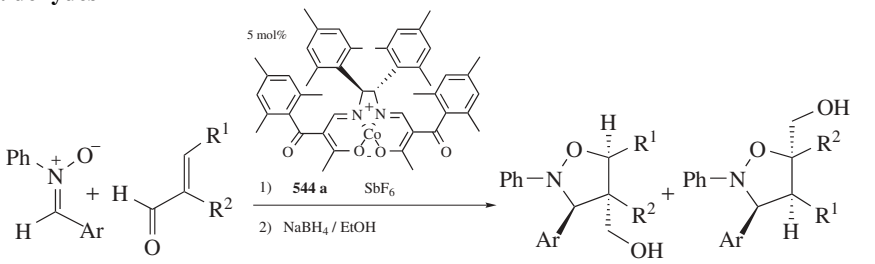
Entry	R	Time (h)	Yield (%)[b,c]	ee (%)[d]
1	Ph	24	94	93
2	4-MePh	24	81	94
3	4-MeOPh	40	76	88
4	4-ClPh	39	85	88
5	2-naphthyl	24	92	93
6	Bu^t	14	90	97
7	cyclohexyl	24	62	70
8		24	86	97

[a] The reaction of nitrones and acrolein (1.5 equiv) was carried out in the presence of chiral bis-Ti(IV) oxide (*S,S*)-**543** in CH_2Cl_2 at –40°C.
[b] Isolated yield.
[c] Only the endo isomer was detected by 1H NMR spectroscopy.
[d] Determined by HPLC analysis using chiral column (Chiral-pak OD-H, Daicel Chemical Industries, Ltd.).

It has been reported that diiron acyl complexes (**564**) undergo stereo- and regioselective 1,3- cycloadditions with a variety of nitrones (Scheme 2.260). These complexes are then oxidatively converted to synthetically useful thio esters (769).

Dipolarophile D6. A complete theoretical study of the 1,3-dipolar cycloaddition reaction of D-glyceraldehyde nitrone (**N**) to methyl acrylate (**MA**) has been

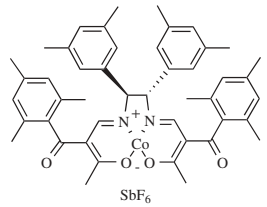
Table 2.23 1,3-Dipolar cycloaddition of nitrone and various α, β-unsaturated aldehydes



Entry	Aldehyde	R^1	R^2	Yield (%)[a]	Rs(a/b)[b]	endo/exo[b]	ee (endo) (%)[c]
1		-$(CH_2)_3$-		Quant	>99/1	>99/1	87
2[d]		H	H	90	89/11	>99/1	79
3		CH_3	H	94	>99/1	98/2	63
4[e]		H	CH_3	91	5/95	>99/1	82
5[f]		H	$C_6H_5CH_2$	93	1/99	>99/1	92

Reaction time: 24 – 144 h. *Reaction temperature:* –40°C.

544 b



[a] Isolated after the reduction with $NaBH_4$.

[b] Determined by ^1H NMR analysis.

[c] Determined by HPLC analysis using Daicel Chiralpak AD-H *or* Chiralce OD-H.

[d] *Reaction temperature:* –78°C.

[e] Eight mole percent complex **544 b** was employed at –60°C and five portions of nitrone was added at 24 h intervals.

[f] Complex **544 b** was employed.

carried out using density functional methods (B3LYP/6-31G*). Both *ortho* and *meta* channels, leading, respectively, to 3,5- (**P1**) - (**P4**) and 3,4- (**P5**) - (**P8**) disubstituted isoxazolidines were considered (Scheme 2.261) (770). *Endo* and *exo* approaches by *Re* and *Si* faces were considered in the study. Starting from transition states (**TS1**) to (**TS8**), the minima associated with the final cycloadducts, (**P1**) to (**P8**) have also been located. In all cases, the cycloaddition reactions are exothermic in the range of −20 to −17 kcal/mol, the most stable product being the

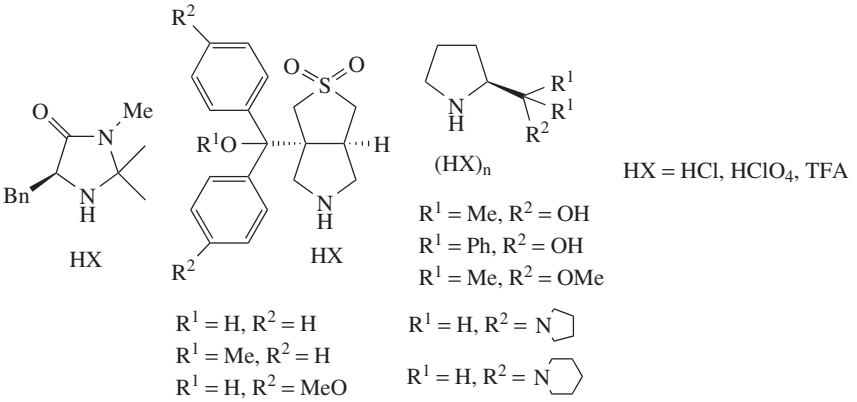
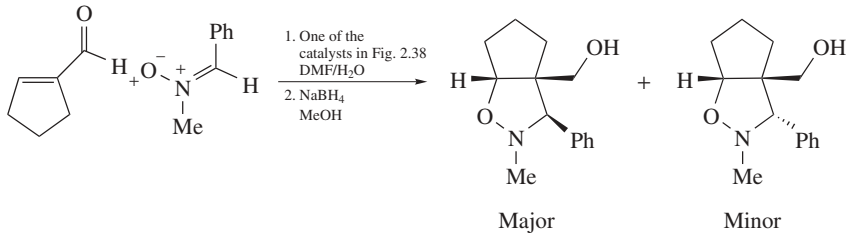
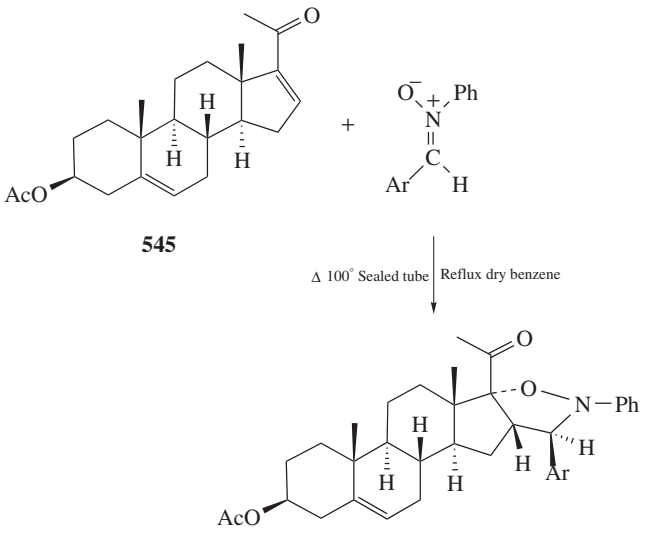


Fig. 2.38 Catalysts used in 1,3-dipolar cycloadditions of nitrones.



Scheme 2.256



Scheme 2.257

Table 2.24 Reactions of 16-DPA 545 with α-aryl-N-phenylnitrones

Ar	% Yield of 546 (reaction time) Reflux (h)	δ Sealed tube (h)
Ph	80 (65)	85 (36)
p-NO_2Ph	82(64)	83(30)
p-ClPh	82(70)	85(37)
p-MeOPh	74(43)	74(24)
3-Furanyl	73(72)	83(32)

(3*R*,5*S*)-isomer. Slightly higher energy differences were observed for 3,5-cycloadducts (*ortho* channel) than for 3,4-cycloadducts (*meta* channel). Clearly, the most favored reaction channel corresponds to the *ortho* one, through an *endo* approach by the *Si* face of the nitrone.

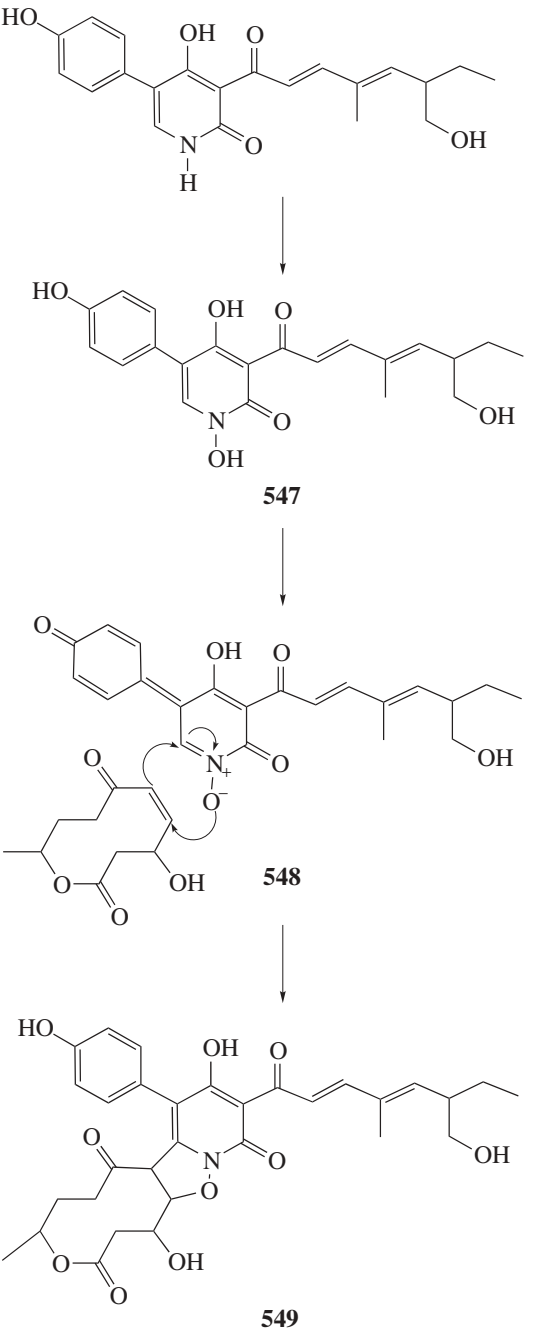
To carry out 1,3-dipolar cycloadditions with alkyl acrylates, nitrones of various structures such as ferrocenylnitrones (141), nitrones derived from chiral amino acids (210), L-serine-derived nitrones (660) and *N*-substituted *C*-phosphorylated nitrones (263) have been used.

Chiral nitrones derived from L-valine (**62a–c**) react with methyl acrylate to afford the corresponding diastereomeric 3,5-disubstituted isoxazolidines (**565a–c**) to (**568a–c**). The dibenzyl substituted nitrone (**62a**) also gave 3,4-disubstituted isoxazolidine (**569**) in 4% yield. The stereoselectivity was dependent on the steric hindrance of the nitrone and on reaction conditions. High pressure decreased the reaction time of the cycloadditions. The major products were found to have the C-3/C-6 *erythro* and C-3/C-5 *trans* configuration (Scheme 2.262) (771).

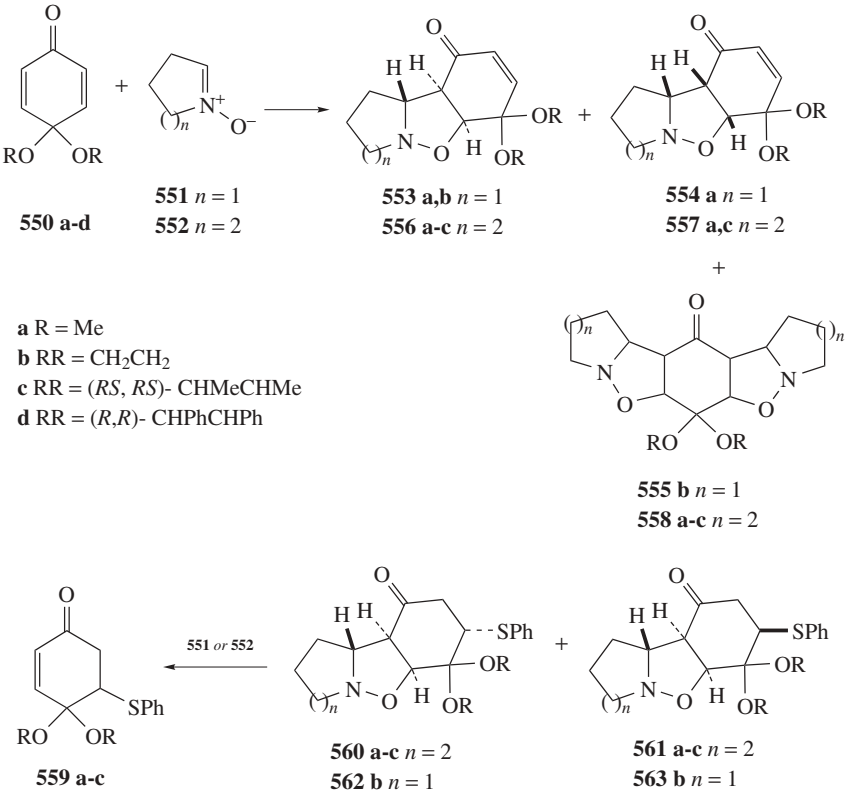
Highly selective 1,3-dipolar cycloaddition reactions of nitrone (**154**) with acrylates have been used in the total syntheses of pyrrolizidine alkaloids, 7-deoxycasuarine (**572**) and hyacinthacine A_2 (**573**) (Scheme 2.263) (772).

1,3-Dipolar cycloaddition reactions between three *N*-benzyl-*C*-glycosyl nitrones and methyl acrylate afforded key intermediates for the synthesis of glycosyl pyrrolidines. It was found that furanosyl nitrones (**574**) and (**575**) reacted with methyl acrylate to give mixtures of all possible 3,5-disubstituted isoxazolidines (**577**) and (**578**). On the other hand, the reaction with pyranosyl nitrone (**576**) was much more selective and cycloaddition at ambient temperatures afforded only one of the possible *Re-endo* adducts (**579a**). The obtained isoxazolidines were transformed into the corresponding *N*-benzyl-3-hydroxy-2-pyrrolidinones (**580–582**) on treatment with Zn in acetic acid (Scheme 2.264) (773).

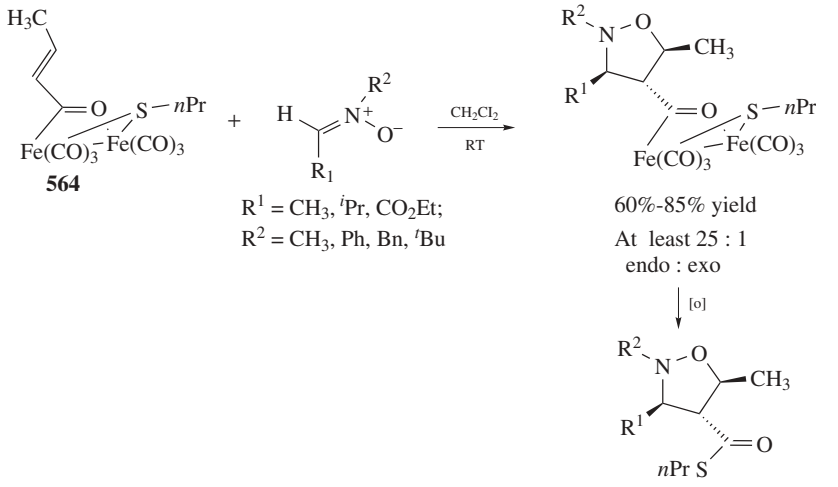
The influence of electronic factors on the regioselective cycloadditions of nitrones (**551**), and (**583**) to (**585**) to acrylates has been demonstrated by using dipolarophiles with electrophilic substituents at the β-carbon of the alkene in γ-bromo α,β-unsaturated esters and lactones (774) and in ethyl 2-hydroperfluoro-2-alkenoates (**586**) (775). The reactions of enoates (**586**) with nitrones are regiospecific and afford isoxazolidines with the CO_2Et and R_F groups in C-4 and C-5


HO
OH
O
N
H
O
OH
HO
OH
O
N
O
OH
OH
547
O
OH
O
N+
O
O−
O
O
OH
548
O
HO
OH
O
O
N
O
O
OH
O
O
OH
549

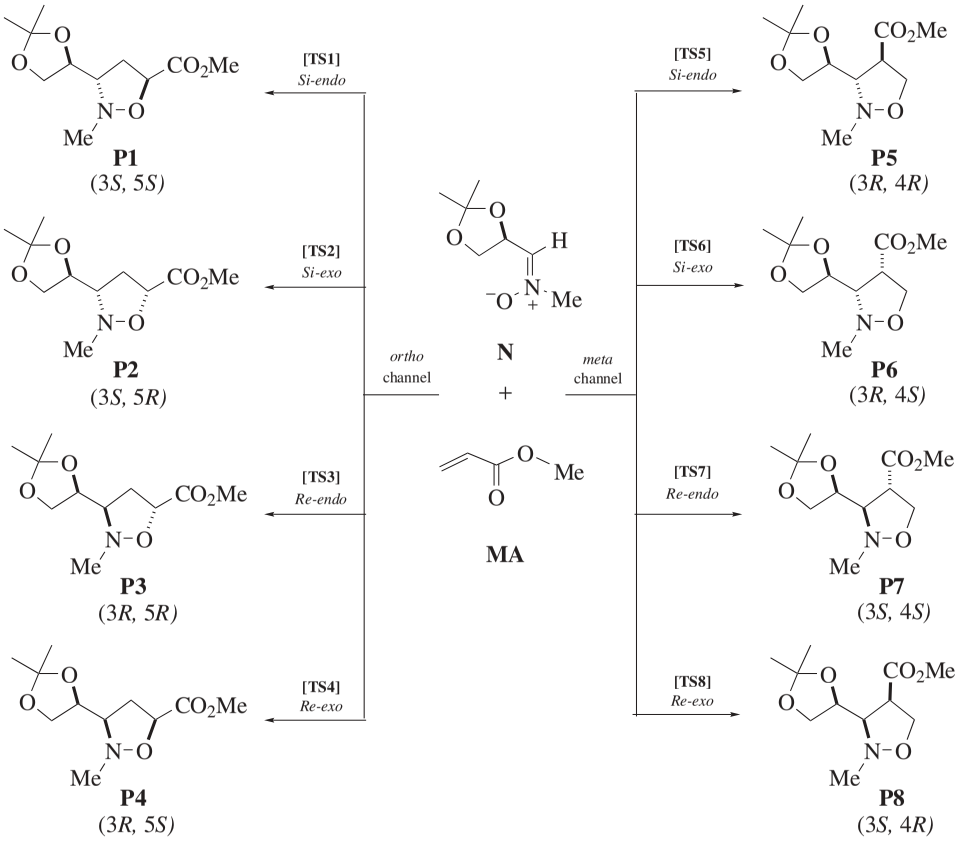
Scheme 2.258



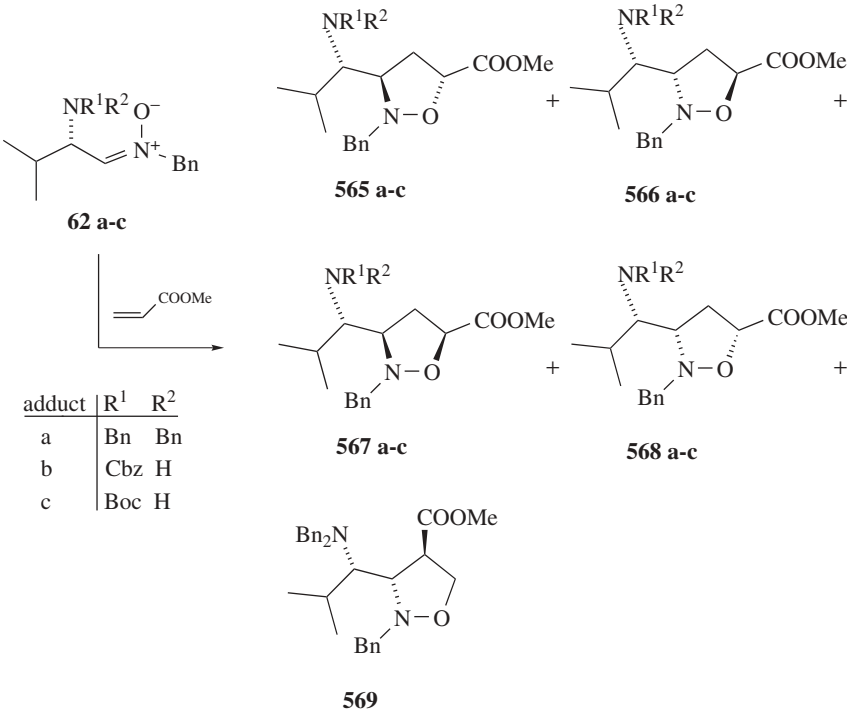
Scheme 2.259



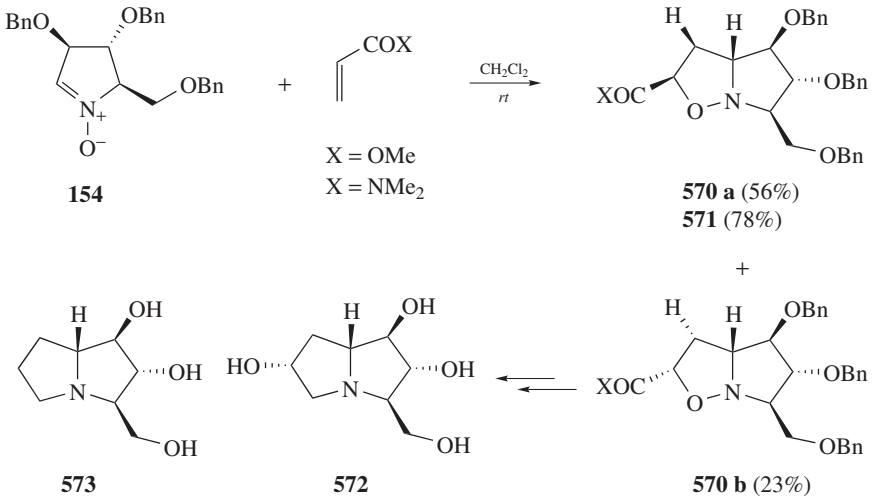
Scheme 2.260


[TS1]
Si-endo
[TS2]
Si-exo
[TS3]
Re-endo
[TS4]
Re-exo
ortho
channel
N
+
MA
meta
channel
[TS5]
Si-endo
[TS6]
Si-exo
[TS7]
Re-endo
[TS8]
Re-exo
P1
(3S, 5S)
P2
(3S, 5R)
P3
(3R, 5R)
P4
(3R, 5S)
P5
(3R, 4R)
P6
(3R, 4S)
P7
(3S, 4S)
P8
(3S, 4R)

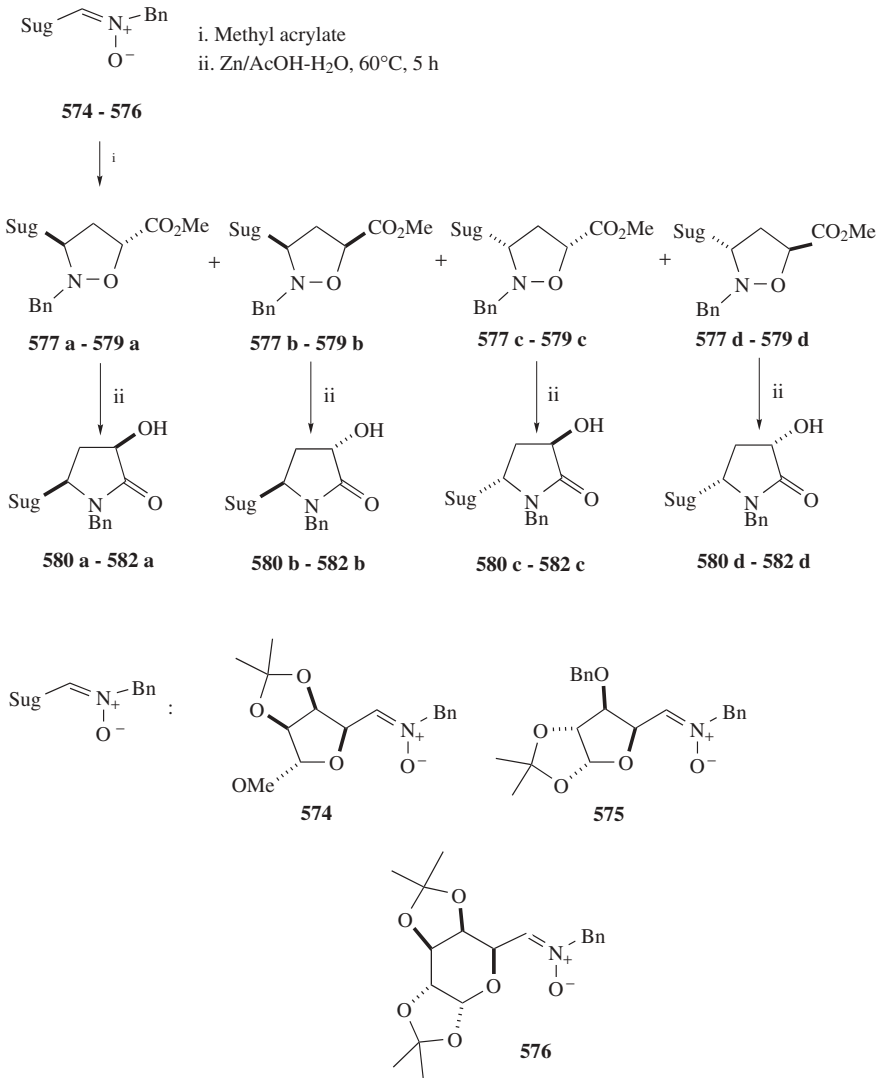
Scheme 2.261



Scheme 2.262



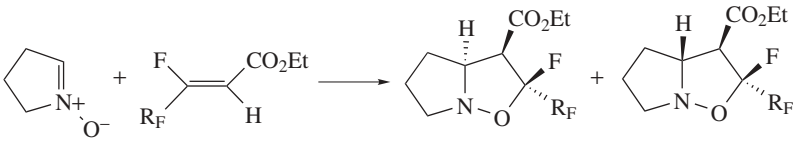
Scheme 2.263



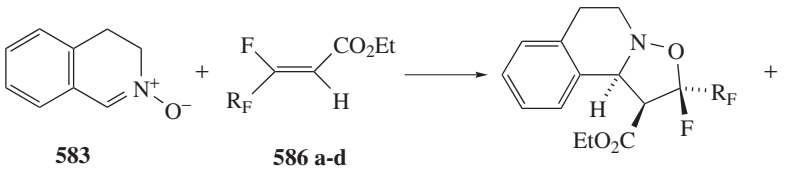
Scheme 2.264

positions. This is caused mainly by electronic factors. The more electron-deficient end of the dipolarophile adds to the nitrone oxygen atom. As illustrated in Scheme 2.265, all reactions gave *cis* and *trans* cycloadducts (**587**) to (**594**) (775).

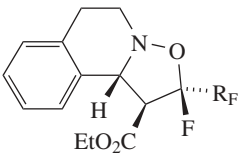
Recently, an example of green chemistry in the formation of a nitrone in aqueous medium, using a surfactant, was reported in 1,3-dipolar cycloadditions to ethyl acrylate (776). The control of regioselectivity in this reaction favors the formation of *trans*-5-substituted isoxazolidines.



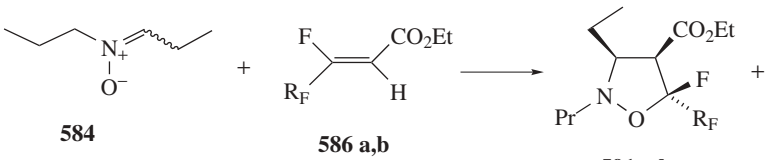
551 586 a 587 a 588 a



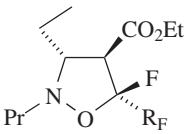
583 586 a-d 589 a-d



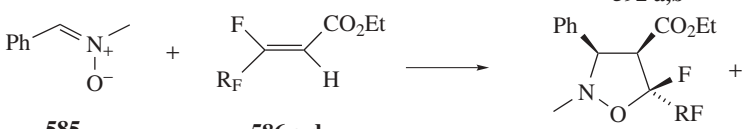
590 a-d



584 586 a,b 591 a,b

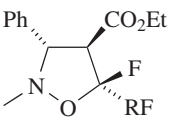


592 a,b



585 586 a,d 593 a,d

a: $R_F = Cl(CF_2)_3$; **b:** $F(CF_2)_5$; **c:** $BrCF_2$; **d:** $Cl(CF_2)_5$

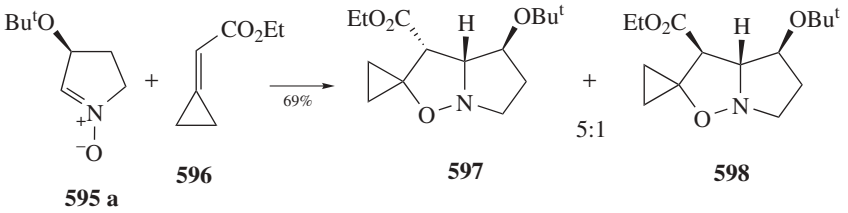


594 a,d

Scheme 2.265

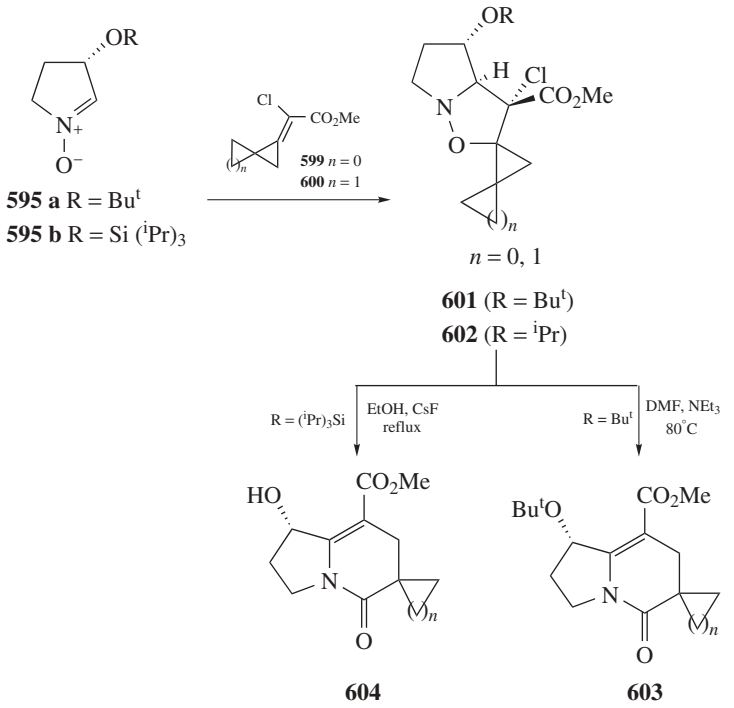
Cycloaddition of the nitrone (**595a**) with ethyl cyclopropylideneacetate (**596**) gave diastereomeric adducts (**597**) and (**598**) in good yield. They were obtained in a 5:1 ratio via *anti-endo* and *anti-exo* approaches (Scheme 2.266) (777).

2-Chloro-2-cyclopropylideneacetate (**599**) and its spiropentane analog (**600**) undergo cycloaddition to enantiopure, five-membered cyclic nitrones (**595a**) and (**595b**) to give, quantitatively, the corresponding 4'-chlorospirocyclopropane-1,5'-isoxazolidines (**601**) and (**602**). These compounds undergo cascade ring enlargements to yield indolizidinone derivatives (**603**) and (**604**) in 53% to 70% yield (Scheme 2.267) (778).



595 a **596** **597** **598**

Scheme 2.266



604 **603**

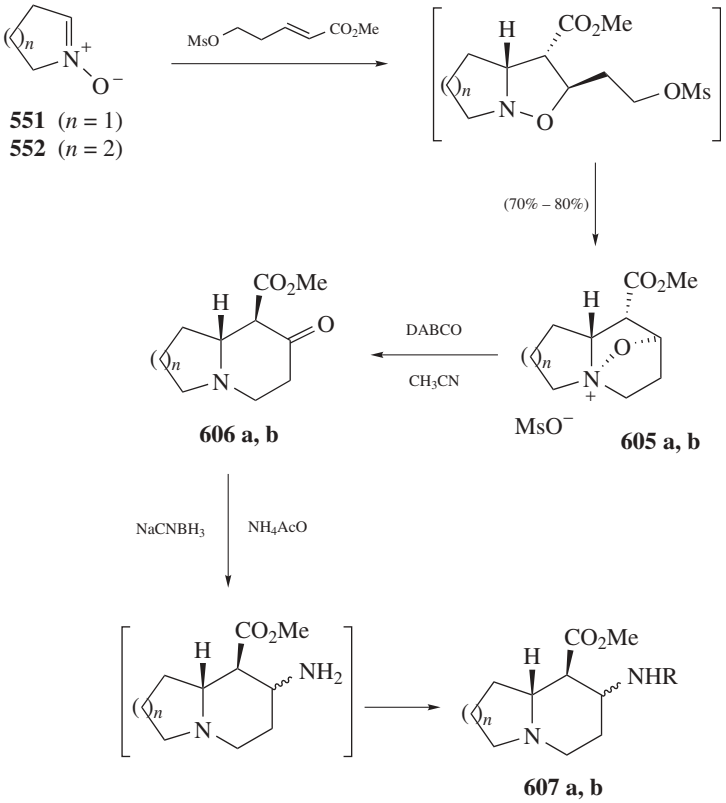
Scheme 2.267

Two protected β-amino acids, containing indolizidine and quinolizidine skeletons (**607a,b**), have been synthesized by using 1,3-dipolar cycloaddition of nitrones (**551**) and (**552**) to methyl (*E*)-5-mesyloxy-2-pentenoate. The key steps of this approach is demonstrated by novel syntheses of indolizidinone and quinolizidinone derivatives (**606a,b**) and by the ring opening of the tricyclic 1,3-dipolar cycloaddition products (**605a,b**) (Scheme 2.268) (779).

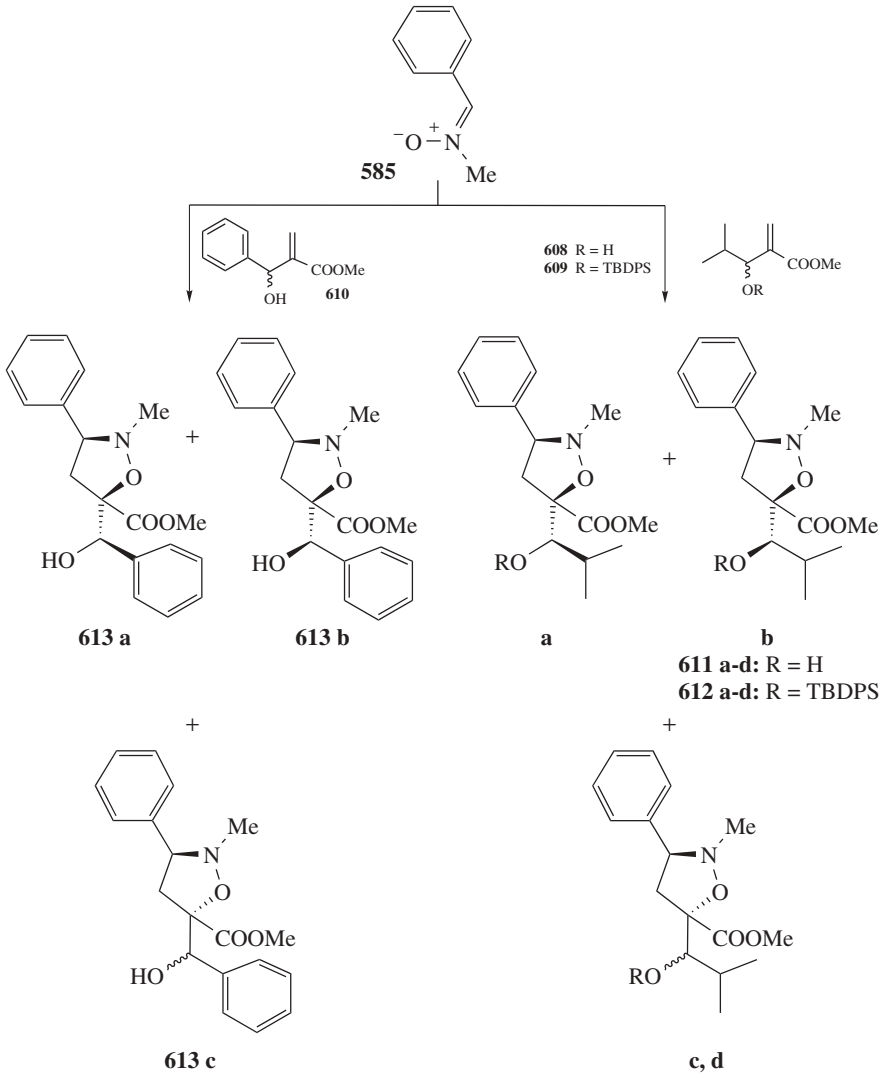
1,3-Dipolar cycloadditions of *C*-phenyl-*N*-methylnitrone (**585**) to Baylis-Hillman adducts such as (β-hydroxy-α-methylene esters) (**608–610**) proceed with complete regioselectivity in good yields to afford the corresponding diastereomeric 3,5,5-trisubstituted isoxazolines (**611–613**) (Scheme 2.269). Attack by the dipole in (**585**) from the less sterically hindered side of dipolarophiles (**608–610**) affords C-3/C-5 *cis* isoxazolidines (**611a,b-613a,b**) as the major products (780).

Dipolarophile D7. Recently, dipolarophiles **D7** (Fig. 2.39) have been widely used in 1,3-dipolar cycloadditions to various nitrones (Fig. 2.40) (72, 781–787).

1,3-Dipolar cycloadditions of nitrone (**614**) to α,β-unsaturated δ-lactones, such as nonchiral **D7a**, racemic mixture **D7c/D7 d**, enantiopure D-*glycero* **D7c**, and



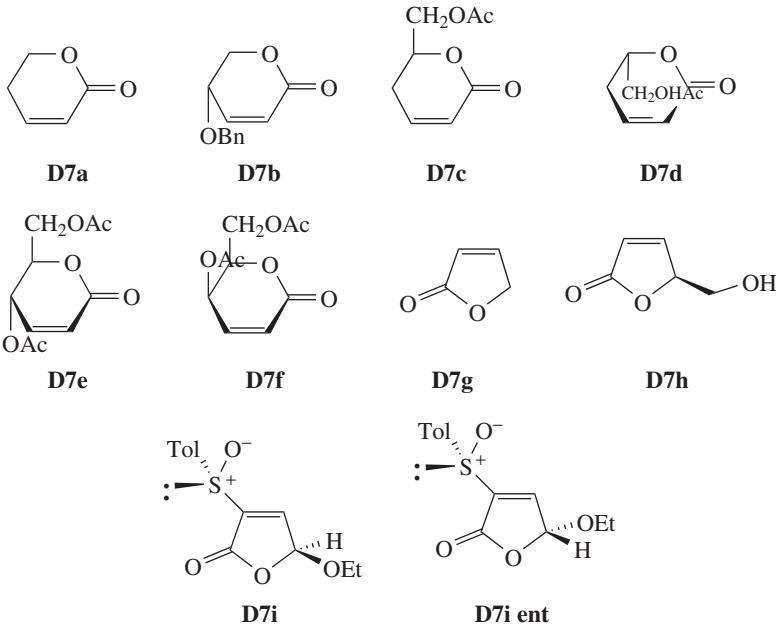
Scheme 2.268



Scheme 2.269

L-*glycero* **D7 d** proceed with high stereoselectivity in the cases of **D7a, D7c** and **D7 d**. They yield the corresponding adducts (**616**), (**617**) and (**618**) (Scheme 2.270). In the case of the racemate **D7c/D7 d**, the cycloaddition proceeds with a significant kinetic resolution (783).

In all these reactions only the *exo* approach of the dipole (**614**) has been observed. The high steric requirements of the *tert*-butoxy groups precluded the *endo* geometry of the transition state (Fig. 2.41).

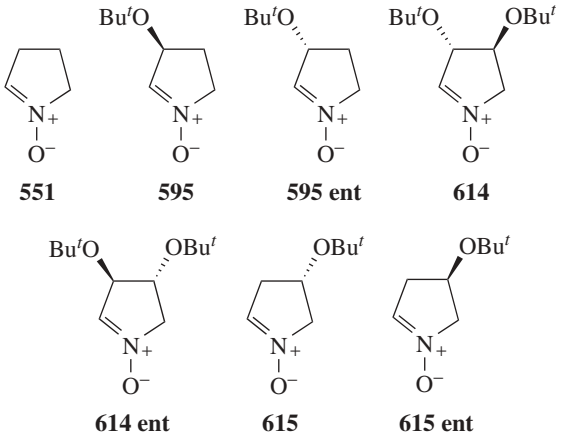


D7a **D7b** **D7c** **D7d**

D7e **D7f** **D7g** **D7h**

D7i **D7i ent**

Fig. 2.39

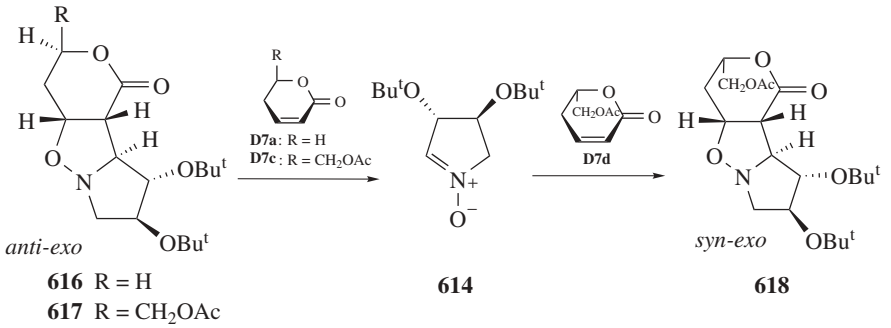


551 **595** **595 ent** **614**

614 ent **615** **615 ent**

Fig. 2.40

Also, the effectiveness of 1,3-dipolar cycloadditions to α,β-unsaturated δ-lactones **D7a, D7c**, **D7 d** (784) and **D7f**, (785) in controlling the configuration of the stereogenic centers around the formed isoxazolidine ring, was demonstrated in reactions with nitrones (**595**).



616 R = H
617 R = CH_2OAc

614

618

Scheme 2.270

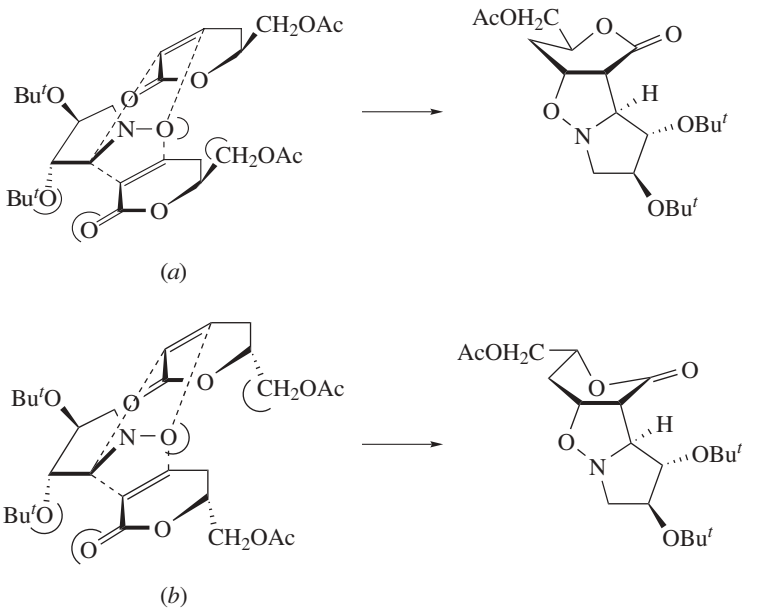
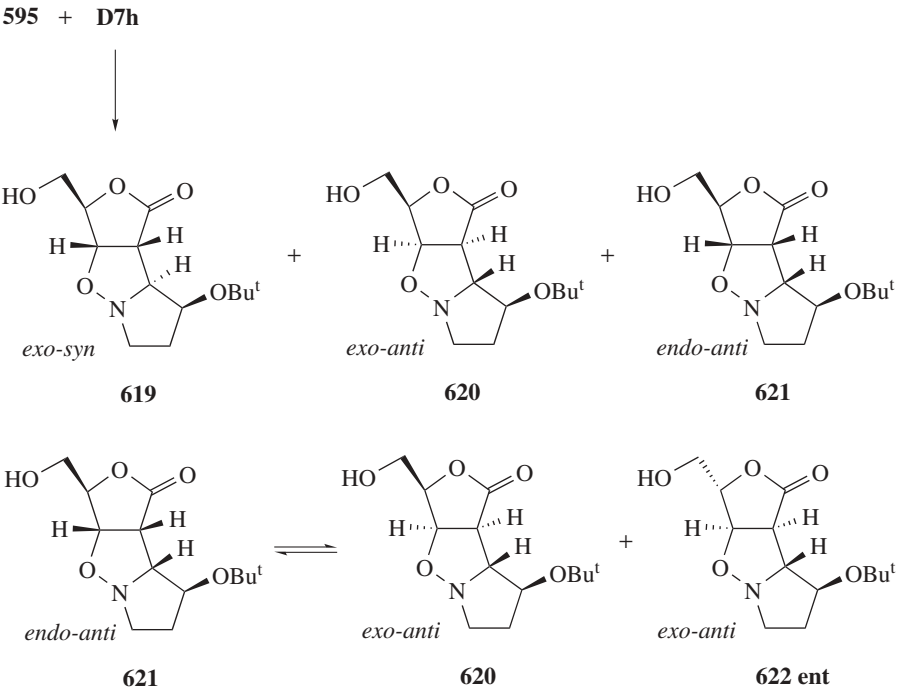


Fig. 2.41 Schematic pathway of 1,3-dipolar cycloaddition of nitrone **614** to lactones **D7c** (a) and **D7d**(b).

The 1,3-dipolar cycloadditions of nitrones (**551**), (**595**), (**614**), (**615**) and their enantiomers (**595 ent**), (**614 ent**), (**615 ent**) (Fig. 2.40) to α,β-unsaturated γ-lactones, such as achiral **D7 g** and D-*glycero* **D7 h**, provide an interesting example of double asymmetric inductions. The reactions are kinetically controlled. However, on heating and at longer reaction times, the reversibility of the cycloaddition (**595** + **D7 h**) was observed, and the presence of a more stable thermodynamic product (**620**) was detected. Moreover, in the case of lactone **D7 h**, a



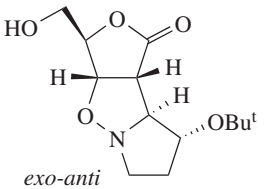
Scheme 2.271

partial racemization did occur and consequently adduct (**622 ent**), derived from **D7 h ent**, was formed (Scheme 2.271) (785).

Contrary to additions involving δ-lactones, where only the *exo* approach of the reactants was observed, γ-lactones reacted with nitrones in *exo*- and *endo*-modes. High preference of *anti*-addition to the terminal hydroxymethyl group in lactone **D7 h** and to the 3-*tert*-butoxy group of the nitrone was observed. In these reactions, the 4-*tert*-butoxy substituent plays a secondary role. The *endo* addition of the reactants is energetically more demanding than the *exo* addition, and occurs, if the substituents, present in the lactone or nitrone, impede such an approach. Because of complex steric interactions only a single product (**623**) or (**624**) was formed in reactions (**595ent**)**/D7 h** and (**614**)**/D7 h** (Scheme 2.272). In one case, (**614**)**/D7 g**,a high preponderance toward the formation of a single adduct was observed (785).

The reaction of morphantridine *N*-oxide (**26**) with 5-ethoxy-3-*p*-tolylsulfinyl-2-furan-(5*H*)-one (**D7i)** yields a mixture of three adducts (**625**) (Scheme 2.273). The major one, *anti*-**625**-*endo*, when reactions were performed at ambient temperature, was obtained in a low diastereomeric ratio: the relative proportion of *anti*-**625**-*endo, syn*-**625**-*endo* and *anti*-**625**-*exo* was 43:36:19. However, the relative proportion changed significantly (72:19:9) when the reaction was conducted at 100°C. Finally, *anti*-**625**-*endo* was obtained in 72%, isolated, yield. The

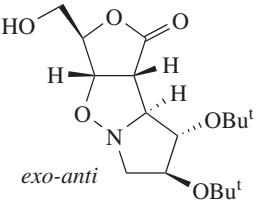
595 ent + **D7h**



exo-anti

623

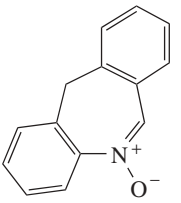
614 + **D7h**



exo-anti

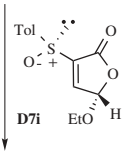
624

Scheme 2.272

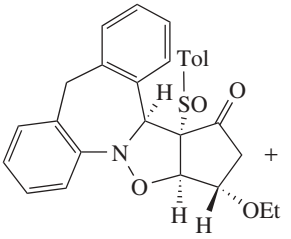


26

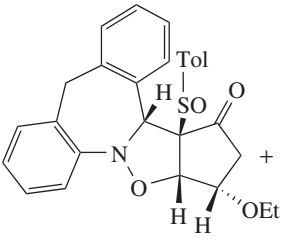
Toluene



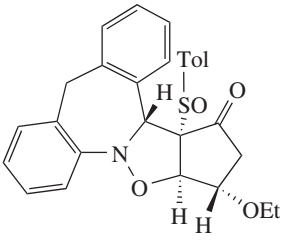
D7i



anti-**625**-*endo*



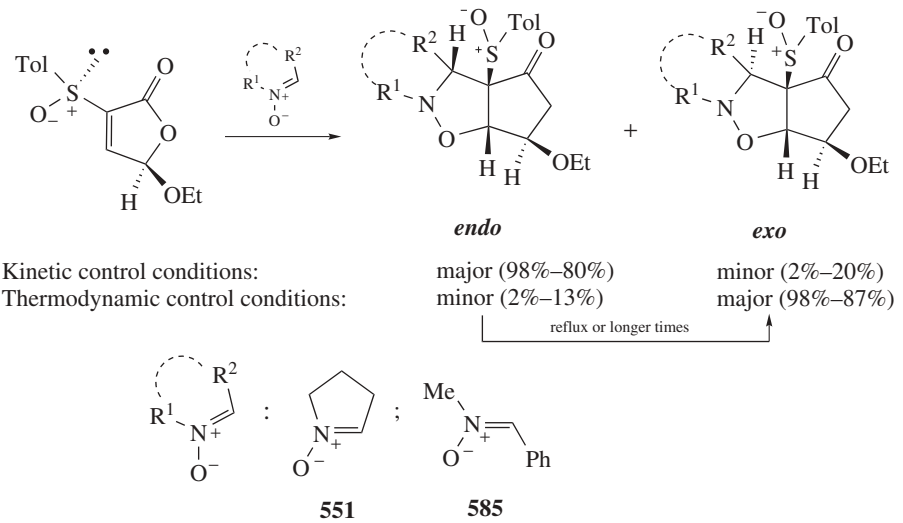
syn-**625**-*endo*



anti-**625**-*exo*

rt	43	38	19
100°C	72	19	9

Scheme 2.273



Scheme 2.274

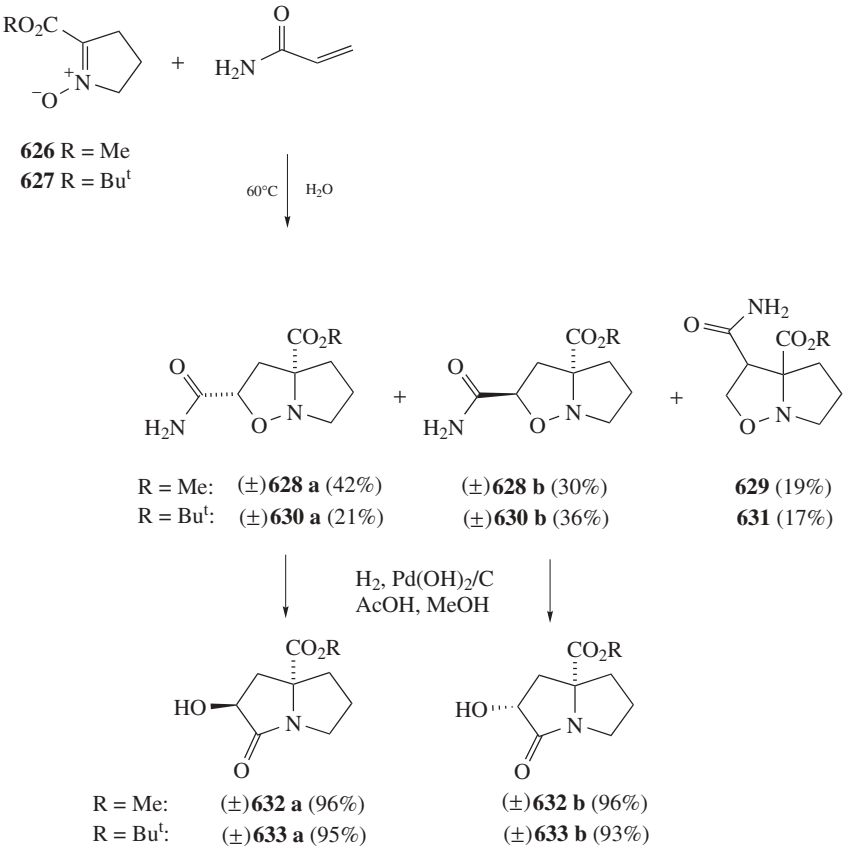
stereoselectivity of these reactions suggests that the sulfinyl group plays a significant role by facilitating the cyclo-reversion (787).

Cyclo-reversions proceed readily in reactions of enantiopure **D7i** and **D7i ent** with cyclic (**551**) and acyclic (**585**) nitrones. The sulfinyl group in lactones **D7i** and **D7i ent** controls the π-facial selectivity and is also controller of the *endo/exo* selectivity (Scheme 2.274) (788).

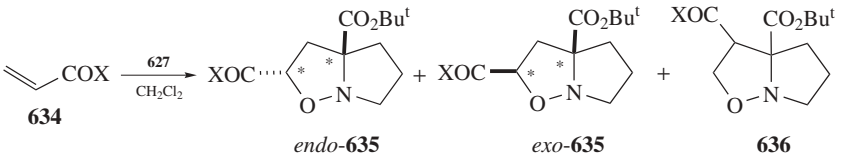
Dipolarophiles D8. 1,3-Dipolar cycloadditions of acrylamide with cyclic nitrones (**626**) and (**627**) have been employed in the synthesis of new dipeptide isosteres with a pyrrolizidinone skeleton (789). Treatment of nitrones (**626**) and (**627**) with acrylamide (2 equiv) in water at 60° for 14 h afforded a mixture of adducts with similar regioselectivity, favoring the 2-substituted adducts (**628, 630**). The *trans*-(**632a, 633a**) and *cis*-(**632b, 633b**) pyrrolizidinones were readily obtained from the *exo*-(**628a, 630a**) and *endo*-(**628b**, **630b**) adducts by hydrogenation in the presence of a catalytic amount of $Pd(OH)_2$ and 10 mol equiv. of AcOH (Scheme 2.275).

1,3-Dipolar cycloadditions of 2-*tert*-butoxycarbonyl-1-pyrroline *N*-oxide (**627**) with several chiral acrylamides (**634a–f**) (Scheme 2.276) followed by hydrogenolysis of cycloadducts (**635**) and (**636**) has been used in the synthesis of enantiopure *tert*-butyl (2*R*,7a*R*)- and (2*S*,7a*S*)-2-hydroxy-3-oxo-tetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylates, useful intermediates for the synthesis of Gly-(*s-cis*)Pro dipeptide mimetic (790).

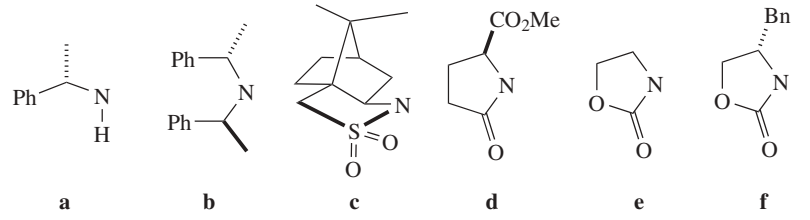
The regioselectivity and diastereoselectivity of these reactions were strongly dependent on the chosen chiral auxiliary **X**. Regioisomeric ratio (**635**)/(**636**) changed depending on the acrylamide structure: (**a**) 77:23, (**b**) 86:14, (**c**) 67:33, (**d**) 69:31, (**e**) and (**f**) 100:0. In all cases a substantial *endo* selectivity in



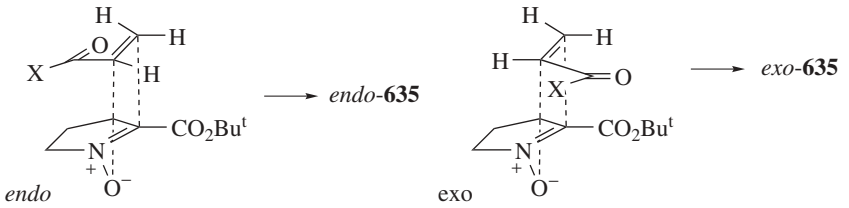
Scheme 2.275



*Relative configuration:



Scheme 2.276



Scheme 2.277

the formation of (**635**) (Scheme 2.277) was generally detected. Ratio (*endo*-**635**)/(*exo*-**635**) changed from 50:50 up to 100:0; (**a**) 64:36, (**b**) 66:34, (**c**) 87:13, (**d**) 100:0, (**e**) 67:33 and 55:45, and (**f**) ratio changed from 50:50 up to 75:25 (depending on the reaction conditions). Obviously, the main reason of the preferential *endo*-approach is the steric interactions induced by the bulky $CO_2{}^tBu$ group in the *exo* approach (Scheme 2.277) (794).

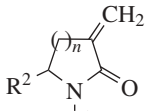
Recently, a series of cycloadducts possessing unusual flipping modes have been isolated from the 1,3-dipolar cycloaddition of 3,4,5,6-tetrahydropyridine *N*-oxide to piperidides of cinnamic acid and para-substituted cinnamic acids (791).

Dipolarophiles D9. Various α-methylenelactams **D9^n** (n = 0,1,2) with four- to six-membered rings (Table 2.25), in reactions with nitrones (**637**), (Table 2.26) afforded good yields of spiro adducts (**638**) and (**639**) via regiospecific 1,3-cycloadditions (Scheme 2.278). Owing to the creation of at least two new asymmetric centers, mixtures of diastereoisomers were obtained (792).

Four asymmetric carbon atoms (structures **641** and **642**) were created in the reaction of nitrone (**637a**) with bislactam (**640**) (Scheme 2.279).

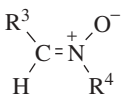
Dipolarophiles D10. Many different catalysts have been used in asymmetric 1,3-dipolar cycloadditions of nitrones (**643**) to olefins **D10** (Scheme 2.280) (793).

Table 2.25 Structures of α-methylenelactams D9^n

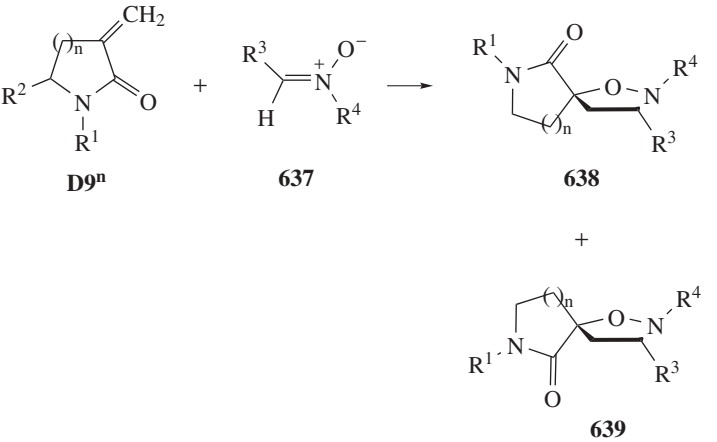


R^1	*n*	R^1	R^2
$D9^0$	0	*p*-MeO-C_6H_4-	-H
$D9^0$	0	*p*-Me-C_6H_4-	-H
$D9^0$	0	*p*-O_2N-C_6H_4-	-H
$D9^1$	1	-CH_3	-H
$D9^1$	1	-CH_3	Ph
$D9^2$	2	-CH_3	-H
$D9^2$	2	Ph-CH_2-	-H

Table 2.26 Structures of nitrones 637



	R^3	R^4
a	PhCO-	Ph-
b	Ph-	Ph-
c	Ph-	$PhCH_2$-
d	Ph-	Bu^t
e	Ph-	Me-



D9^n **637** **638** **639**

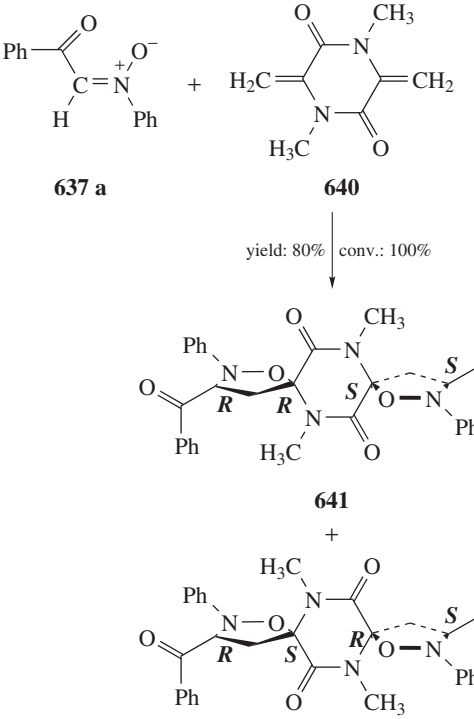
Scheme 2.278

For example, cycloaddition of nitrone (**643**, $R^1 = Ph$, $R^2 = Me$) to **D10**, catalyzed by chiral phosphine-palladium complexes (Fig. 2.42), gave isoxazolidines (**644**) in high yield with high enantioselectivity (794).

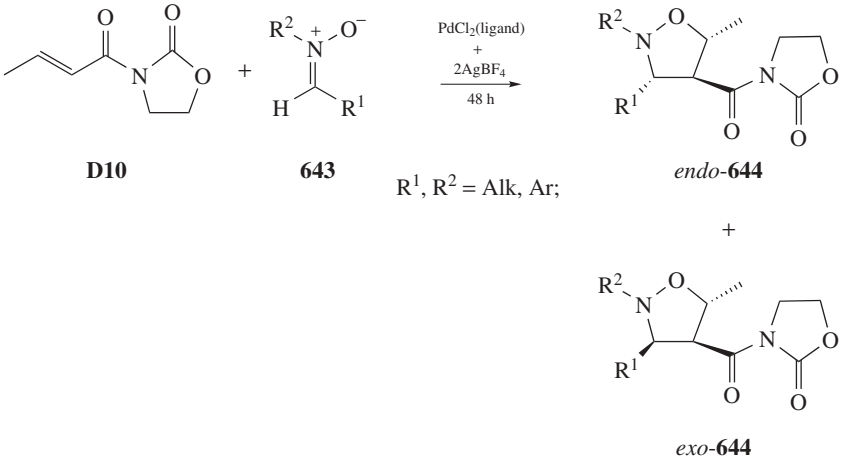
Cycloaddition reactions of alkenes **D10** with nitrones were also catalyzed by $Yb(OTf)_3$, by $Sc(OTf)_3$ (795), by chiral 2,6-bis(4 R-trialkylsiloxymethyl-oxazolinyl)pyridine/Ni(II) (pybox) (Fig. 2.43) (796a), and by chiral bis(2-oxazolinyl)xanthene (xabox) (Fig. 2.44) (796b).

The utility of a new fluorine supported chiral auxiliary was established in a series of catalyzed and uncatalyzed 1,3-dipolar cycloaddition reactions with diphenylnitrone (**637b**) (Scheme 2.281) (797). The yields and selectivities of the cycloadducts (**645a–d**) compare favorably with those obtained with conventional Evans-type auxiliaries (798). Purification of the products was greatly improved by using fluorous solid phase extraction (FSPE).

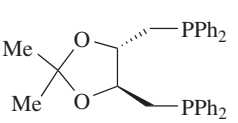
The cyclo-adducts were removed from the auxiliaries by reductive cleavage. The auxiliary group was readily re-functionalized and reused in subsequent



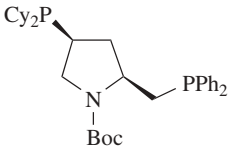
Scheme 2.279



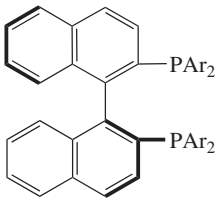
Scheme 2.280



(+)-**DIOP**

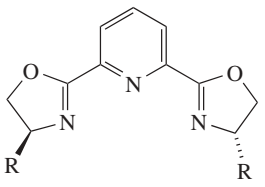


BCPM

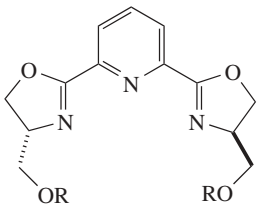


(*S*)-**BINAP** : Ar = Ph
(*S*)-**TolBINAP** : Ar = *p*-Tol
(*S*)-**MeOBINAP** : Ar = *p*-$MeOC_6H_4$
(*S*)-**ClBINAP** : Ar = *p*-ClC_6H_4

Fig. 2.42

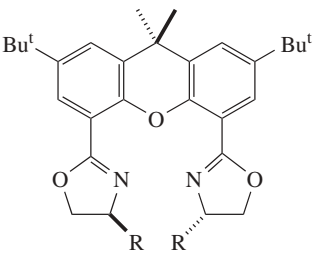


a: R = Pr^i (pybox-Pr^i)
b: R = Bu^t (pybox-Bu^t)



a: R = H (pybox-*hm*)
b: R = Sit-$BuMe_2$ (pybox-*tbdmsom*)
c: R = $Si(Pr^i)_3$ (pybox-*tipsom*)
d: R = Sit-$BuPh_2$ (pybox-*tbdpsom*)

Fig. 2.43

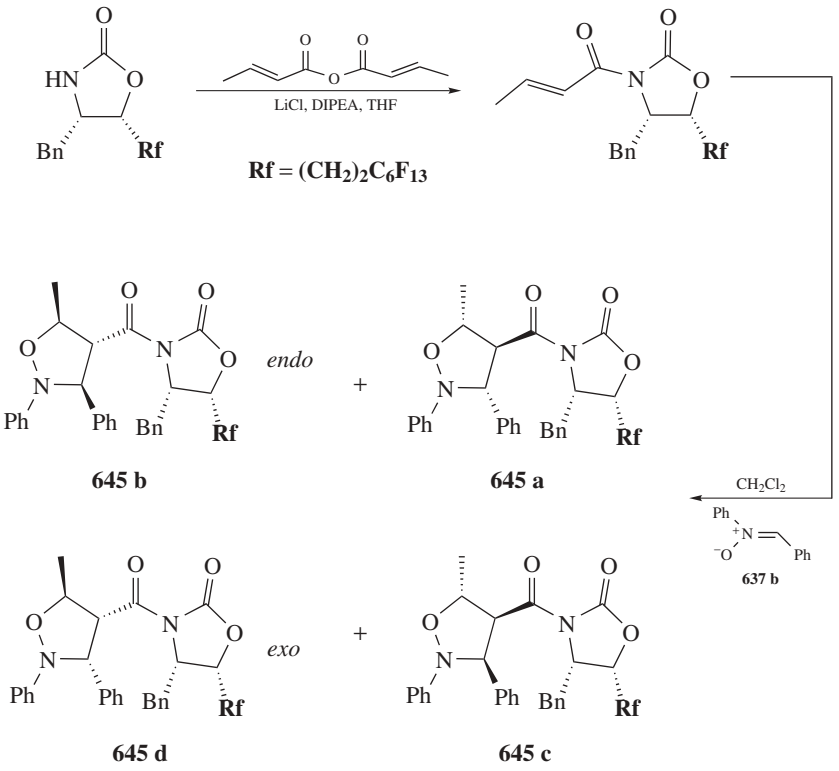


xabox - R
a: R = Pr^i
b: R = Ph
c: R = Bn

Fig. 2.44

cycloaddition reactions, with no change in the yields or selectivities (Scheme 2.282).

Dipolarophiles D11 . In the 1,3-dipolar cycloadditions of electron-rich olefins, such as vinyl ethers, with nitrone (**585**), common palladium (II) catalysts were used (Fig. 2.45). Reactions proceeded smoothly under mild conditions and in good yield, affording isoxazolidines (**646**) (Scheme 2.283) (799).

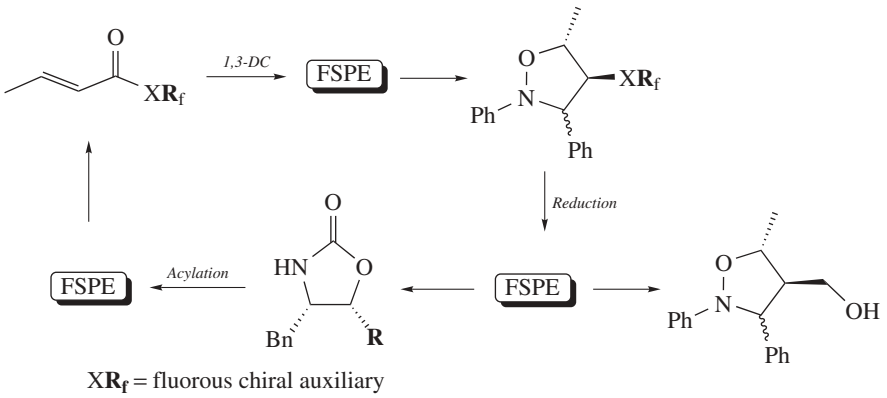


Scheme 2.281

The 1,3-dipolar cycloaddition of nitrones to vinyl ethers is accelerated by Ti(IV) species. The efficiency of the catalyst depends on its complexation capacity. The use of $Ti(^{i}PrO)_2Cl_2$ favors the formation of trans cycloadducts, presumably, via an endo bidentate complex, in which the metal atom is simultaneously coordinated to the vinyl ether and to the cyclic nitrone or to the Z-isomer of the acyclic nitrones (800a). Highly diastereo- and enantioselective 1,3-dipolar cycloaddition reactions of nitrones with alkenes, catalyzed by chiral polybinaphtyl Lewis acids, have been developed. Isoxazolidines with up to 99% ee were obtained. The chiral polymer ligand influences the stereoselectivity to the same extent as its monomeric version, but has the advantage of easy recovery and reuse (800b).

It was shown (801) that the diastereoselectivity of α-fluoroalkyl nitrones is reversed to that of the corresponding α-alkyl nitrones. This fact supports the conclusion that the conformation, due to the relief of the dipole repulsion between the fluorine atom and the oxygen atom of the nitrone is preferred in α-fluoroalkyl nitrones.

The addition of nitrones (**647**) and (**312**) to 4-pentenofuranoside (**648**) derived from D-ribose, followed by reductive opening of the isoxazolidine ring in (**649**)



Scheme 2.282

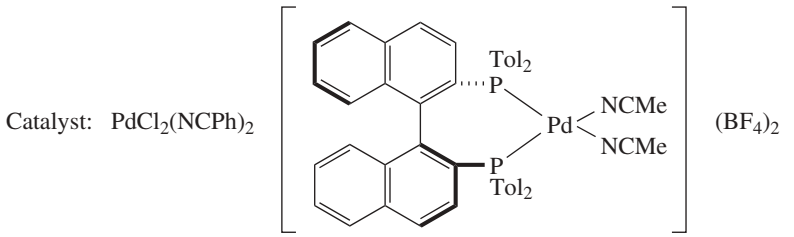
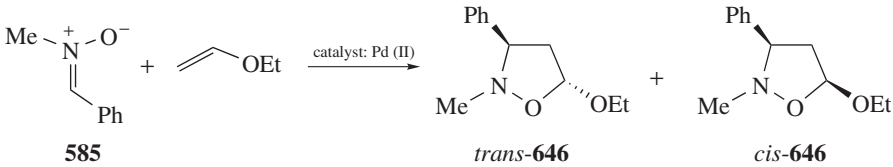


Fig. 2.45



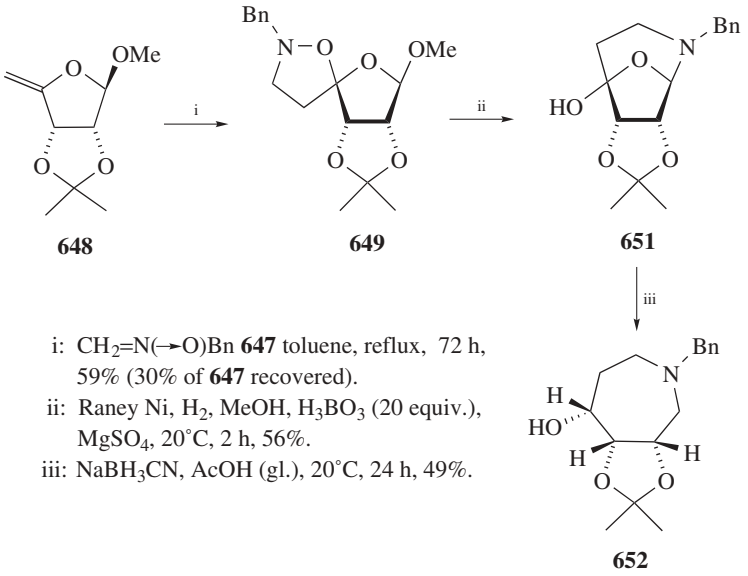
585 *trans*-**646** *cis*-**646**

Scheme 2.283

and (**650**), constitutes a new method for preparing hydroxy azepanes, such as monocyclic (**652**) (Scheme 2.284) or azepanes fused to a pyrrolidine ring (**653**), (**654**) (Scheme 2.285) (802).

1,3-Dipolar cycloadditions of nitrones with vinyl acetate leads to 5-acetoxy-isoxazolidines, which can be easily transformed to isoxazolidinyl nucleosides by the Vorbrüeggen methodology (803).

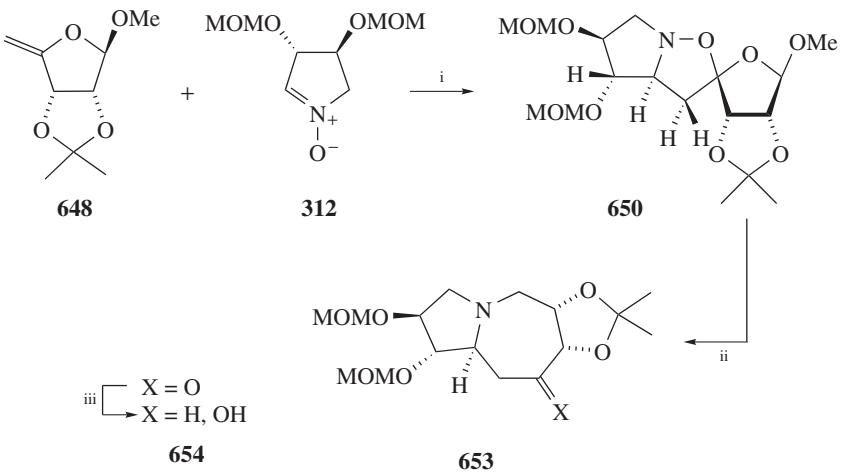
Cycloadditions of nitrones (**655**) and (**656**) to vinyl acetate proceed regioselectively and lead to the isoxazolidines (**657**) and (**658**) as a mixture of diastereomers (Scheme 2.286) (Table 2.27) (206).



648 **649** **651** **652**

i: CH_2=N(→O)Bn **647** toluene, reflux, 72 h, 59% (30% of **647** recovered).
ii: Raney Ni, H_2, MeOH, H_3BO_3 (20 equiv.), $MgSO_4$, 20°C, 2 h, 56%.
iii: $NaBH_3CN$, AcOH (gl.), 20°C, 24 h, 49%.

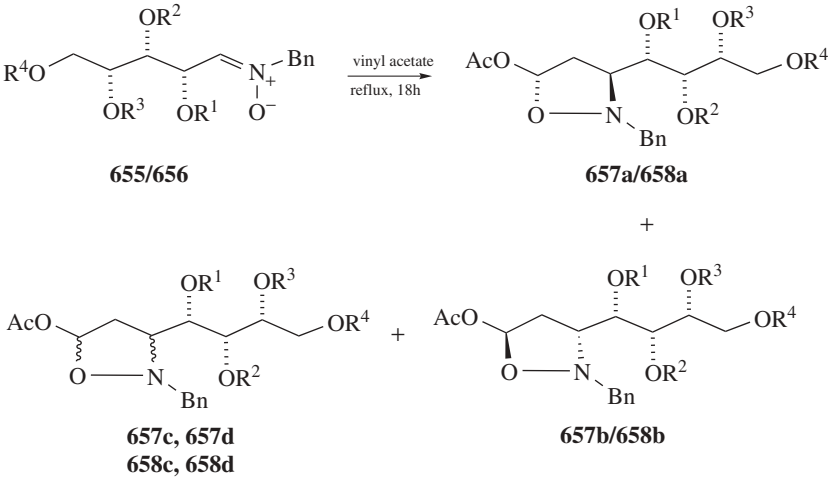
Scheme 2.284



648 **312** **650** **654** **653**

i: Toluene, reflux, 48 h, 96%.
ii: Raney Ni, H_2, MeOH, H_3BO_3 (20 equiv), $MgSO_4$, 20°C, 24 h, 43% of **653** and 56% of **654** (as a ca. 1:1 mixture of epimers).
iii: $NaBH_3$, EtOH, 20°C, 4 h, 98% (as a ca. 1:1 mixture of epimers).

Scheme 2.285



655/656 **657a/658a** **657c, 657d 658c, 658d** **657b/658b**

655, 657 R^1, $R^2 = R^3$, $R^4 = CMe_2$;
656, 658 R^1, $R^2 = CMe_2$, R^3 = Bz, R^4 = TBDPS

Scheme 2.286

Table 2.27 1,3-Dipolar cycloadditions of nitrones 655 and 656 to vinyl acetate

Entry	Nitrone	Total yield (%)	Adduct	a:b:c:d[a]
1	**655**	90	**657**	70:13:9:8
2	**656**	73	**658**	71:15:14:-

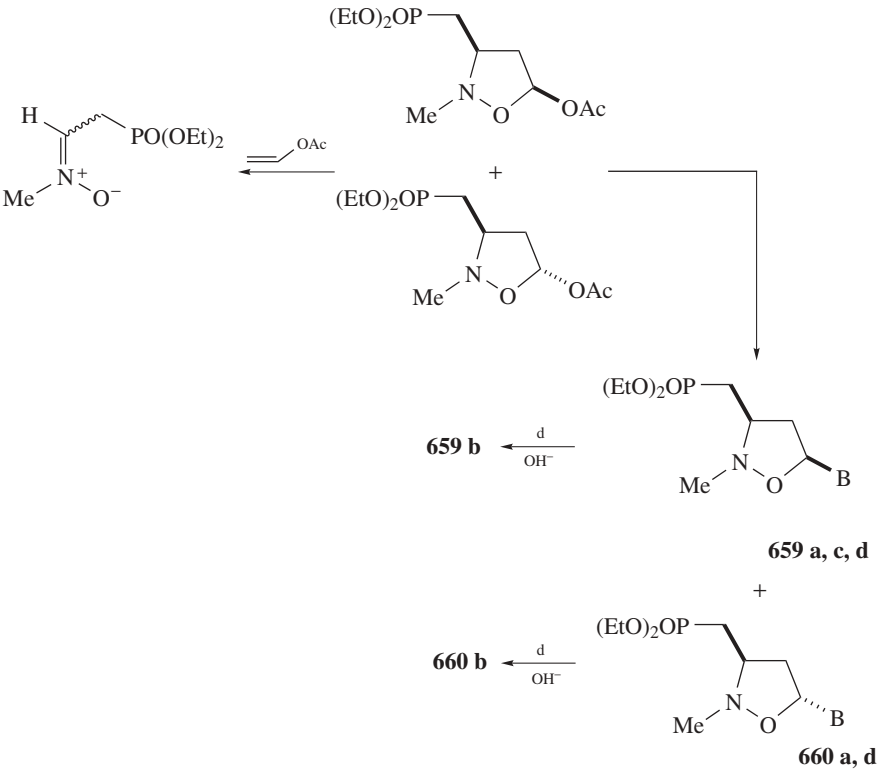
[a]Ratios were determined by ^{1}H-NMR and ^{13}C-NMR (400 MHz) on the crude reaction mixture.

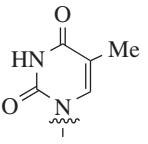
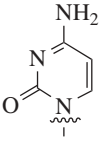
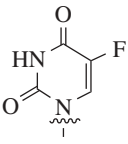
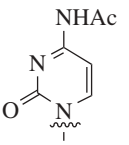
Phosphonated *N,O*-nucleosides (**659**) and (**660**), containing thymine (**a**), *N*-acetylcytosine (**d**) and fluorouracil (**c**) have been synthesized in good yields by the 1,3-dipolar cycloaddition methodology (Scheme 2.287) (152).

Cycloadditions of pyrroline *N*-oxides (**662**) to glycals (**663**) afford aza-C-disaccharides (**661**) (Scheme 2.288) (804).

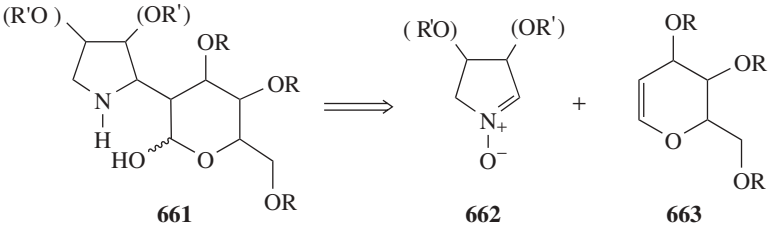
Cycloaddition of 3-methylenephthalide with α,*N*-diphenylnitrone gave two diastereoisomers of 2,3-diphenyl-2,3-dihydrospiro[1,3-oxazole-5(4*H*)1′(3′H)-2-benzofuran]-3′-one (805). The 1,3-dipolar cycloaddition reaction of *N*-benzyl-*C*-(2-furyl)nitrones with electron-rich alkenes gave preferentially *trans*-3,5-disubstituted isoxazolidines (*endo* approach). These experimental results are in good qualitative agreement with those predicted from semiempirical (AM1 and PM3) and *ab initio* (HF/3-21G) calculations (806).

Dipolarophiles D12. Heteroatom substituted alkenes of general formula **D12** have been sparingly used as dipolarophiles when compared to vinyl ethers **D11** (*see* Fig. 2.33). Comparative studies between common heating and microwave



	a	b	c	d
B				

Scheme 2.287

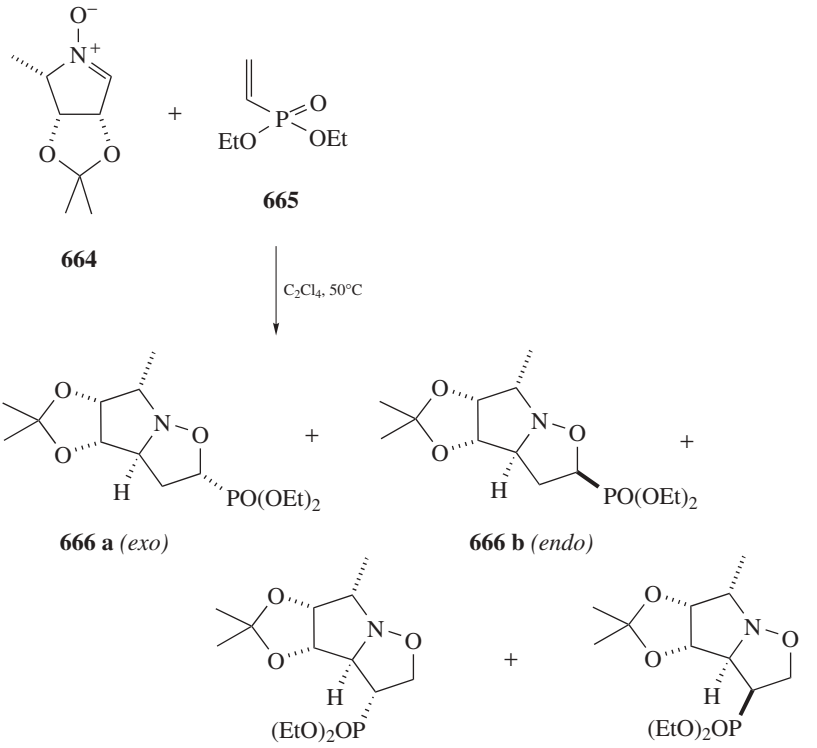


Scheme 2.288

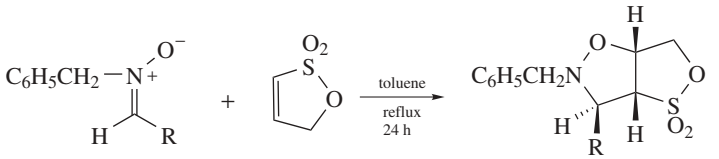
irradiation of 1,3-dipolar cycloadditions of 3-methylene-*N*-substituted isoindolones and nitrones, showed increase of reaction rates and yields, when microwave irradiation was used (807). 4′-*Aza* analogs of 2′3′-dideoxythymidine have been obtained by 1,3-dipolar cycloadditions of methylene nitrones [CH_2=N(O)R], prepared *in situ* from *N*-aryl- and *N*-alkylhydroxylamines and paraformaldehyde, to 1-*N*-vinyl-thymine (808). Computer-assisted design of asymmetric 1,3-dipolar cycloadditions between dimethylvinylborane and chiral nitrones showed excellent regioselectivities in the formation of 5-borylisoxazolidines, due to the presence of a strong secondary orbital interaction between the boron of the vinylborane and the oxygen of the nitrones (809).

Thermal reaction of vinylphosphonate (**665**) with nitrone (**664**) gave respectively, two pairs of *exo* and *endo* regio-adducts (**666a,b**) and (**667a,b**) in 30:52 and 13:6 proportions, the major isomer was the *endo* adduct (**666b**) (Scheme 2.289) (689).

1,3-Dipolar cycloadditions of nitrones with unsaturated alkyl- and arylsulfones have been found to occur with high regioselectivity. They give a single



Scheme 2.289



668 **669** **670**

R = Et, Bu^t, Ph, 2-Furyl

Scheme 2.290

or dominant heterocycle substituted at position four by an electron-withdrawing group (810–812). A remarkably high degree of regioselectivity and stereoselectivity was also observed in reactions of 1-propene-1,3-sultone (**669**) with nitrones (**668**) (Scheme 2.290) (813).

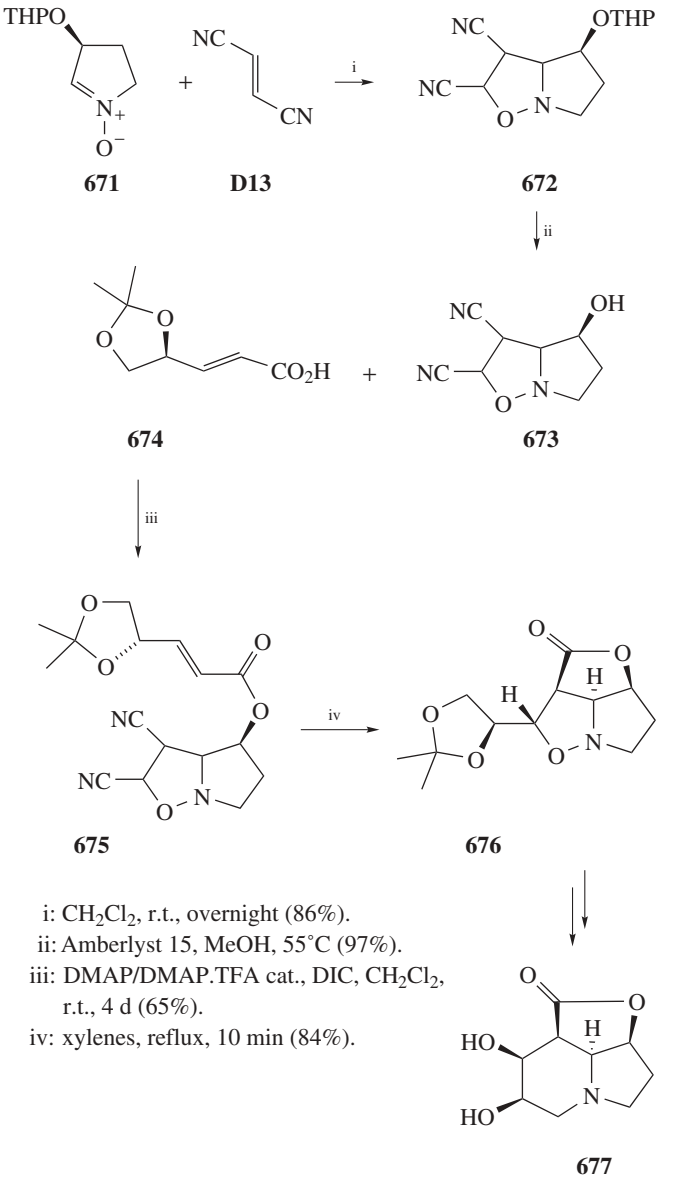
Cycloaddition reactions of vinyl trimethylsilane with *C*-glycosyl nitrones gave moderate to good yields (67%–74%). Estimation of diastereoselectivities from isolated yields showed total *endo* preference for the reaction of the D-*galacto* nitrone. High *endo* preference was observed for the D-*ribo* analog, but *exo* preference for the D-*xylo* one (814).

Recently, *dipolarophile D13* (fumaronitrile) (777) has been used in the synthesis of indolizine lactone (**677**). Both, intermolecular and intramolecular cycloadditions were studied. Intermolecular 1,3-cycloaddition of nitrone (**671**) to **D13** led to the formation of isoxazolidine (**672**). Subsequent deprotection and esterification of the obtained alcohol (**673**) with (**674**) gave isoxazolidine (**675**) in 65% yield. Ester (**675**), when refluxed in xylene for 10 min, after elimination of fumaronitrile by cyclo-reversion, underwent spontaneously intramolecular cycloaddition to give the tricyclic cycloadduct (**676**) in 84% yield (Scheme 2.291).

Dipolarophiles D14. The 1,3-dipolar cycloaddition of nitrones to dimethyl maleate and dimethyl fumarate is widely used in the synthesis of polyhydroxy alkaloid derivatives of dihydroindolizidinone (81), pyrrolizidine (119), (−)-codonopsinine, and (+)-hyacinthacines A_1 and A_2 (312). In cases of unstable nitrones, syntheses of cycloadducts are performed *in situ* (81).

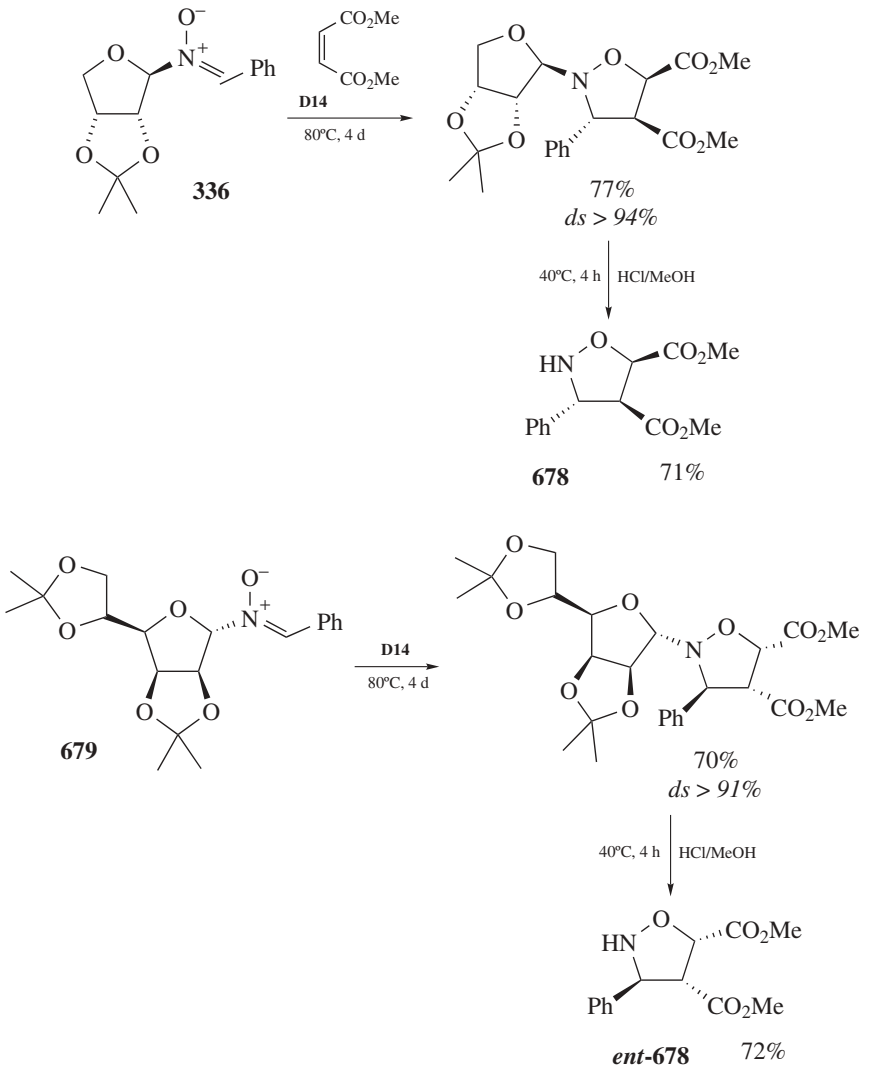
The highly stereoselective 1,3-dipolar cycloaddition of *C*-phenyl-*N*-glycosylnitrones (**336**) and (**679**) to dimethyl maleate **D14**, with the sugar moiety acting as a chiral auxiliary, has been used in enantioselective syntheses of isoxazolidines (**678**) and (**678 ent**) (Scheme 2.292) (118).

Cycloaddition reaction of nitrone (−)-(**394**) with dimethyl maleate **D14** has been used for the synthesis of two new polyhydroxyl pyrrolizidines (**687**) and (**688**) (Schemes 2.293, 2.294). These compounds are analogs of alkaloids rosmarinecine and crotanecine, which were assayed for their inhibitory activities toward 22 commercially available glycosidase enzymes. One of them ((−)-7a-*epi*-crotanecine) (−)-(**688**) is a potent and selective inhibitor of α-mannosidases (310). The reaction of (−)-(**394**) with dimethyl maleate gave a 9.6:6:1 mixture of cycloadducts (−)-(**680**), (+)-(**680**), and (−)-(**681**), which arise from *anti-exo*,



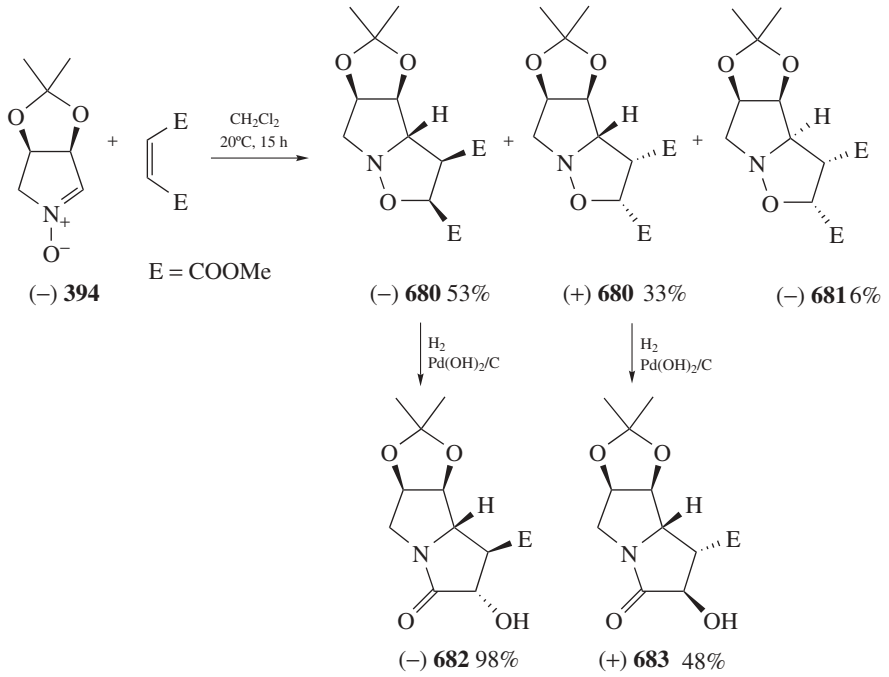
Scheme 2.291

anti-endo, and *syn-exo* approaches (Scheme 2.293). The main cycloadducts (−)-(**680**) and (+)-(**680**) were converted into pyrrolozidinones (−)-(**682**) and (+)-(**683**) by hydrogenolysis in the presence of $Pd(OH)_2$. Treatment of (−)-(**682**) with $LiAlH_4$ in THF, followed by workup with HCl in MeOH, provided the



Scheme 2.292

hydrochloride of (−)-(**687**)·HCl in 79% yield. The selective reduction of lactam (−)-(**682**) with $BH_3 \cdot SMe_2$ in THF gave the β-hydroxy ester (+)-(**685**) in 81% yield. After esterification of the alcohol (+)-(**685**) with methanesulfonyl chloride in CH_2Cl_2 and subsequent treatment with DBU at 20° C, the α,β-unsaturated ester (+)-(**686**) was isolated in 81% yield. The reduction of ester (+)-(**686**) with DIBALH ($(i\text{-}Bu)_2AlH$) in CH_2Cl_2, followed by workup with HCl in MeOH, provided 7a-*epi*-crotanecine hydrochloride (−)-(**688**·**HCl**) in 82% yield (Scheme 2.294).



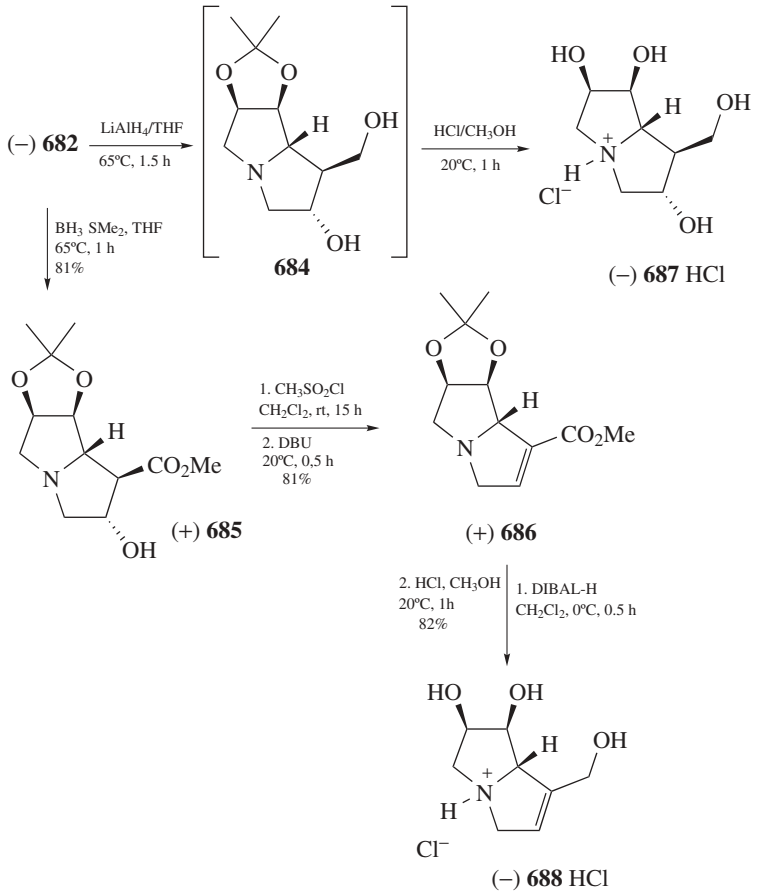
Scheme 2.293

Dipolarophiles D15. Several examples employing *N*-alkyl- and *N*-arylmaleimides as dipolarophiles in the 1,3-dipolar addition to nitrones have been presented (257, 295b, 815, 816).

Nitrones derived from cyclic acetals of D-erythrose (**479**) and (**689**) and of D-threose (**480**) and (**690**), reacted with *N*-phenylmaleimide **D15a** to afford the corresponding diastereomeric isoxazolidines (**691–706**) (Scheme 2.295). The stereoselectivity is dependent on the substituents in the nitrone. In the case of nitrones (**479**) and (**689**) the cycloaddition is *exo*-selective. It was observed that microwave irradiation decreased the reaction times of the cycloadditions dramatically. For example, for nitrone (**689**) and dipolarophile **D15a** the reaction time decreased from 11 h to 8 min and for nitrone (**690**) and **D15a** it decreased from 3 h to 10 min. Moreover, microwave irradiation reversed the ratio of erythro-*trans*/erythro-*cis* adducts from 63:37 to 39:55, see compound (**689**). Cycloadditions of the chiral maleimides **D15b** and **D15c** are less stereoselective (817).

2.8.2. Cycloaddition of Alkynes

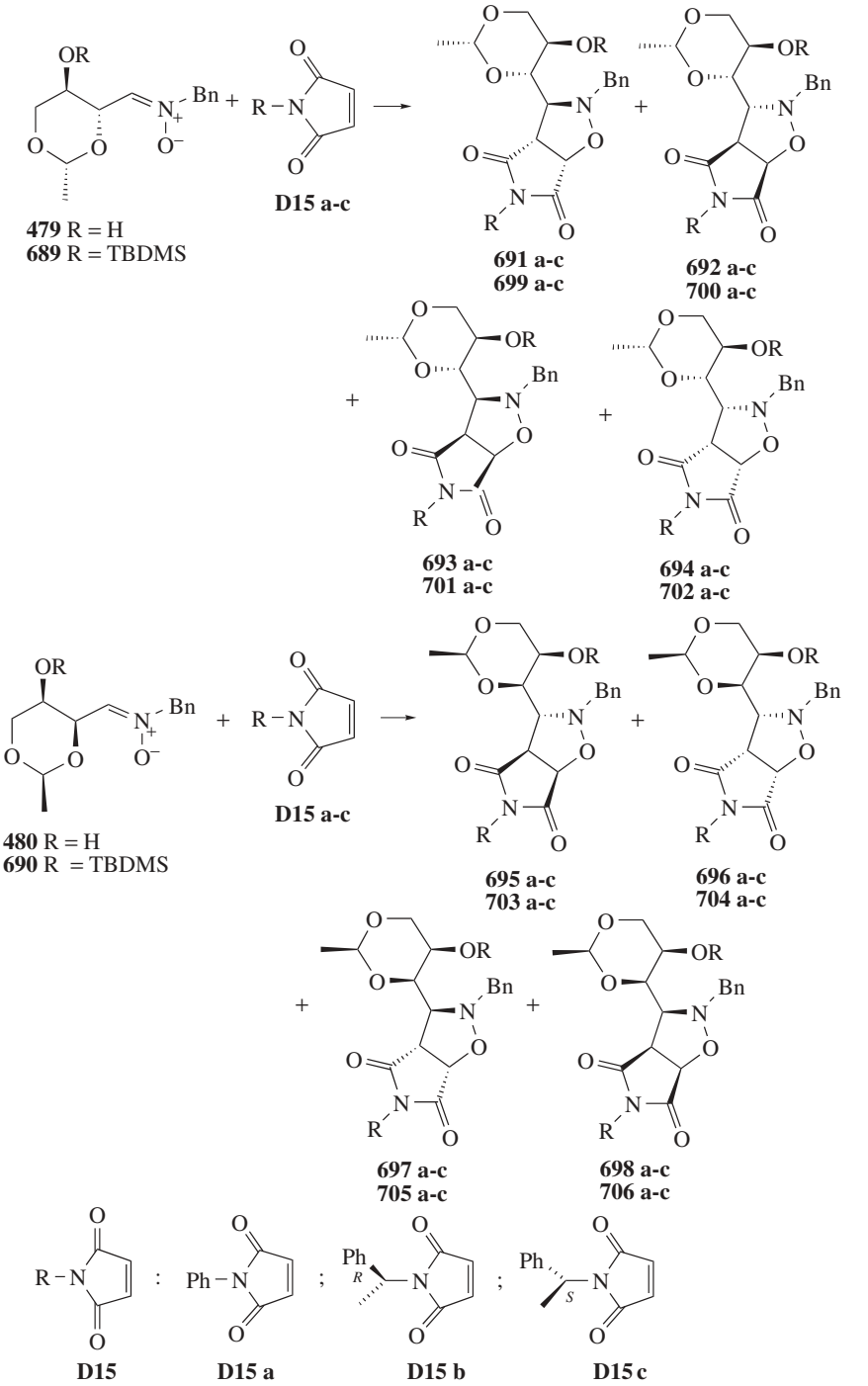
In the frequency of their use in 1,3-dipolar cycloadditions to nitrones, alkynes constitute the second group of dipolarophiles after alkenes. They are of particular interest due to the fact that isoxazolines, the products of initial cycloadditions,



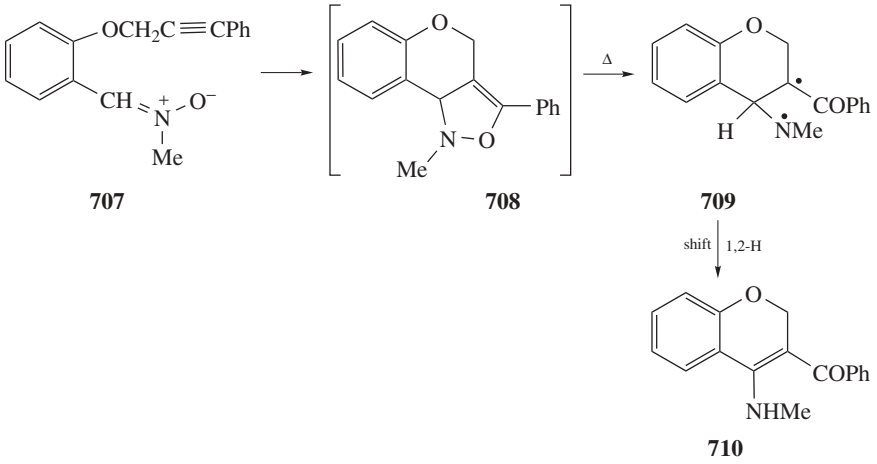
Scheme 2.294

undergo facile, rearrangements and provide ready access to a variety of novel heterocyclic systems in synthetically useful yields.

2.8.2.1. Intramolecular Reactions Intramolecular 1,3-dipolar cycloadditions of nitrones with alkynes are illustrated in Schemes 2.296, 2.297, 2.298 (818, 819). Heating of *N*-methyl-α-[2-(3-phenyl-2-propynyl-1-oxy)benzylidenyl]nitrone (**707**) in toluene at 120°C for 2 hours gave a single rearranged product, the structure of which has been assigned as 3-benzoyl-4-*N*-methylamino-2*H*-1-benzopyran (**710**). In these reactions, intramolecular dipolar cycloaddition produces 4-isoxazoline (**708**) which undergoes preferential N–O bond scission affording diradical (**709**). Subsequent rearrangement, by way of a 1,2-hydrogen shift ultimately gives benzopyran (**710**). Alternatively, the isomerization of (**708**) to (**710**) could follow an acid catalyzed path.

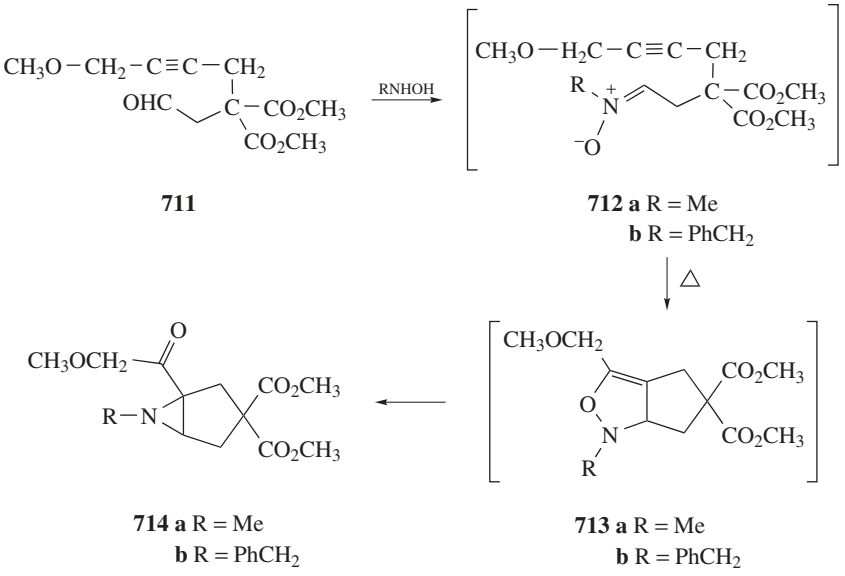

479 R = H
689 R = TBDMS
D15 a-c
691 a-c
699 a-c
692 a-c
700 a-c
693 a-c
701 a-c
694 a-c
702 a-c
480 R = H
690 R = TBDMS
D15 a-c
695 a-c
703 a-c
696 a-c
704 a-c
697 a-c
705 a-c
698 a-c
706 a-c
D15
D15 a
D15 b
D15 c

Scheme 2.295



707 **708** **709** **710**

Scheme 2.296



711

712 a R = Me
b R = $PhCH_2$

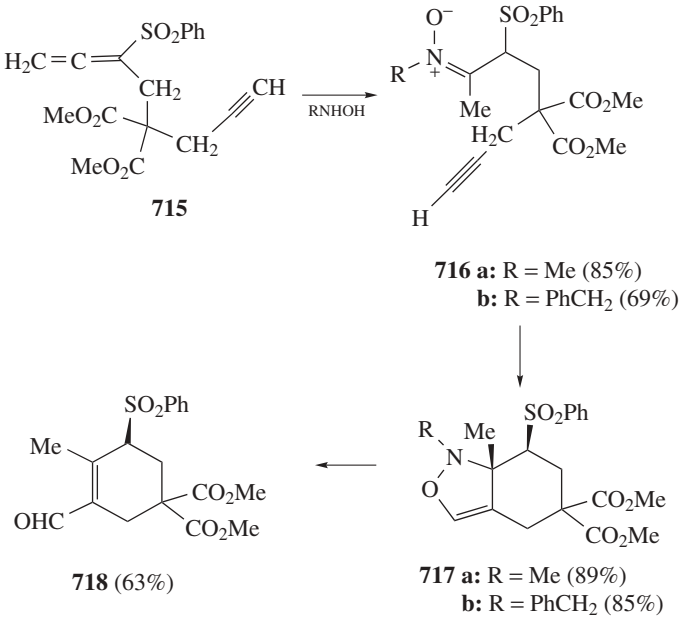
713 a R = Me
b R = $PhCH_2$

714 a R = Me
b R = $PhCH_2$

Scheme 2.297

Heating of (**711**) with *N*-methyl- and *N*-benzylhydroxylamine gave azabicyclo[3.1.0]hexanes (**714a,b**). Formation of these compounds can be explained by an intramolecular cycloaddition process, followed by a subsequent rearrangement of the resulting cycloadducts (**713a,b**) (Scheme 2.297).

Upon treating the acetylenic allene (**715**) with *N*-methyl- or *N*-benzylhydroxylamines, 4-isoxazolines (**717a,b**) were obtained. The initially formed



Scheme 2.298

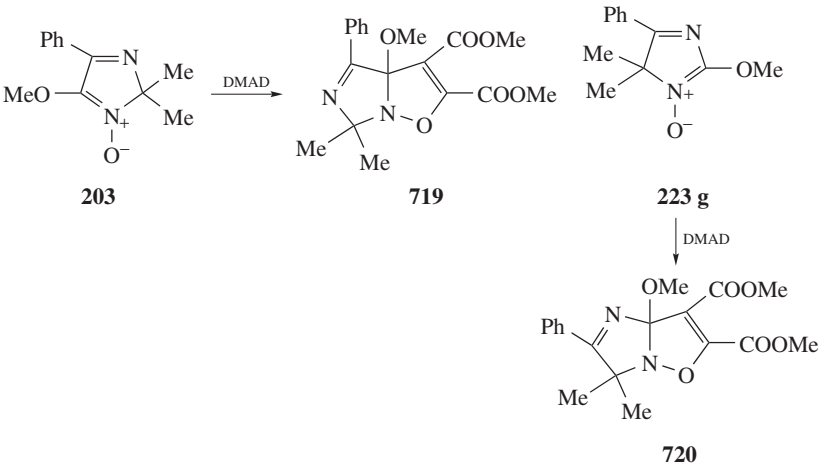
nitrones (**716a,b**) were isolated. Catalytic hydrogenation of 4-isoxazoline (**717b**) resulted in N–O bond cleavage. Then, spontaneous benzylamine elimination gave ultimately the cyclohexenyl substituted aldehyde (**718**) in 63% yield (Scheme 2.298).

2.8.2.2. Intermolecular Reactions Dimethyl acetylenedicarboxylate (DMAD) is frequently used as an alkyne dipolarophile (23, 24, 126b, 152, 241, 333).

Reactions of α-methoxynitrones (**203**) and (**223 g**, $R = OCH_3$) with DMAD give imidazoisoxazoles (**719**) and (**720**) (Scheme 2.299).

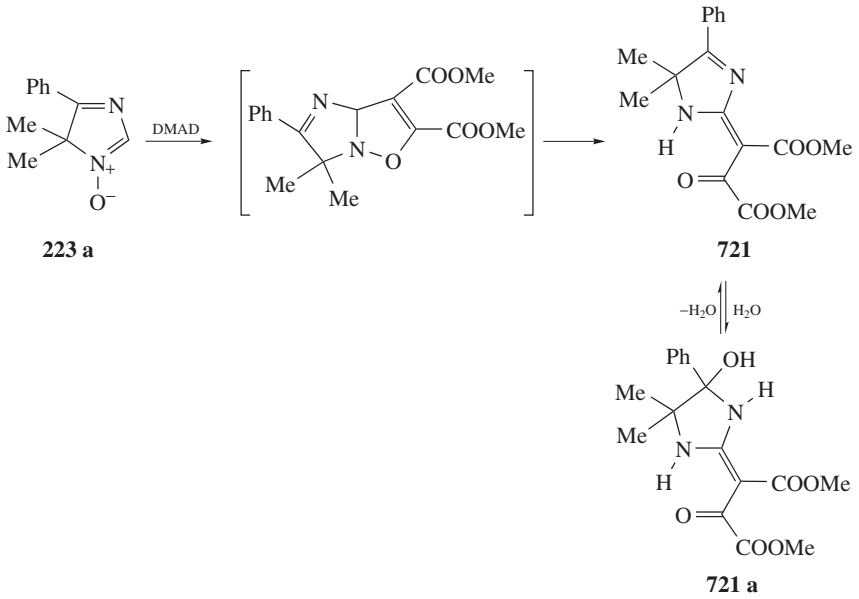
Unlike α-methoxynitrones (**203**) and (**223 g**), the reaction of the corresponding aldonitrones (**223a**) (Scheme 2.300) and (**167**) (Scheme 2.301) proceeds beyond the cycloaddition step. It undergoes ring opening, affording enamine ester (**721**). Compound (**721**) adds reversibly a molecule of H_2O to give the hydrate (**721a**). In the reaction of compound (**167**) with DMAD, apart from enamino ester (**722**), trimethyl 3,3-dimethyl-1-phenyl-3H-pyrrolo[1,2-c]imidazole-5,6,7-tricarboxylate (**723**) was isolated (816).

Enamino ester (**722**) does not react with DMAD under these reaction conditions, while the reaction of nitrone (**167**) with DMAD gives both products (**722**) and (**723**) in approximately equal amounts, irrespective of the amount of DMAD used. This implies that the two reaction pathways are independent of each other. The cycloadduct produced initially undergoes either ring opening to give enamino ester (**722**) or isomerizes to yield 1,3-diazabicyclo[3.1.0]hex-3-ene (**724**).



203 **719** **223 g** **720**

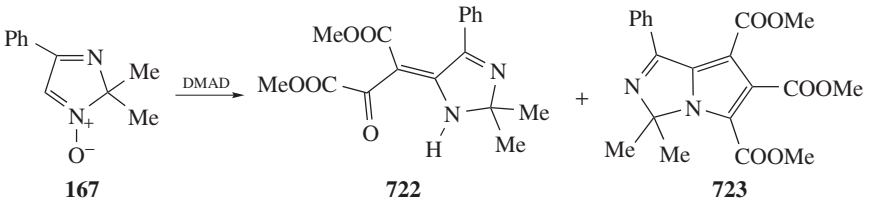
Scheme 2.299



223 a **721** **721 a**

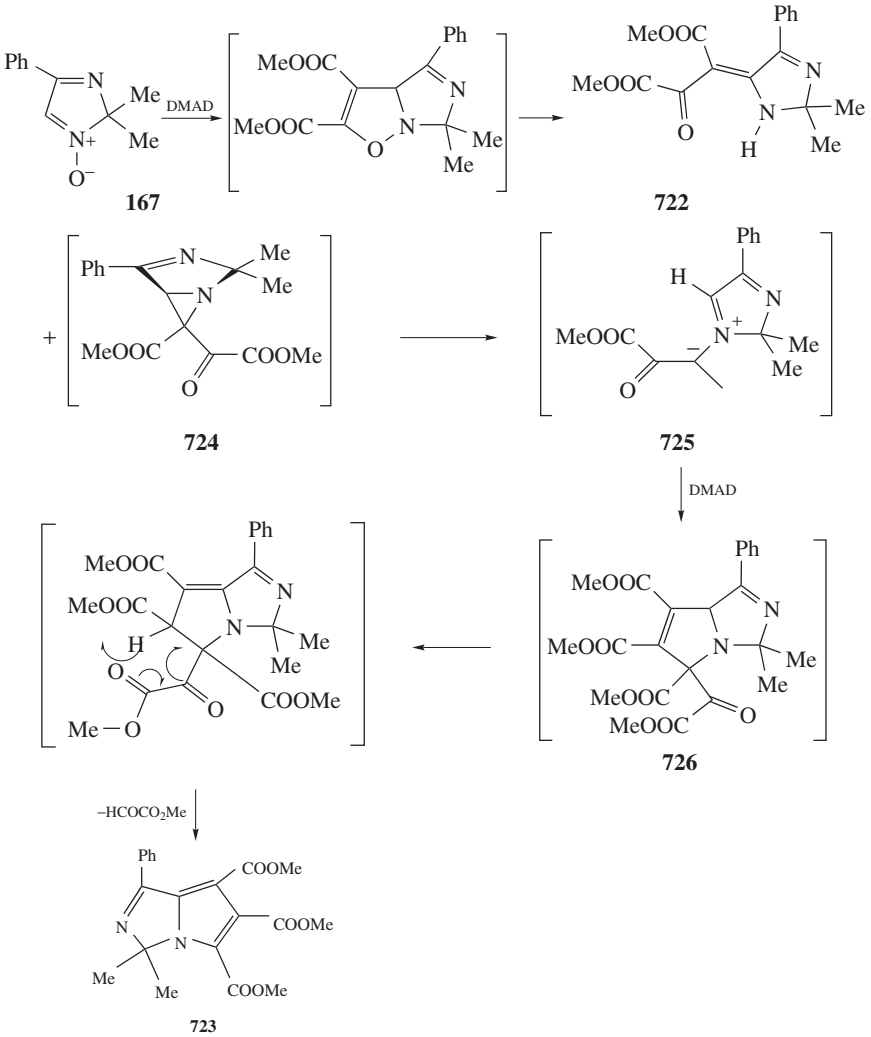
Scheme 2.300

The latter reacts with a second DMAD molecule to give cycloadduct (**726**). The reaction proceeds via opening of the aziridine ring to give compound (**725**). The cyclo-adduct (**726**) undergoes a 1,3-sigmatropic shift and aromatization to give compound (**723**) (Scheme 2.302) (816).



167 **722** **723**

Scheme 2.301



167 **722** **724** **725** **726** **723**

Scheme 2.302

Similarly, in a 1,3-dipolar cycloaddition of DMAD to the conformationally locked cyclic α-alkoxycarbonylnitrone (**727**), bicyclic ring systems, containing a nitrogen atom at the bridgehead position have been synthesized. A mechanistic interpretation of the origin of the fused pyrroles (**729**) includes the intermediate formation of the aziridine ring in (**728**) (Scheme 2.303) (820).

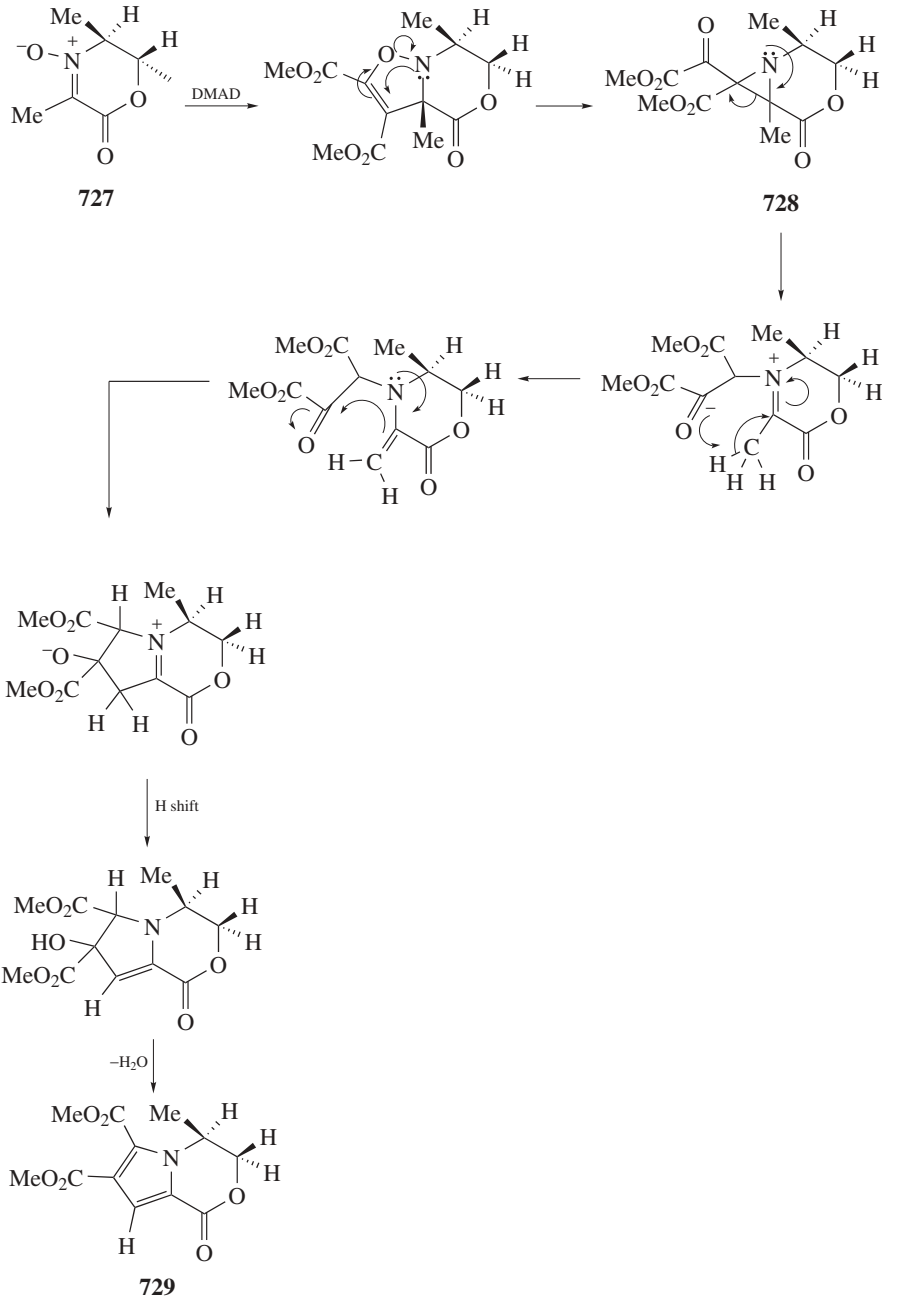
Treatment of 3,4-dihydroisoquinoline-2-oxides (**730**) with DMAD in toluene at room temperature gave the corresponding isoxazolo[3,2-a]isoquinolines (**731**). On heating in toluene, they were converted to the corresponding ylides (**732**) in high yields (Scheme 2.304) (27b).

The 1,3-dipolar cycloaddition reaction of bridged nitrones, incorporated in a homoadamantane ring system (**733**), with electrone-deficient alkynes proceeded regiospecifically at 0°C to give 4-substituted isoxazolines (**734a–d**). The cycloadducts (**734a–d**) were further converted to homoadamantane-fused pyrroles (**735a–d**) (Scheme 2.305) (54).

Nitrone cycloaddition reactions with alkynes have been widely used for the synthesis of imidazolidine nitroxides (**736**) and (**737**), containing chelating enamino ketone groups (821). Different heterocyclic systems were obtained, such as 3-(2-oxygenated alkyl)piperazin-2-ones (**738**) (822), also compounds containing the isoxazolo[3,2-i]indole ring system (**739**) (823) and a new class of ene-hydroxylamino ketones- (*R*)-2-(1-hydroxy-4,4,5,5-tetraalkylimidazolidin-2-ylidene)ethanones (**740**) (824) (Fig. 2.46).

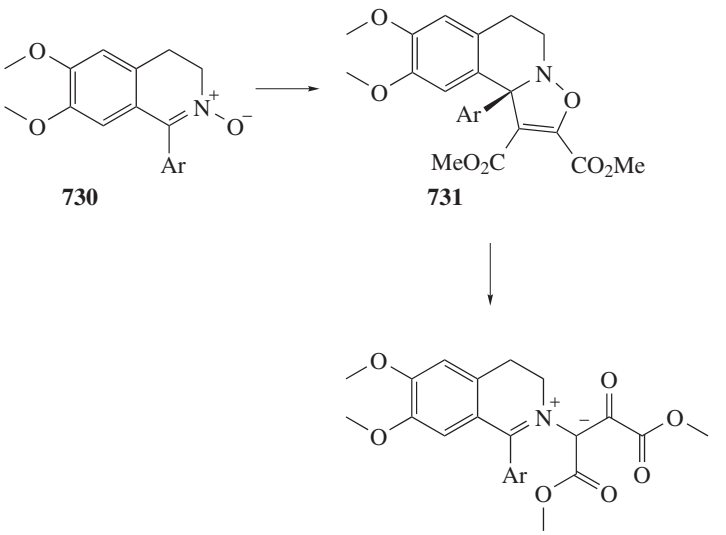
4,5-Dihydro-1*H*-imidazole 3-oxides (**741**), bearing different substituents at positions 1 and 2 of the heterocycle reacted with a wide range of acceptor-substituted alkynes, forming the corresponding cycloadduct derivatives of 1,2,3,7a-tetrahydroimidazo[1,2-b]isoxazole(**742**). A high regioselectivity of this reaction, due to conjugation of the nitrogen atom with the nitrone group was observed (Scheme 2.306) (825–827).

Recently, the first example of a regioselective and organo-catalyzed 1,3-dipolar cycloaddition reaction (**1,3-DCR**) between conjugated alkynoates and nitrones "on water" has been described. A new catalytic system, based on the in situ generation of reactive β-phosphonium (or ammonium) allenolates was used. A plausible catalytic mechanism, accounting for the observed results, has been proposed (Scheme 2.307) (828). The catalytic cycle is triggered by the addition of the catalyst (**Nu**) to the alkynoate, generating the zwitterionic allenoate (**743**). Regioselective 1,3-dipolar cycloaddition of this dipolarophile intermediate to the nitrone affords the zwitterionic cycloadduct intermediate (**744**). Then elimination of a molecule of catalyst generates the 2,3-dihydroisoxazole ring (**745**), re-initiating the cycle. Remarkably, in spite of the marked electronic and structural differences between tertiary phosphines and amines, they perform the same catalytic task, by generating the reactive dipolarophile allenoate (**743**). Preliminary theoretical calculations support the proposed catalytic model, with the zwitterionic allenoate (**743**) acting as the reactive dipolarophile (828).



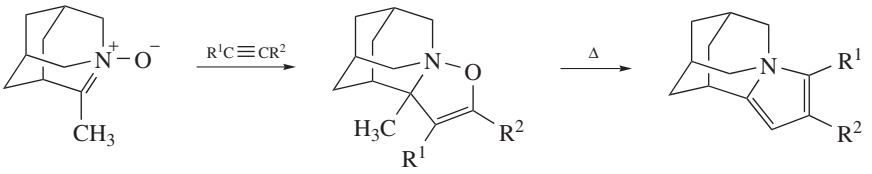
727 728 729

Scheme 2.303



730 731 732

Scheme 2.304



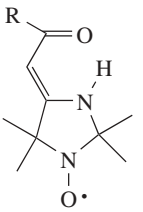
733 734 a-d 735 a-d

	R^1	R^2
a	COOMe	H
b	CN	H
c	COOMe	COOMe
d	H	Ph

Scheme 2.305

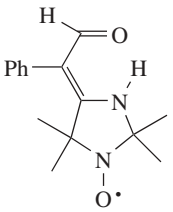
2.8.3. 1,3-Cycloaddition to Nitriles

The use of nitriles as dipolarophiles in 1,3-dipolar cycloaddition reactions is scarce because of their relative inertness in such reactions. Indeed, nitriles with electron-donor substituents do not react with nitrones even under harsh conditions. Hence, an additional activation of the reactants is required. This can be achieved, either by activating the nitrile (dipolarophile) or the nitrone (dipole), or both of them. For example, the reaction of electron-difficient nitriles such as

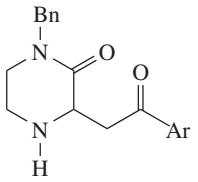


736 a-c

a: R = Ph
b: R = CHO
c: R = AcO

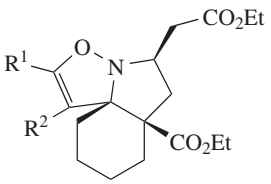


737

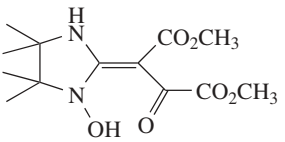


738 a,b

a: R = Ph
b: R = Tol



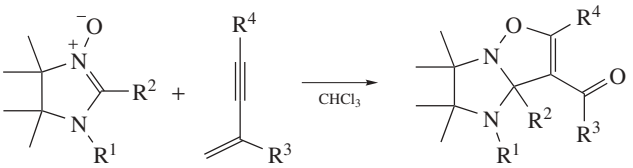
739 a,b



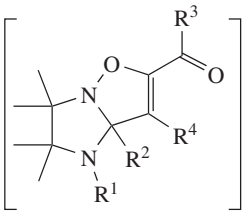
740

a: R = R^1 = CO_2Me, R^2 = COMe
b: R = R^1 = COMe, R^2 = CO_2Me

Fig. 2.46

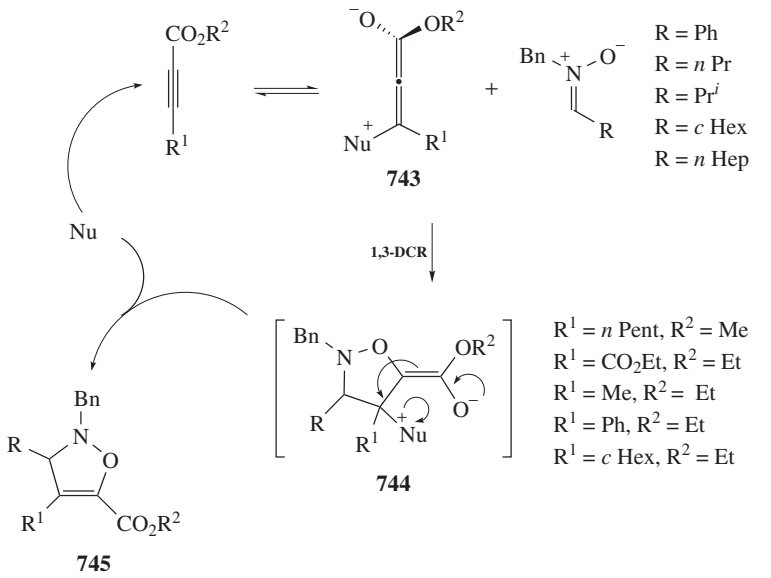


741 **742**

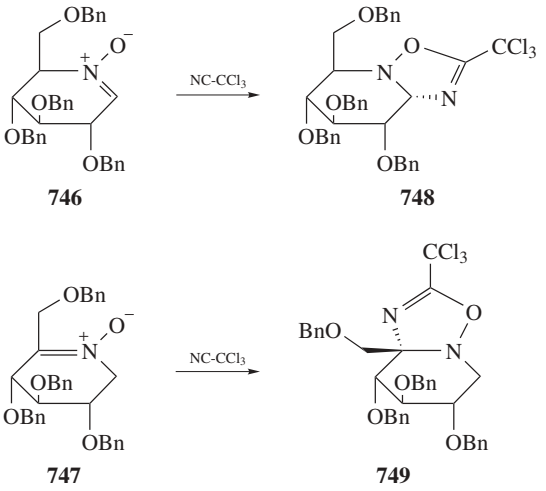


R^1 = H, OH, Me;
R^2 = H, Me, CF_3, Bu^t, Ph, 2,4-$(Me)_2$-C_6H_3; 2,4,6-$(Me)_3$-C_6H_2; 4-NO_2-C_6H_4; 3-NO_2-C_6H_4; 4-MeO-C_6H_4; CH=CHC_6H_5;
R^3 = OMe, H, Me, Ph, OEt; R^4 = H, CO_2Me; Ph; CF_3.

Scheme 2.306

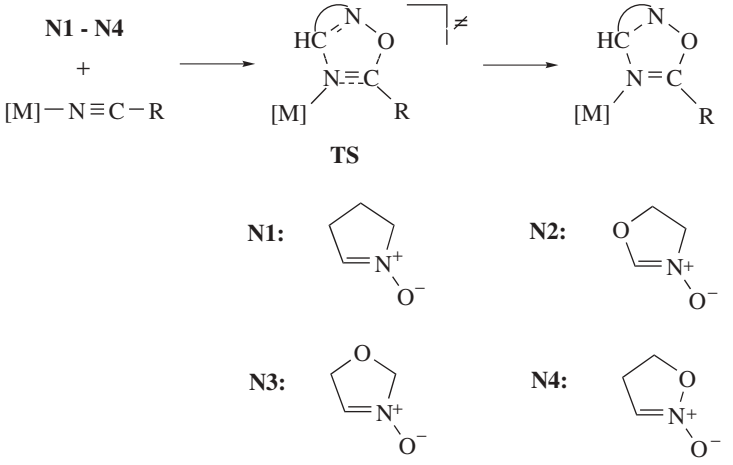


Scheme 2.307



Scheme 2.308

CF_3CN and CCl_3CN leads to the corresponding substituted oxadiazolines (74, 829). Thus, reactions of (**746**) and (**747**), derived from 1-deoxynojirimycin with trichloroacetonitrile in toluene at room temperature leads to bicyclic compounds (**748**) and (**749**) (Scheme 2.308).



R = CH_3; CF_3; [M] = *no*

R = CH_3; [M] = *trans*-[$PtCl_n(NCCH_3)$]; *n* = 2 (**750**) and 4 (**751**)

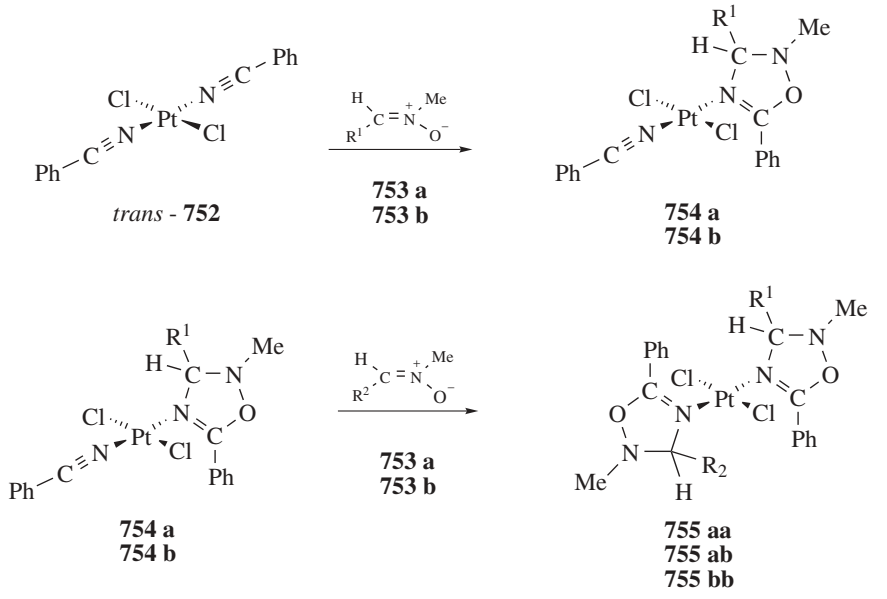
Scheme 2.309

Experimental and theoretical studies of 1,3-dipolar cycloadditions of nitrones to organonitriles, RCN—both free (R = CH_3, CF_3), or ligated to Pt^{2+} and Pt^{4+} (in the complexes *trans*-[$PtCl_2(NCCH_3)_2$ (**750**) and *trans*-[$PtCl_4(NCCH_3)_2$(**751**)] have been performed. The effectiveness of two types of dipolarophile activation, (by introducing a strong electron-acceptor group R and by coordinating to a metal center) has been analyzed and compared (830, 831). The reaction proceeds through the formation of a five-membered cyclic transition state (**TS**) (Scheme 2.309).

The reactivity of dipoles and dipolarophiles increases along the series **N4** < **N1**~**N3** < **N2** and $CH_3CN < CF_3CN <$ **(750)** < **(751)**. The latter demonstrates that the coordination of RCN to a Pt center provides an even higher activation effect upon cycloaddition than the introduction of a strong electron-acceptor group R, such as CF_3. The higher reactivity of the cyclic dipole **N1** than of acyclic nitrones (e.g., $CH_3CH{=}N(CH_3)O$) is interpreted to be a result of its existence in a more strained and hence more reactive *E*-configuration rather than *Z*-configuration. Consideration of solvent effects shows an increase of the activation barriers. Such enhancement is less pronounced for the nonpolar or low polar solvents. On the basis of kinetic and thermodynamic considerations heterocyclic nitrones with the oxygen atom at the sixth position of the ring, such as, **N2**) are predicted to be even more reactive than **N1** in reactions with nitriles. Thus, use of cyclic nitrones of the **N2**-type on one hand, and of the metal-bonded nitriles on the other hand, is the most efficient and promising way for the acceleration of the nitrone-to-nitrile 1,3-cycloaddition reactions. However, the nitronate **N4** is found to be less reactive toward nitriles than the acyclic nitrones (830e).

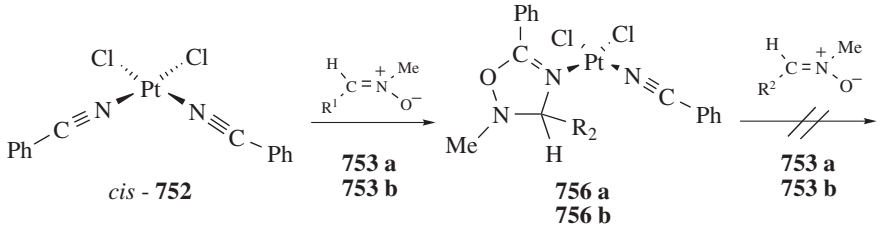
Ligand influence in the 1,3-dipolar cycloaddition reactions of nitrones, exerted by the complexes *cis*- and *trans*- $[PtCl_2(PhCN)_2]$ (**752**), has been used for selective syntheses of mono-oxadiazoline and mixed bis-oxadiazoline complexes under thermal and microwave conditions (832). Microwave irradiation enhances the reaction rates of the cycloaddition considerably. It favors the selectivity toward the mono-cycloadduct. For the first cycloaddition step is accelerated to a higher extent than the second one. The reaction of the *trans*-substituted mono-oxadiazoline complexes (**754**) with nitrone (**753**), different from the one used for the first cycloaddition step, leads to a mixture of bis-oxadiazoline compounds composed of *trans*- [$PtCl_2$(oxadiazoline-**a**) and (oxadiazoline-**b**)] (**755**) (Scheme 2.310). The corresponding *cis*- complexes (**756**), however, do not undergo further cycloaddition (Scheme 2.311). All of the reactions described occur without isomerization of the stereochemistry around the platinum center, regardless, whether thermal or microwave heating was applied.

The reaction between the nitrone (**753b**) and trans-$[PdCl_2(RCN)_2]$ (R = Ph, Me) in the corresponding RCN (or of the nitrone in neat RCN in the presence of $PdCl_2$) proceeds at 45°C with (R = Ph) or reflux with (R = Me). It affords Δ^4-1,2,4-oxadiazoline complexes of structure, similar to (**755**), but with Pd instead of Pt. The reaction time can be drastically reduced by focused microwave irradiation of the reaction mixture (833).



a: R^1, R^2 = Ph; **b:** R^1, R^2 = *p*-MeC_6H_4

Scheme 2.310



a: R^1, R^2 = Ph; **b:** R^1, R^2 = *p*-MeC_6H_4

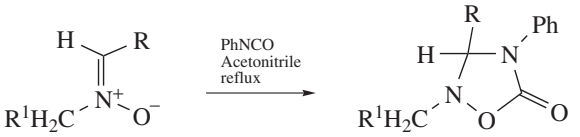
Scheme 2.311

2.8.4. Cycloaddition to Isocyanates, Isothiocyanates, and Ketenes

Cycloaddition of nitrones with electron-donating substituents R (**757a,c,f**) to phenyl isocyanate proceeds readily, in high yields, to give the corresponding 1,2,4-oxadiazolidinone (**758a,c,f**). Nitrones with electron-withdrawing substituents (**757b,d,e,g**) give the corresponding oxadiazolidinone (**758b,d,e,g**) in moderate yields after prolonged heating (Scheme 2.312) (834).

The interaction of imidazoline nitroxide (**759**) with isocyanates leads to oxadiazolidines (**760**), which can be easily transformed into 4*R*-amino-3-imidazoline-1-oxyls (**761**) on treatment with nucleophilic reagents (Nu = NaI, NaN_3, NH_4OH, AcONa, NaH) (Scheme 2.313) (835).

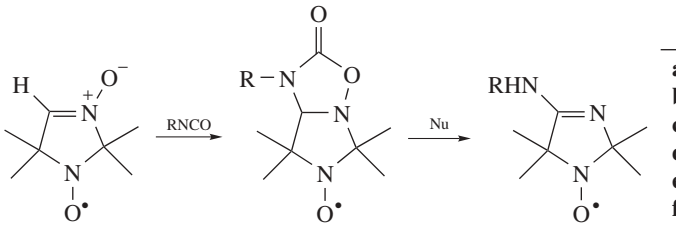
Cyclic α-methoxynitrones (**225f**) and (**223 g**) react respectively with isocyanates and isothiocyanates at ambient temperature, giving 1,3-dipolar cycloaddition products (**763**) and (**764**) (Scheme 2.314). Under similar conditions, the reaction of aldonitrone (**223a**) proceeds much more slowly to give cycloadducts



757 **758**

a: R = 3,4-$(MeO)_2C_6H_3$; R^1 = H
b: R = 2-$NO_2C_6H_4$; R^1 = H
c: R = Ph, R^1 = Ph
d: R = 2-$NO_2C_6H_4$; R^1 = 2,3-$(MeO)_2C_6H_3$
e: R = 2-$NO_2C_6H_4$; R^1 = Ph
f: R = 2,3-$(MeO)_2C_5H_3$; R^1 = Ph
g: R = 3-$NO_2C_6H_4$; R^1 = Ph

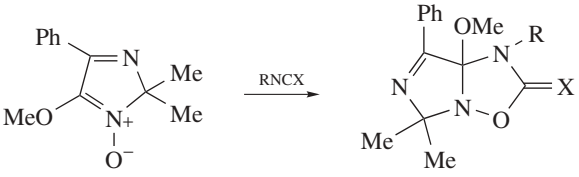
Scheme 2.312



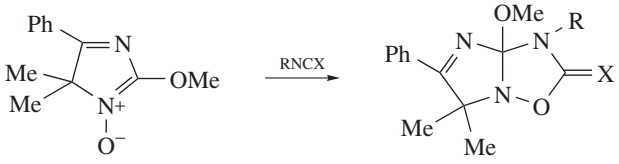
	R
a	C_6H_5
b	$ClCH_2CH_2$
c	$CH_3O_2CCH_2CH_2$
d	CH_2=CHCH
e	α-naphthyl
f	C_2H_5

759 **760** **761**

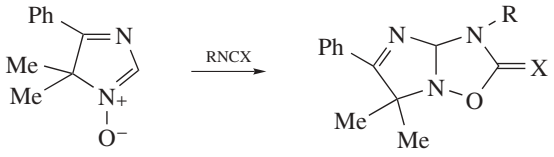
Scheme 2.313



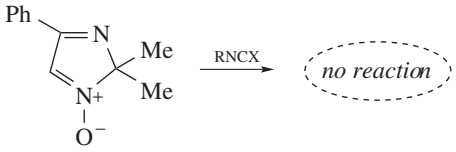
225 f **762 a-d**



223 g **763 a-d**

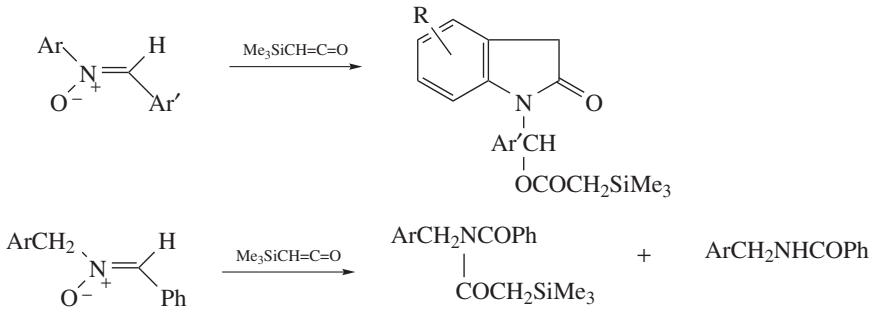


223 a **764 a-d**



225 e R = Ph (**a, b**), $ClCH_2CH_2$ (**c**), α-*naphthyl* (**d**);
X = O (**a,c,d**), S (**b**)

Scheme 2.314



Scheme 2.315

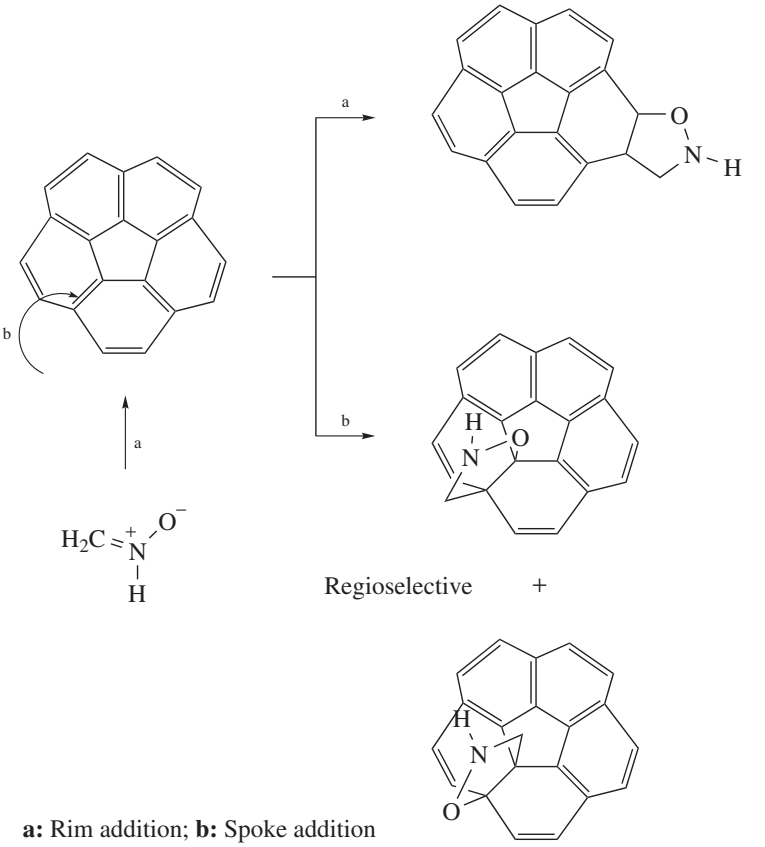
(**764**), while aldonitrone (**225e**) does not react at all. Thus, the reactivity of nitrones in 1,3-dipolar cycloaddition to isocyanates and isothiocyanates increases with an alkoxy substituent in the α-position of the nitrone. The addition of isothiocyanates to nitrones can involve both, the C=N and C=S bonds. In the reactions of compounds (**223a,g**) and (**225e,f**) with PhNCS, only addition products at the C=N bond were isolated (816).

Trimethylsilylketene reacts smoothly with α,*N*-diarylnitrones to give oxoindoles in good yields. On the other hand, the reaction of trimethylsilylketene with *N*-arylmethylnitrones gives a mixture of *N,N*-diacylamines and *N*-acylamines (Scheme 2.315) (836).

2.8.5. Cycloaddition to Corannulene, Fullerenes, and Porphyrins

Corannulene undergoes 1,3-dipolar reactions with nitrones via its rim (a) and spoke (b) π bonds. The rim addition yields "one possible" adduct, whereas two "regioselective" adducts are formed by the spoke addition (Scheme 2.316). Mechanisms of these reactions have been investigated at the B3LYP/6-31G(d) level. Computations show that both, rim and spoke additions prefer concerted pathways that lie 2 to 5 kcal/mol lower in energy than the stepwise paths. The rim bond of corannulene is more flexible to distortion and also has a stronger double bond (i.e., π-character) than the spoke bond. This favors rim addition over spoke addition. Deformation energy analyses also confirm the higher deformation in corannulene in the spoke additions than in the rim additions. Computed activation energies suggest that corannulene acts as a deactivated dipolarophile when compared to ethylene (837).

1,3-Dipolar cycloadditions of fullerene C_{60} to nitrones have been studied. Their mechanism, regiochemistry, and nature of addition have been investigated. All of the reactions lead to the formation of fullerene fused heterocycles. Theoretically, these reactions can lead to four types of additions, such as closed [6,6], open [5,6], closed [5,6], and open [6,6] additions (Scheme 2.317). Energetics and thermodynamic analyses of these reactions show that closed [5,6] and open [6,6]



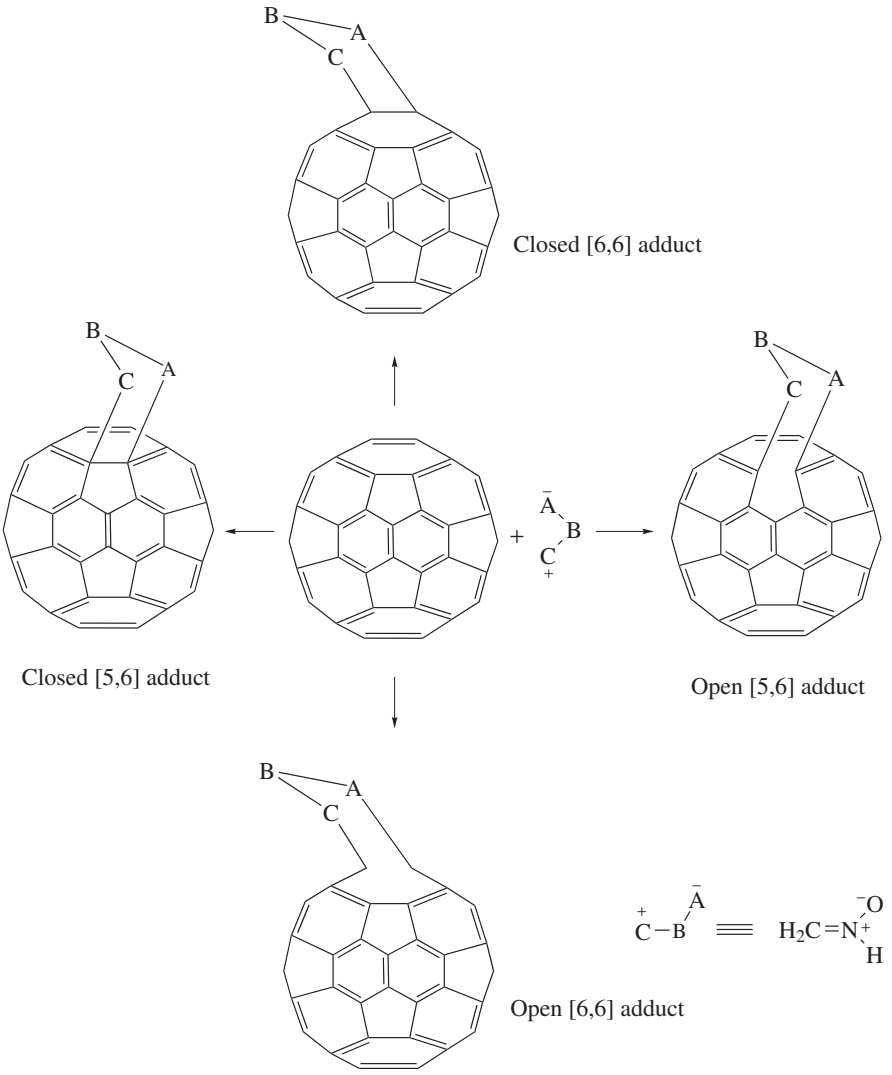
Scheme 2.316

additions are not probable and that closed [6,6] additions are the most favored ones, and follow a concerted mechanism (838).

Glyco-conjugated isoxazolidine-fused chlorins (**768**) and (**769a–d**) were prepared in moderate to good yields by 1,3-dipolar cycloaddition reactions of *meso*-tetrakis(pentafluorophenyl) porphyrin (**765**) with *in situ* generated methylene nitrone (**766**) and glycosyl nitrones (**767a–d**) (Scheme 2.318) (839, 840). Porphyrin glyco-conjugates are of special importance due to their strong absorption in the visible region above 700 nm. It makes these compounds very promising for their potential application as photosensitizers in the photodynamic therapy (PDT) of cancer.

2.9. KINUGASA REACTION ([2 + 2] CYCLOADDITION)

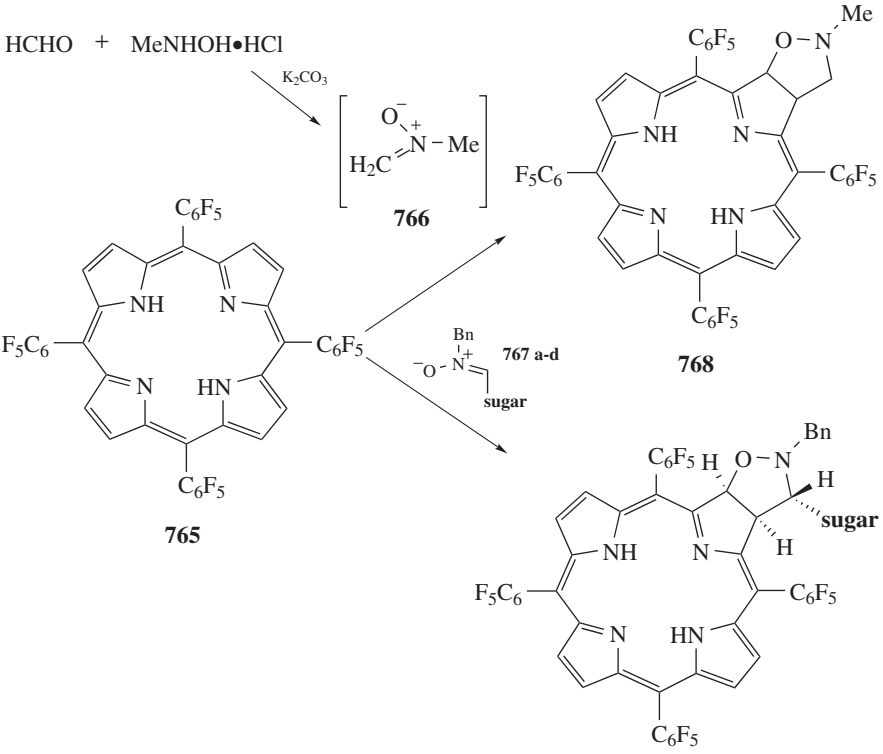
In 1972, Kinugasa and Hashimoto (841) reported the reaction of copper (I) phenylacetylide with α,*N*-diphenylnitrone in dry pyridine. It has provided an

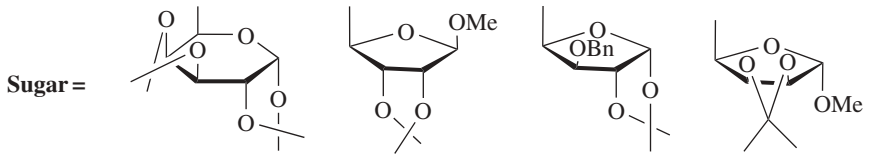


Scheme 2.317

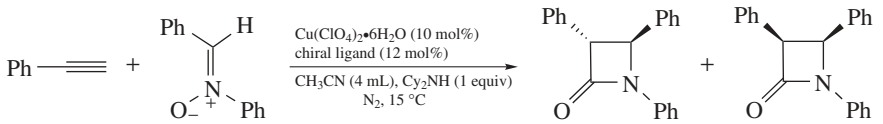
economical and a facile way to the synthesis of β- lactams. Asymmetric Kinugasa reactions also provide an easy access to optically pure β-lactams (**770**) (Scheme 2.319) (842–847).

Copper (II) salts proved to be efficient catalysts in the Kinugasa reaction, and this allowed the reaction to be performed under practical and convenient conditions. Amines strongly influence diastereoselectivity, enantioselectivity, and reaction rate. Bulkier amines always give better diastereoselection and, generally, tertiary amines provide higher diastereoselectivity than secondary ones, and the





Scheme 2.318



Scheme 2.319

latter are better than primary ones. For, example, both, 1,2,2,6,6-pentamethylpiperidine and diisopropylethylamine give largely a single *cis*-isomer, but *iso*-butylamine only gives the products of moderate diastereoselectivity. Compared with tertiary and primary amines, secondary ones afford the desired products with higher enantioselectivity but lower diastereoselectivity. Use of dicyclohexylamine (Cy_2NH) gives the most satisfactory result. Compared with alkylamines, aromatic amines, such as *N,N*-dimethylaniline and aniline, do not catalyze this reaction at all. The reaction of phenylacetylene with α,*N*-diphenylnitrone proceeds readily in a number of solvents, providing the *cis*-isomer (**770 cis**) as the major product. Acetonitrile has been found to be the best solvent in these reactions. In methanol, no reaction was observed. Lowering the temperature slightly increases both, the yield and the *cis*-selectivity in CH_3CN (847b).

The electronic character of aromatic groups at the α-C of nitrones affects both, the yields and the stereoselections (Table 2.28). Electron-rich aromatic groups increase enantioselectivities but decrease the yields (entries 1-3). Electron-deficient ones slightly decrease enantioselectivities but increase the reaction rates (entries 4 and 5). The electronic properties of *N*-bound aromatic groups of nitrones has almost no obvious impact on the enantio-selections (entries 6–10). Both, electron-deficient and electron-rich aromatic groups afford good enantioselectivities and diastereoselectivities. Nitrone with a *N*-bound furyl group furnishes, in moderate yield, the best ee but the lowest diastereoselectivity (entry 9). α-Alkyl and *N*-alklyl nitrones fail to react (entries 11 and 12).

Oxazoline-type chiral ligands $\mathbf{L}^1$ and $\mathbf{L}^2$ (Fig. 2.47) are used as catalysts in these reactions leading to products with good to high enantioselectivities (up to 93% ee) and with high *cis*-diastereo selections.

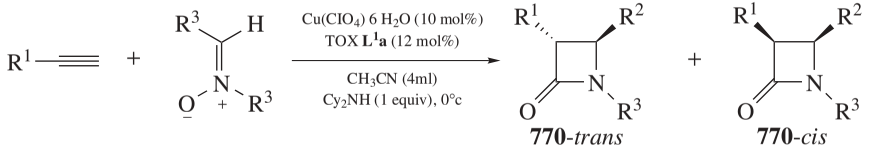
Bisoxazolines (BOX) ($\mathbf{L}^2$**a-d**) give lower reaction rates and enantioselectivities than trioxazolines (TOX) ($\mathbf{L}^1$**a-m**). The proposed reason is that trioxazolines provide a stronger chelation with the copper center than bisoxazolines, effectively preventing phenylethynyl copper from its polymerization (847b).

To explain the formation of β-lactam formation two plausible mechanisms have been suggested (Scheme 2.320).

Path I was proposed to proceed via a [3 + 2] cycloaddition reaction, followed by a rearrangement to give the β-lactam. Considering that imines have formed as a byproduct in some reactions, described above, and that nitrones with *N*-bound electron-withdrawing substituents gave better yields than those with *N*-bound electron-rich substituents (Table 2.28, entries 4 and 5 versus entries 1–3) led to the suggestion of another mechanism (path II). It was proposed that cycloadduct **A** decomposes into intermediate ketene **C**, followed by an intramolecular, nucleophilic cyclization to give enolate **D**. Protonation of **D** gives the desired β-lactam (847b).

A general synthetic route to β-lactam-fused enediynes (Scheme 2.321) has been successfully developed (848). When nitrone (**771**) was subjected to Kinugasa reaction conditions, two β-lactam containing products were obtained: the elimination product (**772**) and the *trans* fused compound (**773**).

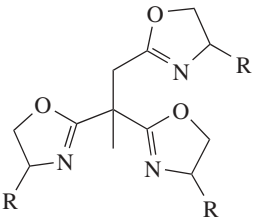
Table 2.28 Asymmetric synthesis of β-lactams[a]



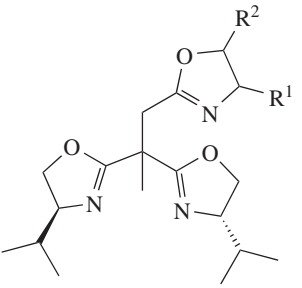
770-*trans* **770**-*cis*

Entry	R^1	R^2	R^3	Lactam	Yield (%)[b]	cis/trans[c]	ee (%)[d]
1	C_6H_5	C_6H_5	C_6H_5	**770 a**	56	15/1	82
2	C_6H_5	C_6H_5	*p*-MeC_6H_4	**770 b**	36	19/1	82
3	C_6H_5	C_6H_5	*p*-$MeOC_6H_4$	**770 c**	36	31/1	84
4	C_6H_5	C_6H_5	*p*-BrC_6H_4	**770 d**	70	13/1	74
5	C_6H_5	C_6H_5	*p*-$EtO_2CC_6H_4$	**770 e**	98	10/1	70
6	C_6H_5	*p*-MeC_6H_4	C_6H_5	**770 f**	50	18/1	82
7	C_6H_5	*p*-$MeOC_6H_4$	C_6H_5	**770 g**	58	18/1	83
8	C_6H_5	*p*-$F_3CC_6H_4$	C_6H_5	**770 h**	75	14/1	82
9	C_6H_5	α-furyl	C_6H_5	**770 i**	56	2/1	85
10	C_6H_5	*p*-$F_3CC_6H_4$	*p*-$MeOC_6H_4$	**770 j**	35	25/1	84
11	C_6H_5	cyclohexenyl	C_6H_5	no reaction			
12	C_6H_5	C_6H_5	$C_6H_5CH_2$	no reaction			
13	*p*-$F_3CC_6H_4$	C_6H_5	C_6H_5	**770 k**	65	3/1	73
14	1-cyclohexenyl	C_6H_5	C_6H_5	**770 l**	33	13/1	72
15	Me_3Si	C_6H_5	C_6H_5	no reaction			
16	EtO_2C	C_6H_5	C_6H_5	**770 m**	25	1/6	46[e]
17[f]	EtO_2C	C_6H_5	C_6H_5	**770 m**	45	1/5	48[e]
18[g]	EtO_2C	C_6H_5	C_6H_5	**770 m**	67	1/6	50[e]
19[g]	EtO_2C	C_6H_5	*p*-$EtO_2CC_6H_4$	**770 n**	80	1/4	51[e]
20[g]	EtO_2C	α-furyl	C_6H_5	**770 o**	78	1/8	45[e]

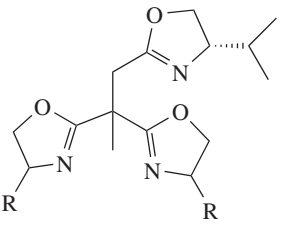
[a] Reactions were run at 0°C using 12 mol % TOX **L[1]a** and 10 mol % of $Cu(ClO_4)_2 . 6H_2O$ under air atmosphere on 0.25 mmol scale.
[b] Total isolated yield of cis- and trans-isomers. [c] Determined by 1H NMR. [d] ee of the cis-isomer determined by chiral HPLC.
[e] ee of the *trans*-isomer determined by chiral HPLC. [f] Using 6 mol % of TOX **L[1]a**, 5 mol % of $Cu(ClO_4)_2 . 6H_2O$, and 20 mol % of $^i Pr_2NEt$.
[g] Using 6 mol % of BOX **L[2]b**, 5 mol % of $Cu(ClO_4)_2 . 6H_2O$, and 20 mol % of $^i Pr_2NEt$.



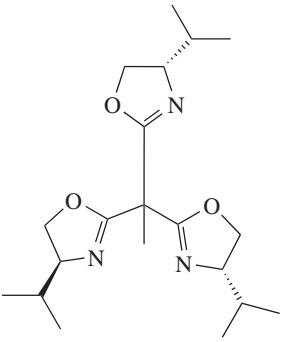
L¹ : **a**: R = (S)-Pr^{i}
b: R = (S)-Bu^{s}
c: R = (S)-Bu^{t}
d: R = (R)-Ph



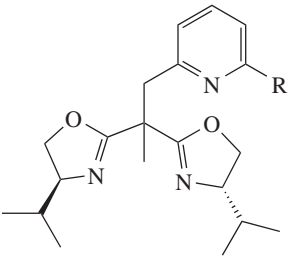
L¹ : **e**: R^1 = (S)-Bu^{s}; R^2 = H
f: R^1 = (S)-Bu^{t}; R^2 = H
g: R^1 = (S)-Bn; R^2 = H
h: R^1 = (S)-Ph; R^2 = H
i: R^1 = (R)-Ph; R^2 = H
j: R^1 = R^2 = (S, R)-$C_6H_4CH_2$-



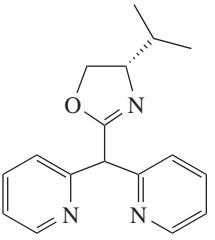
L¹ : **k**: R = (S)-Ph;
l: R = (R)-Ph;



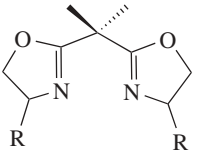
L¹ m



L¹ : **n**: R = H
o: R = Me

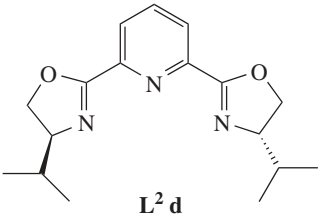


L¹ p



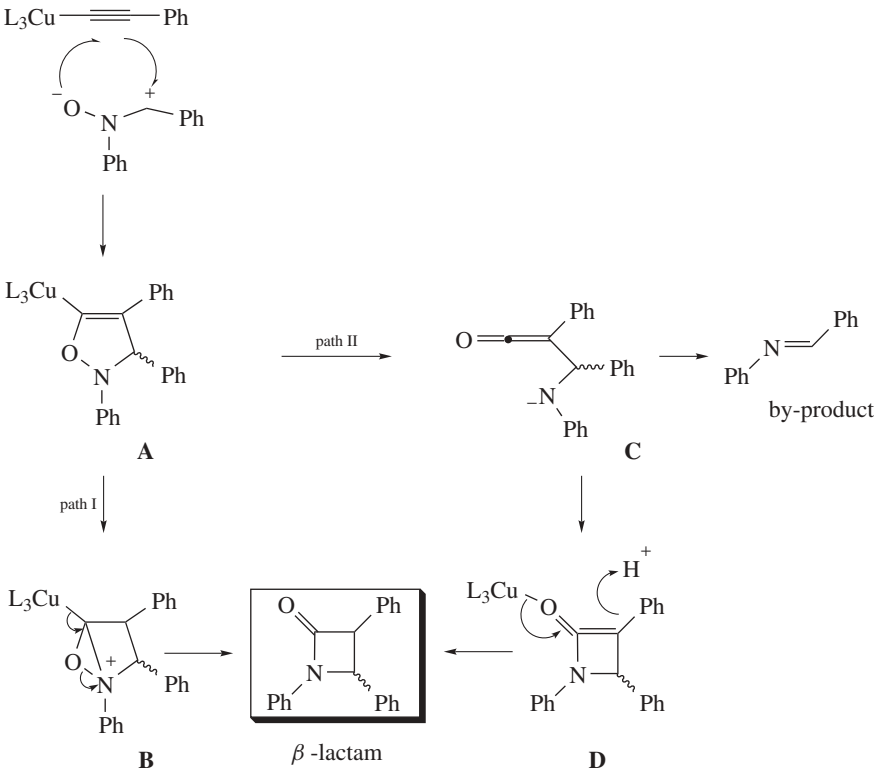
L² a

L² : **a**: R = (S)-Pr^{i}
b: R = (S)-Bu^{t}
c: R = (R)-Ph



L² d

Fig. 2.47 Chiral oxazoline ligands $\mathbf{L}^1$ and $\mathbf{L}^2$.



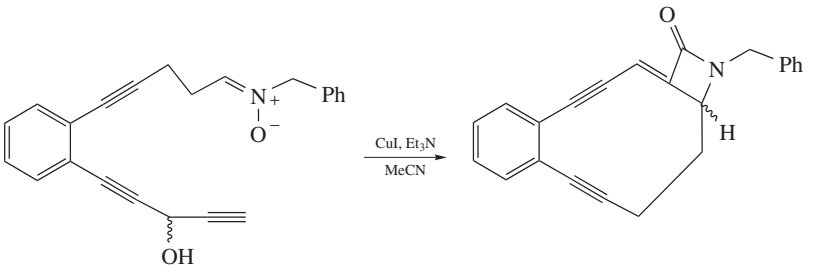
Scheme 2.320

2.10. 1,7- DIPOLAR CYCLIZATION REACTIONS

1,7- Electro-cyclization reactions of conjugated enynyl nitrones (**774**) constitute novel synthetic methods to 6,6,6,5-(**775**) and 6,6,5,5- (**776)** ring steroid analogs (Scheme 2.322). Cyclizations with (**774a–d**) were performed by heating ca10^{-2} M solutions of (**774**) in benzene in a 100-mL autoclave apparatus. In the case of the phenyl derivatives (**774a**) and (**774 d**) the 6,6,6,5-(**775a,d**) and 6,6,5,5-(**776a,d)** ring steroid analogs were obtained. In contrast to the results with (**774a,d**), thermal treatment of the silyl derivatives (**774b,c**) afforded almost exclusively the 6,6,6,5-steroids (**775e**) with only traces of the corresponding C-nor-analog (**776e**) (849).

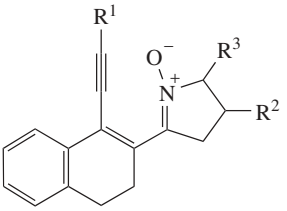
Treatment of various o-propargyl-aryl nitrones (**777a–p**) with potassium hydroxide or sodium methoxide in methanol at room temperature provides 1,2-dihydro[c]benzazepin-3-ones (**778a–p**) (Scheme 2.323) (850, 851). The high yields and the surprisingly mild reaction conditions are particularly remarkable in view of the complex mechanistic pathway involved in the overall transformation.

Similar transformations of benzopentenyl nitrones into 1,2-dihydrobenz[c] azepin-3-ones has been extended to the synthesis of structurally different systems,

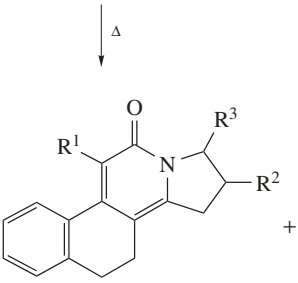


771 **772** + **773**

Scheme 2.321



774 a-e

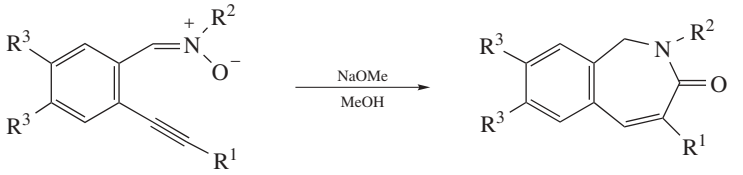


	R^1	R^2	R^3
a	Ph	C_6H_5	H
b	$Si(CH_3)_3$	C_6H_5	H
c	$Si(i\text{-}C_3H_7)_3$	C_6H_5	H
d	C_6H_5	H	CH_3
e	H	C_6H_5	H

775 a (15%)
775 d (24%)
775 e (59%, from **774 b**)
(54%, from **774 c**)

776 a (71%)
776 d (60%)
776 e (<1%, from **774 b,c**)

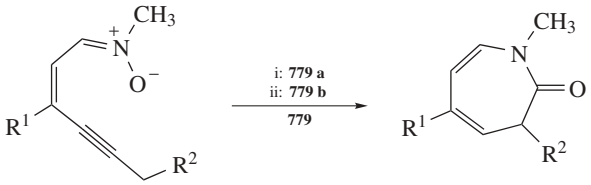
Scheme 2.322



777 a-p **778 a-p**

	a	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**	**k**	**l**	**m**	**n**	**o**	**p**
R1	H	H	H	TMS	TMS	Me	Me	C_6H_5	C_6H_5	C_6H_5	*p*MeC_6H_4	H	H	TMS	*p*MeC_6H_4	Br
R2	Me	C_6H_5	CMe_3	Me	C_6H_5	Me	C_6H_5	Me	C_6H_5	CMe_3	Me	Me	C_6H_5	Me	Me	Me
R3	H	H	H	H	H	H	H	H	H	H	H	OMe	OMe	OMe	OMe	H

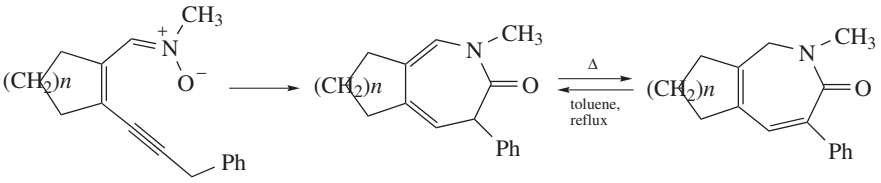
Scheme 2.323



779 a (94%) ($R^1 = R^2 = Ph$) **780 a** (94%) ($R^1 = R^2 = Ph$)
779 b (28%) ($R^1 = CH_3$, $R^2 = H$) **780 b** (28%) ($R^1 = CH_3$, $R^2 = H$)

i) MeONa, MeOH, 30 min, room temp.; ii) NaH, DMF, 22 h, 60°C

Scheme 2.324

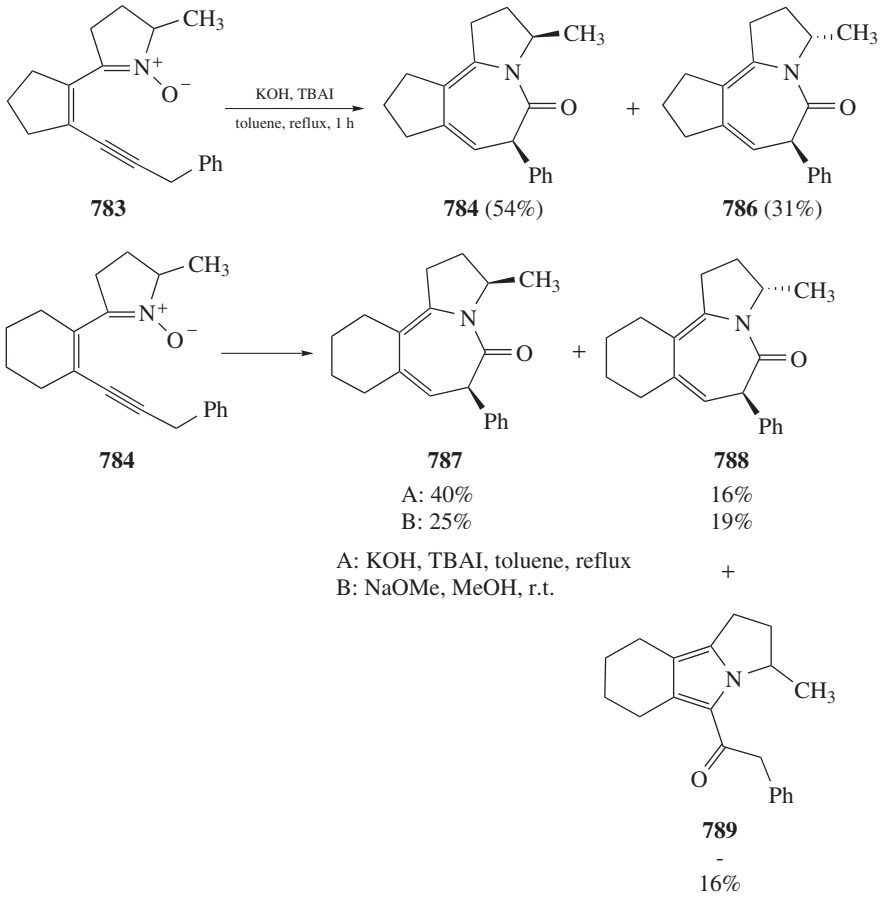


781 a-d **782 a-d**

a) n = 1; b) n = 2; c) n = 3; d) n = 4

Scheme 2.325

such as the monocyclic derivatives (**780a,b**) from the linear systems (**779a,b**) (Scheme 2.324), the bicyclic azepinones (**782a–d**) from monocyclic precursors (**781a–d**) (Scheme 2.325), and the tricyclic heterocycles (**785–789**) from bicyclic precursors (**783**) and (**784**) (Scheme 2.326) (139).

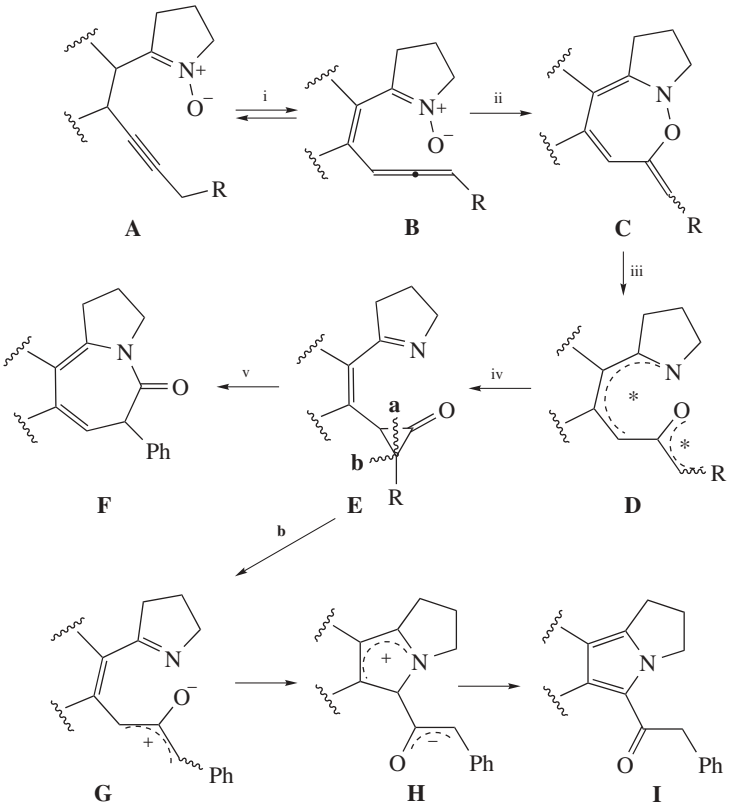


Scheme 2.326

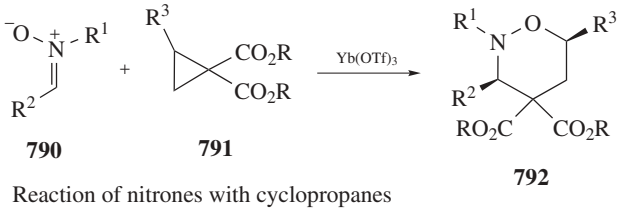
A possible mechanism for the observed transformation includes the sequence outlined in Scheme 2.327: (i) propargyl (**A**) – allene (**B**) tautomerization, (ii) 8π-cyclization (**C**), (iii) N–O cleavage (diradical **D**), (iv) diradical recombination (cyclopropanone derivative **E**), and (v) one or two step cyclizations of the azadienyl cyclopropanone into azepinone **F**. The occurrence of cyclopropanones (type **E**), as intermediates, is supported by the formation, in some cases, of isoindoles (type **I**) (**789**) as minor products (Scheme 2.327) (139, 850, 851).

2.11. REACTIONS WITH CYCLOPROPANES

Reaction of nitrones (**790**) with 1,1-cyclopropanediesters (**791**) in the presence of $Yb(OTf)_3$ affords tetrahydro-1,2-oxazines (**792**) via a homo $3+2$ dipolar cycloaddition (Scheme 2.328) (852).



Scheme 2.327

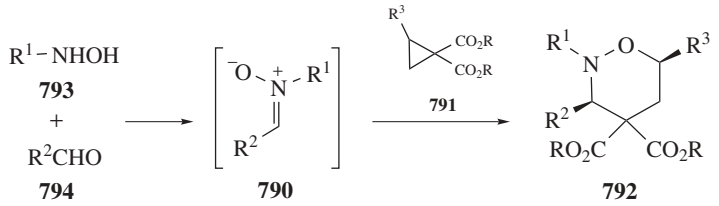


Reaction of nitrones with cyclopropanes

R^1, **R**^{2}, **R**^{3} : *see* Fig 2.48

Scheme 2.328

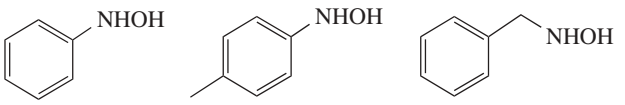
In these reactions, nitrones (**790**) can be formed in situ by the reaction of hydroxylamines (**793**) with aldehydes (**794**) (Scheme 2.329) (Fig. 2.48). This three-component coupling of (**793**), (**794**), and (**791**) allows for the formation of a diverse array of cycloadducts (**792**) with excellent diastereoselectivity (> 95%) and yields (66%–96%) (853).



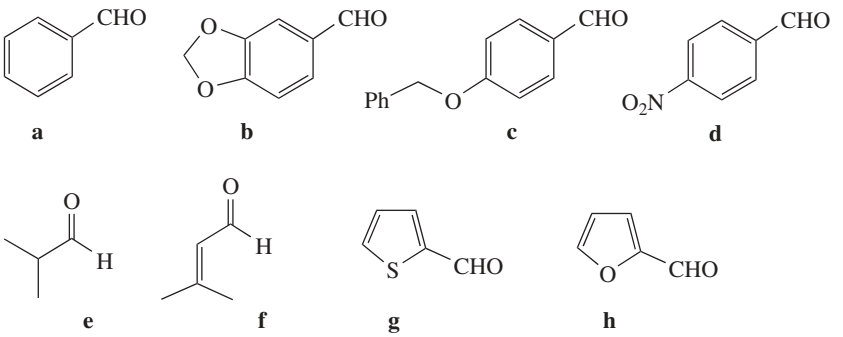
Three component coupling

Scheme 2.329

Hydroxylamines **793**



Aldehydes **794**



Cyclopropanediesters **791**

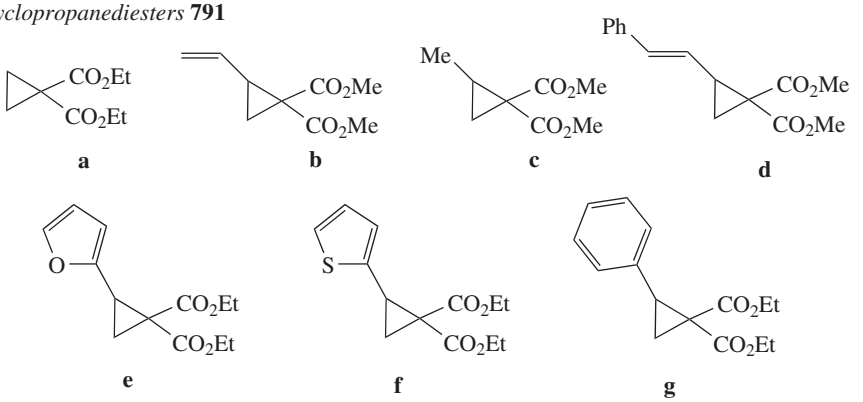
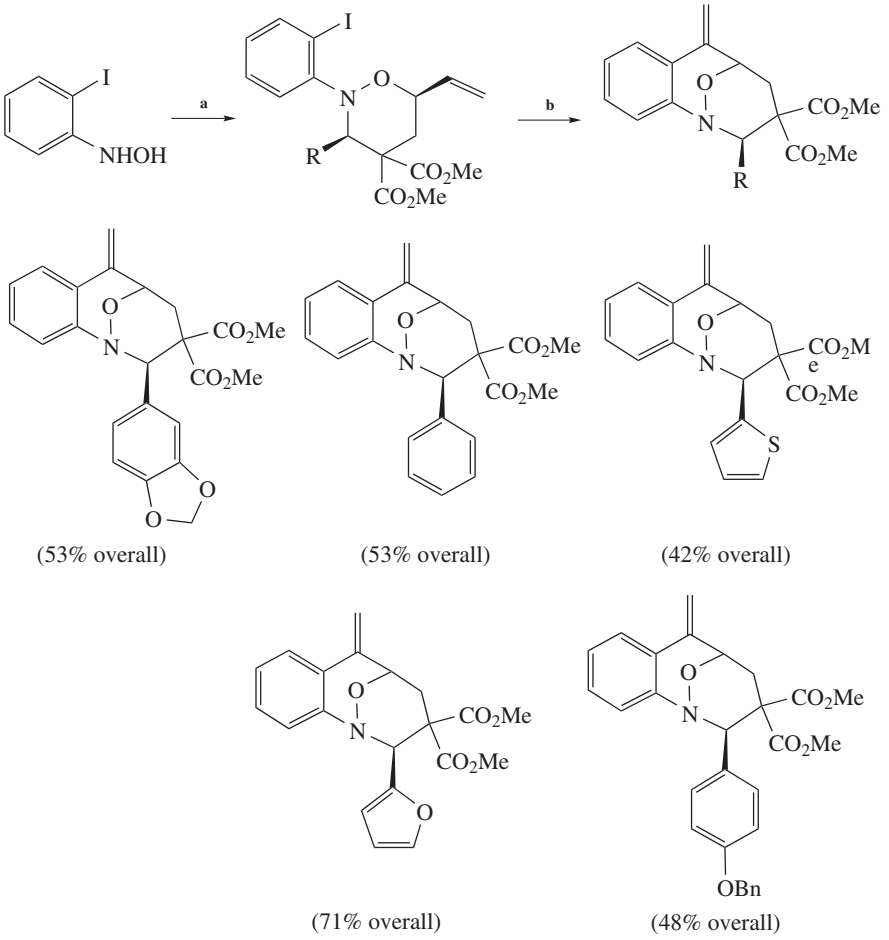


Fig. 2.48 Substrates for three-component coupling reactions.

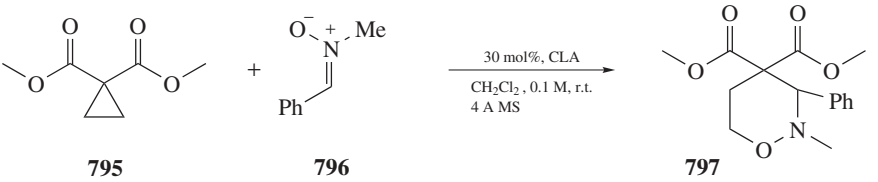


a: **794** (**a-c**, **g** *or* **h**), 10 mol% $Yb(OTf)_3$, 4Å MS, toluene, 25°C, 30 min, then **791** (**b**) 18 h
b: 20 mol% $Pd(PPh_3)_4$, Et_3N, CH_3CN,80°C, 18 h

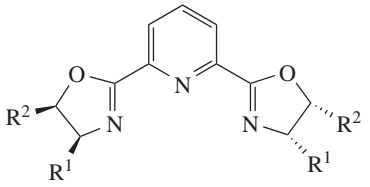
Scheme 2.330

This coupling method is useful for the preparation of interesting new molecular intermediates as well as for the synthesis of "FR900482" skeletal congeners (Scheme 2.330)

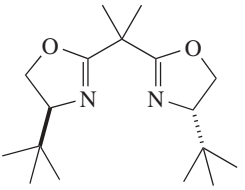
Anhydrous magnesium iodide (MgI_2) has been shown to be an effective promoter of homo $3+2$ dipolar cycloadditions of nitrones with 1,1-cyclopropane diesters. In almost all cases the products, tetrahydro-1,2-oxazines, are formed in excellent yields (854). Lewis acids assist ring opening by stabilizing the malonate anion. The low *cis/trans* diastereoselectivity (but high enantioselectivity) is in contrast to the *cis*-selectivity on using achiral $Yb(OTf)_3$. (852), It suggests



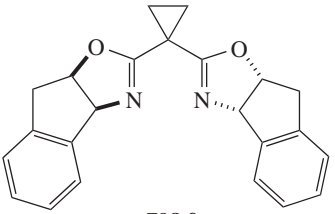
795 **796** **797**



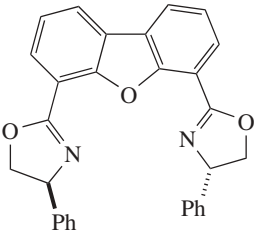
798 **a** R^1 = *i*-Pr; R^2 = H
b R^1 = *i*-Pr; R^2 = H
c R^1 = Ph; R^2 = H
d R^1 = R^2 = H



798 e



798 f



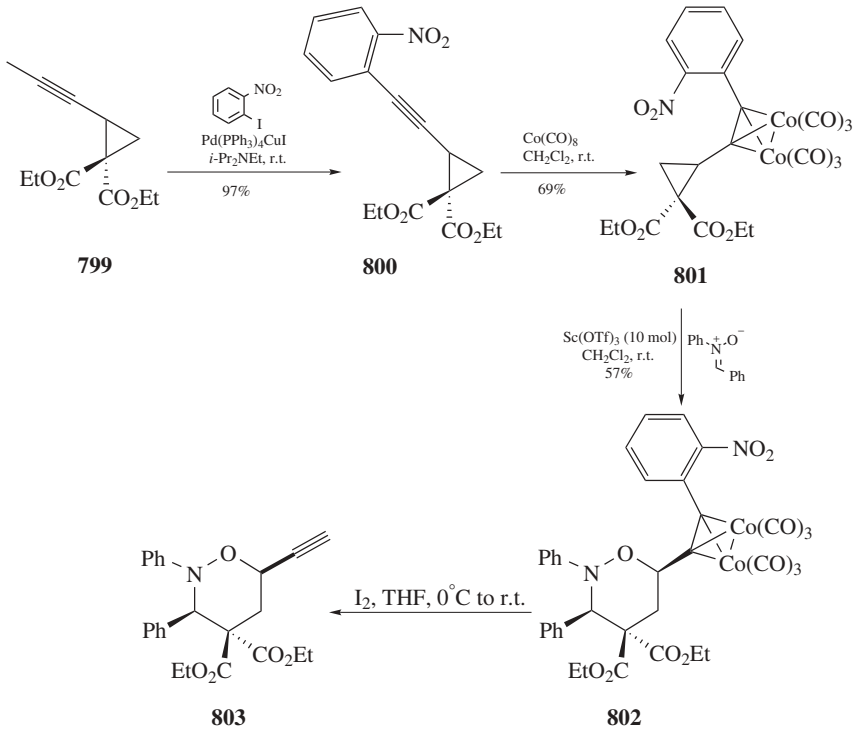
798 g

Entry	Lewis acid	Ligand **798**	time/days	Yield (%)[a]	ee (%)[b]
1	$Yb(OTf)_3$	**a**	3	50	28
2	$Yb(OTf)_3$	**b**	6	90	10
3	$Yb(OTf)_3$	**c**	3	76	02
4	$Yb(OTf)_3$	**d**	3	87	18
5	$Cu(OTf)_2$	**e**	7	-	-
6	$Cu(OTf)_2$	**f**	6	47	37
7	MgI_2	**f**	6	75	34
8	$Ni(ClO_4)_2$	**g**	2	96	89
9[c]	$Ni(ClO_4)_2$	**g**	2	51	89
10[d]	$Ni(ClO_4)_2$	**g**	2	88	90

[a] Isolated yield
[b] Determined by chiral HPLC
[c] No MS 4 Å
[d] THF as a solvent with MS

Scheme 2.331

that capture of the zwitterion by the nitrone occurs stepwise (855). Comparative analysis of chiral catalysts (CLA) in enantioselective addition of nitrone (**796**) to 1,1-cyclopropane diesters (**795**) has been made (855). Reactions with ytterbium triflate as a Lewis acid, and of a variety ligands led to low enantioselectivity



Scheme 2.332

in the tetrahydro-1,2-oxazine products (**797**) (entries 1-4). The use of bisoxazoline ligands (**798e**) and (**798f**) with $Cu(OTf)_2$ and MgI_2 was also ineffective (entries 5-7). The chiral Lewis acid system, derived from nickel perchlorate and ligand (**798 g**), proved to be very effective (96% yield, > 80% ee, entry 8). Molecular sieves were important for obtaining good yields (entry 9). THF as a solvent also gave good results, as long as molecular sieves were included (entry 10) (Scheme 2.331) (855).

The cyclopropane diester (**800**) bearing a vicinal acetylenic moiety, when treated with $Co_2(CO)_8$, affords the formation of the dicobalt hexacarbonyl complex (**801**). It undergoes a smooth cycloaddition with α,*N*-diphenylnitrone, in the presence of $Sc(OTf)_3$, to form the corresponding dicobalt hexacarbonyl complex of tetraydro-1,2-oxazine (**802**). De-complexation of adduct (**802**) gives 6-ethynyltetrahydro-1,2-oxazine (**803**) (Scheme 2.332) (856).

2.12. CONCLUSION

The analysis of the literature on nitrone chemistry shows that these organic compounds are still of special interest for researchers due to their diversity in chemical

properties and synthetic utility. Because of their electronic structure, nitrones are able to react with electrophilic, nucleophilic and radical reagents in addition and substitution reactions. Also, they are used as dipoles in various cycloaddition reactions and are easily subject to various rearrangements, for example, on light exposure. The readiness of nitrones to undergo oxidation and reduction reactions enables their use in chemical or electrochemical oxidative-reductive activations, using a large number of reagents. As a consequence, the range of chemical transformations increases. All this allows us to view nitrones as interesting and promising compounds for fundamental studies and as useful building blocks in various synthetic strategies.

The ability of nitrones to enter 1,3-dipolar cycloadditions seems to be the most useful aspect of their chemistry. There is a great deal of literature concerning this reaction (see[1]) and a high intensity of studies in this area (Section 2.8; ref.: 703–840). This branch of nitrone chemistry is certainly one of the highly developed and widely used aspects, due to its application in molecular design and planned syntheses of various compounds, including a great number of nitrogen-containing heterocyclic natural products.

Great attention has been drawn to the reactions of nucleophilic addition, which allow the syntheses of a whole range of derivatives from hydroxylamines, amines and stable nitroxyl radicals when other ways are unsuccessful. These and many other aspects of nitrone chemistry, including the newly emerging ones, such as electrophilic substitution at α-C via the formation of dipole-stabilized carbanions, and oxidative activation of nucleophilic substitution by generating radical cations (Section 2.6.3), allow one to arrive at the conclusion that nitrone chemistry has not yet been studied in depth. The wide range of nitrone chemistry shows no signs of having reached its limits, and we fully expect new and novel applications to appear in the future.

2.13. ACKNOWLEDGMENT

The author expresses his gratitude to Dr. Nataliya Tkacheva for informative support of this work; Elena Tapilina for translating the original into English; Tatyana Mitereva for drawing illustrative schemes, figures, and tables; Henry Feuer whose careful and gifted editing skills made this book better. My particular thanks are due to all contributors, whose names are mentioned in the references for their invaluable contributions, which made all of this possible.

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3 Nitronates

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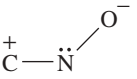
3.1. INTRODUCTION

Aliphatic nitro compounds (AN) are readily available and exhibit various reactivities due to which they have found wide use in organic synthesis (1–4).

A detailed consideration of this problem could be the subject of several monographs. Here, we briefly discuss quite another aspect. There are several reasons for which such different derivatives as nitrile oxides, nitrones, and nitronates are compiled in this monograph.

First, all these classes of compounds are 1,3-dipoles, that is, they serve as the starting reagents in 1,3-dipolar cycloaddition reactions, which can be considered as a modern powerful method for the synthesis of various heterocyclic and polyfunctional compounds (5). All three dipoles have the common reactive fragment:



And consequently, all three dipoles generate derivatives of the same heterocyclic system, viz., isoxazoles, in the reactions with C,C multiple bonds.

It is also worthy of note that all three 1,3-dipoles can readily be generated from AN.

Actually, nitronates are the closest related derivatives of nitronic acids, that is, aci forms of AN, which exist in labile equilibrium with "true" AN. Some derivatives of nitronic acids, $-CH{=}N(O)OX$, where OX is the good leaving group, are evident intermediates in the most well-developed procedures for the synthesis of nitrile oxides from primary AN. In this chapter, special emphasis is given to particular nitronates, which are generated from α-functionalized AN and can also be considered as precursors of α-functionalized nitrile oxides.

Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis: Novel Strategies in Synthesis, Second Edition, By Henry Feuer
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One of the processes most generally used for the synthesis of nitrones is based on reduction of AN to hydroxylamines followed by oxidation of the resulting intermediates. In this process, the nitrogen atom of the nitro group remains in the target nitrones. Another possible approach to the synthesis of nitrones from AN, which involves the replacement of the nitrogen atom that is present in AN, will be described later in this chapter.

Therefore, AN can be considered as convenient nearest precursors of nitrile oxides, nitrones, and nitronates.

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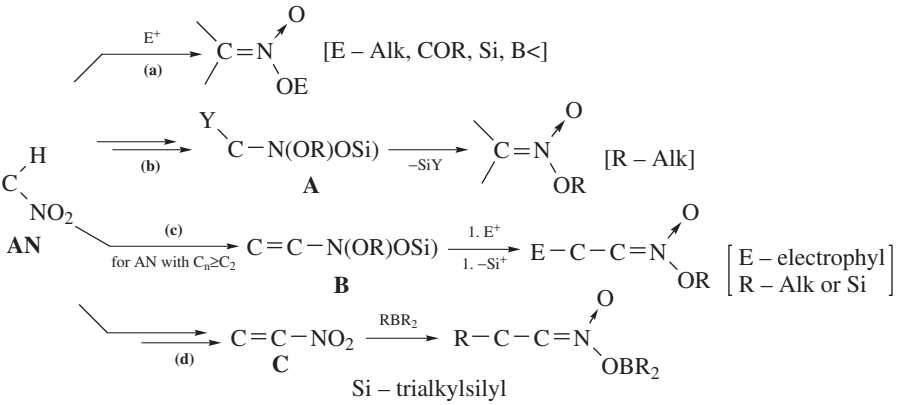
3.2. SYNTHESIS OF NITRONATES

Four general approaches to the synthesis of nitronates from AN are known (Scheme 3.1).

The first most commonly used approach (path ***a***) involves the direct interaction of AN with electrophilic reagents. In this case, the most fundamental property of AN, that is, their ability to act as ambident nucleophiles in organic reactions, is exploited. To synthesize nitronates, it is necessary that AN behave



Scheme 3.1

as O-nucleophiles. (It should be noted that AN, on the contrary, should act as C-nucleophiles in C,C-coupling reactions, such as Henry or Michael reactions, which are most important in the chemistry of AN.)

The second method (path ***b***) involves the initial transformation of AN into nitroso acetals **A** containing the good leaving group **Y** followed by 1,3-elimination of the *SiY* fragment from the above mentioned intermediate to form the target nitronates. The use of this method in the synthesis of only five-membered cyclic nitronates has been documented (see Section 3.2.1.2.1.2). However, there are no obvious obstacles to the extension of the scope of this method.

The third approach (path ***c***) requires that a chain containing at least two carbon atoms be present in AN. As a rule, AN can be smoothly transformed into ene nitroso acetals **B**, which (like standard enamines) can react with electrophiles to give the target nitronates through elimination of the Si^+ fragment (for more details, see Section 3.5.4).

Finally, the fourth approach (path ***d***) involves the generation of conjugated nitro olefins **C** from the starting AN by known methods. The latter are involved in the conjugated [1,4]-addition to give target nitronates. This process is of most importance for the synthesis of six-membered cyclic nitronates (see Section 3.2.1.2.2). This method was also used to prepare a small series of boryl-, silyl- and acyl nitronates (see Sections 3.2.3 and 3.2.4). It is beyond reason to believe that all possibilities of the approach (***d***) are exhausted by these examples.

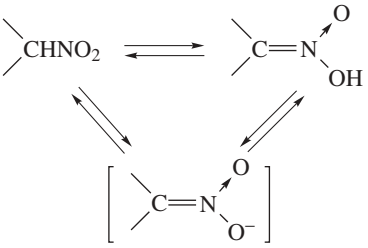
3.2.1. Synthesis of Acyclic Alkyl Nitronates

All four approaches to the synthesis of nitronates presented in Scheme 3.1 were used in one way or another for the preparation of target derivatives and will be considered in more detail in the corresponding subsections.

Nowadays the main method for the synthesis of alkyl nitronates is based on alkylation of the corresponding AN.

3.2.1.1. Alkylation of Nitro Compounds In solution, AN exist in labile equilibrium (the so-called Hantzsch triangle, Scheme 3.2) (1).

The synthesis of nitronates involves coordination of an electrophile (E) at the oxygen atom of any component of the Hantzsch triangle. If AN or aci-AN



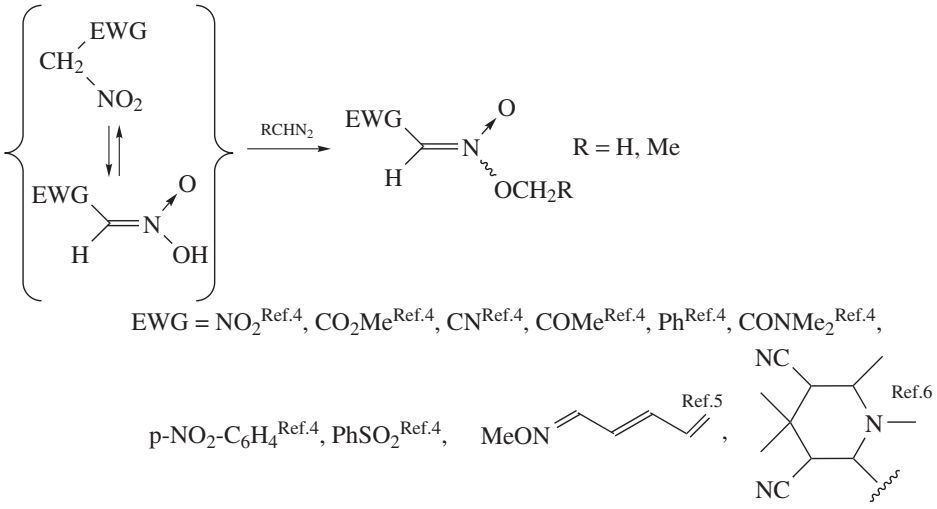
Scheme 3.2

and E^+ are involved in the reaction, it is necessary to perform deprotonation of the resulting cationic intermediate. If the third component of the triangle, the anion, reacts with the neutral molecule of the electrophile E–X, elimination of the leaving group X^- from the coupling product is required to complete the synthesis.

The relationships between the components of the Hantzsch triangle were considered in-depth in the monograph 2 and references therein. Although the problem of reactivity of ambident substrates has been studied over many years and from different points of view, the complexity of the starting system and its numerous reaction pathways do not allow one to reliably predict the results of O-alkylation in each particular case, because it is necessary to take into account the rates of numerous reversible and irreversible processes as well as the thermodynamic factors responsible for the position of the equilibrium; it is necessary to take solvent effects into consideration when estimating the thermodynamic factors. All accumulated observations are approximated by several empirical rules included in monographs 2 and 3.

Diazo compounds and oxonium salts are the most efficient alkylating agents in the synthesis of alkyl nitronates. It is assumed that diazo compounds are inserted into the O–H bond in the aci forms of the corresponding AN, whereas oxonium salts generally react with AN anions.

3.2.1.1.1. Alkylation with Diazo Compounds Diazomethane or diazoethane are commonly used as diazo compounds. The reactions of these alkylating agents proceed smoothly only with AN containing electron-withdrawing groups (EWG) adjacent to the α-C atom (4–6) (Scheme 3.3).



Scheme 3.3

These reactions produce mixtures of stereoisomeric nitronates, in which the isomer ratio varies in a wide range depending on the structure of the starting AN, the reaction conditions, and the nature of the diazo compound used.

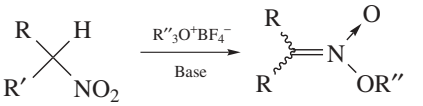
3.2.1.1.2. Alkylation with Oxonium Salts Oxonium salts are the most efficient alkylating agents and can react with both activated and nonactivated AN, including nitromethane and 2-nitropropane (Scheme 3.4).

These reactions also produce mixtures of stereoisomeric nitronates, in which the isomer ratio varies in a wide range (4, 7–9).

The starting trialkyloxonium salts can be rather simply prepared from the corresponding dialkyl ethers. However, only trimethyl-and triethyloxonium borofluorides have been used in the synthesis of nitronates to prepare O-methyl and O-ethyl nitronates, respectively.

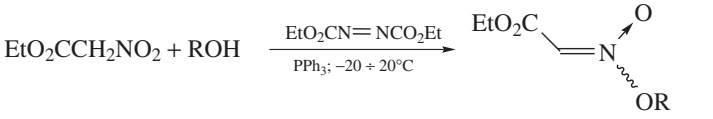
3.2.1.1.3. Use of other Alkylating Agents Rather recently, a procedure has been developed for the preparation of alkyl nitronates containing various substituents adjacent to the oxygen atom under mild conditions with the use of the corresponding alcohols as the alkylating agents (Mitsunobu reaction (10, 11)). Unfortunately, for now, the efficiency of this method in the synthesis of alkyl nitronates has been demonstrated only for nitroacetate derivatives (Scheme 3.5).

Conventional alkylating agents (alkyl halides, sulfates, etc.) are rather rarely used in the synthesis of alkyl nitronates. This is associated with relatively low reactivity of these compounds which, combined with low thermal stability of nitronates (for more details, see Section 3.3.1.1), does not allow one to isolate target products in the individual state.



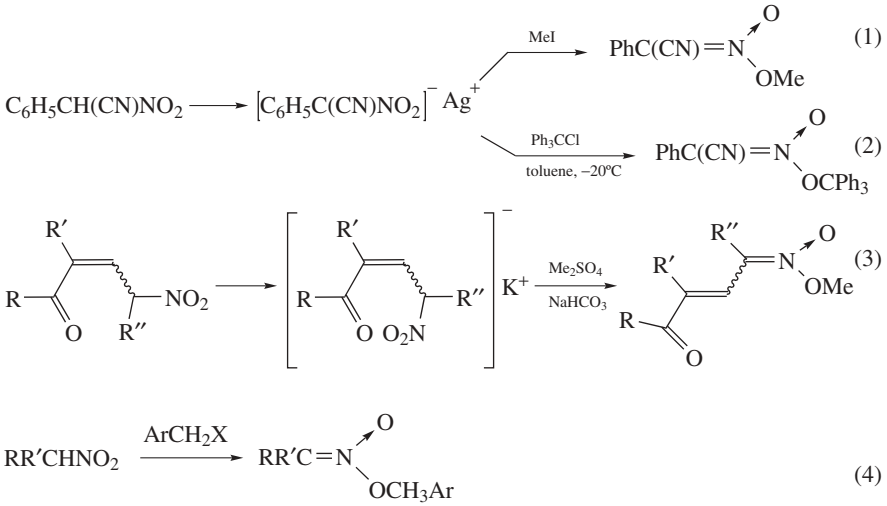
R = R′ = H, R″ = Et[Ref.6]; R = H, R′ = $(CH_2)_3NO_2$, R″ = Et[Ref.7]; R = H, R′ = Alkyl, EWG, R″ = Et[Ref.4]; R = H or Alkyl, R″ = Et[Ref.8]

Scheme 3.4

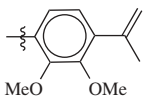


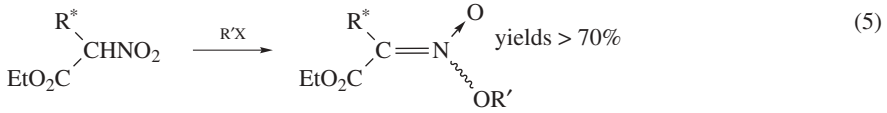
R = Me (82%)[Ref.10]; $C_6H_5CH_2CH_2$ (27%)[Ref.11]; n-$C_{14}H_{29}$ (19%)[Ref.11]

Scheme 3.5



R = H, R′ = CO_2Me, Ar = Ph, X = Br [$KHCO_3$/Et_3BzN, DMF, 60°C, yield 70%]

R = R′ = Me, Ar =  [Na/EtOH, 20°C]



R^* – enantiopure fragment

R′X – MeI, EtI, n-BuBr ,n-PrBr, n-$C_{12}H_{25}Br$, BzCl

Scheme 3.6

However, there are examples of the successful use of intermolecular alkylation of AN with these reagents (Scheme 3.6) (for intramolecular alkylation of AN, see Section 3.2.2).

Successful O-alkylation of the Ag salt of phenylnitroacetonitrile with CH_3I (12) and triphenylchloromethane (13) was documented (Scheme 3.6, Eqs 1 and 2).

Severin and coworkers advantageously used dimethyl sulfate for the preparation of O-methyl nitronates from a representative series of conjugated vinyl ketones containing the nitro group in the allylic position (14) (Scheme 3.6, Eq. 3).

It was demonstrated that benzyl halides can smoothly alkylate salts of particular primary (15) and secondary (16) AN (Scheme 3.6, Eq. 4).

Studies performed by Chinese researchers are of most interest in the context of the problem under consideration. In these studies, various alkylating agents were efficiently used in the synthesis of enantiomerically pure nitronates and ethyl nitroacetate derivatives (17) (Scheme 3.6, Eq. 5).

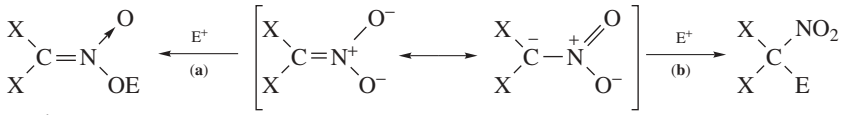
It should be noted that the configuration of the C=N bond in most of the above considered nitronates, which were prepared from AN RR'CHNO$_2$ (R≠R'), was not determined.

3.2.1.1.4. Acyclic Nitronates Derived from Polynitro Compounds Since AN anions are ambident, alkylation can occur either at the oxygen atom of the nitro group to form target nitronates (Scheme 3.7, path ***a***) or at the carbon atom bearing the nitro group (Scheme 3.7, path ***b***). This process is undesirable in the synthesis of nitronates although, at the same time, it provides the basis of the synthetically important Henry, Michael, and Mannich reactions involving analogous AN.

The introduction of powerful electron-withdrawing substituents (NO$_2$, CN, a polynitrogen heterocycle) at the α-C atom of AN stabilize anions of AN, thus facilitating their generation. At the same time, stabilization of anions of AN leads to a decrease in their reactivity and such anions act as milder nucleophilic agents. It will be seen from the following that this leads to an increase in the contribution of C-alkylation.

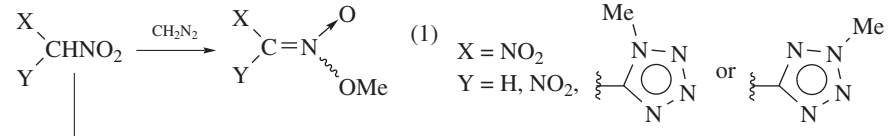
Here, the term polynitro compounds refers to AN in which the α-C atom contains at least two nitro groups. Scheme 3.8 presents data on their successful *O*-alkylation.

For example, the use of diazomethane makes it possible to synthesize the corresponding *O*-methyl nitronates from dinitromethane (18), trinitromethane (19), and two isomeric *N*-methyltetrazolyldinitromethanes (20) (Scheme 3.8, Eq. 1)



X – H, or power EWG (NO$_2$, CN, N-(alkyl)-tetrazolyl)

Scheme 3.7



Scheme 3.8

It should be noted that in the latter case, stereoisomers of O-nitronates were isolated and identified (20).

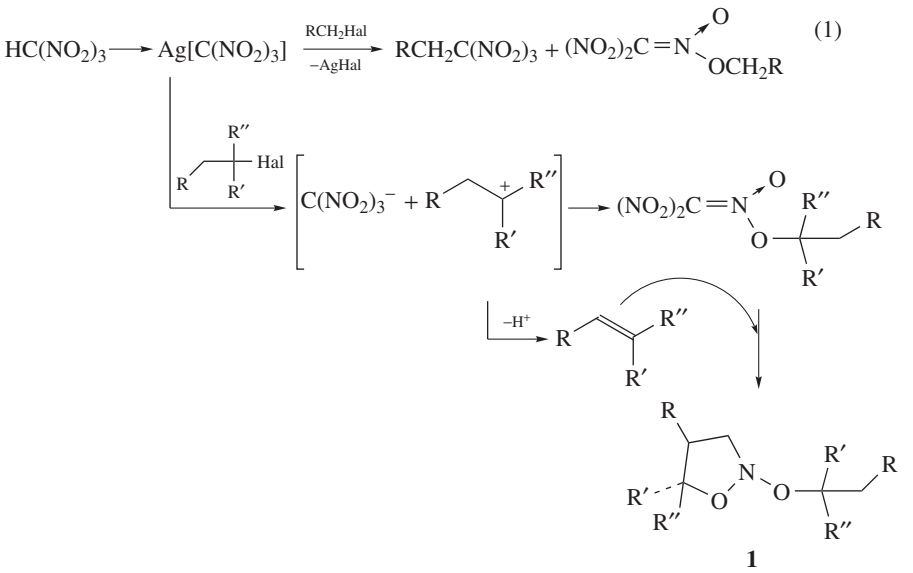
In reactions of certain alkyl halides with salts of polynitromethanes, C-alkylation can also be diminished and target *O*-nitronates can be prepared in satisfactory yields (21, 22) (Scheme 3.8, Eq. 2). Of special note is the study by Kim and Adolph (22), who prepared numerous nitronates by alkylation of salts of dinitromethane, cyanodinitromethane, and trinitromethane with a representative series of α-chloro-substituted (including functionalized) ethers.

Very interesting results were obtained by Russian researchers in alkylation of the Ag salt of trinitromethane with alkyl halides (Scheme 3.9) (23–25).

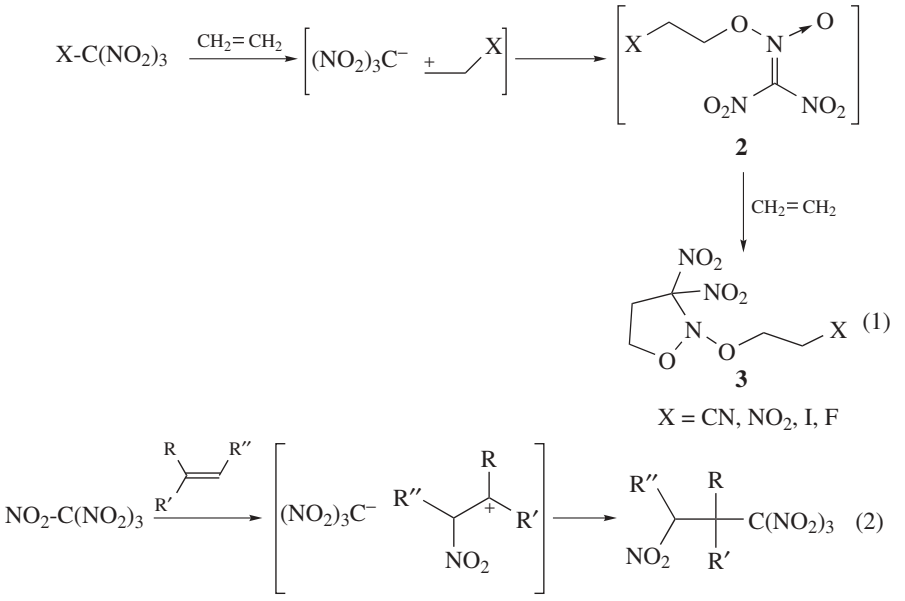
Both C-alkylation products and the corresponding *O*-alkyl nitronates were detected in the reaction mixture prepared by the reactions of above mentioned salt with primary alkyl halides (Scheme 3.9, Eq. 1). However, isoxazolidines (**1**) are the main identified products of the reactions with secondary or tertiary alkyl halides. The possible pathway of their formation is shown in Scheme 3.9. Here, the key event is generation of the corresponding olefins from alkyl halides. These olefins can be trapped with *O*-nitronates that are simultaneously formed in [3 + 2]-cycloaddition reactions. Presumably, these olefins are generated through deprotonation of stabilized cationic intermediates (see Scheme 3.9).

In this manner, the Ag salt of trinitromethane is involved in cascade reactions with branched alkyl halides to give unexpected products.

Equally interesting processes occur in the reactions of tetranitromethane and some of its derivatives with olefins (Scheme 3.10).



Scheme 3.9



Scheme 3.10

Tetranitromethane (X=NO_2) acts as an electrophile toward olefins to give the corresponding ion pairs. Their further behavior depends on the nature of olefin. In the case of ethylene (26, 27), allyl ethers (28), and other monosubstituted alkenes (29–31), nitronates (**2**) that are generated through C,O-coupling of preceding ionic intermediates are involved in [3 + 2]-addition reactions with olefins that are present in the reaction mixture to give isoxazolidines (**3**) in moderate yields (Eq. 1). (Rather large amounts of intermediate nitronates (**2**) can be detected in reaction mixtures prepared with the use of particular branched olefins (30) or dienes (28).)

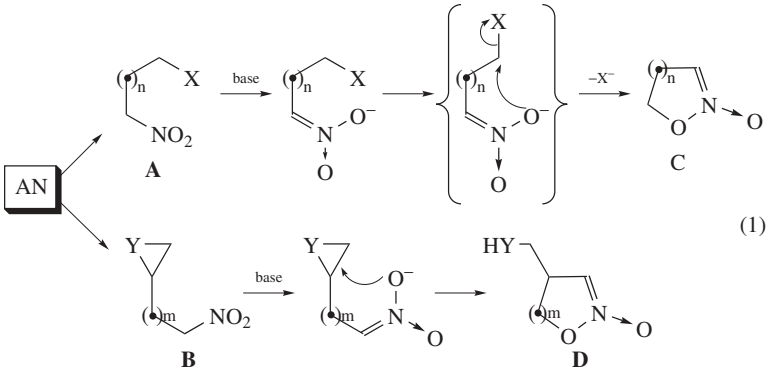
To the contrary, only C-alkylation of the trinitromethane anion with these intermediates is observed (32, 33) if the cations in the ion pair are stabilized by one or two alkyl substituents at the α-carbon atom (Eq. 2).

Other trinitromethane derivatives (X=CN (34), I (35), or F (36)) are involved in analogous processes.

3.2.2. Synthesis of Cyclic Nitronates

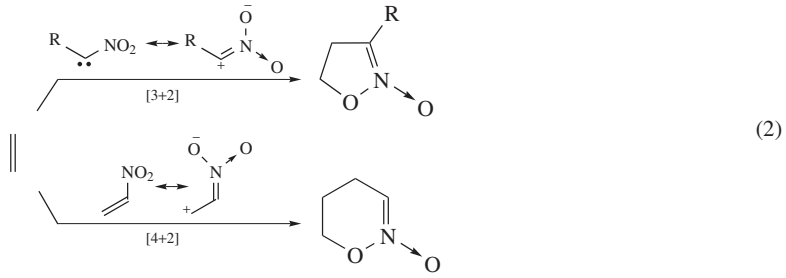
Five- and six-membered cyclic nitronates are generally considered as cyclic nitronates. Scheme 3.11 presents two most general approaches to the synthesis of such compounds.

One of these methods involves intramolecular cyclization of specially prepared precursors **A** or **B** (Eq. 1). These precursors can be synthesized from readily available AN by classical reactions, many of which will be considered in detail below.



(1)

for **A, C** : n = 1, 2; X = I, Br, Cl, NO_2, OTs, OH, SR_2; for **B, D** : m = 1, 2; Y = O, NR



(2)

Scheme 3.11

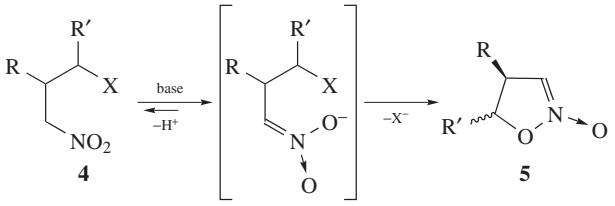
Cyclization of **A** and **B** occurs under the action of bases, whose function is to generate stabilized α-nitro carbanions from the starting AN by well-known reactions, and these carbanions push out the leaving group X^- from substrates **A** or break the strained **C–Y** bond in substrates **B** to form the target cyclic nitronates **C** or **D**, respectively. Evidently, both reactions generally proceed by the S_{N2} mechanism. Intramolecular C,C cyclization of precursors to form the corresponding nitrated carbocycles should be discussed as the main side process.

Another approach to the synthesis of cyclic nitronates is based on cycloaddition reactions (Scheme 3.11, Eq. 2), where two bonds (C–C and C–O) are simultaneously formed. This strategy allows one to perform stereoselective processes with the use of very simple precursors. However, this approach to the synthesis of five-membered cyclic nitronates implies that reactive and very unstable nitrocarbenes are involved in the process.

The synthesis of both five- and six-membered cyclic nitronates have specific features and, hence, these approaches will be considered separately.

3.2.2.1. Synthesis of Five-membered Cyclic Nitronates

3.2.2.1.1. Intramolecular Cyclization of γ-Functionalized AN The most commonly used procedure for the synthesis of five-membered cyclic nitronates (**5**) is



base: AlkONa/AlkOH; AcONa/EtOH; AcONa/DMF;K_2CO_3/THF; NH_3/EtOH; Et_3N; Et_2NH; pyridine; imidazole; DBU/CH_2CL_2; Zn–glycine/DMSO; X – NO_2; Cl; Br; I; OTs; SMe_2; $SeMe_2$

Scheme 3.12

based on intramolecular cyclization of the corresponding primary or secondary AN (**4**) containing a good leaving group **X** in the γ-position (Scheme 3.12).

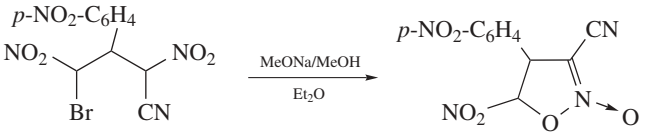
Until recently, this method has been the only synthetically significant method for the preparation of target nitronates (**5**).

The starting functionalized AN (**4**) are rather readily available although the general strategy for their synthesis is lacking. Cyclization occurs through α-nitro carbanions, which are, as a rule, generated in the presence of bases, such as solutions of metal alkoxides in alcohols (sodium ethoxide in ethanol (37), sodium methoxide in methanol (38, 39)), sodium acetate in ethanol (40) or dimethylformamide (DMF) (41), K_2CO_3 in tetrahydrofuran (THF) (42), ammonia in ethanol (43, 44), and various amines (triethylamine (45), diethylamine (46), pyridine (47), or imidazole (48)). Evidently, 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) in aprotic solvents is one of the most efficient catalysts (49). In the presence of the latter, the reaction is completed within a few minutes to give target nitronates in high yield, and even unstable nitronates (**5**) unsubstituted at the C-3 atom can be detected (49). A zinc complex with glycine (10% mol) is very efficient as the catalyst (50).

Cyclization of salts of 1,1-dinitro compounds containing good leaving groups **X** at C-3 can be performed in aqueous or alcoholic solutions in the absence of basic catalysts (51, 52).

In this process, the nitro group (38, 41, 43, 46, 50, 53–56), Cl (37, 42, 49, 52, 57), Br (39, 40, 45, 47, 48, 51), I (49), the tosyl or mesyl radicals (48), as well as neutral Me_2S (58–62) and Me_2Se (63) molecules are generally used as the leaving group (**X**). The relative rates of the intramolecular replacement of various leaving groups **X** by α-nitro carbanions have not been studied systematically. However, it can be concluded that elimination of the Br^- anion occurs faster than elimination of the nitrite anion (39) (Scheme 3.13).

In some cases, the reaction (**4**→**5**) can be combined with the synthesis of starting AN (**4**) from simpler molecules. As mentioned above, there are no general methods for the synthesis of AN (**4**). Several most commonly used schemes for the synthesis of functionalized AN (**4**) are given below (most often, there are cascade reactions).



Scheme 3.13

In some cases, five-membered cyclic nitronates can be prepared by the chemoselective replacement of one of two different halogen atoms in 1,3-dihalopropanes (**6**) by the nitro group followed by intramolecular O-alkylation of the resulting intermediates (Scheme 3.14, Eq. 1).

Another approach is based on the Henry condensation of activated primary AN (**7**) with aldehydes followed by dehydration and addition of the second molecule (**7**) to the resulting Michael substrate (Scheme 3.14, Eq. 2). This process is particularly convenient for the synthesis of five-membered cyclic nitronates (**5**) containing identical functional groups at the C-3 and C-5 atoms.

The third strategy for the synthesis of (**5**) involves the Michael addition of primary AN (**8**) to conjugated α-halo-enones followed by cyclization of the resulting intermediates (Scheme 3.14, Eq. 3).

Yet another approach to the synthesis of five-membered cyclic nitronates (**5**) is based on the Henry condensation of α-halo-substituted aldehydes (**9**) with primary AN followed by cyclization of nitroaldols (Scheme 3.14, Eq. 4) to give five-membered nitronates containing the hydroxy group at the C-4 atom.

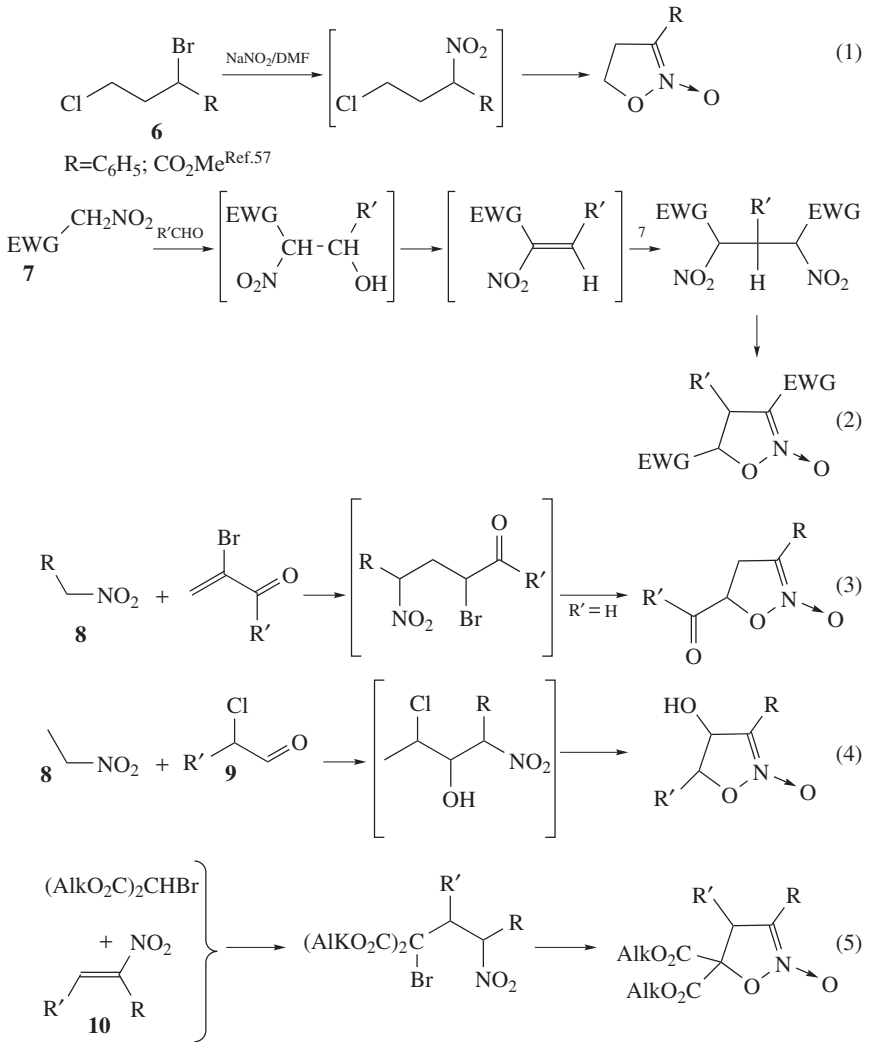
Finally, Scheme 3.14 presents the Michael addition of bromomalonic ester to conjugated nitro olefins **10**. This approach allows one to synthesize five-membered cyclic nitronates (**5**) doubly functionalized at the C-5 atom (Scheme 3.14, Eq. 5).

In the synthesis of nitronates (**5**), longer reaction sequences can also be successfully used. For example, Scheme 3.15 presents the synthesis of trisubstituted nitronates (**5**) from functionalized primary AN (**11**) (exemplified by methyl nitroacetate) and alkyl iodides RCH_2I (56).

The reaction requires an excess of (**11**) and proceeds through intermediate acyclic alkyl nitronates **A**. Thermal decomposition of the latter affords aldehydes RCHO, whose condensation with the starting nitro compounds (**11**) (cf. Eq. 2 in Scheme 3.14) gives target cyclic nitronates (**5**) in 35% to 45% yield. In spite of the fact that the starting compounds **11** are readily available, the evident drawback of this strategy (the use of a large excess of **AN 11**) seems to be not as strong.

In all the above examples, the synthesis of nitronates (**5**) is rather chemoselective. In any case, data on the formation of their structural isomers, viz, the corresponding nitrocyclopropanes (**13**), are lacking. However, the synthesis of five-membered nitronates (**5**) with the use of sulfur or selenium ylides is not chemoselective (see Scheme 3.16).

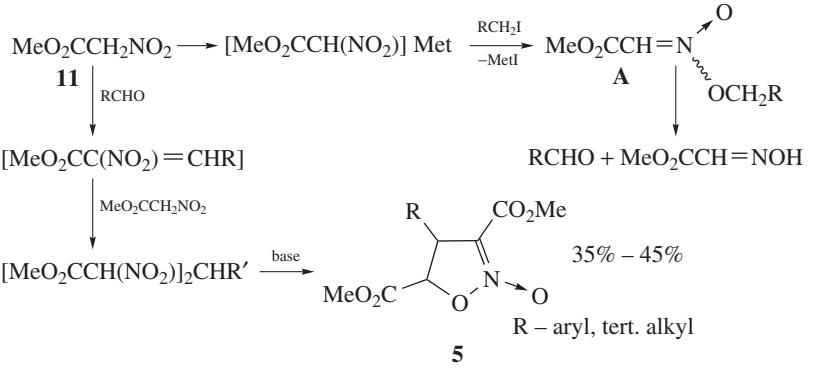
Nitronates (**5**) can be synthesized by the Michael addition of *in situ* generated sulfur or selenium ylides (**12**) (58–60, 62, 63) to conjugated nitroalkenes



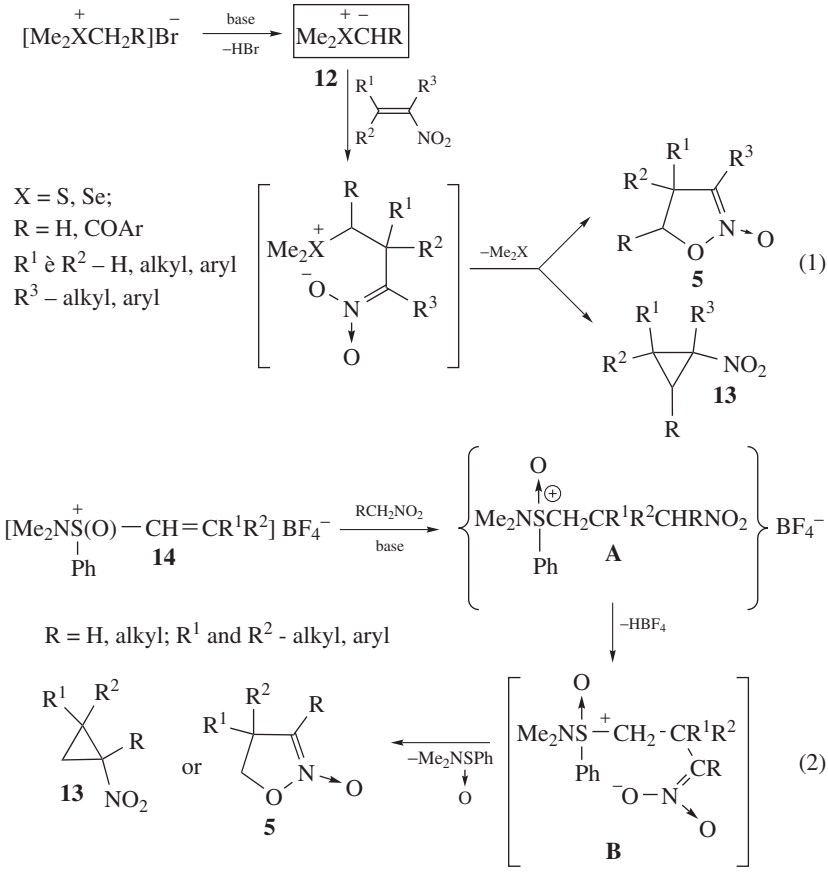
Scheme 3.14

followed by elimination of dimethyl sulfide (or selenide), but this process gives a mixture of target nitronates (**5**) and nitrocyclopropanes (**13**) (Eq. 1). For sulfur ylides, the ratio of structural isomers **5:13** drastically depends on the nature of substituents in both reacting substrates and cannot be predicted in advance. By contrast, selenium ylides give only nitronates (**5**) (63), but operations with selenium derivatives cause inconveniences. There are data, although scarce, on possibility of the chemoselective synthesis with the use of sulfur ylides (58).

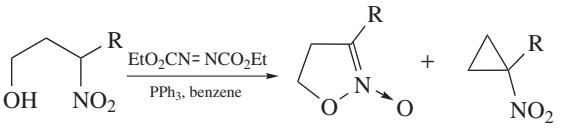
There is also another approach to the use of sulfur ylides in the synthesis of cyclic nitronates (**5**) (see Eq. 2 Ref. 61). Salts (**14**) as Michael substrates add



Scheme 3.15



Scheme 3.16



5 **13**

R = Ph (yield for **5** = 98%); SO_2Ph (yield for **5** = 15%; for **13** = 82%)

Scheme 3.17

primary AN RCH_2NO_2 to give *in situ* ylides **A**, which undergo cyclization to the corresponding nitronates **5**. The chemoselectivity of this reaction is also low and it is accompanied by generation of isomeric cyclopropanes (**13**).

The process shown in Scheme 3.16 is rather interesting. It should be noted that in most cases this reaction is very stereoselective with respect to the arrangement of the substituents at C-4 and C-5 atoms. In light of recent data on the possible isomerization of nitrocyclopropanes (**13**) to form five-membered cyclic nitronates (**5**) (for more details, see Section 3.2.2.1.2), low chemoselectivity of many reactions involving sulfur ylides does not seem to be so fatal.

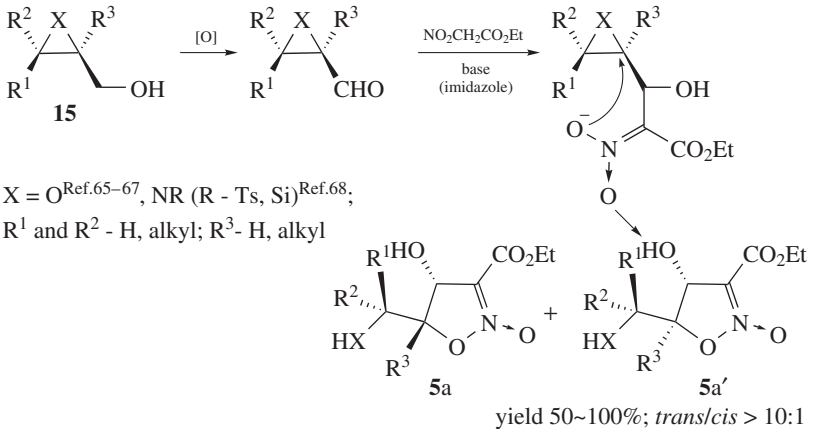
When discussing the specific features of various leaving groups in the synthesis of nitronates presented in Scheme 3.12, the possibility of the use of the OH group as the leaving group should be separately discussed. As in the synthesis of acyclic nitronates, the Mitsunobu procedure (10) is apparently suitable for intramolecular cyclization of acyclic γ-nitro alcohols (Scheme 3.17).

Unfortunately, only two attempts were made to use this approach in the synthesis of five-membered cyclic nitronates (**5**), and only one of them could be considered as successful. In the latter case, isomeric nitrocyclopropane was obtained as the major product. Only α-functionalized nitro alcohols are readily involved in the Mitsunobu cyclization. However, the possibility of isomerization of by-products, nitrocyclopropanes, which was mentioned in the discussion of Scheme 3.16, caused the revision of this process as a procedure for the synthesis of five-membered cyclic nitronates. (A new approach to the synthesis of initial γ-nitro alcohols from readily available AN was documented in Reference 64)

Recently, Italian researchers have developed a new procedure for the synthesis of five-membered cyclic nitronates with the use of enantiomerically pure epoxides (65–67) and aziridines (68) as the starting substrates (**15**) (Scheme 3.18, see also substrate **B** in Scheme 3.11, Eq. 1).

A series of enantiomerically pure stereoisomeric nitronates (**5a**) and **5a'** was successfully prepared by varying the reaction conditions (the nature of the group X, the catalyst, etc.) and using the solid-phase Merrifield synthesis (68).

In the synthesis of five-membered cyclic nitronates (**5**), the problem of stereoselectivity is in preparing these products with desired relative configurations of the stereocenters at the C-4 and C-5 atoms (see Scheme 3.12). Generally, the *trans* configuration of these substituents is most preferable. Several procedures giving exclusively this configuration were documented (see,e.g. (50, 55, 58, 63, 68)).



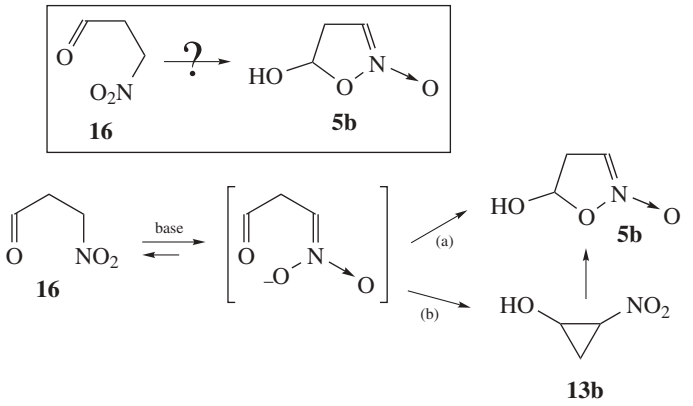
Scheme 3.18

Several studies dealt with the synthesis of enantiomerically pure nitronates (**5**) (46, 48, 50, 68). These products were isolated by sophisticated chromatographic technique. Carbohydrate derivatives are mainly used as sources of asymmetric induction.

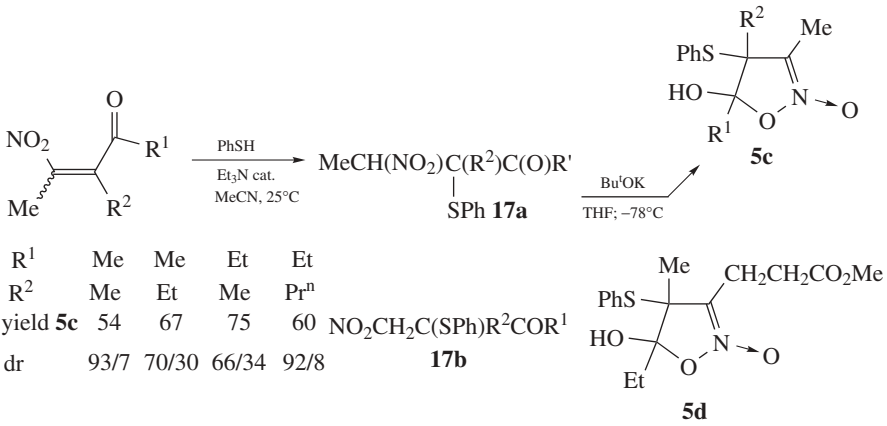
Next, we will briefly consider some intramolecular cyclization reactions, which are not described by Equation 1 in Scheme 3.11.

First, an approach based on intramolecular cyclization of readily available β-nitro ketones (**16**) (Scheme 3.19) deserves attention.

In fact, cyclization (**16**→**5b**) is an intramolecular modification of the classical Henry reaction. It should be noted that the Henry reaction generally occurs as C,C-coupling (path (b)), but the reaction can be forced to proceed by path (a) due to steric hindrance or other factors.



Scheme 3.19



Scheme 3.20

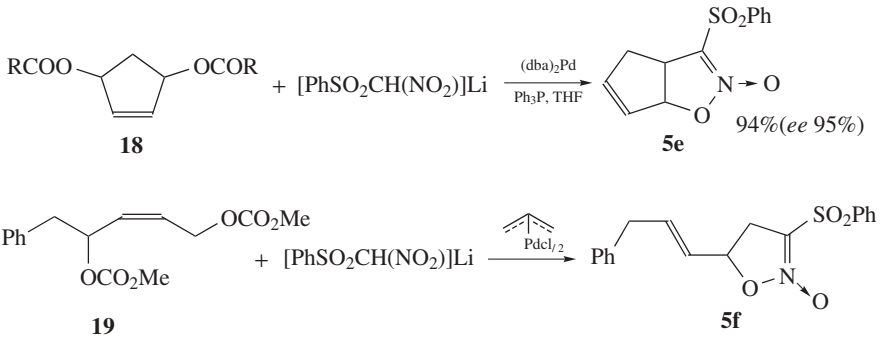
In addition, cyclopropanes (**13b**) can be subjected to isomerization to form target nitronates (**5b**) (see Section 3.2.1.2.1.2)

In spite of the obvious simplicity, this approach has not been examined in practice until recent years. In the very recent past, French researchers demonstrated that this approach can be used for the synthesis of five-membered nitronates **5c,d** starting at least from nitro ketones (**17a**) containing the PhS substituent at C-2. These ketones have been generated from the corresponding β-nitroenones (Scheme 3.20) (69).

Taking into account that nitronates (**5c,d**) have hemiacetal's fragment at the C-5 atom, it is necessary to perform their generation under very mild conditions (THF, -78°C). Nitronate (**5 d**) cannot be isolated in individual state. However, the latter compound can be detected by spectroscopic methods. Nitro ketones (**17b**) containing the $-CH_2NO_2$ fragment are recovered after attempts to perform cyclization, which can be attributed to evidence that cyclization is reversible. Finally, the role of the PhS-fragment in nitro ketone subjected to cyclization remains unclear. In other words, an interesting process presented in Schemes 3.19 and 3.20 requires a more detailed study.

In 1981, it was demonstrated (70) that anions of nitro compounds can be involved in C,C-coupling with allyl acetates at the allylic carbon atom with the use of metal complex catalysis. For many years, this observation did not come to the attention of chemists interested in the synthesis of cyclic nitronates. However, Trost demonstrated (71) that this process can be used in the synthesis of five-membered cyclic nitronates from olefins (**18**) containing two acyl groups in the different allylic positions (Scheme 3.21).

Evidently, this interesting reaction starts with coordination of Pd by the allylic fragment at the site of attachment of one of the acyloxy groups. Then the anion of the nitro compound is involved in C,C-coupling with olefin (**18**) followed by successive ionization of the nitro fragment. Finally, Pd is mediated in O,C-coupling



Scheme 3.21

of the anionic intermediate with the C,C double bond accompanied by the displacement of the second acyloxy group. Special experiments with the use of olefin (**19**) demonstrated that the reaction is regioselective, that is, the sterically least hindered acyloxy group is initially displaced. The reaction of olefin (**19**) with the involvement of Pd coordinated to enantiomerically pure ligands is highly enantioselective (ee > 97%). Therefore, this approach holds promise in the synthesis of enantiomerically pure nitronates similar to (**5f**).

Lastly, the radical inter- and intramolecular cyclizations in the presence of one-electron oxidizing agents as a procedure for the synthesis of five-membered cyclic nitronates can be considered. Radical oxidation of α-nitro ketones (**19**) in the presence of disubstituted olefins under the action of $Mn(OAc)_3$ was documented (72a) (Scheme 3.22, Eq. 1).

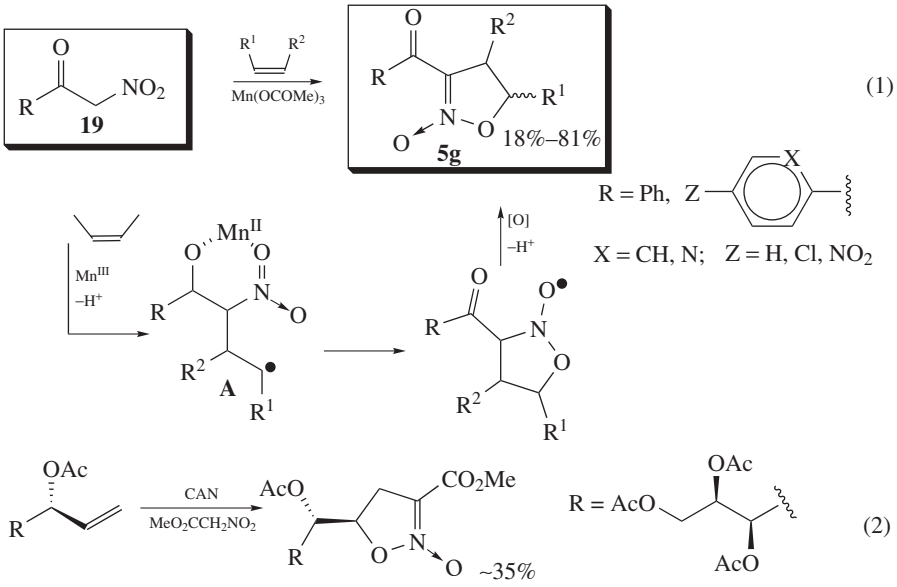
The initially formed nitronate radical reacts with olefin R′C=CR″ to give an "elongated" radical **A** whose successive cyclization and oxidation affords target nitronates (**5 g**) in 18% to 81% yields. Manganese triacetate is regenerated by electrochemical methods.

A similar process can be performed with the use of cerium ammonium nitrate (CAN) for generation of radicals from another CH acid, viz., methyl nitroacetate (72b) (Scheme 3.22, Eq. 2).

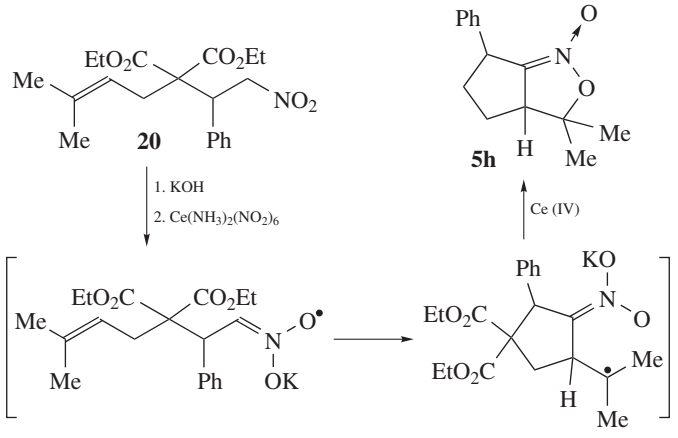
Analogous intramolecular cyclization can be carried out by performing the reaction of CAN with nitro olefin (**20**) (73) (Scheme 3.23). However, this reaction is unlikely to be useful in the synthesis of a broad range of cyclic nitronates because the starting nitro compounds (similar to (**20**)) are difficult to prepare.

3.2.2.1.2. Synthesis of Five-membered Cyclic Nitronates by Cycloaddition Reactions

[3 + 2]-Cycloaddition of Nitrocarbenes. Scheme 3.24 presents possible approaches to the synthesis of five-membered cyclic nitronates (**24**), where [3 + 2]-cycloaddition of intermediate nitrocarbenes (as dipoles **B**) to olefins as trapping agents is the key step.



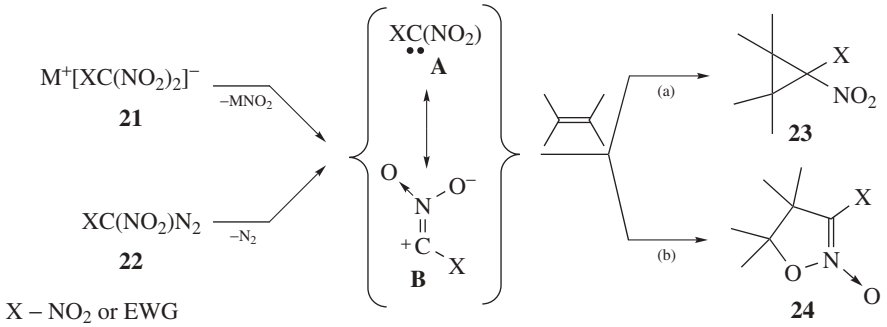
Scheme 3.22



Scheme 3.23

Target nitronates (**24**) are 1,3-dipoles and, consequently, can also be involved in [3 + 2]-cycloaddition reactions with olefins. However, it can *a priori* be expected that the rate of the second cycloaddition will be substantially lower.

Anions of polynitro compounds (**21**) or neutral nitrodiazo compounds (**22**) can be considered as possible precursors of nitrocarbenes (**A**↔**B**) by analogy with other functionalized carbenes. Nitrocarbenes can react with a double bond



Scheme 3.24

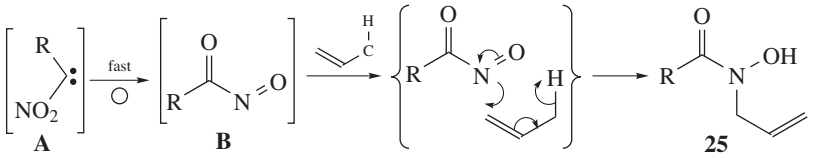
in their classical form **A** by the [1 + 2]-cycloaddition mechanism (path a) to give nitrocyclopropanes (**23**). However, we are interested in another reaction pathway, path (b), which involves the [3 + 2]-cycloaddition reaction of carbene intermediates as 1,3-dipoles **B** leading to five-membered cyclic nitronates (**24**).

It has been expected that trinitromethane derivatives of the general formula $(NO_2)_3C-M$ (M is K, Cs, $SiMe_3$, or $SnBu^n_3$) can generate dinitrocarbene through solvolysis, and the latter can react as a 1,3-dipole with some olefins (74). However, a next study (75) demonstrated that this interpretation of the processes is erroneous at least for $M{=}SiMe_3$. Attempts to detect nitrocarbenes in cycloaddition reactions during thermolysis or photolysis of aliphatic nitrodiazo compounds also failed (76).

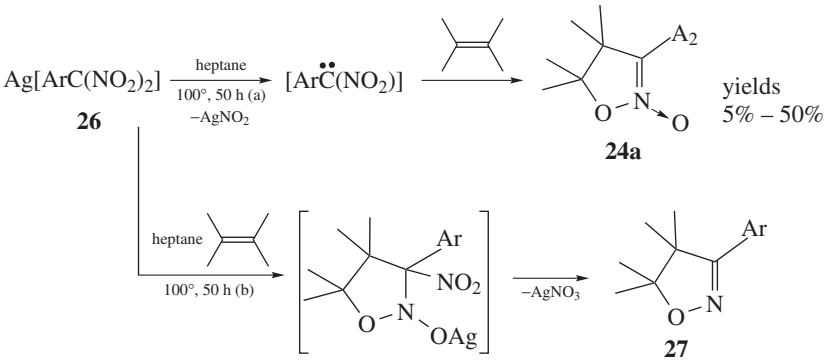
Calculations of the reactivity of model nitrocarbenes (77a) demonstrated that these species **A** much more rapidly undergo a rearrangement to give nitrosocarbonyl intermediates **B** than are involved in [3 + 2]-cycloaddition with an external trapping agent. Shortly thereafter, this fact was confirmed experimentally (77b) because, at the same time, intermediates **B** can be detected in ene reactions with certain olefins to give hydroxylamines (**25**) (Scheme 3.25).

Taken together, these facts demonstrate that the "nitrocarbene approach" to the synthesis of nitronates (**24**) cannot be considered as a promising method for their synthesis.

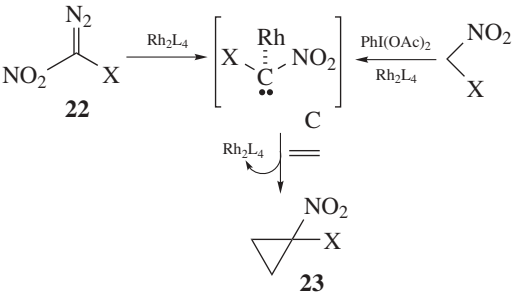
A more recent study (78) on thermolysis of silver salts of aryldinitromethanes (**26**) did not change a negative attitude toward the approach shown in Scheme 3.26, because target nitronates (**24a**) are generated in low yields and are



Scheme 3.25



Scheme 3.26



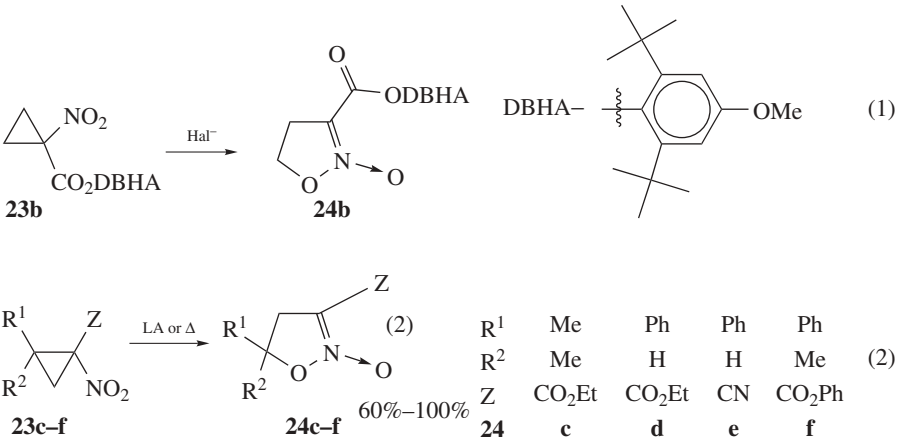
Scheme 3.27

prepared nonselective. The appearance of a noticeable amount of isoxazolines (**27**) as by-products was not adequately interpreted.

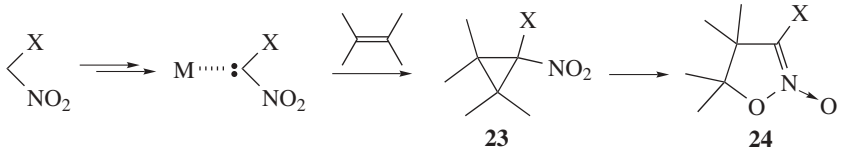
In following years, it was found that stability of nitrocarbene intermediates can be increased by their complexation with variable-valence metals (79, 80), $Rh_2(OAc)_4$ being most widely used for this purpose (Scheme 3.27).

In addition to conventional generation of carbenes from nitrodiazo compounds (**22**) (79), target intermediates **C** can be prepared by oxidation of functionalized AN CH_2XNO_2 with phenyliodonium diacetate. The reactions of Rhodium intermediates with certain olefins afford the corresponding cyclopropanes (**23**). The cycloaddition reaction was performed in the presence of a catalyst. (The successful synthesis of nitrocyclopropanes from trinitromethane derivatives and nitroacetic ester was also documented (81)).

Here, we have already noted that cyclopropanes (**23**) are structural isomers of five-membered cyclic nitronates (**24**). There was evidence that functionalized cyclopropane (**23b**) can be isomerized to give the corresponding five-membered cyclic nitronate (**24b**) under the action of halide anions (82) (Scheme 3.28, Eq. 1). Moreover, the in-depth study (79) demonstrated that the above mentioned



Scheme 3.28



Scheme 3.29

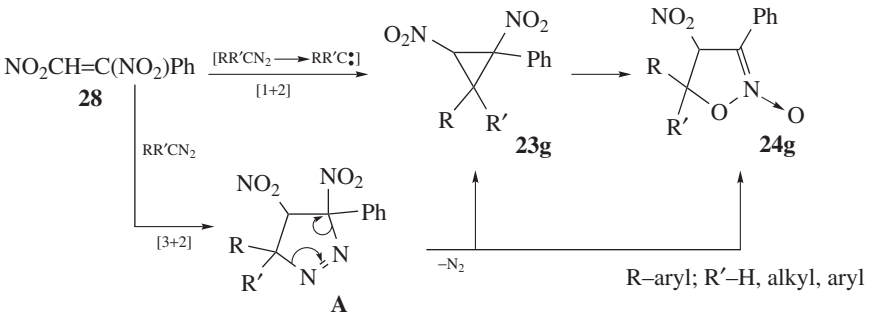
cyclopropanes (**23c–f**) presented in Scheme 3.28 undergo smooth thermal or Lewis acid catalyzed isomerization to give the corresponding nitronates (**24c–f**) (Eq. 2).

In particular, keeping cyclopropane (**23b**) in boron trifluoride etherate at 20°C leads to a quantitative isomerization to give the corresponding nitronate (**24b**).

In cyclopropane, the C,C bond between the atom bearing the nitro group and the most substituted atom of the ring is cleaved.

Therefore, all prerequisites are present for the development of a general strategy for the synthesis of nitronates (**24**) from α-functionalized primary AN through stabilized carbenium intermediates and nitrocyclopropanes (**23**). This approach allows the stereoselective synthesis of nitronates (**24**) from simple molecules (Scheme 3.29).

Cycloaddition of Carbenes to conjugated Nitro Olefins (28). From the above it is evident that there is another synthetic route to nitronates (**24 g**) with the use of carbenium intermediates based on [1 + 2]-cycloaddition of carbenes RR^1C: to conjugated nitro olefins (**28**) followed by isomerization of intermediate nitrocyclopropanes (**23 g**). However, this strategy was used only in one study (see Scheme 3.30).



Scheme 3.30

It was demonstrated (83) that the reaction of dinitrostyrenes (**28**) with aryl diazo compounds RR'CN_2 afford nitronates (**24 g**) in good yields. These products contain the nitro group at the C-4 atom in the *trans* position with respect to the substituent at C-5 (if R′=H). Since the reaction mechanism remains unknown, the direct formation of cyclic nitronates (**24 g**) from pyrazolines **A** without the intermediate formation of cyclopropanes also cannot be ruled out.

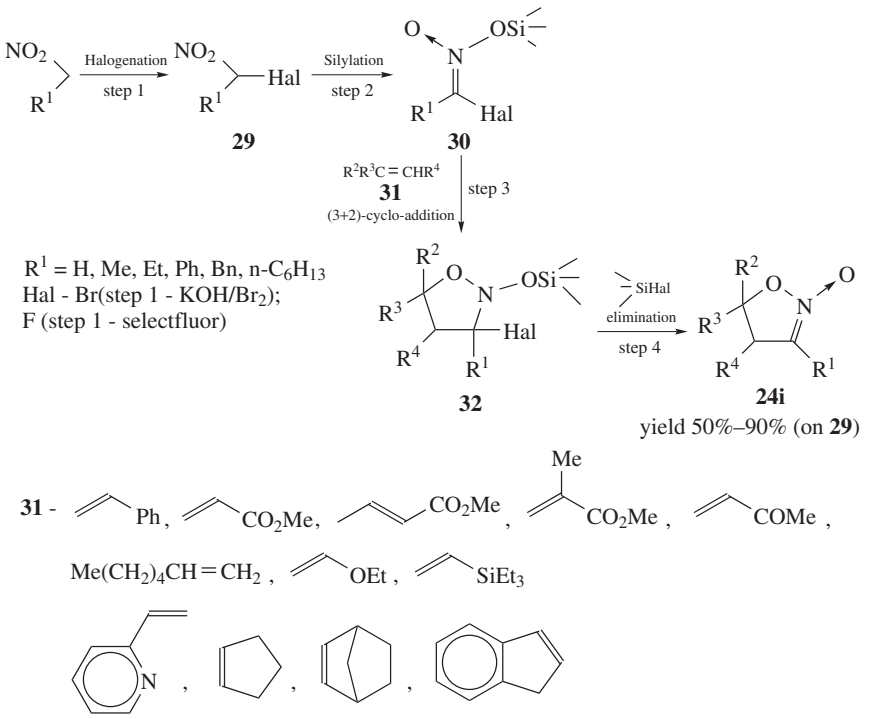
Apparently, the synthesis of 3-cyanoisoxazoline-2 N-oxide from diazomethane and cyanodinitromethane derivatives also occurs through cycloaddition of diazomethane to intermediate 1-cyano-1-nitroethylene (84).

Synthesis of Five-membered Cyclic Nitronates from α-Halogen-substituted AN. The key step of this approach is presented in Scheme 3.1, path (b). Until recently, this synthetic route to nitronates (**24**) has been of no preparative interest, because only two examples, such as elimination of trimethylsilyl nitrite (75) and 1,2-dinitrophenylethane (85) from the corresponding nitroso acetals were documented.

Recently, a novel general four-step strategy has been developed for the synthesis of nitronates (**24i**) from primary AN RCH_2NO_2 and olefins (**31**) (Scheme 3.31) (86, 87). The first step involves halogenation (bromination or fluorination) of initial AN. Bromination was performed according to a standard procedure, whereas fluorination was carried out with the use of the special reagent "Selectfluor" (88). Halonitroalkanes (**11**) (Hal=Br) have attracted attention only as reagents in one-electron transfer reactions (see,e.g.,Ref. 89), because in other transformations the halogen atom in these products was "passivated" by the nitro group.

The second step involves silylation of halonitroalkanes (**29**) with standard silylating agents *Si*Cl/Et_3N(*Si* is Me_3Si or Me_2Bu^tSi). Silyl nitronates **30** can be detected by physicochemical methods.

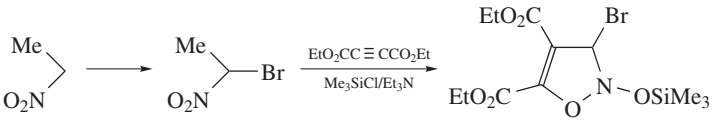
However, the step 2 in this procedure was technologically performed simultaneously with step 3 giving rise to cycloadducts **32**. For Hal=Br, step 3 is the rate-determining step, the scope of the process being limited to terminal alkenes (**31**) (R^4=H); the cycloaddition of even some of them under normal conditions



Scheme 3.31

requiring 1 month for completion (86). According to quantum chemical calculations, the nature of Hal-atom in nitronates (**30**) has the following effect on the rate of step 3: I < Cl∼Br < < F, the replacement of the bromine with fluorine leading to an increase in the cycloaddition rate by approximately one-and-a-half order. Test experiments demonstrated that calculations qualitatively reflect the rate of a true cycloaddition process. Hence, in spite of a high cost of the fluorinating agent, it is advantageous to use only α-fluoro-substituted nitro compounds (**29**) in the synthesis of cyclic nitronates substituted at C-4 (from internal olefins (**31**)). However, one must take into account the unexpectedly low stability of the corresponding α-fluoronitronates (**30**). For this purpose, a special procedure was developed, which provides a low running concentration of α-fluorine-substituted nitronates (**30**) in the course of cycloaddition to olefins (87).

The rate of step 4 involving elimination of halosilane also depends on the nature of the halogen atom but in the inverse order: F < < Br. For Hal=Br, intermediates (**32**) are impossible to detect. By contrast, for Hal=F, elimination of *Si*F is the rate-determining step, which requires a special procedure, for example, refluxing of intermediate (**32**) (Hal=F) in acetonitrile for 1 h. (Preliminary data show that the microwave technology makes it possible to sharply decrease the time required for completion of step 4 (90)). A decrease in the elimination rate in the series F < < Br is evidence that this reaction is not



29a **33**

Scheme 3.32

concerted but involves the initial elimination of the bromide or fluoride anion from intermediate cycloadducts (**32**).

The strategy presented in Scheme 3.31 substantially supplements the known approaches to the synthesis of five-membered cyclic nitronates.

Finally, the reaction with the use of ethyl acetylenedicarboxylate instead of olefin in step 3 produced surprisingly the corresponding isoxazoline (**33**) (Scheme 3.32) (87).

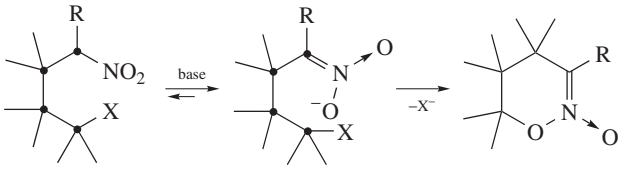
3.2.2.2. Synthesis of Six-membered Cyclic Nitronates

3.2.2.2.1. Intramolecular Cyclization of δ-functionalized AN One of the procedures for the synthesis of six-membered cyclic nitronates (**35**) containing the proton, the alkyl group, an electron-withdrawing substituent, or the nitro group at C-3 is based on intramolecular S_{N2} substitution of the halogen atom in the corresponding δ-halo-substituted nitro compounds (**34**) in the presence of bases (Scheme 3.33).

The chloride (70, 91, 92), bromide (91–97), or iodide (49) anions were used as the leaving group X^-.

For X=OH and R=EWG group or alkyl, the Mitsunobu reaction (10) is evidently the most convenient procedure for the synthesis of the corresponding nitronates (**35a**) (Scheme 3.34).

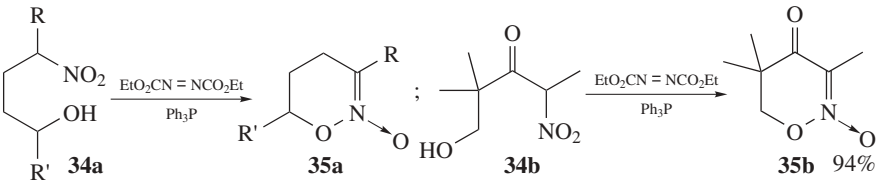
This reaction is characterized by very high yields of target products (**35a**) and the almost complete absence of side reactions, including C-alkylation. It should be noted that the six-membered cyclic nitronate (**35b**), in which the C-4 atom is involved in the carbonyl group, was synthesized only according to this scheme.



34 **35**

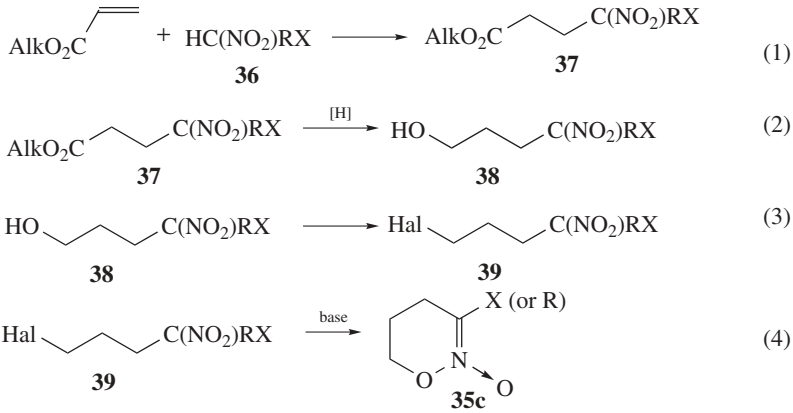
X = Cl[Ref.70,90,91,59,96,97], Br[Ref.91,92,97,98], I[Ref.49,50]; R – H, alkyl, NO_2, EWG

Scheme 3.33

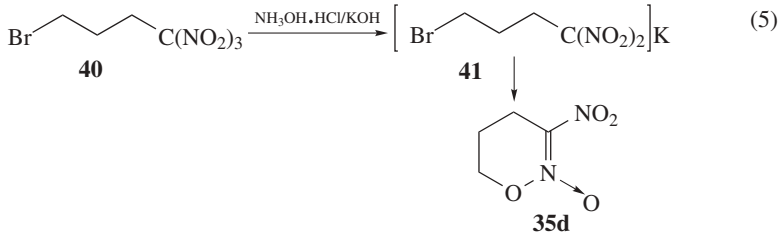


R' = H, R = Ph (93%); SO_2Ph (91%); cyclohexen-l-yl (81%); R' = Me, R = CO_2Et (94%)

Scheme 3.34



R – H, alkyl; X – H, EWG, NO_2 (R or X = H); Hal Cl, Br, I



Scheme 3.35

Precursors of six-membered cyclic nitronates (**35c**), viz., compounds (**39**), can be synthesized in three steps from the simplest nitro compounds (**36**) by the Michael reaction (Scheme 3.35).

The first step (1) gives rise to nitrocarboxylic acid esters (**37**) (If R=X=H, special conditions are required to prevent the double addition of the Michael substrate to reagents (**36**)).

Selective reduction of the ester function in products (**37**), step (2), affords nitro alcohols (**38**), which are either transformed into halo-containing compounds

(**39**) (see Scheme 3.33) or are directly transformed into target nitronates (**35c**) according to the Mitsunobu procedure (see Scheme 3.34).

If trinitromethane (R=X=NO_2) is used as starting compound (**40**), the steps (1) to (3) give rise to product (**40**), from which cyclic nitronate (**35 d**) can be prepared by denitration of the $C(NO_2)_3$ group and cyclization of bromide (**41**) (Eq. 5).

There are other synthetic routes to halides similar to compounds (**39**), which are direct precursors of six-membered cyclic nitronates (**35**) (Scheme 3.36).

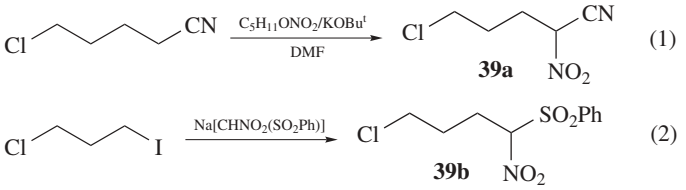
Sometimes, the nitro group can be introduced via nitration into functionalized halo-containing compounds at the α position with respect to the functional group (91) (Eq. 1).

Selective C-alkylation of the $Na[CH(NO_2)SO_2Ph]$ salt with 1-chloro-3-iodopropane (Eq. 2) followed by cyclization of product (**39b**) was documented (70).

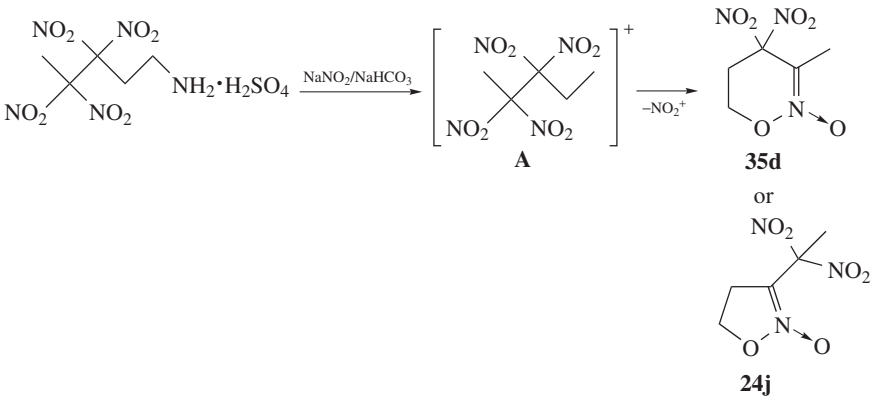
Interesting data were reported in Reference 98 on the transformation of the sulfuric acid salt of amine under conditions of nitrosation (Scheme 3.37).

Apparently, this reaction initially produces unstable diazo compound, which gives cation **A**.

The latter is involved in the intramolecular alkylation of one of the nitro groups accompanied by elimination of the nitronium cation. It was not rigorously established whether the reaction afforded six-membered cyclic nitronate (**35 d**) or



Scheme 3.36



Scheme 3.37

isomeric five-membered cyclic nitronate (**24j**). The significance of this approach in the methodology of the synthesis of six-membered cyclic nitronates is unclear.

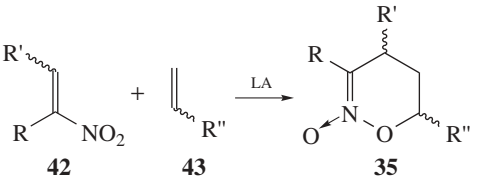
3.2.2.2.2. Synthesis of Six-membered Cyclic Nitronates by the [4 + 2]-cycloaddition Reaction The [4 + 2]-cycloaddition reaction of conjugated nitroalkenes (**42**) with olefins (**43**) is the most powerful and widely used method for the synthesis of six-membered cyclic nitronates (**35**) (Scheme 3.38).

There are several advantages of this method over other approaches to the synthesis of nitronates (**35**). First, direct precursors (**42**) and (**43**) are readily available. Second, this process is simple and versatile. Finally, in many cases high selectivity of the method allows the synthesis of diastereometrically and enantiometrically pure nitronates (**35**).

The reaction presented in Scheme 3.38 is involved in the novel [4 + 2][3 + 2] tandem strategy for the use of nitroalkenes (**42**) in target organic synthesis (for details, see Section 3.4.4). Taking into account the great contribution of Prof. S. Denmark the in investigation of different aspects of this strategy, the latter can be classified as Denmark's approach. The principal aspects of [4 + 2]-cycloaddition of nitro olefins were summarized in two fine reviews (99, 100).

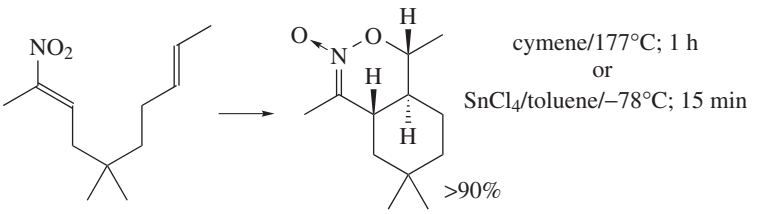
Although the reaction under consideration can be performed in the absence of Lewis acids (LA), the presence of the latter leads to a substantial increase in the reaction rate (101) (e.g., see Scheme 3.39).

$SnCl_4$, $Ti(OPr^i)_2Cl_2$, and methyl acetylenedicarboxylate (MAD) (bis(2,6-*tert*-butyl-4-methylphenoxy)-methyl-aluminum) are most often used as LA. Meanwhile, nonconventional procedures, for example, the reaction in water (102 and references therein), can be used to perform cycloadditions of nitroalkenes.



42 **43** **35**

Scheme 3.38

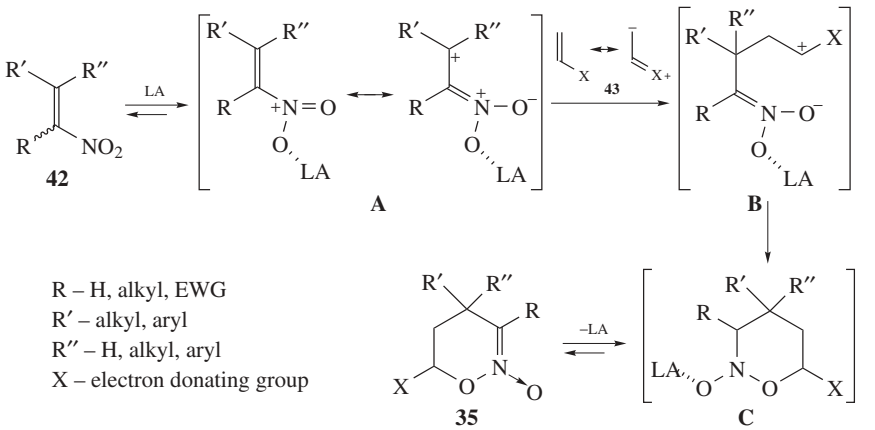


Scheme 3.39

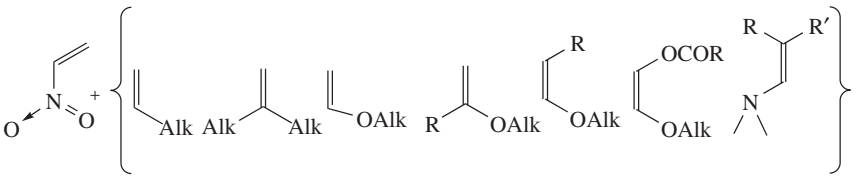
In the reaction presented in Scheme 3.38, nitroalkenes (**42**) act as acceptors. Consequently, the lowest unoccupied molecular orbital (LUMO) of these compounds should be considered in terms of the frontier molecular orbital (FMO) method as defined. The introduction of electron-withdrawing substituents at the β-C atom of nitro olefine (**42**) should decrease the energy of LUMO of the latter compound, thus decreasing the highest occupied molecular orbital (HOMO) HOMO–LUMO energy gap and facilitating [4 + 2]-cycloaddition. However in fact, the rate of the reaction of 4-methoxynitrostyrene with cyclopentene in the presence of $SnCl_4$ is 400 times faster than that of 4-trifluoromethylnitrostyrene (103). Evidently, the reactivity of a particular heterodiene (**42**) in the cycloaddition reaction depends most strongly on the concentration of a complex with LA, which, in turn, should be decreased in the presence of electron-withdrawing substituents in the diene.

The behavior of complexes of nitroalkenes (**42**) with LA toward conjugated dienes is yet another factor underlying the role of these complexes. Conjugated nitroalkenes (**42**) are considered as active dienophiles in classical Diels–Alder reactions (104, 105). On the contrary, in the presence of $SnCl_4$, nitroalkenes (**42**) react with cyclopentadiene and 1,3-cyclohexadiene exclusively at one double bond (103). Therefore, it is highly probable that the **42 + 43** cycloaddition proceeds by a nonconcerted mechanism in the presence of LA (see Scheme 3.40).

Initially, a complex of nitroalkene (**42**) with LA (**A**) is reversibly formed. The efficient concentration of the latter is determined by the reaction conditions and the nature of heterodiene (**42**) and LA. This complex acts as a Michael substrate and adds alkene (**43**) to give bipolar adduct **B**, which undergoes cyclization to give cationic intermediate **C**. The latter eliminates LA to yield target nitronate (**35**). In the case of nonconcerted cycloaddition, ionic intermediate **B** can undergo different isomerization reactions, some of which are considered below. The stereoselectivity of the process depends on the reactive conformation



Scheme 3.40



42 **43**

Scheme 3.41

(or conformations) of intermediate **B**. In actuality, the stereoisomeric composition of the resulting mixture depends most strongly on the nature of LA. As a rule, stereoisomers of the target nitronate can be separated by chromatography.

As follows from above, the rate of [4 + 2]-cycloaddition of nitroolefin (**42**) is determined by the nature of partner (**43**) and decreases in the following series of olefines: electron-rich > electroneutral > electron-deficient (100).

The **42 + 43** cycloaddition is characterized by high regioselectivity, and the reagents react in a head-to-head fashion. The most typical positions of the reagents with respect to each other are shown in Scheme 3.41.

For example, substituents in terminal olefins (**43**) in the resulting nitronates (**35**) are generally adjacent to the C-6 atom. The alkoxy and siloxy substituents from vinyl ethers and silyl enolates respectively, as well as the amino group from enamines, are oriented in the same positions. In the case of tris-substituted olefins, C-6 is the most crowded atom in the resulting nitronates.

The involvement of olefins containing vicinal alkoxy- and acetoxy groups in this synthesis always leads to the formation of nitronate (**35**) containing the alkoxy group at the C-6 atom.

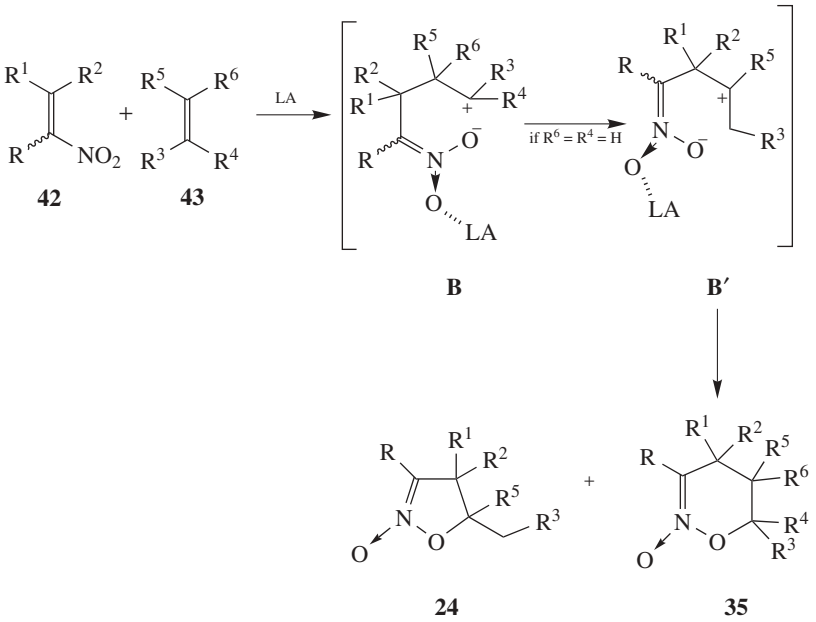
Some characteristic features of the reactions of conjugated nitro olefins (**42**) with various olefins will briefly be considered in following text.

Reactions with alkenes and nonconjugated dienes have been described in many publications (101, 103, 106–111). Various alkenes, such as cycloalkenes as well as acyclic alkenes, up to tetrasubstituted derivatives, can react with nitroalkenes (**42**) (110). Only one double bond is involved in the reactions of heterodienes (**42**) with nonconjugated dienes (111), whereas the second double bond can be used in subsequent transformations of target nitronates (**35**). The reactions of heterodienes (**42**) with inactivated alkenes require the presence of LA as catalyst.

Since inactivated alkenes do not contain the substituent X stabilizing the positive charge in intermediate **B** (see Scheme 3.40), the latter can undergo a hydride shift to form a more stabilized cationic center (intermediate **B′** in Scheme 3.42), which finally gives rise to an impurity of five-membered cyclic nitronate (**24**).

It should be noted that this reaction pathway confirms its nonconcerted character.

Reactions of nitroalkenes with enamines (**43a**) were studied in-depth (112–125). These reactions can produce Michael adducts (when nitroalkenes



Scheme 3.42

(**42**) without substituent R^1 are used) (112). In this case C-alkylation occurs, viz., cyclobutane derivatives (**44**) are obtained as by-products (Scheme 3.43) (114).

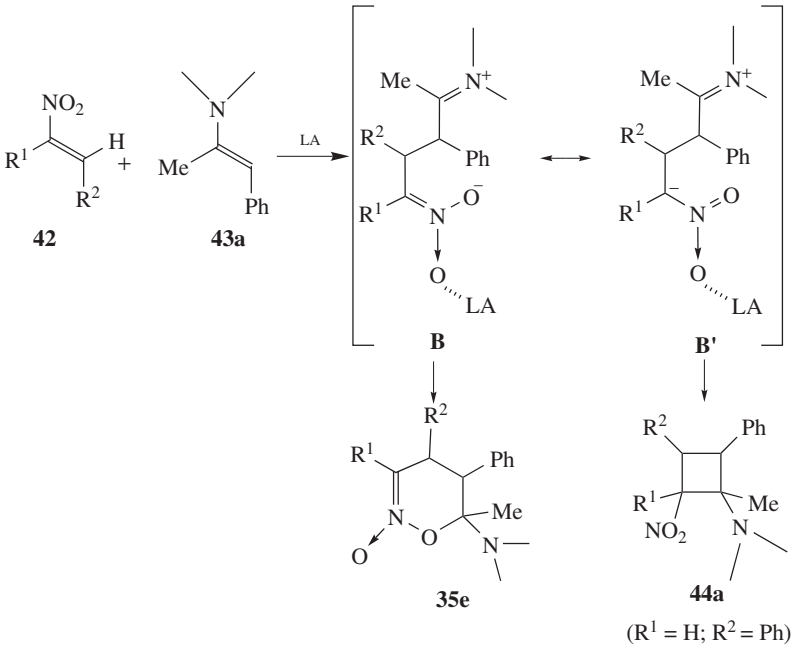
The formation of nitrocyclobutanes (**44**) is attributed to the contribution of the structure **B‴** to the reactivity of stabilized zwitterionic intermediate **B**. The contribution of C-alkylation decreases due to steric hindrance caused by the presence of substituents at the α-position of the initial nitroalkene (**42**).

The reactions of **nitroalkenes** (**42**) with various **enols** (**43b**) (vinyl ethers, silyl, and acyl enolates, ketene acetals) have been studied in most detail (110, 111, 125–154). As a rule, these reactions proceed smoothly to give the corresponding nitronates (**35f**) in yields from high to moderate. As in the reactions with enamines, the formation of compounds (**44b**) is attributed to the ambident character of the anionic centers in zwitterionic intermediates analogous to those shown in Scheme 3.43.

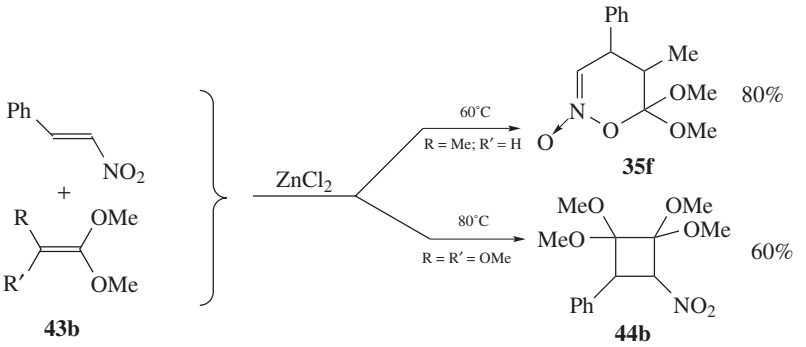
However, the reactions performed under drastic conditions sometimes produce the corresponding nitrocyclobutanes (**44b**) instead of the target cyclic nitronates (**35**) (see Scheme 3.44).

Terminal olefins (**43c**) (Scheme 3.45, Eq. 1) containing two substituents with opposite electronic effects at a single carbon atom can react stereoselectively with heterodienes (**42**) in a head-to-head fashion in the absence of LA (123, 155).

Denmark and coworkers demonstrated (156) that allenes (e.g., (**43 d**)) can selectively react at one of two bonds with conjugated nitro olefins (**42a**)



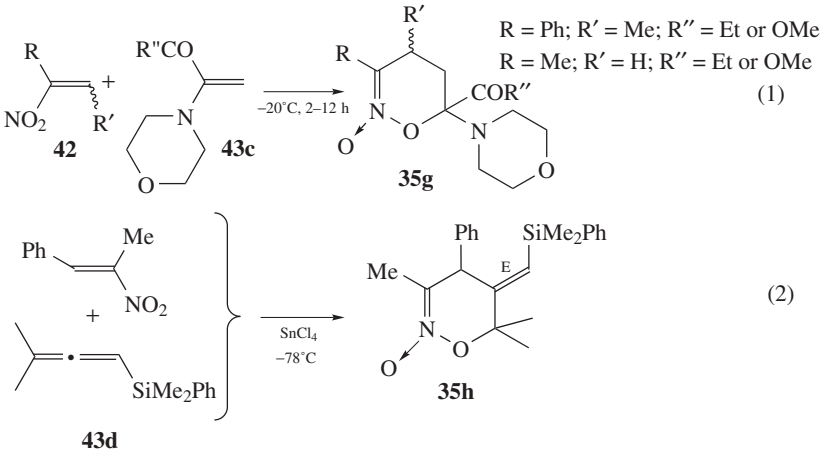
Scheme 3.43



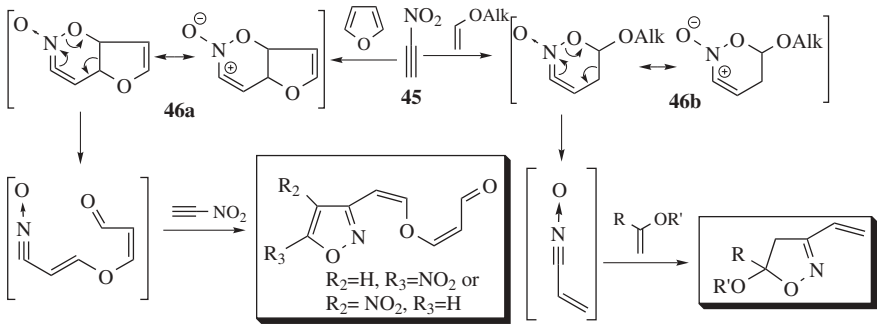
Scheme 3.44

(Scheme 3.45, Eq. 2) through the most stabilized zwitterion to give only one stereoisomer of target 5-methylene-substituted nitronate (**35 h**).

In the synthesis of six-membered cyclic nitronates (**35**) by the (**42 + 43**) cycloaddition, facial discrimination can be achieved by introducing enantiomerically pure chiral fragments into nitro olefin (**42**) (147, 157) enamine (117), or enol (134). In addition, Prof. Seebach (96) and postgraduate students supervised by Prof. Denmark (158) successfully used chiral LA for facial discrimination.



Scheme 3.45



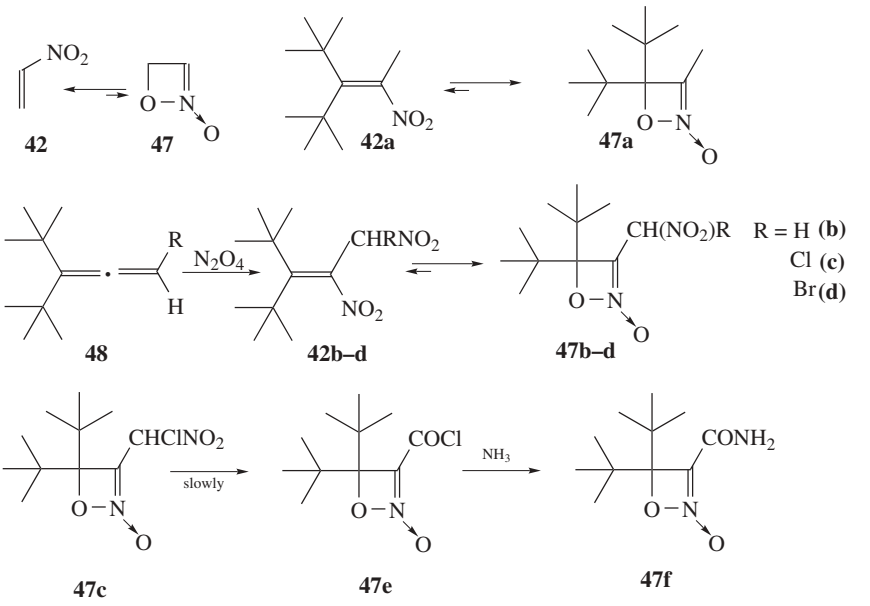
Scheme 3.46

The above described approaches were used in the several studies (96, 137, 138, 140, 150, 159–163) to prepare a representative series of enantiometrically pure six-membered cyclic nitronates (**35**).

To conclude this section, let us note an interesting study by Eaton and coworkers (164), who examined the reactions of solutions of nitroacetylene (**45**) with vinyl ethers and furan (Scheme 3.46); he reasonably suggested that very unstable nitronates (**46a**) and (**46b**) are generated and that these intermediates undergo unusual fragmentation resulting in generation of vinylated nitrile oxides, which give [3 + 2]-cycloaddition products with nitroacetylene or vinyl ether.

3.2.2.3. Synthesis of Unusual Cyclic Nitronates

3.2.2.3.1. Synthesis of Four-membered Cyclic Nitronates Conjugated nitro alkenes (**42**) (Scheme 3.47) can be considered as structural isomers of



Scheme 3.47

four-membered cyclic nitronates (**47**), viz., oxazete N-oxides. Clearly, the equilibrium is virtually completely shifted toward nitroalkenes due to large strains in molecule (**47**). Isomers (**47**) were discussed only as reactive unstable intermediates in thermal (165) and photochemical (166) destruction of α-nitroalkenes (**42**).

However, the introduction of sterically hindered substituents at the β-carbon atom of nitroalkene (**42**) completely changes the ring-chain tautomerism of conjugated nitroalkenes. Apparently, steric hindrance caused by two bulky Bu^t groups in product (**42a**) (Scheme 3.47) prevents effective conjugation of the π systems of the C,C double bond and the nitro group, thus causing its deviation from the plane of the C=C bond as a result of which isomer (**47a**) becomes thermodynamically more favorable.

As a result, nitroalkene (**42a**) is almost completely isomerized into N-oxide (**47a**), which is stable up to 100°C (167). Isomerization proceeds smoothly both in solutions and the solid state. The isomerization rate is approximated by the first-order equation and depends on the polarity of the solvent (isomerization in hexane occurs 70 times more slowly than that in ethanol).

Nitronate(**47a**) is not the only oxazete derivative. For example, sterically hindered nitroalkenes (**42b–d**) can be prepared by nitration and halogenation of readily available allenes (**48**). Compounds (**42b–d**) are rather smoothly isomerized into the corresponding four-membered cyclic nitronates (**47b–d**) by the first-order reaction equation (168). Storage of nitronate (**47c**) is accompanied by its slow transformation into acid chloride (**47e**) from which amide (**47f**) can be easily synthesized.

3.2.2.3.2. Synthesis of Seven-membered Cyclic Nitronates Cyclic nitronates containing more than four carbon atoms in the ring remain virtually unknown. Convenient procedures for the synthesis of these compounds are lacking. In particular, intramolecular alkylation of 5-bromo-1-nitropentane affords nitrocyclopentane rather than the corresponding seven-membered cyclic nitronate (169) (Scheme 3.48).

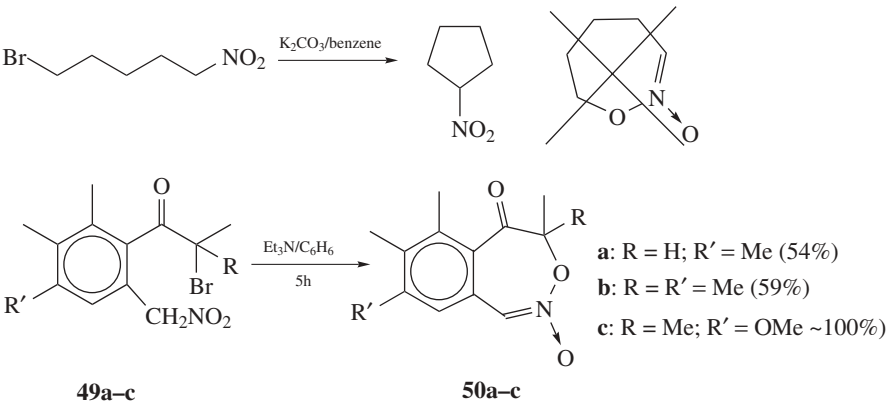
However, intramolecular O-alkylation can be performed under particular conditions leading to of annelation of a seven-membered heterocycle. Japanese researchers (170) prepared the corresponding seven-membered cyclic nitronates (**50a–c**) in good yields by the reaction of triethylamine with brominated aryl ketones (**49a–c**) containing the nitromethyl group in the *ortho* position.

3.2.3. Synthesis of Trialkylsilyl Nitronates

Owing to the fact that silyl esters of nitronic acids (SENAs) are readily available, rather stable, and exhibit various reactivities, these compounds have attracted considerable interest in the chemistry of nitronates.

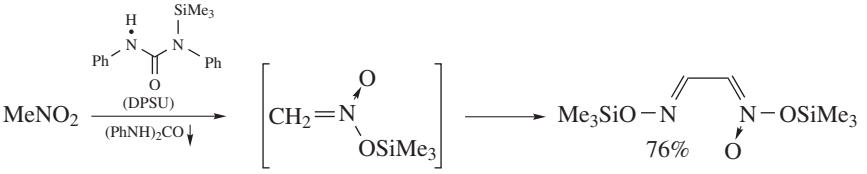
First SENA was prepared by Klebe in 1964 by the reaction of nitromethane with *N*-trimethylsilyl-*N,N'*-diphenylurea (171) (Scheme 3.49).

The resulting bis-silylated derivative of methazonic acid contained the SENA fragment and, in the author's opinion, was produced by condensation of two

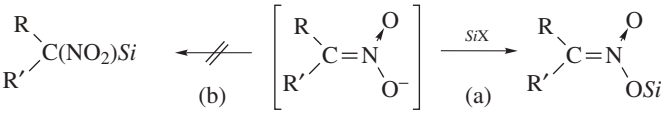


49a–c **50a–c**

Scheme 3.48



Scheme 3.49



*Si*X – silylating agent, *Si* – trialkylsilyl

Scheme 3.50

molecules of intermediate trimethylsilylmethanenitronate. Almost simultaneously, Polish researchers reported on the synthesis of silyl derivatives of nitro alkanes in the Proceedings of the International Symposium on Chemistry of Nitro Compounds, but no details were mentioned (172).

The formation of trimethylsilyl methanenitronate in the reaction of nitromethane with trimethylchlorosilane in the presence of pyridine was also postulated without any experimental evidence (173).

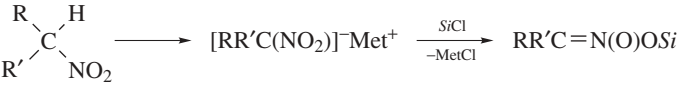
The chemistry of SENA originated 35 years ago. Since that time, extensive experience in handling these hydrolytically unstable but very useful derivatives of AN has been accumulated. Although no systematic investigation of the mechanism of silylation of AN has been made, the transfer of the trialkylsilyl group from the silylating agent to the AN anion is presumably the key step of this process (Scheme 3.50).

Silylation of AN is chemoselective (path (a)); that is, in no case does the silicon atom form the Si–C bond (path (b)). Moreover, if the initial AN contains a functional group at the α-C atom, the trialkylsilyl fragment in the resulting SENA is bonded, as a rule, to the oxygen atom of the nitro group.

The total diversity of methods for silylation of AN lies in varying the nature of the silylating agent *Si*-X and variants of providing an effective concentration of the anions of the silylated nitro compound.

3.2.3.1. Silylation of Salts of AN α-Functionalized AN **52a–c** (trinitromethane, dinitroethane, dimethyl nitromalonate, nitroacetates, etc.) can form salts, which are quite stable. It should be noted that stability of silver and mercury salts can be increased by complexation with neutral molecules (e.g., with dioxane). Hence, for these AN it is advantageous to prepare salts **A**, which react with halosilanes to smoothly form the corresponding SENAs **51a–c** (Scheme 3.51) (174–177).

Potassium nitroacetate **53a** reacts with Me_3SiCl in aprotic solvents to give SENA (**51a**) in moderate yield. At the same time, the introduction of yet another electron-withdrawing group (NO_2 or CO_2Me) stabilizes the anion of salt (**53**) to an extent that it does not react with Me_3SiCl by the S_{N2} mechanism without electrophilic assistance. Hence, K or Na salts **53b, c** are inert with respect to halosilanes, and silver or mercury salts are required for the preparation of the corresponding nitronates. The latter salts are much safer to use as dioxanate complexes. These complexes react with halosilanes in inert aprotic solvents



52a–c **53a–c** **51a–c**

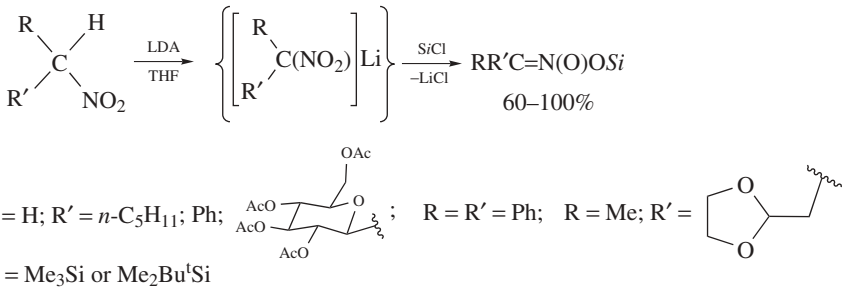
a: R = H; R′ = CO_2Me; Met = K; *Si* – $SiMe_3$ (55%) [Ref.174]

b: R = R′ = CO_2Me; Met = Ag; *Si* – $SiMe_3$ (50%) [Ref.175]

c: R = R′ = NO_2; Met = Ag; Ag•L; $HgC(NO_2)_3$•L_2 (67–90%)

Si – $SiMe_3$, $SiMe_2Ph$, $SiMePh_2$, $SiPh_3$ [Ref.176,177]

Scheme 3.51



Scheme 3.52

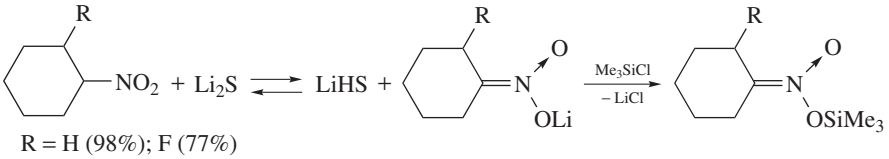
(1,4-dioxane, CH_2Cl_2, toluene, benzene). In hexane, this reaction occurs much more slowly apparently due to the very low solubility of the reacting salt.

3.2.3.2. Silylation of AN in the Presence of Bases Salts of unfunctionalized so-called simplest AN with carbon skeleton C_1-C_4 actively react with halosilanes to give target SENAs. However, operations with these reagents are dangerous. Hence, special procedures are generally used to generate *in situ* anions from the above mentioned AN with the use of bases involved in the silylating agent. For example, Prof. Seebach and coworkers (178, 179) suggested to treat AN with lithium diisopropylamide (LDA) in THF followed by the reaction of the resulting lithium nitronates with trialkylsilanes to prepare target SENAs generally in high yields (Scheme 3.52).

However, this procedure is not good in the case of silylation of vinylnitromethane, 2-nitropropane, and nitrocyclopentane (the yields of respective SENAs are 15%–35%).

A procedure developed by Prof. Olah based on the use of lithium sulfide as a base is well suitable for silylation of nitro derivatives of the cyclohexane series (180, 181) (Scheme 3.53).

However, attempts to use this method for silylation of primary AN led to mixtures of unidentified products.



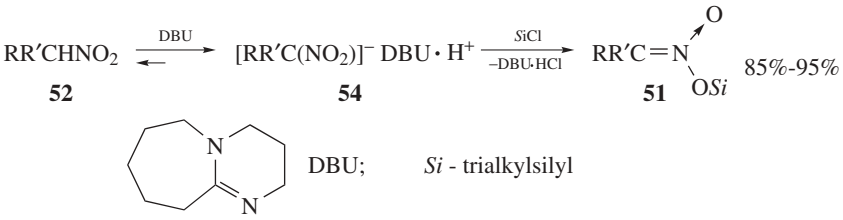
Scheme 3.53

Sodium hydride in THF can be used with advantage to deprotonate nitro derivatives of carbohydrates in the presence of Bu^tMe_2SiCl (182, 183). In these cases, the yields of respective SENAs are 60% to 80%.

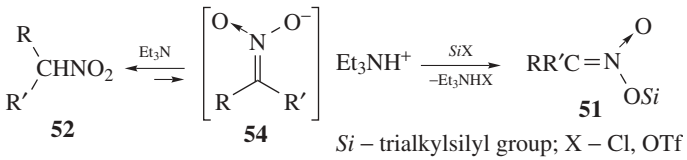
However, a strong nitrogen base–DBU– is the silylating agent of choice for silylation of AN (Scheme 3.54) (184). This procedure is versatile and allows one to rapidly synthesize most of the target anions with a high degree of conversion of the starting AN. The resulting anions of nitro compounds (**54**) rapidly react with trialkylhalosilane to give SENA(**51**) in high yield.

Nevertheless, silylation of AN with a Et_3N/SiX mixture is nowadays most widely used (Scheme 3.55, Table 3.1).

Apparently, the **52**⇆**54** step is the rate-determining step of this reaction, the equilibrium being shifted toward undissociated AN **52** due to low acidity of unfunctionalized AN. In most cases, silylation products can be prepared with the use of appropriate solvents and olefins as trapping agents. However, the conversion of many AN into the corresponding SENAs in the absence of trapping agents in benzene is low (see Table 3.1). It is particularly difficult to prepare SENAs from secondary AN (see, e.g., entry 7 in Table 3.1). The reaction with the use of triethylamine in the presence of a catalytic additive of 4-dimethylaminopyridine

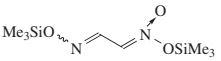
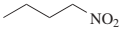
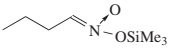
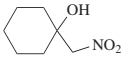
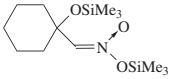
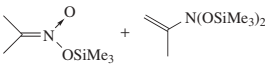
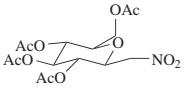
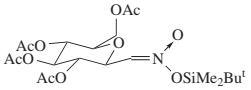
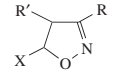
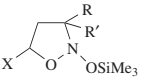
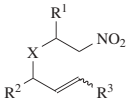
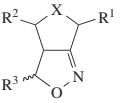
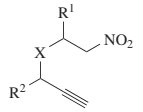
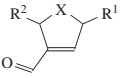


Scheme 3.54



Scheme 3.55

Table 3.1 The silylation of AN by Et_3N/SiX

Entry	AN	*Si*X	Solvent	The product of silylation	Yield, %%	Ref.
1	$MeNO_2$	Me_3SiCl	C_6H_6	 $MeCH{=}N(O)OSiMe_3$ $EtCH{=}N(O)OSiMe_3$	—	185
2	$EtNO_2$	Me_3SiCl	C_6H_6	$MeCH{=}N(O)OSiMe_3$	64	185
3	Pr^nNO_2	Me_3SiCl	C_6H_6	$EtCH{=}N(O)OSiMe_3$	79	185
4		Me_3SiCl	C_6H_6		—[a]	186
5		Me_3SiCl	C_6H_6		—[a]	186
6	Me_2CHNO_2	Me_3SiCl	C_6H_6	$Me_2C{=}N(O)OSiMe_3$	0	186
7	Me_2CHNO_2	Me_3SiCl	MeCN		72[b]	187
8		Bu^tMe_2SiCl	CH_2Cl_2		30[b]	183
9	$R(CF_3)CHNO_2$[c]	$R'Me_2SiCl$	Et_2O	$R(CF_3)C{=}N(O)OSiMe_2R'$[c]	40-66	133
10	$MeO_2CCH_2NO_2$	Me_3SiOTf	Et_2O	$MeO_2CCH{=}N(O)OSiMe_3$	85	188
11	RCH_2NO_2 (R–H or alkyl)	Me_3SiCl	C_6H_6[d]		55-70[b,c]	186
12	$RR'CHNO_2$ (R–H or alkyl; R' – alkyl)	Me_3SiCl	MeCN[d] or $MeCN/C_6H_6$		50-96	189
13	 R^1,R^2,R^3 – H, alkyl, aryl; X – O, S, NCH_2, $CH{=}CH_2$	Me_3SiCl	C_6H_6 or CH_2Cl_2		70-90[e]	190–196
14	 $R^1 = H,Ph$; $R^2 = H,Me$; $X = O,CH_2$	Me_3SiCl	C_6H_6		21-98[e]	190

[a] low conversion;
[b] by NMR;
[c] R= Me, Et; R'= Me, Bu^t, Pr^i;
[d] with addition $XCH{=}CH_2$ or $XCH{=}CHR^1$ (X= CN, CO_2Me, Ac; R^1=H, alkyl);
[e] after treatment of adducts with TsOH, HCl, KF or $Bu^n{}_4NF$.

(DMAP) provides the only approach to silylation of nitroalkanes containing perfluoroalkyl substituents at the α-C atom (133).

The use of more polar solvents instead of benzene makes it difficult to separate the triethylamine salt formed as a by-product, but can substantially accelerate silylation. For example, the use of CH_2Cl_2 increases the yields of silyl esters of primary AN (188).

An increase in electrophilicity of ***Si*X** (e.g., the use of silyl triflates) is possible only in the absence of protons bonded to the β-C atom in silylated AN (see entry 10 in Table 3.1).

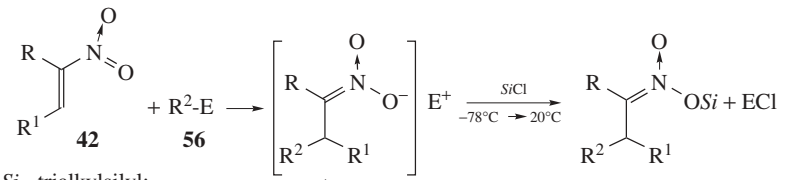
In other cases, the use of silyl triflates leads to double silylation of the starting AN. (This process will be considered separately in Section 3.5.1. Silylation of AN containing functional groups at the β-carbon atom will also be considered separately in Section 3.5.5.)

3.2.3.3. Silylation of Products of Conjugated Addition of Nucleophiles to α-Nitroolefins Nitroalkane anions can be generated not only by deprotonation of nitroalkanes (various modifications of these process were considered above) but also by the conjugated addition of nucleophiles **56** to α-nitroalkenes (**42**) (Scheme 3.56, Table 3.2).

In this approach, the SENA skeleton is assembled from nitroalkene (**42**) and nucleophile **56**.With the exception of two examples (entries 1 and 2 in Table 3.2), the reaction does not stop at SENA **51**, which either undergoes intramolecular cyclization through [3 + 2]-cycloaddition to give fused heterocycles (as a rule after elimination of trimethylsilanol) (198–200) or is involved in [3 + 2]-cycloaddition with specially added methyl vinyl ketone or methyl acrylate to form (after elimination of silanol) substituted isoxazolines in rather high yields (201).

Generally, anionic intermediates **A** smoothly react with trialkylchlorosilanes as the temperature is raised to room temperature. To improve the solubility of intermediate magnesium nitronates (**A** in scheme 3.56), it is advantageous to add HMPA to the reaction mixture. The addition of Et_3N stabilizes SENAs as intermediate.

Cunico and Motta reported (202) on the very interesting one-pot synthesis of SENAs, such as β-nitrocarboxylic acid *N,N*-dimethylamides derivatives, from silylated *N,N*-dimethylformamides **57a,b** and conjugated nitroalkenes (Scheme 3.57).



Scheme 3.56

Table 3.2 The preparation of SENAs from conjugated nitro alkenes (Scheme 3.56)

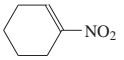
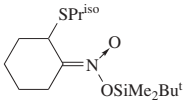
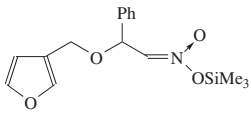
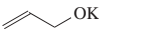
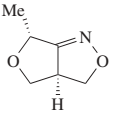
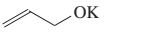
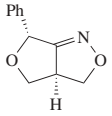
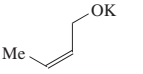
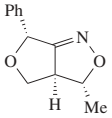
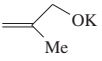
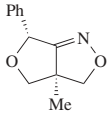
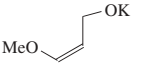
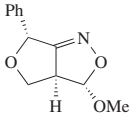
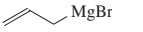
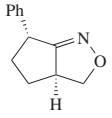
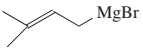
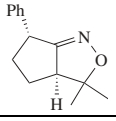
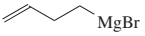
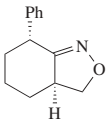
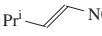
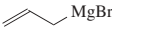
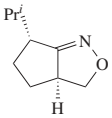
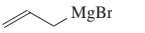
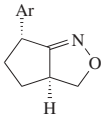
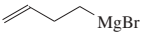
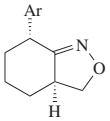
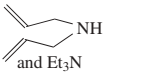
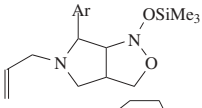
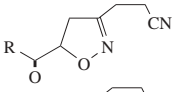
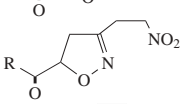
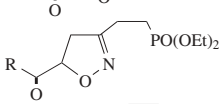
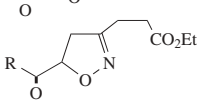
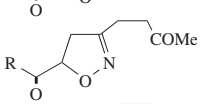
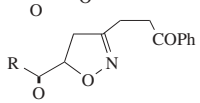
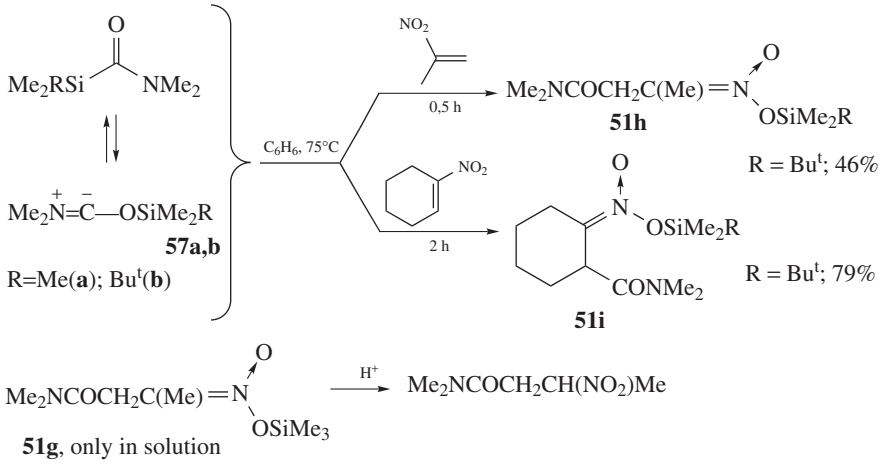
Entry	Nitroalkene (**42**)	Nucleophil (**56**)	*Si*	SENA **51** or product of its trapping	Yield %%	Ref.
1		Me_2CHSLi	Me_2Bu^tSi		96	197
2	*trans*-$PhCH=CHNO_2$		Me_3Si		70[a]	198
3	*trans*-$MeCH=CHNO_2$		Me_3Si		30[d]	198
4	*trans*-$PhCH=CHNO_2$		Me_3Si		84[d]	198
5	*trans*-$PhCH=CHNO_2$		Me_3Si		79[d]	198
6	*trans*-$PhCH=CHNO_2$		Me_3Si		40[d]	198
7	*trans*-$PhCH=CHNO_2$		Me_3Si		30[d]	198
8	*trans*-$PhCH=CHNO_2$		Me_3Si		41[d]; 66[b,d]	199
9	*trans*-$PhCH=CHNO_2$		Me_3Si		53[d]	199

Table 3.2 (*continued*)

10	*trans*- PhCH = CHNO$_2$		Me_3Si		62[d]	199
11			Me_3Si		18[d]	199
12	*trans*- ArCH = CHNO$_2$ (Ar−4-*MeO*-Ph)		Me_3Si		43[d]	199
13	*trans*- ArCH = CHNO$_2$ (Ar−4-*MeO*-Ph)		Me_3Si		58[d]	199
14	*trans*- ArCH = CHNO$_2$ (Ar−4-*MeO*-Ph)		Me_3Si		60	200
15		$NCCH_2Li$[c]	Me_3Si		84(R = Me)[d]; 66(R = OMe)[d]	201
16		$CH_2 = N(O)OLi$	Me_3Si		50[d] (R = Me); 55[d] (R = OMe)	201
17		$(EtO)_2P(O)CH_2Li$	Me_3Si		65[d] (R = Me); 53[d] (R = OMe)	201
18			Me_3Si		65[d] (R = Me); 61[d] (R = OMe)	201
19			Me_3Si		78[d] (R = Me); 65[d] (R = OMe)	201
20			Me_3Si		72[d] (R = Me); 66[d] (R = OMe)	201

[a] Not involved in intramolecular cycloaddition.
[b] With addition hexamethylphosphoramide (HMPA).
[c] With addition RCOCH=CH$_2$ for intermolecular trapping of SENA.
[d] After elimination of Me_3SiOH from [3 + 2]-cycloaddition's product.



Scheme 3.57

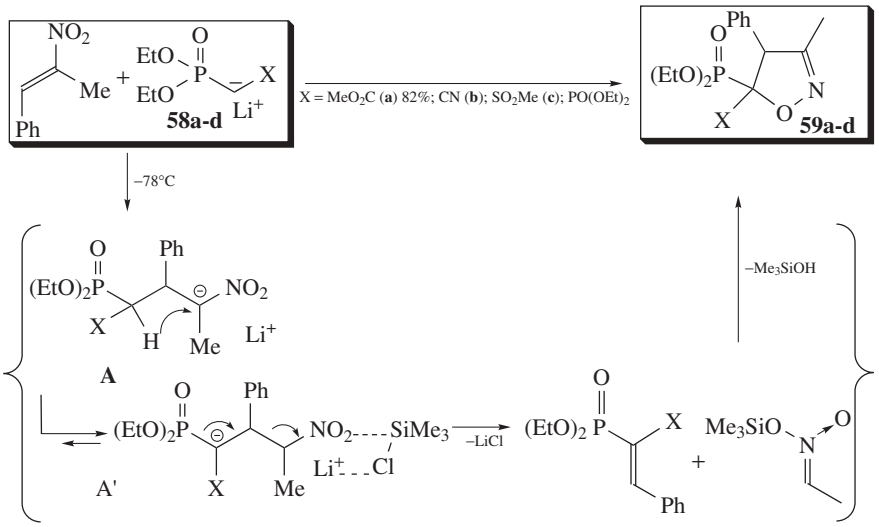
This result was considered by the authors in terms of C,C-coupling of silyl derivatives (**57**) with Michael substrates, such as electron-deficient alkenes, the NO_2 group being the most activating of all the substituents examined (EtCO, EtO_2C, CN, etc.). The mechanism of this process remains unknown. Among other approaches, the authors suggested the single electron transfer (SET) procedure involving the formation of an activated complex of the reagents as the first step. It was noted that more hindered silyl derivative (**57b**) reacts more rapidly than trimethylsilyl analog **57a** (202).

SENAs (**51 h**) and (**51i**) are quite stable, whereas derivative (**51 g**) can be detected only by physicochemical methods in solution (^{1}H NMR) or (after protodesilylation) as β-nitrobutyric acid *N,N*-dimethylamide.

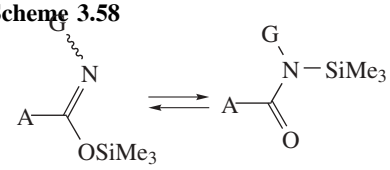
The use of strongly stabilized nucleophiles, for example, of $[(EtO)_2P(O)CHX]^-Li^+$ **58a–d**, where X is a powerful EWG group, such as MeO_2C, CN, SO_2Me, or P(O) $(OEt)_2$, in the conjugated addition with α-nitroolefins gives rise to more complex processes (201b) (Scheme 3.58).

Probably, at high temperature, the initially formed anion **A** undergoes the 1,3-proton shift to give apparently more stable anion **A′**, which is silylated at the oxygen atom of the nitro group to form (after elimination of LiCl) two new intermediates—trimethylsilyl methylmethanenitronate and substituted styrene, which are involved in [3 + 2]-cycloaddition followed by elimination of trimethylsilanol to give isoxazolines **59a–d**. One of these products (**59a**) was obtained in very high yield. (The C,C bond cleavage in anionic intermediate **A′** could alternatively occur through silylation of the group X followed by the transfer of the *SiMe*$_3$ fragment to oxygen of the nitro group.)

3.2.3.4. Silylation of AN with Silylated Amides One of the most important approaches to the synthesis of SENAs is based on silylation of AN with neutral silylating agents, that is, in the absence of bases. *N*-Silylated amides presented



Scheme 3.58



A – Me, G – $SiMe_3$ (BSA); A – CF_3, G – $SiMe_3$ (BSTFA); A– PhNH, G – Ph (DPSU)

Scheme 3.59

in Scheme 3.59 can be used as such agents. This approach was used for the introduction of the trimethylsilyl group, although there are no principal obstacles to the introduction of other triorganosilyl fragments.

All three amides are evidently mixtures of tautomers. It should be noted that the nitrogen atom in the imide form is sterically unhindered and sufficiently basic to provoke deprotonation of silylated AN

DPSU is a rather weak silylating agent, which has found use for silylation of the hydroxy group. The advantage of this reagent is that it does not give by-products of silylation in solution because *N,N′*-diphenylurea is insoluble in most organic solvents and can be almost completely separated by filtration.

Silylation of AN with BSA and BSTFA produces as by-products *N*-trimethylsilylacetamide (bp 70°C/35 mm Hg) and *N*-trimethylsilyltrifluoroacetamide (bp 60°C/35 mm Hg), respectively. Owing to high volatility typical of fluorinated hydrocarbons, distillation of BSTFA from the reaction mixture seems to be more favorable, although their high casts should also be taken into account.

Silylation with *N*-trimethylsilylamides is generally performed at room or higher temperature (but not higher than 100°C). More drastic heating leads to

decomposition of silylating agents (e.g., BSA is transformed into a mixture of hexamethyldisiloxane and acetonitrile).

To inhibit this decomposition, it is necessary to add a small amount of triethylamine to BSA.

Table 3.3 summarizes examples of the successful use of DPSU for silylation of AN.

As can be seen from this table, it is advantageous to use DPSU only for silylation of α-functionalized AN.

Principal results of the use of BSA and BSTFA are given in Table 3.4.

The mechanism of silylation of AN with silylated amides was not systematically studied, but some data on this problem have been reported (204).

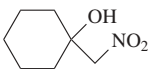
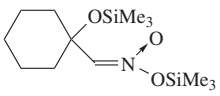
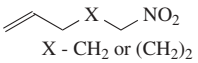
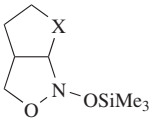
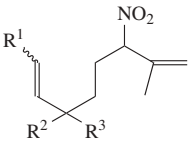
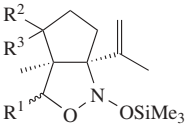
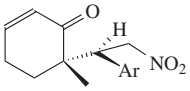
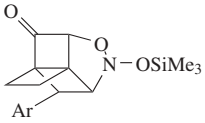
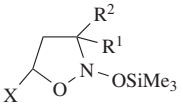
It could be suggested that silylation of AN occurs through multicenter transition states **A** or **B**(Chart 3.1).

However, certain facts contradict this interpretation. For example, the silylation of AN with BSA was accelerated after addition of triethylamine, which facilitates AN ionization (185). Besides, the addition of 1,1-dinitroethane leads to an increase in the rate of silylation of methyl nitroacetate with a deficient amount of DPSU. At the same time, the silylation of 1,1-dinitroethane by itself, taken separately with DPSU, occurs faster than silylation of $MeO_2CCH_2NO_2$ (204). Apparently, this is accounted for by the higher nucleophilicity of methyl nitroacetate compared to that of 1,1-dinitroethane. (A separate experiment demonstrated that silyl aci-dinitroethane does not react with methyl nitroacetate.)

Table 3.3 The silylation of AN with DPSU

Entry	AN	Conditions	SENAs	Yield,%	Ref.
1	$MeNO_2$	35°C	$SiMe_3ON{=}CHCH{=}N(O)O\ SiMe_3$	76	171
2	$HON{=}CHCH_2NO_2$	35°C	$SiMe_3ON{=}CHCH{=}N(O)O\ SiMe_3$	> 90	171
3	$MeO_2CCH_2NO_2$	20°C, 15 h, C_6H_6	$MeO_2CCH{=}N(O)O\ SiMe_3$	90	203
4	$CH_2(NO_2)_2$	20°C, 0.3 h, C_6H_6	$NO_2CH{=}N(O)O\ SiMe_3$	90	203
5	$MeCH(NO_2)_2$	20°C, 0.3 h, C_6H_6	$MeC(NO_2){=}N(O)O\ SiMe_3$	90	204
6	$(MeO_2C)_2CHNO_2$	20°C, 0.6 h, C_6H_6	$(MeO_2C)_2C{=}N(O)O\ SiMe_3$	97	175
7	$HC(NO_2)_3$	0°C, 0.3 h, tolyene	$(NO_2)_2C{=}N(O)O\ SiMe_3$	69 (by NMR)	176
8	$PhCH_2NO_2$	80°C, 1 h, C_6H_6	$PhCH{=}N(O)O\ SiMe_3$	0	204
9	$PhCH{=}N(O)OH$	20°C, 0.5 h, C_6H_6	$PhCH{=}N(O)O\ SiMe_3$	80	204

Table 3.4 The silylation of AN with BSA and BSTFA

Entry	AN	Conditions	SENAs	Yield,%[a]	Ref.
1	$MeNO_2$	BSA, C_6H_6, 20°C	$CH_2=N(O)O\ SiMe_3$	90[b]	205
2	$CH_3CH_2NO_2$	BSA, 65°C, 2 h	$CH_3CH=N(O)O\ SiMe_3$	90	205
3	$EtCH_2NO_2$	BSA, 70°C, 2 h	$EtCH=N(O)O\ SiMe_3$	90	205
4	$PhCH_2NO_2$	BSA, C_6H_6, 20°C, 0.3 h	$PhCH=N(O)O\ SiMe_3$	81	205
5	$BrCH_2NO_2$	BSA, CH_2Cl_2, 20°C, 0.1 h	$BrCH=N(O)O\ SiMe_3$	70	204
6	$HOCH_2CH_2NO_2$	BSA, C_6H_6, 80°C, 2 h	$Me_3SiOCH_2CH=N(O)OSiMe_3$	90	186
7		BSA, C_6H_6, 80°C, 4 h		69	186
8	$MeCH(Cl)NO_2$	BSA, C_6H_6, 80°C, 24 h	$MeC(Cl)=N(O)OSiMe_3$	90[b]	186
9	Me_2CHNO_2	BSA, 105°C, 3 h	$Me_2C=N(O)OSiMe_3$	85	205
10		BSTFA, C_6H_6, 80°C, 1 h		55[c] (X = CH_2) 60[c] (X = $(CH_2)_2$)	186,206
11		BSA, C_6H_6 or toluene/MeCN, 80 or 110°C, 3 h		60–80[c]	207–211
12	 Ar – 4-MeO-C_6H_4-	BSA, Pr^iNEt_2		67[c,d]	96
13	$R^1R^2CHNO_2$, R^1,R^2–H, alkyl, aryl	BSA, C_6H_6, 20–110°C, 1–5 h[e]		70–100	205
14	$C_6H_5NHCH_2CH_2NO_2$	BSA, 0→20°C, 1 h	$PhN(SiMe_3)CH_2CH{=}N(O)OSiMe_3$	80	212

[a] Product distilled.
[b] By NMR calculation.
[c] After intramolecular [3 + 2]-cycloaddition.
[d] Enantiomeric pure product.
[e] After [3 + 2]-cycloaddition with $XCH{=}CH_2$ (X= CO_2Me, Ph).

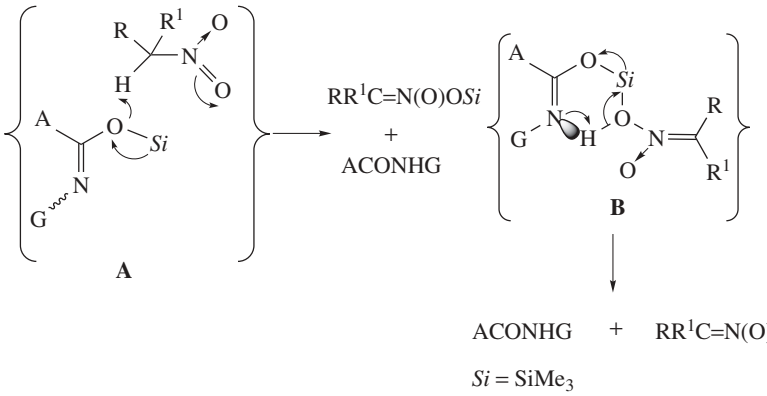


Chart 3.1 A possible mexanistic models for electrocyclic silylation of *AN with N-silyl-amides*.

The silylation:

Deprotonation	Ph⟨ NO$_2$	>> MeNO$_2$	>> EtNO$_2$	> Pr^{n}NO$_2$	>> Me$_2$CHNO$_2$
K (mol^{-1}sec^{-1})	144	30	5.6	4.7	0.26

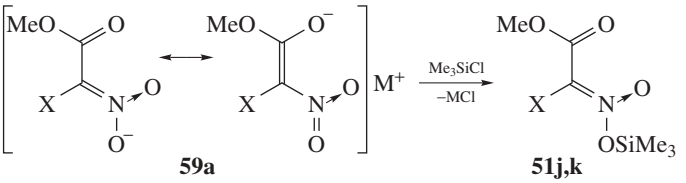
Chart 3.2 The competition of the rates of silylation and deprotonation of various AN.

The rates of silylation of AN with BSA (Chart 3.2) were estimated by the competitive reaction method (204). These rates change in parallel with the rates of deprotonation of these AN, determined by treatment with NaOH in aqueous methanol (213).

It is most likely that silylation of AN with silyl derivatives of amides, like the processes considered in Section 3.2.3.2, involve the formation of α-nitrocarbanions as the key step. It is also possible that only aci forms of AN can react with DPSU. This is evidenced by a comparison of the results of entries 8 and 9 in Table 3.3.

However, this process is multistep, many steps are reversible, and the reactions are heterophase in the case of DPSU. These circumstances do not allow one to give a general interpretation. It cannot be ruled out that the rate-determining step in the reaction with DPSU differs from that with bis-trimethylsilylacetamides.

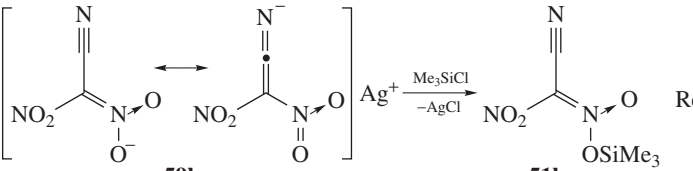
3.2.3.5. Silylation of Functionalized AN Silylation of α-functionalized AN can afford not only "classical" SENAs but also their structural isomers, in which the silyl group is bound to the electronegative atom of the functional group. This could occur due to the possible stabilization of the negative charge by its transfer to functional groups (Scheme 3.60). However, only the corresponding SENAs occur (isolated or detected) as products of silylation of functionalized AN (e.g., see Eqs 1 and 2 in Scheme 3.60). Apparently, this is associated not with kinetic



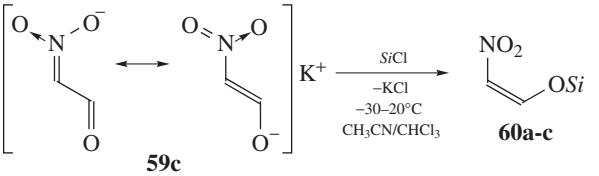
59a **51j,k** (1)

X = H[Ref. 174, 176]; CO_2Me[Ref. 175]

M = K, Ag



59b **51l** Ref. 49 (2)



59c **60a-c** Ref. 152, 214, 215 (3)

a, *Si* = MeO_2C $Si(Pr^i)_2$ (60%); **b**, *Si* = $Si(Pr^i)_2$ (62%);

c, *Si* = O—$Si(Pr^i)_2$ (85%)

Scheme 3.60

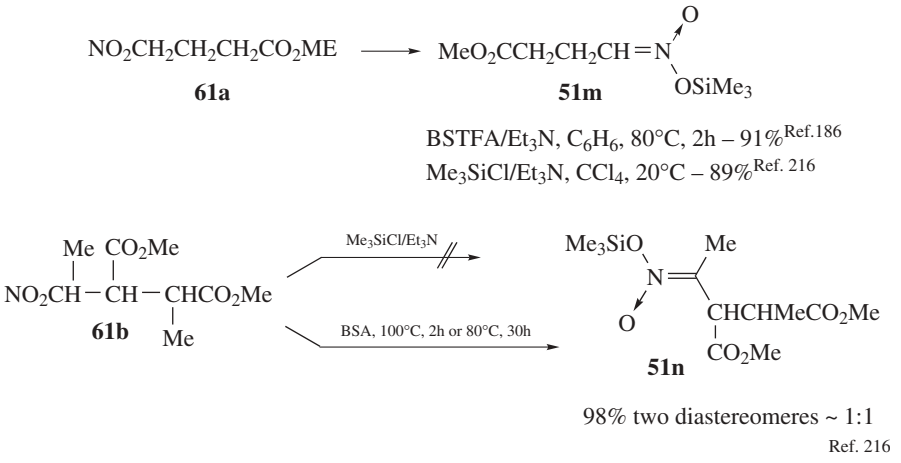
but with thermodynamic factors, because it is known that the trialkylsilyl group is prone to low-barrier silylotropy (for details, see Section 3.3.4.1).

However, an opposite situation is observed for α-nitroaldehyde salt (**59c**) (Eq. 3 in Scheme 3.60). Denmark and coworkers succeeded in isolating thermodynamically more favorable β-siloxynitroehtylenes (**60**) by silylation of these products (152, 214, 215).

It should be emphasized that all silylated products presented in Scheme 3.60 are detected as the only stereoisomer.

Silylation of β-functionalized AN will be considered separately because of the complexity of this process, which involves various and very fast transformations of the initial SENAs.

γ-Functionalized AN can be silylated independently both at the nitro and functional fragments. The character of the resulting product depends on many factors, such as the nature of the functional group, its basicity, the acidity of the $CHNO_2$ fragment and on the strength of the silylating agent. Here, we consider only one example (Scheme 3.61).

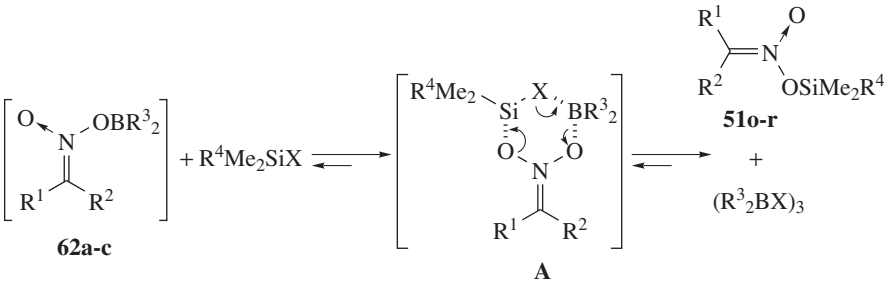


Scheme 3.61

AN (**61a**), which is easily generated from nitromethane and methyl acrylate by the Michael reaction, is smoothly silylated by both Me_3SiCl/Et_3N (211) and amide BSTFA (182) to give the corresponding SENA (**51 m**) in high yield. However, its sterically hindered analog, viz., product (**61b**), does not react with Me_3SiCl/Et_3N and gives the corresponding SENA (**51n**) in the reaction with BSA only under very drastic conditions. The removal of the Me substituent from the α or γ position of (**61b**) leads to a sharp increase in the silylation rate and a change in the character of the process.

3.2.3.6. Synthesis of Silyl Nitronates by the Replacement of an Heteroorganic Fragment in Organoboron Nitronates An alternative procedure for the synthesis of SENAs is based on the replacement of a elementorganic fragment in elementorganic derivatives of nitronic acids with specially selected silylating agents. Evidently, these reactions are reversible and can proceed only if the formation of new bonds is energetically favorable. This approach was studied only as applied to boron derivatives of alkanenitronic acids (217) (Scheme 3.62).

For example, the reactions of silylamines with dimeric dialkylboron nitronates (**62a–c**) rapidly afford the corresponding SENA (**51o–r**) in satisfactory yields, and these products can be isolated and purified by distillation. Evidently, the gain in energy due to the replacement of the weak Si–N bond by the stronger Si–O bond is the driving force of the process. Besides, there is apparently an additional gain in energy in the case of trimeric borylated amines compared to dimeric nitronates (**62**) because of the stronger coordination bond, although the energy of the > B–O single bond (544 kJ/ mol) is substantially higher than that of the B–N single bond (443 kJ/ mol) (218). Interestingly, as opposed to the reaction of silylamine presented in Scheme 3.62, the reaction with the corresponding silyl halide does not occur. On the contrary, the backward reaction with the



$R^1 = R^2 = R^3 = Me$, $R^4 = Et$, $X = NMe_2$ (50%);
$R^1 = H$, $R^2 = CMe_2CO_2Me$, $R^3 = Me$, $R^4 = Et$, $X = NMe_2$ (55%);
$R^1 = R^2 = Me$, $R^3 = Pr^i$, $R^4 = Et$, $X = NMe_2$ (55%)

Scheme 3.62

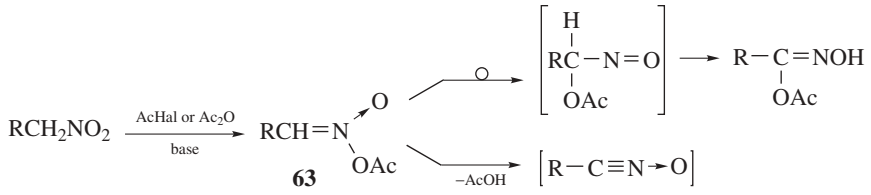
involvement of silyl nitronates and the corresponding boron halides takes place (for more details, see below in Section 3.2.4.2).

3.2.4. Synthesis of other Types of Nitronates

3.2.4.1. Synthesis of Acyl Nitronates The most general approach to the synthesis of acyl nitronates is based on the reactions of anions of the corresponding AN with acyl halides or carboxylic acid anhydrides in the presence of bases. Here, we will not consider a series of studies, where the formation of intermediate *O*-acyl nitronates was postulated without conclusive proof or by detection of their decomposition products.

Acyl nitronates (**63**) derived from primary AN are characterized by two types of such transformations: the rearrangement into α-acetoxy aldoximes (219) and elimination of the corresponding carboxylic acids to form nitrile oxides (Scheme 3.63).

As a rule, acyl nitronates derived from secondary AN are more stable. For example, the reaction of acetic anhydride with the Na salt of 2-nitropropane in the presence of K_2CO_3 afforded the corresponding acyl nitronate in a yield lower



Ac–acyl.

Scheme 3.63

than 20%. This product was isolated, its boiling point and refraction index were determined, and a satisfactory elemental analysis was obtained, (220). (As far as is known, these are first reliable data on isolation of acyl nitronates.)

More recently, the synthesis of relatively stable chiral acyl nitronates by the reactions of acetic anhydride and pyridine with secondary nitro sugar derivatives has been documented (221).

Approximately at the same time, Shevelev and coworkers studied the reactions of trinitromethane and 1,1-dinitroethane salts with RCOCl (R=Me or Ph) and detected the corresponding acyl nitronates on the basis of decomposition products and by trapping with various E–X reagents (222) (Scheme 3.64).

There are two interesting aspects in these studies. First, an original fragmentation path accompanied by elimination of ketene was proposed for acetyl nitronates. This is evidenced by the appearance of a considerable amount of the starting 1,1-dinitroethane in the reaction mixture, when the reaction is performed with acetyl chloride, whereas dinitroethane is not produced in the reaction with benzoyl chloride. Second, in the reactions of various trapping agents with *in situ* generated acyl nitronate **A**, the electrophilic moiety of these reagents is coupled with the α-C atom of the acyl intermediate **A**.

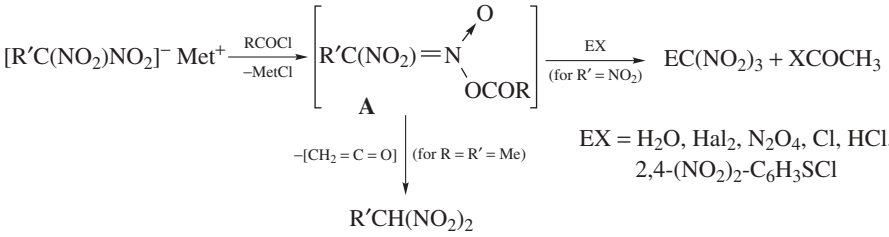
Mckillop (223) confirmed the existence of acetyl nitronate **A** derived from nitroethane by its trapping as a 1,3-dipole in the reaction with dimethyl acetylenedicarboxylate (Scheme 3.65).

The author presented conclusive evidence that the generation of the resulting isoxazole (**64**) does not occur through the intermediate acetonitrile oxide.

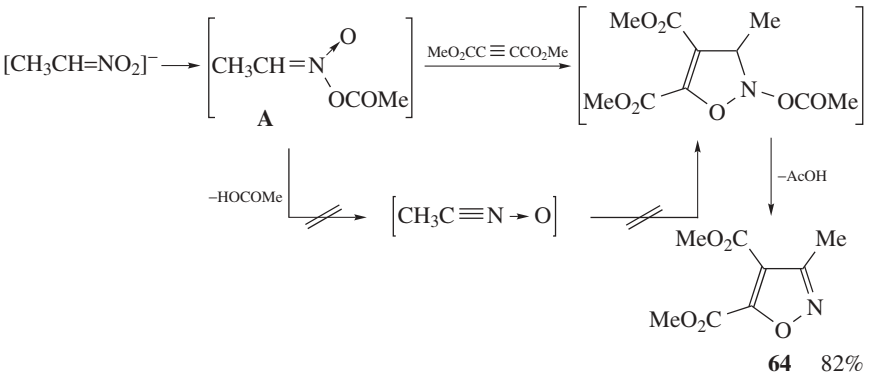
There is also evidence that conjugation of the nitronate fragment with π systems can stabilize acyl nitronates. For example, Perekalin and coworkers (224) isolated a very stable nitronate (**63a**), which was prepared by acetylation of 1,4-dinitrobut-2-ene salts (**65**) in a mixture with the corresponding C-acylation product (**66**) (Scheme 3.66), by column chromatography.

Even more stable acyl nitronates (**68**) were prepared from conjugated nitroalkenes (**67**) (Scheme 3.67) (224). Nitronates (**68**) were characterized by elemental analysis, mass, and IR spectroscopy.

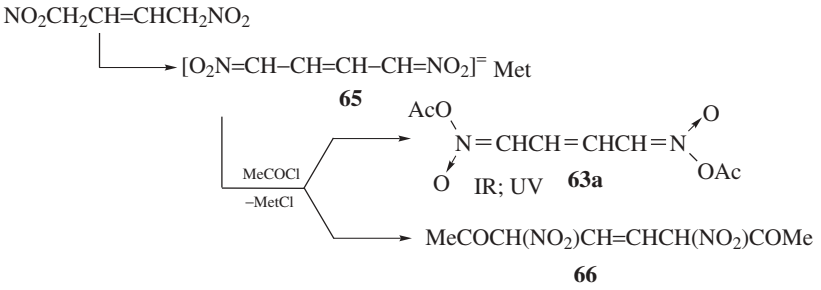
However, taking into account the unusually high stability of the resulting acyl nitronates shown in Schemes 3.66 and 3.67, additional data are required to confirm their structures.



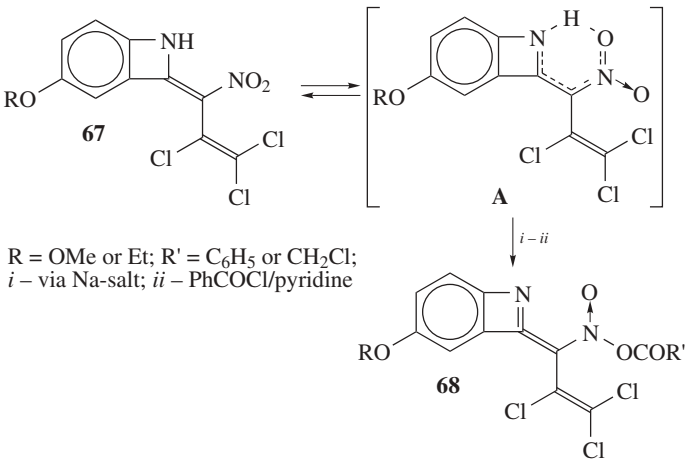
Scheme 3.64



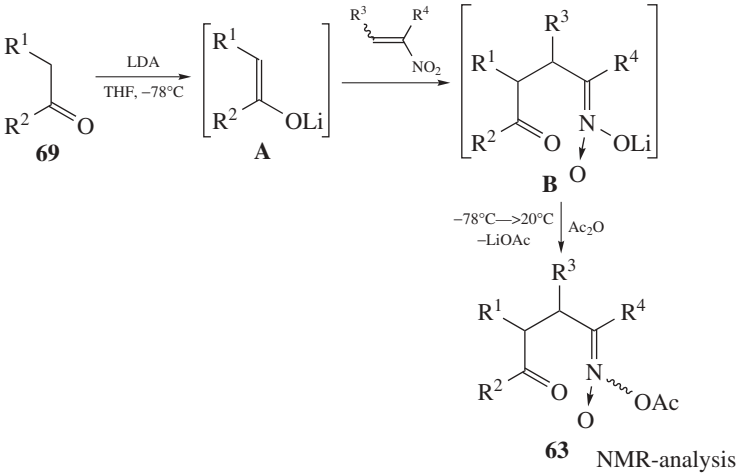
Scheme 3.65



Scheme 3.66



Scheme 3.67



Scheme 3.68

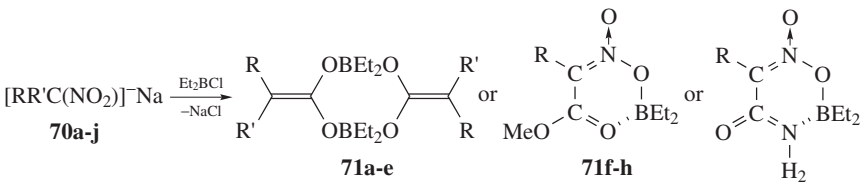
An interesting approach to the synthesis of acyl nitronates was developed by the Japanese research group headed by Yoshikoshi (226–228) (Scheme 3.68).

This method is analogous to the synthesis of silyl nitronates from conjugated nitro olefins (see Section 3.2.3.3). According to this strategy, acyl nitronates (**63**) derived from secondary AN are constructed in one step from carbonyl compounds (**69**) and conjugated nitroalkenes with LDA and acetic anhydride. Initially, *Li* derivatives **A** are generated from carbonyl compounds and then these derivatives are transformed at low temperature into the corresponding *Li* nitronates **B**. The latter are acylated at the oxygen atom to give acyl nitronates (**63**) in moderate yields. These products can be purified by flash-chromatography and are used in further transformations (226–228). Study by ^{1}H NMR spectroscopy demonstrated that acyl nitronates (**63**) are mixture of stereoisomers at the C,C double bond.

3.2.4.2. Synthesis of Dialkylboryl Nitronates Approaches to the synthesis of boryl nitronates are similar to the strategy for the synthesis of silyl nitronates developed in more detail (see Section 3.2.3). However, only four studies have dealt with the synthesis of boryl nitronates (217, 229–231). The absence of interest in this class of compounds is apparently attributed to the fact that they are not involved in 1,3-dipolar cycloaddition reactions and, consequently, are unlikely to find use in organic synthesis.

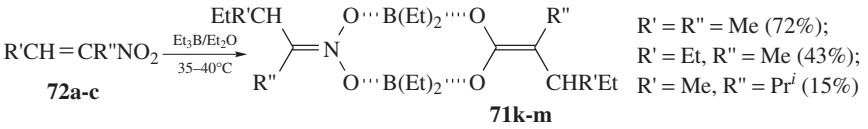
The reactions of salts of nitro compounds **70a–j** with diethyl borochloride allow one to prepare a wide range of boryl nitronates **71a–e**, **71f–h**, and **71i,j** (229, 230) (Scheme 3.69).

As can be seen from Scheme 3.69, the resulting nitronates have different structures (**71a–e** are dimers, whereas **71f–h** and **71i,j** are chelates). Low yields of some target substrates are attributed to their low thermal and hydrolytic stability.



a: R = Me, R' = CHMeEt, Br instead Cl (42%); **b**: R = R' = Me (42%);
c: R = H; R' = Me (54%); **d**: R = H, R' = C_3H_7 (21%); **e**: R = Me, R' = Ph (42%);
f: R = H, R' = CO_2Me (84%, crude); **g**: R = Me, R' = CO_2Me (97%, crude);
h: R = R' = CO_2Me (86%, crude); **i**: R = H, R' = $CONH_2$ (94%);
j: R = Me, R' = $CONH_2$ (60%).

Scheme 3.69



Scheme 3.70

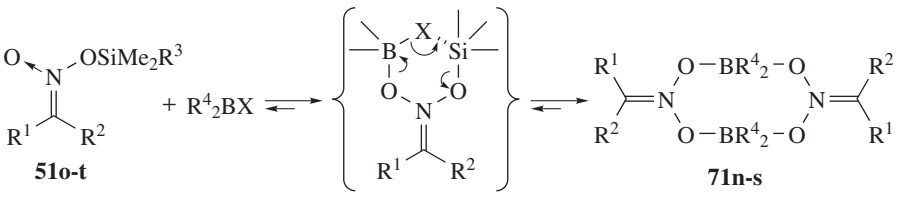
Another synthetic route to boryl nitronates (**71k–m**), which is, however, poorly developed (231), is based on the reaction of trialkylborons (exemplified by triethylboron) with α-nitroolefins (**72a–c**) proceeding by the 1,4-addition mechanism (Scheme 3.70, cf. Scheme 3.56).

Unfortunately, an increase in the size of substituents at the α- and β-C atoms of nitro olefin (**72**) leads to a sharp decrease in the yield of target nitronates. It casts doubt on the importance of this method or at least on the procedure suggested.

Finally, boryl nitronates can be synthesized by a method based on the replacement of the trialkylsilyl fragment in SENAs (217) (Scheme 3.71).

To successfully apply this approach, it is necessary to use boron halides as reagents. This equilibrium process (cf. Scheme 3.61), is being shifted to the right toward dimeric nitronates (**71n–s**) because the energy of the B–O bond (544 kJ/mol) (218) is higher than that of the B–Cl bond (489 kJ/mol) (218). The fact that there is an additional gain in energy in dimeric nitronates (**71n–s**) because boron is tetracoordinate, is of first importance. It should be emphasized that boron polyhalides (e.g., BF_3) can also be involved in exchange reactions, which extends the range of available boron derivatives of nitronic acids. Besides, this exchange process occurs under very mild conditions.

In this section, we considered virtually complete data on the preparation of covalent nitronates. Data on nitronates including other elements are scarce (see, e.g., Ref. 232) but they refer to either salts or nitro compounds in which the elementorganic fragment is bound to the carbon atom bearing the nitro group or to intermediates of unknown structures.



51o-t **71n-s**

71n: $R^1 = R^2 = CO_2Me$, $R^3 = Me$, $R^4 = X = F$ (80%);
71o; $R^1 = R^2 = CO_2Me$, $R^3 = Me$, $R^4 = H$, $X = Cl$ (80%);
71p: $R^1 = H$, $R^2 = CMe_2CO_2Me$, $R^3 = Me$, $R^4 = Et$, $X = Cl$ (70%);
71r: $R^1 = R^2 = Me$, $R^3 = Me$, $R^4 = Et$, $X = Cl$ (95%);
71s: $R^1 = R^2 = Me$, $R^3 = Pr^i$, $R^4 = Et$, $X = Cl$ (59%).

Scheme 3.71

3.3. PRINCIPAL PHYSICOCHEMICAL DATA AND CHARACTERISTICS

Since covalent nitronates contain several reaction centers, these compounds have versatile reactivity. On the one hand, high reactivity of these derivatives offers considerable scope for their use in organic synthesis. However, on the other hand, high reactivity is to a large extent responsible for the instability of nitronates. As a result, these compounds require special handling and special conditions for their storage. Hence, it is appropriate to begin this section with a discussion of stability of nitronates, as their main property, which is to a larger extent responsible for the possibility of practical use of these derivatives.

3.3.1. Stability of Nitronates

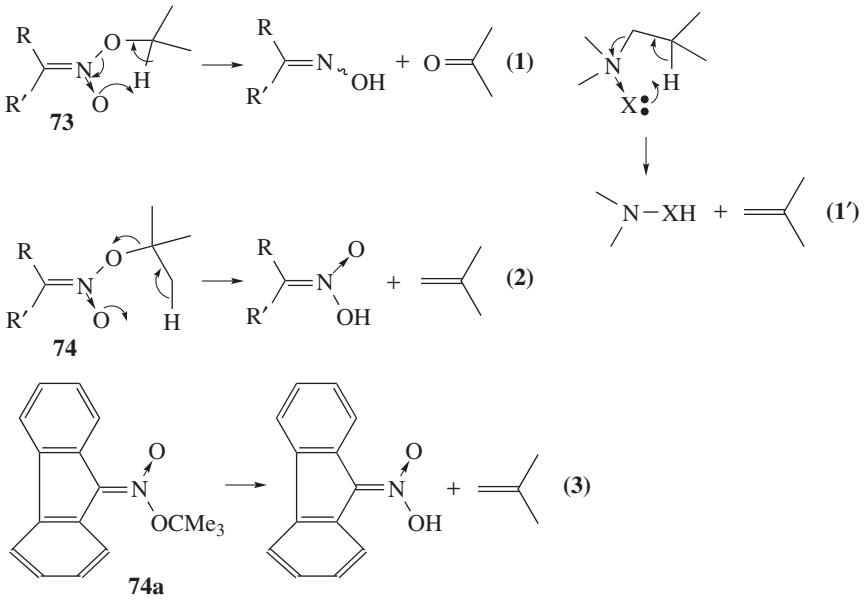
Since different types of nitronates decompose through different pathways, their stability will be considered separately.

3.3.1.1. Stability of Acyclic Alkyl and Acyl Nitronates A weak point of acyclic alkyl nitronates is their thermal instability because these compounds can be involved in two electrocyclic reactions presented in Scheme 3.72.

According to the first process, acyclic alkyl nitronates (**73**) afford corresponding oximes and carbonyl compounds (**3**) (Eq.1). This process is similar to the well-known Cope rearrangement (Eq.1′) (233).

However, if protons at the α-carbon atom of the O-alkyl fragment are absent, another process can occur resulting in elimination of olefin and generation of the respective aci-nitro compound (Eq.2). In particular, this "anomalous" decomposition was found by Nenitzescu and Isacescu (234) for nitronate **74a** (Eq. 3).

Spectrophotometric study of the decomposition kinetics of nitronate $(MeO_2C)_2C{=}N(O)OMe$ (**73a**) demonstrated that this compound decomposes at 25°C by a first-order reaction according to Equation 1 (Scheme 3.72) to give the

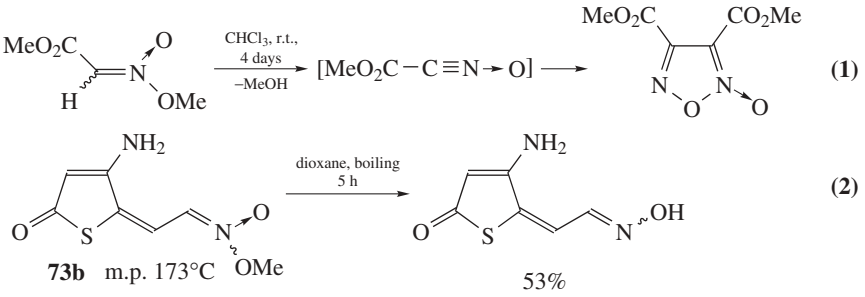


Scheme 3.72

corresponding oxime $(MeO_2C)_2C{=}N{-}OH$ in 80% to 90% yield (235). Decomposition of (**73a**) was studied in protic and aprotic solvents of different polarity (CH_2Cl_2, methanol, ethanol, dioxane, acetonitrile, monoglyme, ethyl acetate, and DMF). It was found that the reaction rate is virtually independent of the nature of the solvent ($k \approx 5{\cdot}10^{-4}{-}10{\cdot}10^{-4}\ min^{-1}$). Therefore, the results of the study (235) fully confirm that thermal decomposition of nitronate (**73a**) occurs as a monomolecular electrocyclic reaction. More than 30 years later, thermal decomposition of nitronate (**73a**) was reinvestigated by Japanese researchers (49), who obtained very close results. These authors also stated that thermal decomposition of nitronate (**73a**) is completely inhibited by the addition of 10% mol. boron trifluoride etherate, which however causes spontaneous decomposition of both isomers of nitronate $(MeO_2C)CH{=}N(O)OMe$ giving rise to bis-carbomethoxyfuroxan rather than the corresponding oxime $(MeO_2C)CH{=}N{-}OH$ (see Eq. 1 in Scheme 3.73).

Data on the chemistry of acyclic nitronates confirms that the process described by Equation 1 in Scheme 3.72 has a general character (see, e.g., Ref. 56) or the results of thermolysis of nitronate (**73b**) (236) described by Equation 2 in Scheme 3.73).

It should be noted that the mechanism of thermal decomposition of acyclic nitronates was not studied in detail. It is known that *cis* isomers of alkyl nitronates derived from primary AN are much less stable than the analogous *trans* isomers (49, 237a).



Scheme 3.73

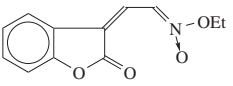
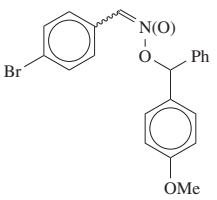
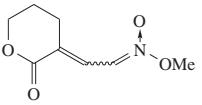
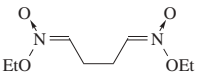
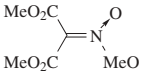
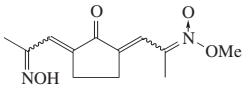
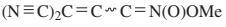
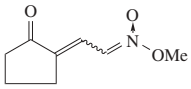
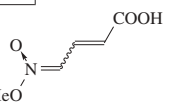
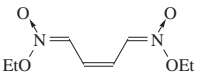
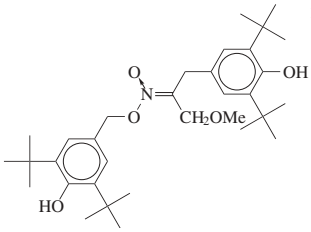
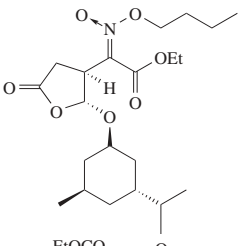
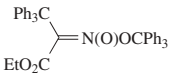
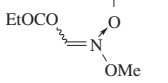
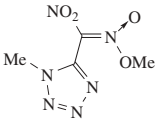
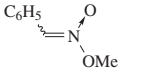
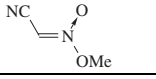
Kanemasa and coworkers demonstrated (49) that the above mentioned nitronate $(MeO_2C)CH{=}N(O)OMe$ in chloroform decomposes not through the standard pathway (Eq. 1, Scheme 3.72) but with elimination of methanol and formation of nitrile oxide, which undergoes dimerization to form the corresponding furoxan (Eq. 1, Scheme 3.73). However, these data directly contradict the results obtained by another Japanese research team (56), who used the standard fragmentation of nitronates $(MeO_2C)CH{=}N(O)OAlk$ for the *in situ* generation of aldehydes required for the synthesis of five-membered cyclic nitronates (Scheme 3.15). Probably, these essentially contradictory results can be reconciled by assuming, in accordance with the hypothesis (237b), that stability and the character of decomposition of alkyl nitronates derived from primary AN substantially depend on the nature of the solvent and, consequently alkyl nitronates can be used as precursors of the corresponding aldehydes only in polar solvents (DMF, *N,N*-dimethylacetamide) (56).

Table 3.5 gives the most typical examples of acyclic nitronic esters, which have unusually high thermal stability. These data contradict the known data on fast thermal decomposition of alkyl nitronates derived from the simplest nitroalkanes (237) and relatively low thermal stability of nitronate (**73a**). On the basis of the available data, the following empirical rule can be derived: an extension of the conjugation chain of the nitronate fragment increases stability of nitronates.

O-Acyl nitronates are much less stable than alkyl nitronates. The mechanism of thermal decomposition has not been studied systematically. It should be noted that acyl nitronates derived from primary AN are considered as precursors of nitrile oxides. The use of these nitronates in organic synthesis is hardly probable. However, acyl nitronates which have no protons at the α-C atom are convenient intermediates for the synthesis of nitrogen-containing heterocycles (see Refs (226–228)). As in the case of alkyl nitronates, the insertion of the nitronate fragment into the conjugation chain leads to a very strong increase in stability of acyl nitronates (224). Typical examples of stable acyl nitronates are given in Table 3.6.

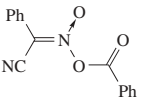
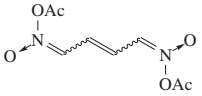
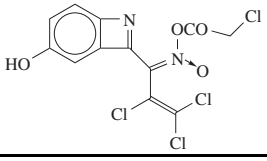
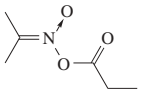
3.3.1.2. Stability of Silyl- and Boryl Nitronates SENAs cannot decompose through pathways characteristic of alkyl nitronates (see Scheme 3.72).

Table 3.5 Physical characteristics of acyclic alkyl nitronates

Entry	Nitronate	M.p., °C	Ref.	Entry	Nitronate	M.p., °C	Ref.
1		100	238	11		192	244
2		134	238	12		72	8
3	 **73a**	68	239	13		173–178	245
4		105	139	14		86–88	245
5		172	240	15		120	14c
6		155	241	16		92	8
7		221–222	242	17		89–90	17a
8		146–147	243	18		84/25[a]	246
9		78–80	20b	19		117/15[a] 83/1.5	247
10		122–123	5	20		52/0.08[a]	248

[a] b. p. °C/mm Hg

Table 3.6 Physical characteristics of typical acyl nitronates

Entry	Nitronate	M.p., °C	Ref.	Entry	Nitronate	M.p., °C	Ref.
1		115.8	249	3		174–175	224
2		188–190	225a	4		50/1	220

Actually, in these derivatives the silicon atom bonded to the oxygen atom of the nitro group contains no protons. Hence, decomposition according to Eq. 1 is impossible. The fragmentation according to Eq. 2 is also unlikely because the Si=C double bond is thermodynamically unfavorable.

These effects undoubtedly increase thermal stability of SENAs (many of these compounds are distilled *in vacuo* at temperatures higher than 100°C, see Table 3.7). At the same time, SENAs are hydrolytically highly unstable (see Section 3.4.2.2.). Besides, these compounds can undergo spontaneous decomposition for unknown reasons. It is known that acidic impurities facilitate these processes, whereas triethylamine, on the contrary, stabilizes SENAs (191). Hence, SENAs are recommended to be either stored in a refrigerator with full protection from atmospheric moisture or used *in situ*.

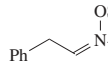
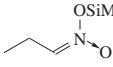
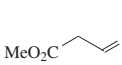
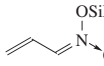
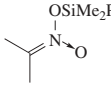
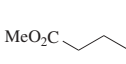
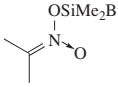
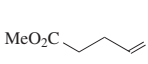
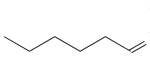
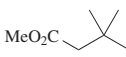
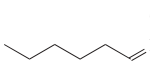
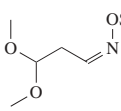
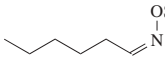
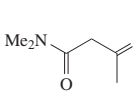
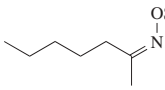
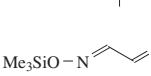
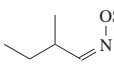
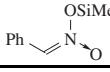
Typical physical characteristics of SENAs are given in Table 3.7. Gareev and coworkers synthesized a large number of phosphoryl-containing SENAs and characterized these compounds by densities and refractive indexes (255, 256).

Boryl nitronates (**75–78**), (217, 229–231) which have been poorly studied, are as a rule unstable. It should be noted that dimers (**75**) are crystalline compounds, which decompose in the solid state within a few days to give boron-containing heterocycles (**79**) (Scheme 3.74).

Other boryl nitronates (**76–78**), in which boron is coordinated to the functional group, are as a rule characterized by extraordinary high hydrolytic instability. Complexes (**77**) are exceptions. They melt without decomposition at temperatures higher than 100°C and are easily isolated from solutions.

3.3.1.3. Stability of Cyclic Nitronates For steric reasons, fragmentation of five- and six-membered cyclic nitronates cannot follow pathways presented in Scheme 3.72. Hence, stability of these compounds can be substantially higher than that of alkyl nitronates. These compounds generally exist in the crystalline state and can be purified by recrystallization or liquid chromatography. Selected melting points of nitronates are given in Table 3.8.

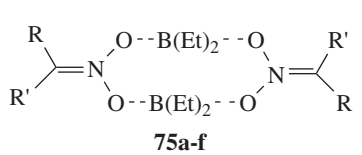
Table 3.7 Physical characteristics of SENAs

Entry	Nitronate	b.p. °C/torr	Ref	Entry	Nitronate	b.p. °C/Torr	Ref.
1		65–67/17	205	12		85–87/0.5	205
2		67/17	205	13		62/0.5	252
3		72–77/18	205	14		80–90/20	178
4		43/0.5	217	15		92–94/1	186
5		120–140/10	178	16		140–150/ 0.01 82/0.03	178, 253
6		65/0.01	178	17		110/10	217
7		70–72/0.35	250	18		67–68/0.03	254
8		140/0.005	178	19		116/0.05	202
9		90–100/ 0.01	178	20		150/0.01 (m.p. 68–69)	178
10		49–51/0.5	171	21		110/0.03[a]	253
11		63–65/0.3	251				

[a] enantiomerically pure $[\alpha_d] = +119^\circ$

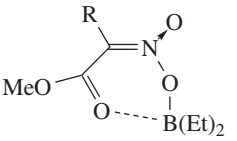
4,5–Disubstituted 4,5-dihydroisoxazole *N*-oxides and 5,6-dihydro-[4*H*]-oxazines containing at least two substituents at the C-4,C-5, and C-6 atoms have stereoisomers, which can as a rule be separated by liquid chromatography. Several strategies for diastereo- and enantioselective synthesis of cyclic nitronates are known. These strategies will be discussed in detail in Sections 3.4.4 and 3.4.5. For unknown reasons, unsubstituted cyclic nitronates are much less stable than their substituted analogs. However, six-membered nitronate are stable (see entry 20 in Table 3.8). Apparently, fragmentation of these compounds is associated with initial cleavage of the weak endocyclic N–O bond.

Chart 3.3 shows selected physical characteristics of rare strained four-membered as well as seven-membered cyclic nitronates.



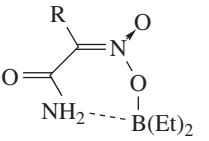
75a-f

R = H, R'=Me (**a**), Pr^n(**b**), Ph (**c**) (oils);
R = R'=Me (**d**) (mp 64–66°C),
R = Me, R'=Pr^i (**e**) (mp 62–65°C),
R = Me, R'=CHMeEt (**f**) (mp 63–65°C).



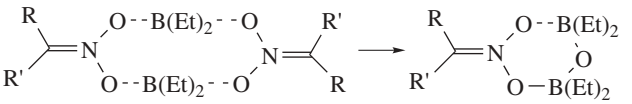
76a-c

R = H(**a**), Me (**b**), CO_2Me (**c**) (only in solutions)

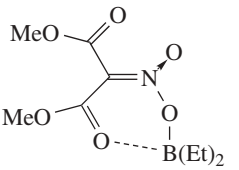


77a-b

R = H(**a**) (mp 110°C), Me (**b**) (mp 109–115°C)



75 **79**



78a
(only in solution)

Scheme 3.74

These data confirm the general conclusion about high thermal stability of cyclic nitronates.

3.3.2. Spectral Characteristics of Nitronates

During the period of more than four decades of extensive development of chemistry of covalent nitronates, at least a thousand of these compounds have been synthesized. Their overwhelming majority has been spectroscopically characterized. Hence, a consideration of all spectral characteristics of these products within the framework of this short section is of no significance, the more so as some data have been summarized in a recent monograph 3.

A discussion of problems, which could be solved by physicochemical studies of nitronates, seems to be much more useful.

In this respect, ways of detecting the nitronate fragment in substrates under study are considered first.

However, in our opinion, the rigorous assignment of products to covalent nitronic esters rather than to their structural isomers, which are true nitro compounds or ionic salts, is a more important and complex problem. This problem involves difficulties, because ambident anions of nitro compounds (which are evident precursors of nitronates) have comparable O- and C-nucleophilicities and, therefore, the resulting substrates can belong to any of the above mentioned series. Incorrect structure assignments of derivatives of polynitro compounds prepared from tetranitromethane were made in former studies. In addition, the structures of nitronates assigned to some products in early studies, should not have been accepted without the use of modern spectral methods.

Table 3.8 Physical characteristics of cyclic nitronates

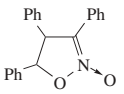
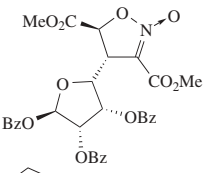
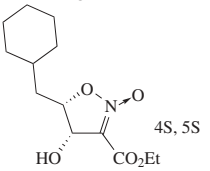
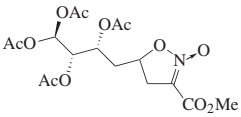
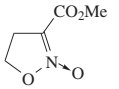
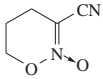
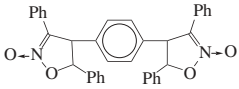
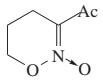
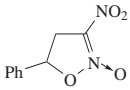
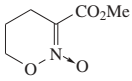
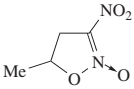
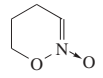
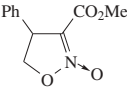
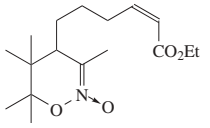
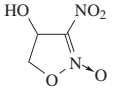
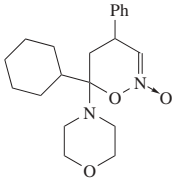
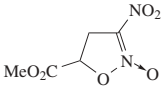
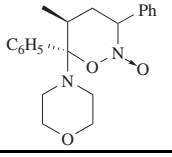
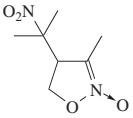
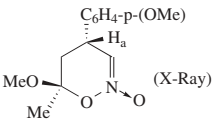
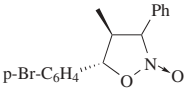
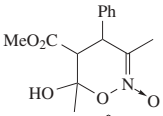
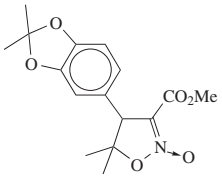
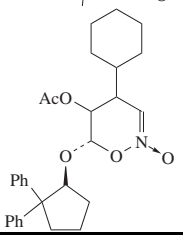
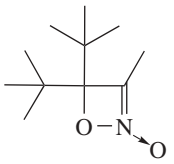
Entry	Cyclic nitronate	M.p. °C	Ref	Entry	Cyclic nitronate	M.p. °C	Ref.
1		161–162	44	14		97.5–99	262
2		96–97	19	15		85–87	48
3		122–123	57	16		163–164	72b
4		79	57	17		62–63	263
5		253–254 dec.	257	18		27–28	91
6		84–85	258	19		62–63	94
7		39–40	259	20		n_d^{20} = 1.5125[a]	92,49
8		82–84	61	21		52–53	110
9		129–130	52	22		53–54	119
10		71–72	260	23		126–128	114

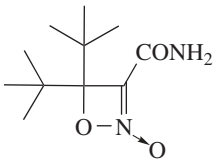
Table 3.8 (*continued*)

Entry	Cyclic nitronate	M.p. °C	Ref	Entry	Cyclic nitronate	M.p. °C	Ref.
11		77–78	37	24		115–117	264
12		213–215	44	25		104–105	265
13		185	261	26		187–189	137

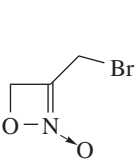
[a] unstable



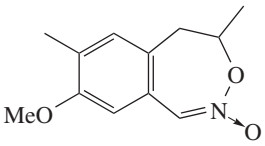
m.p. 85°C
$t_{subl.}$ 50°/0.001
t_{dec} > 100°C



m.p. 146°C



m.p. 98°C[Ref.167, 168]



m.p. 148-149°C[Ref.170]

Chart 3.3 Some physical characteristics of rare cyclic nitronates.

In studies of alkyl- or silyl nitronates, the problem of comparison of covalent and ionic structures is not urgent because it is impossible to imagine a stable product containing alkyl- or trialkylsilyl cations. However, this is not so evident for other elementorganic nitronates, and special studies were required to solve these questions (see, e.g., Ref. 232).

Another problem, which is as a rule solved by physicochemical studies, is the determination of the configuration of the C=N double bond in "nonsymmetrical" nitronates and the determination of the configurations of the stereocenters.

Finally, conformational analysis and investigation of the stereodynamics of nitronates are of importance.

The lack of systematic studies of the two last-mentioned problems hinders elaboration of modern mechanistic concepts, which are very useful for the development of the chemistry of nitronates.

The physicochemical characteristics of different types of nitronates were considered in detail in a review (266). Many data on this problem were included in a recent monograph (267).

3.3.2.1. UV and IR Spectroscopy of Nitronates Table 3.9 contains selected data from UV and IR spectroscopy of different types of nitronates. It is quite evident that characteristic spectral parameters are virtually independent of the nature of the fragment bound to the oxygen atom of the nitro group.

The UV spectra of nitronates, which are not functionalized at the α-C atom, have an intense absorption at 230 to 240 nm, which is very similar in characteristics to UV absorption of salts of nitro compounds and solutions of aci-nitro compounds in protic solvents. Since standard alkyl- or silyl nitronates cannot have ionic structures, the presence of the above mentioned absorption in the UV spectra of nitronates, unambiguously confirms, that these compounds have the structures of O-esters.

The introduction of substituents, which have a mesomeric effect and extend the chain of conjugation, at the α-C atom of nitronates leads to a shift of the absorption 260 to a maximum of 320 nm. It should be noted that the UV spectra of dimers of dialkylboron nitronates (entry 8) are virtually identical to those of other types of nitronates.

The IR spectra of unfunctionalized nitronates show an intense C=N stretching band between ν_{as} of the nitro group (1550–1560 cm^{-1}) and the C=N stretching band in oximes (1650–1685 cm^{-1}) (269).

This band in the spectra of acyclic nitronates is moderate in intensity, whereas the intensity of this band in the spectra of cyclic nitronates is substantially higher.

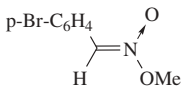
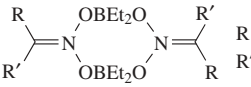
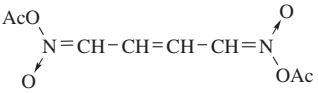
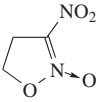
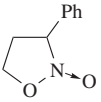
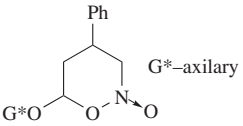
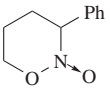
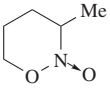
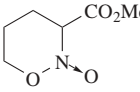
In Reference 267, the vibrational frequencies of nitrones, nitronates, and oximes were compared and it was concluded that the C=N vibrational frequency in the IR spectra of these derivatives decreases in the following series: oximes > nitronates > nitrones.

In the analysis of nitronates containing substituents, which extend the conjugation chain, the IR spectroscopic data are uninformative for the structural assignment because C=N absorption is shifted to lower frequencies (see entries 3, 6, 7, 9, 13, and 15), whereas the ν_{as} band of the nitro group is, on the contrary, slightly shifted to higher frequencies with the result that the characteristic ranges of these vibrations overlap. However, study of nitronate $MeO_2CCH{=}N(O)OMe$ (see entry 6) demonstrated that the C=N stretching band can be revealed by Raman spectroscopy (203). Actually, this band is clearly observed in the Raman spectrum of the nitronate, whereas the intensity of the ν_{as} band of the nitro group in the spectra of analogous nitro compounds is, on the contrary, very low.

IR spectroscopy can be used with advantage for the determination of the coordination site of the boron atom in boryl nitronates (230) (see Chart 3.4).

In the IR spectrum of nitronate (**76b**), the $\nu_{stretch.C=O}$ band is shifted to lower frequencies by approximately 150 cm^{-1} accompanied by a decrease in the intensity of this signal by more than twice due to coordination of the boron atom at the carbonyl group.

Table 3.9 Characteristic UV and IR absorbance for various nitronates.[a]

Entry	Nitronate	λ_{max} nm (ϵ)	$IR_{C=N}$ cm^{-1}	Ref.
1	$MeCH{=}N(O)OSiMe_3$	240 ($5.1{\cdot}10^3$)	1622	205
2	$Me_2C{=}N(O)OSiMe_3$	240 ($7.0{\cdot}10^3$)	1626	205
3	$PhCH{=}N(O)OSiMe_3$	280 ($7.0{\cdot}10^3$)	1590	205
4		288 ($32.7{\cdot}10^3$)	1610–1620	237
5	$CF_3CH{=}N(O)OSiMe_3$	—	1610	132
6	$MeO_2CCH{=}N(O)OSiMe_3$	265 ($10.0{\cdot}10^3$)	1590 1739 (C=O)	203
7	$(MeO_2C)_2C{=}N(O)OSiMe_3$	271 ($\sim 5.0{\cdot}10^3$) [b], [c]	1580 1750 (C=O)	268
8	 R = H or alkyl; R′ = alkyl	228–235 ($(10.2-10.7){\cdot}10^3$)	1615–1650	229
9		272 ($26{\cdot}10^3$)	1585	224
10		320 ($8.3{\cdot}10^3$)	1620	259
11		—	1620	57
12	 G*–axilary	—	1626	140
13		288 ($11.6{\cdot}10^3$)	1590	92
14		234 ($5.0{\cdot}10^3$)	—	92
15		—	1570	92

[a] For nitroalkanes: $\lambda_{max} = 210$ nm ($\epsilon \sim 1{\cdot}10^4$) and λ_{max} 270–280 nm ($\epsilon \sim 20$); $\nu_{as} \sim 1550-1560\ cm^{-1}$ 266.
[b] For nitronate **73a** $\lambda_{max} = 265$ nm ($\epsilon = 11.0{\cdot}10^3$) 235
[c] In KR-spectra $\nu_{C=N} = 1590\ cm^{-1}$ ($\rho = 0.44$) 203

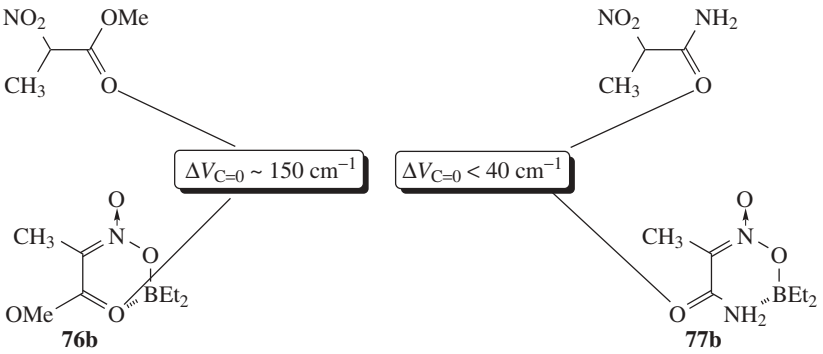


Chart 3.4

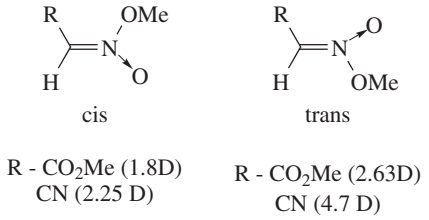


Chart 3.5

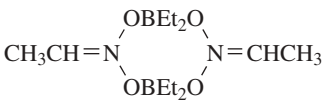
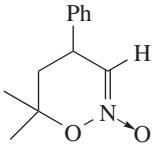
By contrast, the analogous low-frequency shift in the spectrum of nitronate (**77b**), in which the boron atom is coordinated at the nitrogen atom of the amide group, is no larger than 40 cm^{-1}. (In addition, coordination at nitrogen is confirmed by the low-field shift and splitting of the signals of the protons of the NH_2 fragment in the ^1H NMR spectrum of product **77b** (7.8 and 8.2 ppm) compared to their signal in the ^1H NMR spectrum of the starting amide (7.2 ppm, one broadened signal).

French scientists (270) suggested that the configurations of stereoisomeric acyclic alkyl nitronates can be determined from the relative dipole moments which for *trans*- isomers of nitronates containing EWG at the α-C atom are substantially larger than those of the *cis* isomers (Chart 3.5).

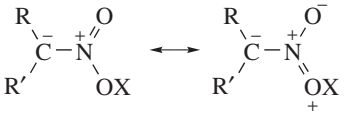
3.3.2.2. NMR Spectroscopy of Nitronates Due to the informativeness of NMR spectra and the fact that it is relatively easy to measure these spectra on modern NMR instruments, NMR spectroscopy is the most important and useful method for structural and stereoisomeric assignments of nitronates.

Tables 3.10 to 3.13 contain principal characteristic NMR parameters for different types of nitronates. In spite of evident differences in the structures of the model compounds used, their ^1H and ^{13}C NMR spectra have many common features.

Table 3.10 ^{1}H NMR resonances for nitronates[a]

Entry	Nitronate	ppm	Notes	Ref.
1	$CH_2{=}N(O)OSiMe_3$	5.50		266
2	$MeCH{=}N(O)OSiMe_3$	6.00	$^{2}J\ (H,^{15}N) = 0$	266
3	*trans*-$MeCH{=}N(O)OMe$	6.20		266
4	*cis*- $MeCH{=}N(O)OMe$	5.90		271
5		6.95	$^{2}J\ (H,^{15}N) = 2.9$	271
6	*trans*-$MeO_2CCH{=}N(O)OSiMe_3$	6.33	$^{2}J\ (H,^{15}N) = 0$	272
7	*trans*-$MeO_2CCH{=}N(O)OMe$	6.79	$^{2}J\ (H,^{15}N) = 0$	271 274;
8	*cis*- $MeO_2CCH{=}N(O)OMe$	6.43	$^{2}J\ (H,^{15}N) = 1.8$	270 274;
9	$MeO_2CCH{=}N(O)OBEt_2$	6.82		272
10	$CHBr{=}N(O)OSiMe_3$	6.96		266
11	$PhCH{=}N(O)OSiMe_3$	6.70		272
12	$CF_3CH{=}N(O)OSiMe_2Bu^t$	6.51(br)		132
13		6.36		274

[a]For CH_3NO_2 – 4.28 ppm; $MeCH_2NO_2$ – 4.38 ppm; $[MeCH(NO_2)]^-$ – 6.14 ppm 266.



A **B**

Chart 3.6

Since the α-C atoms in C-nitro compounds are sp^3 hybridized, whereas these atoms in nitronates are sp^2 hybridized, the signals for both the α-C atom and the protons bonded to this atom are shifted in nitronates to lower field. However, all of the above mentioned signals in the NMR spectra of nitronates $RR'C{=}N(O)OX$ do appear at higher field than the corresponding signals for analogous oximino derivatives $RR'C{=}N{-}O{-}$ due to the contribution of resonance structures **A** and **B** shown in Chart 3.6.

This rule is equally applicable to all types of true nitronates and is the most characteristic parameter of the $C{=}N{\rightarrow}O$ fragment. This is particularly typical of the ^{13}C NMR signals of the α-C atoms, which are shifted to higher field by more than 30 ppm compared to the analogous signals of the corresponding oximes.

Nitronates, in which the *N*-oxide fragment is absent, are characterized by strong paramagnetic shifts of the signals of the α-C atom and the proton bound to this atom (see, e.g., entry 5 in Table 3.10 and entries 2 and 9 in Table 3.11).

It is possible to choose between the structures of the true nitro compound and nitronate based on direct spin–spin coupling constants $^{1}J^{13}C,^{15}N$ which increase in nitronates by near to twice with reference to true AN (see entry 3, Table 3.12).

The question as to whether the boron atom is coordinated to the carbonyl group in boryl nitronates can be solved by analyzing the chemical shifts of the C=O fragment. For example, the signals of the coordinated and uncoordinated carbonyl groups in the spectrum of boryl nitronate (entry 6 in Table 3.11) differ by 12 ppm, although these signals in the spectrum of analogous alkyl nitronate (entry 7 in Table 3.11) are very close to each other. At the same time, the signals of two carbonyl groups in another boryl nitronate (entries 9,10 in Table 3.11) are also very similar. This unambiguously demonstrates that the boron atom in the latter nitronate is not coordinated to the carbonyl group.

The configurations of two isomers of nitronates derived from primary AN can be unambiguously determined by comparing the chemical shift of the proton bound to the α-C atom. The signal of this proton in the *cis* isomer appears at higher field (*cf*. entries 3 and 4 or entries 7 and 8 in Table 3.10). (It should be noted that the signals of the α-C-**H** protons in the spectra of SENAs are slightly shifted to higher field compared to the corresponding signals in the spectra of analogous alkyl nitronates). If only one stereoisomer exists, its configuration can be determined based on the presence (for *cis* isomers) or the absence (for *trans* isomers) of the constant $^{2}JH,^{15}N$ (see entries 2, 5, and 6–8, Table 3.10). An analogous dependence is observed also for oximes (223).

The related configurations of stereocenters in substituted cyclic nitronates can be determined by analyzing the spin–spin coupling constants between the vicinal protons in the stereoisomer discussed (Chart 3.7) (276). If needed, the results of this analysis are supplemented by special NOE experiments.

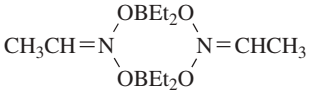
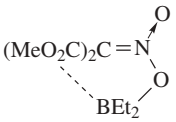
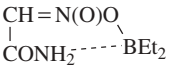
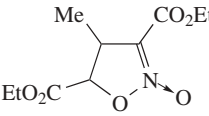
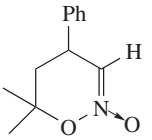
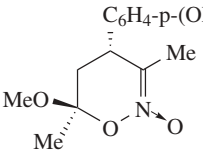
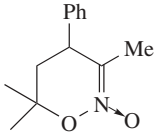
Analysis of nitronates by ^{14}N and ^{15}N NMR spectroscopy has an auxiliary character (see Table 3.12). The ^{14}N NMR signals are often broadened and, hence, are difficult to observe and are poorly informative, although magnitudes of their chemical shifts could in principle help in distinguishing between covalent nitronates and salts. It is difficult to observe ^{15}N NMR signals in natural-abundance NMR spectra of nitronates, while an introduction of a label is an expensive procedure.

For most of SENAs, the ^{29}Si chemical shifts can easily be measured by the *Insensitive Nuclei Enhanced by Polarization Transfer (INEPT)* method (see Table 3.13).

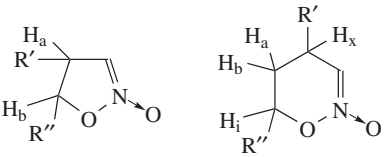
These shifts are similar to the ^{29}Si chemical shifts in the spectra of silyl derivatives of analogous oximes. This is evidence for the absence of essential additional coordination of silicon in SENAs. The qualitative and quantitative analyses of the ^{29}Si NMR signal can be considered as a simple method of NMR monitoring of SENAs in solution.

The ^{11}B NMR chemical shifts (Table 3.13) demonstrate that the boron atom in all known nitronates is tetracoordinated, that is, it is additionally coordinated by

Table 3.11 ^{13}C NMR resonances for nitronates[a]

Entry	Nitronate	δ(C − α) ppm	Notes	Ref.
1	$MeCH=N(O)OSiMe_3$	109.8	$^1J(^{13}C,^{15}N) = 27.4$ Hz	277
2		134.9	$^1J(^{13}C,^{15}N) = 27.5$ Hz	272
3	$MeCH=N(O)OBEt_2 \cdot NC_5H_5$ (−30°C)	114.3	$^1J(^{13}C,^{15}N) = 27.0$ Hz	272
4	$Me_2C=N(O)OSiMe_3$	118.3		277
5	$(MeO_2C)_2C=N(O)OSiMe_3$	114.2	δ_{CO} 158.8 ppm	277,278
6		111.7	δ_{CO} 158.1 and 170.1 ppm	272
7	$(MeO_2C)_2C=N(O)OMe$	111.8	δ_{CO} 158.5 and 159.5 ppm	266
8	$MeOCOC(Me)_2CH=N(O)OSiMe_3$	120.2	δ_{CO} 172.5 ppm	272
9	$[MeOCOC(Me)_2CH=N(O)OBEt_2]_2$	139.9	δ_{CO} 172.9 ppm	272
10	$MeOCOC(Me)_2CH=N(O)OBEt_2 \cdot NC_5H_5$	121.9	δ_{CO} 174 ppm	272
11		105.8	δ_{CO} 168.9 ppm	272
12		112.4		270
13		113.4		274
14		123		267
15		121.9		274

[a]For $MeCH_2NO_2$: $\delta_{CH2NO2} = 69.3$ ppm; for $[MeCH(NO_2)]^-$ $\delta_{\alpha-C} = 115.7$ ppm;[266]
for $(MeO_2C)_2CHNO_2$: $\delta_{CHNO2} = 88.2$ ppm; for $[(MeO_2C)_2CNO_2]^-$ $\delta_{\alpha-C} = 111.7$ ppm 266;
for PhCH=NOH: $\delta_{\alpha-C} = 146.4$ (syn), 149.6 (anti) ppm; for Me_2C=NOH: $\delta_{\alpha-C} = 154.3$ ppm 279



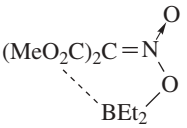
A **B**

Chart 3.7

Table 3.12 ^{14}N and ^{15}N resonances for nitronates

Entry	Nitronate	$\delta_{=N(O)O-}$ (^{14}N, ppm)	Hz	Ref.	Notes
1	$MeCH{=}N(O)OSiMe_3$	-83 ± 5	270 ± 20	277	
2	$Me_2C{=}N(O)OSiMe_3$	-97 ± 10	550 ± 30	277	
3	$MeC(NO_2){=}N(O)OSiMe_3$	-74 ± 8	350 ± 50	272,277	-12 ± 2 ($\Delta \approx 100$ Hz)$-NO_2$ ^1J (^{13}C, ^{15}N) = 21.4 and 39.7 Hz

Table 3.13 ^{29}Si and ^{11}B resonances for nitronates

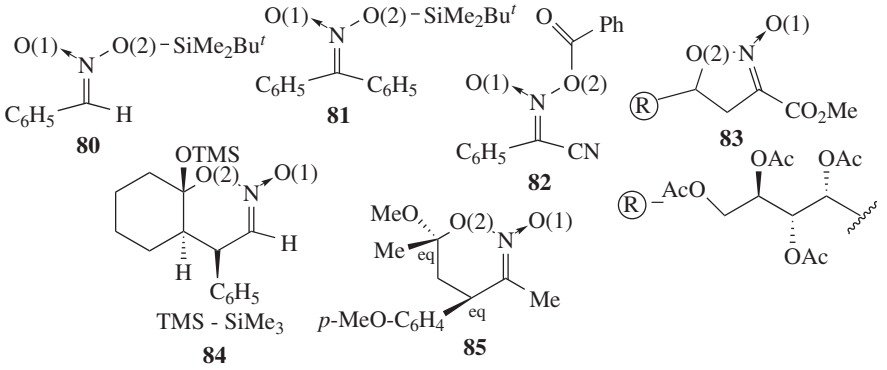
Entry	Nitronate	δ (^{29}Si) ppm	δ (^{11}B) ppm	Ref
1	$MeCH{=}N(O)OSiMe_3$	22.6		277
2	$Me_2C{=}N(O)OSiMe_3$	21.1		277
3	$(MeO_2C)_2C{=}N(O)OSiMe_3$	32.7		277
4	$Me_2C{=}NOSiMe_3$	21.2		267
5	$(MeO_2C)_2C{=}NOSiMe_3$	33.8		277
6	$[Me_2C{=}N(O)OBEt_2]_2$		12.0	229
7			15.8	230

the *N*- oxide oxygen atom, by the functional group, or by on external complexing agent (pyridine) (in addition, see Tables 3.10 and 3.11).

3.3.3. Character of Bonds in the Nitronate Fragment (X-ray and Calculation Data)

Nitronates have not been adequately studied by X-ray diffraction and calculation methods. Characteristic X-ray diffraction data for different types of nitronates are given in Table 3.14.

Table 3.14 X-ray diffraction data for nitronates



X-ray data	**80**[Ref.179]	**81**[Ref.178]	**82**[Ref.280]	**83**[Ref.263a]	**84**[Ref. 267]	**85**[Ref.264]
N—O(1)- bond (Å)	1.259	1.271	1.232	1.241	1.258	1.268
N—O(2)- bond (Å)	1.411	1.400	1.455	1.468	1.434	1.429
N—C- bond (Å)	1.302	1.309	1.318	1.302	1.296	1.302
O(1)—N—C- angle (grad.)	129.7	130.0	130.3	135.61	127.8	127.3
O(2)—N—C- angle (grad.)	114.1	114.7	114.0	110.64	120.6	121.5
O(1)—N—O(2)- angle (grad.)	116.2	115.3	115.6	113.70	111.5	111.2

Except for slight differences in the bond lengths and bond angles, the structure of the nitronate fragment weakly depends on the nature of the substituents at the carbon and oxygen atoms. The lengths of analogous bonds for related types of compounds, such as nitrone (**86**) and *O*- methyl ester oxime (**87**), are included for comparison (281) (Chart 3.8).

As expected, the nitronate fragment is planar in all nitronates. The C=N bond is shortened (in comparison with standard C–N bond), and its length is similar to the C=N bond lengths in reference structures (**86**) and (**87**). Two

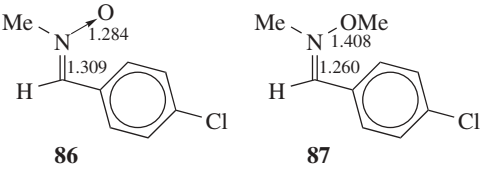


Chart 3.8 X-ray diffraction data for related structures 278.

N–O bonds in nitronates (**80 to 85**) strongly differ in length. One of these bonds (semipolar) is shortened and its length in all nitronates is even smaller than that in reference nitrone (**86**). To the contrary, another N–O bond length is similar to that in oxime derivative (**87**). As expected, the latter bond length is most sensitive to the electronegativity of the substituent, the higher the electronegativity, the larger being the bond length. Accordingly, this bond in acyl nitronate (**82**) is the weakest one, which facilitates generation of the corresponding nitrile oxide after elimination of the OAc-group and the proton from the α-C atom.

The sum of the bond angles at the nitrogen atom in nitronates (**80 to 85**) is close to 360°, which correlates with sp^2 hybridization of the nitrogen atom in these derivatives. However, all three angles substantially deviated from "classical" 120° (see Table 3.14). The O–N–O and O(2) –N–C angles are smallest. Evidently, a decrease in the O–N–O angle reflects a decrease in the grade of *s* character of the nitrogen atom on these orbitals. It cannot be ruled out that the O(1)–N–C angle increases due to a stereoelectronic repulsion between the substituent at the α-C atom and the O(1)- atom. (Analogous destabilizing interactions have been discussed earlier in connection with isomerization of sterically hindered α-nitroalkenes (167, 168).) The destabilizing repulsion between the phenyl substituent at C-3 and the O(1) atom in nitronate (**81**) causes rotation of this substituent so that it becomes orthogonal to the plane of the nitronate fragment, whereas another phenyl ring is in the plane of the nitronate fragment and is conjugated with this fragment. These are very fine effects because after removal of the "planar" phenyl ring, the remaining phenyl substituent (nitronate **80)** returns to the plane of the π system of nitronate to provide efficient conjugation with its π system.

In six-membered cyclic nitronates (e.g., in (**85**)) adopting a half-chair conformation, the C-6 and C-5 atoms deviate from the plane of four atoms in the opposite directions, the deviation of the C-6 atom being substantially larger (the deviation of the C-5 atom. The latter is generally at most 0.05 Å). It should be noted that one six-membered cyclic nitronate adopts a half-boat conformation (data from the Cambridge Structural Database, see also Fig. 3.2 and its discussion).

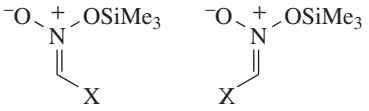
The geometry of nitronates has not been adequately studied by quantum-chemical calculations. For example, the bond lengths in nitronate $Me_2C{=}N(O)OMe$ were calculated by the INDO method for ideal geometry (248).

Dil'man has optimized the geometry of several model α-halogen-substituted SENAs by the B3LYP/6–31G(d) method (87, 282) (Table 3.15).

The calculated bond lengths and bond angles are in satisfactory agreement with the X-ray diffraction data for the nitronate fragment in model SENAs (Table 3.14) although the introduction of the halogen atom clearly leads to a slight change in the bond lengths and bond angles. Interestingly, the structural parameters of stereoisomers of α-halogen-substituted silyl nitronates are somewhat different. This is particularly true for the O←N=C angle. The latter is substantially larger in the *E* isomer, which apparently minimizes the destabilizing interaction between the oxygen and halogen atoms.

Table 3.15 Selected bond length and angles of α-halosubstituted silylnitronates[a]

Z-isomer *E*-isomer



For *Z*-isomer					
X	H	F	Cl	Br	I[b]
C=N (Å)	1.302	1.299	1.307	1.307	1.306
N→O (Å)	1.248	1.258	1.254	1.254	1.254
N—O (Å)	1.404	1.394	1.385	1.386	1.386
C—X (Å)	1.078	1.329	1.716	1.869	2.090
O←N=C (°)	128.62	126.03	125.36	125.40	125.38
O—N=C (°)	114.29	114.81	116.39	116.46	117.05
O—N—O (°)	117.08	119.15	118.25	118.14	117.57
For *E*-isomer					
X	H	F	Cl	Br	I[b]
C=N (Å)	1.302	1.299	1.307	1.306	1.306
N→O (Å)	1.248	1.250	1.245	1.245	1.243
N—O (Å)	1.404	1.409	1.404	1.403	1.406
C—X (Å)	1.079	1.328	1.712	1.864	2.082
O←N=C (°)	128.62	128.42	129.17	129.15	129.79
O—N=C (°)	114.29	112.21	112.35	112.59	112.56
O—N—O (°)	117.08	119.37	118.48	118.27	117.65
$\Delta(E_E\text{-}E_Z)$, kcal/mol		−0.2	−1.1	−0.9	−1.9

[a] Calculated at the level B3LYP/6-31G(d) unless otherwise mentioned.
[b] Combined basis set was used: LanL2DZ for iodine, 6-31G(d) for all other atoms.

The energetically favorable conformations of model alkyl nitronate (**88**) and related compounds (**89 to 91**) (283) were determined by the B3LYP/6−31G(d) method (see Chart 3.9). It appeared that the marked conformations with the minimized dipole moments are energetically most favorable for compounds (**88−91**) (the use of the dipole−dipole interaction model in conformational analysis was also described in the publication (284)). Calculations including $n-\pi$ interactions (see Fig. 3.1) did not change this situation because the contribution of this effect is equal in magnitude for both limiting conformations shown in Chart 3.9.

In addition, the character of the overall curve 1 indicates that rotation of the O−Me fragment about the N−O bond, in the range from 0° to 50°, leads to an insignificant change in the total energy of the conformation due to compensation of two effects similar in magnitude but opposite in the sign.

For steric reasons, cyclic nitronates cannot adopt the energetically most favorable conformation marked on Chart 3.9. Calculations by the B3LYP/6−31G(d) method for model unsubstituted six-membered cyclic nitronate (283) gave two most favorable conformations with approximately equal energies. These conformations are shown in Fig. 3.2.

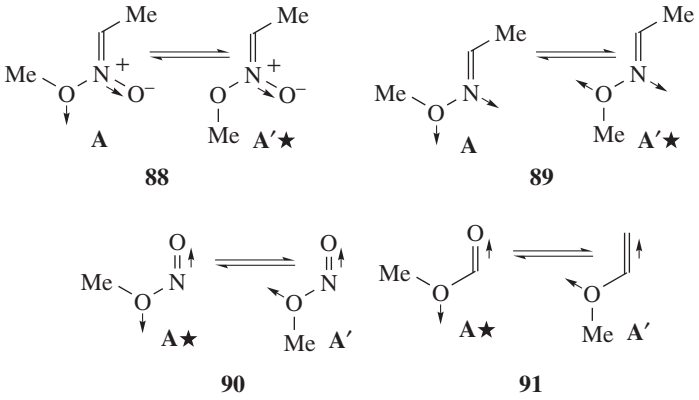


Chart 3.9

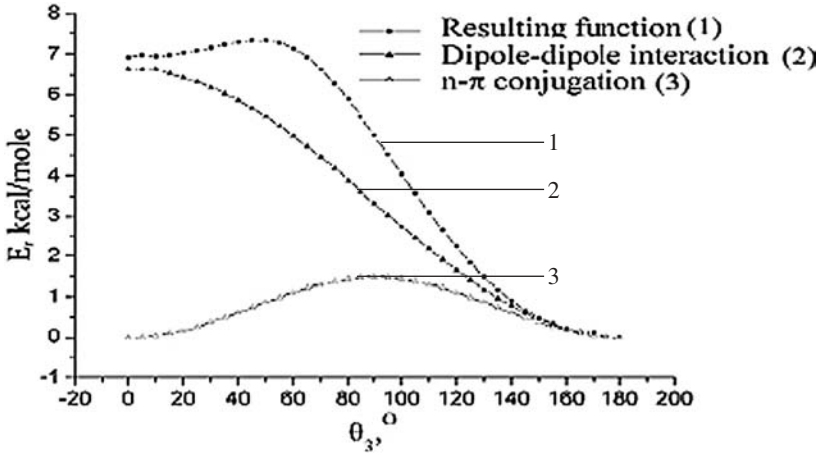
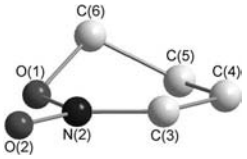
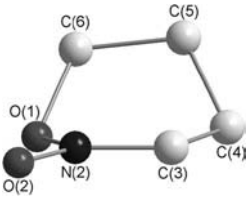


Fig. 3.1 The dependence of energies of conformations of model nitronates and related compounds from the value of rotation about the N–O bond (dihedral angle θ_3)

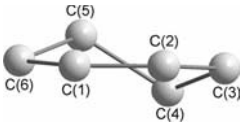
The conformation **A** is a half-chair, in which all atoms, except for the C-6 atom, are virtually in a single plane, from which the C-6 atom deviates due to rotation about the N–O(1) bond. The C(3)–N(2)–O(1)–C(6) dihedral angle θ^1 characterizes the degree of rotation. The N(2)–C(3)–C(4)–C(5) dihedral angle θ^2 corresponds to rotation about the C(3)-C(4) bond, which can occur independently of the first process and leads to a deviation of the C-5 atom from the plane of the nitronate fragment in the direction opposite to the C-6 atom. For the conformation **A**, $\theta^1 = 24.3^\circ$ and $\theta^2 = 6.5^\circ$,that is, $\Delta = /\theta^1/ - /\theta^2/$, which characterizes the difference in the degree of rotation about two bonds, is 17.8° (for cyclohexene, $\Delta = 0$). It should be noted that the results of these calculations are



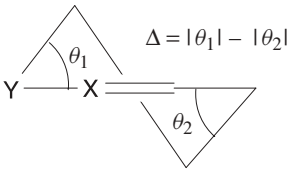
Conformation **A**



Conformation **B**



Cyclohexene



Conformation	θ_1,°	θ_2,°	Δ,°
A	24.3	6.5	17.8
B	53.7	–46.6	7.1

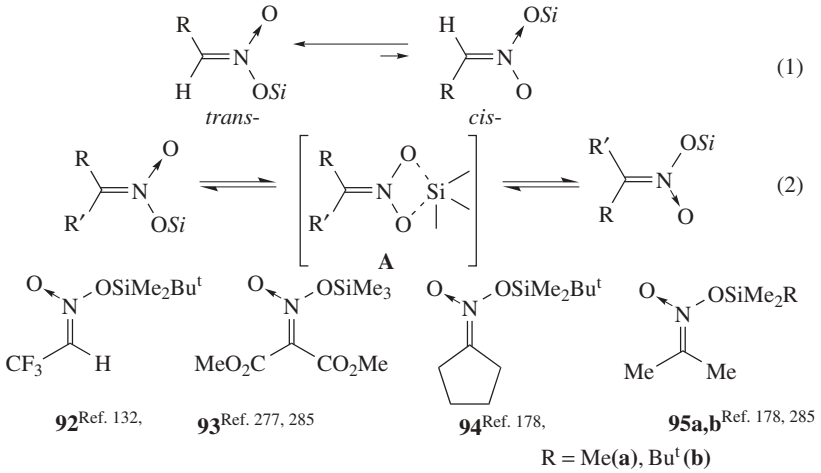
Fig. 3.2 Calculations of conformations for six-membered cyclic nitronate

in qualitative agreement with X-ray diffraction data from the Cambridge Structural Database for most of six-membered cyclic nitronates. Since the degree of rotation about the N–O bond in the range from 0° to 50° has virtually no effect on the energy of the conformation (see Fig. 3.1), the molecules of six-membered cyclic nitronates can minimize steric and electronic interactions of substituents by varying the deviation of the C-6 atom from the plane of the nitronate fragment over a wide range.

The conformation **B** (Fig. 3.2) is a half-boat, in which the C-5 and C-6 atoms deviate in the same direction from the plane of the nitronate fragment but at different angles ($\theta^1 = 53.7°$ and $\theta^2 = -46.6°$, that is, $\Delta = 7.1°$). The discussion of the conformation **A** is valid for the conformation **B**. Interestingly, X-ray data for one six-membered cyclic nitronate adopting the conformation **B** are available in the Cambridge Structural Database.

3.3.4. Stereodynamics of Nitronates

3.3.4.1. Intramolecular Migrations of the Trialkylsilyl Fragment As was mentioned in Section 3.3.2.2., acyclic alkyl nitronates are characterized by two sets of signals in the NMR spectra corresponding to the *E* and Z isomers, that is, the C=N bond in these products is configurationally stable under usual conditions. To the contrary, SENAs are, as a rule, characterized by one set of signals under usual conditions. For example, spectroscopic data suggest that silyl derivatives



for **92**: $\Delta H^{\neq} = 36.4$ kj/mol; $\Delta S^{\neq} = -75.4$k j/mol; $\Delta G^{\neq}_{298k} = 58.9$ kj/mol; $\Delta G^{\circ}_{293k} = 2.07$ kj/mol;

for **93**: $\Delta H^{\neq} = 47.4$ kj/mol; $\Delta S^{\neq} = -30.2$ kj/mol; $\Delta G^{\neq}_{298k} = 56.4$ kj/mol;

for **94**: $E_A = 42.0$ kj/mol.

Scheme 3.75

of primary AN are *trans* isomers, as evidenced by a number of characteristic features (see Tables 3.10 and 3.11). However, in some cases, *cis*- isomers of the starting nitronates were identified based on the configurations of the resulting products generated in 1,3-dipolar cycloaddition reactions (for more details, see Section 3.4.3.4.4). Consequently, a fast exchange process occurs in these derivatives (Scheme 3.75, Eq. 1), and *trans* isomers are thermodynamically more favorable due to steric factors.

Product (**92**) containing the CF_3 group in the α position is the only compound, in which the contribution of the *cis* isomer of SENA is rather high, and both isomers can be observed by ^{19}F NMR spectroscopy. However, the *trans* isomer of this compound is also thermodynamically more favorable.

For symmetric nitronates **93 to 95** (Scheme 3.75), the substituents at the α-C atom in the NMR spectra are equivalent under usual conditions, that is, they give one set of signals. However, at lower temperature, the signals of two MeO_2C and α-CH_2 fragments in the spectra of products (**93**) and (**94**), respectively, become nonequivalent (178, 285, 277). The kinetic parameters of the process described by Equation 2 and the kinetic and thermodynamic parameters of equilibrium (1) for product (**92**) (see Scheme 3.75) were determined by dynamic NMR. The presence of pentacoordinated silicon in products presented on Scheme 3.75 can be ruled out based on the ^{29}Si chemical shifts in the spectra of these SENAs. Hence, the stereodynamic process described by Equation (1) can be explained only as a 1,3−O,O-migration of the silyl fragment. The real rate of this migration is independent of the concentration of the respective SENA and is weakly sensitive

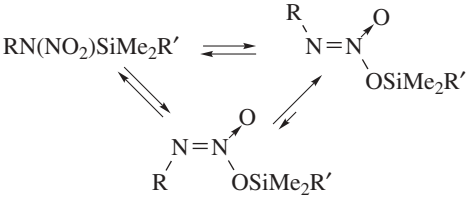
to the nature of the solvent. All of these factors correspond to an intramolecular process and the transition state **A** presented in Scheme 3.75 (Eq. 2).

This character of the process is indirectly confirmed by the X-ray diffraction data for compounds (**80**) and (**81**) (Table 3.14), in which the distance from the silicon atom to the valence bound O(1) atom is approximately 0.8 Å smaller than the sum of the van der Waals radii of these atoms. It should be noted that the bond angles at the silicon atom are somewhat distorted. For example, the $O-Si-CMe_3$ angle is substantially smaller than the tetrahedral angle (100.6° and 97.5°, respectively). The $Si-CMe_3$ and Si–O bonds are slightly elongated. In the authors' opinion (178), a distortion of the geometry of the silyl fragment in the crystals of (**80**) and (**81**) cannot be attributed to a steric factor. This distortion is evidence for the orientation of the silyl fragment in the field of the oxygen atom, which is not bonded to this fragment. The same intermediate structure should lie on the path from SENA to the transition state **A** for a concerted process (Scheme 3.75, Eq. (2)). The relatively high negative entropy of activation of the process also suggests that this process is electrocyclic.

Interestingly, the migration rate of the Si group in nitronates (**95a,b**) (Scheme 3.75) is so high that the methyl groups cannot be distinguished by the NMR method by lowering the temperature at which the spectra are measured to -100°C. (Now the migrations of organosilyl fragment in different organic compounds were studied (286–288). A decrease in the 1,3-XY-migration rates of the silyl group in the presence of electronegative substituents was documented (286).)

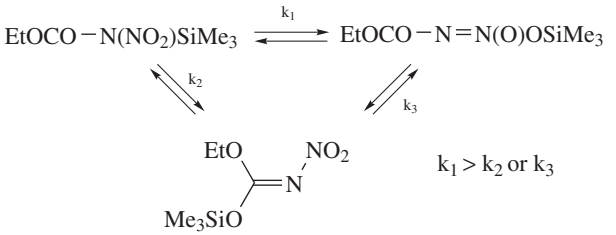
It should be emphasized that in no case were derivatives of AN containing the C–Si bond detected, although the formation of these compounds in certain silylation reactions as kinetic products cannot be ruled out. In particular, this can be expected for nitronates (**51 h,i**) (Scheme 3.57) generated in the reactions of silylated dimethylformamides with conjugated nitro olefins (202), because this reaction with other Michael substrates affords products with the C–Si bond.

It is notable, that a reversible migration of the silyl fragment from oxygen to the nitrogen atom bearing the nitro group occurs in silyl derivatives of *N*-nitroamines (Scheme 3.76) (289). The mechanism of 1,3-N,O-migration of the silyl fragment is analogous to that of 1,3-N,O-migration of the silyl fragment in SENAs (through a cyclic transition state), and both of these processes are characterized by similar kinetic parameters.



R - Me, Et, $NCCH_2CH_2$; R′ - Me, Pr^i, Bu^t

Scheme 3.76



Scheme 3.77

If a functional group in N-nitro derivatives attaches to the nitrogen atom, a two processes which are presented in Scheme 3.77 and proceed at different rates, can be observed by dynamic NMR (290).

These processes are 1,3-N,O-migration of the $SiMe_3$ fragment between oxygen of the nitro group and the nitrogen atom bonded to nitro group and 1,3-N,O-migration of the $SiMe_3$ fragment between the nitrogen atom and oxygen of the functional group (or 1,5-N,O-migration of the $SiMe_3$ group between the oxygen atoms of the nitro group and the functional fragment).

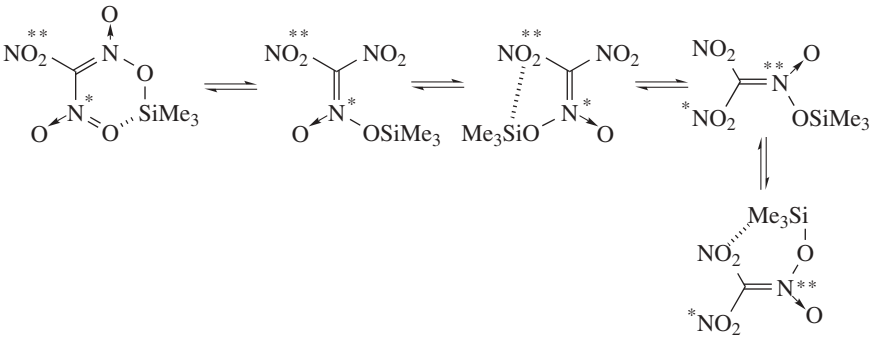
As mentioned above, in no case was the reversible exchange of the $SiMe_3$ fragment between oxygen of the nitro group and the functional group bound to the α-C atom observed. The silyl fragment is, as a rule, located at the nitronate group.*

However, the situation may be changed if the α-C atom is bound with several nitro groups. For example, the fast exchange of the trimethylsilyl fragment between all three nitro groups was detected for nitronate $(NO_2)_2C{=}N(O)OSiMe_3$ by the NMR method with the use of the ^{15}N label; for only one spin-spin coupling constant $^1J13_{C,}15_N$ (33.6 Hz) was observed in the temperature range from −60°C to 20°C (272). Evidently, three different coupling constants $^1J13_{C,}15_N$ are averaged due to the fast 1,5−O,O-shift of the $SiMe_3$ group. Apparently, this exchange can occur for the nitronate fragment only with the *cis*-nitro group as shown in Scheme 3.78. (It was established that the 1,5−O,O-shift of the silyl fragment with the *trans* carbonyl group in silyl derivatives of β-dicarbonyl compounds does not take place (288).)

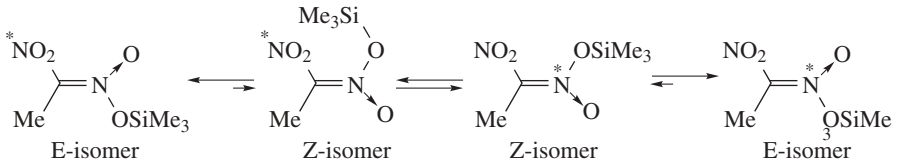
At the same time, two different coupling constants $^1J13_{C,}15_N$ were observed in the spectrum of the $SiMe_3$ derivative of 1,1-dinitroethane, in which the sterically hindered *Z* isomer is present at very low concentration. By this reason, the process of 1,5−O,O-migration of the $SiMe_3$ group is unobservable on the NMR time scale (272) (Scheme 3.79).

At 20°C: $^3J_{H,}15_N = 2.1$ Hz and 2.3 Hz; $^1J_{H,}15_N = 21.4$ and 39.7 Hz.

*It should be noted that selective silylation of the carbonyl group bound to the atom, which bears the nitro group, was documented (see products **60** Scheme 3.60, Eq. 3 (152, 214, 215),). It cannot be ruled out that silylation of other α-functionalized AN also affords initially intermediates silylated at the functional group, and that these intermediates rapidly and irreversibly isomerize into the respective thermodynamically preferable silyl nitronates.



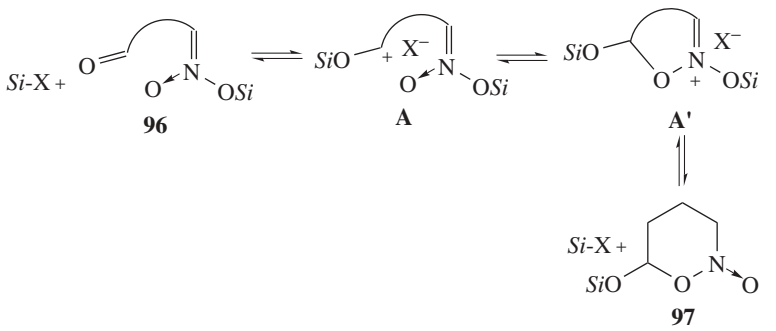
Scheme 3.78



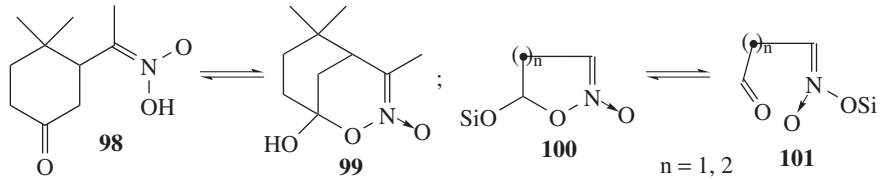
Scheme 3.79

3.3.4.2. Ring-chain Tautomerism of Nitronates and Derived Iminium Cations In these studies (291, 292), the ring-chain tautomerism of silylated cations **A**, prepared by reversible silylation of the above mentioned nitronates (**96**) was suggested as an explanation for the observed transformations of γ-keto-functionalized SENAs **96** (Scheme 3.80).

The same tautomeric equilibrium can be obtained in the silylation of six-membered cyclic nitronates (**97**) containing the siloxy or alkoxy group at C-6, which stabilizes the cationic center at the C-6 atom (293) (for more details, see Section **3.5**).



Scheme 3.80

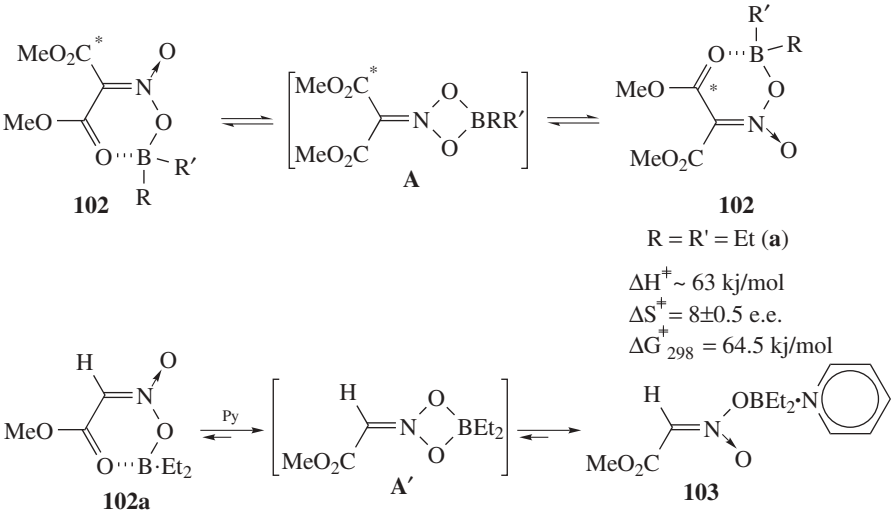


Scheme 3.81

Analogous tautomerism **98**⇄**99** has been observed earlier for similar functionalized nitronic acids (294) (Scheme 3.81).

Evidently, the cleavage of the weak endocyclic N–O bond is the driving force of the ring opening. The nucleophilicity of the *N*-oxide oxygen atom in nitronates facilitates the backward cyclization reaction (in the case of minimization of steric hindrance). With regard to the above mentioned one cannot exclude the tautomerism between cyclic nitronates **100** and "open" (or chain) isomers **101**.

3.3.4.3. Migrations of Dialkylboron Fragments in Acyclic Nitronates In dialkylboron derivative of diethyl nitromalonate (**102**) (Scheme 3.82), in which the boron atom is tetracoordinated due to bonding with one of the carbonyl groups, the nonequivalence of the carboxy groups observed in the ^{1}H and ^{13}C NMR spectra disappears with increasing temperature. Since the rate of exchange of the BEt_2 group between the carboxy groups is virtually the same in both acetonitrile and dichloromethane (285), the existence of the cationic intermediate $[BEt_2(NCMe)_2]^+$ in this process can be excluded with reasonable confidence, and



Scheme 3.82

consequently, the exchange occurs through the cyclic transition state **A** shown in Scheme 3.82.

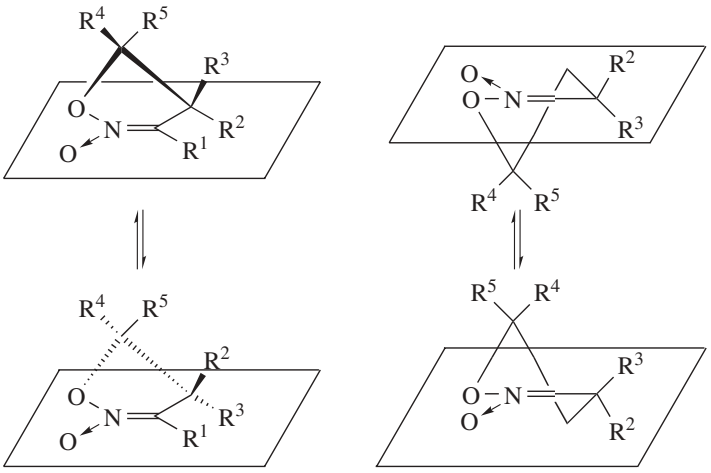
The kinetic parameters of the exchange process in product (**102a**) are similar to those of the corresponding exchange process in the related trimethylsilyl derivative (285).

In the dialkylboron derivative of nitroacetic ester (**102a**) adopting the *Z*- configuration, the tetracoordinated boron atom is bonded with the carbonyl group (NMR spectroscopic data) (230). Also, a complex of this product with pyridine (**103**) has the *E*- configuration (272). Apparently, the reaction of (**102a**) with pyridine also proceeds through the cyclic transition state **A′** (Scheme 3.82).

3.3.4.4. Stereodynamics of Cyclic Nitronates From general considerations and according to X-ray diffraction data (263a), molecules of five-membered cyclic nitronates should adopt an envelope conformation with the C-5 atom deviating from the plane. This atom fluctuates together with its substituents (R^4 and R^5) (Scheme 3.83, process ***a***).

An analogous situation was observed for the C^5 and C^6 atoms in six-membered cyclic nitronates (Scheme 3.83, process ***b***).

Both of these processes have no effect on the configuration of nitronates. Owing to low energy barriers, they are unobservable on the NMR time scale. (The ring-inversion barrier in cyclohexane (295) is 22 kJ·mol^{-1}; the calculated inversion barrier for unsubstituted six-membered cyclic nitronate (293) should also be not higher than 20 to 25 kJ/mol.). Hence, the NMR data reflect averaged most favorable thermodynamical conformations of cyclic nitronates.



Scheme 3.83

3.4. REACTIVITY OF NITRONATES

3.4.1. General Principles

The π-electron density distribution in nitronates can be described by borderline resonance structures **A–D** (Scheme 3.84).

Structure **B** is of most interest. It is responsible for the activity of nitronates as 1,3-dipoles in [3 + 2]-cycloaddition reactions. This is the most important aspect of the reactivity of nitronates determining the significance of these compounds in organic synthesis (see e.g., Ref. 267). In addition, this structure suggests that nitronates can show both, *O*-nucleophilic properties, that is, react at the oxygen atom with electrophiles, and α-C-electrophilic properties, that is, add nucleophiles at the α-carbon atom.

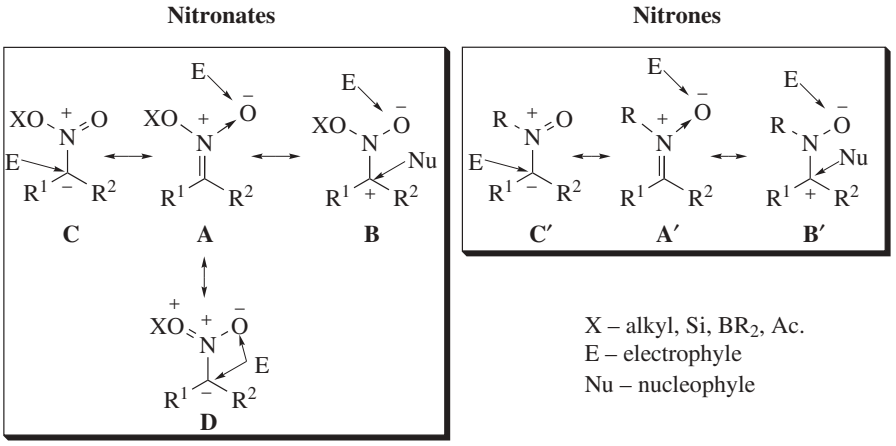
Structures **C** and **D** show that nitronates can also add electrophiles at the carbon atom.

The resonance structures of nitronates are most similar to those of nitrones, but nitronates have the additional structure **D**. Strange as it may seem, the contribution of this structure more likely slightly diminishes α-C-electrophilic activity of nitronates, move than is favorable for the appearance of the nucleophilic properties. In any case, no transformations, in which nitronates unambiguously act as C-nucleophiles, have been rigorously established.

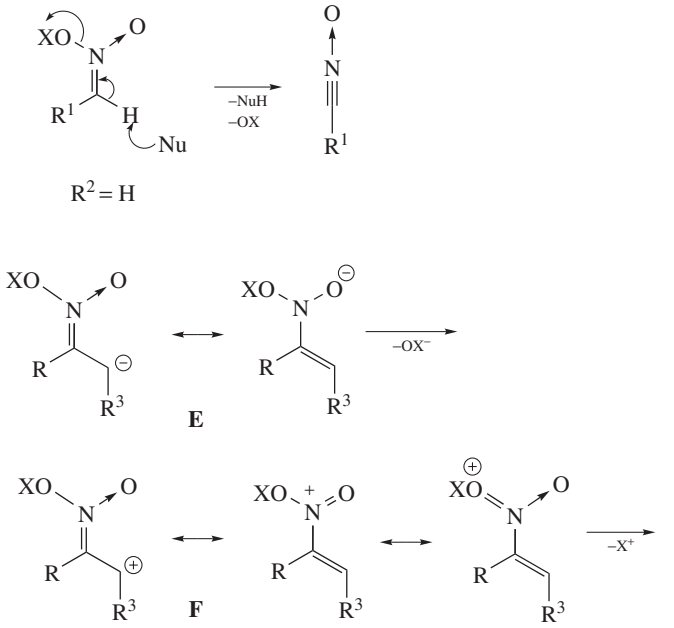
The addition of electrophiles at the oxygen atom could activate nitronates as C-electrophiles, analogously to that in the case of the carbonyl group (297). However, this aspect of reactivity of nitronates has remained unknown until very recent times.

Scheme 3.85 illustrates deprotonation of nitronates.

Here both deprotonation of the α-carbon atom followed by generation of nitrile oxides and deprotonation of the β-carbon atom can occur, giving rise to stabilized



Scheme 3.84



Scheme 3.85

anions **E**. However, in the presence of a good leaving group OX^-, the latter can become kinetically unstable and rapidly transform into the corresponding conjugated nitrosoalkenes. The problem of generation and efficient trapping of these anions still exists.

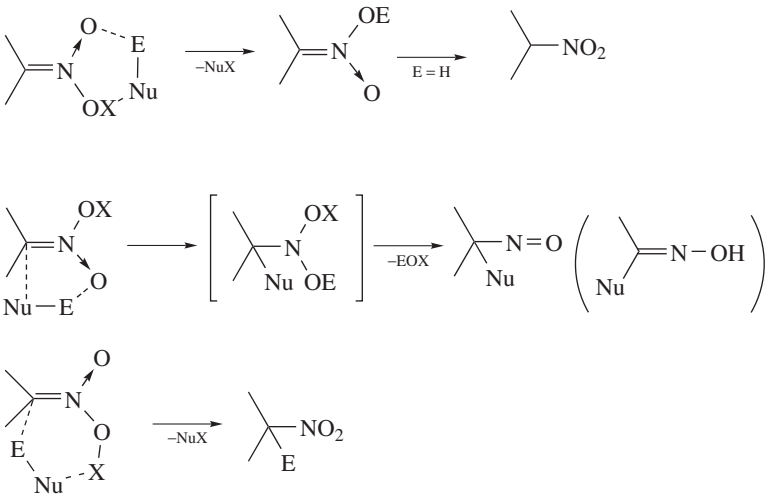
It should be noted that nitronates can stabilize not only a negative but also a positive charge on the β-carbon atom to give stabilized cations **F**. The latter, however, can also be kinetically unstable in the presence of a good leaving group **X**. It must be noted that this aspect of chemistry of nitronates also remains to be studied.

From the above it follows that, in spite of numerous potential possibilities, nitronates would not be "good reagents" in charge-controlled reactions. However, the structures of these compounds are favorable for concerted reactions, which are schematically shown in Scheme 3.86.

But, these processes can give rise to modified nitro or nitroso compounds or their isomeric oximes.

Since many of these processes occur through six-membered cyclic transition states, they can be highly stereoselective. However, for these reactions to proceed, not only high steric demands but also good leaving groups X are required. In this respect, silyl and acyl nitronates are *a priori* most preferable.

In the reactions of cyclic nitronates, the leaving groups that are generated upon cleavage of endocyclic N–O bonds are not eliminated and can be involved in further transformations.



Scheme 3.86

Therefore, it is evident that the group X to a large extent determines the specific features of the behavior of different types of nitronates. Hence, all aspects of the chemistry of these compounds (except for [3 + 2]-cycloaddition) will be considered separately for the main types of nitronates.

3.4.2. Reactions of Nitronates with Nucleophilic and Electrophilic Agents

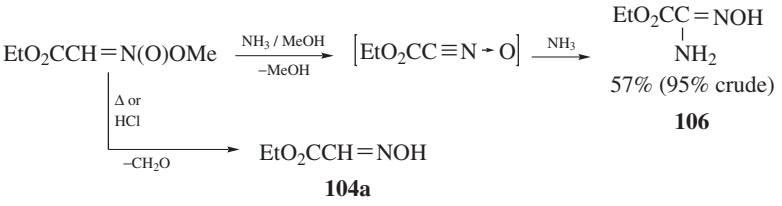
3.4.2.1. Acyclic Alkyl Nitronates The reactions of this type of nitronates with nucleophiles and electrophiles have not been systematically studied. It is most likely that this is associated with the low thermal stability of acyclic alkyl nitronates (see Section 3.3.1.1).

It was demonstrated that treatment of nitronate $MeO_2CH{=}N(O)OMe$ with HCI (246), as well as heating (298) affords oxime (**104a**) as a result of standard thermal decomposition of alkyl nitronates, which occurs via a Cope rearrangement (233) (Scheme 3.87).

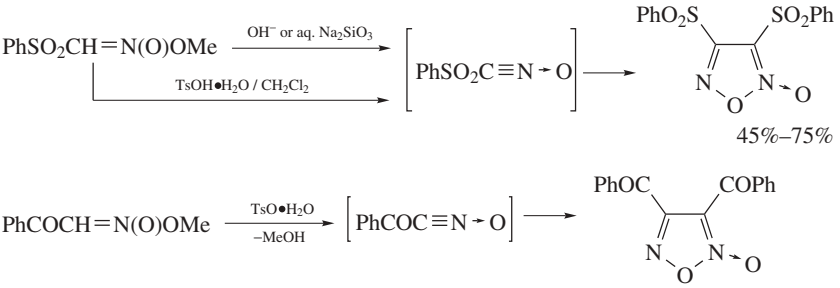
Refluxing of α,α-disubstituted nitronate (**105**) in water also gives rise to the corresponding oxime (**104b**) (299). However, treatment of the above mentioned nitronate with methanol saturated with ammonia produces amino oxime (**106**) in good yield (298). The latter is most likely formed through 1,3-addition of ammonia to the intermediate nitrile oxide. This is in good agreement with the scheme of decomposition of the initial nitronate suggested by Japanese researchers (49).

As can be seen from Scheme 3.88, nitrile oxides can be generated in the reactions of acids or bases with other alkyl nitronates derived from α-functionalized nitro compounds (300, 301).

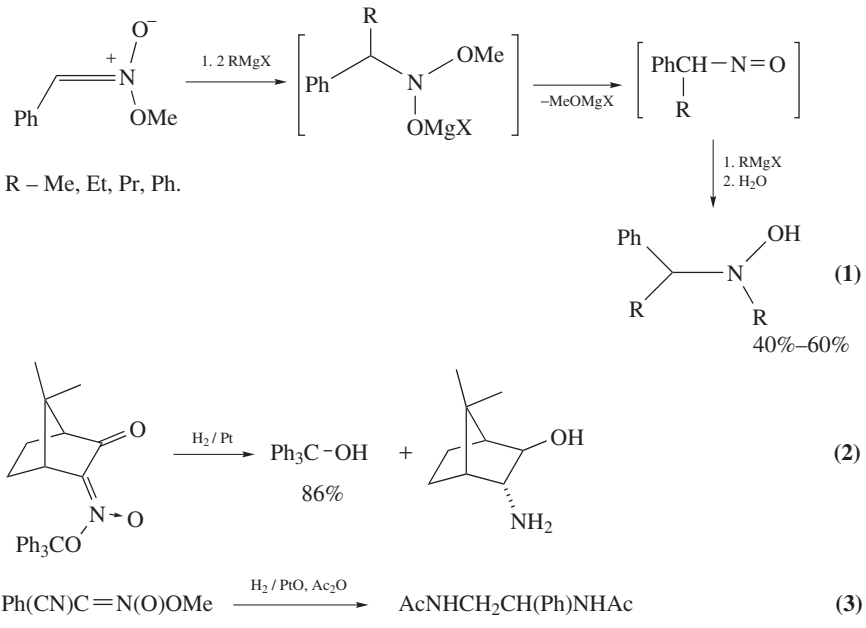
The 1,3-addition of Grignard reagents to the O-methyl ether of phenylnitromethane (Eq. (1), Scheme 3.89) was documented (302). However, this strategy has not been developed in succeeding years.



Scheme 3.87



Scheme 3.88



Scheme 3.89

Two examples of successful hydrogenation of the nitronate group were described (12, 220b) (Scheme 3.89), fully, but the authors did not isolate the target amino alcohols in individual state and their yields were not reported.

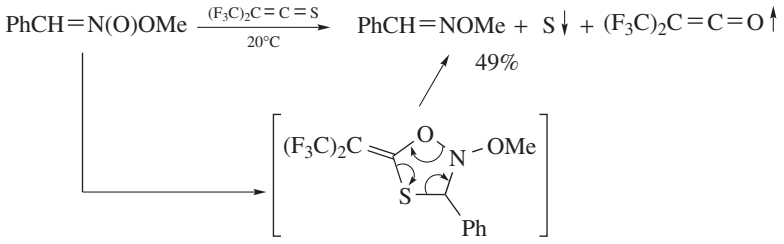
An interesting procedure for deoxygenation of O-methyl ether of phenylnitromethane with bis-trifluomethylthioketene was developed by Rash (303) (Scheme 3.90).

Apparently, the reaction involves cycloaddition of nitronate at the C=S double bond of thioketene. This approach can be useful for deoxygenation of labile nitronates.

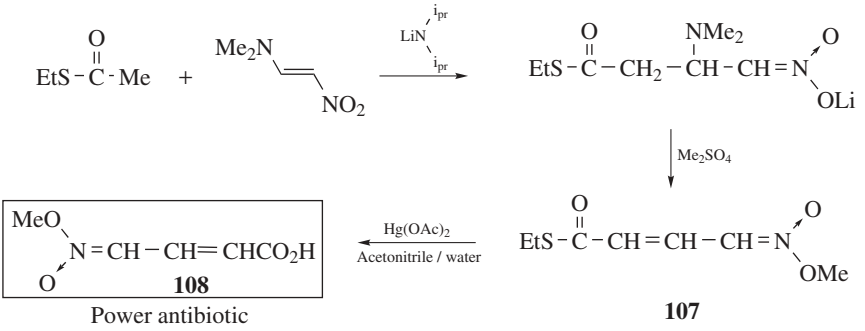
Severin and coworkers (14c) performed the facile synthesis of alkyl nitronate (**108**) (304), which is an analog of the powerful antibiotic enteromycin (305) (Scheme 3.91).

For this purpose, nitronate (**107**) containing the EtSCO- fragment was synthesized followed by selective saponification of this fragment with mercury acetate in water, which occurred with retention of the nitronate structure.

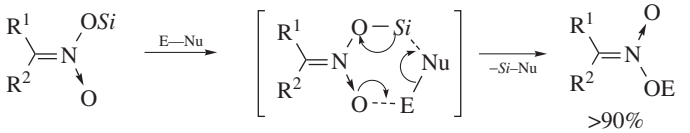
3.4.2.2. Silyl Nitronates The reactions of SENA with nucleophilic and electrophilic agents substantially differ in the character and the resulting products from the analogous reactions with acyclic alkyl nitronates. The differences are due to the fact that the O*Si* fragment is a good leaving group and that the



Scheme 3.90



Scheme 3.91



R^1 – alkyl, EWG – group;
R^2 = H, alkyl, EWG – group; *Si* – trialkylsilyl

$R^1R^2CHNO_2$

E-Nu = H-OH[Ref. 174,203-205]; H-OMe[Ref. 175,203-205];
H-Cl[Ref. 175,204,205]; H-NEt[Ref. 175,204]; Na-OH[Ref. 204]; XMg-Alk[Ref. 306]

Scheme 3.92

O-*Si* bond can also be cleaved in the presence of *Si*-active nucleophiles. Hence, eliminations play the major role in reactions of SENAs.

SENAs are readily desilylated by reagents containing an active proton (175, 203–205) and by sodium ethoxide (204, 306) (Scheme 3.92).

In these reactions, the starting AN are generally recovered in good yields or their salts are generated.

Unlike alkyl nitronates (302), their silyl analogs react with Grignard reagents at the silicon atom rather than at the α-C atom (306). All these processes may be represented as electrocyclic.

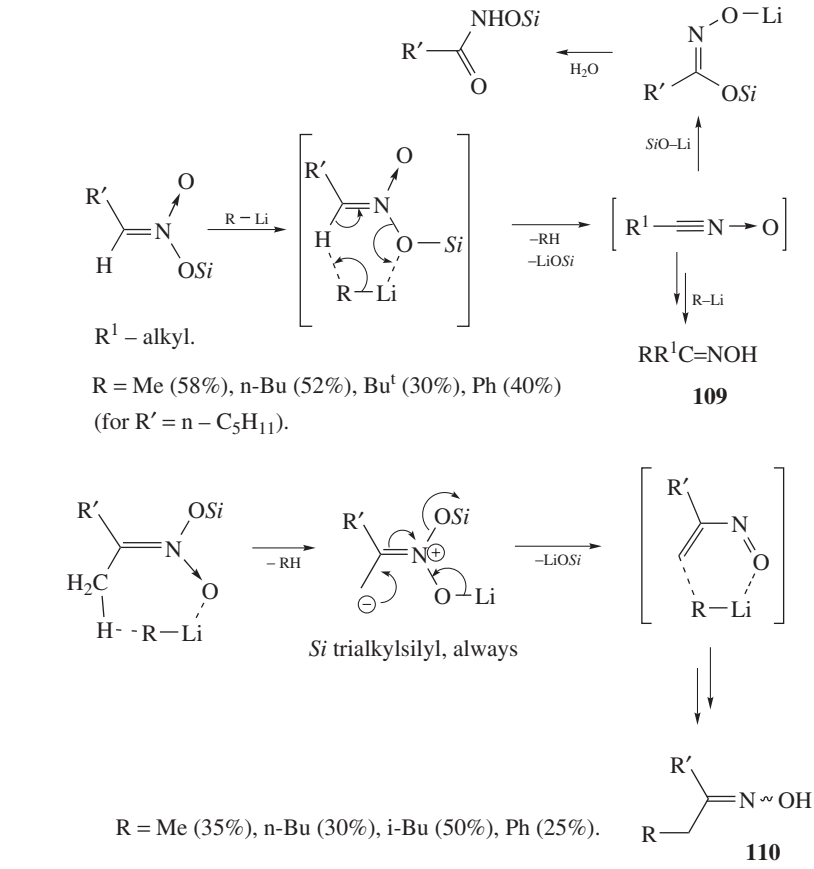
Organolithium reagents cause deprotonation of the α-C atom of SENA (306). If these protons are absent, deprotonation occurs at the β-carbon (Scheme 3.93). These transformations produce oximes (**109**) or (**110**), respectively.

The formation of the latter compounds can be attributed to the result of the direct attack of the nucleophile R on the α- or β-carbon atoms of SENAs after elimination of the corresponding protons. However, it is most likely that the reaction proceeds through nitrile oxides or conjugated nitrosoalkenes (see Scheme 3.93). This interpretation is evidenced by generation of silyl esters of hydroxamic acids R'CONHO*Si* as by-products. The reactions with more saturated solutions give the latter compounds as the major products.

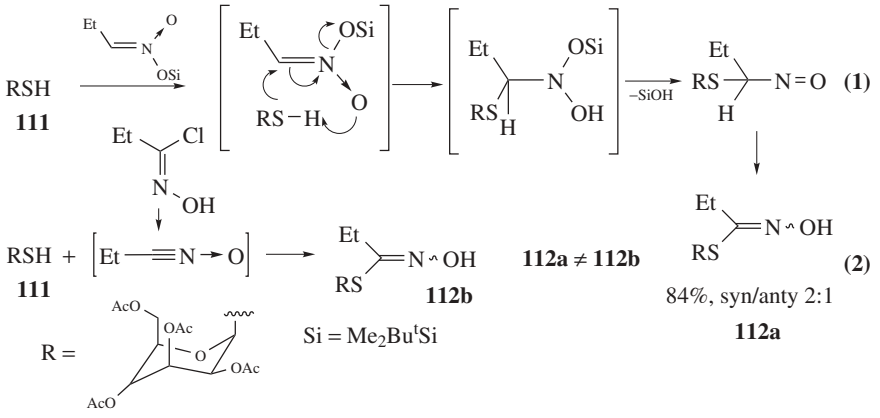
By contrast, softer nucleophiles, such as thiols (**111**), evidently do react with SENAs at the α-C atom (307) (see Scheme 3.94). This interpretation is confirmed by a substantial difference in the configuration of thiohydroxamate **112a** isolated in the reaction with silyl nitronate (**a**) and analogous product **112b** (**b**) prepared from authentic nitrile oxide.

The reactions of salts of nitro compounds (**113**) (Scheme 3.95) with silylated thiols (308), hexamethyldisilathiane (308, 309), and hexamethyldisilane (310) afford oximes (**114**), thiohydroxamates (**115**), or thiohydroxamic acids (**116**) as final products depending on the structures of the starting nitronates and the reagents used.

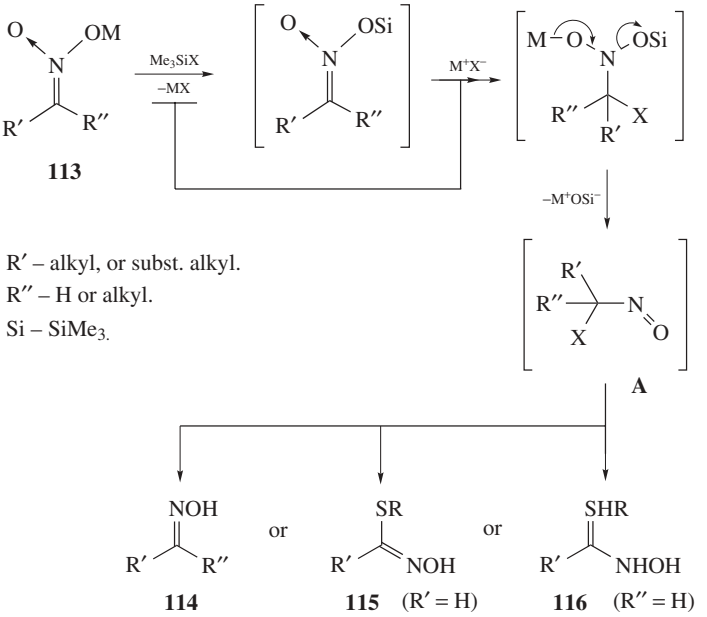
All reactions initially produce silyl nitronates, which react with nucleophiles to give nitroso intermediates **A**. The latter give products **114 to 116** either during the reaction or upon aqueous treatment.



Scheme 3.93



Scheme 3.94



113 **A**

114 **115** (R′ = H) **116** (R″ = H)

Met = K	X = SR (R - Me, $SiMe_3$)	yield **114** - 68%–96%
Met = K	X = $SiMe_3$	yield **116** - 50%–92%
Met = Li	X = SR^2 (R^2 - Me, Ph)	yield **115** - 61%–78%
Met = K	X = $SiMe_3$	yield **114** - 40%–73%

Scheme 3.95

Therefore, most nucleophilic agents do not react with SENAs at the α-C atom.

This situation is retained in the reactions with electrophilic agents. In particular, deoxygenation of SENAs with $P(OMe)_3$ also occurs at the oxygen atom to give the corresponding silyl derivatives of oximes in good yields (311).

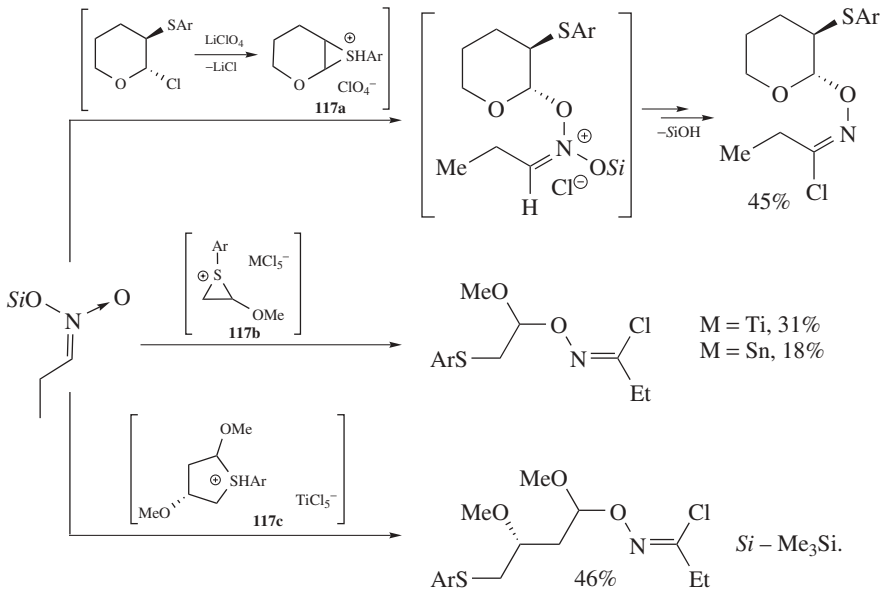
Evidently, thia-stabilized carbocations (**117a–c**) react with nitronates also at the *N*-oxide oxygen atom (312) (Scheme 3.96).

Variations in the nature of LA, which is required for the generation of cations, led neither to an increase in the yield of the target product nor to a change in the reaction pathway.

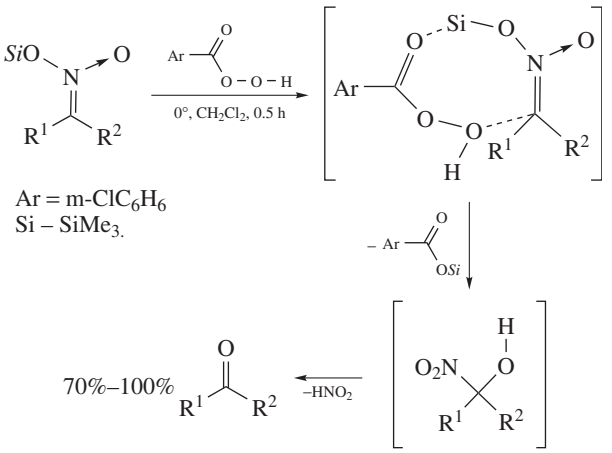
The attack of a cation on the oxygen atom of SENA should give rise to iminium cations, which can be stabilized by deprotonation or desilylation. (These possibilities will be considered in detail in Section 3.5.)

The reactions of SENAs with boron-containing LA also occur at the silicon atom and provide a route to boryl nitronates (see Scheme 3.71)

It cannot be ruled out that the reactions of SENAs with *meta*-chloroperbenzoic acid (184) involve the cationic attack on the α-C-atom of the nitronate (Scheme 3.97).



Scheme 3.96

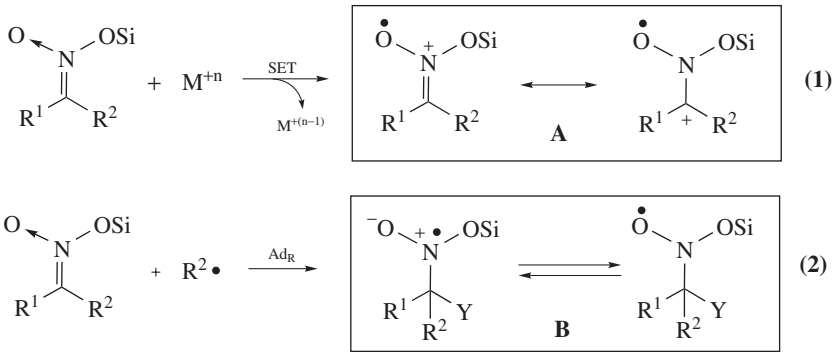


Scheme 3.97

It should be noted that this reaction is one of the mildest and most convenient methods of transforming secondary AN into ketones.

SENAs are convenient substrates for radical reactions (Scheme 3.98). This is due to several factors.

First, SENAs should be rather readily oxidized in one-electron transfer reactions. For example, MeCH=N(O)OSiMe$_2$Bu^t gives an oxidation peak in the

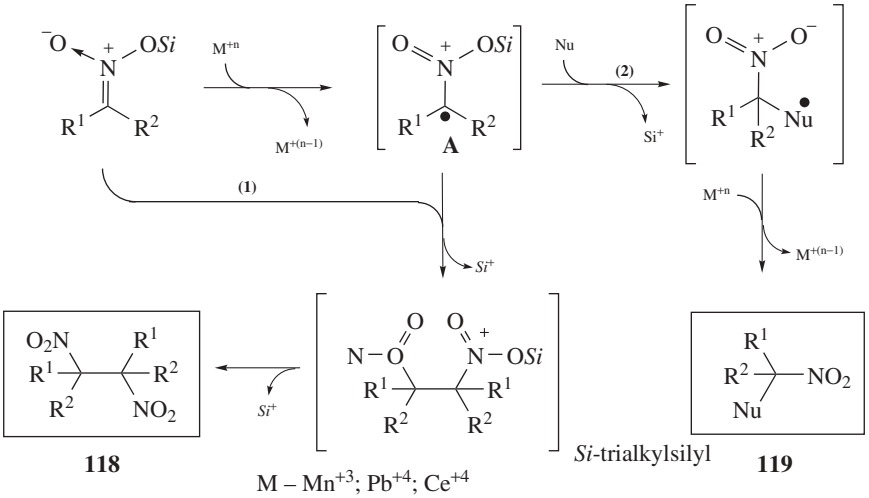


Scheme 3.98

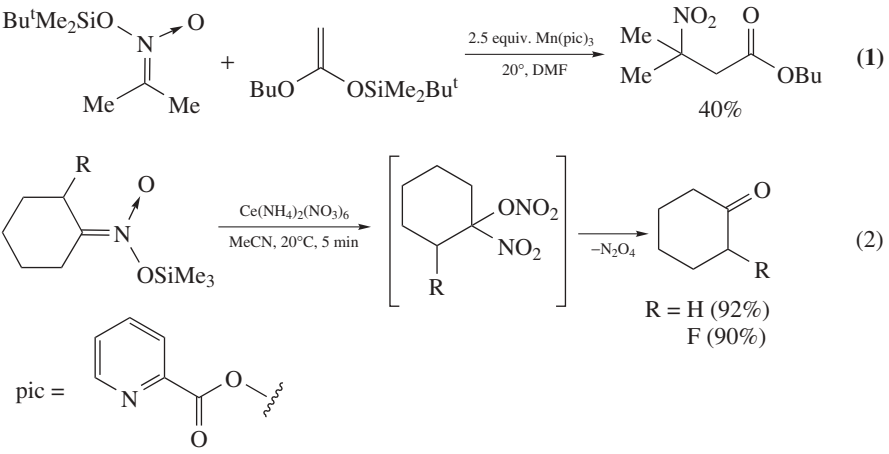
cyclic voltammogram at 2.1 V, whereas nitroethane shows no peaks lower than 3 V (313).

Second, nitroxyl radicals, which are generated either by a one-electron oxidation of SENAs (Eq. 1, Scheme 3.98) or by the addition of radical species to silyl nitronates (Eq. 2, Scheme 3.98), are rather stable and, consequently, can act as kinetically independent species.

SENAs can be oxidized by Mn (III) (313), Pb (IV) (314), or Ce(IV) (181) salts. The resulting cation radicals **A** (Schemes 3.98 and 3.99) either react with their precursors (313, 314) to give vicinal dinitro compounds (**118**) in low yields (pathway (**1**) in Scheme 3.99) or are trapped by an external nucleophile Nu (181, 313) (pathway (**2**) in Scheme 3.99) to give, after a one-electron oxidation, adducts (**119**).



Scheme 3.99



Scheme 3.100

This reaction was studied in most detail by Narasaka and coworkers (313). These authors demonstrated that silyl nitronates can be oxidized by different trivalent manganese salts (acetate, acetylacetonate, etc.), but $Mn(pic)_3$ is the oxidizing agent of choice.

Silyl enolates, enamines, or vinyl sulfides can serve as trapping agents.

A typical example of this reaction giving rise to β-functionalized nitro compounds is shown in Scheme 3.100 (Eq. 1). Here silyl ketene acetal was used as the trapping agent.

The nitrate anion can also serve as the trapping agent for radical cations (181) (Eq. 2).

The addition of C-centered radicals to the C=N bond giving rise to radicals **B** (Scheme 3.98) can be used for organization of radical C-alkylation of primary nitro compounds containing the sulfo group at the α-position (315).

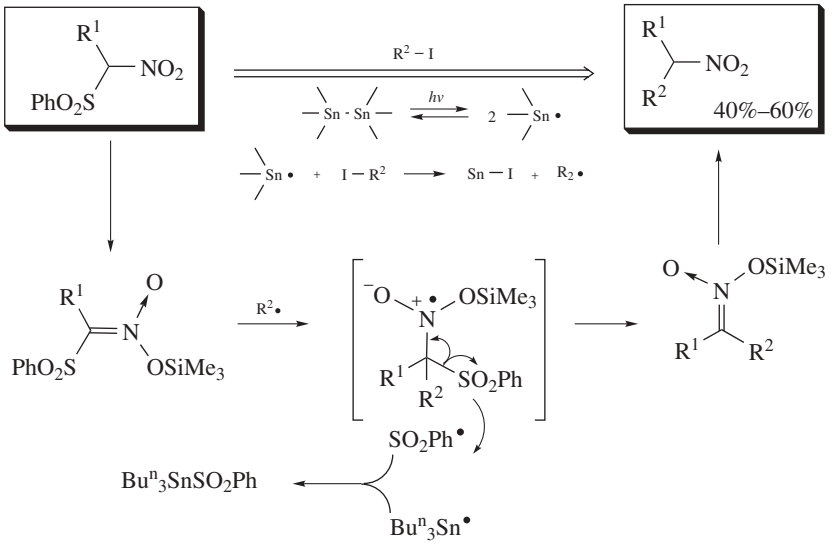
The radicals R can be generated by different iodides and hexaalkyldistannanes (Scheme 3.101).

In this case, radical intermediates eliminate stable sulfene radicals that recombine with the triorganostannyl radicals.

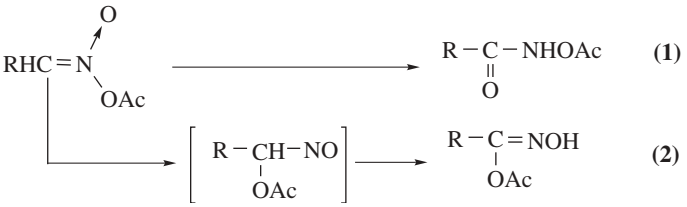
Secondary AN are produced in moderate yields.

3.4.2.3. Acyl Nitronates In spite of the fact that acyl nitronates have been known for many years (Jones, ***Am.Chem.J***., 20, 1 (1898)), the chemistry of these compounds remains poorly developed. This is most probably due to the very low stability of acyl nitronates derived from primary and α-functionalized nitro compounds (for more details, see Section 3.3.1.1).

For acyl nitronates of the general formula RCH=N(O)OAc, two types of rearrangements were suggested (Scheme 3.102), which are associated, respectively, with 1,2-migrations of the N-oxide oxygen atom (223) or the OAc fragment (219).



Scheme 3.101



Scheme 3.102

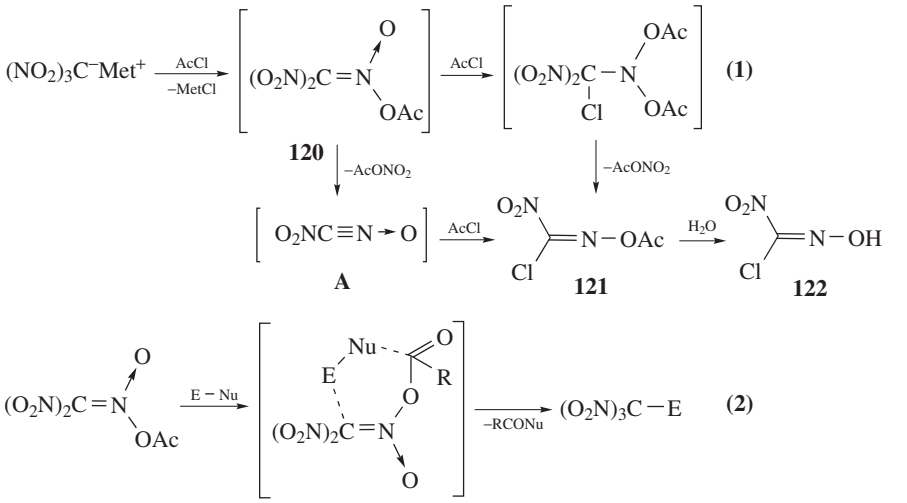
They give rise to N,O-diacylhydroxylamine derivatives (Eq. 1) or hydroxamic acid derivatives (Eq. 2).

No convincing evidence for these rearrangements was reported in these studies (219, 223).

The chemistry of O-acyl derivatives of trinitromethane was studied in more detail. By analogy with O-silyl ethers of trinitromethane, for intermediate (**120**) (Scheme 3.103, Eq. 1) it was suggested (222a) that the reaction involves elimination of acetyl nitrate to form the very unstable N-oxide **A**, which adds acetyl chloride to give derivative (**121**). Saponification of the latter affords isolable oxime (**122**).

However, this oxime can be generated via another pathway involving 1,3-addition of acetyl chloride to nitronate (**120**) followed by elimination of acetyl nitrate.

The latter interpretation is supported by rather successful attempts to trap very unstable nitronate (**120**) by various *E–Nu* reagents (222c) (see Eq. 2 in



Scheme 3.103

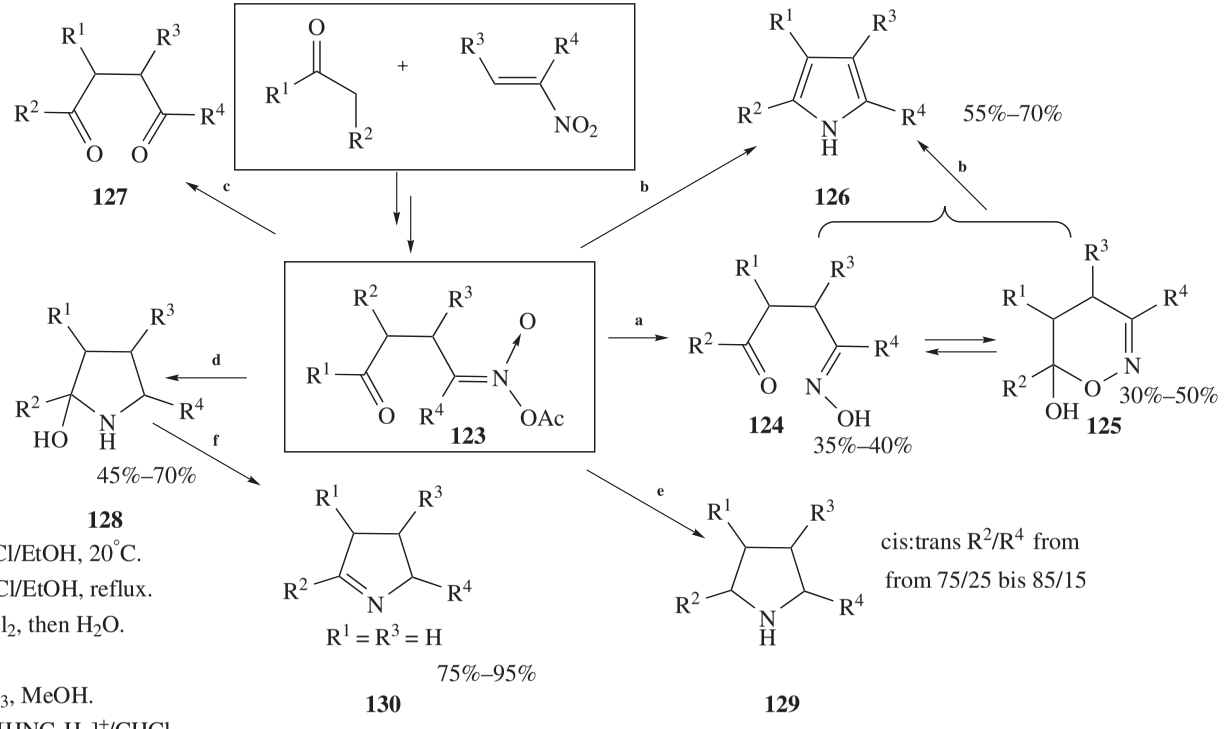
Scheme 3.103). In these experiments, a representative series of trinitromethane derivatives $(NO_2)_3C-E$ was isolated in various yields.

The chemistry of acyl nitronates derived from secondary AN has received much more attention. Yoshikoshi and coworkers (226–228) developed a reliable procedure for the synthesis of these derivatives from readily available precursors (ketones and α-nitroalkenes), they demonstrated that the resulting acyl nitronates (**123**) are convenient reagents for the preparation of various heterocyclic and acyclic derivatives (226) (Scheme 3.104).

For example, the reaction of nitronates (**123**) with a zinc copper pair in ethanol followed by treatment of the intermediate with aqueous ammonium chloride **a** to give an equilibrium mixture of ketoximes (**124**) and their cyclic esters **125**. Heating of this mixture **b** affords pyocoles (**126**). Successive treatment of nitronates (**123**) with boron trifluoride etherate and water **c** affords 1,4-diketones (**127**). Catalytic hydrogenation of acyl nitronates (**123**) over platinum dioxide **d** or 5% rhodium on aluminum oxide **e** gives α-hydroxypyrrolidines (**128**) or pyrrolidines **129**, respectively. Finally, smooth dehydration of α-hydroxypyrrolidines (**128**) into pyrrolines (**130f**) can be performed.

Each transformation shown in Scheme 3.104 involves consecutive reactions, for which optimal procedures were found. For example, path **b** involves four transformations: successive reduction of the nitronate fragment to the oximino group and then to the imino group followed by keto imino condensation and dehydration of intermediate pyrroline.

A more detailed consideration of these reactions is beyond the scope of chemistry of nitronates.


127
126
55%–70%
123
124
35%–40%
125
30%–50%
128
45%–70%
130
75%–95%
129
cis:trans R2/R4 from
from 75/25 bis 85/15
a: Zn/Cu, aq. NH4Cl/EtOH, 20°C.
b: Zn/Cu, aq. NH4Cl/EtOH, reflux.
c: BF3·Et2O, CH2Cl2, then H2O.
d: H2/PtO2, AcOH.
e: H2/ 5% Rh/Al2O3, MeOH.
f: p-Me-C6H4SO3−[HNC5H5]+/CHCl3

Scheme 3.104

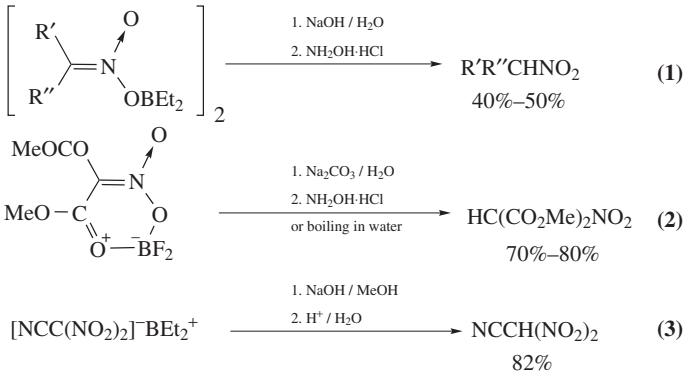
3.4.2.4. Dialkylboryl Nitronates In spite of an interesting structure, this class of nitronates remains poorly known. The lack of interest in boryl nitronates is apparently attributed to the fact that these compounds are inert to [3 + 2]-cycloaddition reactions.

Regardless of the coordination mode of the boron atom, boryl nitronates are rather smoothly subjected to alkaline hydrolysis to give, after acidification, the corresponding nitroalkanes (217, 230, 316). Depending on stability of the aci form, the yields of nitroalkanes obtained vary from moderate to high (Scheme 3.105).

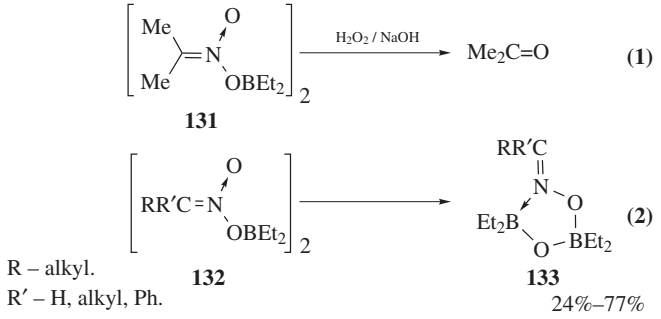
Oxidation of dimeric nitronate **131** with hydrogen peroxide in an alkaline medium generates acetone, whose yield was not determined (229) (Scheme 3.106).

Upon storage in solution or in its individual state, dimeric boryl nitronates (**132**) are transformed into heterocycles **133** (Scheme 3.106, Eq. 2) (229, 230, 316).

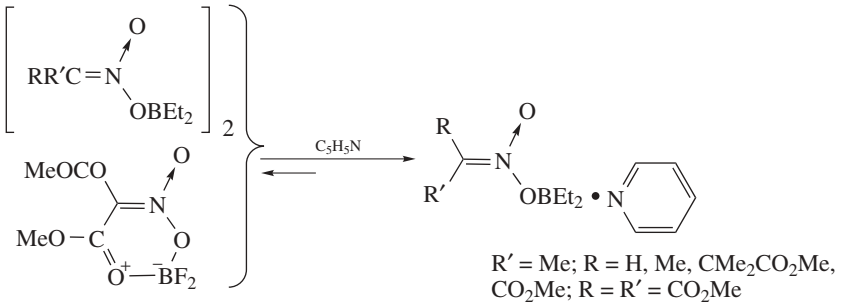
Interestingly, complexes, which are formed upon treatment of all boryl nitronates with pyridine, regardless of the coordination mode of the boron atom,



Scheme 3.105



Scheme 3.106



Scheme 3.107

are thermodynamically more stable than the starting nitronates (317). (Scheme 3.107).

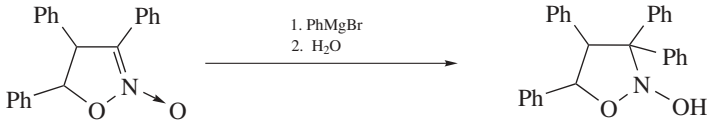
3.4.2.5. Cyclic Nitronates The chemistry of cyclic nitronates substantially differs from the chemistry of their acyclic analogs. Cyclic nitronates are involved predominantly in various rearrangements rather than in elimination reactions. The character and pathways of these rearrangements are determined not only by the nature of the reagent used but also by the character of the heterocycle and the nature of the substituents attached to the heterocycle.

Therefore, data on these compounds are difficult to summarize. Since certain five- and six-membered nitronates are easily assembled from simple molecules, some of the transformations considered in this section can be used for the development of new promising strategies for organic synthesis.

3.4.2.5.1. Reactions with Nucleophilic and Electrophilic Agents Examples of 1,3-addition of these reagents to cyclic nitronates are virtually lacking. To our knowledge, the reaction of phenylmagnesium bromide with 3,4,5-triphenylisoxazoline 2–N-oxide giving rise to the corresponding nitroso hemiacetal (318) (Scheme 3.108) is the only exception.

It is unlikely that this reaction is of general character. In any case, alkylmagnesium bromides give quite another product. The question whether other cyclic nitronates can be involved in this reaction also remains to be established.

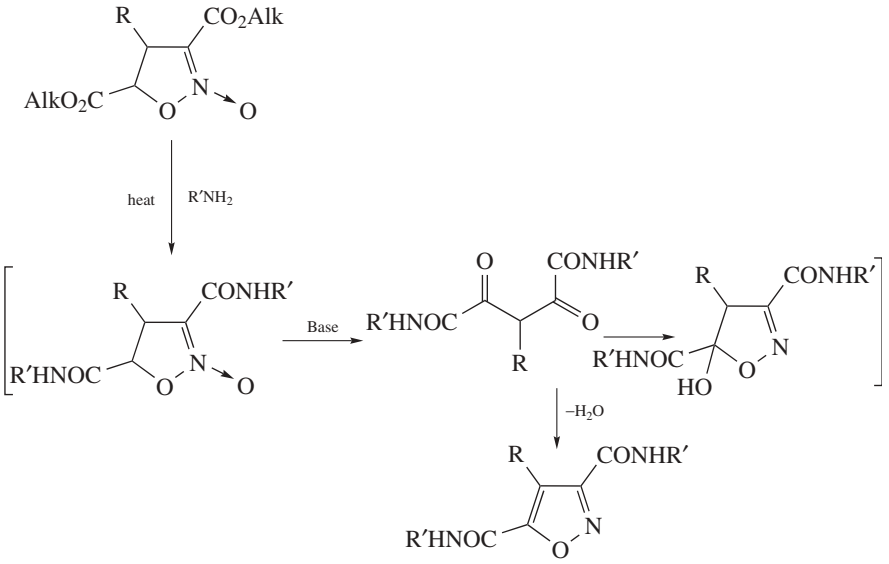
The reactions of ammonia or primary amines with five-membered cyclic nitronates containing the *EWG*-group at the C-5 atom involve deoxygenation of the nitronate fragment, aromatization of the ring, and amidation of the ester

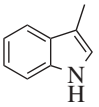


Scheme 3.108

groups present as substituents (41, 237b, 319). Selected details and the possible pathway of this reaction are shown in Scheme 3.109.

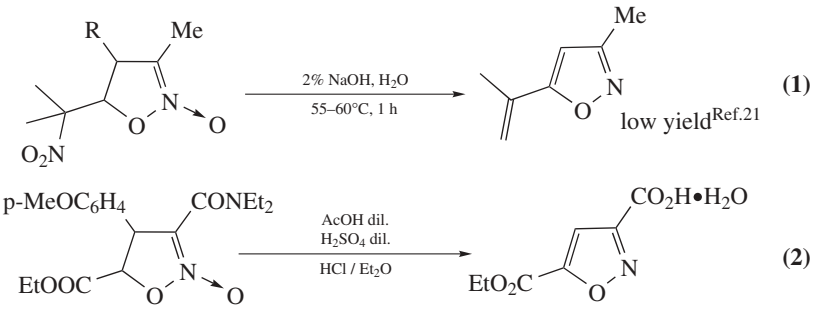
Five-membered cyclic nitronates can be subjected to aromatization by alkali (21) or dilute acids (37, 319) (Scheme 3.110).



$R'NH_2 - NH_3$ R – p–$MeOC_6H_4$[Ref.319](33%);  [Ref.41] (61%);

$R'NH_2 - Bu^nNH_2$; R – alkyl[Ref.237b] (50%–65%).

Scheme 3.109



Scheme 3.110

Yields and details of this reaction, described in the study (319) (Eq. 2), were not reported.

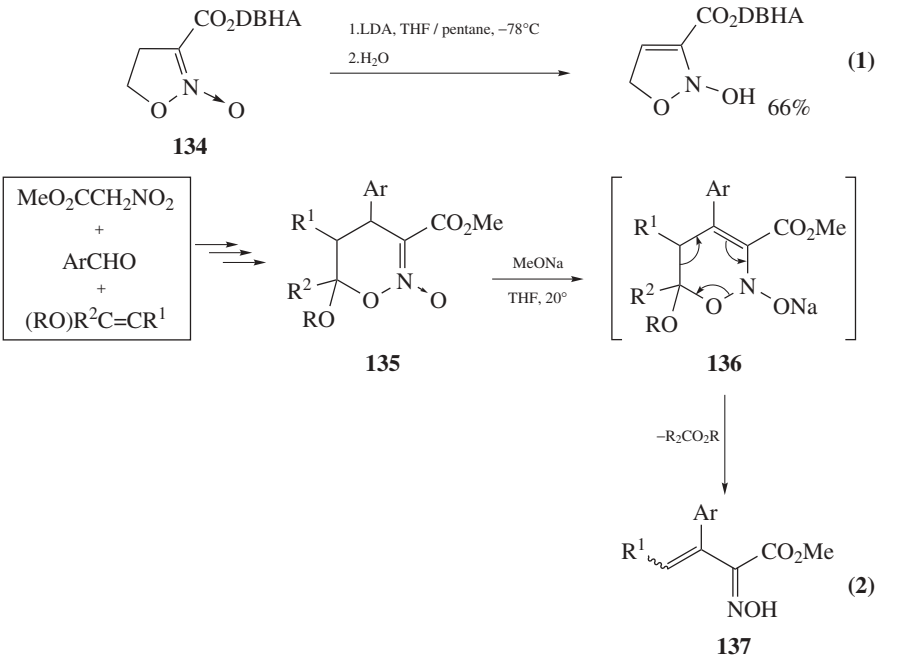
The reactions of strong nucleophiles and electrophiles with cyclic nitronates can be accompanied by more extensive transformations.

For example, the reaction of lithium diisopropylamine (82) with N-oxide (**134**) leads to a rather selective deprotonation at the C-4 atom (Scheme 3.111, Eq. 1). An analogous transfer of double bond was observed for six-membered cyclic nitronates **135** (Eq. 2) (143). However, intermediates (**136**) that formed in the latter case undergo fast fragmentation and give conjugated ene-oximes (**137**) as the final products.

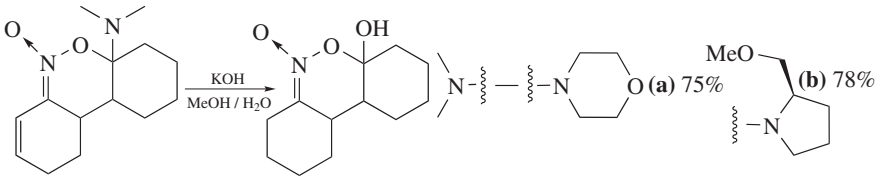
The reactions of aqueous ethanolic alkali with tricyclic six-membered nitronates (**138a,b**) containing the dialkylamino group at the C-6 atom result in the selective replacement of this group to give the corresponding nitronates (**139a,b**) containing the hemiacetal fragment at the C-6 atom (117) (Scheme 3.112).

The mechanism of this process remains unknown. The reaction employing nitronate containing auxiliary(**138b**), produces the corresponding optically active nitronate (**139b**), but its optical and diastereomeric purity was not determined (117).

After acidic treatment of six-membered cyclic nitronates containing amino or alkoxy groups at C-6, the corresponding functionalized 1,4-dicarbonyl compounds (124, 145) can be isolated in good yields (Scheme 3.113).

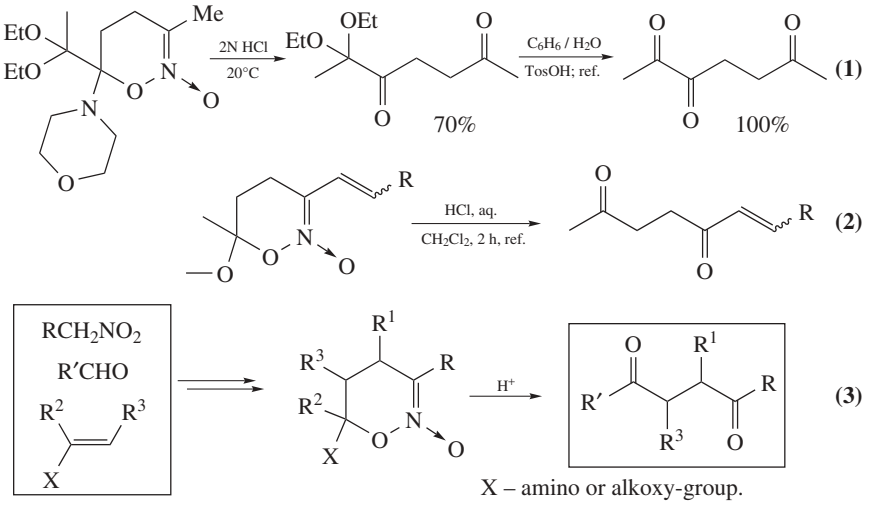


Scheme 3.111



138a,b **139a,b**

Scheme 3.112



Scheme 3.113

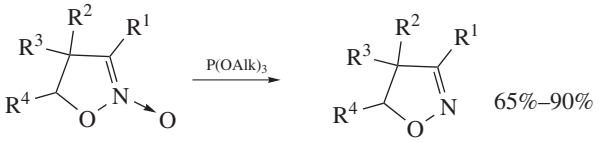
This approach can be used for the development of a versatile and facile procedure for the synthesis of functionalized 1,4-dicarbonyl compounds from very simple precursors (Scheme 3.113, Eq. 3).

3.4.2.5.2. Deoxygenation of Cyclic Nitronates Since cyclic nitronates are readily available and are rather stable compounds (see Sections 3.2 and 3.3), simple approaches for their deoxygenation with retention of the configuration of stereocenters can be used for the synthesis of cyclic esters of functionalized oximes.

The main procedure for deoxygenation of similar nitronates is based on their reaction with trialkyl phosphites (Scheme 3.114). These reactions readily proceed with five- (45, 55, 320, 321) and six- membered (143) cyclic nitronates.

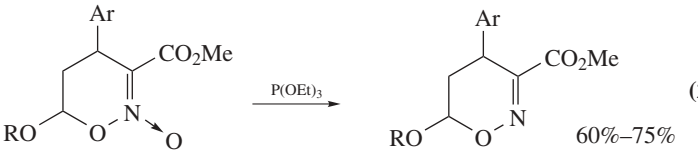
It should be noted that the configurations of the substituents in the starting cyclic nitronates are retained upon deoxygenation as well.

Trost and coworkers (71) used tin dichloride for deoxygenation of annelated five-membered cyclic nitronates (**140a,b**) with retention of stereocenters (Scheme 3.115).



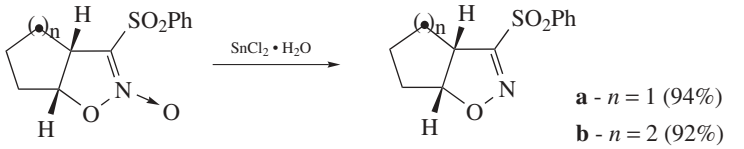
(1)

Alk – Me, Et; R^1 – CO_2Alk; R^2 – $OSiAlk_3$, aryl, Bu^t;
R^3 – H or alkyl; R^4 – AlkylCO or $AlkylO_2C$.



(2)

Scheme 3.114



140a,b **141a,b**

Scheme 3.115

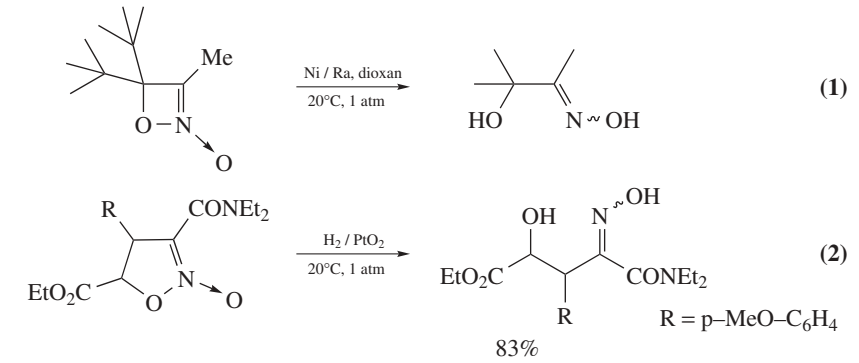
3.4.2.5.3. Hydrogenolysis of Cyclic Nitronates Since hydrogenolysis of substituted cyclic nitronates afford polyfunctional derivatives, this reaction is of interest for the development of a methodology of organic synthesis. However, this process has been poorly studied.

Generally, hydrogenolysis involves cleavage of the endocyclic N–O bond as the first step. For example, four-membered cyclic nitronates can be reduced successively to α-hydroxy-oximes (167) (Scheme 3.116, Eq. 1). Unfortunately, the yield of the target product was not reported.

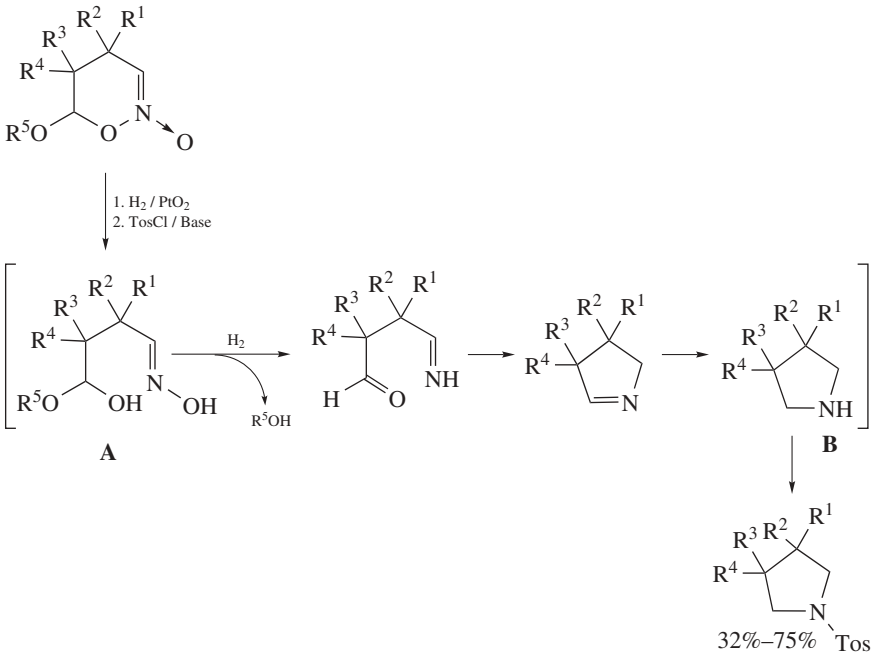
An analogous result was obtained by the hydrogenation of five-membered cyclic nitronate. The latter reaction afforded α-oximino-γ-hydroxypentane-1,5-dicarboxylic acid derivative (Scheme 3.116, Eq. 2) in high yield (83%) (319).

Professor Denmark studied in detail hydrogenolysis of six-membered cyclic nitronates containing the alkoxy group at the C-6 atom (137, 139). The mechanistic interpretation of the reaction is given in Scheme 3.117.

Here hydrogenolysis also starts with the cleavage of the endocyclic N–O bond; however, the resulting oximes **A** undergo the following transformations: hemiacetals at the C-6 atom are transformed into the carbonyl group, and the oximino fragment is successively hydrogenated to imine and then to amine followed by condensation of the amino group with the carbonyl group. The resulting imine is reduced to pyrrolidine **B**. Unstable pyrrolidines **B** are immediately tosylated in



Scheme 3.116



Scheme 3.117

the reaction mixture to give isolable tosyl derivatives. The following two facts should be mentioned.

First, both the configuration and optical purity of the stereocenters of the starting nitronates are retained in pyrrolidines **B**. If R^5O is an auxiliary, the degree of recovery of the corresponding alcohol R^5OH and the optical purity of the isolable pyrrolidine are higher than 95%.

Second, for unknown reasons, the yield of the target product substantially depends on the nature of the base used. For example, using triethylamine instead of DBU leads to an increase in the yield of any pyrrolidine by almost 20%.

3.4.2.5.4. Ozonolysis of Cyclic Nitronates This very interesting approach to cleavage of the nitronate fragment has been recently demonstrated by Linker and coworkers using two optically pure five-membered cyclic nitronates as an example (263a) (Scheme 3.118).

In this reaction, the nitronate is transformed into the β-hydroxycarbonyl fragment with complete retention of the stereo- and optical configuration. If the generality of this procedure will be demonstrated, it will play an important role in chemistry of cyclic nitronates.

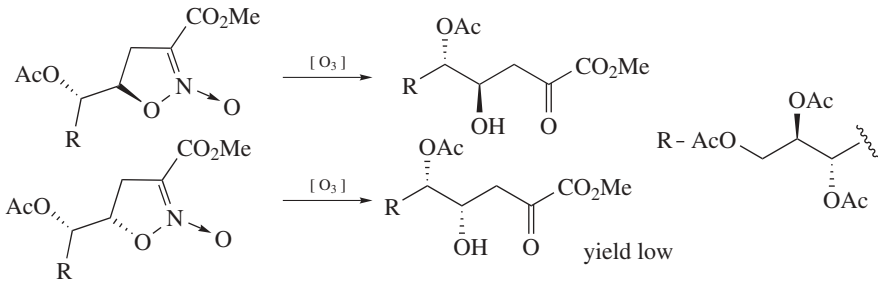
3.4.2.5.5. Modification of Substituents and Functional Groups of Cyclic Nitronates At an ambient temperature, four-membered cyclic nitronate containing the chloronitromethyl group at the C-3 atom is gradually transformed into the corresponding acid chloride even under solvent-free conditions, and treatment of the latter with aqueous ammonia affords amide (168) (Scheme 3.119, Eq. 1).

The ester groups in five-membered cyclic nitronates were successfully subjected to different transformations. Treatment of nitronates containing the methoxycarbonyl groups at positions 3 and 5 with butylamine at 20°C afforded the corresponding diamides (237b) (Scheme 3.119, Eq. 2). Their yields depend dramatically on the nature of the substituent R (further transformations of these products are shown in Scheme 3.109).

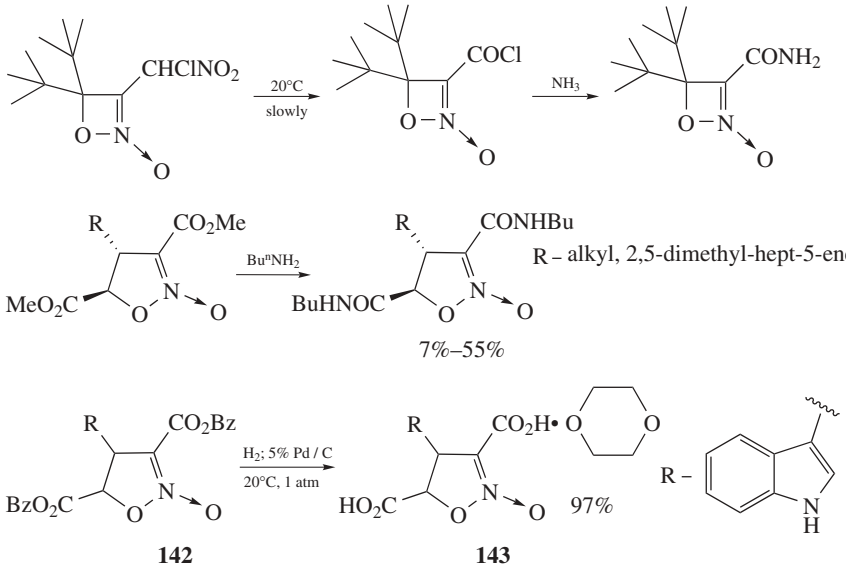
Hydrogenolysis of dibenzyl ether (**142**) containing the indolyl substituent at C-4 produced the corresponding acid (**143**) as the dioxonate complex in very good yield (41) (Scheme 3.119, Eq. 3). However, the structure of this interesting product was not rigorously established.

Only the methoxycarbonyl group at position 5 was reduced in good yield upon treatment of nitronates (**144**) (Scheme 3.120, Eq. 1) with sodium borohydride (55).

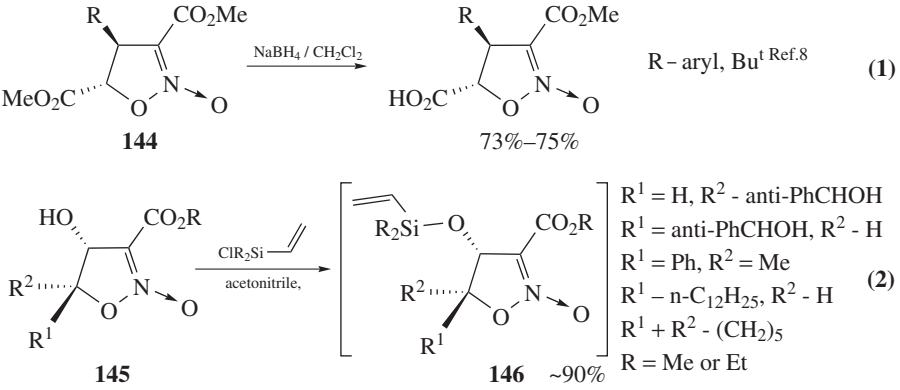
Silylation of the hydroxy group in nitronates (**145**) (Scheme 3.120, Eq. 2) with $ClSiR_2CH{=}CH_2$ (R = Me or Ph) generates nitronates (**146**) in high yields. The



Scheme 3.118



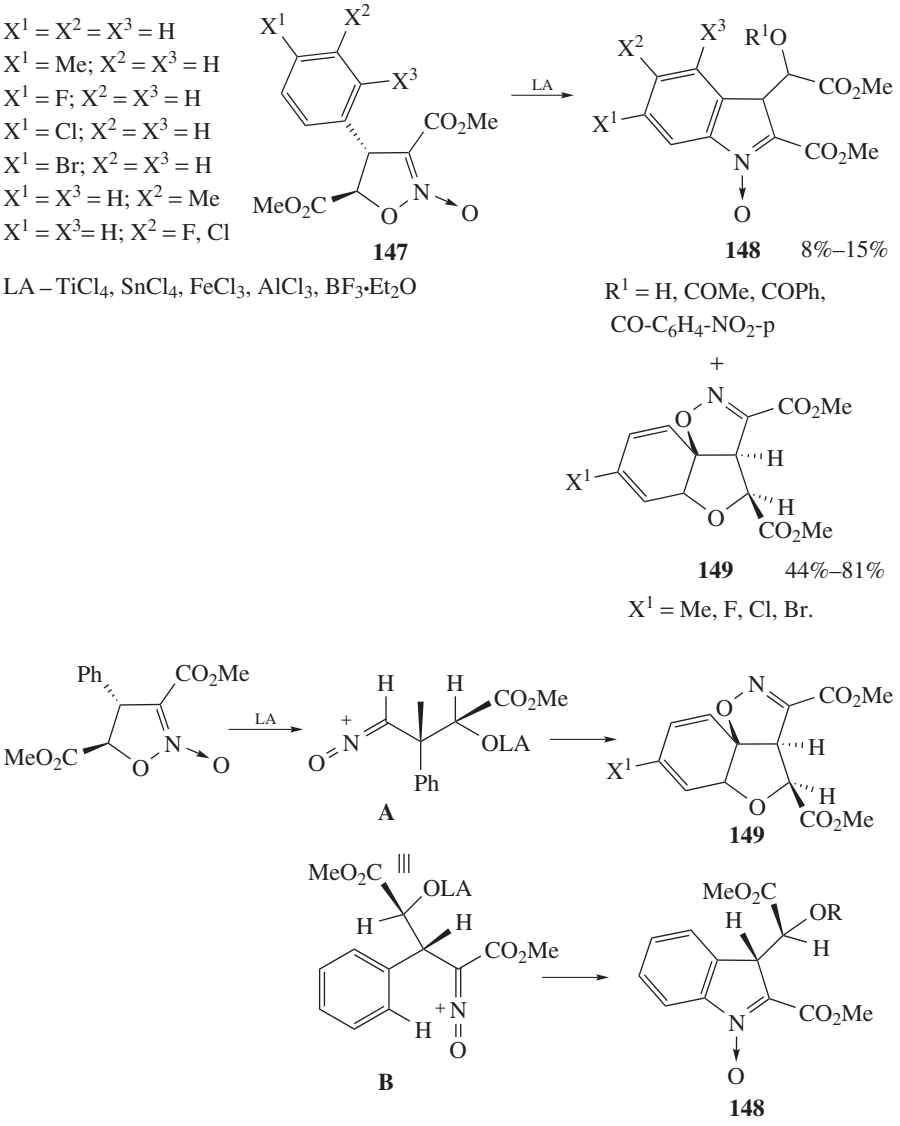
Scheme 3.119



Scheme 3.120

latter can be considered as efficient intermediates for intramolecular [3 + 2]-cycloaddition reactions (66).

3.4.2.5.6. Rearrangements of Cyclic Nitronates Many rearrangements of cyclic nitronates occur under the action of LA and involve the interaction with the negative end of the dipole as the initial step. If an aryl substituent is bound to the C-4 atom, deep skeletal rearrangements, including annelation, are possible. Japanese researchers (321) systematically studied the reactions of a representative



Scheme 3.121

series of 3,5-bis-methoxycarbonylisoxazoline-2 *N*-oxides (**147**) (Scheme 3.121) containing substituted aryl groups at position 4 with different LA.

Depending on the nature of the substituents X^1, X^2, and X^3, the reactions produced nitrones (**148**) (as indole derivatives) or annelated isoxazolines (**149**). The authors performed a series of experiments (including one with the use of a deuterium label) and suggested a mechanistic scheme for the interpretation

of the observed transformations. The main characteristic feature of this process is generation of the nitrosonium cation **A** after cleavage of the endocyclic N–O bond. These cations are ambident and can be involved in intramolecular reactions with nucleophilic aryl fragments either through the nitrogen atom or through the oxygen atom to give nitrones (**148**) or heterocycles (**149**), respectively. In the authors' opinion, the presence of substituents X^1 in the *para* position of nitronate (**147**) facilitates the reaction pathway to form products (**149**).

Japanese researchers varied aryl substituent at C-4 in nitronate (**147**), LA, and the reaction conditions, they used successfully diastereomerically pure nitronates (**147**) (Scheme 3.121) for the synthesis of various fused-ring systems, such as benzofuro-[3,2-d]-1,2-oxazines (322), furo-[3,4-d]-isoxazoles (323–326), indolo-[2,3-b]-1-pyrroline 1-oxides (327), 4*H*-1,2-benzoxazines (328), benzofuro-[2,3-c]-tetrahydropyrans (329), and monocyclic 1,2-oxazines (330).

All of these processes are interpreted through intermediate nitrosonium cations, which are generated upon cleavage of the endocyclic N–O bond with LA. A detailed consideration of all these transformations is beyond the scope of the present monograph.

The transformation of *N*-oxides (**150a,b**) into butyrolactone derivatives (**151a,b**), accompanied by the formation of oximes (**152**) as by-products, is yet another example (331) (Scheme 3.122).

In the authors' opinion, the nitrosonium cations **A** are chlorinated by $TiCl_4$(LA) and undergo cyclization with one of the methoxycarbonyl groups to give butyrolactones (**151**). This process can be accompanied by *ortho*-cyclization giving rise to oximes (**152**) as by-products.

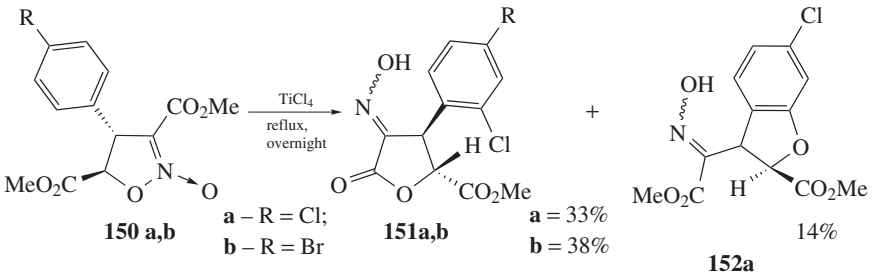
Six-membered cyclic nitronates can undergo rearrangements accompanied by cleavage of the endocyclic N–O bond or by cleavage of the endocyclic C–O bond. The latter fact is evidently associated with the presence of substituents, which efficiently stabilize the positive charge, at the C-6 atom. This occurs upon treatment of nitronates (**154a,b**) with silicon dioxide (Scheme 3.123) (117).

The reactions of the resulting stabilized ions **153a,b** with silicon dioxide produces isolable polyfunctional compounds **155a,b**. It should be emphasized that the configuration of the stereocenters in nitronate (**153**) remains unchanged in the course of the transformation and the reaction is stereoselective with respect to the new stereocenter at the atom bearing the nitro group.

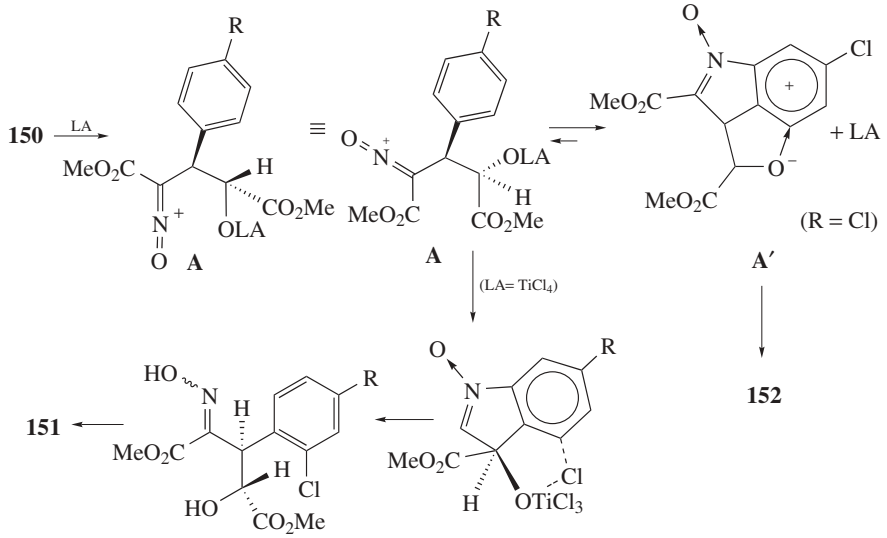
Interestingly, the character of the isolable products strongly depends on the nature of the substituent R^3. In the presence of the piperidine radical instead of the morpholine group, the resulting acyclic ions (**157a,b**) are again involved in cyclization giving rise to a new C,C bond and annelated bicyclic compounds (**158a,b**). This reaction is also rather diastereoselective.

Similar tautomeric rearrangements of intermediate six-membered cyclic nitronates were described by Huffman and coworkers (116) (Scheme 3.124).

By contrast, six-membered cyclic nitronates **A** containing the trimethylsilyl group at the C-6 atom are apparently stabilized through cleavage of the N–O



Mechanistic consideration:



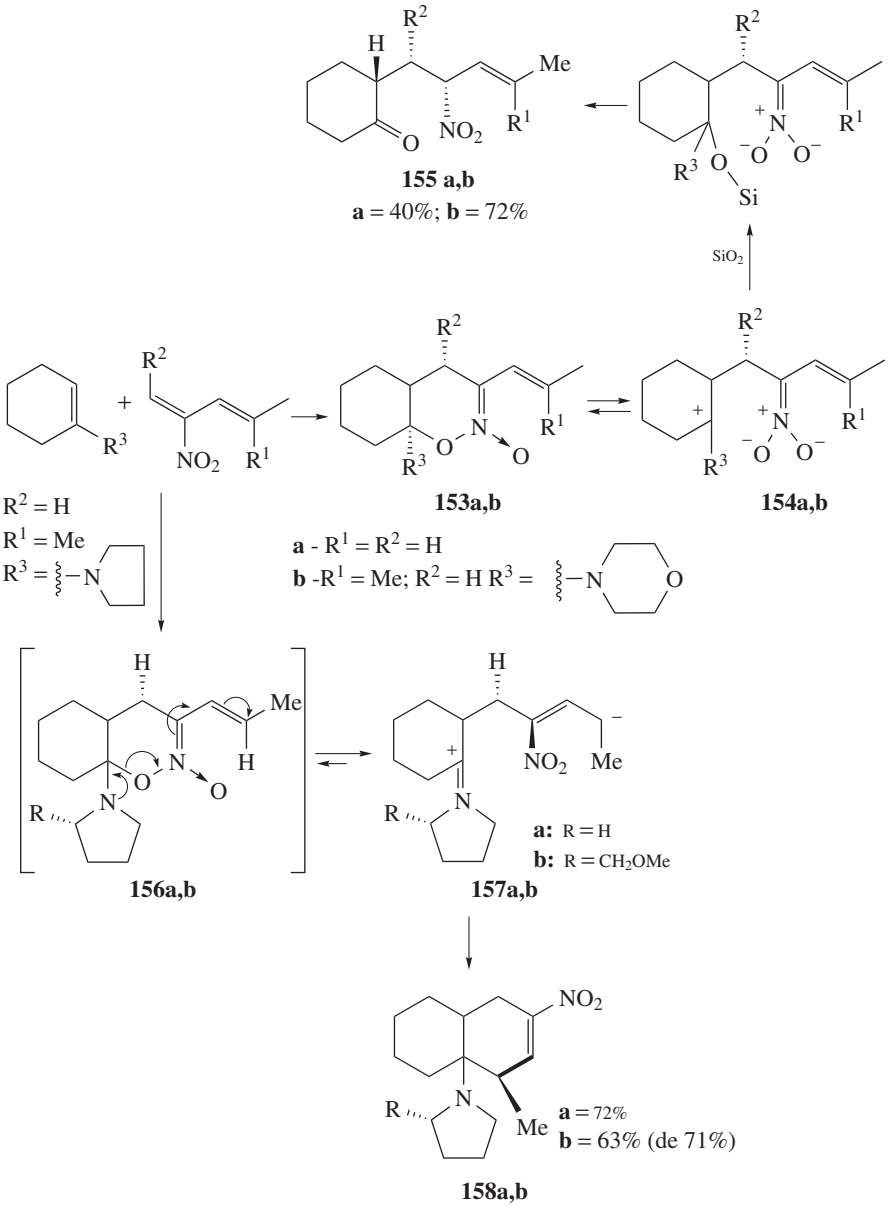
Scheme 3.122

bond to give the corresponding functionalized oximes (332). The mechanistic interpretation of this transformation is shown at the bottom of the Scheme 3.124.

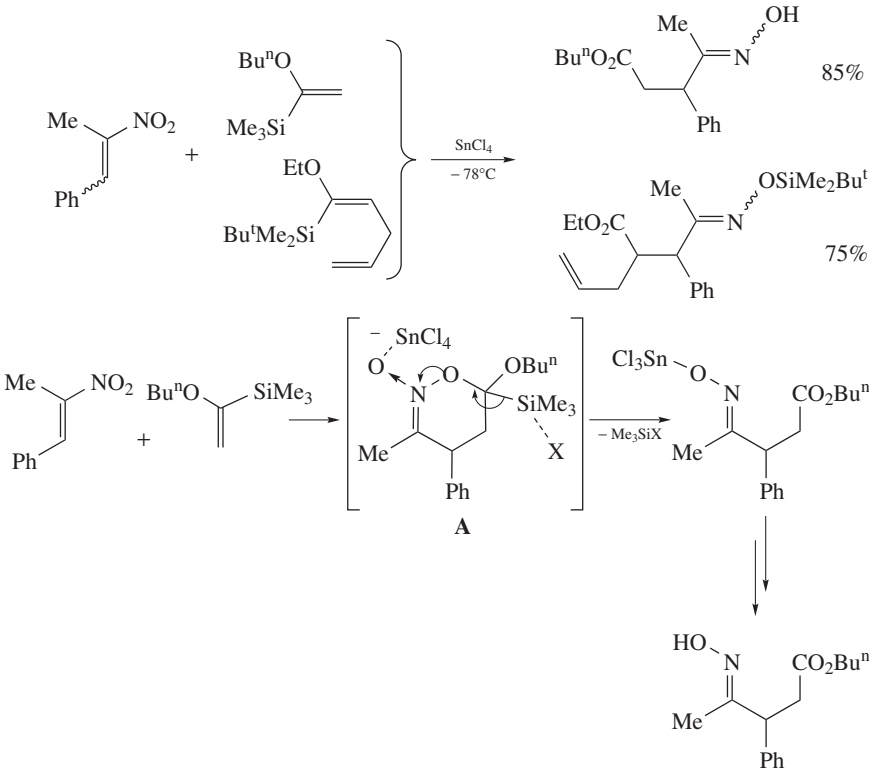
Finally, the rearrangement of seven-membered cyclic nitronate (**159**) (170) accompanied by the ring contraction to form oxime (**160**) was documented (Scheme 3.125). Details of this transformation were not reported.

3.4.3. Nitronates in [3 + 2]-Cycloaddition Reactions

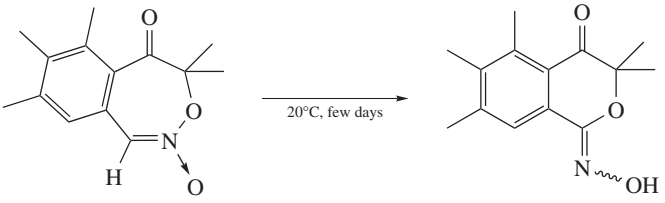
Examples of [3 + 2]- (or 1,3-dipolar) cycloaddition reactions have been known for many years. However, only after the main principles of this type of transformations have been formulated by Huisgen (333), [3 + 2]-cycloaddition became one of the most important tools in organic synthesis (334, 335). Actually, the simultaneous formation of two new bonds makes it possible to efficiently assemble a complex molecule from simple and readily available precursors. Due to


155 a,b
a = 40%; b = 72%
SiO2
153a,b
154a,b
R2 = H
R1 = Me
a - R1 = R2 = H
b -R1 = Me; R2 = H R3 =
156a,b
157a,b
a: R = H
b: R = CH2OMe
a = 72%
b = 63% (de 71%)
158a,b

Scheme 3.123



Scheme 3.124

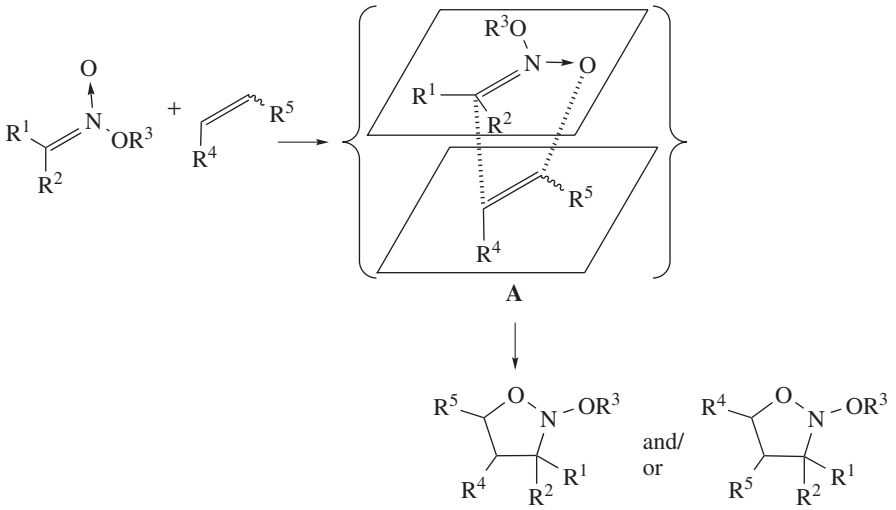


159 **160**

Scheme 3.125

a wide field of application and high regio- and stereoselectivity of the process, it can be used in modern strategies for the design of complex organic molecules.

Nitronates are among the most readily available and rather reactive 1,3-dipoles. The structure **B** in Scheme 3.84 is responsible for the reactivity of nitronate molecules.



R^3 – alkyl, Si $\equiv R^3$+ R^2 – alkylene C_2 or C_3, R^1, R^2, R^4, R^5 – H, alkyl, aryl, EWG or electron donating groups.

Scheme 3.126

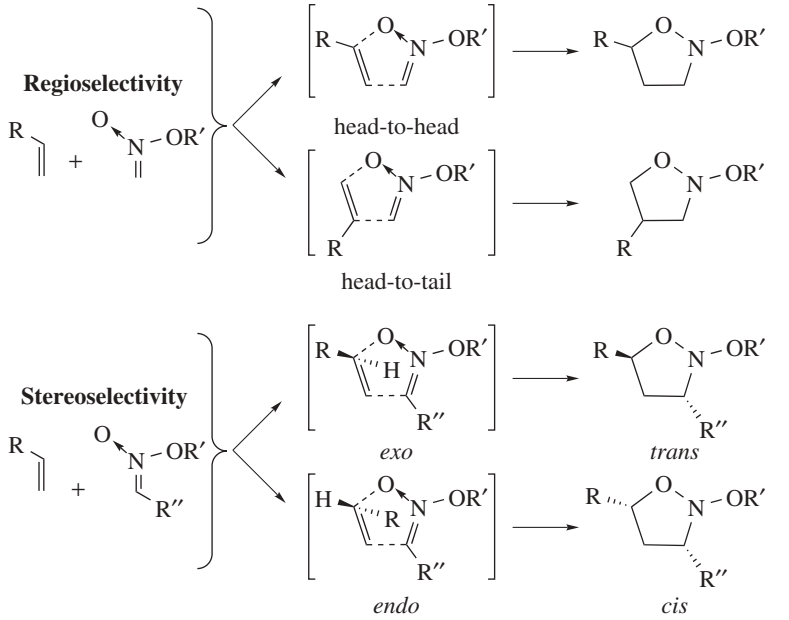
Nowadays, it is commonly accepted that [3 + 2]-cycloaddition is a concerted process, and that the C,C double bond serves as the main type of dipolarophiles (Scheme 3.126).

Regio- and stereoselectivity of the process depend on the nature of its participants and are determined by the character of the approach of the dipolarophile to the dipole. (In Scheme 3.127, this is demonstrated for the reaction of monosubstituted nitronates with monosubstituted olefins.)

For the overwhelming majority of nitronates, the reactions with monosubstituted olefins are characterized by the head-to-head approach of the olefin, that is, the substituent R is present at the C-5 atom. A general conclusion about stereoselectivity of this reaction (endo or exo approach of olefin to the dipole (Scheme 3.127)) cannot be drawn. However, the exo approach prevails for nitronates. (Possible factors responsible for discrimination of the facial approach will be discussed below in Section 3.4.3.5).

3.4.3.1. Intermolecular [3 + 2]-Addition of Nitronates to Olefins Of all known types of nitronates (see Section 3.2), alkyl- and silyl nitronates as well as cyclic C_5-C_6 nitronates are involved in [3 + 2]-cycloaddition reactions. Detailed comparative kinetic studies for different types of nitronates have not been reported. However, a few data (162, 336, 337) allow one to deduce some sequences (Chart 3.10).

In spite of the fact that these series are conventional, the choice of the optimal conditions for concrete [3 + 2]-addition reactions can be guided by these series to a first approximation.



Scheme 3.127

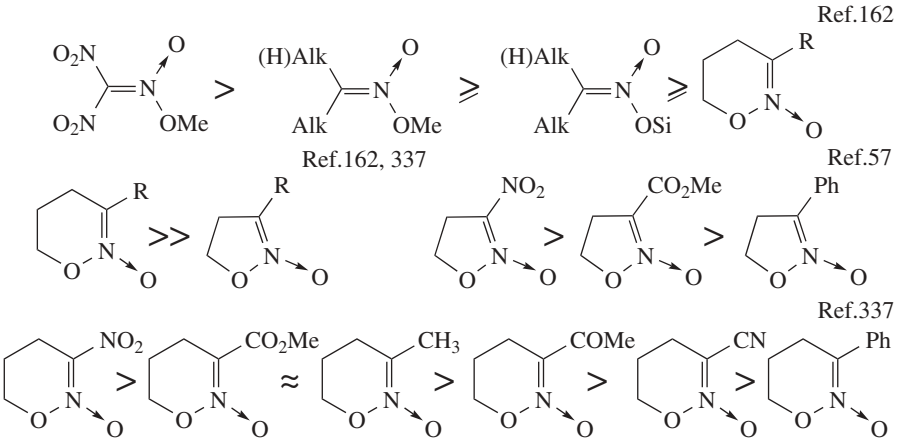
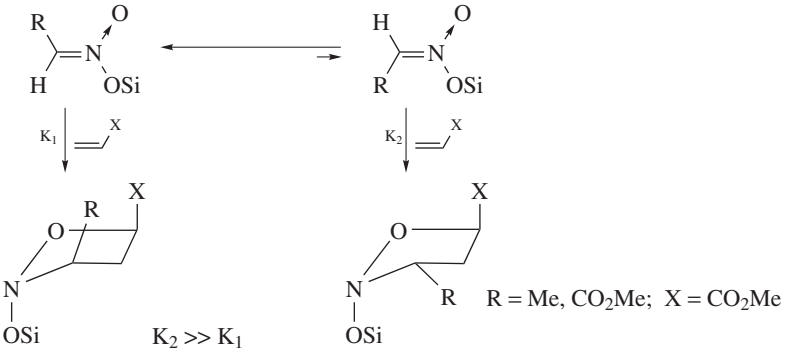


Chart 3.10

On the whole, the introduction of alkyl substituents at the α-carbon atom leads to a sharp decrease in the rate of [3 + 2]-cycloaddition, that is, nitronates derived from primary AN react much faster than nitronates derived from analogous secondary AN. The introduction of functional EWG groups leads to a substantial increase in the rate of [3 + 2]-cycloaddition. It can also be noted that



Scheme 3.128

six-membered cyclic nitronates are involved in this reaction much faster than analogous five-membered nitronates.

For acyclic nitronates, the reaction rate can depend on the configuration of the dipole. On the basis of ^{15}N NMR spectroscopic data, it was demonstrated (338a) that thermodynamically more favorable *trans* isomers of nitronates (**1**) are much less reactive in [3 + 2]-addition to methyl acrylate (Scheme 3.128).

Analogous data on O-methyl derivatives of methyl nitroacetate were reported in the study (338b).

Evidently, this situation determined by the influence of the steric factors should also be observed in reactions of analogous nitronates with other dipolarophiles.

3.4.3.1.1. Alkyl Nitronates In spite of the low stability of acyclic alkyl nitronates, these compounds were rather extensively studied in [3 + 2]-addition reactions with various alkenes (9, 18, 28, 49, 300, 301, 306, 307, 338b–354) (Chart 3.11).

Regardless of the nature of substituents in monosubstituted and α,α-disubstituted alkenes, these compounds are involved in regioselective addition in a head-to-head fashion to give the corresponding isoxazolidines substituted at the C-5 atom (for transformations of cycloadducts, see the special Section 3.4.3.4.). In the case of α,β-di- or trisubstituted olefins, the regioselectivity of the approach of olefin and the regioselectivity of cycloaddition depend on the nature of substituents in the olefin. As a rule, the EWG groups of olefin appear at the C-5 atom in the resulting cycloadduct. To estimate the preferable approach of the olefin responsible for the attachment of the discussed substituent at the C-4 atom, one can use the series H > Si > C > O suggested by Prof. Denmark (162) for cycloadditions of disubstituted olefins to six-membered cyclic nitronates.

It is of no benefit to analyze, stereoselectivity, the reaction under consideration in the general case. However, it should be noted that the *exo* approach of olefin is preferable in more cases. As can be seen from Chart 3.11, if olefin molecules contain two different double bonds or a double bond and a triple bond, only one double bond can be selectively involved in the reaction with acyclic nitronates.

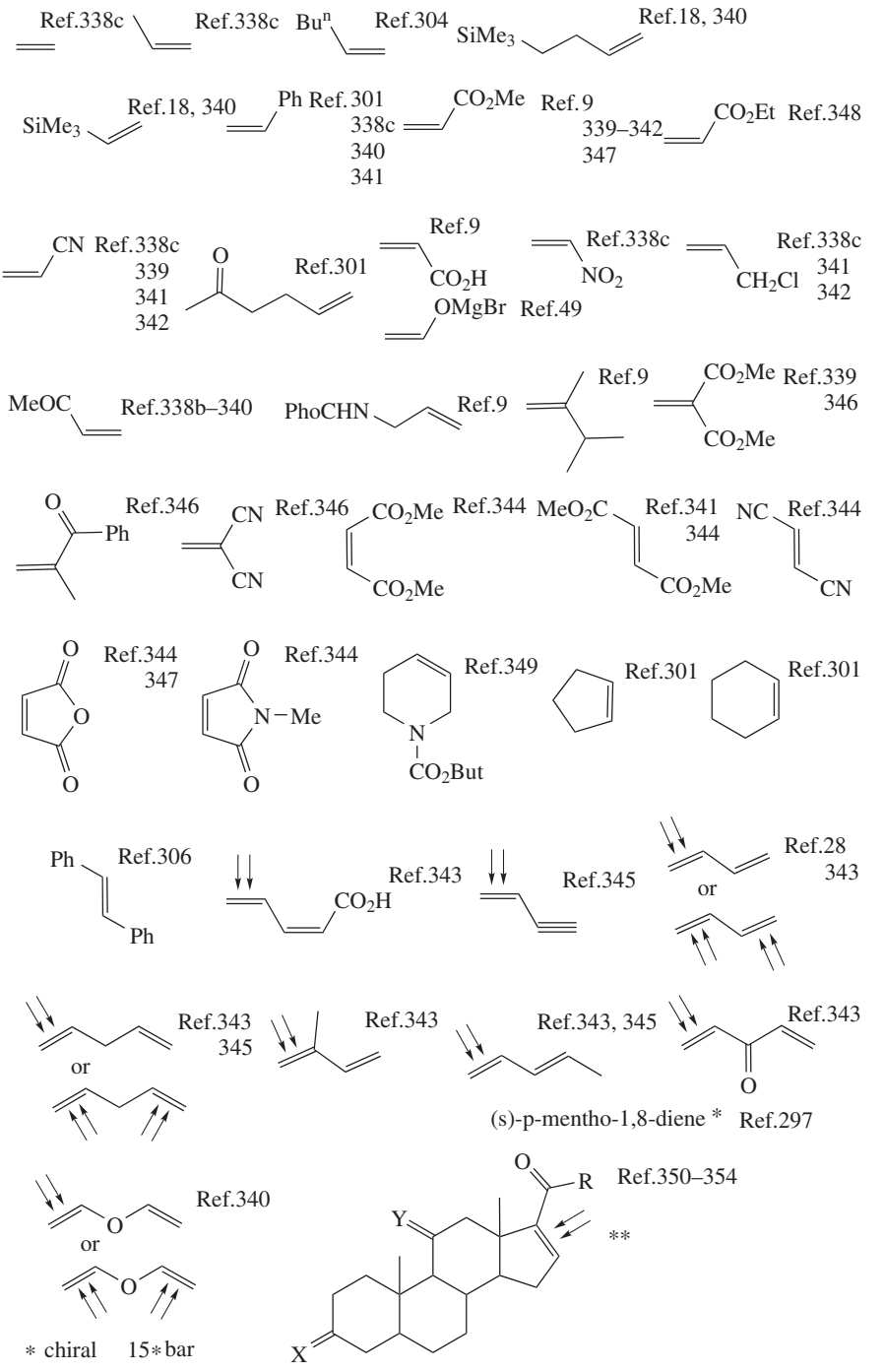


Chart 3.11 [3 + 2]Reactivity of acyclic alkyl nitronates.

3.4.3.1.2. Silyl Nitronates The characteristic features of the behavior of SENAs in [3 + 2]-addition reactions (75, 133, 175–177, 185, 186, 189, 201a, 203, 205, 206, 216, 355–362c) are virtually identical to those of acyclic alkyl nitronates considered in the previous section. As mentioned above, minor but more reactive *Z*-tautomers of SENAs derived from primary AN can be detected by cycloaddition reactions (see Section 3.3.4.1 and Scheme 3.128).

Chart 3.12 shows the most characteristic olefins involved in [3 + 2]-addition reactions with SENAs.

Here two facts can be mentioned. For example, cycloaddition of nitronate $(MeO_2C)CH{=}N(O)OSiMe_3$ to ethylene was observed (203), whereas its *O*-methyl analog does not react with ethylene. It is hardly probable that this fact is due to the high reactivity of the silyl nitronate. More likely, the negative result for alkyl nitronate is attributed to low stability of this derivative.

Second, fullerene C_{60} was involved in the standard reaction with very reactive nitronate $CH_2{=}N(O)OSiMe_3$ (362b).

Cycloaddition of SENAs to sulfonyl-substituted allene (362a) or vinyl phosphonates (362c) is worthy of notice.

3.4.3.1.3. Five-membered Cyclic Nitronates In spite of the fact that five-membered cyclic nitronates are known for more than a hundred years and are classified as the most stable representative of this class of compounds, their

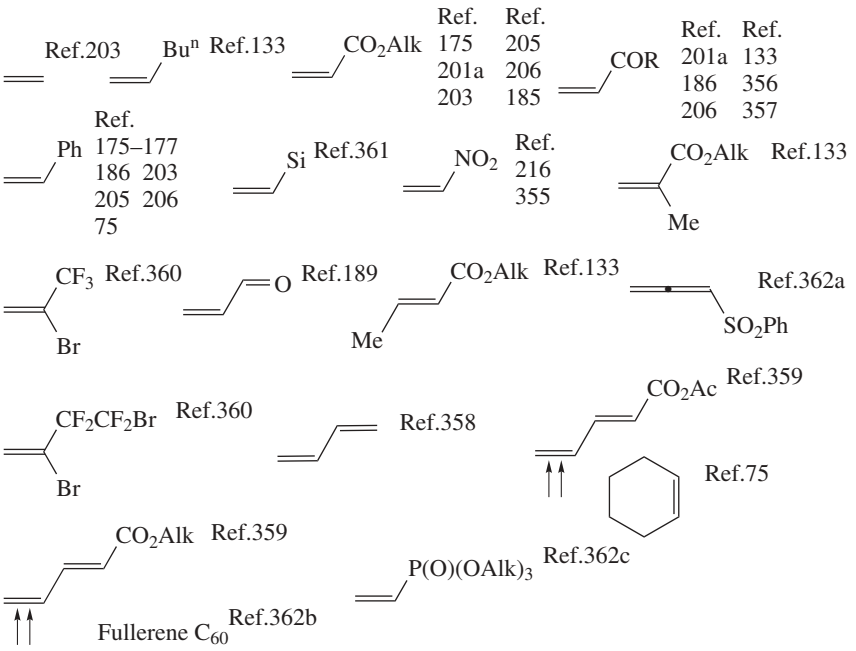


Chart 3.12 [3 + 2]Reactivity of silyl nitronates.

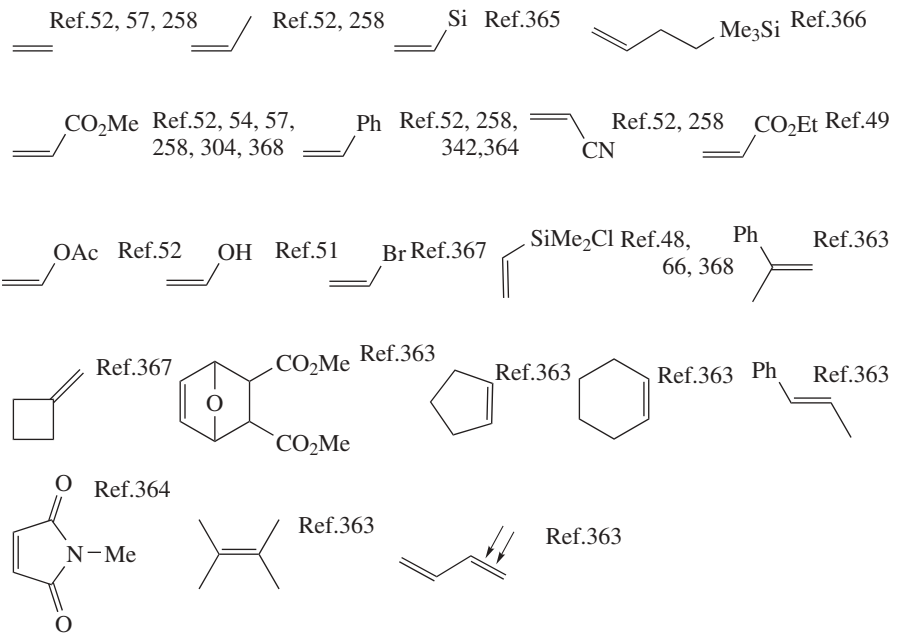


Chart 3.13 [3 + 2]Reactivity of five-membered cyclic nitronates.

behavior in [3 + 2]-cycloaddition reactions is the least known (48, 49, 51, 52, 54, 57, 66, 258, 363–369) (Chart 3.13).

Most of the [3 + 2]-cycloaddition reactions considered here were performed at high temperature. The rules of regioselectivity, which were formulated in two previous sections, are also true for these reactions.

It should be noted that tetramethylethylene was involved in the [3 + 2]-cycloaddition with five-membered cyclic nitronates (363).

3.4.3.1.4. Six-membered Cyclic Nitronates As can be seen from Chart 3.14, the range of olefins involved in intermolecular [3 + 2]-cycloadditions with six-membered nitronates, is substantially wider (49, 91, 92, 97, 138, 143, 146, 151, 156, 160–162, 370–373) compared to five-membered nitronates.

The behavior of six-membered cyclic nitronates in this process was studied more systematically.

Let us remember the rule of orientation of substituents in viz. disubstituted olefins directed to the C-4 atom of the cycloadduct: H > Si > C > O (162) (the atom of the substituent in olefin bound to C-4 in the resulting adduct). As in the previous case, many reactions proceed at high temperature. It should be emphasized that unsubstituted 5,6-dihydro-[4*H*]-oxazine *N*-oxides were successfully involved in [3 + 2]-cycloaddition. Professor Chlenov was the first to perform this reaction with the use of styrene (the yield was 21%) (337). More recently, the

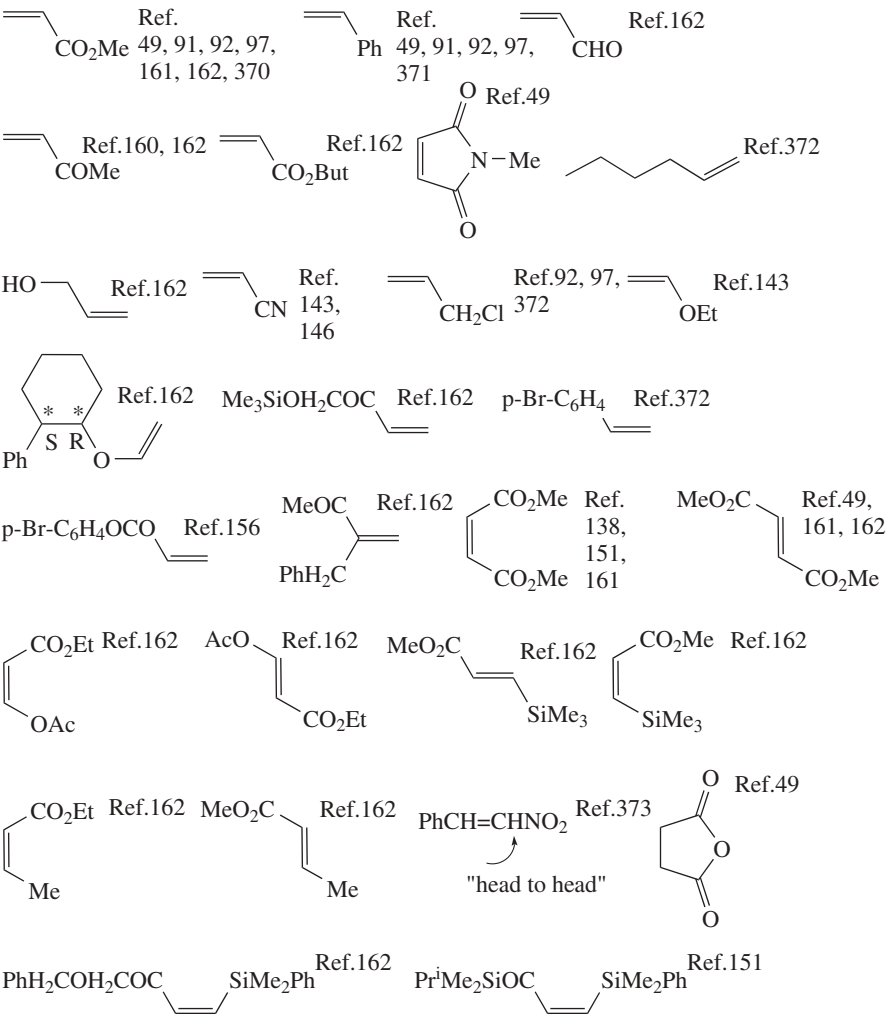
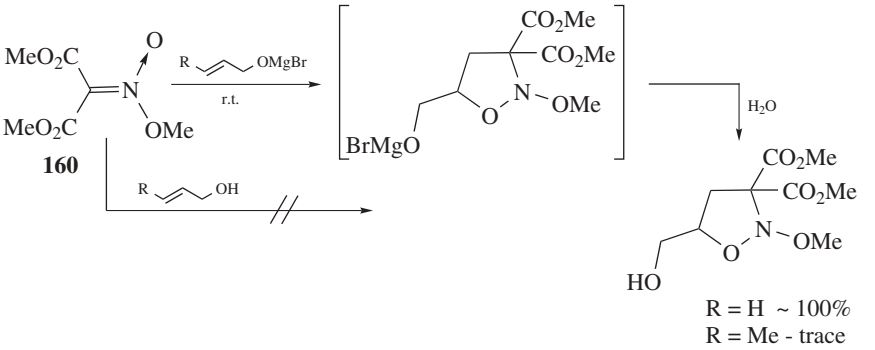


Chart 3.14 [3 + 2]Reactivity of six-membered cyclic nitronates.

improved procedure was applied to a series of mono- and α,β-disubstituted olefins containing EWG groups (49).

3.4.3.1.5. Attempts to Catalyze [3 + 2]-Cycloaddition of Nitronates to Olefins In Section 3.2.1.2.2.2, it was noted that [4 + 2]-cycloaddition reactions of nitroalkenes and alkenes proceed much faster in the presence of LA. At the same time, in the presence of LA, nitronates can rapidly decompose (49) or undergo rearrangements (see Section 3.4.2.5.6.). Hence, it is not surprising that catalysis of 1,3-dipolar cycloaddition reactions of nitronates with alkenes by LA has attracted little attention until very recent times. An exception is the study by the Japanese



Scheme 3.129

researchers (49), who demonstrated that magnesium ions drastically accelerate [3 + 2]-cycloaddition of allyl alcohol to nitronate **160** (Scheme 3.129).

However, both the mechanism of this reaction and its general character remain unknown.

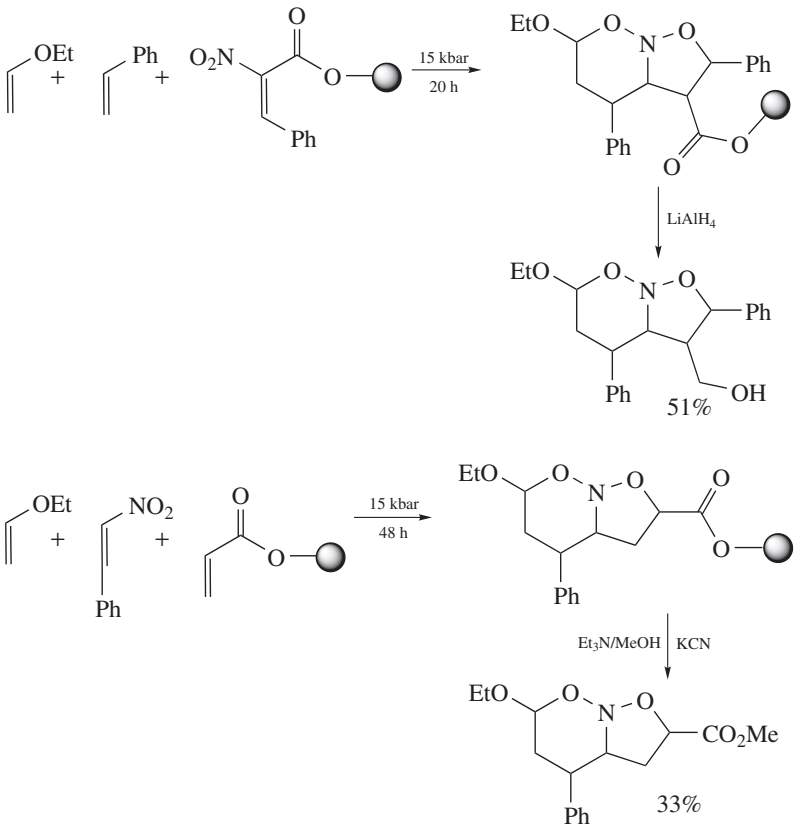
In modern organic chemistry, efficient procedures are being developed for the most important processes. In particular, improvements, such as the use of super-high pressure (374a, b) or microwave (374c), may be advantageous for cycloaddition reactions. The latter methodology in [3 + 2]-addition processes involving nitronates has not been used. Super-high pressure was efficiently used in the pioneering study by Kamernitskii and coworkers (349), who used compounds belonging to steroids as dipolarophiles.

More regularly, super-high pressure (15 kbar) was used in the tandem [4 + 2] [3 + 2] process, in which six-membered cyclic nitronates, generated *in situ* as intermediates, are involved in [3 + 2]-addition to specially chosen dipolarophiles (364, 373, 375). It should be emphasized that this reaction does not require the use of LA as catalysts.

The use of super-high pressure combined with a special resin, for which nitroalkene or one of olefins are partners, in the tandem [4 + 2][3 + 2] process, was also documented (376, 377) (Scheme 3.130).

The yields of the target products are as yet moderate. However, the preparative significance of both [3 + 2]-addition of six-membered cyclic nitronates and the tandem [4 + 2][3 + 2] processes with the involvement of these intermediates can be enhanced provided that this methodology will be improved.

3.4.3.1.6. Other Types of Nitronates in [3 + 2]-Cycloaddition Reactions with Olefins As mentioned above, of all known types of nitronates, only alkyl and silyl nitronates can be involved in [3 + 2]-cycloaddition reactions with olefins. However, furoxans (**161**), which can also be considered as cyclic nitronates, can react with active dipolarophiles under extreme conditions to give nitrosoacetals (**162**) (Scheme 3.131, Eq. 1).

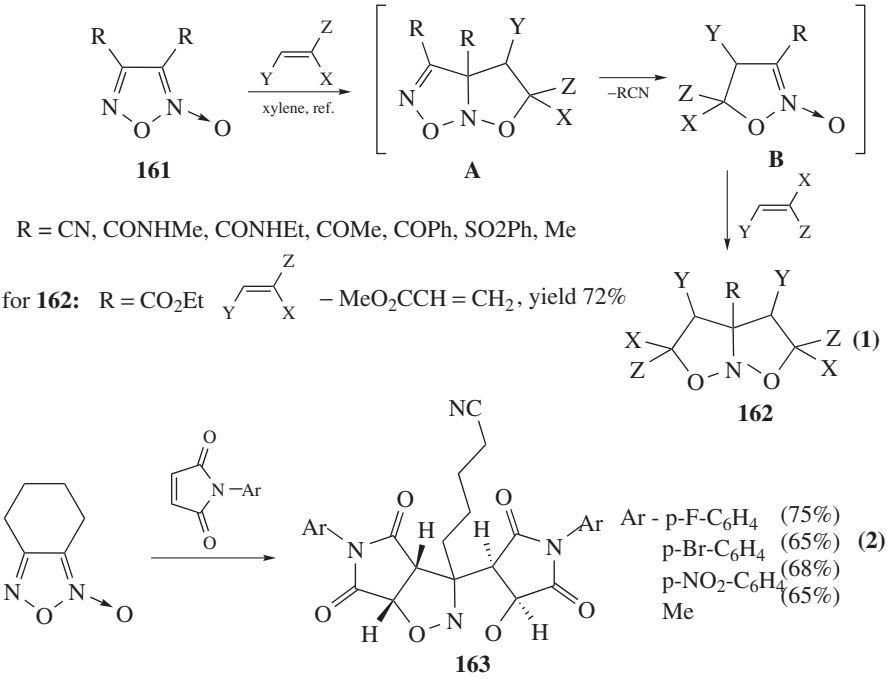


Scheme 3.130

This process is of a rather general character, and different types of olefins, such as normal olefins, Michael substrates, inverted and strained olefins, can be involved in such reactions. However, the interaction shown in Scheme 3.131 is accompanied by a number of side reactions, and consequently, the scope of the transformation (**161**→**162**) and the yield of nitrosoacetals (**162**) substantially depend on the nature of the substituent R.

The mechanism of this reaction has not been studied in detail. However, it can be represented as a sequence of reactions. The first reaction is, in fact, [3 + 2]-cycloaddition of olefin to furoxan (**161**). Under severe conditions, the resulting intermediate **A** undergoes fragmentation to give five-membered cyclic nitronate **B**. The latter is involved in the usual addition reaction with an excess of olefin to form isolable bicyclic product (**162**) (301, 378, 379).

An interesting example of the use of this process for the convenient stereoselective synthesis of functionalized nitrosoacetals (**163**) was described in the study (380) (Scheme 3.131, Eq. 2).



Scheme 3.131

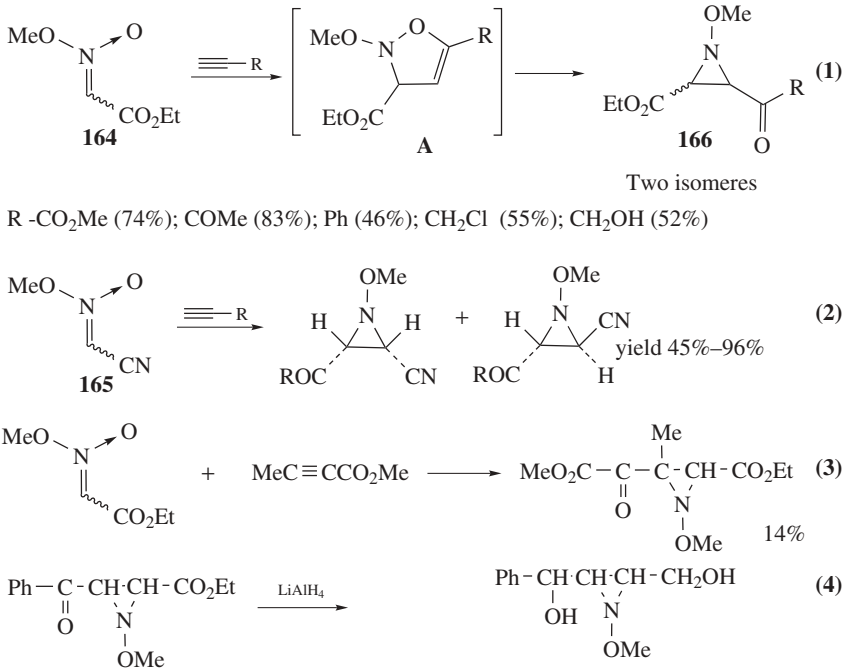
3.4.3.2. Intermolecular [3 + 2]-Addition of Nitronates to other Dipolarophiles

3.4.3.2.1. Intermolecular [3 + 2]-addition to a triple bond The [3 + 2]-addition reactions of acetylenes with nitrones never afford normal adducts; instead, they produce the corresponding aziridines (381). An analogous situation is observed for most of nitronates (93, 95, 382 (Scheme 3.132).

The reactions of alkyl nitronates (**164**) or (**165**) derived from α-functionalized primary AN with monosubstituted acetylenes produce mixtures of diastereomeric aziridines (**166**) in moderate to high yields. Most probably, the first step of this process involves normal concerted cycloaddition to give the corresponding intermediates **A**, which were not detected due to their fast rearrangement to give acyl-substituted aziridines (**166**). The reaction is regioselective and stereospecific. The latter fact was demonstrated by French researchers (95).

This interaction can be performed with the involvement of internal acetylenes, which was exemplified by the reaction of $MeC{\equiv}CCO_2Me$ with nitronate (**164**) (382) (Scheme 3.132, Eq. 3). This reaction is also regioselective, but the yield of the target aziridine is low. Nitronate $(MeO_2C)_2C{=}NO(OMe)$ also reacts with acetylenes (382). The carboxyl group in isolable *N*-alkoxyaziridines can be selectively reduced (Scheme 3.132, Eq. 4).

Interestingly, the character of the reaction with cyclic six-membered nitronates is similar. For example, *N*-oxide (**167**) reacts with monosubstituted acetylenes



Scheme 3.132

to give diastereomerically pure aziridines (**168**) in high yield (94). The latter compounds adopt a configuration shown in Scheme 3.133.

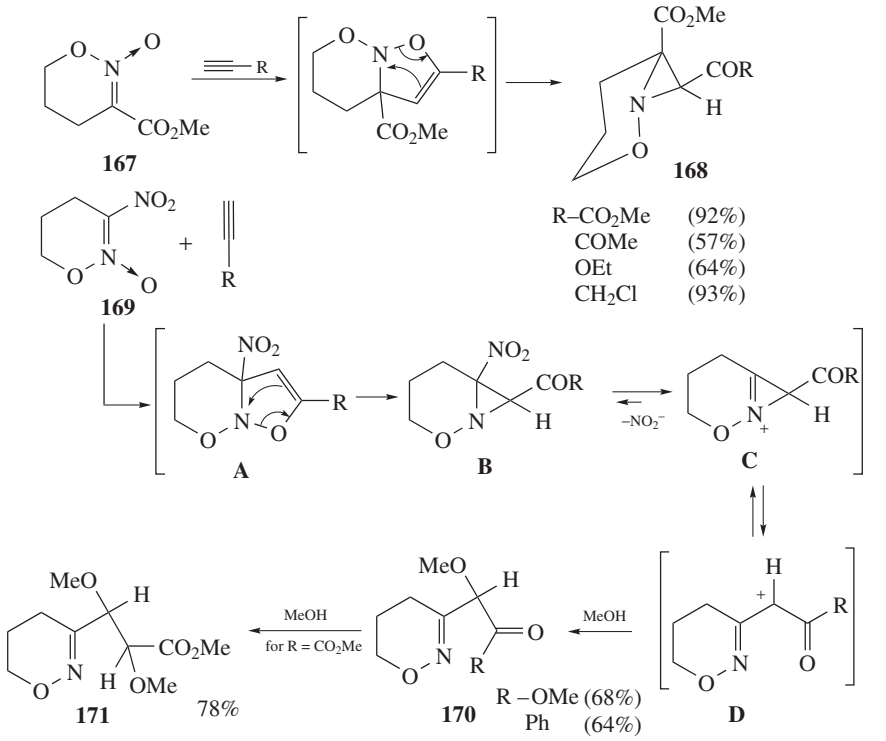
However, the character of the reaction of 3-nitro-substituted *N*-oxide (**169**) with the C,C triple bond is changed 371. Apparently, the first step affords the normal cycloadduct **A**, which is successively rearranged into aziridine **B**. Elimination of the nitronate anion from the latter compound gives rise to ambident cations **C** and **D**, which, after quenching with methanol, form dihydrooxazines (**170**) or (**171**) depending on the nature of the substituent R.

The reaction of chiral six-membered cyclic nitronates with internal and terminal acetylenes was used with advantage in the synthesis of enantiomerically pure fused substituted aziridines containing several stereocenters (96) (Scheme 3.134).

The reaction of the C,C triple bond with nitronates leads to several unexpected results.

For example, it was reported (223) that unstable acyl nitronate (**172**) was detected by its trapping with dimethyl acetylenedicarboxylate (**DMAD**) (Scheme 3.135).

In this reaction, isoxazole (**173**) rather than the corresponding aziridine was isolated in good yield. It was stated (223) that acyl nitronate (**172**) rather than the corresponding nitrile oxide is a precursor of isoxazole (**173**). This interpretation is supported by the fact that the corresponding nitrile oxide dimer (furoxan (**174**))



167 **168** **169** **A** **B** **C** **D** **170** **171**

Scheme 3.133

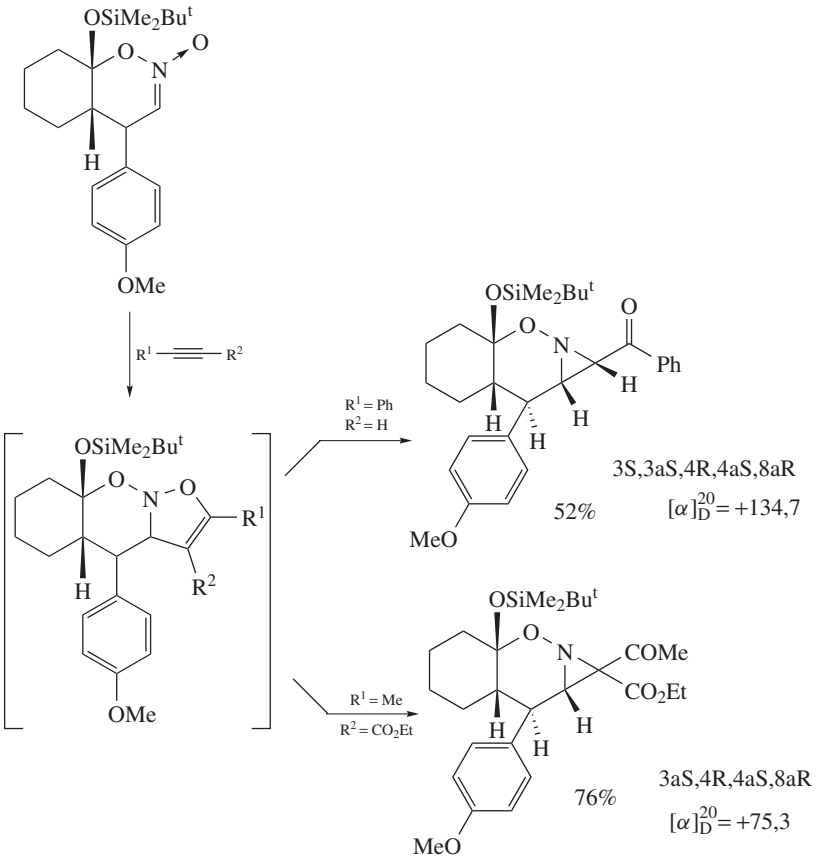
is absent among the reaction products as well as by the fact that isoxazoles cannot be detected among products of trapping of nitronate (**172**) by other acetylenes. All the same, it is rather surprising that acyl nitronate (**172**), which smoothly reacts with DMAD, does not form adducts with any other compound containing a multiple bond, including maleic anhydride.

Interestingly, the reaction of nitronate $MeCBr=N(O)OSiMe_2Bu^t$ with DMAD also produces substituted dihydroisoxazole (**175**) in good yield rather than the corresponding isomeric aziridine (**176**) (Scheme 3.136), which was confirmed by IR spectroscopic data (87).

Presumably, isoxazoline (**175**) is thermodynamically more favorable than overcrowded aziridine (**176**) due to π,π conjugation. Elimination of the bromide anion from intermediate (**175**) is also hindered due to instability of the carbocation that formed.

3.4.3.2.2. Intermolecular [3 + 2]-Addition to other Dipolarophiles Data on this problem are scarce and concern primarily interactions of SENAs with the C,S double bond. (383–386)

Dipolarophiles (**178**) containing this fragment can easily be generated by irradiation of thio derivatives of acetophenone **177** (Scheme 3.137). (Special



Scheme 3.134

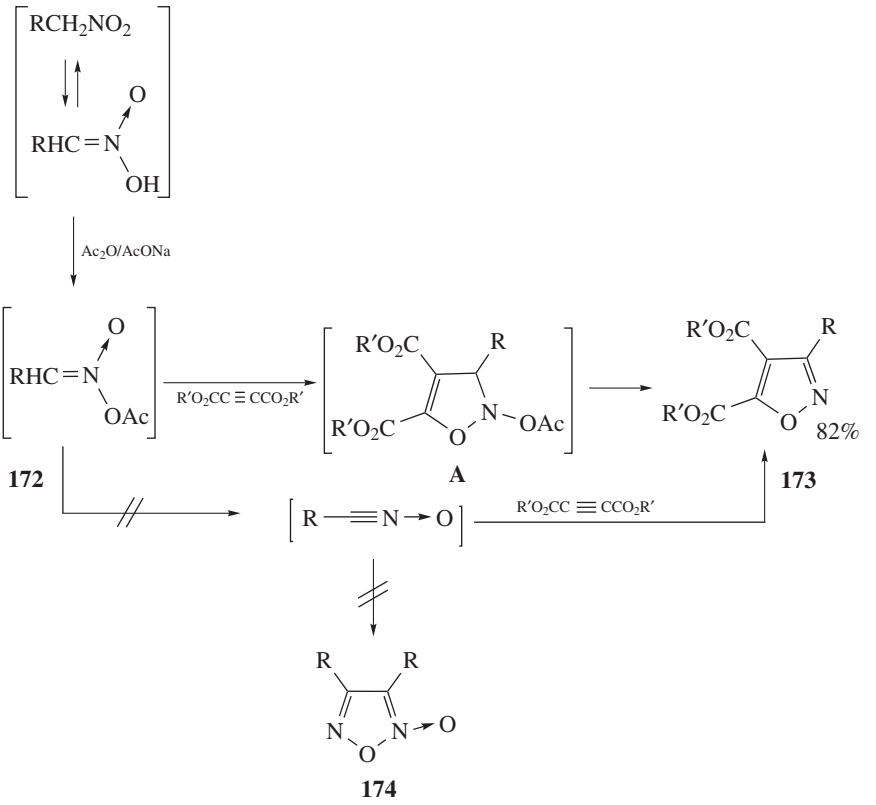
investigations demonstrated that thia aldehydes (**178**) exist in equilibrium with isomeric trimers.)

Thio aldehydes (**178**) *in situ* smoothly react with silyl ether of nitroethane, and regioselectively form cycloadducts (**179**) as one isomer or as a mixture of stereoisomers in high yields.

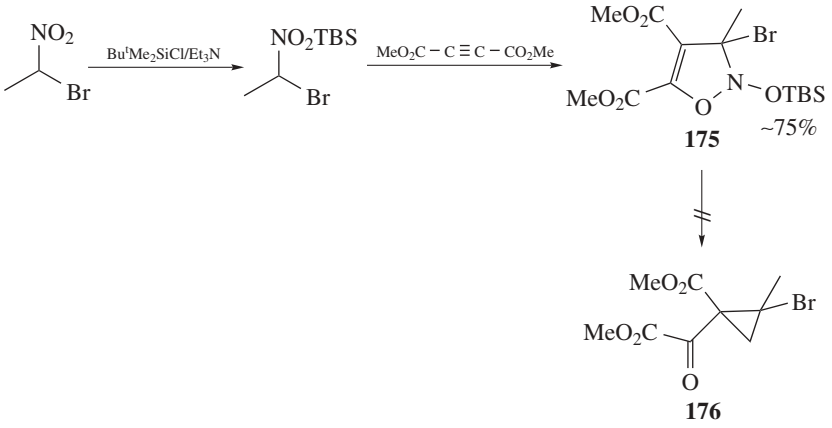
This reaction was used as the basis for the development of a procedure for the synthesis of carbonyl compounds (**182**) from acetophenone derivatives (**180**) (386) (Scheme 3.138).

The process involves one technological step. Tetrabutyl- or triethylammonium fluorides can serve as reagents for the cleavage of cycloadducts (**181**). For this purpose, *N*-chlorosuccinimide in aqueous THF can also be used.

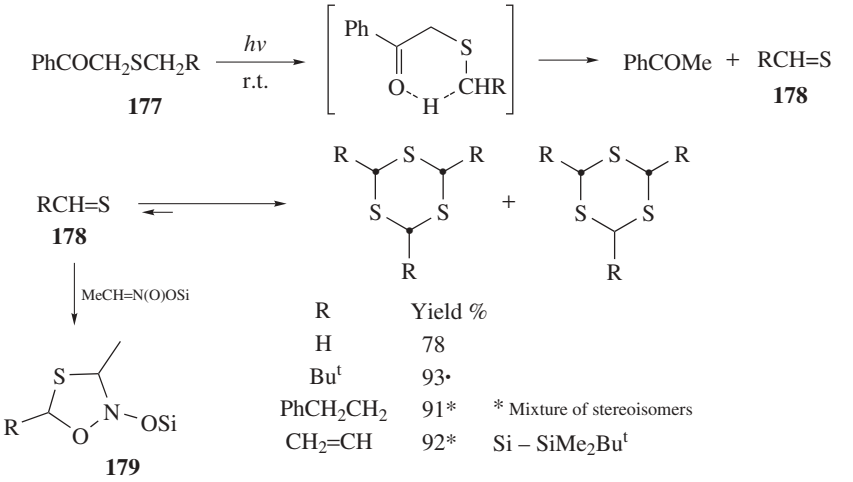
As mentioned above (303) (Scheme 3.90, Eq. 1), bis-trifluoromethyl thioketene has the deoxygenating ability toward alkyl nitronates, which is also based on cycloaddition to the C=S bond.



Scheme 3.135



Scheme 3.136



Scheme 3.137

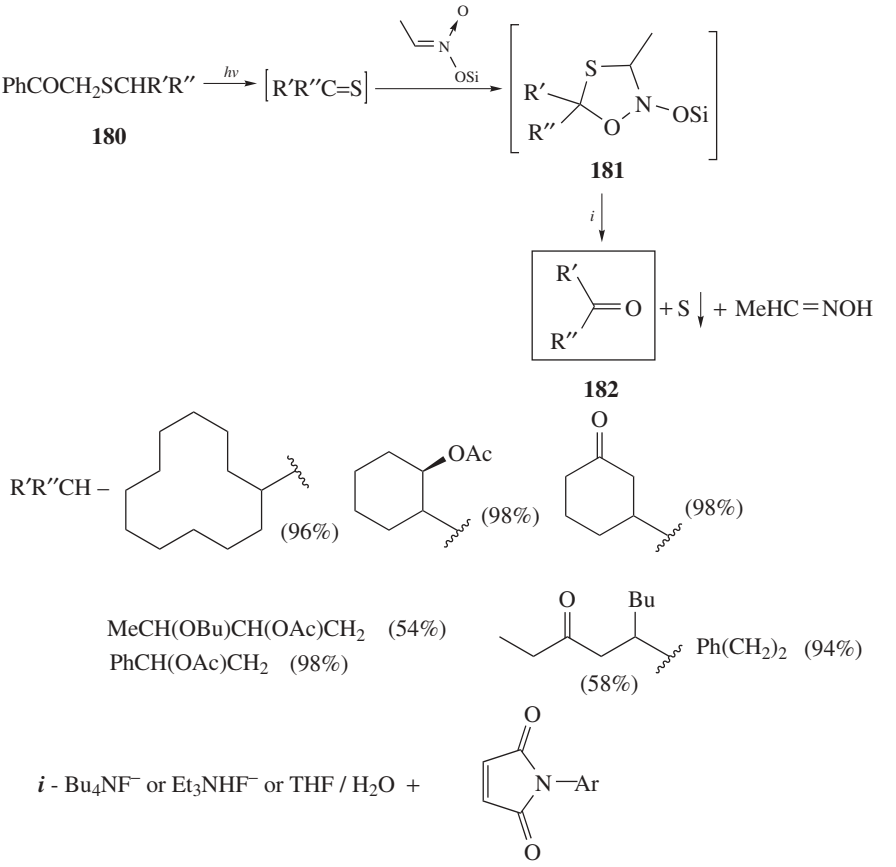
It was reported (387) that decomposition of nitronate (**183**) afforded isoxadiazole **184** (Scheme 3.139).

It was suggested that this product was formed by [3 + 2]-cycloaddition of nitronate (**183**) and oxime of benzaldehide, which was generated upon decomposition of the above mentioned nitronate, followed by elimination of water and methanol. However, direct evidence for the occurrence of cycloaddition of nitronates to the C,N double bond of oximes is lacking.

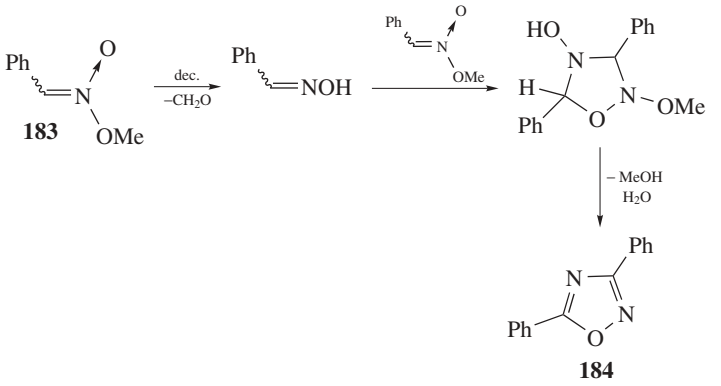
3.4.3.3. Intramolecular [3 + 2]-Cycloaddition of Nitronates These reactions are more efficient than analogous intermolecular transformations of nitronates as [1,3]-dipoles, and, consequently, activation of the "dipolarophilic" fragment is not required. However, another problem arises, that is, the construction of the starting substrate combining the nitronate fragment and the C,C double bond in the required positions.

A rather general strategy was developed for the construction of such substrates (Scheme 3.140).

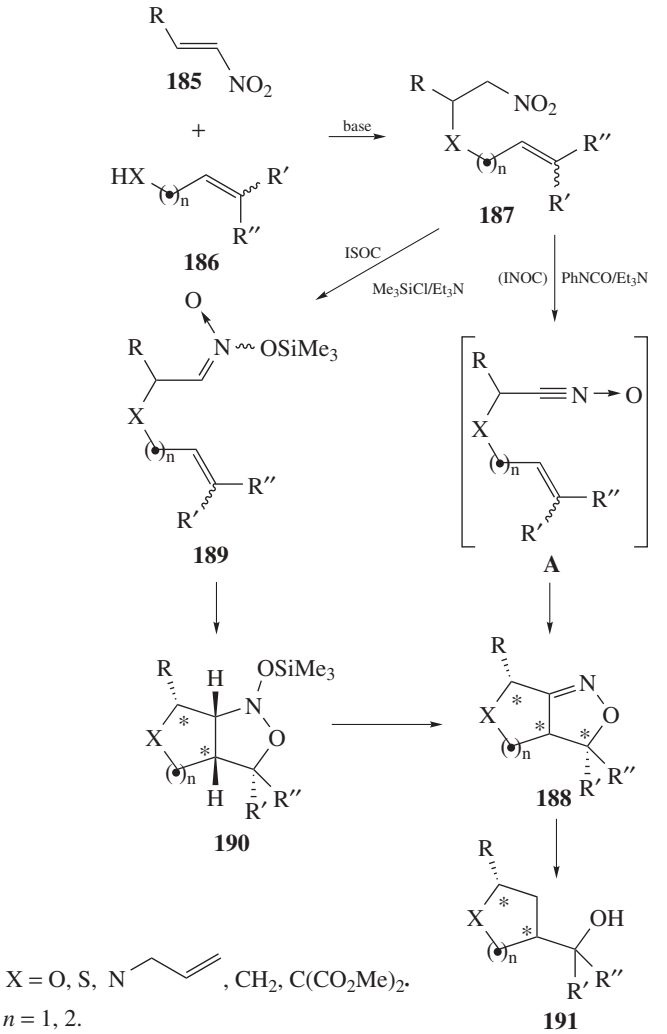
This approach involves the Michael reaction of readily available α-nitroalkenes (**185**) with various nucleophiles (**186**) containing the C,C double bond. (Generally, it is necessary to activate the nucleophile by particular bases, such as amines, metal hydrides, organomagnesium compounds, etc.) As a result, a wide range of target nitro derivatives **187**, which differ primarily by the length and composition of the tether between the $>CH(NO_2)$ fragment and the C,C double bond, can be obtained. This tether (n = 1 or 2) can consist only of carbon atoms (X = > C) (186, 191, 199) or include one oxygen atom (X=O) (192), (194–196, 198), a nitrogen atom (X = N–Alk or NH) (200), or the sulfur atom (X=S) (195, 388, 389). Nitro compounds (**187**) are transformed into nitrile oxides **A**, which are subjected to intramolecular cycloaddition to give bicyclic derivatives **188**



Scheme 3.138



Scheme 3.139



Scheme 3.140

(**intramolecular nitrile oxide cycloaddition (INOC)** process) or undergo silylation to form SENAs (**189**), as subjects of intramolecular cycloaddition, giving rise to fused isoxazolidines (**190**) (**ISOC** process). The latter can be smoothly transformed into bicyclic isoxazolines (**188**). Products (**188**) are readily reduced to the corresponding γ-amino alcohols **191**. It should be noted that the configurations of the labeled stereocenters are retained upon the transformation (**190**→**188**) due to which, the stereochemistry of the **INOC** and **ISOC** processes can be compared.

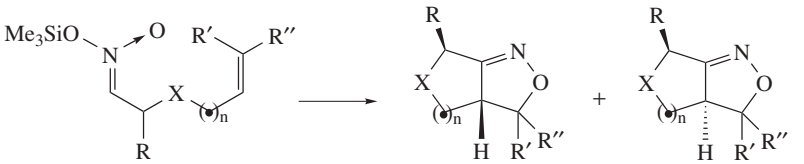
Both of these processes are regioselective, and are different from intermolecular [3 + 2]-cycloadditions of nitronates in that the terminal carbon atom of the C,C double bond is bound to the oxygen atom of the nitronate fragment regardless of the degree of its substitution.

The stereoselectivity of the **INOC** process substantially differs from that of the **ISOC** process, the stereoselectivity of the **ISOC** process being generally much higher. Evidently, this is due to a considerable differentiation of the transition states. It gives to different stereoisomers due to higher hindrance of the nitronate dipole compared to the linear nitrile oxide dipole.

It does not help to discuss the influence of substituents in nitro substrate (**187**) on the stereoselectivity and stereodirection of [3 + 2]-cycloaddition in the general case, because this effect is determined by the sum of different factors and, hence, it depends on the number and nature of the above mentioned substituents.

At the same time, the stereoselectivity and stereodirection of the **ISOC** process substantially depend on the tether length (Scheme 3.141).

If the tether consists of three atoms (-RCH–X-$(\cdot)_n$- (n = 1)), the stereoselectivity of the process is very high, and *trans* isomer **188a** prevails among the reaction products, regardless of the composition of the tether, due to the *endo* approach of the tether to the *Z* isomer of the nitronate. An increase in the length of the tether to four atoms (n = 2) leads to a sharp decrease in selectivity of cycloaddition, and *cis* isomer (**188b**) prevails among the reaction products. Evidently, the latter isomer is formed as a result of the *exo* approach of the tether to the nitronate.



Entry	R	R’	R”	X	n	dr **a/b**	Ref.
1	C_6H_5	H	H	CH_2	1	99:1	199
2	4-MeO-C_6H_4	H	H	CH_2	1	99:1	199
3	*i*-Pr	H	H	CH_2	1	99:1	199
4	C_6H_5	Me	Me	CH_2	1	99:1	199
5	C_6H_5	H	H	CH_2	2	1:2.6	199
6	*i*-Pr	H	H	S	1	99:1[a]	388
7	C_6H_5	H	H	S	1	99:1[b]	388
8	4-MeO-C_6H_4	H	H	$C(CO_2Me)_2$	1	99:1[c]	200
9	C_6H_5	H	H	S	2	5:3	388

[a] INOC – 1:1; [b] INOC – 3:2; [c] INOC – 1:5.

Scheme 3.141

References to Scheme 3.141 exemplify that the selectivity decreases or even the stereodirection is inverted in going from the **ISOC** process to the **INOC** process (see entry 8, Scheme 3.141).

An interesting example was cited in Reference 196 (Scheme 3.142).

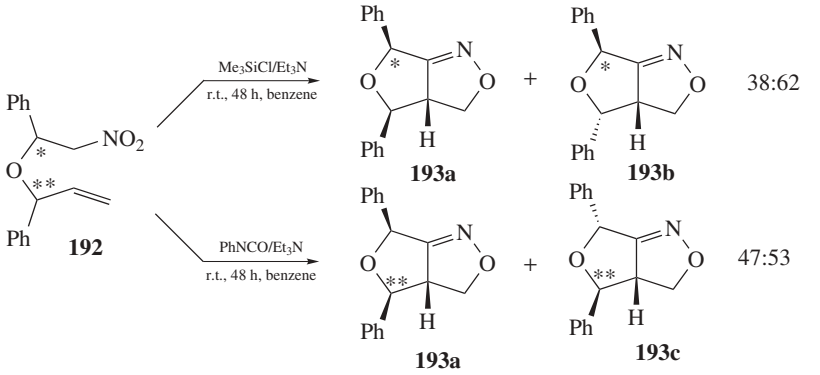
The authors demonstrated that the stereocontrol in the **ISOC** process as applied to nitro compound (**192**) is influenced by the phenyl substituent at the C* atom to give, respectively, stereoisomers **193a** and (**193b**), whereas the stereocontrol in the **INOC** process is provided by the substituent at the C** atom. This corresponds to a decrease in the effect of the "dipole" in going to the INOC process.

The **INOC** and **ISOC** processes, taken together, cover a wide range of substrates and generally give the target bicyclic products in yields from high to moderate. It should be noted that the reaction conditions for the INOC process are milder and the yields of bicyclic products are somewhat higher, while the **ISOC** process is substantially more selective.

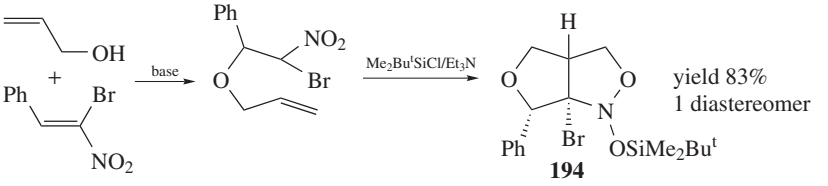
An increase in the tether length requires substantially more severe reaction conditions. For tethers containing more than five atoms between the reacting fragments, intramolecular [3 + 2]-cycloaddition reactions remain unknown.

Recently, β-bromo-β-nitrostyrene has been successfully involved in the **ISOC** process (Scheme 3.143) (390).

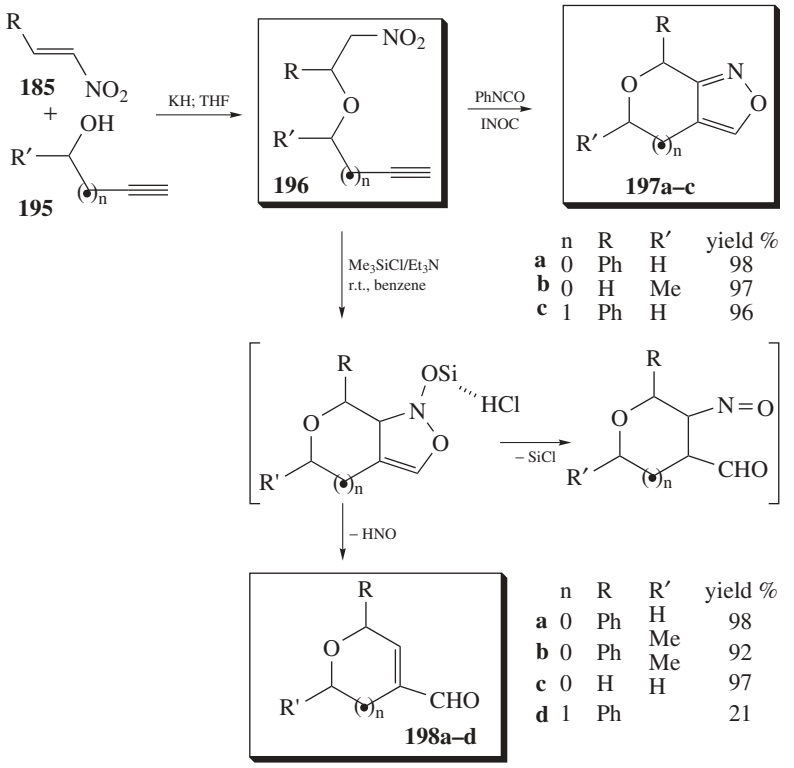
In this case, unlike the above considered examples, Bu^tMe_2SiCl was used as the silylating agent and the target isoxazolidine (**194**) was isolated in high yield



Scheme 3.142



Scheme 3.143



	n	R	R′	yield %
a	0	Ph	H	98
b	0	H	Me	97
c	1	Ph	H	96

	n	R	R′	yield %
a	0	Ph	H	98
b	0	Ph	Me Me	92
c	0	H	H	97
d	1	Ph		21

Scheme 3.144

as one stereoisomer. The relative configurations of the carbon atoms were reliably established, whereas the configuration of the nitrogen atom (containing a pseudoequatorial lone pair) can be assumed only by analogy with *N*-siloxyisoxalidines described earlier.

The intramolecular interaction of SENAs with the C,C triple bond was documented (190). The starting substrates were constructed with the use of the strategy shown in Scheme 3.140, alcohols containing the C,C triple bond being used as nucleophiles (**195**) (Scheme 3.144).

The resulting nitro compounds (**196**) were involved in intramolecular [3 + 2]-cycloaddition according to the **INOC**. This method (for n = 0) produced fused ene aldehydes (**198a–c**) also in good yields in the case of **ISOC** strategies. The **INOC** method gave usual fused isoxazoles (**197a–c**) in high yields, whereas with the **ISOC** longer tether (n = 1), the corresponding aldehyde (**198a–d**) can also be prepared, but in low yield. The reaction pathway yielding aldehydes (**198**), which was suggested in the Reference 190 is shown at the bottom of Scheme 3.144. (It should also be noted that only one example of intermolecular addition of SENAs to the C,C triple bond is known; see Scheme 3.136.)

In addition to the general procedure for the construction of the starting substrates for intramolecular [3 + 2]-cycloaddition (see Schemes 3.140 and 3.143), several other routes to these products are known.

A procedure developed by Moiseenkov, Veselovskii, and coworkers (207–211, 391) (Scheme 3.145) is of most interest.

Here substituted acyclic dienes (**199**) serve as the starting reagents. The method involves:

a. The introduction of the nitro group with retention of both C,C double bonds in the molecule;
b. Silylation of the nitro fragment in substrate (**200**) with BSA;
c. Intramolecular cycloaddition giving rise to fused isoxazolidine (**201**);
d. Cleavage of the isoxazolidine ring to form conjugated oxime (**202**).

This method is very original. Intramolecular cycloaddition to the double bond remote from the nitro fragment can be considered as the key step (step c). This step is regio- and stereoselective. Cleavage of the isoxazolidine ring with fluoride ions was accompanied by an interesting allyl migration of the nitroso group (**B**→**C**), which allows one to synthesize conjugated ene oximes (**202**). The latter are very convenient reagents for the formation of the iridane skeleton involved in a series of biologically active substrates.

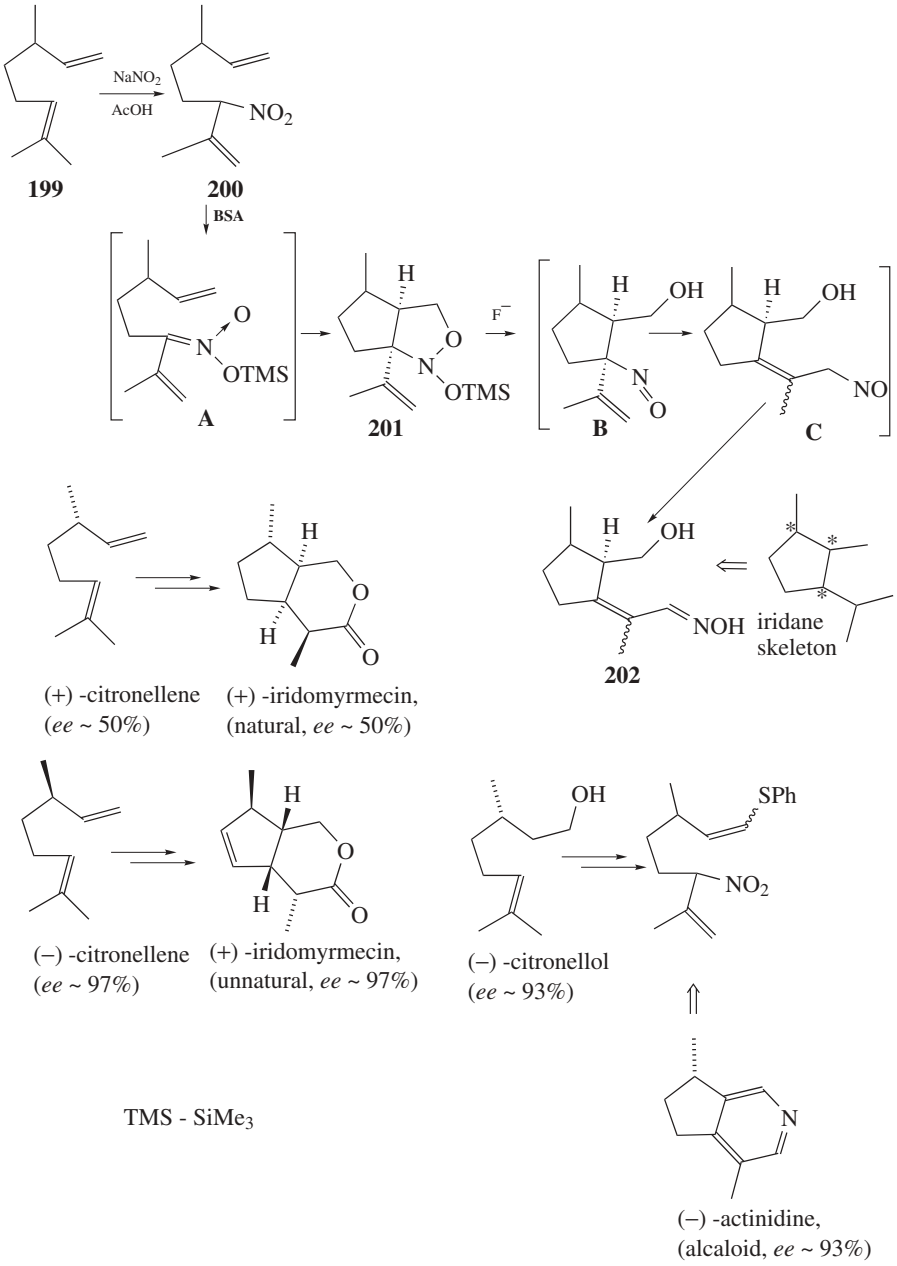
Russian researchers applied this scheme to readily available chiral dienes or their precursors and prepared several enantiomerically pure target substrates, the enantioselectivity of intramolecular [3 + 2]-cycloaddition being virtually complete.

Professor Seebach and coworkers (96) used silyl enolate (**203**) containing an additional C,C double bond in the Michael reaction with α-nitroalkene (**204**) in the presence of chiral LA (Scheme 3.146).

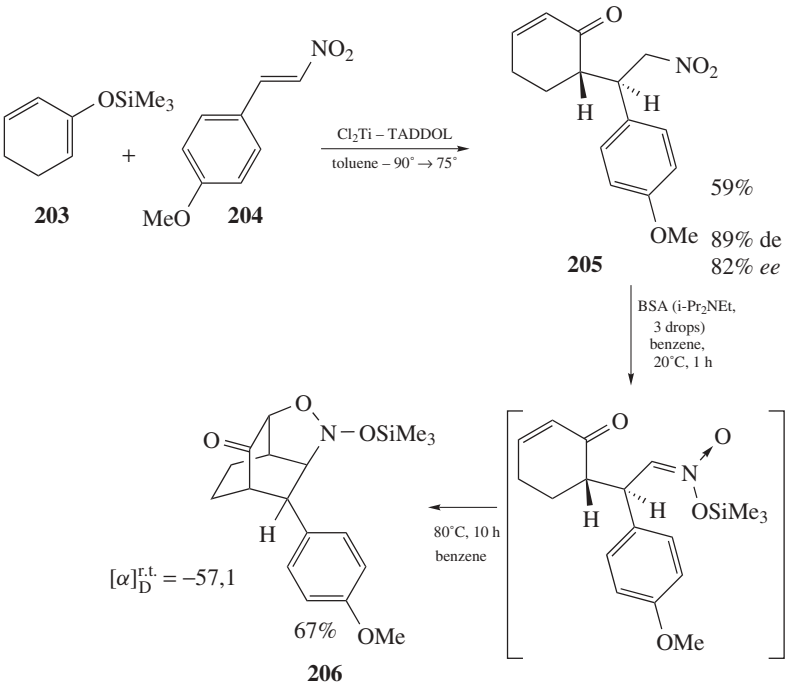
As a result, diastereo- and enantiomerically pure functionalized nitro derivative (**205**) was synthesized in satisfactory yield. This compound was used in the **ISOC** procedure, which gave diastereo- and enantiomerically pure isoxazolidine (**206**) in good yield. The latter compound can be considered as a possible reagent for asymmetric synthesis. It should be noted that silylation in this procedure, like that described above (Scheme 3.145), was performed with the use of BSA as the silylating agent in the presence of a small amount of Hunig's base, the latter being evidently added for acceleration of silylation and stabilization of intermediate silyl nitronate.

Taiwan researchers (392) described the transformation of fused dihydrofurans (**207**), in the presence of LA, giving rise to 3-benzofuryl-substituted formaldoximes (**208**) in good yields (Scheme 3.147).

A long reaction sequence was suggested for this very unusual transformation. In this process, the key step (**A**→**B**) involves intramolecular [3 + 2]-cycloaddition of SENA **A**, which was generated through 1,5–C,O-migration of the trimethylsilyl group in compound (**207**). Then the tricyclic system **B** is rearranged to give


NaNO2
AcOH
NO2
199
200
BSA
O
N
OTMS
A
H
O
N
OTMS
201
F−
H
OH
N
O
B
H
OH
NO
C
H
OH
NOH
iridane
skeleton
202
(+) -citronellene
(ee ~ 50%)
(+) -iridomyrmecin,
(natural, ee ~ 50%)
(–) -citronellene
(ee ~ 97%)
(+) -iridomyrmecin,
(unnatural, ee ~ 97%)
OH
SPh
NO2
(–) -citronellol
(ee ~ 93%)
TMS - SiMe3
N
(–) -actinidine,
(alcaloid, ee ~ 93%)

Scheme 3.145



Scheme 3.146

isoxazoline **E**, which undergoes isomerization to form conjugated nitrosoalkene **F**. The 1,5-proton shift in the latter gives rise to isolable oxime (**208**).

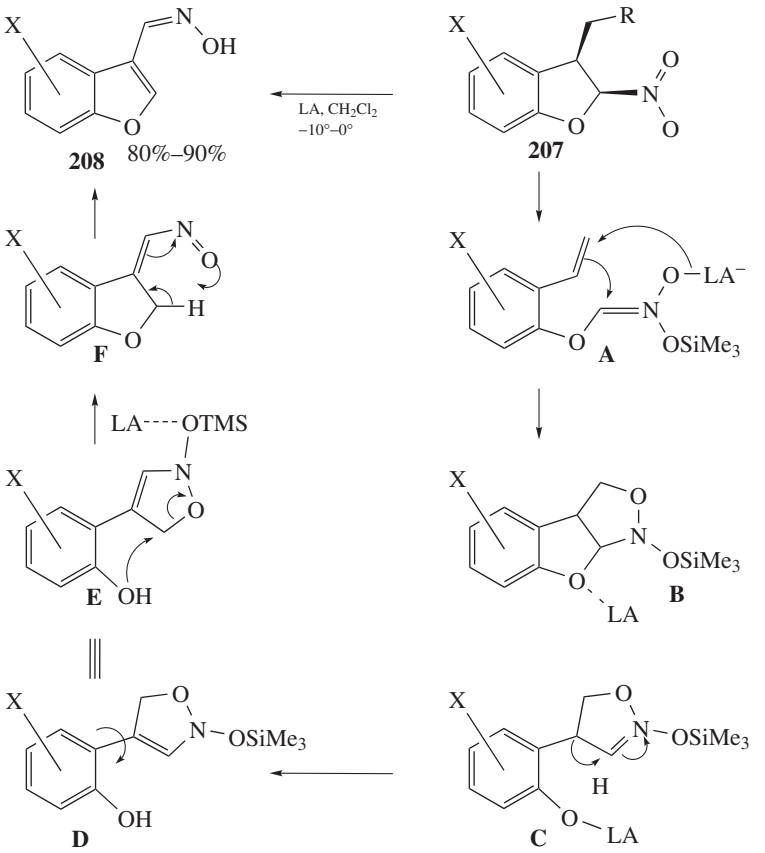
Not all of the steps of this scheme are justified. However, it was successfully extended to the synthesis of 2-nitrobenzothiophene (392) (Scheme 3.148). It is known that an attempt to use this strategy for the preparation of unfused 2-nitro-3-(trimethylsilylmethyl)dihydrofuran led to the selective formation of another product.

The behavior of SENAs in intramolecular [3 + 2]-cycloaddition was studied also with a Si-containing tether (193, 194).

In particular, a series of isoxazolines (**211**) fused to the five-membered ring was synthesized (193) (Scheme 3.149, Eq. 1). As a rule, the reactions are characterized by high stereoselectivity (dr > 20:1).

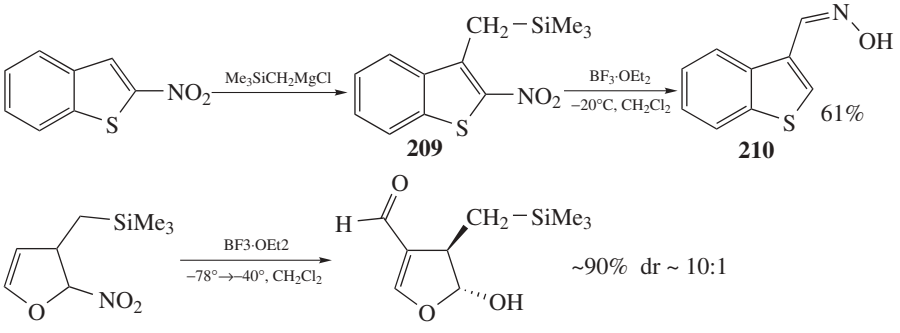
Products (**211**) can be hydrogenated over Ni/Ra, which is accompanied by opening of both rings, the configurations of the stereocenters being retained.

In the **ISOC** process, a longer Si-containing tether was also used (194) (Scheme 3.149, Eq. 2). As expected, the use of a longer tether requires more severe reaction conditions and leads to a decrease in stereoselectivity of the process. However, the results of the study (194) show that the stereoselectivity of the reaction additionally depends on the bulkiness of the substituent R (cf. the 2/2′ ratio for (**212a**) and (**212b**) respectively).

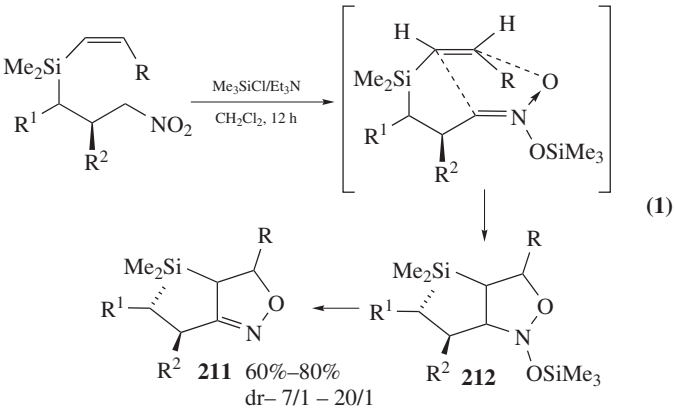


R = $SiMe_3$; X = H; 5-Br; 5-OMe; 7-OMe;
LA – $AlCl_3$, $TiCl_4$, $BF_3{\cdot}OEt_2$, $SnCl_4$.

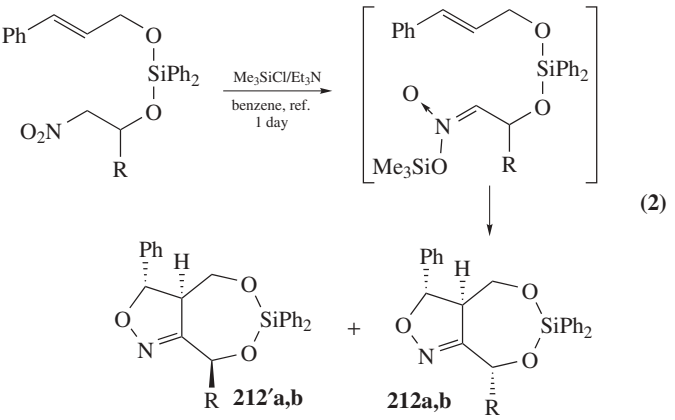
Scheme 3.147



Scheme 3.148



R and R^2 – H or Me; R^1 – $BuO(CH_2)_2$; n-Pr; n-Hex; $BuOCH_2CHMe$



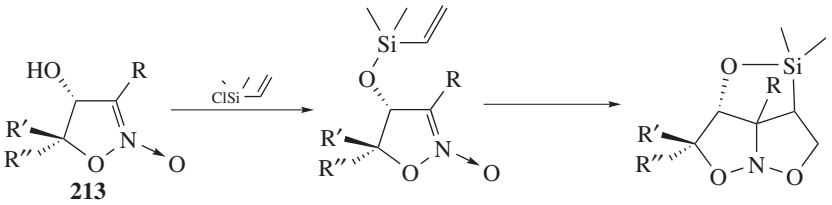
a–R = Me, 45%, 2/2′ = 7:3
b–R = Ph, 23%, 2/2′ = 9:1

Scheme 3.149

In the **INOC** process, the stereoselectivity of both reactions shown in Scheme 3.149 is substantially lower compared to that in **ISOC;** however, the yield of isoxazolines (**211**) and (**212a,b**) is noticeably higher.

In intramolecular [3 + 2]-cycloaddition reactions of five-membered cyclic nitronates, only a Si-containing tether was used (393) (Scheme 3.150, see also Scheme 3.120 and references therein).

This process was carried out with the use of diastereomerically and enantiomerically pure five-membered cyclic nitronates (**213**). After selective silylation of the hydroxy group and intramolecular cycloaddition, these compounds give enantiomerically pure fused systems, which are similar precursors of enantiomerically pure hydroxyamino acids and other polyfunctional compounds possessing potential biological activity.



Scheme 3.150

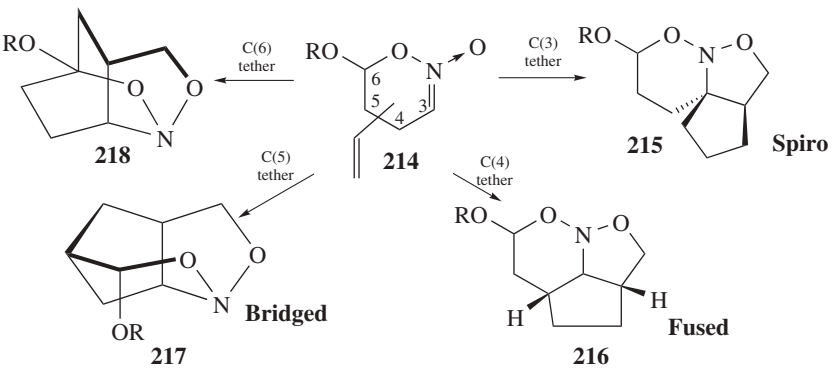
Intramolecular [3 + 2]-cycloaddition of six-membered cyclic nitronates was extensively studied by Prof. Denmark and coworkers for the tandem [4 + 2] [3 + 2]-cycloaddition reactions of nitroalkenes. Detailed considerations of this problem were summarized in two reviews (394a, b). Most data were comprehensively discussed in Reference 394b. It is unnecessary to repeat this information; however, it is worthwhile to briefly review the available data.

At the outset, it should be noted that, as in the above-considered intramolecular [3 + 2]-cycloaddition reactions, the regioselectivity of the process is retained, that is, the terminal (or more removed) atom of the C,C double bond is always bonded to the oxygen atom of the nitronate.

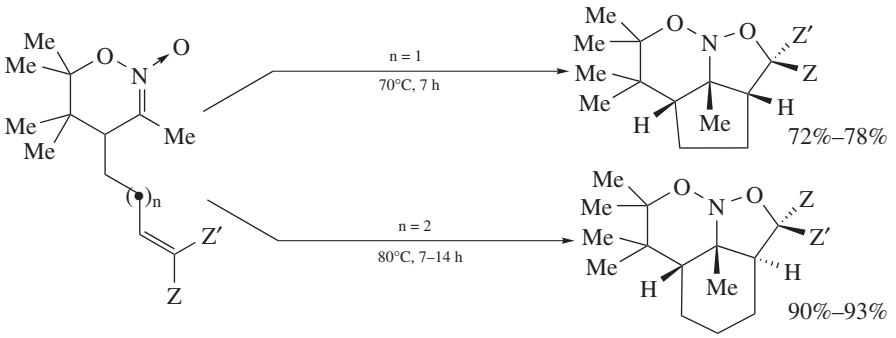
The character of the resulting fused system completely depends on the site of attachment of the tether to the six-membered ring (Scheme 3.151).

If a tether is attached to the C(3) atom of nitronates (**214**), the reaction gives rise to spiro systems (**215**). For these systems, generating a linkage containing three atoms between the six-membered ring and the C,C double bond is a case of choice. It necessarily leads to *cis*-fusion of two five-membered rings.

If a tether is bound to the C(4) atom, annelated (fused) systems (**216**) are formed. In this case, two atoms can be present in the above mentioned linkage, the protons in product (**216**) being in the *cis* position.



Scheme 3.151



Scheme 3.152

If a tether is bound to the C(5) or C(6) atoms, bridged systems (**215**) and (**216**), respectively, are formed, and the number of atoms between the six-membered ring and the double bond can be reduced to one.

If a tether is considered as a linkage between the reacting fragments (nitronate and the C=C bond), it contains three atoms in all cases.

Tethers attached to C(4) were studied in most detail because the corresponding starting substrates are readily available. It appeared that if the reacting fragments are linked to each other by three or four atoms, there is no substantial difference in the reaction conditions and the yields of the target products. However, the approach of the reactive C,C double bond to the nitronate fragment changes (110) (Scheme 3.152).

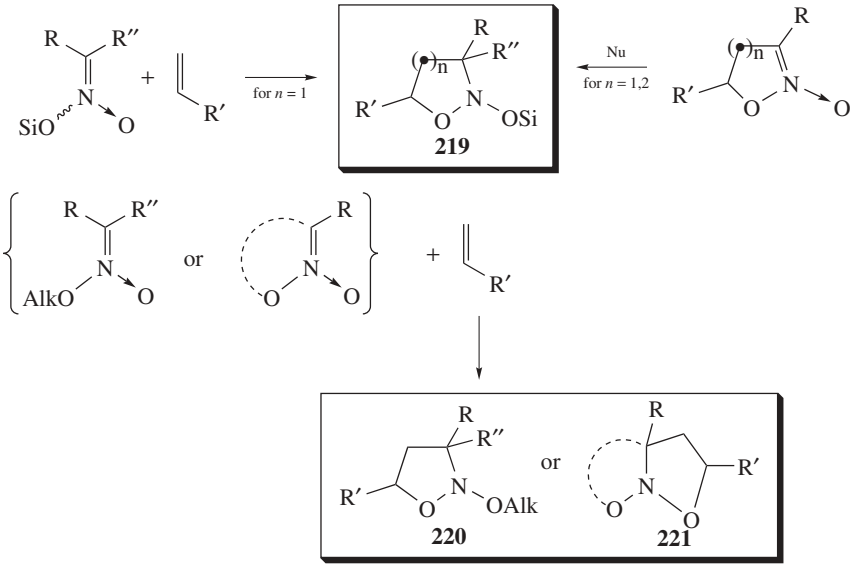
At the same time, cycloaddition does not occur when the tether length is increased by one more atom (110). The stereoselectivity of cycloaddition depends on both the tether length (n = 1 or 2) and the configuration of the reacting C,C double bond, which was established in several reactions (110).

For tethers bound to the C(5) and C(6) atoms, the optimal reaction conditions, as well as the yields and configurations of the products, depend on numerous factors and cannot be generalized and described by simple relationships.

Therefore, in spite of extensive investigations, it is difficult to *a priori* predict the stereochemical outcome of the intramolecular [3 + 2]-cycloaddition reaction involving six-membered cyclic nitronates as well as to find optimal reaction conditions.

3.4.3.4. Main Aspects of Chemistry and Stereochemistry of Cyclic Nitroso Acetals Chemistry of cyclic nitroso acetals or nitrosals (the term was introduced by Prof. Seebach) has attracted interest only after the discovery of the 1,3-dipolar cycloaddition reaction of nitronates with olefins in 1962 by the research group of Prof. Tartakovsky. (Principal data on nitroso acetals up to 1990 were summarized in the review by Rudchenko (395).)

Cyclic nitroso acetals (**219, 220**), and (**221**) (Scheme 3.153) belong to the most interesting group of nitroso acetals, such as derivatives containing the –O–N–O–



Scheme 3.153

fragment. Evidently, these products are unstable due to the presence of weak N–O bonds (energy of about 53 kcal/mol (394)) and to the possibility of antibonding interactions between lone electron pairs of three heteroatoms linked to each other. Hence, main transformations of these derivatives should involve the N–O bond cleavage. In this process, a cyclic structure can be considered as a kind of tether, which makes it possible to avoid the change in the initial molecule after N–O bond cleavage.

Besides, cyclic nitroso acetals have attracted considerable interest because [3 + 2]-cycloaddition of nitronates to olefins provides a simple and efficient procedure for the synthesis of five-membered cyclic nitrosals (see Scheme 3.153). Hence, knowledge of the configurations of these products allows conclusions about the mechanism of this very important process. However, it is impossible to distinguish kinetic and thermodynamic products of [3 + 2]-cycloaddition of nitronates to olefins without studying such a fundamental problem as the stereodynamics of five-membered cyclic nitroso acetals, that is, the ring and nitrogen inversions.

A recently developed general procedure for the synthesis of cyclic nitroso acetals is based on the reaction of cyclic nitronates with C-nucleophiles under conditions of electrophilic catalysis (Scheme 3.153; for more details, see Section 3.5.2.3).

3.4.3.4.1. Transformations of Five-membered Cyclic Nitroso Acetals Containing the N-siloxy Fragment Under the Action of Acids and Nucleophiles These products are characterized by the fact that both the N–O*Si* and O–Si bonds can

easily be cleaved. In the general form, these transformations of nitroso acetals are shown in Scheme 3.154 using isoxazolidines (**223**) as an example.

By the action of protons and some other electrophilic agents, these isoxazolidines eliminate the corresponding silanol to give isoxazolines (**224**). At the same time, nucleophiles can cause elimination of the trialkylsilyl group to form oximino alcohols (**225**).

Selective reduction of the oximino fragment in products (**224**) or (**225**) gives rise to poorly studied γ-amino alcohols (**226**). In addition, desoximation of (**225**) can produce the corresponding β-hydroxycarbonyl derivatives (**227**). In addition, oximino alcohols (**225**) can be oxidized to γ-nitro alcohols (**228**).

Since nitroso acetals (**223**) can be efficiently assembled from very simple molecules and primarily from AN, Scheme 3.154 shows a general strategy for assembling polyfunctional molecules from readily available precursors in a few steps. As will be evident from the preceding data, it is possible to design the stereocenters and chiral molecules.

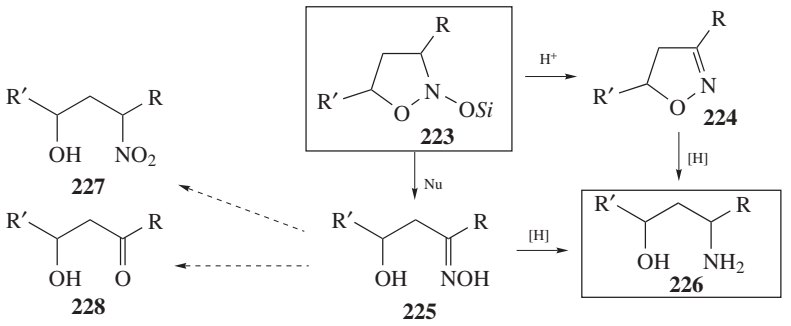
Let us consider the reactions shown in Scheme 3.154 in more detail.

The transformation (**223**→**224**) involves elimination of silanol under acid catalysis followed by stabilization of the cation **A** by proton elimination from the C-3 atom (Scheme 3.155). In this process, the configurations of the stereocenters at the C-4 and C-5 atoms are retained. It should be noted that the siloxy fragment is eliminated from the most favorable axial position.

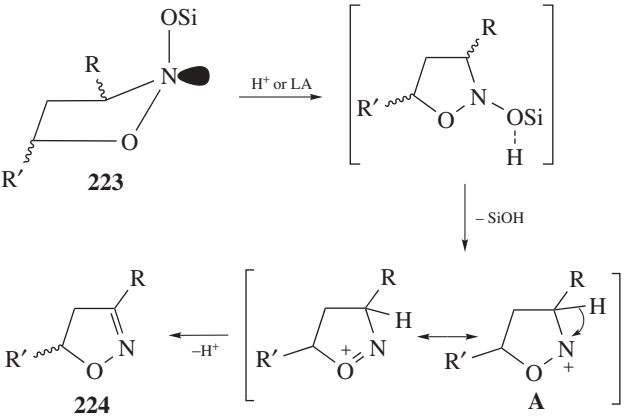
Several procedures were developed for the transformation (**223**→**224**). The most commonly used procedures are based on treatment of the nitroso acetal with benzene saturated with HCl (204, 205) and by the addition of a catalytic amount of *para*-toluenesulfonic acid or trifluoroacetic acid (206). The introduction of branched radicals at the silicon atom decelerates elimination of silanol.

Thermal elimination of trimethylsilanol from *N*-trimethylsiloxyisoxazolidines was also documented (175, 185). Presumably, this process is accelerated by the resulting trimethylsilanol.

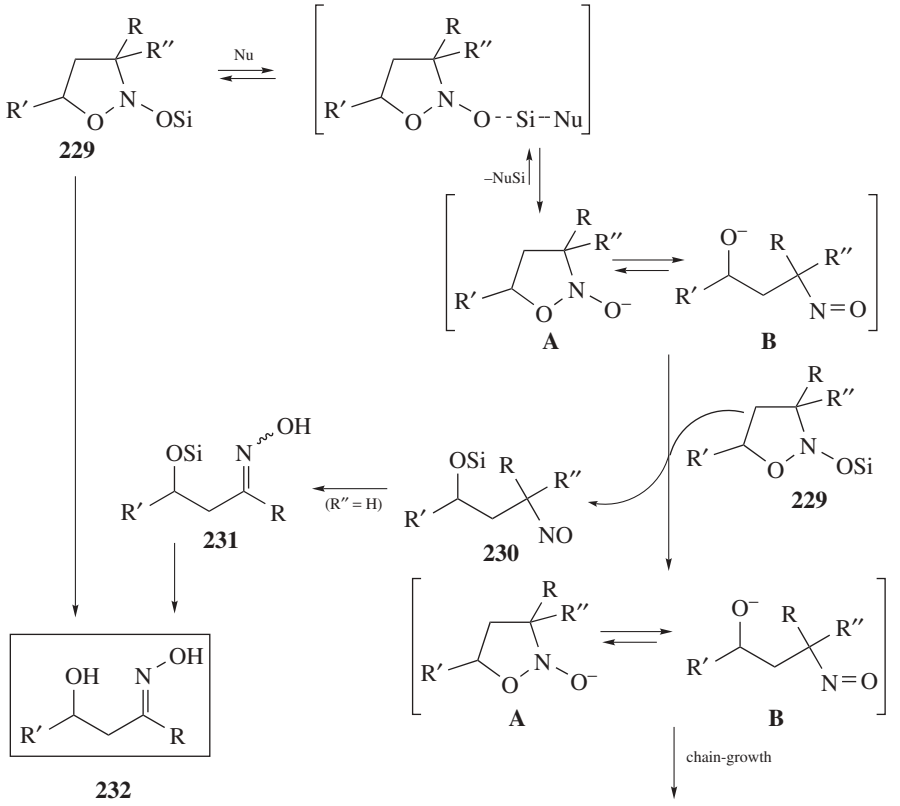
The reactions of isoxazolidines (**229**) with nucleophiles are more complex. Generally, these processes have a pronounced induction period (174, 204). They can be described by the following formal scheme (Scheme 3.156).



Scheme 3.154



Scheme 3.155



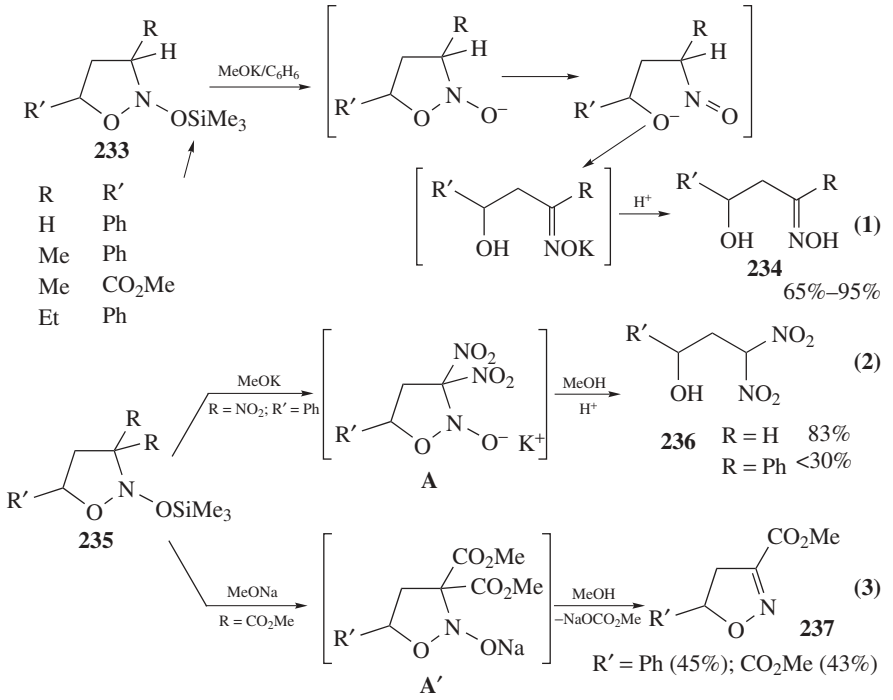
Scheme 3.156

The process is initiated by the reversible reaction of a nucleophile with isoxazolidine (**229**) at the silicon atom. The resulting anion **A** is also reversibly isomerized to form the anion **B**, which is accompanied by cleavage of the endocyclic N–O bond. The anion **B** acts as a nucleophile toward isoxazolidine (**229**), removes the trialkylsilyl group to give nitroso derivative (**230**), and initiates the chain growth. If at least one of the substituents at the C-3 atom is a proton, nitroso product (**230**) undergoes isomerization to give oximino derivative (**231**). The corresponding β-hydroxy oxime (**232**) is the final product in this sequence of transformations. In this case, the relative configurations of the stereocenters at the C-4 and C-5 atoms are also retained.

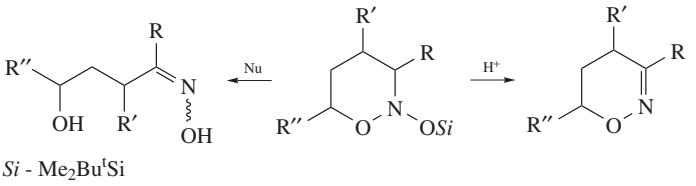
Two procedures were developed for efficient isomerization (**229**→**230**→**232**). One procedure is based on the reaction of fluoride anion, which has pronounced selectivity with respect to the silicon atom (189, 207). Another procedure involves treatment of nitroso acetals (**229**) with methanol containing a catalytic amount of triethylamine (174, 216).

Potassium methoxide in benzene also works well as a nucleophile in the transformation (**233**→**234**), where R=H or alkyl (Scheme 3.157, Eq. 1) (204, 205).

Interesting results were obtained in the reaction of strong nucleophiles with isoxazolidines (**235**) containing two *EWG* groups at the C-3 atom (Scheme 3.157, Eqs. 2 and 3). If R=NO_2, stabilization of the anionic intermediate **A** is



Scheme 3.157



Scheme 3.158

accompanied by C–N bond cleavage and the formation of more stable 1,1-dinitroalkyl anions (176). However, if R=CO_2Me, the analogous anionic intermediates **A′** are stabilized to give the corresponding isoxazolines (**237**) in moderate yield (175).

Preliminary experiments showed (396) that *N*-siloxytetrahydro-4*H*-oxazines (274), which are homologs of the above-considered *N*-siloxyisoxazolidines, can undergo analogous transformations under the action of nucleophilic and electrophilic agents (Scheme 3.158).

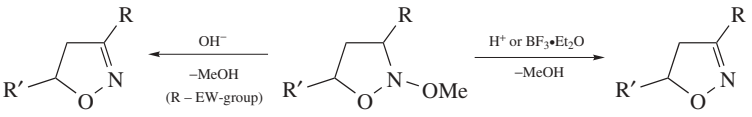
However, the selective action of nucleophilic and electrophilic reagents on these compounds can be complicated by the fact that the conformation with the axial *N*-siloxy fragment is thermodynamically less favorable for these nitroso acetals and that the silicon atom is sterically hindered.

3.4.3.4.2. Transformations of Cyclic and Bicyclic Fused Nitroso Acetals Containing the N-alkoxy Fragment Under the Action of Acids and Nucleophiles Unlike nitroso acetals considered in Section 3.4.3.4.1., *N*-alkoxynitroso acetals do not contain an evident center for nucleophilic attack near oxygen atoms. However, as can be seen from Scheme 3.159, nucleophiles can cause deprotonation of the C-3 atom if the latter bears an *EWG* group. The resulting anion can be stabilized through cleavage of the exocyclic N–O bond to form isoxazolines (**238**) (52, 397).

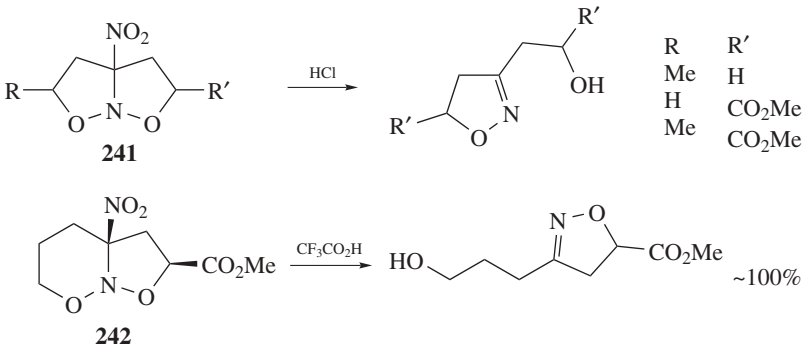
At the same time, the reactions of isoxazolidines (**239**) with soft acids and retain LA (157, 341, 398, 399) resemble an analogous process considered above for *N*-siloxynitroso acetals, which also affords isoxazolines (**240**). Methanol can be eliminated from nitroso acetals (**239**) also upon heating (341).

The reaction (**239**→**240**) for functionalized nitroso acetals is complicated by rearrangements (400).

The most interesting results were obtained in the study of the reaction of fused bicyclic nitroso acetals (**241**) with acids (337) (Scheme 3.160).



Scheme 3.159



Scheme 3.160

Both N–O bonds in this group of nitroso acetals are cleaved with 20% sulfuric acid. By contrast, gaseous hydrochloric acid selectively reacts at one N–O bond and cleaves the ring containing the most electronegative substituent at the C-5 atom. This reaction pathway can be attributed to higher stabilization of the negative charge on the corresponding oxygen atom.

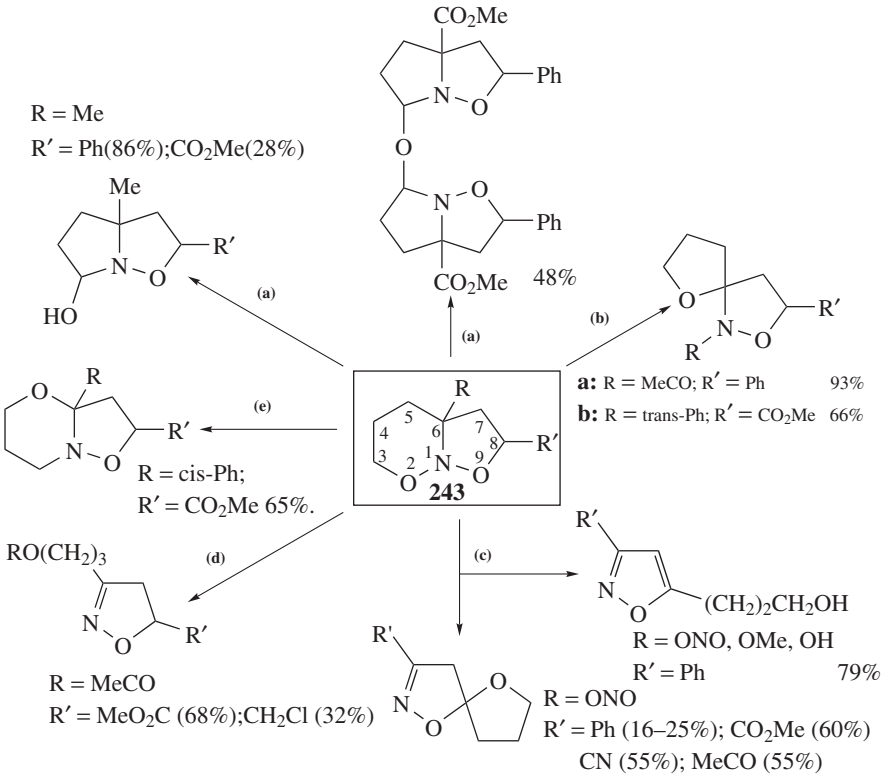
However, treatment of nitroso acetal (**242**) with CF_3CO_2H leads to selective N–O bond cleavage in the unsubstituted six-membered ring (49), in spite of the fact that the five-membered ring contains the –N–O–C(CO_2Me)- fragment, which efficiently stabilizes the negative charge. This result can be attributed to the anomeric effect, because the pseudo-axial position (related to the five-membered cycle) is preferable for the oxygen atom, involved in the six-membered ring (for more details, see Section 3.4.3.4.4.).

Very interesting rearrangements of fused bicyclic acetals (**243**), which occur by the action of boron trifluoride etherate, were found and studied in detail by Chlenov et al. (401) (Scheme 3.161).

In each particular case, the rearrangement pathway depends on the nature of the substituents R and R′. All of these rearrangements involve the N–O bond cleavage in the six-membered ring, but differ in the modes of stabilization of the resulting formal charges on the oxygen and nitrogen atoms.

Rearrangements of type (**a**) lead to binding of the nitrogen atom to the C-3 atom and the proton transfer from the latter atom to oxygen. Rearrangements of type (**b**) are accompanied by migration of the substituent from C-6 to the nitrogen atom, the oxygen atom taking the place of this substituent. Rearrangements of type (**c**) involve the N–(C-8) and O-(C-6) bond formations accompanied by elimination of the substituent from C-6. Rearrangements of type (**d**) involve the formation of the double bond between the nitrogen atom and the C-6 atom with the simultaneous migration of the substituent from C-6 to the oxygen atom. Finally, rearrangements of type (**e**) are characterized by the formation of bonds between nitrogen and C-5 and between oxygen and C-6.

In the author's opinion, the main reaction pathway for nitroso acetals (**243**) is determined by the ease of N–O bond cleavage in the O–N–O fragment.

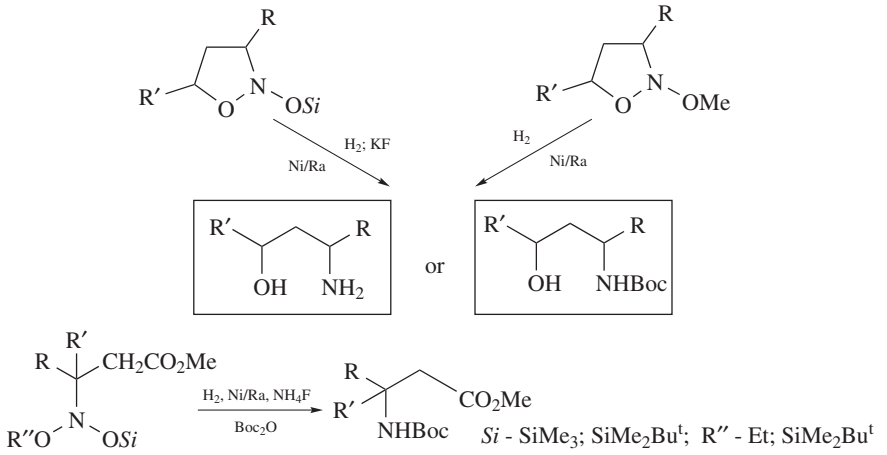


Scheme 3.161

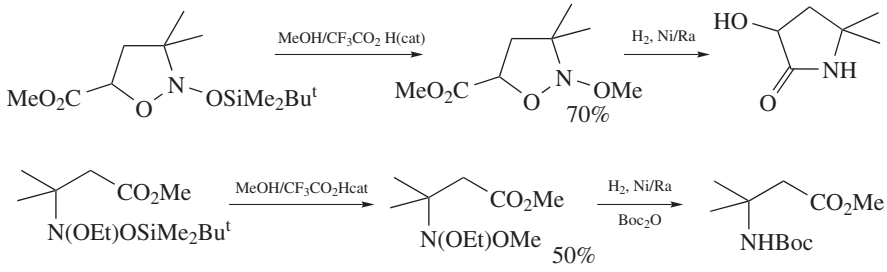
The presence of the bond in the *trans*-antiparallel position with respect to the cleaved N–O bond allows concerted 1,2-migration (a diotropic process). Apparently, the result of these rearrangements is also determined by the fact that the pseudo-axial position is substantially more favorable for the O–2 atom in nitroso acetals (**243**).

3.4.3.4.3. Selective Reduction of the O–N–O Fragment in Cyclic and Bicyclic Fused Nitroso Acetals From the point of development of methodology of organic synthesis, selective reduction of the nitroso acetal fragment and associated processes are the most important reactions of nitroso acetals (also see Scheme 3.154).

Selective reduction of the $-O-N-OSiMe_3$ fragment in *N*-siloxyisoxazolidines with $NaBH_2S_3$ as well as with a solution of diborane in THF was documented (205). However, this approach has not gained wide acceptance. Catalytic hydrogenation of nitroso acetals is used more common. For example, hydrogenation over Raney nickel was used with advantage for the selective hydrogenation of acyclic functionalized nitroso acetals (402), *N*-siloxyisoxazolidines (186, 189, 205, 402), and *N*-alkoxyisoxazolidines (402) (Scheme 3.162).



Scheme 3.162



Scheme 3.163

In this reaction, the role of the fluoride ion is apparently to generate a small amount of HF, which transforms the sterically hindered N–O*Si* fragment into the N–OH fragment. The latter undergoes hydrogenation more rapidly.

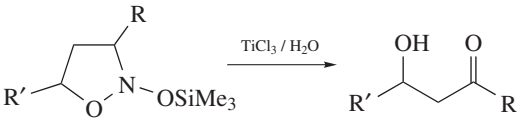
Hydrogenation of *N*-siloxynitroso acetals can also be facilitated by replacing the *N*-siloxy group with the less hindered *N*-methoxy group (402) (Scheme 3.163).

This methodology remains to be optimized, but in the future it will be characterized as a promising procedure for the use of nitroso acetals in organic synthesis.

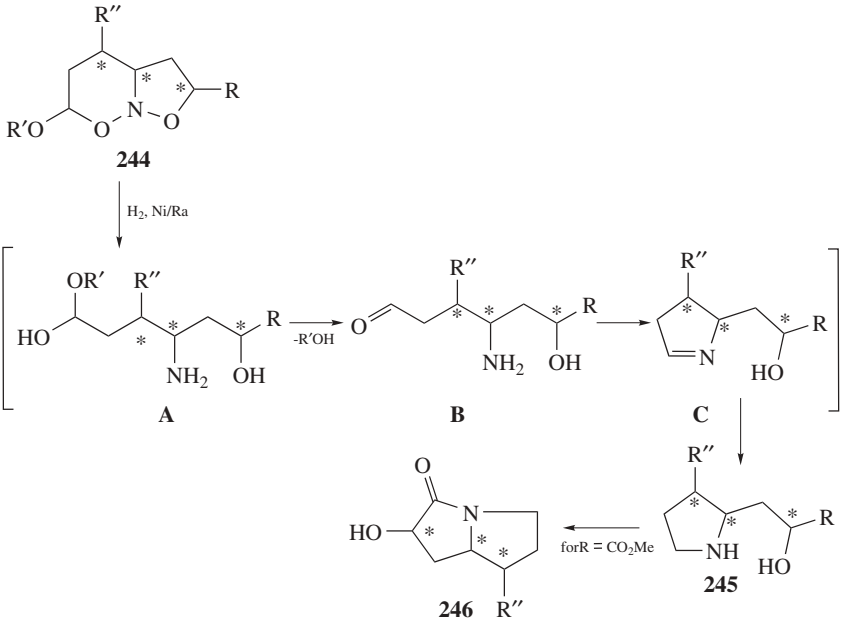
A convenient procedure was developed for transformations of *N*-siloxyisoxazolidines into functionalized β-hydroxycarbonyl compounds with aqueous titanium trichloride (185, 189) (Scheme 3.164).

Therefore, acyclic and monocyclic nitroso acetals are convenient precursors of functionalized β-hydroxy ketones and γ-amino alcohols (see Reference 403).

Catalytic hydrogenation of polycyclic fused nitroso acetals is a more complex reaction sequence. This process was successfully used in the synthesis of natural and biologically active compounds (see, e.g., Refs. 148, 367 and the review 99).



Scheme 3.164



Scheme 3.165

One of the modifications of this sequence is shown in Scheme 3.165.

Hydrogenation of nitroso acetals (**244**) containing the alkoxy substituent at the C-6 atom involves cleavage of both N–O bonds as the first step to give aminodiols **A**, which are successively transformed into carbonyl compounds **B**. The latter are fused to give pyrrolidines **C**, which are hydrogenated at the C=N bond to form isolable pyrrolines (**245**). If R=CO_2Me, the reaction proceeds further with intramolecular condensation of pyrrolidines (**245**) giving rise to fused systems (**246**). It should be noted that the configuration of labeled stereocenters in nitroso acetals (**244**) is retained in isolable products (**245**) or (**246**). Hence, this scheme is of considerable interest for the design of stereo- and enantioselective processes.

A large group of reactions leading to modifications of substituents in cyclic nitroso acetals (66, 152, 159, 160, 190, 214, 215, 367, 404, 405) is not considered because, in our opinion, this aspect of chemistry of nitroso acetals, is beyond the scope of the present section.

3.4.3.4.4. Determination of the Configurations and Study of Stereodynamics of Cyclic Nitroso Acetals This determination is of obvious fundamental importance by itself and, in addition, it is of importance in considering the mechanism of [3 + 2]-cycloaddition and in predicting the configurations of the resulting stereocenters.

The most reliable data on the relative configurations of different types of cyclic nitroso acetals can be obtained by X-ray diffraction (Chart 3.15).

These studies were carried out for five-membered monocyclic *N*-alkoxy- (406–408) and *N*-siloxyisoxazolidines (178) (**A**), for *N*-siloxytetrahydro-4*H*-oxazines (274), and bicyclic fused derivatives containing the isoxazolidine ring (**B**) (99, 157, 337).

These data demonstrate that the nitrogen atom in practically all cyclic nitroso acetals **A** or **B**, containing the isoxazolidine ring, deviates from the plane through the other four atoms (envelope). The nitrogen lone pair always pseudoequatorial.

(The exception is one stereoisomer of bicyclic compound **B**(R=CN, R′ = p–Br–C_6H_4 (*trans*)), in which the C-6 atom rather than the nitrogen atom deviates from the plane through four atoms, and the nitrogen lone pair is pseudoequatorial in this compound as well.) All known *N*-siloxy-tetrahydro-4*H*-oxazines (274) adopt a chair conformation, whereas the nitrogen lone pair can be in either equatorial or axial orientation. In the majority of fused compounds **B**, the six-membered ring also adopts a chair conformation, although the six-membered ring having a skewed boat conformation was found in one compound (157).

Quantum-chemical calculations for model isoxazolidines **C** and **C′** demonstrated that the conformer **C** containing the pseudoequatorial nitrogen lone pair is thermodynamically highly favorable, whereas the conformer **D** with the equatorial

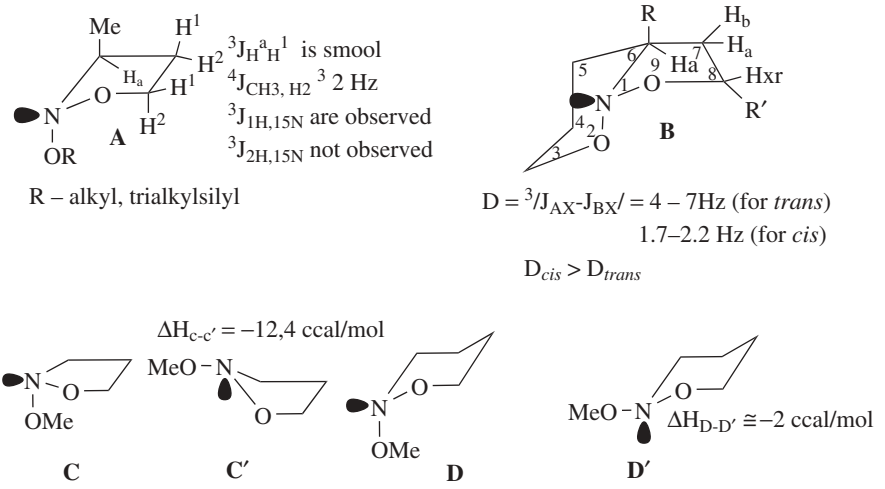


Chart 3.15 Some criteria for determination of configuration of cyclic nitrosoacetals.

orientation of the lone pair for model six-membered nitrosoacetals is thermodynamically much less favorable than the other conformer **D′** (408).

The configurations of five-membered cyclic nitronates **A** in solution were established and conformational analyses were performed by NMR spectroscopy (178, 184, 273, 338a, 338b, 410–414). In most of these studies, the mutual arrangements and positions of the protons were determined with the use of the Karplus dependence $^3J_{vic,H,H}$. However, other evidence, such as NOE_{dif} (410) and the appearance of the small constant $^3J_{H,H}$ allows one to determine the proton at C-3 in the pseudoequatorial position (414). The determination of long-range constants $J_{H,H}$, based on the application of known rules (415), the use of shift reagents (335a) and the long-range constants $J_{H,15N}$ (273, 338a), were also considered. The absolute values of the differences in the vicinal constants appeared to be useful in determining the positions of the protons of ABX systems in fused bicyclic systems (337). In more recent studies, different 2D NMR methods were employed (162, 416). The same indications were used for the determination of the configurations and in conformational analyses of *N*-siloxy-tetrahydro-4*H*-oxazines (274).

Investigations of the stereodynamics of cyclic nitroso acetals and, particularly, different types of isoxazolidines are of great importance.

Only one process was observed in these derivatives by low-temperature NMR (see, e.g., Ref. 417). As a rule, the barrier of this process was very high (133,203, 346); although, for unknown reasons, the introduction of two nitro groups at the C-3 atom leads to a noticeable decrease in the barrier height (see Scheme 3.166).

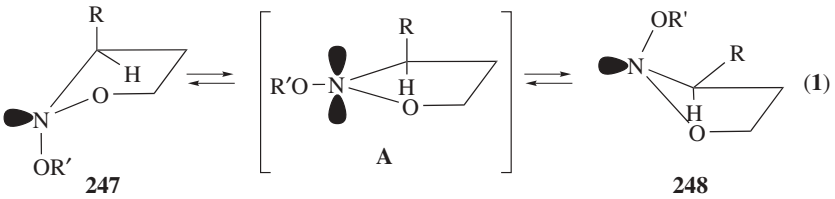
On the basis of all the above mentioned results, Russian researchers provided an explanation for the stereodynamics of isoxazolidines shown in Scheme 3.166. There is a so-called combined inversion-buckling process (417), which occurs through a planar transition state **A** with an unhybridized p electron pair at the nitrogen atom (see Scheme 3.166).

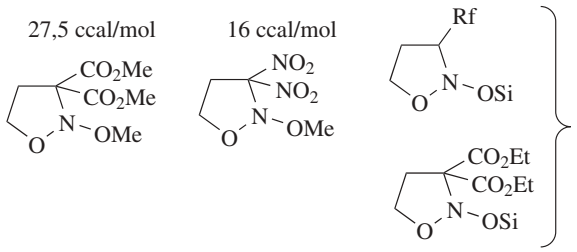
Subsequently, this interpretation has been commonly accepted; however, it does not account for the factors responsible for a decrease in the rate of the fast classical ring inversion. Hence, in our opinion, it is more reasonable to consider the stereodynamics of isoxazolidines as a result of superposition of two processes, a fast ring inversion (I_R) and slow nitrogen inversion (shown in the lower portion of Scheme 3.166) (418).

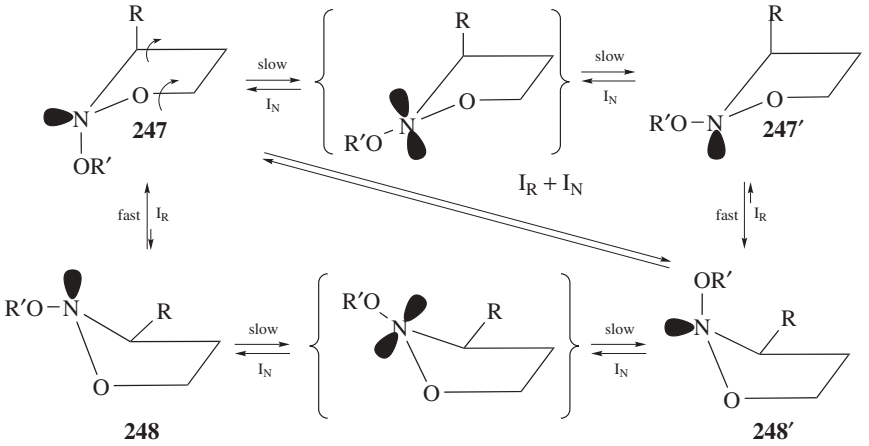
The observed degeneration of the stereodynamic pattern of these processes is due to the fact that all conformers containing the axial lone pair at the nitrogen atom are thermodynamically highly unfavorable. Calculations also confirmed that the axial position of the nitrogen lone electron pair is highly unfavorable (see Chart 3.15).

It should be noted that the equatorial position of the nitrogen lone pair in six-membered cyclic nitroso acetals is not so favorable. Hence, both stereodynamic processes can be observed for these compounds (Scheme 3.167, see also Ref. (274)).

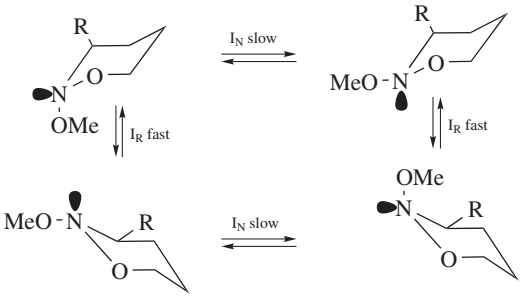
In conclusion, the barrier of nitrogen inversion in cyclic nitrosoacetals is very high. This circumstance allows one to distinguish kinetic and thermodynamic







Scheme 3.166



Scheme 3.167

isomers of isoxazolidines obtained via [3 + 2]-cycloaddition of nitronates with olefins. It enables the determination of the configuration of the transition state of the above mentioned process.

3.4.3.5. Mechanism of [3 + 2]-cycloaddition of Nitronates with Olefins The mechanistic concepts of the [3 + 2]-cycloaddition reaction should not only explain the available results but also have predictive ability. First, it is necessary to obtain answers to the following questions (Chart 3.16):

a. Influence of the nature of substituents in reactants on the rate of [3 + 2]-cycloaddition;
b. Factors responsible for regioselectivity of the process;
c. Factors responsible for stereoselectivity of the process;
d. Factors responsible for the facial preference of [3 + 2]-cycloaddition.

Points b to d should be explained in more detail for intermolecular cycloaddition reactions of acyclic nitronates **A** with monosubstituted olefins. *Regioselectivity* of the process is determined by the character of the approach of olefin to the dipole (head-to-head or head-to-tail, (Chart 3.16, part (**1**)). In the former case, the substituent R′ is bound to the C-5 atom; in the latter case, to the C-4 atom.

Taking into account the data presented in the previous section, stereoisomers of products prepared by cycloaddition reactions of nonsymmetric acyclic nitronates with monosubstituted olefins will differ in the mutual arrangement of the nitrogen atom and the substituents R and R′ (see Chart 3.16, part (**2**)). The mutual arrangement of the substituents R and R′, as well as the orientation of these substituents with respect to the nitrogen atom for one stereoisomer of nitronate **A**, is controlled by the approach of olefin to the dipole (*exo* or *endo* approach). The relationship between the configurations of the starting nitronate and the cycloadduct is exemplified by the *exo* approach. Therefore, the *stereoselectivity* of the [3 + 2]-cycloaddition is controlled by the approach of olefin and the configuration of nitronate.

Facial selectivity of the attack of the olefin on the dipole is characterized by the preference of the approach of the olefin to the plane of the dipole from the top or from the bottom (see Chart 3.16, part (**3**)). This type of selectivity can be determined by introducing chiral substituents into the reactants or by with the use of calculation methods.

The reactions shown in Chart 3.16 are characterized by a head-to-head addition of monosubstituted olefins to nitronates, the *exo* approach of olefins being observed in most cases.

Earlier, [3 + 2]-cycloaddition reactions of nitronates have been described in terms of the FMO theory. For example, French researchers studied reactions of olefins containing EWG groups with nitronates by the FMO–INDO method (248, 338b, 419). Recently, more modern methods have been used for calculations of FMO and the potential energy surfaces for several analogous reactions (87, 399,

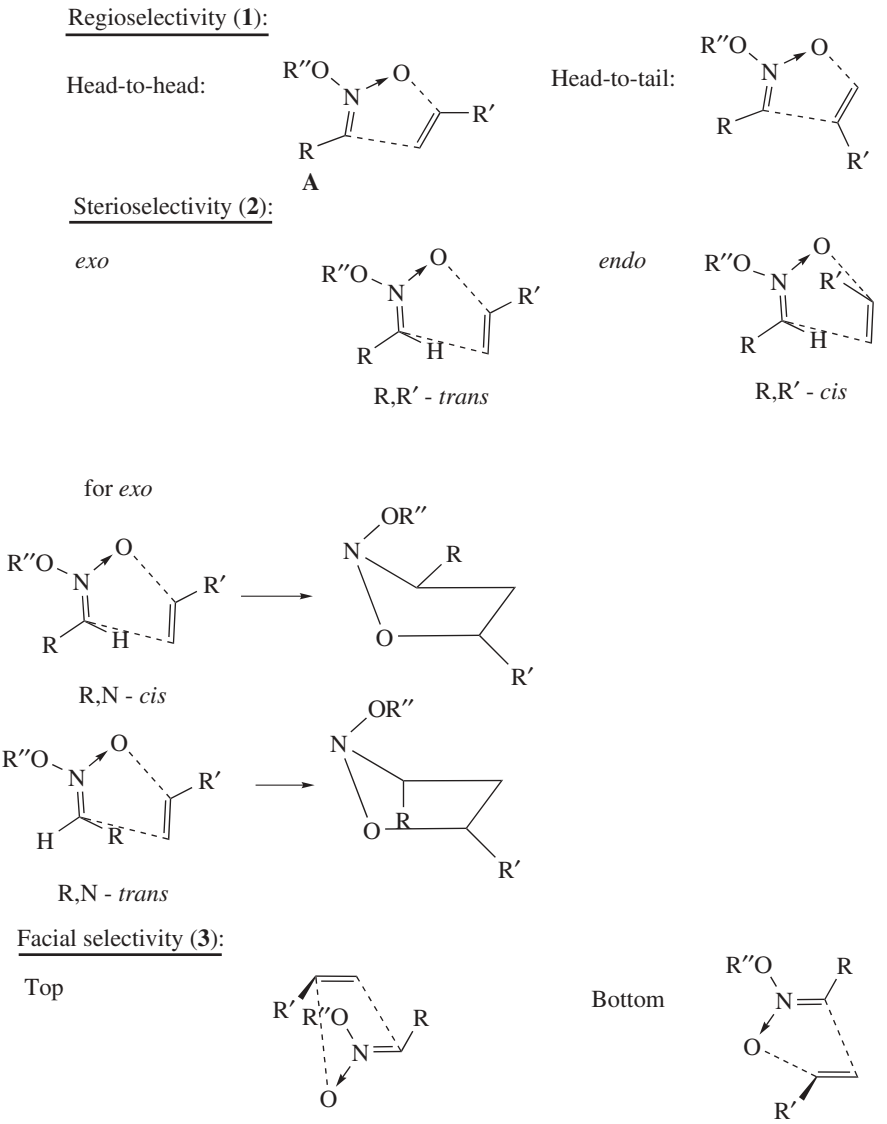
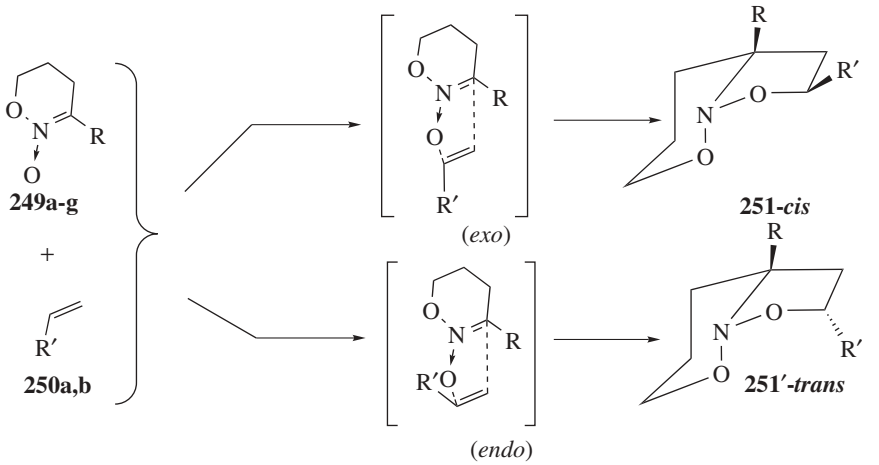


Chart 3.16 Mechanistic interpretations for [3 + 2]cycloaddition of nitronates with olefins.

420, 421). It was demonstrated that the transition state of these processes exhibits a weak zwitterionic character and that secondary orbital interactions facilitate the *endo* approach.

However, the problems of cycloaddition of nitronates with dipolarophiles require systematic studies. Unfortunately, only two studies dealing with these problems have been reported. Let us consider them in more detail.



For **249** R = Me (**a**), Ph (**b**), CO_2Me (**c**), MeCO (**d**), NO_2 (**e**), CN (**f**), H (**g**).
For **250** R = CO_2Me (**a**), Ph (**b**).

Scheme 3.168

The pioneering study (337) was performed more than 25 years ago and, unfortunately, the principal results of this study were not published in reviewed journals. Six-membered cyclic nitronates (**249a–g**) and dipolarophiles (**250a–d**) (Scheme 3.168) were investigated. This appropriate choice of compounds made it possible to eliminate problems associated with stereoisomerism of nitronates.

Cycloaddition reactions produce nitroso acetals (**251**) in high yields. In all cases (R = H, Me, Ph, CO_2Me, COMe, CN, NO_2; R' = CO_2Me, Ph, CN, CH_2Cl), the regioselectivity was very high, that is, the substituent R′ in the five-membered ring is always attached to the carbon atom bonded to the oxygen atom. The stereoselectivity of the reaction substantially depend on the nature of the substituent and was determined by the attack of the olefin on the dipole (see Scheme 3.168 and Table 3.16).

Generally, the *exo* approach of olefins to nitronates dominated in these reactions. For most of nitroso acetals (**251**), the relative configurations of substituents were determined by NMR, on the assumption that the six-membered ring adopts a chair conformation and the fused five-membered ring has an envelop conformation with the nitrogen atom deviating from the plane through the other four atoms of the ring. For one nitroso acetal (**251 g**) (R=CN, R′ = C_6H_4-*p*-Br, (cis)), the validity of the assumptions was confirmed by X-ray analysis. The resulting stereoisomers differ in the related orientation of the substituents R and R′. Selected data on the configurations of stereoisomers of nitroso acetals are given in Table 3.16.

The kinetic and activation parameters for a number of (**249 + 250**) reactions were determined by spectrophotometry and NMR (see Table 3.17) (337).

Table 3.16 Stereochemical results of [3 + 2]-cycloaddition 249 + 250

Entry	Nitronate	R	Olefin	R'	Nitroso acetal	Ratio *cis/trans*	Yield, %%
1	(**249a**)	Me	(**250a**)	CO_2Me	(**251a**)	4:1	90
2	(**249a**)	Me	(**250b**)	Ph	(**251a'**)	*cis*-(100%)	87
3	(**249b**)	Ph	(**250a**)	CO_2Me	(**251b**)	3:1	79
4	(**249b**)	Ph	(**250b**)	Ph	(**251b'**)	*cis*-(100%)	80
5	(**249c**)	CO_2Me	(**250a**)	CO_2Me	(**251c**)	5.5:1	100
6	(**249c**)	CO_2Me	(**250b**)	Ph	(**251c'**)	*cis*-(100%)	100
7	(**249d**)	MeCO	(**250a**)	CO_2Me	(**251d**)	4:1	86
8	(**249f**)	CN	(**250a**)	CO_2Me	(**251f**)	3:1	100
9	(**249e**)	NO_2	(**250a**)	CO_2Me	(**251e**)	*cis*-(100%)	85
10	(**249e**)	NO_2	(**250b**)	Ph	(**251e'**)	*cis*-(100%)	94

Table 3.17 The activation parameters for [3 + 2]-cycloaddition 249 + 250

Entry	Reaction	$\Delta H^{\neq}$ ccal/mol	$\Delta S^{\neq}$ ccal/mol	$\Delta G^{\neq}_{293}$ ccal/mol
1	**249a + 250a**	13.0 ± 1.0	-33.2 ± 3.3	22.73
2	**249b + 250a**	13.8 ± 0.4	-37.3 ± 1.4	24.73
3	**249c + 250a**	11.1 ± 0.3	-38.3 ± 0.9	22.32
4	**249d + 250a**	13.0 ± 0.3	-38.7 ± 0.8	24.34
5	**249e + 250a**	11.5 ± 0.1	-33.1 ± 0.2	21.20
6	**249f + 250a**	15.4 ± 0.7	-30.8 ± 2.3	24.42
7	**249c + 250b**	14.9 ± 1.2	-30.3 ± 4.0	23.95
8	**249d + 250b**	15.6 ± 1.3	-31.9 ± 3.9	24.95
9	**249e + 250b**	14.0 ± 0.7	-27.4 ± 2.3	22.03

On the basis of these data, a series of comparative reactivities toward styrene and methyl acrylate for different types of nitronates were derived (Chart 3.17).

The main drawback of these kinetic studies is that the kinetic measurements were carried out in a narrow temperature range (generally, $20^{\circ}-30^{\circ}C$). However, the study in Reference (337) remains the only direct kinetic investigation of [3 + 2]-cycloaddition of nitronates to the C,C double bond.

The theoretical interpretation of the results was made (334) in terms of the molecular orbital perturbation theory, in particular, of the FMO theory (CNDO−2 method), using the model of the concerted formation of both new bonds through the cyclic transition state. In this study, the authors provided an explanation for the regioselectivity of the process and obtained a series of comparative reactivities of dipolarophiles (methyl acrylate > styrene), which is in agreement with the experimental data. However, in spite of similar tendencies, the experimental series of comparative reactivities of nitronates (**249**) toward methyl acrylate (**250a**) and styrene (**250b**) are not consistent with the calculated series (see Chart 3.17). This is attributed to the fact that calculation methods are insufficiently correct and the

Experimental (for **250a**)	Calculated
For $\Delta H^{\neq}$: **249c≥249e>249a≈249d>249b>249f**	**249a>249f>249c>249e>249d>249b**
For $\Delta G^{\neq}_{293}$: **249e>249c≥249a>249d≥249f>249b**	
Experimental (for **250b**)	Calculated
For $\Delta H^{\neq}$: **249e>249c>249d**	**249a>249f>249c>249d>249e>249b**
For $\Delta G^{\neq}_{293}$: **249e>249c>249d**	

Chart 3.17 The experimental and calculated rates of [3 + 2] cycloaddition of some six-membered cyclic nitronates with model olefins.

difference in the lengths of the bonds formed in the transition state of nitronates discussed.

This approach did not provide a complete explanation for the observed degree of stereoselectivity. On the whole, the *endo* approach of olefin to nitronate is stabilized by secondary orbital interactions but, at the same time, is destabilized due to steric hindrance.

In terms of the approach used, the authors drew a general conclusion that the [3 + 2]-cycloaddition reactions of nitronates with dipolarophiles under study should be considered as either nonconcerted or as those, which substantially differ in the positions of transition states on the reaction coordinate (337).

Another attempt to perform a general mechanistic consideration of [3 + 2]-cycloaddition reactions of nitronates with olefins has been made relatively recently by Prof. Denmark and coworkers (162) using modern quantum-chemical methods, which allow one to correctly calculate the potential energy surfaces for model substrates. Since these data have been summarized in the recent review (335), it is not necessary to consider them as comprehensively as the study in (337).

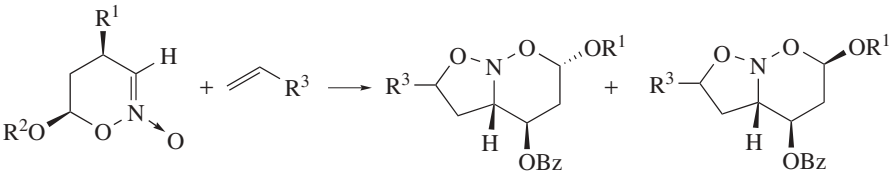
Cycloadditions of six-membered cyclic nitronates (**249i,j**) with various olefins, both monosubstituted (**250a,i,k–n**) (Scheme 3.169) and disubstituted (**253a–g**) (Scheme 3.170), were also investigated.

Kinetic studies were not performed and, consequently, the activation parameters were not determined.

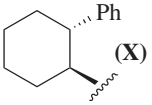
Data on related reactivities of olefins were extracted from competitive reactions. Hence the main emphasis has been given to investigations of regio-, stereo-, and facial preferences.

The structures of the resulting nitroso acetals (**252**) (Scheme 3.169) or (**254 + 255**) (Scheme 3.170) and their stereoisomeric compositions were studied in detail by NMR and X-ray analysis.

As in the above described study (337), the addition of monosubstituted olefins (**250a,i–m**) to nitronates (**249**) occurs strictly regioselectively in a head-to-head



249 i,j **250a,i-m** **252** **252′**

R1 – OBz, R^2 – Bu or  **(X)**

R^1	R^2	R^3	Olefin	Product	Yield,%	d.r 252/252′
OBz	X	CO_2Me	**250a**	**252a + 252a′**	79	7,6/1
OBz	X	CO_2Me	**250a**	**252b + 252b′**	86	6,5/1
OBz	X	CO_2Bu^t	**250i**	**252c + 252c′**	91	11,4/1
OBz	X	COMe	**250d**	**252d + 252d′**	88	6,2/1*
OBz	X	$COCH_2OTDS$	**250j**	**252e + 252e′**	90	5/1*
OBz	X	$COCH_2OBu$	**250k**	**252f + 252f′**	89	5,7/1
OBz	X	CHO	**250l**	**252g + 252g′**	**	1/2
OBz	X	CH_2OH	**250m**	**252h + 252h′**	81	1,3/2

* by NMR

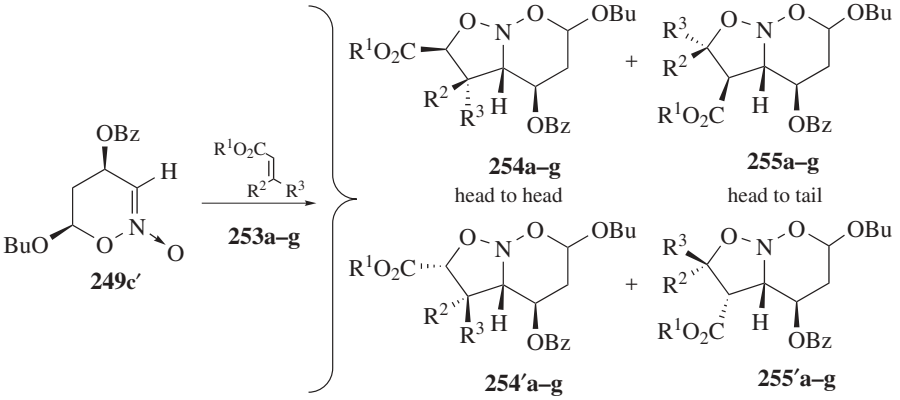
** converted by reduction with $NaBH_4$ into **252h + 252h′** in 62%

Scheme 3.169

fashion. The degree of stereoselectivity depends on the nature of the substituent R^3 (Scheme 3.169) and varies in a wide range (from 11.4/1 to 1/2), the *exo* approach of olefin to nitronate being dominant as a rule.

The reactions of vicinally disubstituted olefins (**253a–g**) (Scheme 3.170) occur nonregioselectively and produce two regioisomers of nitroso acetals ((**254**) and (**255**), respectively). Each regioisomer can have two stereoisomers, which differ in the mutual arrangement of the CO_2R' group and the substituents in the six-membered ring.

For the substituents (R^2 and R^3), the contribution of the head-to-tail approach giving rise to nitroso acetals (**255**) and (**255′**) increases in the series: O > C > Si > H. In the authors' opinion (162) , the FMO theory does not explain all facts and does not have predictive ability for the estimation of the regioselectivity of cycloaddition of 1,2-disubstituted dipolarophiles, because this problem is strongly related to electronic perturbations of dipolarophiles. The parameters, which are generally used to account for the influence of substituents, (422–425) also cannot approximate the regularities of regioselectivity of [3 + 2]-cycloaddition observed for 1,2-disubstituted olefins. In the authors' opinion (162), the so-called polarity index (*P*), which has been recently suggested for explaining of



R^1	R^2	R^3	Olefin	Products	Yield%	d.r. **254/255/ 254′/255′**
Me	H	H	**253a** **253b**	**254a; 255a; 254′a; 255′a**	79	7,6/∗/1/∗
Me	$SiMe_3$	H		**254b; 255b; 254′b; 255′b**	72	2,4/1/∗/∗
Me	H	$SiMe_3$	**253c**	**254c; 255c; 254′c; 255′c**	77	1/1,5/2,1/∗
Et	Me	H	**253d** **253e**	**254d; 255d; 254′d; 255′d**	75	1/1,6/∗/∗
Et	OAc	H		**254e; 255e; 254′e; 255′e**	54	∗/1/∗/∗
Et	H	OAc	**253f**	**254f; 255f; 254′f; 255′f**	78	∗∗
Me	H	CO_2Me	**253g**	**254g; 255g; 254′g; 255′g**	82	1/∗/1/∗

∗ not observed

∗∗ regioselectivity 1/2,7

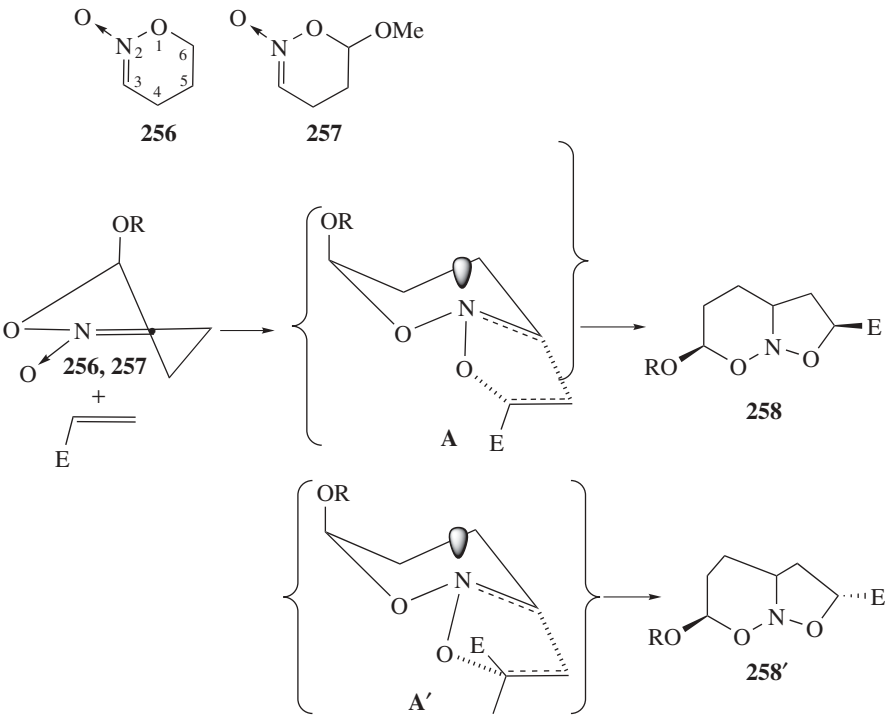
Scheme 3.170

the reactivity of ambident anions (426), is the best for prediction of the regioselectivity of [3 + 2]-cycloadditions of 1,2-disubstituted olefins with nitronates.

However, the use of this interesting approach remains to be tested by experimental methods and from a philosophical position.†

The authors (162) attempted to explain the stereochemical outcome of the reactions (Schemes 3.169 and 3.170) in the terms used earlier (337), that is, by steric factors, which destabilize the *endo* approach of a dipolarophile, and the electronic effect (secondary orbital interactions), which is most typical for electron-rich dipolarophiles and can slightly stabilize the *endo* approach of these olefins.

†It remains unclear why the approach used for the description of ionic processes (426) should be applied to the reaction, which is commonly considered as concerted. In particular, it is unclear how the steric factors, which can play the decisive role in the description of concerted processes with their sterically crowded transition states, are taken into account. Also, whether this explanation of regioselectivity can be extended to other nitronates and monosubstituted olefins.



Scheme 3.171

The most interesting conclusion made in the study (162) is that the facial attack of olefin on six-membered cyclic nitronate from the side of the C-5 atom (or from the side opposite to the C-6 atom) is much more preferable. This result was obtained by calculation methods for model reactions of nitronates (**256**) and (**257**) with ethylene (E=H, Scheme 3.171).

The preference of the distal attack of olefin (ethylene) on nitronate (**257**) could be attributed to steric hindrances due to the presence of the axial alkoxy substituent at the C-6 atom, which shields the proximal attack. These hindrances are absent in nitronate (**256**). However, one could suggest that for nitronate (**256**) adopting a half-chair conformation, the approach of olefin from the side of the C-6 atom is more shielded even if the C-6 atom is unsubstituted because considerably deviates upward from the plane of the C=N bond of the dipole in comparison to the deviation of the C-5 atom in the opposite direction (see Sections 3.3.3 and 3.5.2). It could be worthwhile to combine this approach with a consideration of the facial preference for model nitronates substituted at the C-5 atom also.

It should be emphasized that this consideration may be fruitful in explaining the stereoselectivity of other reactions of six-membered cyclic nitronates and oxime ethers (see, e.g., Section 3.5.2.3.).

3.4.4. Reactions of Tandem [4 + 2][3 + 2] Cycloaddition of Conjugated Nitroalkenes and their Use in Organic Synthesis

One of the main trends in modern organic synthesis is the use of efficient and selective reaction sequences, which make it possible to assemble target molecules from simple precursors with the use of a minimum number of operations (technological steps).

In this respect, tandem [4 + 2][3 + 2] cycloaddition of nitroalkenes (Chart 3.18), which was developed and studied in detail by Prof. Denmark and coworkers, is of most interest for the chemistry of nitronates.

This approach has been comprehensively described in Reference 99 and two monographs 427 and 428. Hence, we will not consider this approach in detail, the more so that selected aspects of [4 + 2]-cycloaddition reactions of conjugated nitroalkenes with olefins were discussed in Section 3.2.1.2.2.2. Many concerned with the synthesis of six-membered cyclic nitronates, many problems of [3 + 2]-cycloaddition of six-membered cyclic nitronates were also considered above (see Sections 3.4.3.1.4 and 3.4.3.3).

However, it is necessary to formulate the most common features of the strategy developed by Prof. Denmark and summarize the most important synthetic results.

This strategy is very useful for the synthesis of natural compounds and their analogs. Let us consider this approach in more detail using sequence **I** (Chart 3.18) as an example.

Initially, after the retrosynthesis of the target substrate, the starting reagents are chosen (for **I**, nitroolefin and two alkenes with opposite demands). Then intermediate six-membered cyclic nitronate (**259**) is synthesized (Scheme 3.172).

Here, the difference in the rates of [4 + 2]- and [3 + 2]-cycloaddition reactions with respect to the second component (olefin) is used. Electron-rich olefins

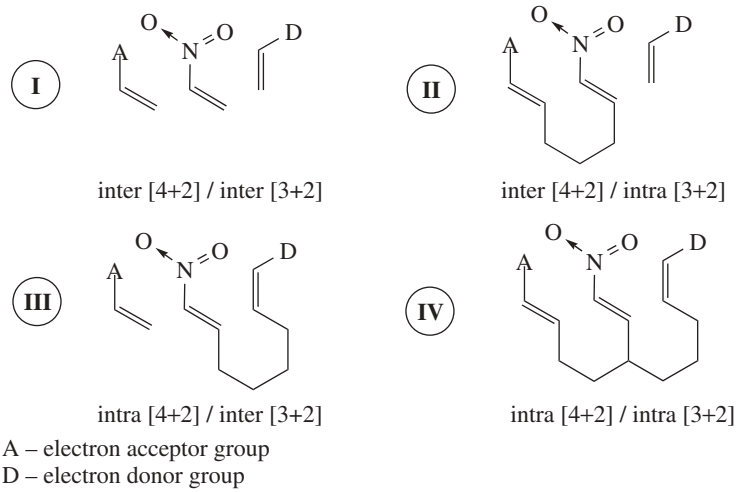
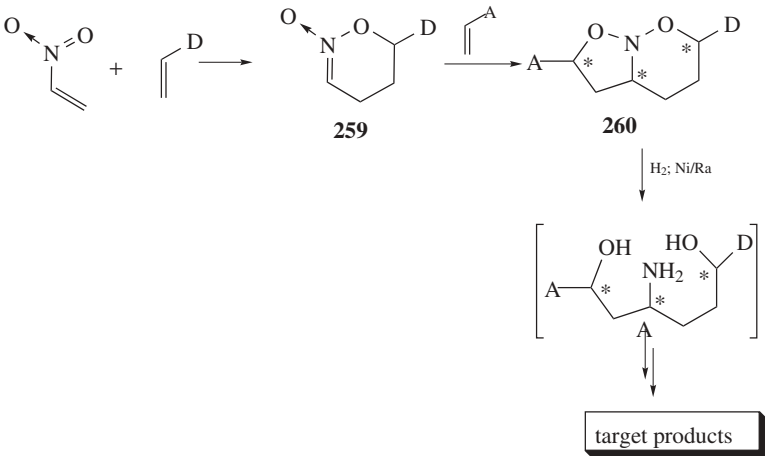


Chart 3.18 Various modes of tandem [4 + 2][3 + 2] cycloaddition of nitroalkenes.



Scheme 3.172

(C=C–D) are most efficient in the former process, whereas electron-deficient olefins (C=C–D) are most efficient in the latter process. Hence, the [4 + 2]-cycloaddition of alkene C=C–D with α-nitroalkene can be successfully performed in the presence of alkene C=C–A. In this step, an auxillary is introduced into the resulting nitronate (**259**) and, if required, enantiomerically pure nitronate (**259**) is isolated. Then the [3 + 2]-cycloaddition reaction of nitronate (**259**) with olefin C=C–A is performed to obtain nitroso acetal (**260**), which is generally followed by reduction of the nitroso acetal fragment. The configurations of the labeled stereocenters generated in the tandem process are retained during the reduction process. The resulting intermediate **A** is transformed into the target product by using standard manipulations of organic synthesis.

When choosing a concrete scheme for the synthesis of a complicated substrate in terms of the strategy proposed by Prof. Denmark, not only the characteristic features of the target product but also other factors should be taken into account. As a rule, intramolecular cycloaddition reactions proceed more easily and are characterized by higher stereoselectivity, but the starting substrates are much more difficult to synthesize.

A representative series of enantiomerically pure alkaloids and other compounds having known biological activity was synthesized using the above described strategy by the group of Prof. Denmark (Chart 3.19).

As mentioned above, not only general principles but also concrete examples of the use of the tandem strategy by Prof. Denmark were considered in two monographs (427, 428). These data should be supplemented by the synthesis of azafenestranes, which has been recently performed by Prof. Denmark and his group (429, 430) (Scheme 3.173).

The *cis,cis,cis,cis*-[5,5,5,5]-1-azafenestrane as complex with BH_3 (**261**) was prepared starting from nitroalkene (**262**), which is difficult to synthesize, using an approach shown in Chart 3.18 and Scheme 3.172. (429)

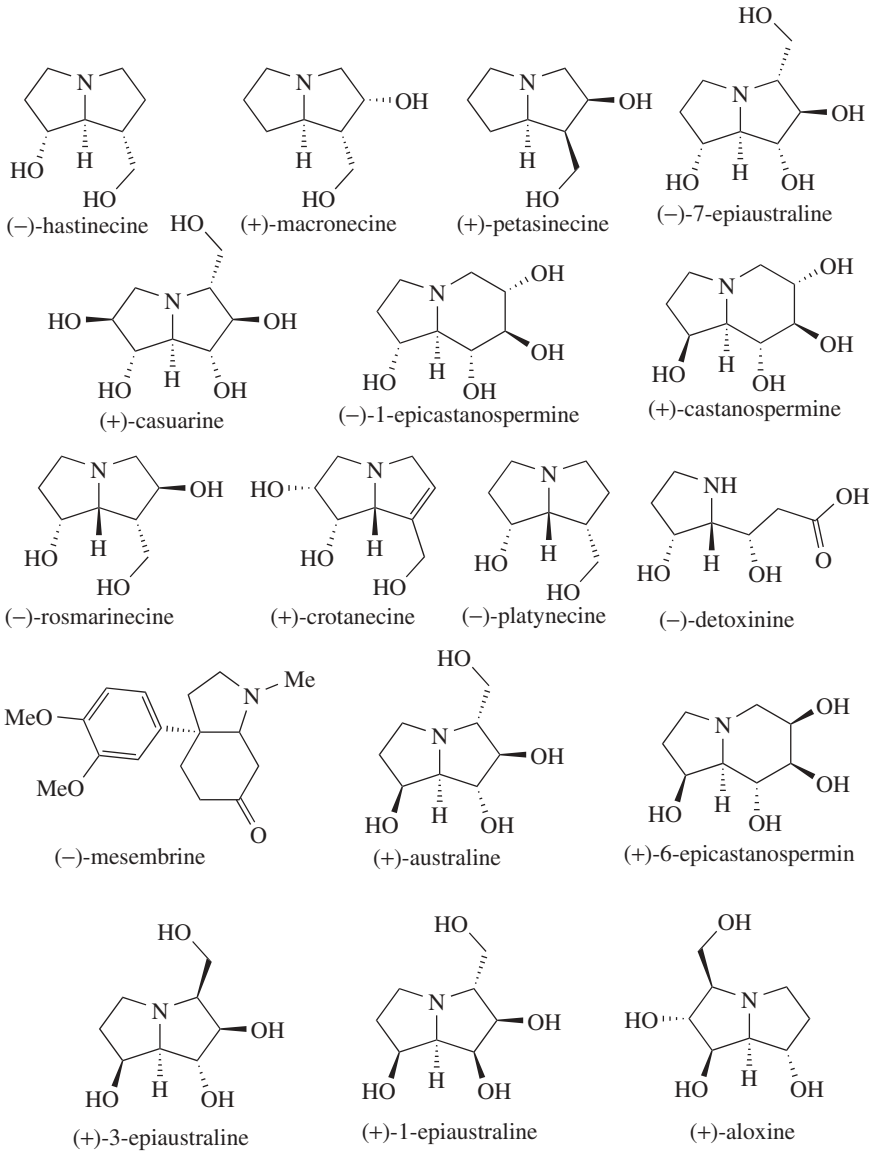
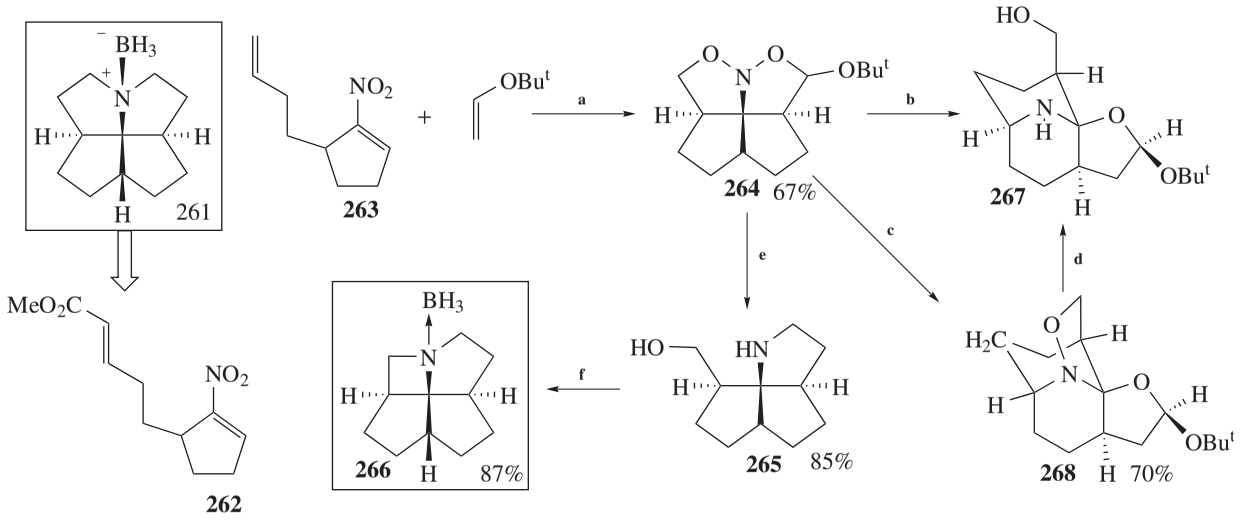


Chart 3.19 Total syntheses realized by employing tandem [4 + 2][3 + 2] cycloaddition of nitroalkenes.

When synthesizing the analogous *cis,cis,cis,cis*-[5,5,5,4]-1-azafenestrane complex (**266**) according to the same strategy, with the use of the more readily available nitrocyclopentene (**263**), the researchers (430) unexpectedly observed the diotropic rearrangement of intermediate (**264**) (**264**→**268**) (pathway **c**), which



a: $AlMe_3$, CH_2Cl_2, −78°C, 1 h, with Al_2O_3.
b: Ni/Ra, H_2, (1 at), MeOH (94%).
c: MeOH, 20°, 3 h.
d: H_2 (26 at) Ni/Ra, EtOAc/H_2O, 20 h (98%).
e: H_2 (26 at) Ni/Ra, EtOAc/H_2O, 20 h.
f: PPh_3; $Pr^iO_2CN{=}NCO_2Pr^i$, CH_2Cl_2, 0°, 0,7 h, then BH_3.THF, −78°→r.t..

Scheme 3.173

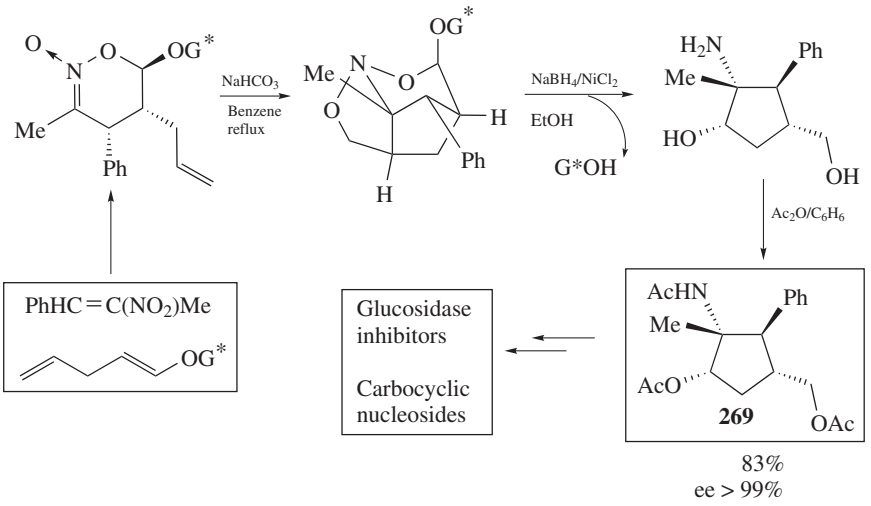
complicated the target hydrogenation of this intermediate (**264**) (430). (For more details about diotropic rearrangements of fused nitroso acetals, see Ref. 401 and Scheme 3.161.) This problem was successfully eliminated by substantially increasing the hydrogen pressure. The latest data on the synthesis and investigation of azafenestranes as compounds with a flattened carbon tetrahedron were summarized in the recent study by Prof. Denmark and coworkers (430b).

In conclusion of this section, let us briefly mention the enantioselective synthesis of functionalized aminocyclopentanes (**269**) which were carried out by the group of Prof. Denmark, starting from very simple compounds containing auxiliaries (332, 431) (Scheme 3.174).

The resulting derivatives (**269**) can be considered as strategically important intermediates in the synthesis of glycosidase inhibitors and carbocyclic nucleosides (150). A new approach to the stereoselective synthesis of the piperidine ring with the use of [4 + 2][3 + 2]-cycloaddition from specially prepared substrates is also very interesting (431)b, c. In the context of this problem, the conditions for the formation of systems containing quaternary vicinal stereocenters were found.

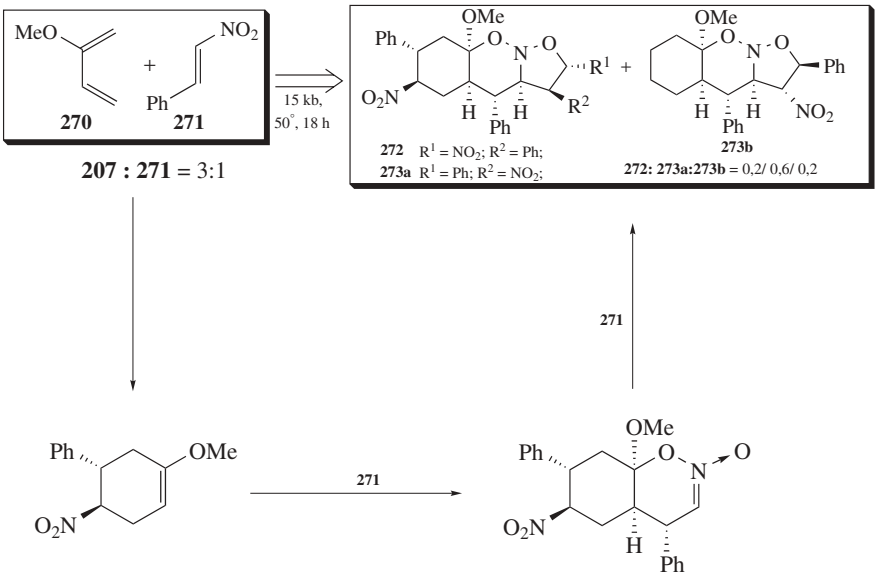
As mentioned above, modern optimization methods and, in particular, superhigh pressure, are little used in [3 + 2]-cycloaddition reactions. However, Netherland researchers used this approach and performed the domino [4 + 2][4 + 2] [3 + 2]-cycloaddition (432) in the absence of Lewis acids (Scheme 3.175).

2-Methoxybuta-1,3-diene (**270**) and several other reagents were involved in this transformation. The process was exemplified in detail by the reaction of diene (**270**) with nitrostyrene (**271**). Initially, nitrostyrene acts as a dienophile to give the corresponding α-methoxycyclohexene, which is involved in the [4 + 2]-cycloaddition reaction with the second nitrostyrene molecule to form the intermediate six-membered cyclic nitronate. The latter reacts with the third nitrostyrene

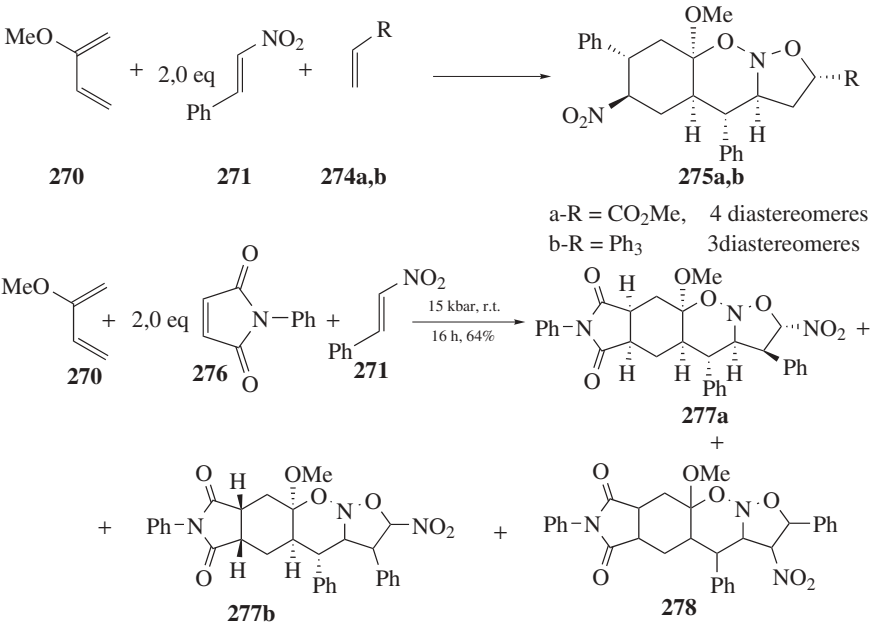


Scheme 3.174

Two component [4+2] [4+2] [4+2] domino cycloaddition

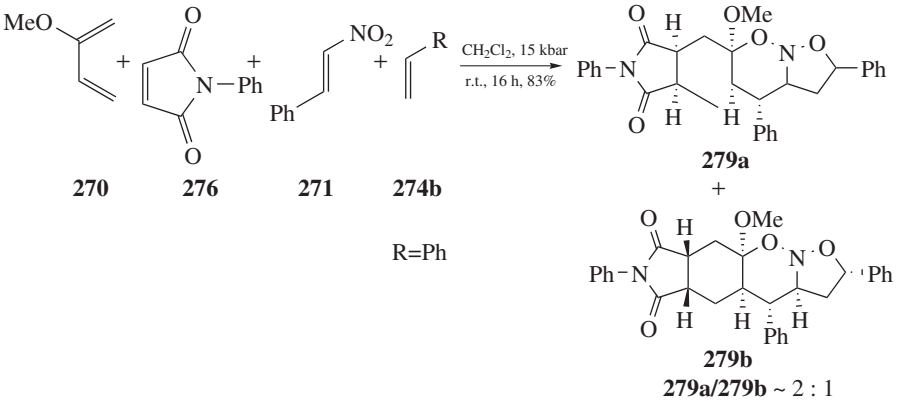


Three component [4+2] [4+2] [4+2] domino cycloaddition



Scheme 3.175

Four component [4+2] [4+2] [4+2] domino cycloaddition



270 **276** **271** **274b**

Scheme 3.175

molecule to give the [3 + 2]-cycloaddition product. According to NMR data, the first two reactions are regio- and stereoselective, and the latter step affords regioisomers (**272**) and (**273**), one of which gives two stereoisomers.

Examples of three- and four-component sequences, each occurring at superhigh pressure with various stereoselectivities, are given in the lower port of Scheme 3.175. Methoxydiene (**270**) and nitrostyrene are necessary participants of these sequences.

This method is expected to find more use in the future.

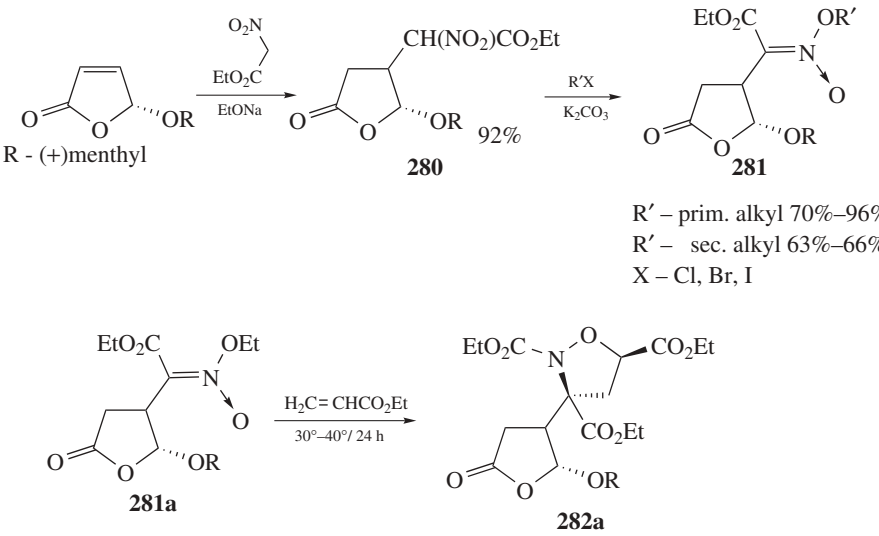
3.4.5. Nitronates in Enantioselective [3 + 2]-Cycloaddition Reactions

This problem has already been touched upon in previous sections. However, taking into account the importance of these reactions in modern organic synthesis, it is worthwhile to consider the main data in a special section.

The enantioselectivity of [3 + 2]-cycloaddition reactions is determined by the preference of a particular facial attack of the reagents containing chiral inductors. Most of such reactions proceed in the absence of a catalyst and, consequently, the inductor should be present in either the dipole or the dipolarophile.

For acyclic alkyl nitronates, only one process of this type has been documented (17) (Scheme 3.176).

Starting nitro compound (**280**) is generated by the Michael reaction with enantiomerically pure dihydrofuranone containing the (+)-menthyl fragment. Stereo- and enantiomerically pure nitronates (**281**) can be prepared and isolated upon alkylation of nitro substrate (**280**). One of nitronates (**281a**, R′ = Et) is readily involved in the [3 + 2]-cycloaddition reaction with ethyl acrylate to give enantiomerically pure isoxazolidine (**282a**) in satisfactory yield. Although the complete configuration of (**282a**) was not determined, it can be concluded that



Scheme 3.176

the enantioselectivity of the [3 + 2]-cycloaddition is associated with discrimination of one of the facial attacks of olefin on 1,3-dipole (**281a**) due to shielding by the menthyl radical.

Silyl nitronates containing chiral inductors have not been as yet used in intermolecular [3 + 2]-cycloaddition reactions. In this case, the facial discrimination was generally created by introducing chiral nonracemic fragments into dipolarophiles (see review 433).

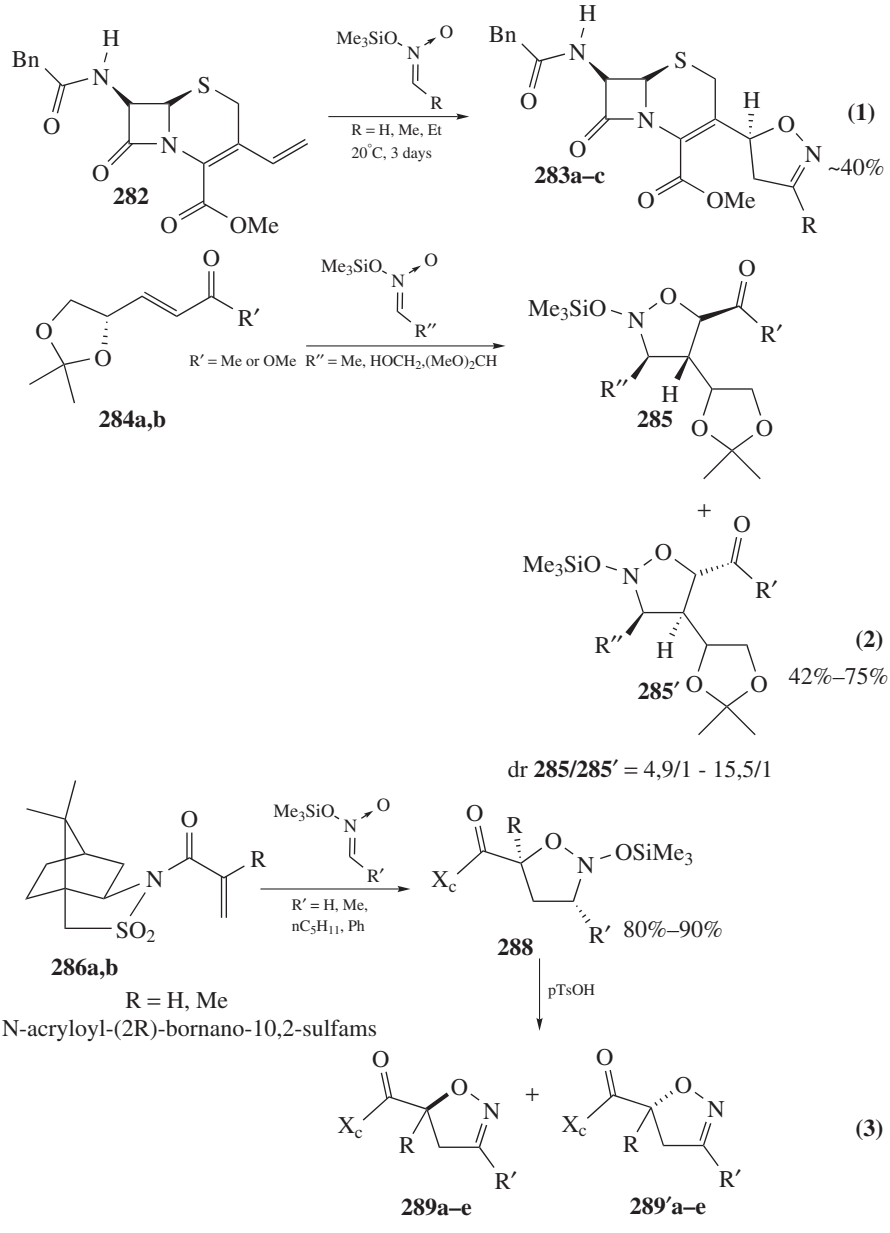
Several SENAs derived from primary AN were involved in the reaction with ceptem (**282**) (Scheme 3.177, Eq. 1) (434) to prepare the diastereomeric pure cycloadducts, which were then transformed into isoxazolines (**283**). However, the configurations of the new stereocenters in products (**283**) were not determined.

The reactions of some SENAs with chiral dipolarophiles (**284a,b**) were also described (411) (Scheme 3.177, Eq. 2). It should be noted that the yields of the target cycloadducts were not always high due to steric hindrance in vicinally substituted dipolarophiles. Also the facial selectivity is rather moderate.

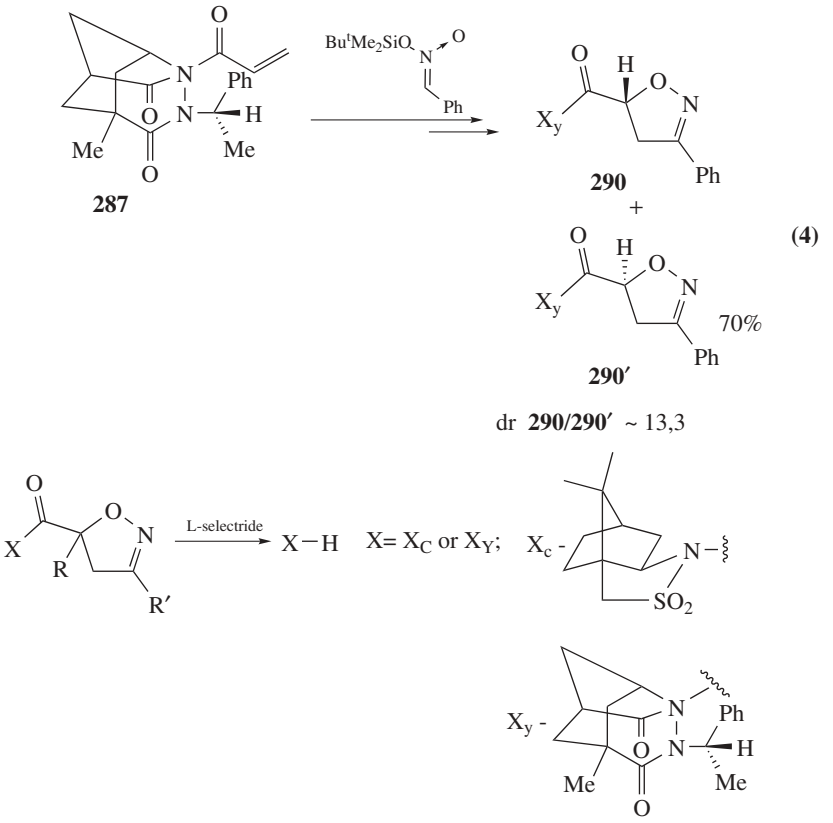
Another approach is based on the use of the so-called Oppolzer's sultams products (**286a,b**), (Scheme 3.177, Eq. 3) (435–437), or on polycyclic lactam (**287**) (Scheme 3.177, Eq. 4) (438) as dipolarophiles.

In the former case, both "antipodes" of sultams were used and the initially formed cycloadducts (**288a–e**) were transformed into more stable isoxazolines (**289a–e**) and (**289′a–e**) with retention of configuration of the new stereocenter at C-5. For Oppolzer's sultam, (435–437) the yields of the target products were high and the ratio of diastereomers was close to 1:10.

Interestingly, nonpolar solvents facilitate an increase in the enantioselectivity of the process, and the introduction of a substituent at C-4, but, leads to a decrease


Bn
H
N
O
S
N
O
O
OMe
282
Me3SiO
N
O
R
R = H, Me, Et
20°C, 3 days
283a–c
~40%
(1)
R′ = Me or OMe
R″ = Me, HOCH2,(MeO)2CH
284a,b
Me3SiO
R′
R″
H
285
285′
42%–75%
(2)
dr 285/285′ = 4,9/1 - 15,5/1
SO2
286a,b
R = H, Me
N-acryloyl-(2R)-bornano-10,2-sulfams
R′ = H, Me,
nC5H11, Ph
Xc
OSiMe3
288
80%–90%
pTsOH
289a–e
289′a–e
(3)
for R = H, dr 289/289′ = 10;for R = Me, dr 289/289′ = 2

Scheme 3.177

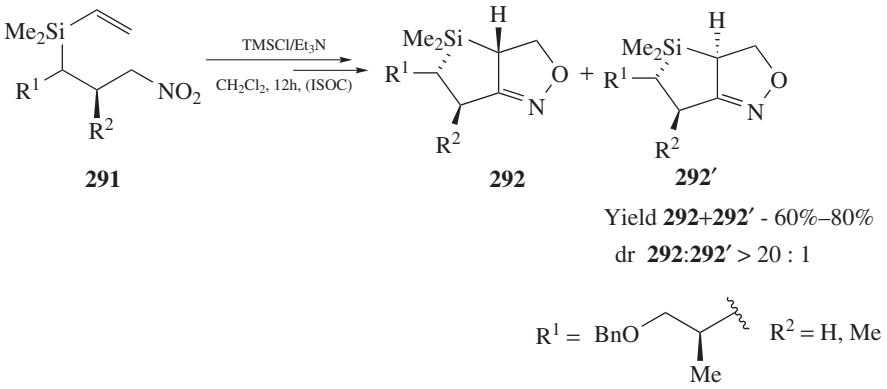


Scheme 3.177

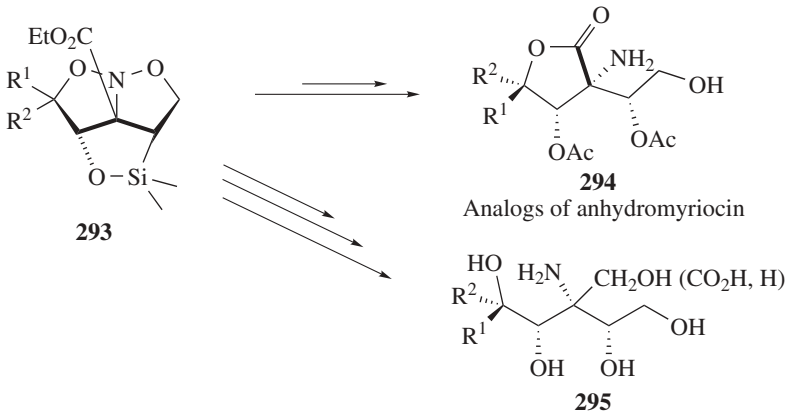
in the enantioselectivity of the reaction. The configurations of the stereocenters were established by the NMR method and confirmed by X-ray diffraction data. On the basis of these data and assuming that only the major *E* isomer of the nitronate is involved in the reaction, it can be concluded that the *Re*-face attack of nitronate on the dipolarophile is preferable, apparently, because of shielding from the *Si* face due to the presence of an auxiliary. The reaction with lactam (**287**) proceeds analogously (438) but is characterized by a somewhat higher enantioselectivity. Reduction of isoxazolines with L-selectride makes it possible to restore auxiliaries. This process was used in the asymmetric synthesis of nonactin and its derivatives. (439–441)

In intramolecular [3 + 2]-cycloaddition reactions, silyl nitronates also lead to substantially higher stereoselectivity than intermolecular reactions (see, e.g., Scheme 3.178) (193).

SENAs containing auxiliaries were successfully used in the **ISOC** procedure for the synthesis of enantiomerically pure polycyclic (96) (Scheme 3.146) and natural (210, 211) (Scheme 3.145) compounds.



Scheme 3.178



Scheme 3.179

In the synthesis of **enantiomerically pure five-membered cyclic nitronates**, (+)-citronellal (237b), carbohydrate derivatives (263a), *D*-mannitol (48), chiral epoxides (65, 68), chiral aziridines (68), and aldehydo sugars (46) were used as auxiliaries (20<dr>1.5).

In addition, chiral five-membered cyclic nitronates can be prepared from optically inactive starting nitronates with the use of ligated palladium (catalyst) as a chiral inductor (71) (ee 97%).

As mentioned above (66, 393), (see Scheme 3.150) silylation followed by intramolecular enantioselective cycloaddition with five-membered cyclic nitronates, containing the hydroxyl group at C-4, can produce chiral polycyclic structures (**293**), which are direct precursors of chiral hydroxyamino acids (**294**) and aminopolyols (**295**) (Scheme 3.179).

Most studies and approaches concern the synthesis and transformations of **enantiomerically pure six-membered cyclic nitronates**. (This problem was considered in Sections 3.2.1.2.2.2 and 3.4.3.5)

Chiral LA are rarely used in the construction of chiral six-membered cyclic nitronates by the Diels-Alder reaction of olefins with α-nitoralkenes (96, 158), in spite of the potential efficiency of the process. Apparently, this is associated with the absence of known common features of the process and, as a consequence, with the necessity to perform special investigations for optimization in each particular case.

Two research groups examined the approach to the synthesis and the use of six-membered cyclic nitronates by introducing chiral inductors into the molecule of the starting α-nitroalkene. (Here, it is incorrect to use the term auxiliaries because the chiral fragment is not eliminated and is involved in the target product.)

The synthesis of chiral α-nitroalkenes (**296**) from galactose was documented (157) (Scheme 3.180).

Then the highly enantioselective synthesis of the optically pure diastereomers of nitronates (**297**) was carried out (*endo* approach, *Re*-face attack of (**296**)). Storage of the latter compound in ethanol in the presence of an excess of vinyl ethyl ether afforded optically active nitroso acetals (**298**) in good yield. Upon storage, compound (**298**) underwent a rearrangement accompanied by cleavage of the N–O bond to give enantiomerically pure isoxazoline (**299**) serving as a convenient building block for asymmetric syntheses.

The synthesis of nitronates (**297**) in the presence of electron-deficient olefins (398) produces optically pure nitroso acetals (**300**) with high optical purity. Interestingly, the use of ethanol as the solvent in the (**296**→**298**) reaction leads to a substantial increase in *de* compared to CH_2Cl_2 (157).

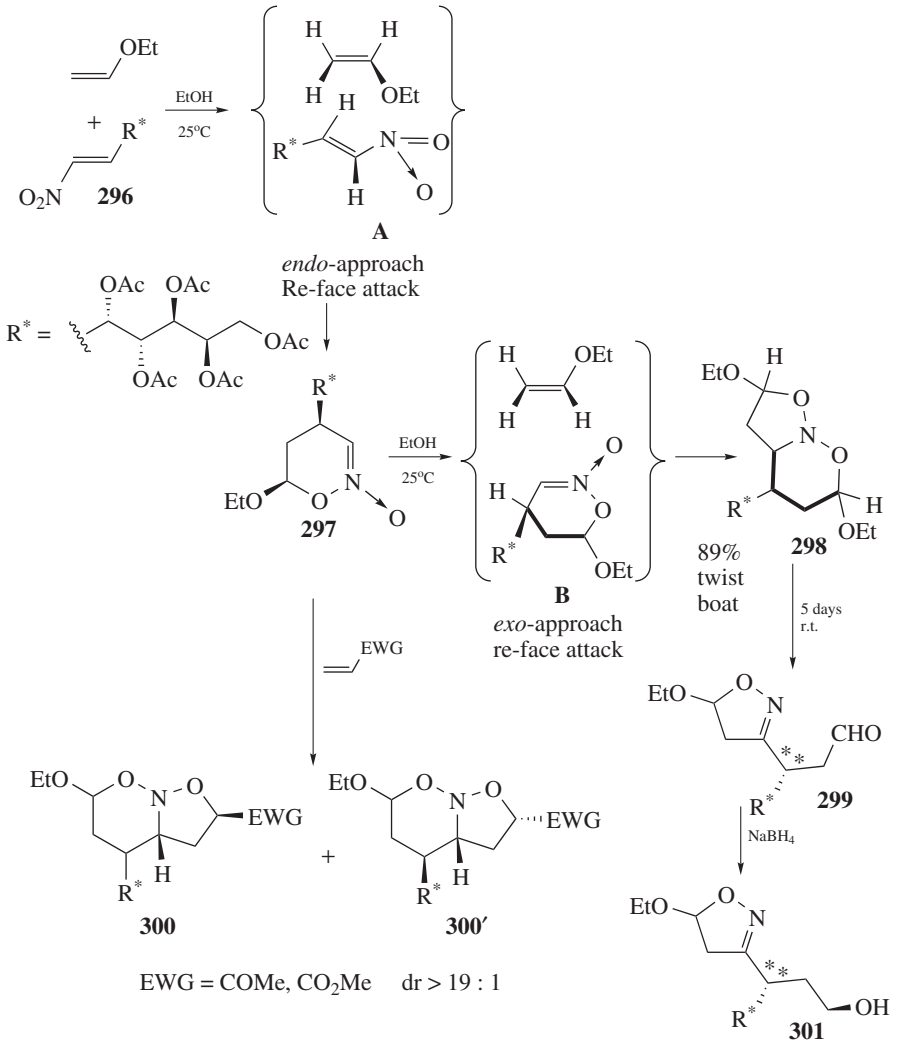
Another research group (147) studied the reaction of vinyl ethyl ether with optically pure α-nitroolefin (**302**) giving rise to enantiomerically pure nitronate (**303**). The reaction of the latter with an excess of the olefin gradually produces nitroso acetal (**304**) (Scheme 3.181).

The optical purity of compound (**304**) is due to the high facial preference of the attack of the olefin on nitronate (**303**) from the distal side with respect to the substituents at the C-4 and C-6 atoms. Modifications of nucleotides provide a promising approach to the synthesis of new anti-HIV drugs.

The asymmetric synthesis of six-membered cyclic nitronates with the use of dipolarophiles containing auxiliaries was studied in more detail. Chiral vinyl ethers are most commonly used for this purpose. This process is schematically shown in Scheme 3.182.

It should be noted that the reactions (**306**→**307**) and (**307**→**308**) can be either inter- or intramolecular, and that the number of substituents attached to the C,C double bond in the olefin can also be varied.

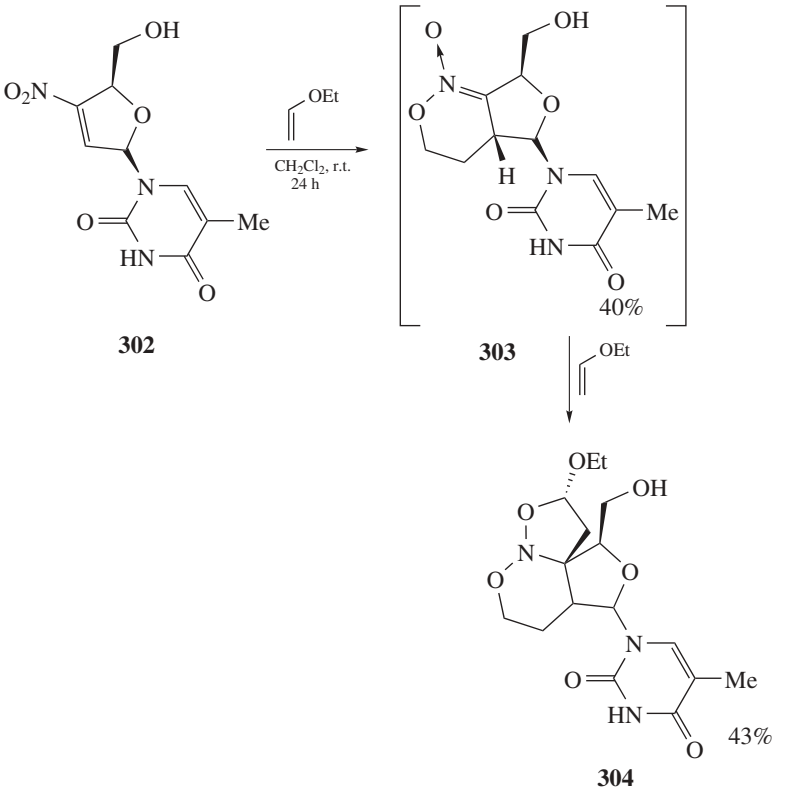
Denmark (442, 443) studied extensively various alcohols (**305**) with the aim of using these compounds as auxiliaries in the process shown in Scheme 3.182 (141, 442) and demonstrated that enantiomers of alcohols (**305a**) and (**305b**) are



Scheme 3.180

highly efficient in most of the tandem [4 + 2][3 + 2] reactions. However, both of these alcohols are difficult to prepare. These enantiomers provide high selectivity of the [4 + 2] step due to the dominant *Re*-face attack of the α-nitroalkene.

Some examples demonstrated (134, 443) that more readily available alcohols of the terpene series can be used instead of (**305a**) and (**305b**) in some cases. These alcohols can be easily prepared as both (+) and (−) isomers. Of special note is that, as was demonstrated by Italian scientists (102, 163), the [4 + 2]-addition of some α-nitroalkenes containing electronegative groups at the atom bearing the nitro group with vinyl ethers containing auxiliaries, which are



Scheme 3.181

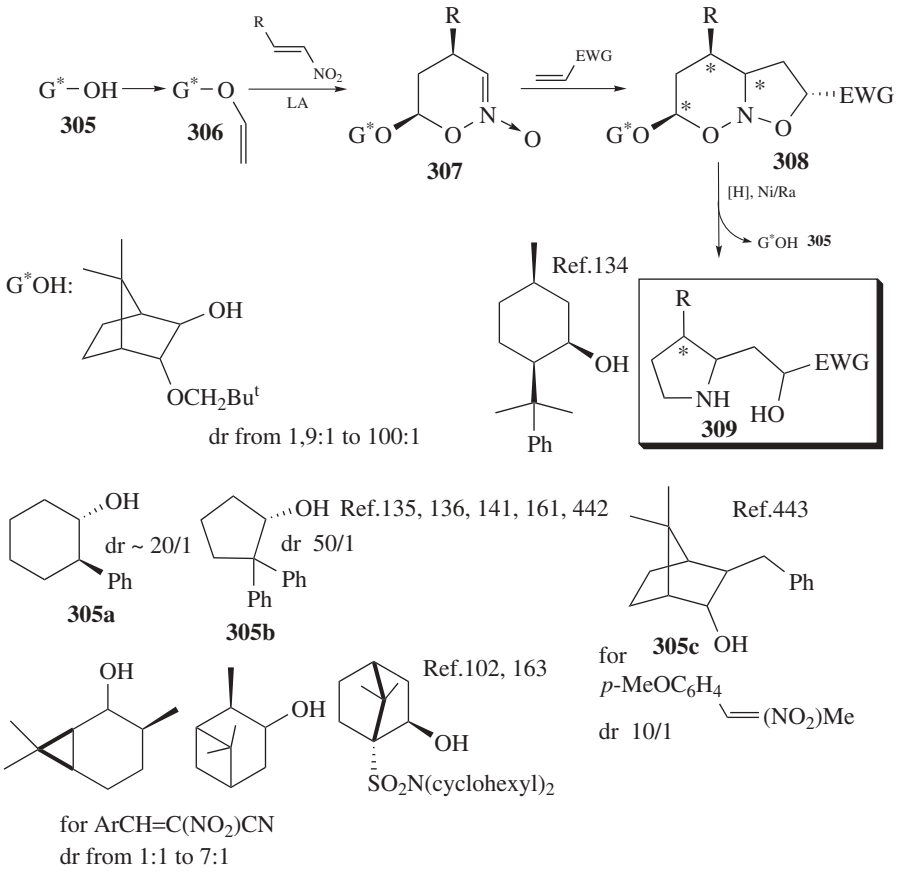
derived from alcohols (**305**) of the terpene series, can be performed stereoselectively in water in the absence of LA as the catalyst. In all of the above mentioned cases, the attack of olefin C=C–EWG on nitronate (**307**) occurs from the side distal to the substituents at the C-4 and C-6 atoms.

The possibilities of the use of enamines containing auxiliaries as dienophiles in tandem [4 + 2][3 + 2] reactions were not studied in detail. However, the results of the study (117) showed that such processes can occur (Scheme 3.183).

The use of enantiomer (**311**) as a dienophile in the [4 + 2]-addition to nitrocyclohexadiene (**310**) made it possible to prepare enantiomerically pure nitronate (**312**), from which an auxiliary can be removed by a simple procedure.

3.5. SILYLATION OF NITRO COMPOUNDS AS A PROCESS

Since simplest AN can be easily synthesized and can exhibit various reactivity, these compounds have attracted attention as the starting reagents for the design of important building blocks in modern strategies of organic synthesis (see,



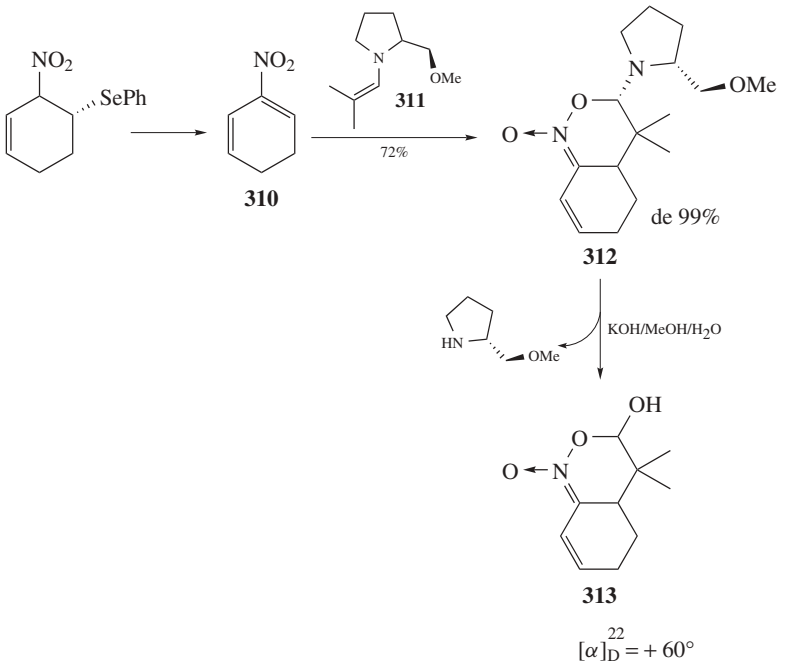
Scheme 3.182

e.g., Refs. 335, 442, 427, 444). However, most approaches involving AN are based on particular changes in the environment about the α-C atom bearing the nitro group. In these transformations, other atoms of the carbon skeleton of AN generally remain intact. In our opinion, this situation substantially reduces the possibilities for the development of efficient procedures with the use of AN.

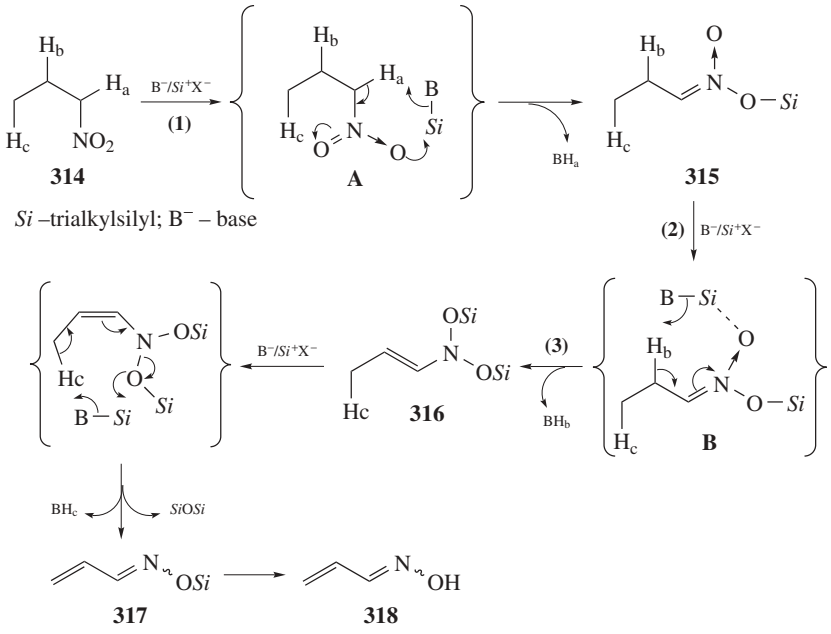
Modern methods for the design of complex organic molecules are based on readily available starting reagents and on the use of highly selective reaction sequences.

As applied to AN, the problem of activation of the carbon skeleton requires first the selective deprotonation of AN. At first glance, this task seems to be impossible to solve, because the acidity of the protons bound to the α-C atom in AN is much higher than that of other protons.

However, the above mentioned problem can be solved with the use of a rather simple algorithm (291, 445) (Scheme 3.184).



Scheme 3.183



Si –trialkylsilyl; B^- – base

Scheme 3.184

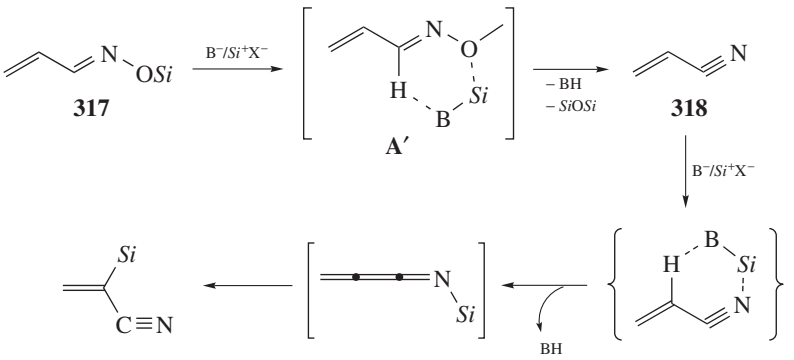
Let us consider the reaction of the standard silylating agent **B/*Si*** with AN (**314**) containing at least three carbon atoms. For simplicity, all processes will be described as electrocyclic schemes, although many of them evidently involve nonconcerted reactions.

In the first step (**1**), the H_α proton having the highest acidity is eliminated as BH_α^+ giving rise to SENA (**315**). However, now the Hβ proton in this substrate becomes flexible because it becomes heteroallylic. Hence, the $BH\beta^+$ fragment is eliminated in the second step (**2**) to give bis(siloxy)enamine (**316**). It should be noted that the Hγ proton in nitroso acetal (**316**) also has high acidity because it becomes allylic. Elimination of the latter proton affords the corresponding conjugated enoxime (**317**).

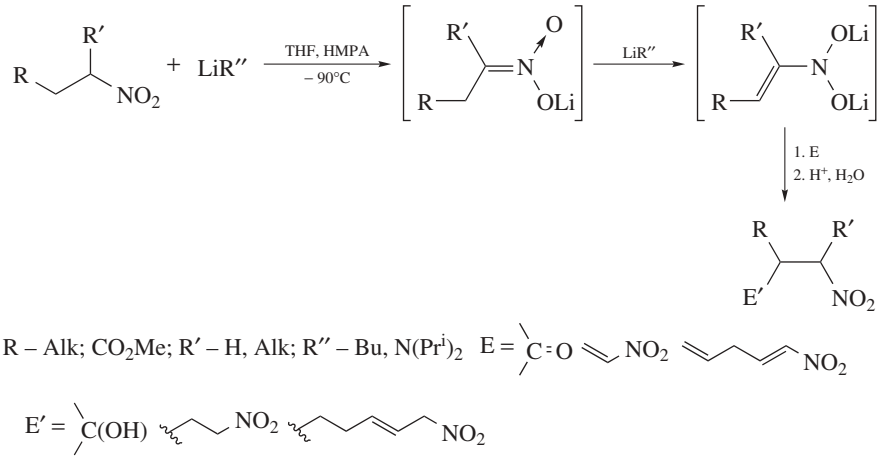
Therefore, AN containing protons at the first three carbon atoms can be considered as sources of SENA, nitroso acetals, and conjugated enoximes. The process shown in Scheme 3.184 is actually a redox process, in which the nitro group is partially reduced, while the carbon skeleton of AN is oxidized, the silylating agent serving as a mediator, which makes it possible to interrupt the sequence in the required step. Actually, the strength of both components in the silylating agent **B/*Si*X** can be varied over a wide range. Substituents at the C_1-C_3 atoms also act as mediators and either facilitate the elimination of the corresponding protons or, on the contrary, hinder the proton abstraction.

It should be noted that enoxime (**317**) in Scheme 3.184 is not always the last one in the reaction sequence under consideration. For primary AN, this sequence can be extended to give finally α-silylated conjugated enenitriles (Scheme 3.185).

Evidently, this approach is not limited to the formation of nitronates, nitroso acetals or enoximes. The rearrangements of these compounds by elimination reactions, the trapping of intermediates and finally their reactions with various reagents are of equal importance. It should be emphasized that silylation of AN as a process in organic chemistry is characterized by an unrivalled completeness and diversity of transformations. Hence, the silylation can be considered as a separate field of application of AN in organic synthesis.



Scheme 3.185



Scheme 3.186

In spite of the evident simplicity, the concept of the development of reaction sequences for activation of the carbon skeleton of AN has been ignored in the literature until recent years. Nevertheless, the data on double lithiation of AN (446, 447) (Scheme 3.186) clearly demonstrated that these ideas hold promise.

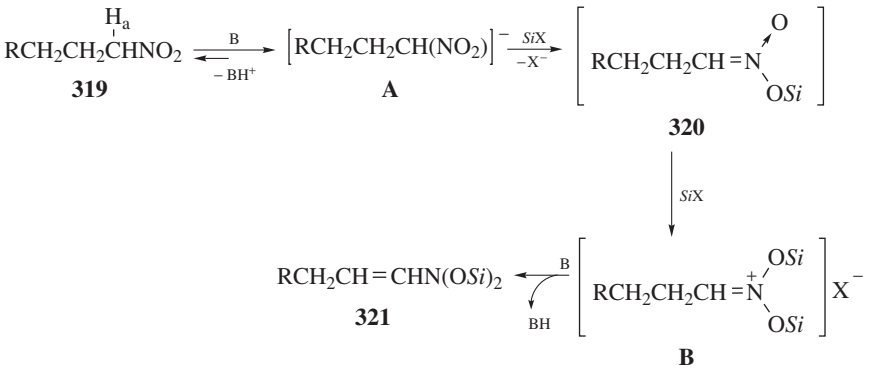
Unfortunately, these studies have not been developed in more recent years, apparently due to problems associated with the instability of *Li* intermediates. It should be emphasized that, unlike *Li* derivatives, trialkylsilyl derivatives of many organic compounds are quite stable. In organic synthesis, the trialkylsilyl group is considered as a standard protecting group (448). Here AN are no exception (for more details, see Section 3.3.1.2.)

3.5.1. Double Silylation of AN

Let us consider the steps (**314**→**315**) and (**315**→**316**) shown in Scheme 3.184 in more detail (Scheme 3.187).

It is evident that these two reactions occur by different mechanisms. Actually, the Hα proton is rather acidic, whereas the basicity of the corresponding AN is low. As a result, the first silylation reaction generally starts with the nucleophilic attack of the starting AN and generation of the anion **A**, which reacts with a silylating agent and pushes out the X^- group to give the corresponding SENA (**320**).

In the second silylation step, the situation is opposite because the basicity of SENA is substantially higher than that of the starting AN. Hence, the second silylation should start with the electrophilic attack of nitronate (**320**) giving rise to the cationic intermediate **B**, whose deprotonation affords nitroso acetal (**321**). (Interestingly, tertiary amines stabilize SENA (**320**) but, at the same time, destabilize nitroso acetals (**321**).)



Scheme 3.187

The above analysis shows that attempts to separate the two silylation steps of AN can be successful due to the difference in the mechanism.

Main problems of monosilylation of AN were considered in detail in Section 3.2.1.3. Transformations of SENAs were described in Section 3.4. Hence, the present section deals only with some aspects of the chemistry of these compounds and derivatives which were not covered in previous sections and which are associated with the process shown in Scheme 3.184.

3.5.1.1. Modeling of Classical Reactions of AN with the Use of Silyl Nitronates

Classical C,C-coupling reactions of AN anions (Henry, Michael, and Mannich) involve complex systems of equilibria and, consequently, generally not performed in protic solvents. The introduction of the silyl protecting group allows one to perform these reactions in an aprotic medium to prepare or retain products unstable in the presence of active protons. In addition, the use of nucleophiles which are specifically active toward silicon (e.g., the fluoride anion) enables one to design a process in which the effective concentration of α-nitro carbanions is maintained low.

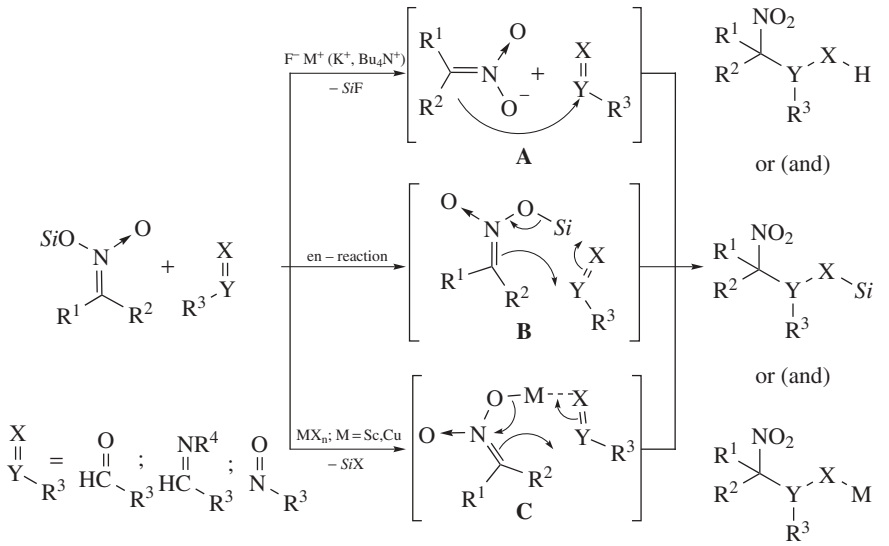
3.5.1.1.1. Silyl Nitronates in Henry Reactions Topologically, condensations of SENAs with carbonyl and nitroso groups, as well as with an imino fragment, belongs to Henry reactions.

In these processes, three transition states are possible (Scheme 3.188)

In the first case, SENAs in the presence of various catalysts (primarily salts containing the fluoride anion) generate the corresponding α-nitro carbanions, which are poorly solvated in aprotic solvents and, consequently, rapidly react with substrates $R^3-Y=X$ to give functionalized nitro compounds through the transition state **A**.

The second type of reactions is an electrocyclic process occurring as the ene reaction (the transition state **B** in Scheme 3.188).

Finally, the possible transition state **C** contains a ligated metal atom and two coordinated reagent molecules, which are involved in the C,C-coupling reaction.



Scheme 3.188

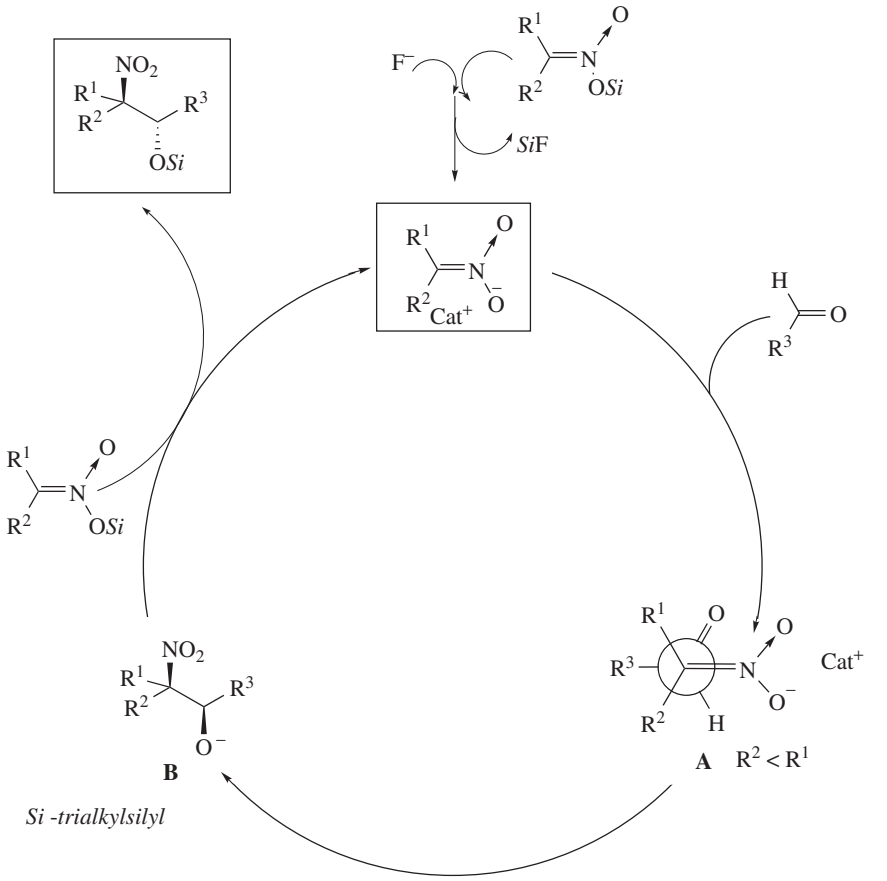
The C,C-coupling reactions of SENAs with carbonyl compounds were studied in most detail (132, 179, 182, 183, 185, 253, 254, 449, 450). Only aldehydes are involved in the Henry reaction with SENAs and activating additives of ammonium fluorides (or triethylamine (185)) are required for this process (Scheme 3.189).

The reaction starts with desilylation of nitronate. The α-nitro carbanion which is eliminated gives (through the transition state **A**) the coupling product, the anion **B**. The latter desilylates the next nitronate molecule to form the target product and continues the chain.

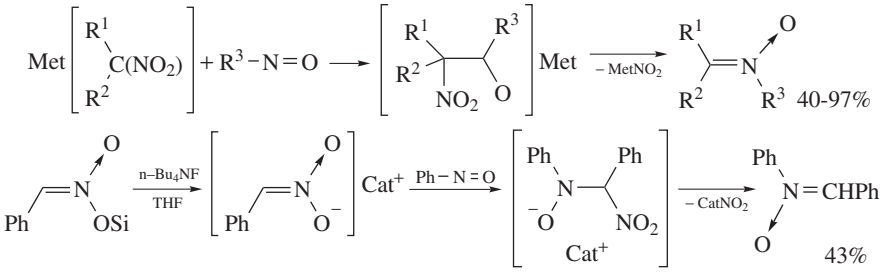
SENAs derived from primary AN are most efficient in this process, *erythro* isomers of β-siloxy-nitro compounds being formed as the major products. (In contrast, the *threo* isomer is primarily generated from $CF_3CH{=}N(O)OSi$ under these conditions (132).) It should be emphasized that the stereoselectivity of this process strongly depends on the quality of tetrabutylammonium fluoride. The latter should be thoroughly dried, because the presence of moisture in the reaction mixture leads to epimerization of the starting products. On the other hand, in some cases the addition of water increases the total yield of the coupling product (182). SENAs derived from secondary AN react with aldehydes with difficulty to give mixtures of silylated and nonsilylated condensation products in low yields.

Recently, C,N condensation of salts of nitro compounds with the nitroso group has been discovered (251, 451) (Scheme 3.190). This reaction can be considered as a convenient procedure for the synthesis of nitrones from AN. The yields of the target products are 40 to 97%.

SENAs can be involved in these reactions but only in the presence of fluoride anion as the catalyst (see the lower part of Scheme 3.190). As can be seen from



Scheme 3.189

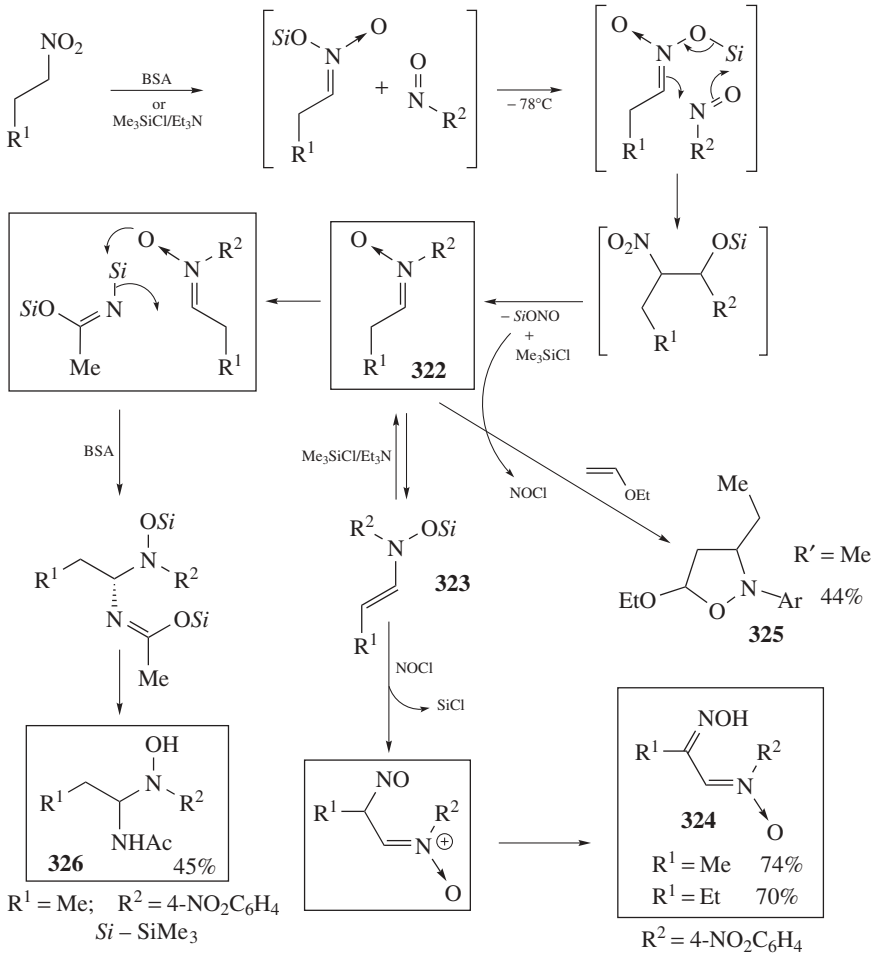


Scheme 3.190

this scheme, SENAs have no obvious advantages over salts of nitro compounds in such processes.

However, reactions of the higher electrophilic nitrosoarene ($R^2 = p\text{-}NO_2\text{-}C_6H_4$, Scheme 3.191) do not require catalysis by fluoride anion, and the C,N-coupling process occurs, apparently, by the ene scheme to give nitrone (**322**) (452, 453). The reaction proceeds under very mild conditions (at $-78^\circ C$). Apparently, in the reaction with the use of a Me_3SiCl/Et_3N mixture as the silylating agent, nitrones (**322**) exist in tautomeric equilibrium with isomeric vinylhydroxylamines (**323**), which are nitrosated by nitrosyl chloride, generated as a by-product, to give isolable functionalized nitrones (**324**).

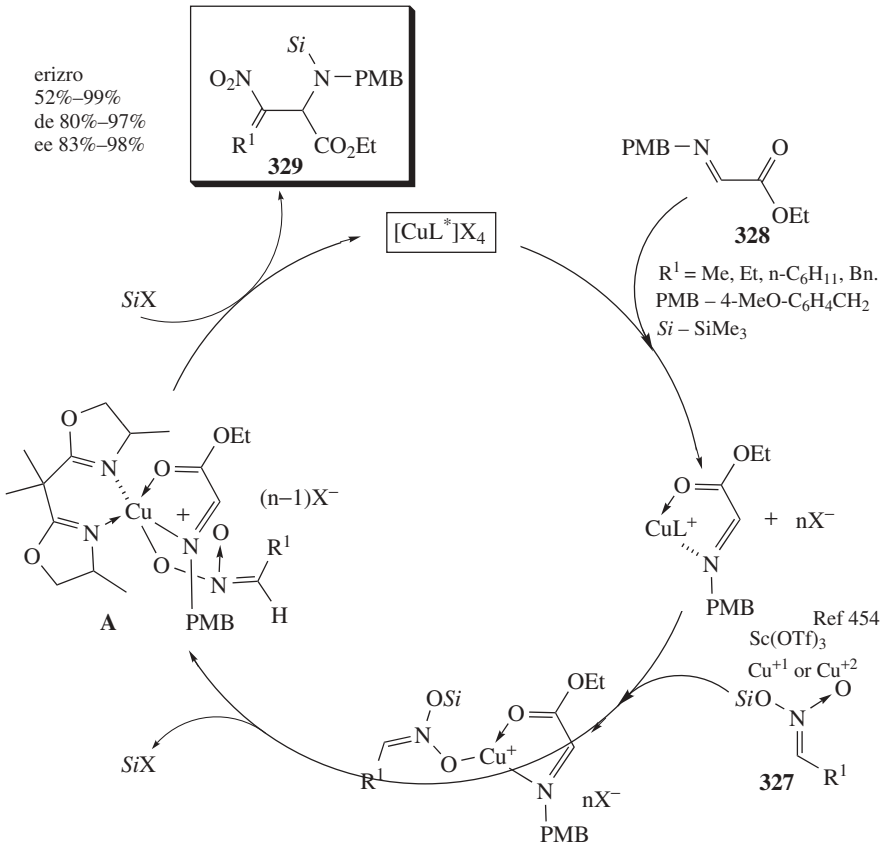
At the same time, nitrones can be trapped by external dipolarophiles to form isoxazolidines (**325**). In the reactions with N,O-bis(trimethylsilyl)acetamide



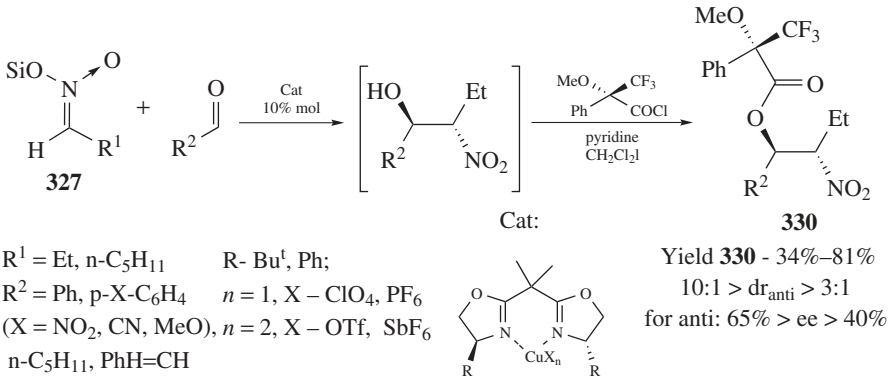
Scheme 3.191

(BSA) as the silylating agent, nitrone (**322**) (R′=Me) can react with the silylating agent at the N–Si bond to give derivative (**326**). Experiments with the use of the ^{15}N label demonstrated that the nitroso group was the source of the nitrogen atom included in nitrones (**322**) and (**324**). The NMR data revealed pronounced chemical nuclear polarization of cycloadduct (**325**). This indicates that the synthesis of the latter compound involves a one-electron transfer step.

In the very recent past, metal complex catalysis has been used with advantage for the stereo- and enantio selective syntheses based on the Henry and Michael reactions with SENAs (454–458). The characteristic features of these transformations can be exemplified by catalysis of the reactions of SENAs (**327**) with functionalized imides (**328**) by ligated trivalent scandium complexes or mono- and divalent copper complexes (454) (Scheme 3.192). Apparently, the catalyst initially forms a complex with imide (**328**), which reacts with nitronate (**327**) to give the key intermediate **A**. Evidently, diastereo- and enantioselectivity of the process are associated with preferable transformations of this intermediate.



Scheme 3.192



Scheme 3.193

This process involves C,C-coupling and silylation of the resulting product with Me_3SiX which is eliminated. The yields of target products (**329**) are 52 to 99%. The excess of the *erythro* isomer *de* = 80 to 97%. The reactions with the use of a catalyst containing a chiral ligand give the *erythro* isomer with an enantiomeric excess of 83 to 98%. To prevent racemization of the target product, the process shown in Scheme 3.192 was optimized with respect to the catalysts at $-100^{\circ}C$. The resulting products (**329**) can be considered as convenient precursors of chiral unnatural amino acids and other biologically active compounds.

The application of this approach to the enantioselective "classical" Henry reaction with SENAs (**327**) is exemplified in Scheme 3.193 (455).

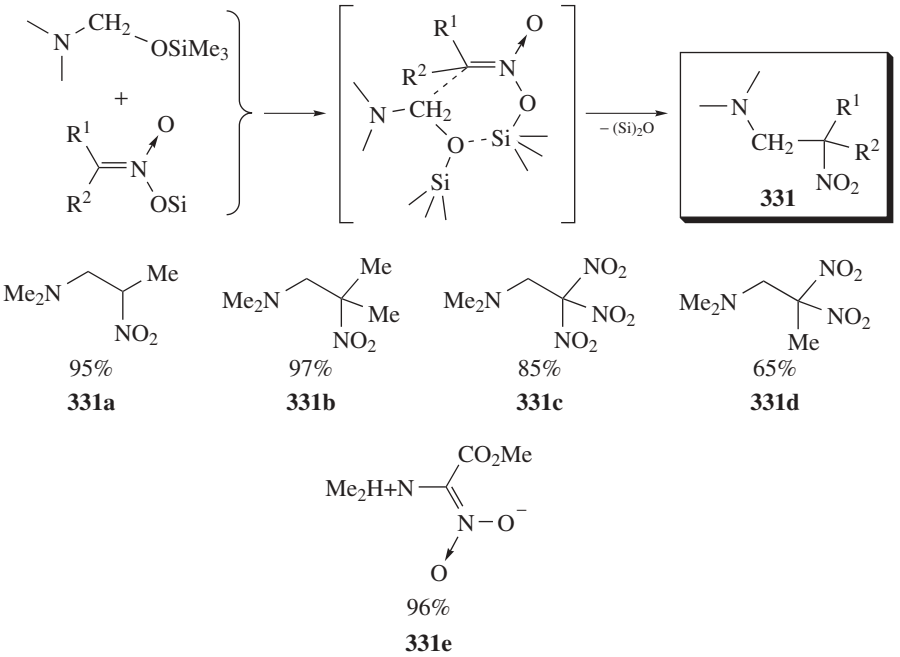
As can be seen from the above data, the enantiomeric excess for target products (**330**) is low. This process requires improvements.

3.5.1.1.2. Silyl Nitronates in the Mannich Reaction The Mannich reaction with SENAs (Scheme 3.194) was also modified (459). This reaction in nonpolar solvents produced previously unavailable β-nitroamines (**331**), which are unstable in water and other protic solvents.

In Scheme 3.194, this process is represented as proceeding through the six-membered cyclic transition state, although C,C-coupling of two ions generated from the starting substrates cannot be ruled out. However, the structure of the nitronate can be varied over a wide range; attempts to modify the siloxymethylene component failed.

It should be noted that the demarcation between metal complex catalysis of the Henry (454–458) and Mannich reactions is arbitrary, and that the catalyzed process is sometimes called the Mannich reaction (see, e.g., Ref. 456).

3.5.1.1.3. Silyl Nitronates in the Michael Reaction The Michael reactions with SENAs were unknown until recently. Competitive [3 + 2]-cycloaddition reactions have been used instead of this process (for more details, see Section 3.4.3.).



Scheme 3.194

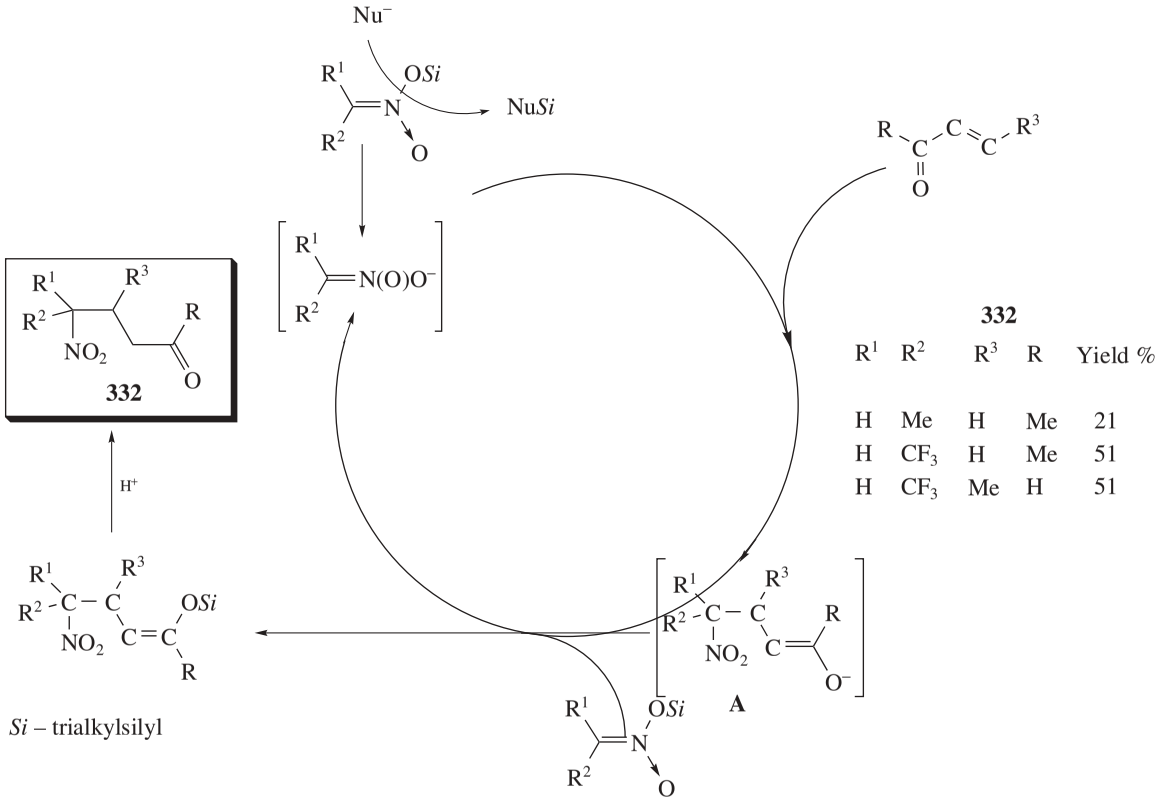
However, Michael addition has been successfully performed in recent years with the use of nucleophilics catalysis (fluoride anion or amines) (132) (Scheme 3.195).

Only few SENAs are involved in reactions with standard Michael substrates, and the yields of the target products are low (see Scheme 3.195). However, a similar process with unstable intermediates, conjugated nitrosoalkenes, was studied in sufficient detail (see Section 3.5.4.2.2.).

Recently, Japanese researchers have performed several asymmetric syntheses with SENAs (460–462) catalyzed by chiral ammonium cations **A** or **A'** (see Scheme 3.196).

Few of these studies (460, 462) dealt with the Michael reaction; one study (461) with the Henry reaction. The efficiency, stereoselectivity, and enantioselectivity of this process are rather high. The mechanism of the transformations is poorly known. Presumably, the chiral cation should shield the *Si* surface of nitronate, thus providing the *Re* approach of the substrate. In addition, the approach of the reagents, resulting in generation of *syn* isomers, is considered less favorable than the approach yielding *anti* isomers.

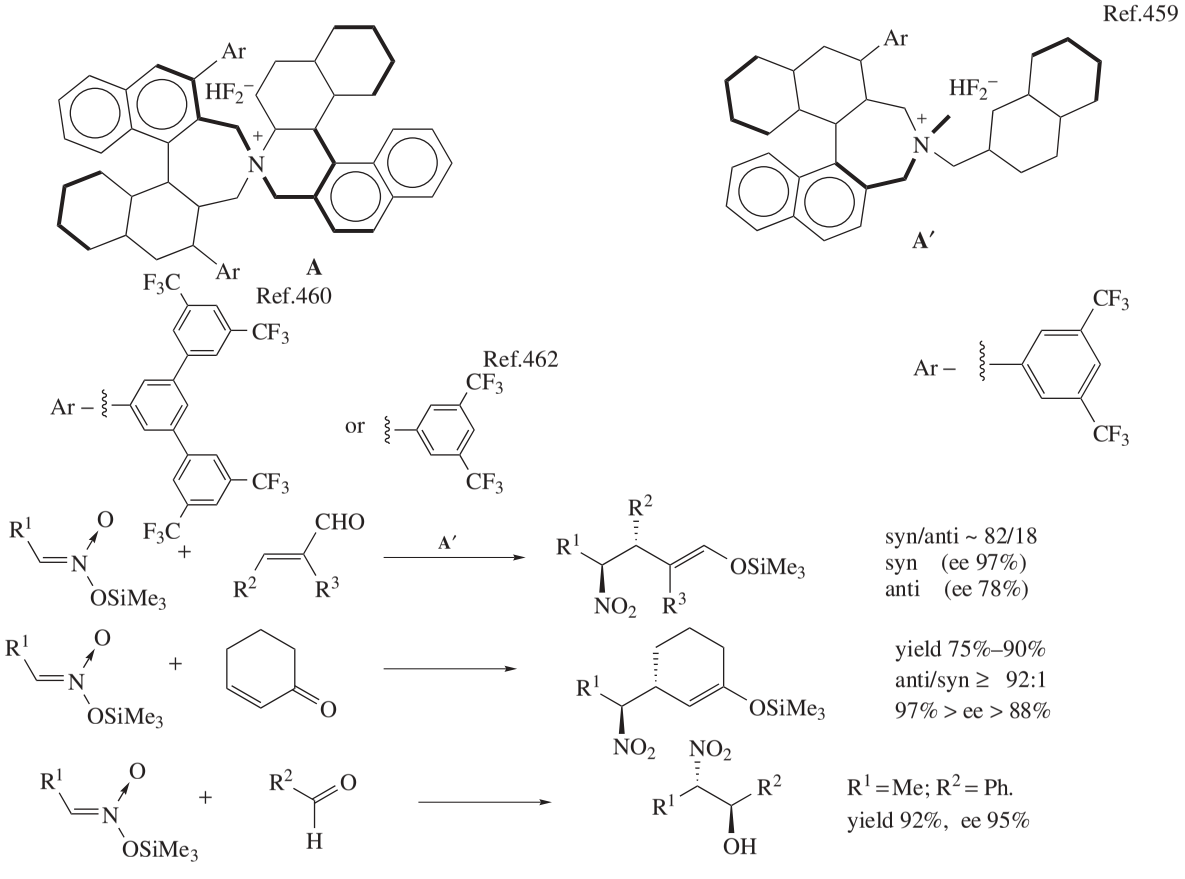
3.5.1.2. Double Silylation of Aliphatic Nitro Compounds–Optimization and Procedures Double silylation of AN with standard silylating agents *Si*X/Base is mechanistically shown in Chart 3.20 as a four-step process.



332

R^1	R^2	R^3	R	Yield %
H	Me	H	Me	21
H	CF_3	H	Me	51
H	CF_3	Me	H	51

Scheme 3.195


Ref.459
Ar
HF2−
N+
Ar
A
Ref.460
F3C
CF3
Ar –
CF3
F3C
or
Ref.462
CF3
CF3
Ar –
CF3
CF3
A′
R1
O
N
OSiMe3
CHO
R2
R3
+
A′
R2
R1
OSiMe3
NO2
R3
syn/anti ~ 82/18
syn (ee 97%)
anti (ee 78%)
yield 75%–90%
anti/syn ≥ 92:1
97% > ee > 88%
O
NO2
NO2
R1
R2
OH
R1 = Me; R2 = Ph.
yield 92%, ee 95%
H

Scheme 3.196

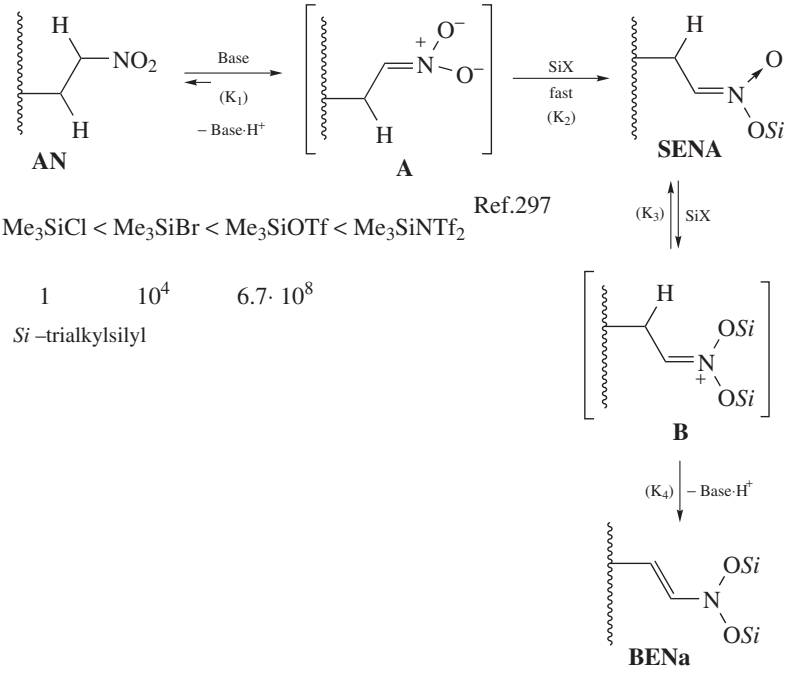


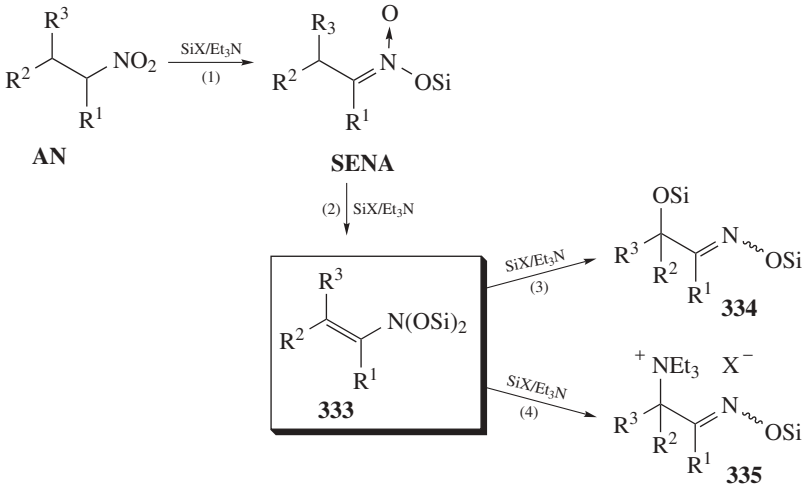
Chart 3.20 The mechanistic interpretation for double silylation of AN.

Under the action of a base, the first step (K_1) reversibly produces the α-nitro carbanion **A**, which then rapidly reacts with *Si*X (K_2) to form SENA. The latter is reversibly silylated by the second equivalent of *Si*X (K_3) to give the cationic intermediate **B**, whose deprotonation with the base (K_4) affords the target nitroso acetal (or BENA).

Therefore, the result of the process depends on the ratio of the rate constants K_1-K_4 and the thermodynamic of two equilibria. The efficiency of generation of SENA is determined primarily by the effective concentration of the α-nitro carbanion **A**, whereas it is difficult *a priori* to distinguish the key step in the **SENA→BENA** process. Assuming that K_3 corresponds to the key step, the efficiency of the overall process is determined by the strength of the silylating agent. (The series of efficiency of the most commonly used silylating agents is shown in Chart 3.20 based on the results of the study (463).) On the whole, analysis of Chart 3.20 leads to the conclusion that the use of a powerful silylating agent, simultaneously with a strong base, should be favorable for double silylation of AN in one technological step. Accordingly, the *Si*OTf/DBU combination is *a priori* the system of choice for this synthesis.

The group of Prof. Simchen was the first to synthesize (188, 464) BENA from AN by the reactions with the *Si*OTf/Et_3N system (Scheme 3.197).

These studies and more recent investigations by Russian researchers (187, 465–467) demonstrated that BENA (**333**) are rather labile compounds, which



Scheme 3.197

can be rapidly rearranged into oximes (**334**) or give quaternary ammonium salts (**335**). (These reactions will be considered in more detail in Section 3.5.4.3.) Stability of BENA (**333**) depends not only on the nature of the silylating reagent used but also on the reaction conditions and the nature of the starting AN.

Interestingly, bases and water have different effect on stability of BENA and intermediate SENA. Additives of tertiary amines stabilize SENAs (191), whereas bases cause spontaneous decomposition of BENAs. SENAs are hydrolytically unstable, whereas BENAs are inert toward water under neutral conditions.

An increase in the strength of silyl Lewis acid leads to an increase in the rate of the AN→BENA process and allows one to use milder conditions. In addition, the rate ratio K_4/K_2 (Chart 3.20) sharply increases. For example, the generation rate of respective BENA is approximately equal to the rate of consumption of the corresponding intermediate SENA in double silylation of 2-nitropropane with Me_3SiCl (187). This SENA was not detected among the products of silylation of 2-nitropropane in the presence of even a smaller amount of Me_3SiOTf.

In special studies, several procedures were developed (465–468) for the one-pot synthesis of the corresponding BENA in good yields from the overwhelming majority of various AN, the amounts of impurities being minimum (Table 3.18).

To increase stability of the target substrates, washing of the resulting reaction mixture with an aqueous $NaHSO_4$ solution was included as a necessary step in standard procedures for the synthesis of BENA.

However, in some cases, it is worthwhile to synthesize BENA in two steps by isolating intermediate SENA (see, in particular, entries 10 and 22, Table 3.18).

It is particularly difficult to synthesize BENA from AN disubstituted at the β-carbon atom.

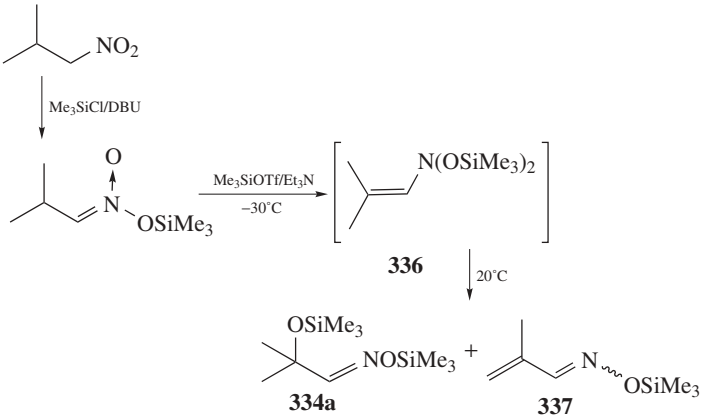
Table 3.18 Double silylation of AN. Optimal procedures for synthesis of BENAs

Entry	R^1	R^2	R^3	*Si*	X	Conditions	Procedure[a]	**BENA 333**	Yield %
1	Me	H	H	Me_3Si	Cl	20°, 70 h	A	**a**	77
2	Me	H	H	Me_3Si	Br	20°, 40 h	B	**a**	92
3	H	H	H	Me_3Si	Br	0°, 20 h	B	**b**	97
4	H	Me	H	Me_3Si	Br	−30°, 48 h	B	**c**	89
5	H	CH_2CO_2-Me	H	Me_3Si	Br	−30°, 92 h	B	**d**	97
6	$(CH_2)_2$-CO_2Me	H	H	Me_3Si	Br	20°, 20 h	B	**e**	90
7	Ph	H	H	Me_3Si	Br	0°, 42 h	B	**f**	88
8	H	CHMe-CO_2Et	H	Me_3Si	Br	−30°, 120 h	B	**g**	79
9	-$(CH_2)_4$-		H	Me_3Si	Br	−30°, 20 h	B	**h**	60
10	$CH(Pr^i)$-$OSiMe_3$	H	H	Me_3Si	Br	20°, 17 days[c]	B	**i**	62
11	CO_2Et	H	H	Me_3Si	OTf	−75°, 5 h	C	**j**	94
12	H	CO_2Me	H	Me_3Si	OTf	−75°, 2.5 h	C	**k**	87
13	CO_2Et	Me	H	Me_3Si	OTf	−50°, 4 h	C	**l**	92
14	H	CO_2Me	H	Me_3Si	OTf	−75°, 5 h	C	**m**	87
15	H	CO_2Me	$PhCOCH_2$	Me_3Si	OTf	−75°, 1.5 h	C	**n**	71
16	Me	CO_2Me	H	Me_3Si	OTf	−30°, 3 h	C	**o**	85
17	H	CH_2=C-$(OSiMe_3)$[c]	H	Me_3Si	OTf	−75°, 2 h	C	**p**	84
18	H	H	H	Me_2Bu^tSi	OTf	0°, 4 h	C	**b'**	92
19	Me	H	H	Me_2Bu^tSi	OTf	0°, 3 h	C	**a'**	93
20	CO_2Et	H	H	Me_2Bu^tSi	OTf	−40°, 2 h	C	**j'**	55
21	H	CHMe-CO_2Et	H	Me_2Bu^tSi	OTf	0°, 3 h	C	**g'**	93
22	$CH(Pr^i)$-$OSiMe_3$	H	H	Me_2Bu^tSi	OTf	20°, 6 days[b]	C	**i'**	78
23	Me	CO_2Me	H	Me_2Bu^tSi	OTf	0°, 3 h	C	**o'**	75
24	Ph	H	H	Me_2Bu^tSi	OTf	0°, 3 h	C	**f'**	85
25	Br	H	H	Me_2Bu^tSi	OTf	0°, 4 h	C	**r'**	72
26	Br	H	H	Me_3Si	OTf	0°, 48 h	C	**r**	85
27	Cl	n-C_5H_{11}	H	Me_2Bu^tSi	OTf	0°, 4 h	C	**s'**	90
28	I	n-C_5H_{11}	H	Me_2Bu^tSi	OTf	0°, 4 h	C	**t'**	75
29	F	n-C_5H_{11}	H	Me_2Bu^tSi	OTf	0°, 24 h	C	**u'**	75

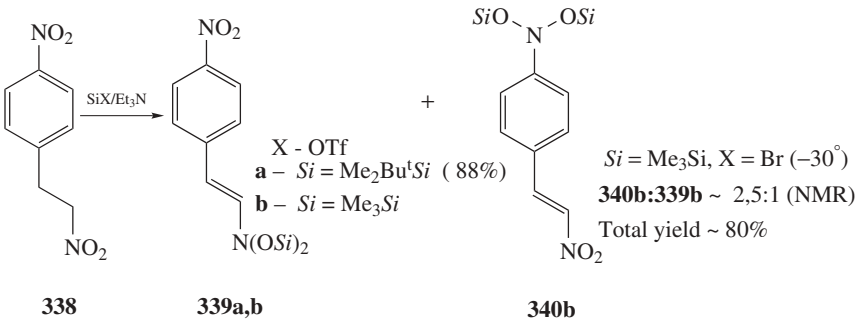
[a] A – Me_3SiCl/Et_3N in MeCN; B - Me_3SiBr/Et_3N in 1,2-dichloroethane; C - *Si*OTf /Et_3N in CH_2Cl_2.
[b] For SENA→BENA (for run 10: Me_3SiCl/DBU, CH_2Cl_2, 0→20°C, 0, 5 h).
[c] Entry 17, for AN, R^2 = MeCO.

For example, BENA (**336**) can be detected only by NMR spectra of the reaction mixture. At higher temperature, this nitroso acetal is transformed in solution into a mixture of oxime (**334a**) (the rearrangement product) and enoxime (**337**) (the elimination product of trimethylsilanol) (469) (Scheme 3.198).

Double silylation of AN (**338**) with Me_3SiBr/Et_3N afforded both the usual BENA (**339b**), and the product of its rearrangement, nitroso acetal (**340b**) (Scheme 3.199), which was detected in the reaction mixture by NMR data.



Scheme 3.198



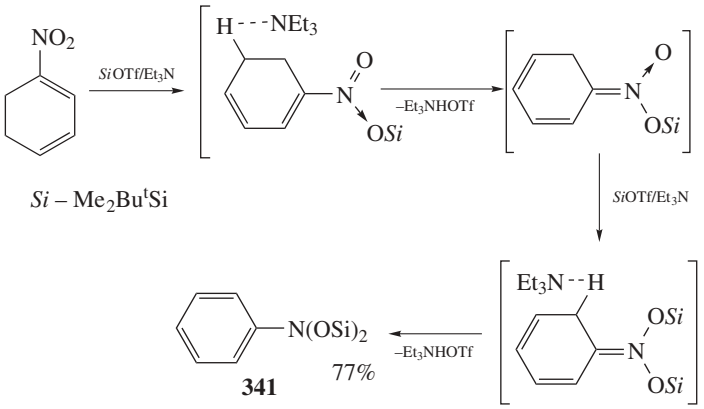
Scheme 3.199

At the same time, the corresponding "normal" BENAs (**339a**) and (**339b**) can be prepared using Me_2Bu^tSiOTf/Et_3N or Me_3SiOTf/Et_3N. (467, 470)

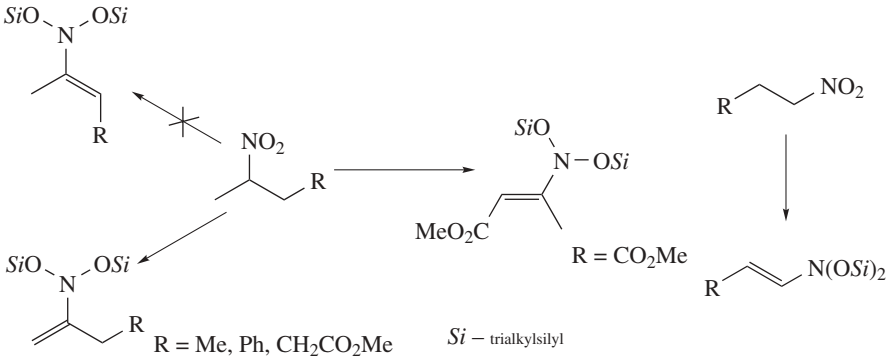
Nitroso acetal (**341**) was synthesized by double silylation of 1-nitro cyclohexa-1,3-diene (471) (Scheme 3.200). Nitrosal (**341**) can be considered as a possible equivalent of nitrosobenzene.

In conclusion of this section, it should be emphasized that double silylation of AN is very regio- and stereospecific. As a rule, the reaction mixtures contain only one structural isomer of the target nitroso acetals. If the starting AN contains the methyl group at the α-C atom, double silylation leads to deprotonation of this group to give terminal BENA regardless of the nature of the substituent R at the β-carbon atom (Scheme 3.201).

Only the introduction of a powerful electron-withdrawing group ($R=CO_2Me$) leads to a change in the deprotonation site and the regioselective generation of the corresponding terminal BENA.



Scheme 3.200



Scheme 3.201

Double silylation of primary AN occurs stereoselectively to give only the *trans* isomer of the corresponding BENA. Only one stereoisomer is detected in tris-substituted BENAs.

3.5.1.3. Silylation of Cyclic Nitronates As can be seen from Chart 3.20 and Scheme 3.197, double silylation of AN necessarily involves silylation of intermediate SENAs. In this connection, silylation of alkyl nitronates as nearest analogous of SENAs is of obvious interest. This reaction would be expected to give "mixed" nitroso acetals containing the >C=C–N(OAlk)O*Si* fragment. Until recently, such derivatives were unknown. However, cyclic nitronates are of particular interest, because cleavage of the endocyclic N–O bond does not lead to simplification of the initial molecule. This provides additional possibilities for the use of these nitroso acetals in organic synthesis.

In recent years, silylation of six-membered cyclic nitronates has been comprehensively studied by Russian researchers in collaboration with Prof. Denmark (264, 472). This process is mechanistically shown in Scheme 3.202.

As in the case of double silylation of AN, the formation of target enamines (**343**) is accompanied by side processes, which should be minimized when developing convenient procedures for the synthesis of nitroso acetals (**343**).

First, it should be noted that the starting nitronates (**342**) or target nitroso acetals (**343**) can undergo stereoisomerization under the action of electrophiles, which can be accompanied by reversible cleavage of the endocyclic N–O bond reactions (**342⇆342'**) or (**343⇆343'**). To suppress these processes, it is necessary to perform the transformation (**342→343**) under conditions as mild as possible and to use a silylating agent containing a small excess of a base.

Second, one should take into account the stability of nitroso acetals (**343**) associated with the possibility of their rearrangement to give oxazines (**344**). In addition, it should be taken into account that cyclic nitroso acetals (**343**) can be transformed into halo derivatives of dihydrooxazines (**345**). (These transformations of nitroso acetals (**343**) will be considered in more detail in Section 3.5.4.3.3.)

Taking into account all the aforesaid, simple procedures were developed for preparation of most six-membered cyclic nitronates. These procedures allow one to stereo- and regioselectively synthesize the corresponding cyclic nitroso acetals (**343**), which retain the configurations of the stereocenters of the starting nitronates (**342**) (see Table 3.19) (264, 472–474). It should be emphasized that, in the presence of the substituent R^1, the internal C,C double bond in the resulting nitroso acetals (**343**) always is of *trans* configuration.

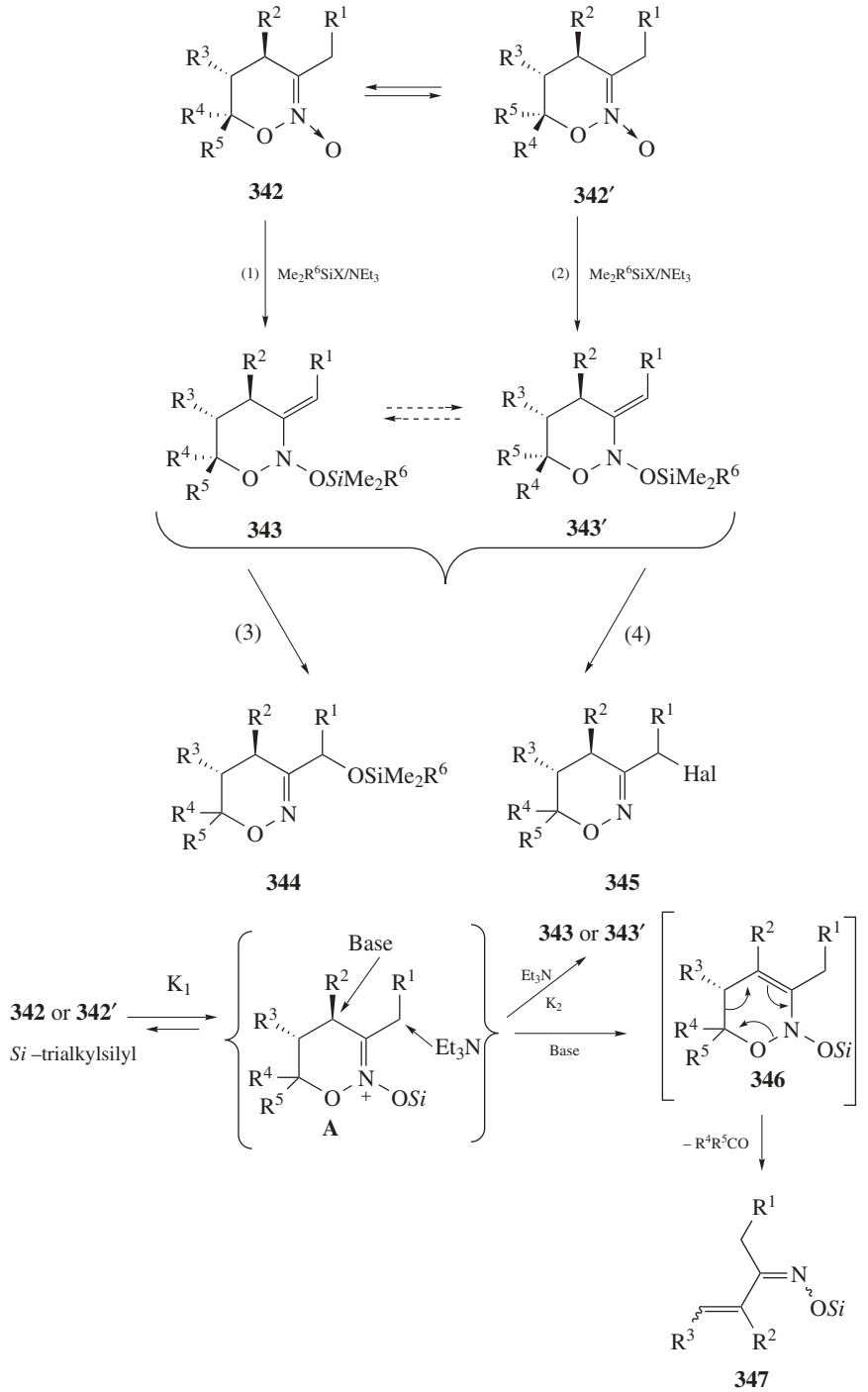
For silylation of six-membered cyclic nitronates (**342**), the influence of the nature of base on the regioselectivity of the synthesis of nitrosals (**343**) was studied in sufficient detail. Intermediate cations **A** can be deprotonated at the α-C atom of the substituent at C-3 as well as the C-4 atom (see Scheme 3.202 and Table 3.20) (264, 474).

It appeared that triethylamine is the base of choice for generating nitrosals (**343**). However, sterically less hindered amines deprotonate the C-4 atom to give, after retro-[4 + 2]-cycloaddition of the intermediate enamines (**346**), the corresponding conjugated enoximes (**347**).

Interestingly, nitrogen bases containing the strongly shielded nitrogen atom give not nitroso acetals but instead the corresponding enamines, which substantially decreases the rate of this reaction (see entries 3 and 4 in Table 3.20). For unknown reasons, silylation of nitronates (**342t,u**) with Me_3SiBr/Et_3N also leads to deprotonation at the C-4 atom.

Silylation of 3-alkyl-substituted five-membered cyclic nitronates remains virtually unknown, although one example of the successful synthesis of the corresponding nitroso acetal was documented (Scheme 3.203) 475.

Recall that, unlike six-membered analogs, N-oxyisoxazolines-3 are quite stable (see Scheme 3.111 and Reference 82).


342
342′
(1) Me2R6SiX/NEt3
(2) Me2R6SiX/NEt3
343
343′
(3)
(4)
344
345
342 or 342′
Si –trialkylsilyl
K1
Base
Et3N
A
343 or 343′
Et3N
K2
Base
346
– R4R5CO
347

Scheme 3.202

Table 3.19 The silylation of six-membered cyclic nitronates. The preparation of ene-nitroso acetals

Entry	Compounds (**342**)	(**343**)	R^1	R^2	R^3	R^4	R^5	R^6	X	Conditions	Yield (**343**) (%%)
1	**a**	**a**	H	4-MeO-Ph	H	OMe	Me	Me	Cl	*i*	60
2	**a**	**a**	H	4-MeO-Ph	H	OMe	Me	Me	Br	*i*	93
3	**a**	**a**	H	4-MeO-Ph	H	OMe	Me	Me	OTf	*iii*	-[a]
4	**a**	**a'**	H	4-MeO-Ph	H	OMe	Me	Et	Cl	*iv*	62
5	**a**	**a"**	H	4-MeO-Ph	H	OMe	Me	^{t}Bu	OTf	*iii*	71
6	**b**	**b**	H	4-MeO-Ph	H	OEt	H	Me	Br	*ii*	98
7	**c**	**c**	H	4-MeO-Ph	H	H	OEt	Me	Br	*ii*	98
8	**d**	**d**	H	4-MeO-Ph	H	Ph	H	Me	Br	*ii*	94
9	**e**	**e**	H	4-MeO-Ph	H	H	Ph	Me	Br	*ii*	96
10	**f**	**f**	H	4-MeO-Ph	-$(CH_2)_4$-		H	Me	Br	*ii*	95
11	**g**	**g**	H	Ph	H	OMe	Me	Me	Br	*ii*	97
12	**g**	**g"**	H	Ph	H	OMe	Me	^{t}Bu	OTf	*iii*	94
13	**h**	**h**	H	Ph	H	Me	Me	Me	Br	*ii*	95
14	**h**	**h"**	H	Ph	H	Me	Me	^{t}Bu	OTf	*iii*	92
15	**i**	**i"**	H	4-NO_2-Ph	-$(CH_2)_4$-		H	^{t}Bu	OTf	*iii*	98
16	**j**	**j**	H	OBn	H	OMe	Me	Me	Br	*ii*	97
17	**k**	**k**	H	OBn	H	Me	OMe	Me	Br	*ii*	97
18	**l**	**l**	H	OBn	H	Me	Me	Me	Br	*ii*	95
19	**l**	**l"**	H	OBn	H	Me	Me	^{t}Bu	OTf	*iii*	92
20	**m**	**m**	Me	4-MeO-Ph	H	OMe	Me	Me	Br	*ii*	85
21	**n**	**n"**	Me	4-MeO-Ph	H	OEt	H	^{t}Bu	OTf	*iii*	80
22	**o**	**o**	Me	Ph	H	OMe	Me	Me	Br	*ii*	95
23	**p**	**p**	4-Cl-Ph	4-MeO-Ph	H	OMe	Me	Me	Br	*ii*	91
24	**r**	**r**	CO_2Me	4-MeO-Ph	H	OMe	Me	Me	Br	*ii*	97
25	**s**	**s"**	CO_2Me	4-MeO-Ph	H	OMe	Me	^{t}Bu	OTf	*iii*	76

[a] Product (**343a**) decomposed in a matter of few hours after preparation.
[b] *i*: CH_2Cl_2, 20^0C, 48 h; *ii*: CH_2Cl_2, -78^0C, 24 h; *iii*: CH_2Cl_2, -78^0C, 1 h; *iv*: MeCN, 20^0 C, 72 h.

3.5.2. *N,N*-Bis(oxyiminium) Cations. Inversion of the Usual Reactivity of Aliphatic Nitro Compounds

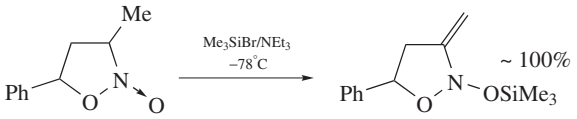
As can be seen from Chart 3.20, the transformation of SENAs into BENAs can include cationic intermediates **B**. In addition to deprotonation of these intermediates giving rise to BENAs, it is worthwhile to consider the possibility of their alternate use and primarily the involvement of these species in C,C-coupling reactions. This problem is directly related to the fundamental problem of "umpolung" of the general reactivity of AN (Chart 3.21).

Actually, the reactions of AN with bases produce reversibly carbanions **A**, which are the major intermediates in the "classical" reactions of AN (Henry, Michael, and Mannich reactions). The reactions of AN with acids afford iminium cations **B** (also reversibly), which are the key intermediates in the Nef reaction

Table 3.20 The effect of nature of base on direction of deprotonation of cationic intermediates derived from six-membered cyclic nitronates

Entry	(**342**, **343**)	(**347**)	R^1	R^2	R^4	R^5	Base	Conditions T, °C/t, h	Yield %,% (**343**)	(**347**)
1	**a**	**a**	H	4-MeO-Ph	OMe	Me	NEt_3	−78/24	93	-
2	**a**	**a**	H	4-MeO-Ph	OMe	Me	Py	−30/24	-	96
3	**a**	**a**	H	4-MeO-Ph	OMe	Me	Py′	−30/72	43	51
4	**a**	**a**	H	4-MeO-Ph	OMe	Me	Py″	0/12	-	28
5	**a**	**a**	H	4-MeO-Ph	OMe	Me	DBU	0/96	-	63[a]
6	**b**	**a**	H	4-MeO-Ph	OEt	H	Py	−30/24	-	91
7	**g**	**b**	H	Ph	OMe	Me	Py	−30/24	-	92
8	**t**	**c**	Me	Ph	OMe	Me	Py	−30/24	-	90
9	**u**	**d**	Me	4-MeO-Ph	Me	Me	NEt_3	−78/24	91	-
10	**v**	**e**	Me	OBn	Me	Me	NEt_3	−78/24	80	-
11	**w**	**f**	Me	4-MeO-Ph	OMe	Me	iPr_2NEt	−78/2.5	52	-

[a]Conversion 80%. *Si*-$SiMe_3$; X=Br; Py-pyridine; Py′-2,6-dimethylpyridine; Py″-2,6-*tret*.butyl-4-methyl-pyridine.



Scheme 3.203

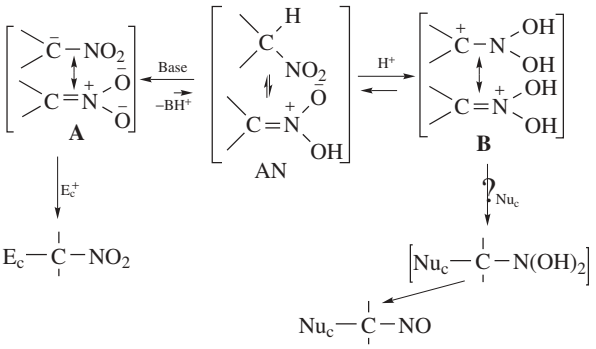


Chart 3.21 Umpolung of reactivity of AN in C,C-coupling interaction.

(427, 476). However, the more important question of whether AN can be used in C,C-coupling reactions with nucleophiles remains open. It should be noted that Japanese researchers demonstrated in several studies that these transformations can be performed for benzene and certain electron-rich arenes (477). Just the same, this procedure requires severe conditions (the use of superacids at high

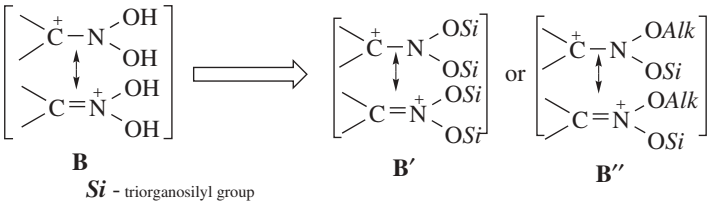


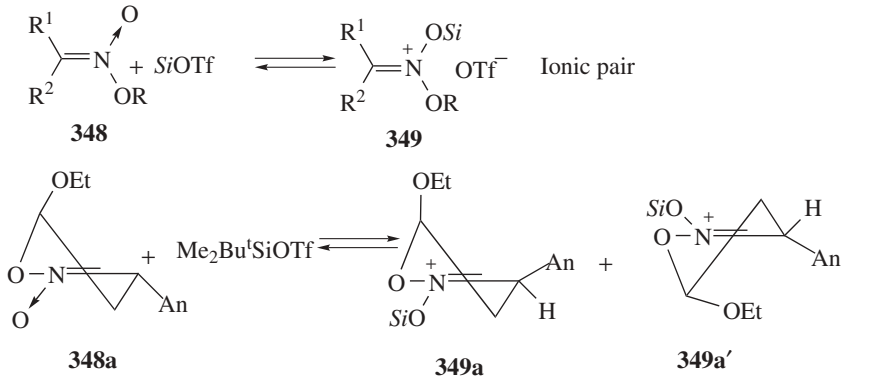
Chart 3.22 New approach to the generation of iminium cations from AN.

temperature) and, consequently, it is not promising as a methodological approach for most of synthetically important carbon-centered nucleophiles $\mathbf{Nu}_c$. In this connection, the use of AN silylation instead of AN protonation and, consequently, the use of aprotic solvents holds considerable promise. Recently, this approach has been developed by Russian researchers (274) (Chart 3.22).

It can easily be seen that intermediates **B′** and **B″** are generated, respectively, in silylation reactions of SENAs (Chart 3.20) or alkyl nitronates (Scheme 3.202). To estimate the efficiency of this approach, it is necessary to reveal whether cationic intermediates **B′** and **B″** can exist as kinetically independent species.

3.5.2.1. Direct Low-temperature Observation of Bis-N,N-Oxyiminium Cations
For this purpose, the reactions of various types of nitronates (**348**) with trialkylsilyl triflates in CD_2Cl_2 were studied by low-temperature NMR spectroscopy. More than 10 iminium cationic intermediates (**349**) were detected (Scheme 3.204) (478).

It should be noted that the signals of the –CH=N fragment in all cations (**349**) are characterized by strong paramagnetic shifts compared to the analogous resonances of the starting nitronates (**348**) (the signal for the proton is shifted



Scheme 3.204

by more than 1.5 ppm, whereas the signal for ^{13}C is shifted by approximately 30 ppm). These chemical shifts are similar to those obtained earlier for cations generated by silylation of nitrones (479).

Seven of the observed cations (**349**) are derivatives of six-membered cyclic nitronates. The predominant conformations of the starting nitronate and the corresponding cation are identical for almost all of these species, the NMR spectra showing only one set of signals for each nitronate and the derived cation. By contrast, silylation of nitronate (**348a**) gives rise to two conformers of cation (**349a**) and (**349a′**), which are observed separately and, consequently, have an abnormally high barrier of the ring inversion.

For four cations (**349b–e**), the thermodynamic parameters of the equilibrium (Table 3.21) and the exponents n in the equation of the equilibrium constant were determined.

These data show that the iminium cations exist in dichloromethane as ion pairs. Apparently, this is the reason why the ring inversion in cation (**349a**) is hindered, taking into account that the ring inversion requires the energy-consuming cleavage of the ion pair.

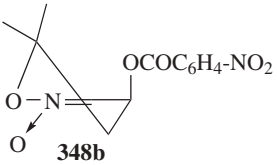
Several facts, which are of importance for the use of cations (**349**) in C,C-coupling reactions, follow from the existence of these cations as ion pairs.

First, a decrease in the concentration of solutions would lead to a shift of the equilibrium (**348**⇆**349**) toward initial nitronates (**348**). Second, high negative ΔS° of the equilibrium demonstrate that an increase in the temperature also would shift the equilibrium (**348**⇆**349**) toward nitronates. Hence, it is advantageous to perform the C,C-coupling reactions of cations (**349**) at low temperatures and at high concentrations of the molecules involved in the reaction.

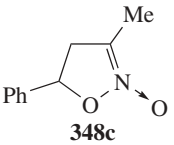
As can be seen from Scheme 3.204, it is necessary to use powerful LA as catalysts for the generation of cationic intermediates (**349**). However, similar acids are hydrolytically very unstable.

Table 3.21 Thermodynamic parameters of equilibrium (348) + SiOTf⇄(349)

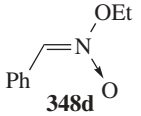
Equilibrium	n (averaged)	Range of T, K	ΔG^0_{293}, kJ/mol	ΔH^0, kJ/mol	ΔS^0, J/mol•K
348b⇆**349b**	0.98 ± 0.05	183 ÷ 207	18.0 ± 1.1	− 35.5 ± 0.4	−182.7 ± 2.4
348c⇆**349c**	1.04 ± 0.08	190 ÷ 220	1.7 ± 3.3	− 29.0 ± 1.3	−104.8 ± 6.7
348d⇆**349d**	1.04 ± 0.06	180 ÷ 210	12.2 ± 2.3	− 26.4 ± 0.9	−131.7 ± 4.8
348e⇆**349e**	0.84 ± 0.05	210 ÷ 240	9.3 ± 2.3	− 59.5 ± 1.0	−234.9 ± 4.3



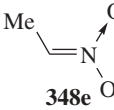
348b



348c

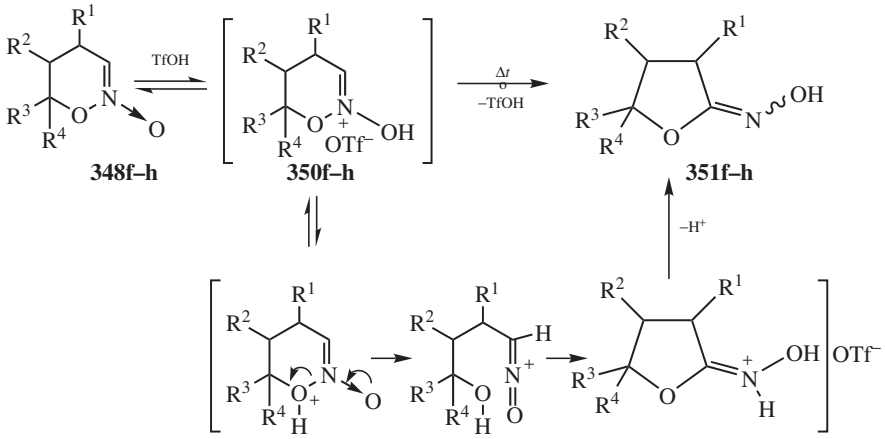


348d



348e

$$K = \frac{[349]^n}{[348]\,[Si\text{OTf}]} \quad (1)$$



348f–h **350f–h** **351f–h**

	R^1	R^2	R^3	R^4	Yield (%) **(351)**
f	Ph	H	Me	Me	93
g	Ph	$-(CH_2)_4-$		H	83
h	Ph	Ph	Ph	H	79

Scheme 3.205

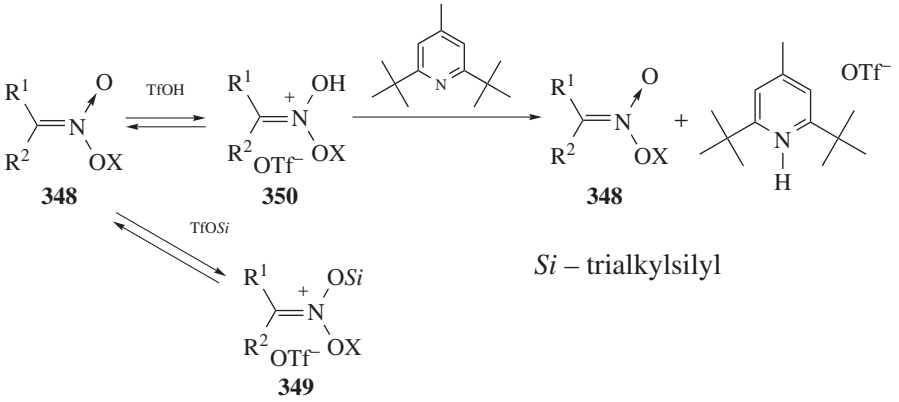
This is responsible for the formation of *N*-hydroxyiminium cations (**350f–h**) as by-products, which was established by silylation of six-membered cyclic nitronates (Scheme 3.205).

In low-temperature NMR spectra, cations (**350f–h**) are observed separately from their *N*-siloxy analogs (**349f–h**). At higher temperatures, cations (**350f–h**) are transformed into respective α-tetrahydrofuranone oximes (**4f–h**), which were not characterized in Reference (480). (An analogous narrowing of the ring in seven-membered cyclic nitronates was described in the study (170) (Scheme 3.125)).

To suppress the side reaction (**348**⇄**350**), which hinders the generation of cations (**349**) and thus their involvement in C,C-coupling reactions, it is advantageous to add Brönsted bases, for example, 2,6-bis(*tert*-butyl)-4-methylpyridine (Scheme 3.206) (478). These bases can efficiently bind triflic acid.

3.5.2.2. Kinetic Studies of C,C-Coupling Reactions of Bis- N,N-Oxyiminium Cations with C-Centered Nucleophiles To estimate the electrophilicity of cationic intermediates (**349**), the reaction kinetics was measured for several test cations with nucleophiles, which were characterized in the study (481) as reference compounds, (Table 3.22) (478).

The kinetic measurements were performed by NMR monitoring of the reaction mixtures in the temperature range from −90 to −40°C. All of the reactions under study were approximated by the second-order rate equation.



Scheme 3.206

The activation parameters and a few other data characterizing the electrophilicity of cationic intermediates (**349**) are given in Table 3.23.

As can be seen from Table 3.23, the electrophilicities ***E***, which were determined according to Mayr's scheme (482), vary in a wide range and depend mostly on the substituents at the C-3 atom (see the last entry in Table 3.23). On the whole, the electrophilicities *E* for bis-oxyiminium cations are in the same range as those for classical iminium cations (482) (e.g., see Ref. 483 for $[C{=}NMe_2]^+$, $E = -6.69$).

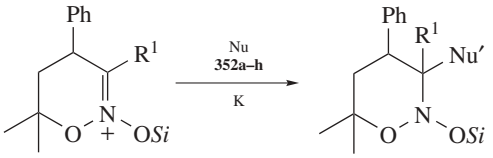
Steric hindrance in the silyl groups of cation (**349**) and nucleophile (**352**) has virtually no effect on the rate constant of the C,C-coupling reaction. Hence, it can be concluded that, at least for silyl-containing nucleophiles (**352**), elimination of the trialkylsilyl group from cationic intermediate **A** is not the rate-determining step of the reaction sequence (Scheme 3.207).

As mentioned in the previous section, the position of the equilibrium between the starting nitronates and the corresponding cationic intermediates are very labile and depend on various factors. However, a preliminary analysis demonstrates that C,C-coupling with nucleophiles can occur for cationic intermediates derived from different types of nitronates.

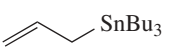
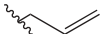
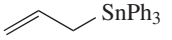
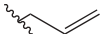
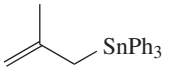
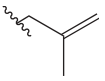
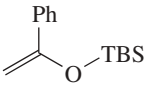
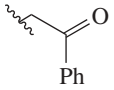
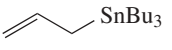
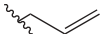
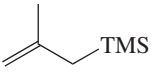
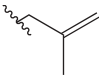
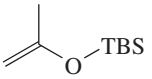
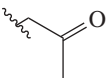
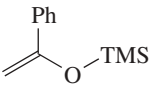
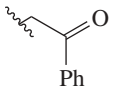
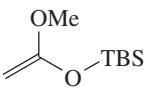
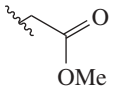
3.5.2.3. Intermolecular C,C-Coupling of Bis-N,N-Oxyiminium Cations with C-Centered Nucleophiles Readily available silyl ketene acetals $CH_2{=}C(OMe)$-O*Si*, where *Si* is Me_3Si or Me_2Bu^tSi, were used as efficient test nucleophiles in C,C-coupling reactions. These reactions with silyl ketene acetal, as well as with other nucleophiles containing *Si* as the leaving group, can be performed under very mild conditions in the presence of catalytic amounts of silyl Lewis acids. (Catalysis of C,C-coupling reactions by silyl Lewis acids was discussed in detail in Reference 297)

Both silyl- and alkyl esters derived from *primary* AN are readily involved in C,C-coupling reactions with silyl ketene acetal (Scheme 3.208, Eq. 1) (484).

Table 3.22 The C,C-coupling of iminium cations 349 with reference nucleophiles



349f,f′,i **353a–h**

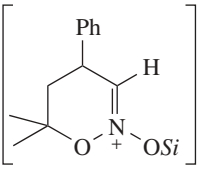
Cation	R^1	*Si*	Nu	Nu'	Product
(**349f**)	H	TBS	 **352a**		(**353a**)
(**349f**)	H	TBS	 **352e**		(**353a**)
(**349f**)	H	TBS	 **352f**		(**353c**)
(**349f**)	H	TBS	 **352g**		(**353 d**)
(**349f′**)	H	TMS	 **352a**		(**353e**)
(**349f′**)	H	TMS	 **352b**		(**353f**)
(**349f′**)	H	TMS	 **352c**		(**353b**)
(**349f′**)	H	TMS	 **352d**		(**353 g**)
(**349i**)	Me	TBS	 **352h**		(**353 h**)

[a] TMS–$SiMe_3$; TBS–$SiMe_2Bu^t$.

Table 3.23 The kinetic and activation parameters for (349 + 352) C,C-couplings

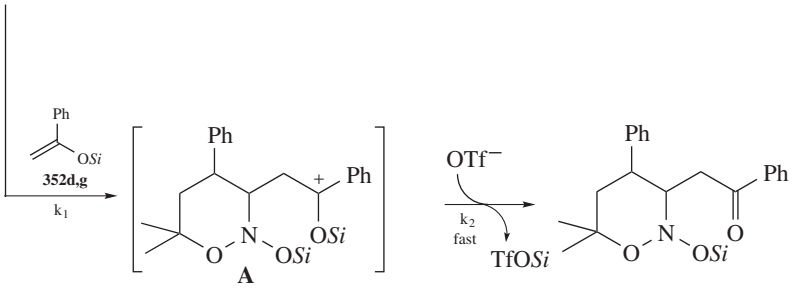
Cat. 4	Nucleo-phile	Product	Ref. N and (s) parameters (481)	E	k(20° C), $mol^{-1} \cdot s^{-1}$	$\Delta G^{\#}_{20C}$, kJ/mol	$\Delta H^{\#}$, kJ/mol	$\Delta S^{\#}$, J/mol·K
	(**352a**)	(**353a**)	5.46 (0.89)	−3.69	37.7	62.9 ± 3.7	42.9 ± 1.5	−68.1 ± 7.4
(**349f**)	(**352e**)	(**353a**)	3.09 (0.90)	−3.37	0.55	73.2 ± 4.0	49.5 ± 1.8	−80.7 ± 7.8
	(**352f**)	(**353c**)	5.13 (0.90)[a]	−4.21	6.55	67.1 ± 4.4	45.2 ± 1.9	−74.9 ± 8.6
	(**352 g**)	(**353 d**)	6.22 (0.96)	−6.08	1.37	70.9 ± 1.7	51.1 ± 0.7	−67.6 ± 3.3
(**349f′**)	(**352a**)	(**353e**)	5.46 (0.89)	−3.70	36.6	63.0 ± 3.6	41.7 ± 1.5	−72.4 ± 7.2
	(**352b**)	(**353f**)	4.41 (0.96)	−4.54	0.74	72.4 ± 2.3	39.2 ± 1.0	−113.6 ± 4.4
	(**352c**)	(**353b**)	5.41 (0.91)	−5.45	0.92	71.9 ± 2.3	43.9 ± 1.0	−95.6 ± 4.3
	(**352 d**)	(**353 g**)	6.22 (0.96)	−5.99	1.65	70.5 ± 1.7	51.7 ± 0.7	−64.1 ± 3.1
(**349i**)	(**352 h**)	(**353 h**)	10.32 (0.79)	−10.21	1.23	71.2 ± 1.1	31.4 ± 0.5	−135.9 ± 2.3

[a] s value for (**352f**) was estimated as the same as for (**352a**) and (**352e**) in Reference 481.



349f,f′

for 349f, 353d: *Si* – Me_2Bu^tSi
for 349f′, 353g: *Si* – Me_3Si

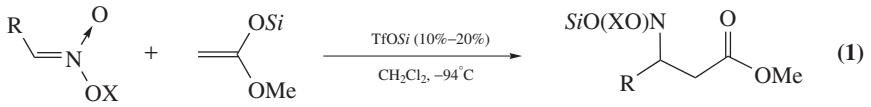


C,C – Coupling k (–50°C, $M^{-1}S^{-1}$)

349f + 352d 353d → $1.38 \times 10^{-3} \pm 2.9 \times 10^{-4}$
349f + 352g 353d → $1.40 \times 10^{-3} \pm 4.0 \times 10^{-4}$
349f′+ 352g 353g → $1.41 \times 10^{-3} \pm 0.4 \times 10^{-4}$

for 352d: *Si* – Me_2Bu^tSi
for 352g: *Si* – Me_3Si

Scheme 3.207

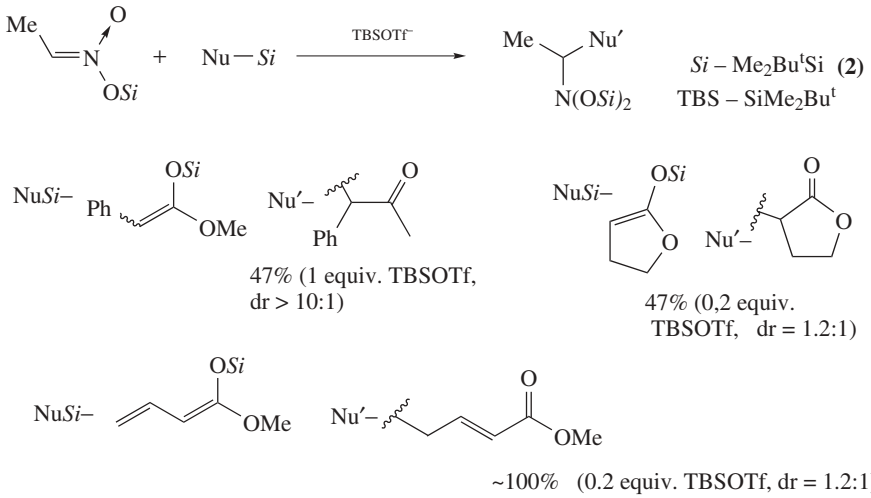


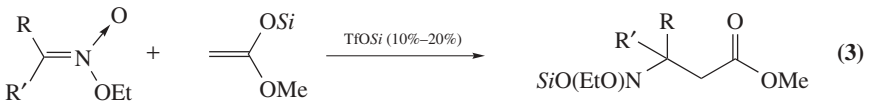
(1)

Si – Me_2Bu^tSi; X = *Si*: R = H (82%)*; Me (86%); Et (87%); $PhCH_2$ (89%); $MeO_2C(CH_2)_2$ (92%); $NO_2(CH_2)_3$ (85%); Ph (89%); 4-$MeOC_6H_4$ (87%); SiO-N = $CH(CH_2)_3$ (58%)**

X = OEt: R = $PhCH_2$ (61%); Et (57%).

*, the nitronate was prepared in situ
**, bis-C, C-coupling





(3)

Si – Me_2Bu^tSi; R = R′ = Me (70%); instead R and R′ – $(CH_2)_4$– (63%); –$(CH_2)_5$– (71%)
R = Me, R′ = $(CH_2)_2CO_2Me$ (43%)

Scheme 3.208

The reaction is performed at −94°C in dichloromethane and, generally, in the presence of catalytic amounts of silyl triflate. Although the reaction can be performed with trimethylsilyl derivatives as well, it is advantageous to use hydrolytically more stable $SiMe_2Bu^t$ derivatives. The reaction of 1,4-dinitrobutane can afford both mono- and bis-C,C-coupling products.

Two procedures were developed for C,C-coupling reactions of silyl esters of primary AN. One approach involves two steps and the synthesis of intermediate SENAs according to standard procedures. Another procedure is based on the one-pot reaction of AN with the DBU/TBSOTf system in a ratio of 1:1.1 followed by the addition of silyl ketene acetal and a catalytic amount of TBSOTf.

SENAs derived from *primary* AN can undergo C,C-coupling reactions with other silyl-containing nucleophiles (Eq. 2), which was exemplified by the reaction of SENA derived from nitroethane. It should be noted that high diastereoselectivity can sometimes be achieved by introducing a substituent at the reaction center of the nucleophile.

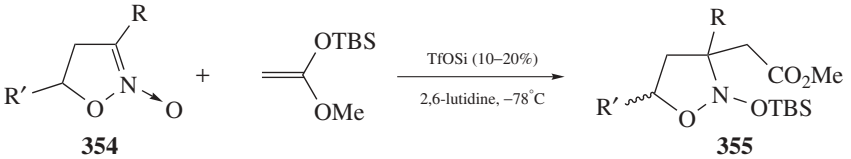
The C,C-coupling reactions of ambident nucleophile $CH_2{=}CHCH{=}(OMe)OSi$ occur regioselectively at the terminal C=C bond, but the reactions are characterized by low stereoselectivity.

SENAs derived from *secondary* AN are not involved in catalytic C,C-coupling reactions with silyl ketene acetals. This is possibly due to a decrease in both the effective concentration of the cationic intermediate (the steric effect) and its lower level of electrophilicity (see the lower entry in Table 3.23).

However, C,C-coupling reactions of sterically less hindered alkyl nitronates derived from *secondary* AN with silyl ketene acetal were successfully performed (Eq. 3). These reactions produced the target "mixed" nitroso acetals in moderate yields.

Catalytic C,C-coupling reactions with *five-membered cyclic* nitronates were reported (485) (Scheme 3.209).

The process was studied in sufficient detail for 3,5-disubstituted nitronates (**354**). 2,6-Lutidine is added to bind TfOH as a by-product. Because of this addition the temperature of C,C-coupling can be raised to −78°C, thus simplifying



354 **355**

R	R′	Yield %	dr
Me	Ph	77	3.5:1
Et	Ph	76	3.6:1
$PhCH_2$	Ph	71	2.3:1
$PhCH_2$	OEt	93	One isomer
n-C_6H_{13}	Ph	91	4:1
Me	CO_2Me	73	10:1
$MeO_2C(CH_2)_2$	Ph	50	3:1

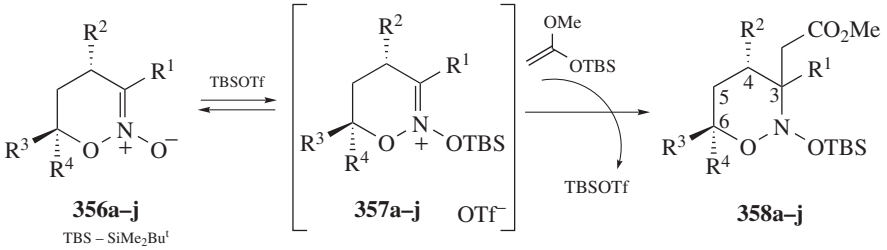
Scheme 3.209

the process. Target isoxazolidines (**355**) were prepared in rather high yields. The diastereoselectivity of the transformation (**354**→**355**) substantially depends on the nature of the substituents.

It should be emphasized that most of isoxazolidines shown in Scheme 3.209 cannot be prepared according to the alternative [3 + 2]-cycloaddition scheme with the use of the corresponding acyclic nitronates (for more details, see Section 3.4.3.1.2).

The C,C-coupling reactions of *six-membered* cyclic nitronates were studied in most detail (274, 478). Here silyl ketene acetal was also used as the test nucleophile. The configurations of most of the starting nitronates and the resulting nitroso acetals were determined by NMR spectroscopy and X-ray diffraction, and also a conformational analysis was performed (see Tables 3.24 and 3.25).

Table 3.24 C–C coupling of nitronates (356a–j) with silylketene acetal. (An–4–MeO–C_6H_4)



Entry	Nitronate **356**	R^1	R^2	R^3	R^4	Oxazine **358**	Yield, %	Ratio of stereoisomers[a]
1	**a**	H	Ph	Me	Me	**a**	91	-
2	**b**	H	Me	Me	Me	**b**	88	-
3	**c**	H	Ph	OMe	Me	**c**	91	-
4	**d**	H	An	H	OEt	**d**	93	-
5	**e**	H	An	OEt	H	**e + e**	88	1.5:1
6	**f**	H	OBz	Me	Me	**f + f' + f**	88	19:1:2[b]
7	**g**	H	OCO-C_6H_4-NO_2-*p*	Me	Me	**g + g' + g**	92	20:1.5:1[c]
8	**h**	Me	H	H	H	**h**	95	-
9	**i**	Me	H	Me	Me	**i**	90	-
10	**j**	Me	Ph	Me	Me	**j**	92	-

[a] Established by quantitative analysis of ^{1}H NMR spectra of crude product.

[b] After column chromatography pure (**358f**) (77%) as well as inseparable mixture of (**358f''**) and (**358f'**) (11%) were isolated (**358f'** : **358f''**) ≈ 1:2. Upon the storage in $CDCl_3$ at r.t. for 3 weeks (**358f**) was partially converted into (**358f''**) (**358f** : **358f''** = 3:2).

[c] After column chromatography pure (**358f**) (82%) and an inseparable mixture of its invertomer. (**358 g''**) and diastereoisomer (**358 g'**) was also isolated in 10% yield (**358 g'** : **358 g''** ≈ 3:2). Upon the storage in $CDCl_3$ at r.t. for 4 weeks (**358 g**) was partially converted into (**358 g''**) (**358 g** : **358 g''** = 1:1).

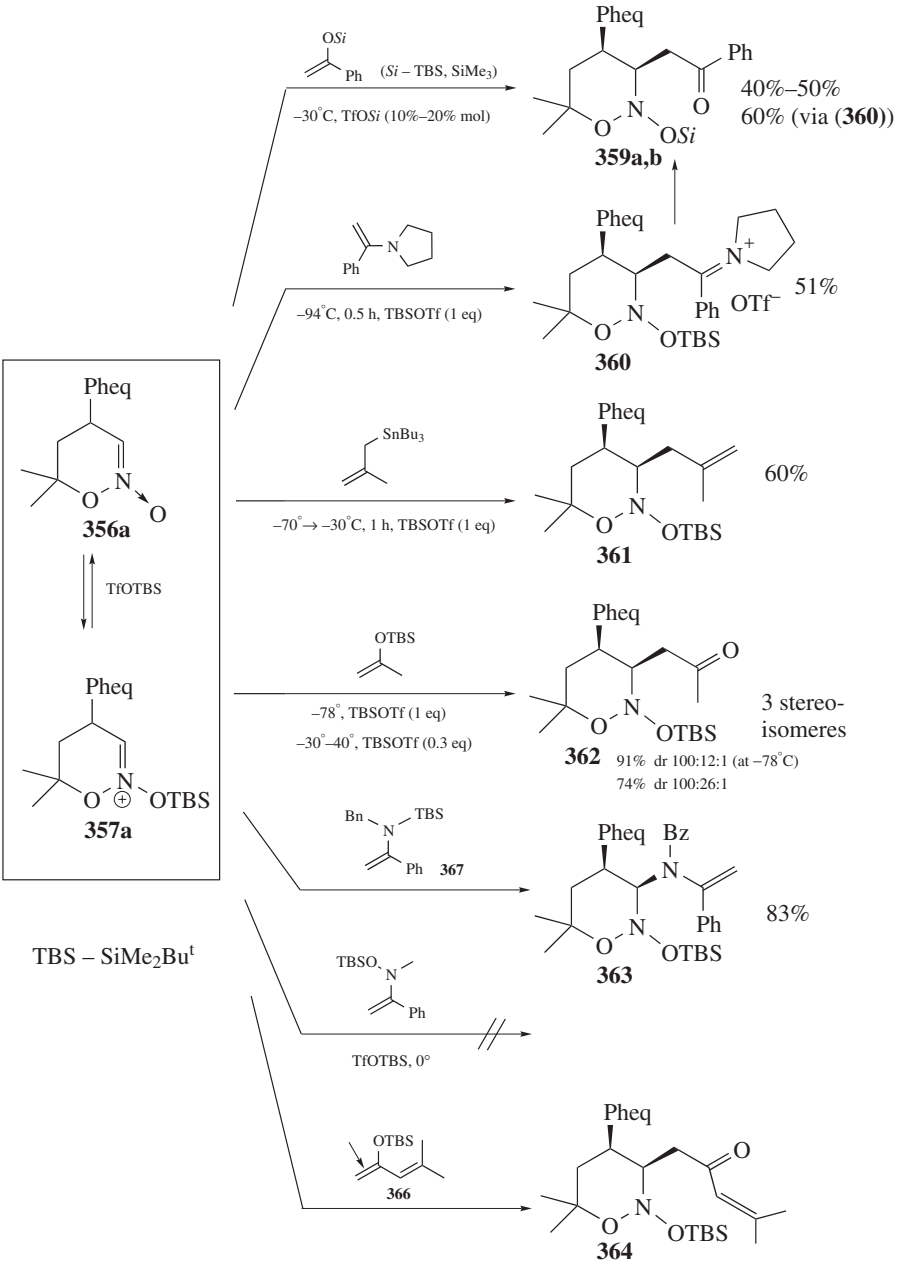
Table 3.25 Stereochemical outcome of coupling of nitronates (356) with nucleophiles (see Table 3.24 and Scheme 3.210)

Entry	Nitronate **356**	R^2 (position)[a]	Tetrahydro [4H]-Oxazines	Configuration of R^1 relatively to R^2 (position of R^1)[a]	Configuration of OSi in relation to R^1 (position of OSi)
1	**a**	Ph (eq)	**358a**	*trans* (eq)	*trans* (eq)[b]
2	**b**	Me(eq)	**358b**	*trans* (eq)	*trans* (eq)[b]
3	**c**	Ph (eq)	**358c**	*trans* (eq)	*trans* (eq)[c]
4	**d**	An (ax)	**358 d**	*cis* (ax)	*trans* (ax)[c]
5	**e**	An (eq)	**358e**	*cis* (eq)	*trans* (eq)[b]
			358e′	*trans* (eq)	*trans* (eq)[b]
6	**f**	OBz (ax)	**358f**	*cis* (eq)[c]	*cis* (eq)[c]
			358f′	*trans* (eq)	*trans* (eq)[b]
			358f′′	*cis* (ax)[d]	*trans* (eq)[d]
7	**g**	OCO-C_6H_4-NO_2-p (ax)	**358g**	*cis* (eq)[d]	*cis* (eq)[d]
			358g'	*trans* (eq)	*trans* (eq)[b]
			358g′′	*cis* (ax)[c]	*trans* (eq)[c]
8	**h**	H	**358h**	-	*trans* (eq)[b]
9	**i**	H	**358i**	-	*trans* (eq)[b]
10	**j**	Ph (eq)	**358j**	*trans* (eq)[c]	*trans* (eq)[c]
11	**a**	Ph (eq)	**359a,b**	*trans* (eq)	*trans* (eq)[b]
12	**a**	Ph (eq)	**360**	*trans* (eq)	*trans* (eq)[b]
13	**a**	Ph (eq)	**363**	*trans* (eq)[c]	*cis* (ax)[c]
14	**a**	Ph (eq)	**361**	*trans* (eq)	*trans* (eq)[b]

[a]Established by NMR.
[b]Established by similarity of NMR data with analogous NMR data of (**358c**)
[c]Established by X-ray data
[d]Stereochemical assignment for (**358f′′**) and (**358g**) were based on the close similarity of their NMR spectral pattern with that of the (**358g′′**) and (**358f**) respectively.

It should be noted that specially purified individual stereoisomers of six-membered cyclic nitronates were used in coupling with silyl ketene acetal. Hence, the mechanistic model of the C,C-coupling reaction can be discussed on the basis of the configurations of the stereocenters of the starting nitronates of intermediate cations (**357**) (see Section 3.5.2.1), and the resulting tetrahydro-oxazines (**358**) (for more details, see below). It should be noted that most of C,C-coupling reactions of six-membered cyclic nitronates with silyl ketene acetal are characterized by a very high diastereoselectivity.

Six-membered cyclic nitronates can be involved in C,C-coupling reactions with other C-centered nucleophiles having high nucleophilicity on Mayr's scale (481). This was demonstrated by the reactions of nitronate (**356a**) (Scheme 3.210).


Pheq
356a
TfOTBS
Pheq
357a
OTBS
TBS – SiMe2But
OSi
Ph
(Si – TBS, SiMe3)
–30°C, TfOSi (10%–20% mol)
Pheq
Ph
O
N
O
OSi
359a,b
40%–50%
60% (via (360))
Ph
N
–94°C, 0.5 h, TBSOTf (1 eq)
Pheq
N+
Ph
OTf–
51%
O
N
OTBS
360
SnBu3
–70°→ –30°C, 1 h, TBSOTf (1 eq)
Pheq
O
N
OTBS
361
60%
OTBS
–78°, TBSOTf (1 eq)
–30°–40°, TBSOTf (0.3 eq)
Pheq
O
N
OTBS
362
91% dr 100:12:1 (at –78°C)
74% dr 100:26:1
3 stereo-isomeres
Bn
N
TBS
Ph
367
Pheq
Bz
N
Ph
O
N
OTBS
363
83%
TBSO
N
Ph
TfOTBS, 0°
OTBS
366
Pheq
O
N
OTBS
364

Scheme 3.210

For example, carbonyl derivatives (**359a,b**) can be prepared by the reaction of cation (**357a**) or by other triorganosilyl analogs with silyl enolates derived from acetophenone. Target nitroso acetal (**359**) can also be synthesized through the intermediate iminium salt (**360**) by C,C-coupling of cation (**357a**) with 1-phenyl-1-*N*-pyrrolidinylethylene.

Among other C,C-coupling reactions shown in Scheme 3.210, the reaction of cation (**357a**) with diene (**366**) can be noted, which occurs regioselectively at the terminal C,C double bond.

The reaction of nitronate (**356a**) with *N*-silylenamine (**367**) is of particular interest. This process also occurs stereoselectively but by N,C-coupling. It should be noted that the resulting product (**363**) has the amino group and the trialkylsiloxy fragment in *trans* configuration.

Detailed configurational and conformational analyses of the starting six-membered cyclic nitronates (**356**) of cationic intermediates (**357**), and C,C-coupling products (**357 + Nu**), taking into account slow nitrogen inversion (I_N) in nitroso acetals (see Section 3.4.3.4.4), made it possible to propose a mechanistic model based on the stereochemical outcome of the C,C-coupling process (Chart 3.23).

Evidently, the stereoselectivity of the process is determined by the preference of the distal approach of the nucleophile (Nu) to the C-6 atom in the predominant conformation of cation (**357**) (Chart 3.23, *a*). In the resulting nitroso acetal, the nitrogen lone pair and the Nu′ fragment are in a *trans* configuration.

It should be noted that exactly the same stereochemical outcome can be obtained after the proximal approach of the nucleophile (Nu) to the C-6 atom in the minor conformation of cation (**357′**) (Chart 3.23, *a*). However, this seems to be unlikely for a number of reasons.

First, the inversion of cations (**357**) has a high barrier (see Scheme 3.204, cation (**349a**)), and two conformers can be independently observed in the temperature range, where their C,C-coupling generally occurs.

Second, the diastereomers ratio in C,C-coupling products of cation (**349**) with silyl ketene acetal exactly corresponds to the conformers ratio for this cation (**349a:349a′**), that is, it is evident that the interaction occurs through the distal approach of silyl ketene acetal to the C-6 atom of observed conformations **a** and **a′** of the above mentioned cation.

Finally, calculations demonstrated (162) that the distal approach of dipolarophiles to the C-6 atom of the dipole is also preferable in [3 + 2]-cycloaddition reactions of six-membered cyclic nitronates.

The *trans* configuration of the nitrogen lone pair and the Nu′ fragment in nitroso acetals can be attributed to the anomeric effect of this pair (see Chart 3.23, *b*).

The most surprising fact is that the N,C-coupling reaction (**356a→363**) leads to a change in the mutual orientation of the respective Nu′ fragment and the nitrogen lone pair. Evidently, conclusions cannot be drawn based on only one example. However, it can be hypothesized that the stereocontrol of this process

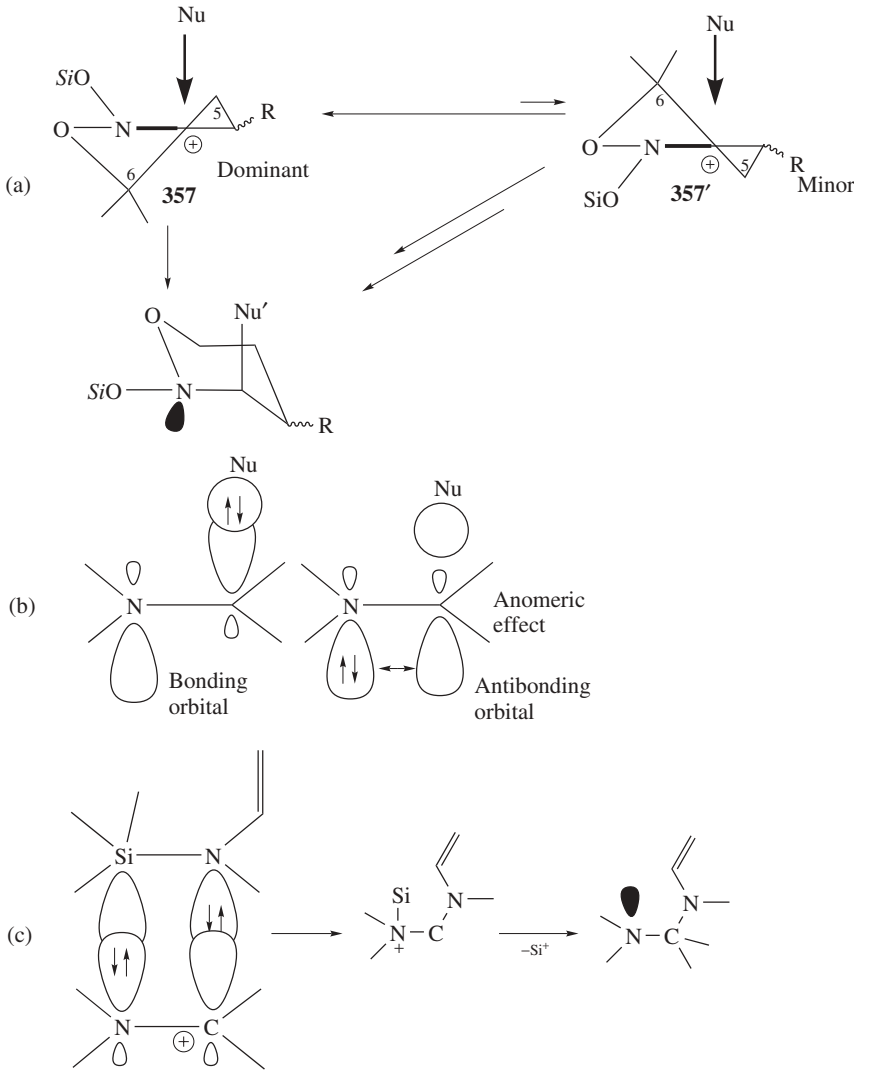
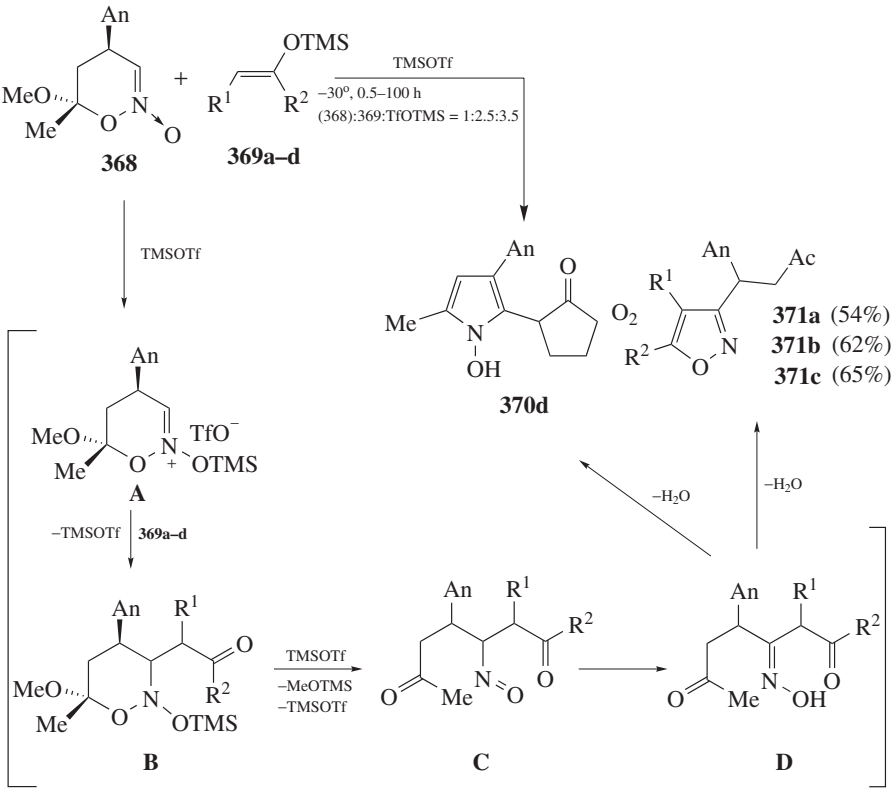


Chart 3.23 Mechanistic interpretation of C,C-coupling of six-membered cyclic nitronates with nucleophiles.

is performed through coordination of the nitrogen lone pair and the silicon atom of the nucleophile in the transition state (see Chart 3.23, *c*).

The influence of catalytic C,C-coupling of six-membered cyclic nitronates can be used, under more drastic conditions, for the construction of nitrogen-containing heterocycles via cascade chemical transformations (see, e.g., the coupling reaction of nitronate (**368**) with silyl enolates (**369a–d**) in the presence of trimethylsilyl triflate (154) (Scheme 3.211)).



An - 4-MeO-C_6H_4; TMS - $SiMe_3$; **369a** - R^1 = H, R^2 = Me; **369 b** - R^1 = H, R^2 = An; **369**c - R^1, R^2 = $(CH_2)_4$; **369d** - R^1, R^2 = $(CH_2)_3$.

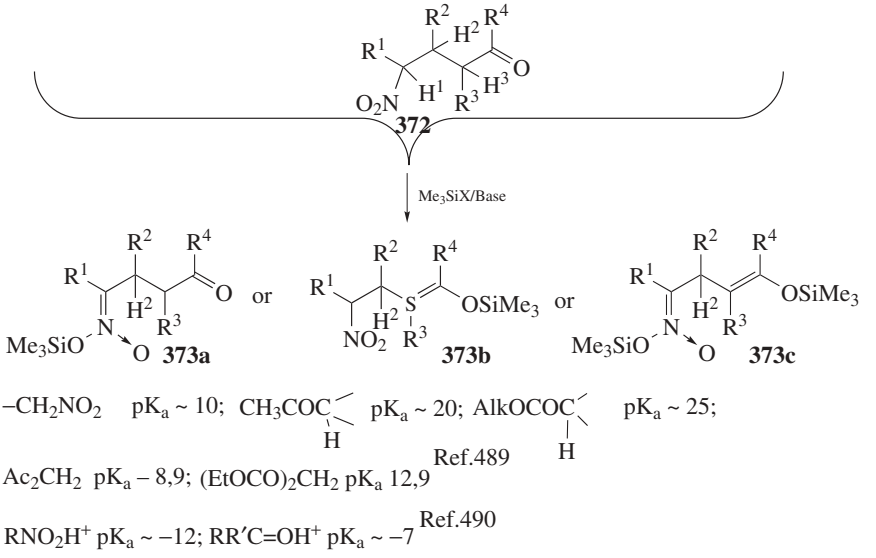
Scheme 3.211

The formation of a new C,C bond (intermediate **B**) is the key step in these transformations. In the presence of Lewis acids, nitroso acetal **B** is rearranged to give diketo oxime **D**.

Depending on the steric effects of the substituents R^1 and R^2, the latter intermediate undergoes cyclization to form either isoxazoles (**371a–c**) or N-hydroxypyrrole (**370 d**) after elimination of water.

3.5.2.4. Intramolecular Trapping of Bis-N,N-Oxyiminium Cations Special γ-functionalized nitro compounds (**372**) were constructed with the aim of performing intramolecular trapping of bis-*N,N*-siloxyiminium cations prepared in process of double silylation of (**372**). Monosilylation of the latter compounds can afford different silyl derivatives (**373a–c**) (Scheme 3.212) (486, 487).

The nature of products (**373**) depends on a number of factors (486, 487). As can be seen from the lower part of the scheme, the reactions of compounds, in which R^3 is H or alkyl, using weak silyl Lewis acids (X is a poor leaving group)



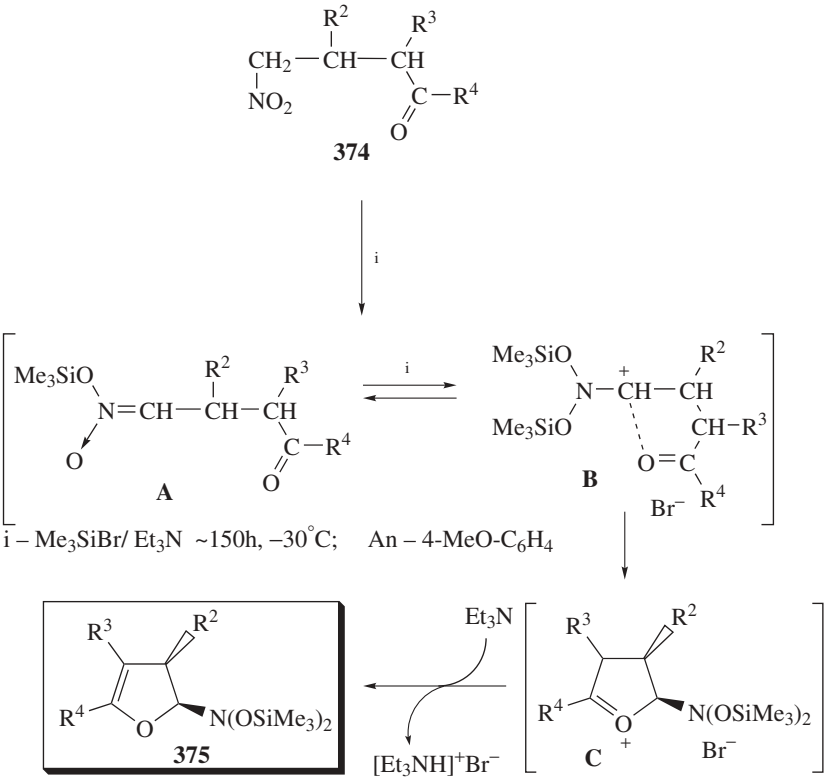
Scheme 3.212

involve deprotonation of the nitro fragment to form SENA (**373a**) as the first step. If R^3 is Ac or CO_2Alk, the rate of deprotonation of the C-1 atom can be similar to that of deprotonation of C-3, and it is difficult to predict the character of the primary silylation product. An increase in the strength of the silylating agent would facilitate the primary attack of a more nucleophilic functional group, whereas the use of a stronger base can, on the contrary, shift the reaction toward initial silylation of the nitro fragment.

Double silylation of the nitro fragment of substrate (**372**) would afford the $[>C{=}N(OSi)_2]^+$ cation, which should be trapped. To hinder deprotonation of this cation, the substrate contains a bulky substituent R^2 at the C-2 atom. *A priori*, based on the data on intermolecular C,C-coupling of the above-mentioned cations, it can be suggested that the introduction of substituents at the C-1 atom should decrease the reactivity of the cation and can adversely affect the thermodynamics of such cations. Consequently, these substituents would hinder the generation as well as trapping of cationic intermediates.

In intramolecular trapping of bis-oxyiminium cations, Me_3SiBr was used as the silylating agent, which makes it possible to smoothly perform silylation of primary AN (see Chart 3.20). A representative group of substrates (**372**) was synthesized for intramolecular trapping of cations (488).

3.5.2.4.1. Intramolecular C,C-Coupling of Bis-N,N-(trimethylsiloxy)Iminium Cations As can be seen from Scheme 3.213, intramolecular C,C-coupling of the nitro fragment and the acetyl group occurs smoothly upon silylation of substrates (**374**) containing the acetyl group at the C-3 atom (153, 292, 470, 489).



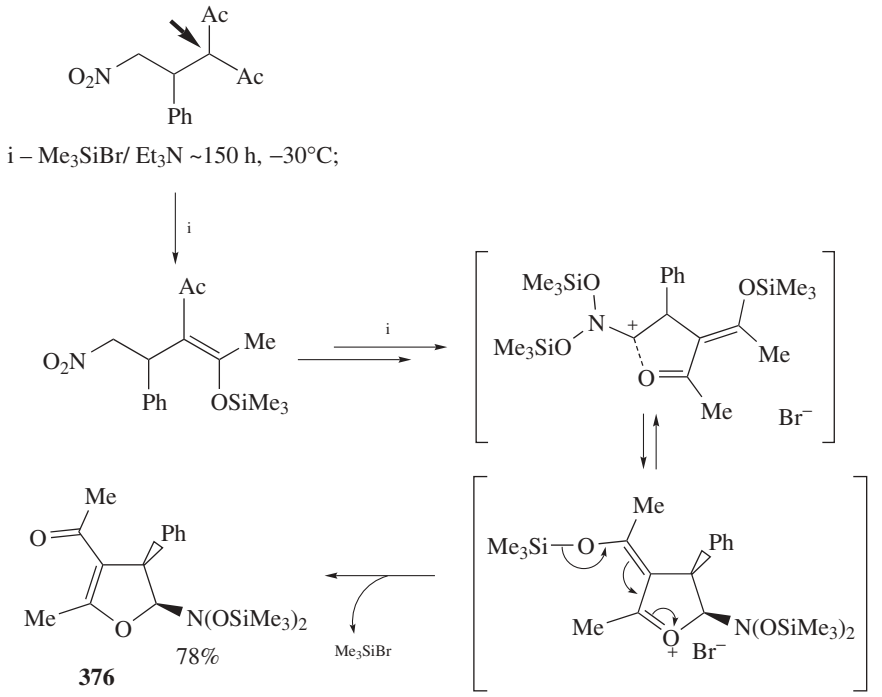
R^2	R^3	R^4	Yield %
An	H	Ph	89
An	H	An	96
An	H	4-NO_2-C_6H_4	23
An	H	4-Me-C_6H_4	92
An	H		85
Ph	Ph	Ph	51
Me	H	Ph	94
Ph	H	Ph	88
4-Cl-C_6H_4	H	Ph	86
4-NO_2-C_6H_4	H	Ph	72

Scheme 3.213

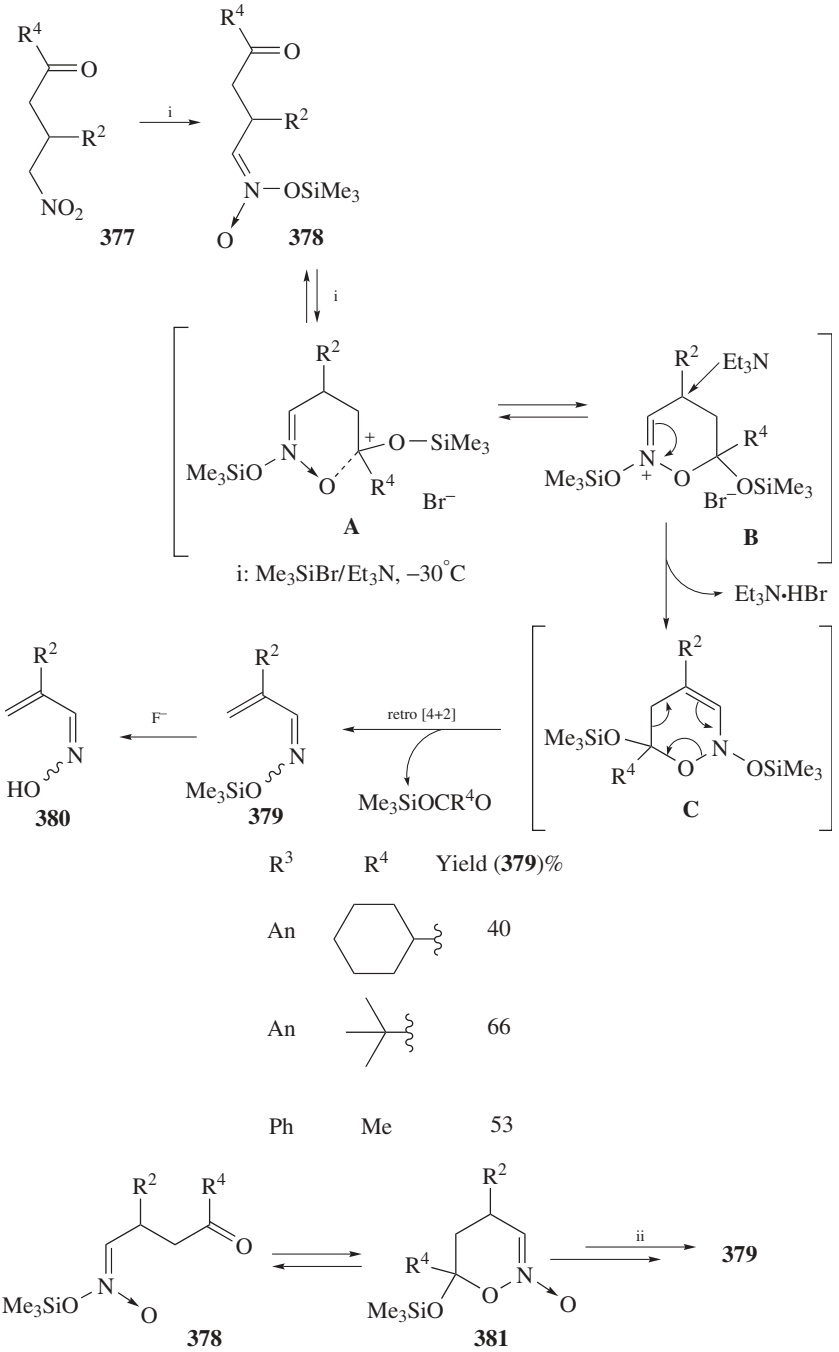
It is reasonable to suggest that SENA **A** is initially generated, and then can undergo a reversible second silylation. The resulting iminium cation **B** undergoes stereoselective intramolecular cyclization to give the cation **C**, whose deprotonation affords dihydrofurans (**375**) containing the nitroso acetal fragment. These target products are generated in high yields, but the substituent R^4 in the starting substrate must necessarily be conjugated with the carbonyl group, thus decreasing the electrophilicity of its carbon atom. If R^2=H, the iminium cation cannot be trapped intramolecularly because of its fast deprotonation.

If two acyl groups are attached to the C-3 atom, the formation of the target dihydrofuran (**376**) occurs apparently through another pathway (Scheme 3.214). In the first step, silylation occurs at the $-CHAc_2$ fragment containing the most active proton. Then the process involves double silylation of the nitro fragment, cyclization of the resulting cation and stabilization of the intermediate accompanied by elimination of trimethylbromosilane (292).

If the substituent R^4 is not conjugated with the carbonyl group (compounds (**377**) in Scheme 3.215), silylation proceeds in a different fashion (153, 292, 470). After the formation of the initial SENAs (**378**), the latter undergo reversible cyclization to give cyclic iminium cations **B**, which are stabilized by deprotonation of the C-4 atom to form the cyclic intermediates 2*H*-5,6-dihydrooxazines **C**.



Scheme 3.214


R4
O
R2
NO2
377
i
N—OSiMe3
O
378
Me3SiO
N
O
+
O—SiMe3
R4
Br–
A
Et3N
R4
OSiMe3
B
i: Me3SiBr/Et3N, –30°C
Et3N•HBr
F–
HO
380
Me3SiO
379
retro [4+2]
Me3SiOCR4O
C
R3
R4
Yield (379)%
An
40
An
66
Ph
Me
53
ii
379
Me3SiO
378
381
ii: silylation and retro [4+2]-cycloaddition

Scheme 3.215

The fragmentation of the latter, after elimination of silyl carboxylate, affords silyl derivatives of conjugated enoximes (**379**) in moderate yields.

Retro-[4 + 2]-cycloaddition of dihydrooxazines of type **C** was considered in Section 3.5.1.3. An analogous process was described for N-alkyl- (490) or N-trimethylsilyl-2*H*- dihydrooxazines (491). However, *2H*- dihydrooxazines dealt with in studies (490, 491) could be isolated or, at least, characterized. At the same time, accumulation of heteroatoms bound to each other dramatically decreases the stability of intermediates **C**.

The process under consideration could be discussed in terms of ring-chain tautomerism of nitronates (**378**⇄**381**) (see the lower part of Scheme 3.215), the more so that such examples were documented for proton analogs of similar SENA (492). However, both nitronates ((**378**) and (**381**)), which were prepared by independent syntheses, are quite stable, and therefore their isomerization in the presence of a silyl Lewis acid should involve ring-chain tautomerism of cations. Evidently, cyclization of nitronate (**378**) is attributed to high electrophilicity of the carbon atom of the carbonyl group, provided that this group is not involved in the conjugation chain.

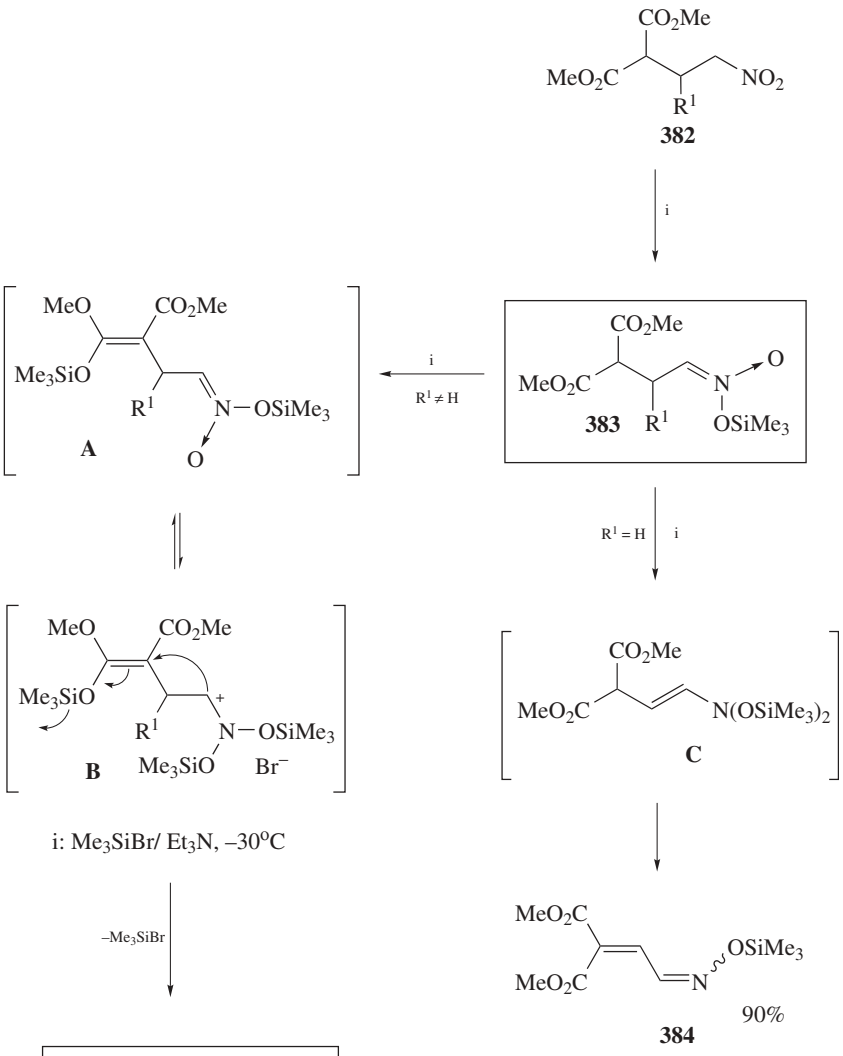
3.5.2.4.2. Intramolecular C,C-Coupling Reactions of Bis-N,N-(trimethylsiloxy) Iminium Cations Here we consider one of the mechanistic schemes of intramolecular C,C-coupling reactions of bis-*N,N*-(siloxy)iminium cations generated by silylation of β-nitroalkylated derivatives of malonic ester (**382**) (Scheme 3.216).

The initially formed SENA (**383a**) (R' = H) undergoes rapid deprotonation at the C-2 atom to give unstable enamine **C** which is rapidly transformed into enoxime (**384**). In the presence of the substituent R′, which shields the C-2 atom, thus hindering its deprotonation, SENAs (**383**) undergo further silylation of both functionalized fragments to give cationic intermediates **B**. The latter undergo intramolecular cyclization accompanied by eliminating trimethylbromosilane to give cyclopropanes (**385**) in good yields (470, 489, 493). The formation of cyclopropanes (**385**) is characterized by strict stereoselectivity (the substituent R′ and the nitroso acetal fragment have a *trans* configuration).

3.5.2.4.3. Selected Features of the Chemistry of N,N-Bis-Trimethylsiloxy-Substituted Cyclopropanes and Dihydrofurans Scheme 3.217 shows selected features of the chemistry of compounds prepared by intramolecular trapping of bis-*N,N*-(trimethylsiloxy)iminium cations.

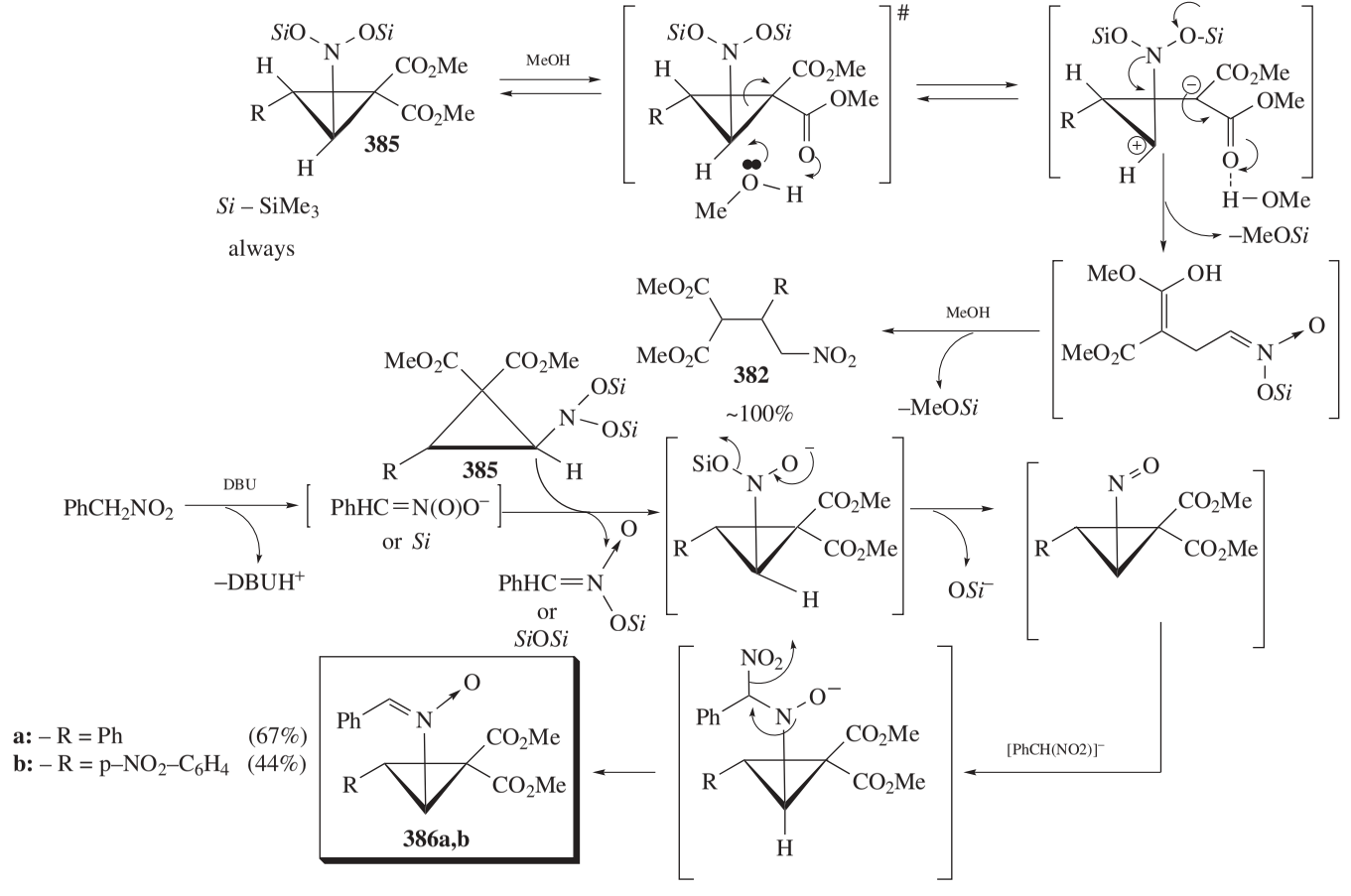
The strained C,C bond in cyclopropanes is prone to heterolysis, particularly, in the presence of substituents stabilizing the resulting charges. These facts can be used to interpret easy methanolysis of cyclopropanes (**385**), resulting in regeneration of the starting functionalized AN (**382**) in high yields (Eq. 1) (493).

The $-N(OSiMe_3)_2$ fragment is an equivalent of the nitroso group. It was demonstrated (493) that cyclopropanes (**385**) can serve as equivalents of the corresponding nitrosocyclopropanes in coupling reactions of the nitroso group with anions of nitro compounds (Eq. 2).

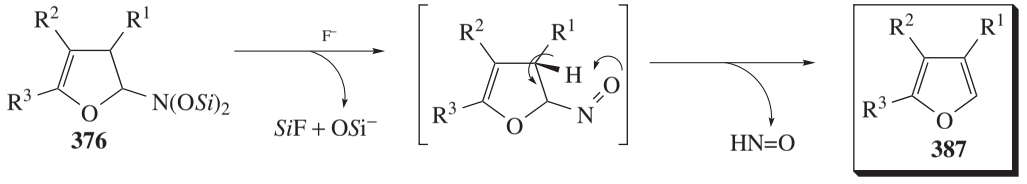


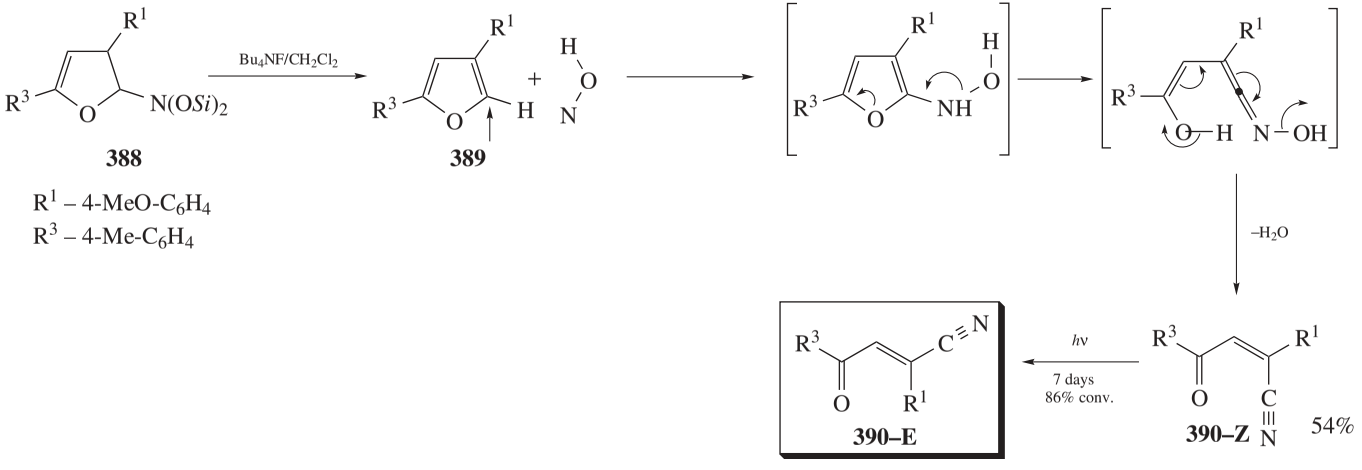
R^1	Yield of (**385**)%
Ph	97
3-MeO-C_6H_4	90
2-MeO-C_6H_4	90
4-MeO-C_6H_4	85
3-NO_2-C_6H_4	95
4-NO_2-C_6H_4	95
4-Cl-C_6H_4	80
4-Me-C_6H_4	96
Me	76

Scheme 3.216


385
MeOH
Si – SiMe3
always
(1)
382
~100%
–MeOSi
DBU
PhCH2NO2
–DBUH+
PhHC=N(O)O–
or Si
PhHC=N
or
SiOSi
OSi–
[PhCH(NO2)]–
(2)
a: – R = Ph (67%)
b: – R = p–NO2–C6H4 (44%)
386a,b

Scheme 3.217





Scheme 3.217 (*continued*)

In the presence of fluoride anion as the catalyst, dihydrofurans (**376**) can also apparently generate the respective nitroso derivatives. The latter eliminate HNO and give the corresponding furans (**387a–h**) in moderate yields (292) (Eq. 3).

Finally, treatment of dihydrofuran (**388**) with fluoride anion in CH_2Cl_2 gives rise to the *Z*- isomer of conjugated ene nitrile (**390-*Z***) rather than the corresponding furan (Eq. 4) (292). Unfortunately, attempts to extend the formation of ene nitriles to other dihydrofurans (**376**) failed.

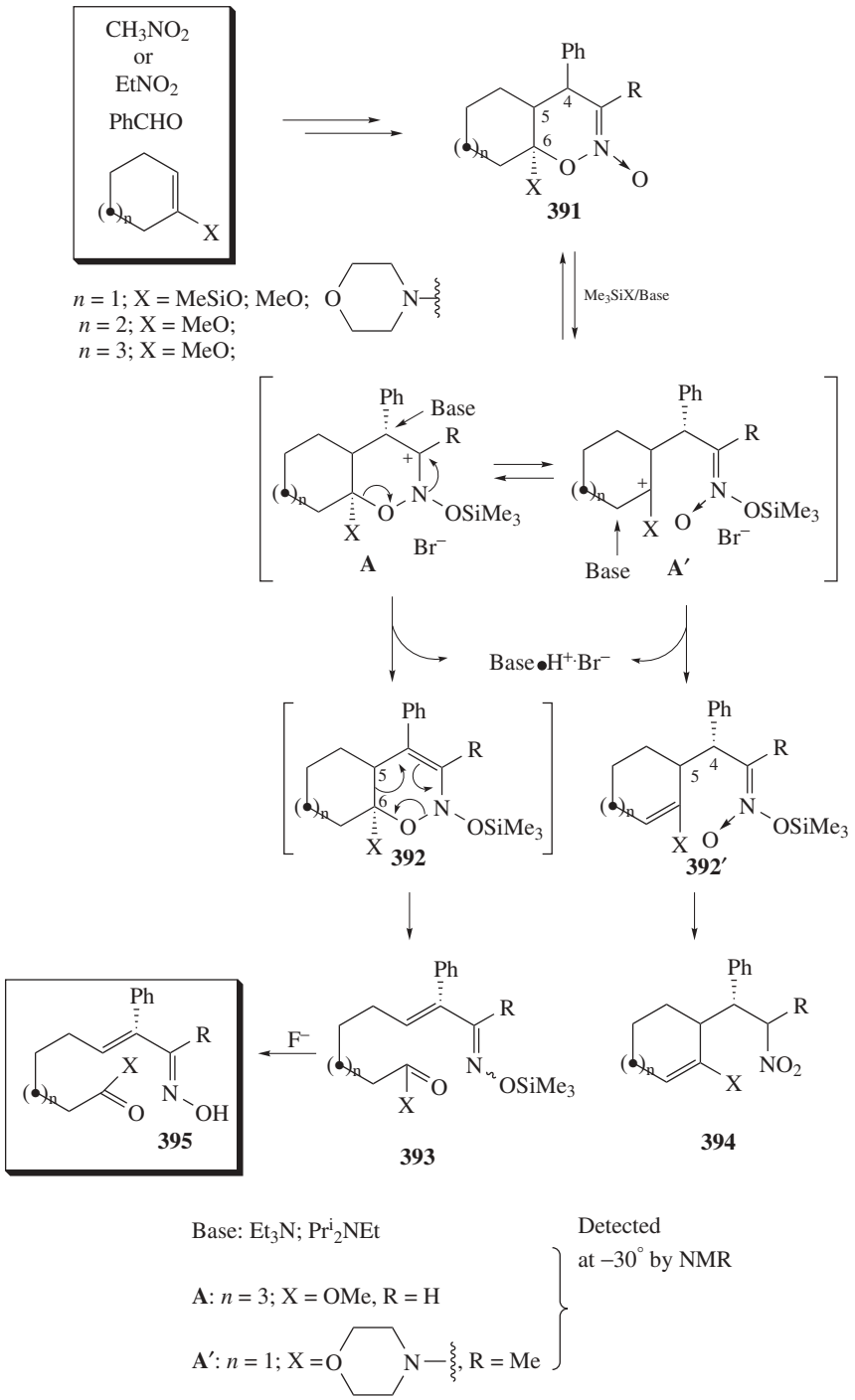
3.5.2.5. Ring-Chain Tautomerism of Bis-N,N-Oxyiminium Cations Scheme 3.215 shows the ring-chain tautomerism of selected bis-*N,N*-oxyiminium cations, which was suggested as an explanation of the reactivity of γ-functionalized AN. This problem is not only of theoretical interest but also of importance for the development of a simple and efficient procedure for the synthesis of conjugated enoximes (**395**) containing a remote functional group (153, 293) (Scheme 3.218).

These enoximes can be prepared through available annelated six-membered cyclic nitronates (**391**) by their silylation giving rise to the iminium cations **A**, whose deprotonation affords annelated 2*H*-5,6-dihydrooxazines (**392**). After the known retro-fragmentation (490), the latter compounds are transformed into the target conjugated en oximes (**395**).

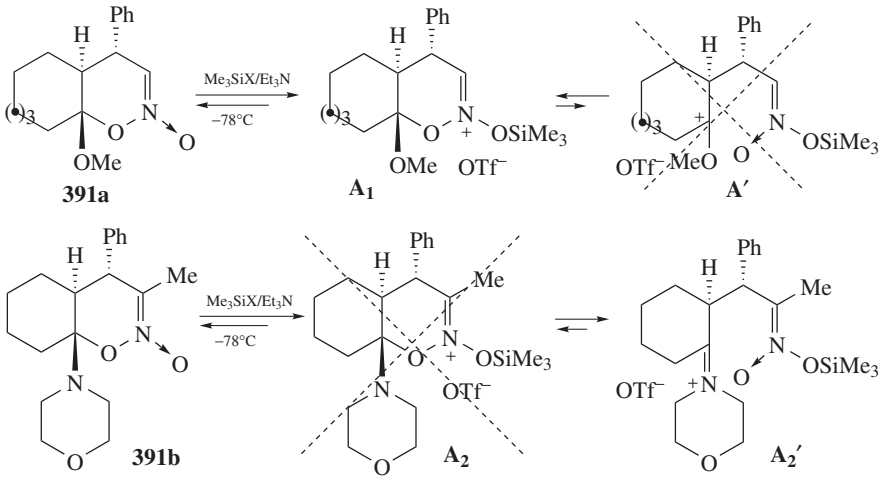
For compounds, in which n = 1 and X = $SiMe_3$ or OMe, silylation was studied in more detail (293). For this purpose, the specially prepared individual stereoisomers of nitronates (**391**) were subjected to silylation. The configuration of the C,C double bond in the resulting oximes (**393**) and (**395**) was determined in each case. It appeared that if the fragmentation (**392**→**393**) is considered as a concerted process (according to Reference 490a), the configuration of the C=C bond in derivative (**393**) does not correspond to the configuration of its direct precursor, oxazine (**392**). This contradiction can be resolved by considering the ring-chain tautomerism of cationic intermediates **A**⇄**A′**, which can lead to a change in the initial configuration of the C-6 stereocenter of (**392**).

Variations in the size of the carbocycle (n = 1–3), the nature of the group X stabilizing the positive charge in the cation **A′**, and the steric hindrance of the base in the silylating agent demonstrated that both the character of silylation products and the configuration of the C,C double bond in oxime (**395**) depend dramatically on these factors. An increase in ring size, the replacement of the alkoxy group at the C-6 atom by the amino fragment, and the use of Hunig's base, sterically more hindered than Et_3N, lead to an increase in the percentage of nitro compound (**394**) in silylation products. The reactions of compounds, in which n = 1 and X is –N-morpholyl or n = 3 and X=OMe, afford nitro compound (**394**) as the only silylation product. The transformation (**391**→**394′**) does not lead to changes in the relative configuration of the stereocenters at the C-4 and C-5 atoms.

Attempts to directly observe the cations **A** and **A′** by low-temperature NMR, developed in the studies 274 and 478, made it possible to detect both types of cations (293) (Scheme 3.219).


CH3NO2
or
EtNO2
PhCHO
n = 1; X = MeSiO; MeO;
n = 2; X = MeO;
n = 3; X = MeO;
391
Me3SiX/Base
Base
A
A′
Base•H+·Br−
392
392′
393
394
395
F−
Base: Et3N; Pri2NEt
A: n = 3; X = OMe, R = H
A′: n = 1; X = O N—, R = Me
Detected
at –30° by NMR

Scheme 3.218



Scheme 3.219

This is indirect evidence for the cationic ring-chain tautomerism shown in Scheme 3.218.

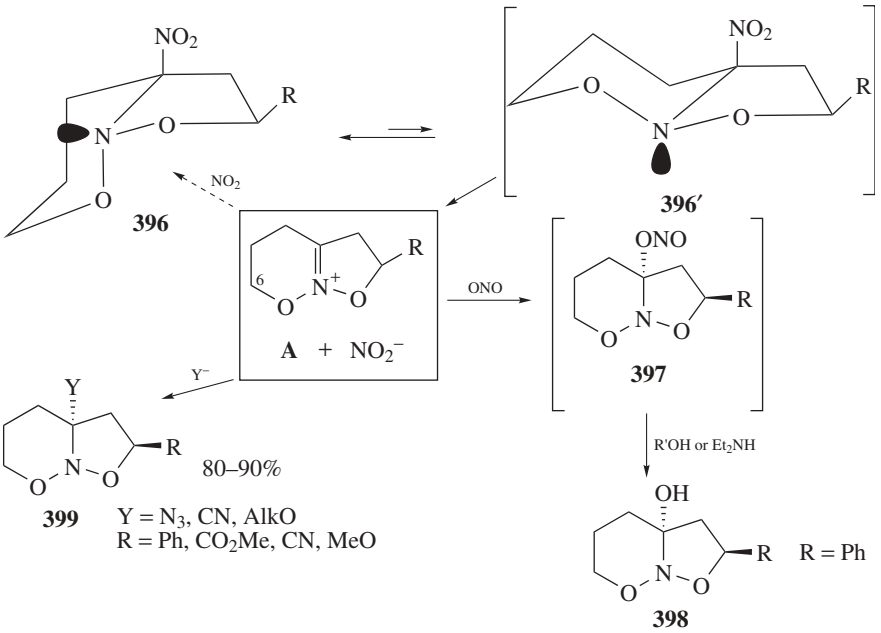
However, a flexible equilibrium $\mathbf{A} \rightleftarrows \mathbf{A}'$ was not detected.

3.5.2.6. Other Procedures for Generation of Bis-N,N-Oxyiminium Cations

Chlenov was the first to consider bis-*N,N*-oxyiminium cations as kinetically independent species (337, 371, 494). He also developed a simple and original procedure for generating intermediates of this type by elimination of the nitro group from bicyclic systems (**396**) (Scheme 3.220).

To generate the cation **A**, it is necessary to invert the predominant conformation of the starting nitroso acetal (**396**) into conformation (**396′**) (I_N), in which the nitrogen lone pair and the nitro group are *trans*-antiparallel. As mentioned above in other isoxazolidines (417), similar inversion can be facilitated by the presence of nitro groups bonded to neighbouring C-atom. Owing to the anomeric effect of the nitrogen lone pair, the nitro group can reversibly eliminate from conformation (**396′**) to give the stabilized cation **A**. The ambident anion, NO_2^- can recombine with the cation **A** by C,O-coupling to form nitrite (**397**), which cannot be isolated in its individual state but can be detected by ^{1}H NMR spectroscopy. Nitrite (**397**) does not eliminate the NO_2^- anion. It was hypothesized (337) that compound (**397**) is stable because of the hindered I_N-process.

Cationic intermediates **A** can react with active nucleophiles $\mathbf{Y}^-$ to give coupling products (**399**) in high yields, with the *trans* configuration of the nucleophile and the substituent R predominating. (As in the case of the [3 + 2]-cycloaddition reactions with six-membered cyclic nitronates (162), this stereoselectivity can be attributed to the favorable approach of the nucleophile to the plane of the cation which is distal with respect to the C-6 atom. It should be noted that this



Scheme 3.220

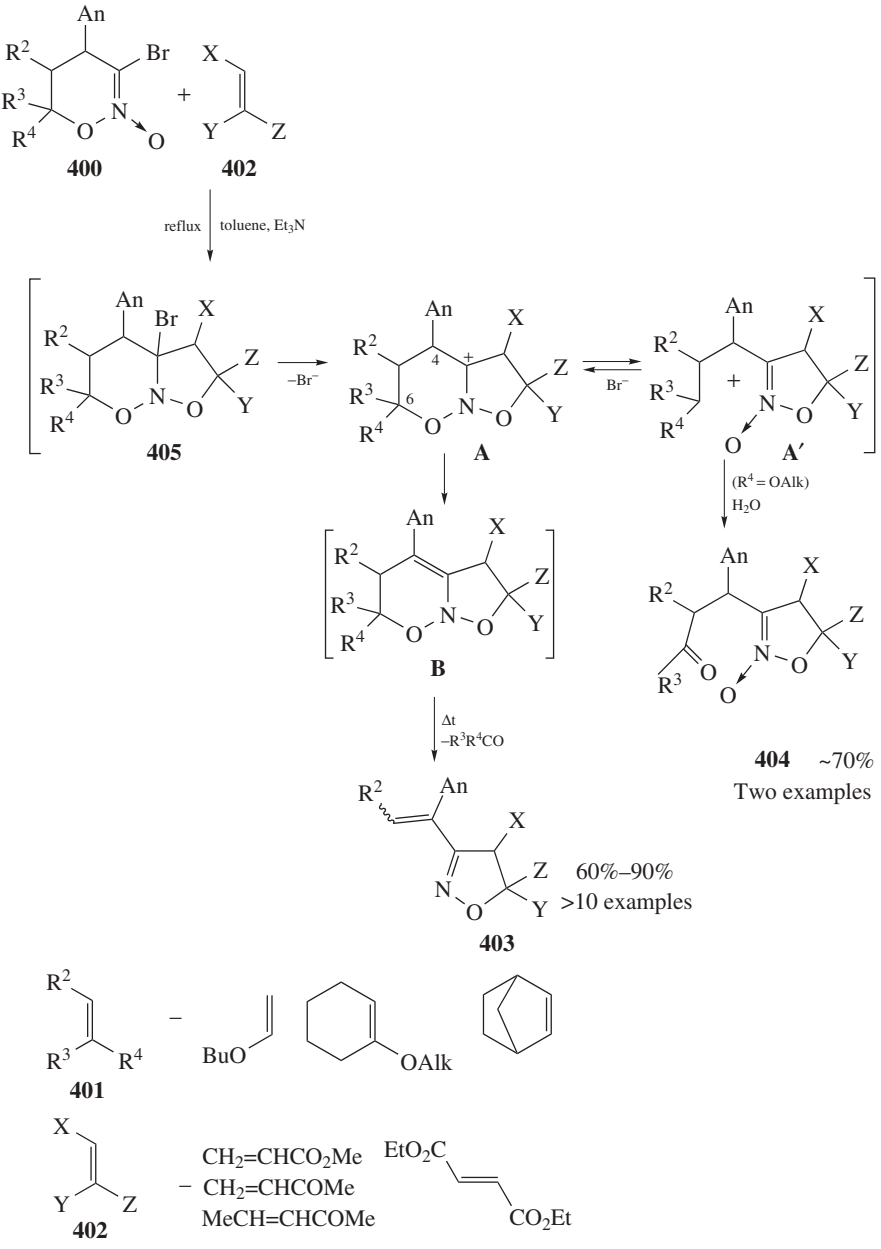
approach of the nucleophile is typical also for catalytic C,C-coupling reactions of six-membered cyclic nitronates with silyl-containing nucleophiles (478).)

Recently, it has been demonstrated (495) that the [3 + 2]-cycloaddition reactions of 3-bromo-substituted six-membered cyclic nitronates (**400**), which are constructed from olefins (**401**) and 1-bromo-1-nitro-2,4′-methoxyphenylethylene, with olefins (**402**) produce 3-vinylisoxazolines (**403**) or five-membered cyclic nitronates (**404**) in good yields (Scheme 3.221).

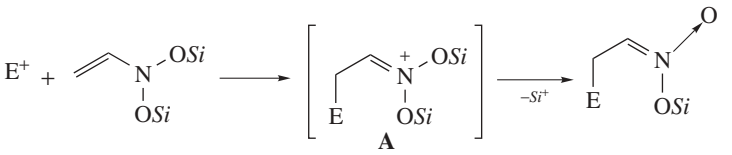
To account for the formation of the final products, a pathway involving the initial generation of cycloadducts (**405**) followed by elimination of the bromide anion to give cations **A** was proposed. The cations can stabilize by deprotonation of the C-4 atom followed by retro-[4 + 2]-cycloaddition of intermediates **B** to give isolable vinylisoxazolines (**403**).

The formation of five-membered cyclic nitronates (**404**) is explained in terms of ring-chain tautomerism of cationic intermediates **A** (**A**⇄**A**′). The presence of the alkoxy substituent (R^4) at the C-6 atom could stabilize the open form (cation **A**′), which finally leads to the formation of functionalized five-membered cyclic nitronates (**404**) probably with the participation of water.

In processes (**400** + **402**)→(**403**) and (**400** + **402**)→(**404**), the possibility of introducing of auxillaries at the C-6 atom is advantageous for the development of new strategies for asymmetric synthesis with participation of six-membered 3-bromo-substituted six-membered cyclic nitronates.


400
402
reflux
toluene, Et3N
405
–Br–
A
Br–
A′
(R4 = OAlk)
H2O
B
Δt
–R3R4CO
404 ~70%
Two examples
403
60%–90%
>10 examples
401
BuO
OAlk
402
CH2=CHCO2Me
CH2=CHCOMe
MeCH=CHCOMe
EtO2C
CO2Et
An – 4-MeO-C6H4;

Scheme 3.221



Si – trialkylsilyl; E^+ – cationic intermediate

Scheme 3.222

Another approach to the generation of bis-*N,N*-oxyiminium cations is shown in Scheme 3.222.

This approach will be considered in more detail in Section 3.5.4.2.1. In these processes, it should be noted, the only aim is to decompose the cations **A** as rapidly as possible by facilitating elimination of Si^+. Hence, the use of this approach to the synthesis of intermediates **A** in C,C-coupling reactions is not promising.

3.5.3. Elimination Reactions with Silyl Nitronates and Ene Nitroso Acetals

Silylation of AN and cyclic nitronates affords SENA and BENA or cyclic *N*-siloxy-ene nitroso acetals as the major primary products (see Sections 3.2.1.3 and 3.5.1). All these relatively unstable derivatives can undergo various elimination reactions, which will be considered in separately.

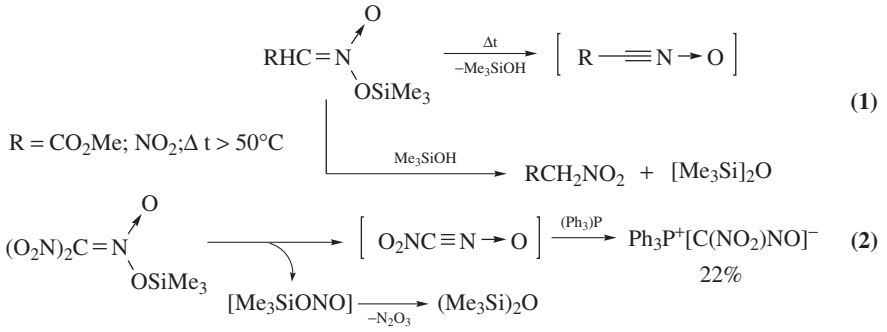
3.5.3.1. Elimination Reactions with Silyl Nitronates Most elimination reactions of SENA involve cleavage of the weak N–O bond or cleavage of the O–Si bond. In the latter case, the reactions could occur with the participation of hypervalent silicon in the transition state, that requires the presence of an external nucleophile.

3.5.3.1.1. 1,2-C,N Elimination These processes are typical of SENA containing an electron-withdrawing substituent at the α-carbon atom and occur at high temperatures (176, 203) (Scheme 3.223).

If such SENA contains the proton at the α-C atom (203), trimethylsilanol is eliminated, which causes partial hydrolysis of the nitronate.

Trimethylsilyl ether of trinitromethane decomposes at ambient temperature (176) to give very unstable trimethylsilyl nitrite. Another decomposition product, nitronitrile oxide, can be trapped in low yield as the adduct with triphenylphosphine.

3.5.3.1.2. 1,3-C,N Elimination Standard SENAs are quite stable at ambient conditions. However, if an activating electron-withdrawing substituent is attached at the β-carbon atom, spontaneous elimination of trialkylsilanol occurs to form the corresponding α-nitrosoalkene **C** (491, 496–498) (Scheme 3.224).



Scheme 3.223

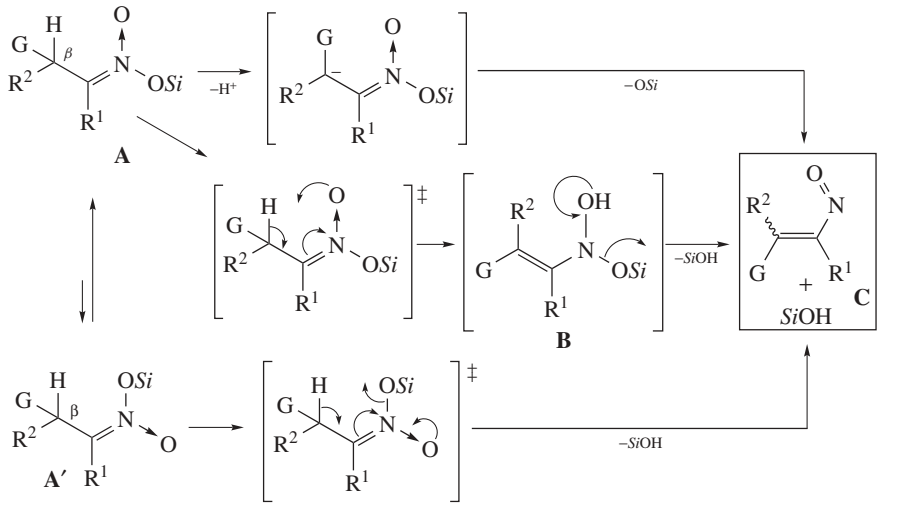
Three possible mechanistic schemes can be suggested for this process. One involves elimination of the proton attached to the β-C atom of nitronate **A** or **A′** followed by elimination of the O*Si*$^-$ group from the intermediate anion (cf. Scheme 3.93). Another mechanism is associated with a 1,4-C,O-transfer of the proton from the β-C atom of nitronate **A** to the oxygen atom of the N→O fragment followed by elimination of silanol from hemiacetal **B**. The third mechanism is based on the concerted elimination of silanol from the minor *cis* isomer of SENA.

On the basis of available experimental data, it is impossible to choose a definite pathway of elimination of silanol. However, study of silylation of methyl β-nitropropionate (**411**) with BSA in the presence of trapping agents rigorously proved that silyl nitronate **D** is initially formed. This compound can be detected in the [3 + 2]-cycloaddition reaction with methyl acrylate product (**413**). If silylation of AN (**411**) is performed in the presence of ethyl vinyl ether, α-nitrosoalkene **E** can be successfully trapped in as heterodiene a Diels-Alder reaction. Dihydrooxazine (**414**) is formed, and its silylation affords isolable product (**415**).

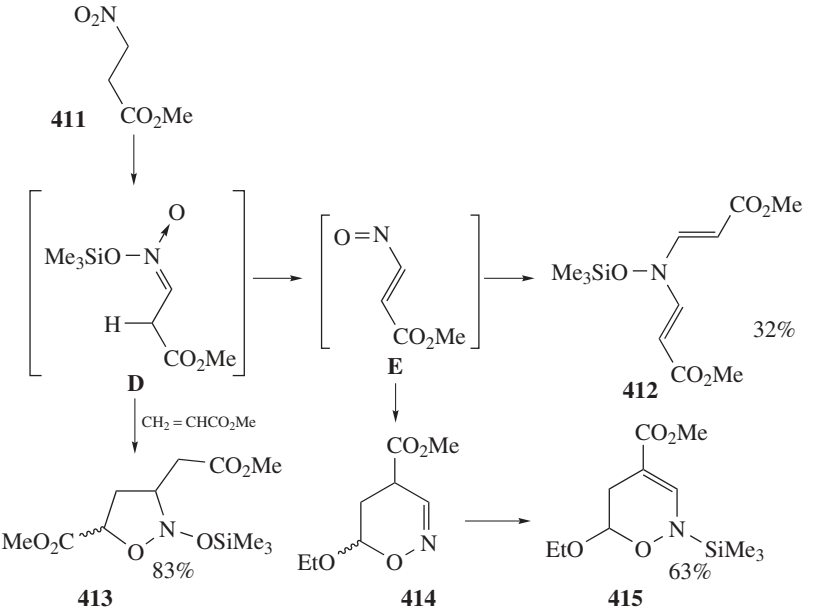
3.5.3.1.3. 1,4-C,O Elimination (δ-Elimination) Silylation of vicinal substituted nitroethanes $XCH_2CH_2NO_2$ demonstrated that if substituent X is highly electronegative, the resulting SENAs **A** rapidly eliminate the corresponding trimethylsilane to give nitroethylene (212) (Scheme 3.225).

If X = AcO, intermediate SENA can be trapped by methyl acrylate in the [3 + 2]-cycloaddition reaction (isoxazolidine (**416**)). If X=Cl, attempts to trap silyl nitronate failed; however, nitroethylene was detected in a Diels-Alder reaction. By contrast, SENAs, in which X=OSiMe$_3$ or NHPh, are quite stable. Therefore, the substituents X can be arranged in the following series of increasing elimination rates of *Si*X: Cl > AcO > > PhNH.

The above described elimination (δ-decay) is an analog of the so-called β-elimination of β-functionalized silanes (X–C–C–*Si* → *Si*X + C=C).

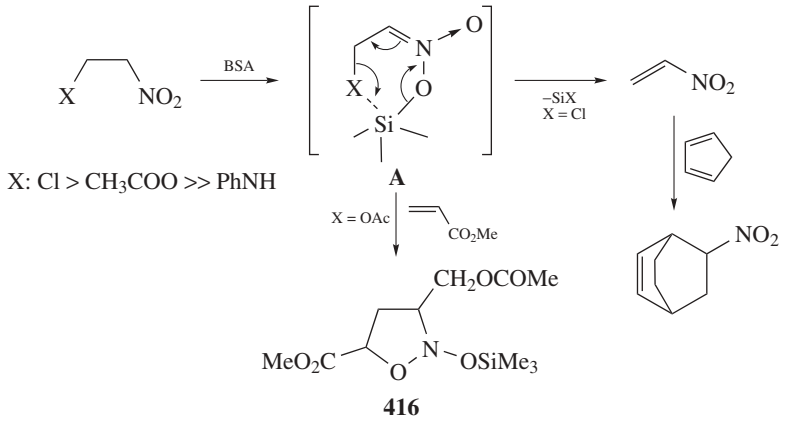


G – EWG-group; *Si* – $SiAlk_3$



412 – BSA, 20°C without solvent; **413** – 20°C, BSA in $CH_2 = CHCO_2Me$
414 – 20°C, BSA in $CH_2 = CHCOEt$.

Scheme 3.224



416

Scheme 3.225

3.5.3.2. Elimination Reactions with N,N-Bis(siloxy)Enamines

3.5.3.2.1. 1,2-N,O Elimination BENAs are chemical equivalents of α-nitrosoalkenes and, consequently, can give very active intermediates under various conditions (Scheme 3.226).

First, α-nitrosoalkenes can be generated from BENAs in the presence of bases, for example, of triethylamine (499), which can initiate chain decomposition of these nitroso acetals (Eq. 1). Then, the more active trialkylsiloxy anion is involved in this process. (Apparently, this is responsible for the well-known spontaneous decomposition of BENA in the presence of nitrogen bases.)

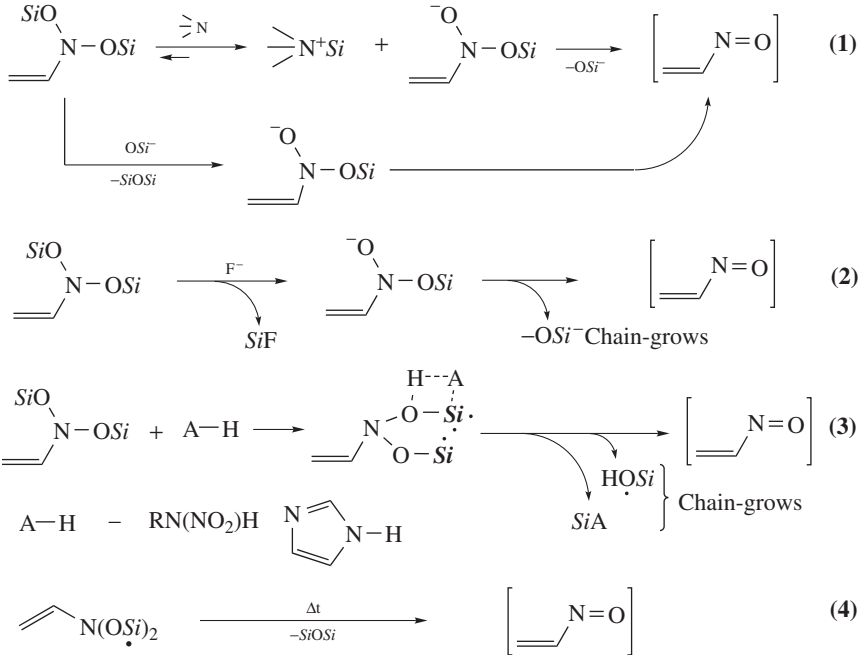
Analogous processes with BENAs also occur in the presence of fluoride anion (500) (Eq. 2).

Evidently, some acids can also initiate similar chain reactions (501, 502) (Eq. 3).

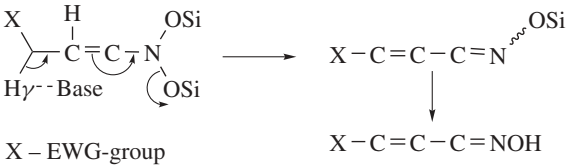
Finally, it is known that BENA are thermally unstable (464). α-Nitrosoalkenes generated from BENAs are very labile intermediates having multiple reactivities (503). Hence, special efforts should be made to choose the reaction conditions under which the transformations of BENA follow the desired pathway.

3.5.3.2.2. 1,4–N,C Elimination The reactions of standard BENAs with bases were considered in the previous section. As a rule, these reactions proceed at the silicon atom of the nitroso acetal fragment. However, if a EWG-group is adjacent to the γ-C atom of BENA, the allylic proton (Hγ) at this carbon atom becomes so labile that it can be eliminated already in the presence of bases at room temperature (504), thus initiating the transformation of such BENA into conjugated en oximes (Scheme 3.227).

To summarize Section 3.5.3, the general conclusion is that depending on the reaction conditions and the nature of the nitro substrate, silylation of AN and cyclic nitronates afford silyl nitronates (**SENA**), bis(siloxy)enamines (BENA, or



Scheme 3.226



Scheme 3.227

cyclic conjugated ene nitroso acetals), conjugated en-oximes, and decomposition products of unstable α-nitrosoalkenes.

3.5.4. Chemistry of *N,N*-Bis(siloxy)Enamines and Conjugated Cyclic Ene-Nitroso Acetals

BENA and their nearest analogs, *cyclic N-siloxyacetals* (see Section 3.5.1.3), can be considered as available AN derivatives, they can easily be generated by double silylation of AN or silylation of cyclic nitronates.

These products have various reactivities (for more details, see below) and undoubtedly will find wide use in organic synthesis. Depending on the nature of substituents, these compounds are colorless oils or crystalline products, which

are resistant to water treatment but undergo rapid and uncontrolled decomposition in the presence of acids or bases. Investigations of their structures and stereodynamics are of considerable interest.

3.5.4.1. Structure and Stereodynamic of Ene- Nitroso Acetals On the one hand, BENA can be considered as close analogs of enamines, in which the nitrogen lone pair is efficiently conjugated with the C,C double bond, resulting in strengthening of the C,N bond and flattening of the nitrogen atom. As a result, the nitrogen inversion is accelerated, whereas rotation about the C=N bond becomes much slower. In enamines containing an *EWG*-group at the β-carbon atom, the activation free energy for rotation about the C,N bond is 40 to 80 kJ/mol (505), whereas the inversion barrier is very low (4–6 kJ/mol (506)).

On the other hand, BENA are nitroso acetals, that is, compounds in which the nitrogen atom is bound to two electronegative substituents. The nitrogen inversion in nitroso acetals is strongly hindered. The barrier for this process is, as a rule, higher than 80 kJ/mol (395), and the nitrogen atom is characterized by a high degree of pyramidalization (508).

Therefore, the nitrogen configuration in BENA and the energy barriers for both stereodynamic processes are influenced by two opposite factors and it is *a priori* difficult to predict the final result.

Preliminary experiments demonstrated that only one slow dynamic process can be generally detected in BENA by dynamic NMR spectroscopy.

The equivalence or nonequivalence of siloxy substituents in BENA in possible dynamic processes and conformations are considered in Fig. 3.3 (467).

Pyramidal nitrogen is favorable for slow inversion. In this case, two methyl groups in the $SiMe_2Bu^t$ fragment are nonequivalent, whereas two $SiMe_3$ groups are, on the contrary, equivalent. However, any two identical substituents at the nitrogen atom become nonequivalent in the presence of the asymmetric center G* attached to the C,C double bond.

A consideration of hindered rotation about the C,N bond is a more complex problem. Here it is necessary to analyze conformations with "planar" or flattened nitrogen. Two frontier situations are possible. In the first, most evident case, the conformations **A** and **C**, in which the nitrogen configuration is favorable for efficient conjugation between the nitrogen lone pair and the C,C double bond, are predominant. In these conformations, the groups R at the nitrogen atoms are always nonequivalent in the case of slow rotation of nitrogen. However, it cannot be ruled out that the conformation **B**, in which the substituents at the nitrogen atom (R = Me or $OSiMe_3$) are equivalent in the case of slow rotation of nitrogen, is predominant.

To study this problem in detail, the structures and stereodynamics of BENA were investigated by several physicochemical methods (X-ray diffraction, quantum chemical calculations and dynamic NMR spectroscopy) (467).

Principal X-ray diffraction data for typical BENAs (**416a–d**) and related compounds **(417)** to **(421)** are shown in Table 3.26 (264, 467, 468, 507–509).

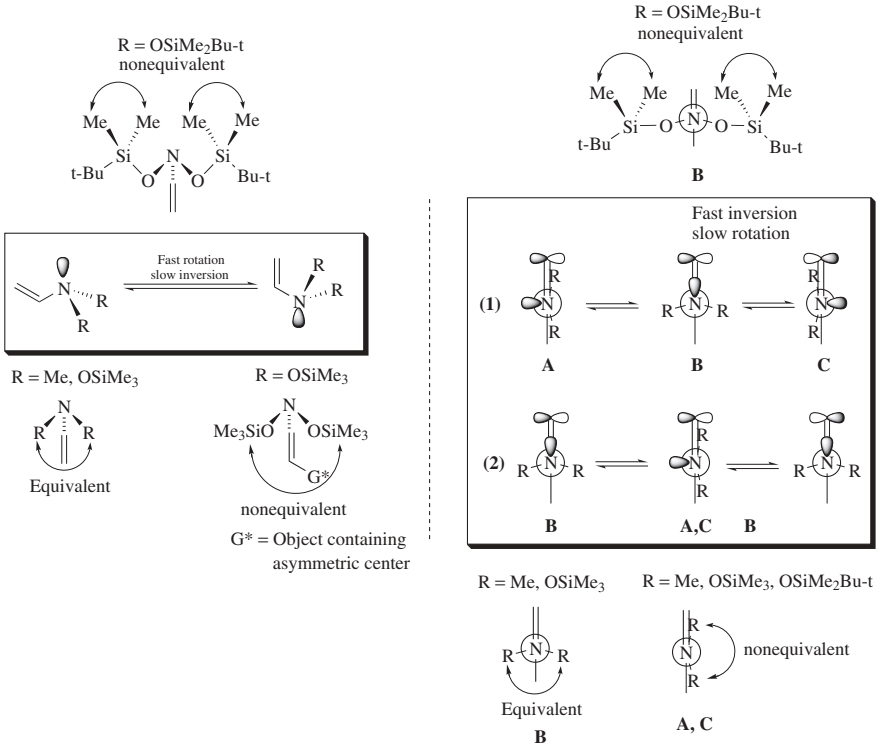


Fig. 3.3 Conformation analysis of BENA stereodynamics

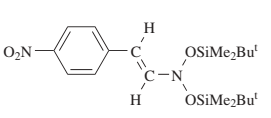
Evidently, in the crystalline state, BENA can adopt one of two conformations (**A** or **B**) presented in Fig. 3.3. Nevertheless, the nitrogen atom is characterized by a high degree of pyramidalization in both conformations, and the C–N bond is substantially elongated compared to similar bond in "classical" enamines (see, e.g., (**417**)). It should also be noted that the C,C double bond in BENA is substantially shortened compared to the analogous bond in standard enamines.

Therefore, X-ray diffraction data provide unambiguous evidence that the structural characteristics of BENA are substantially more similar to those of nitroso acetals (**418**) (Table 3.26) than to enamines and, consequently, the dynamic process observed by NMR spectroscopy is most likely a slow nitrogen inversion.

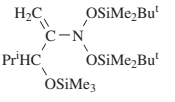
Low efficiency of the $n \rightarrow \pi$ conjugation in BENA is confirmed by a strong hypsochromic shift of the absorption band in the UV spectrum of nitroso acetal (**416b**) compared to product (**417**) (for (**416b**), $\lambda_{max} = 324$ nm ($\log\varepsilon = 4.1$); for (**417**), and $\lambda_{max} = 404$ nm ($\log\varepsilon = 4.0$)) (467).

Quantum chemical calculations by the DFT PBE/TZP method for model nitroso acetals and related compounds (467) are also indicative of nitrogen inversion as the slowest dynamic process in the ene nitroso acetals studied (see Fig. 3.4, Table 3.27).

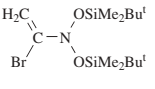
Table 3.26 X-ray data for BENAs and related compounds



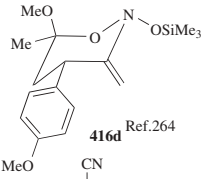
416a Ref.467



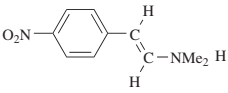
416b Ref.467



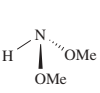
416c Ref.468



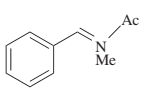
416d Ref.264



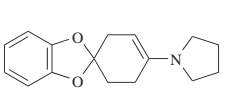
417 Ref.467



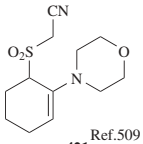
418 Ref.507



419 Ref.508



420 Ref.509



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Entry	Compd.	Conformation[a]	θ_1° C = C-N-R	θ_2° C = C-N-R	$L_{C\text{-}N}$ Ang	$L_{C=C}$ Ang	Sum of angles at N
1	**416a**	B	132.8	−119.5	1.439	1.324	312.0
2	**416b**	A distored	3.8	−106.4	1.450	1.313	316.0
3	**416c**	B	125.08	−125.08	1.433	1.316	315.9
4	**416d**	A distored	16.9	+124.14	1.442	1.318	317.3
5	**417**	A	4.2	177.3	1.351	1.348	359.7
6	**418**	-	-	-	-	-	311.8
7	**419**	A	4.2	178.6	1.398	1.322	359.9
8	**420**	A	6.9	176.0	1.381	1.366	359.2
9	**421**	A distored	7.0	−122.8	1.431	1.353	340.7

[a] see Fig 3.

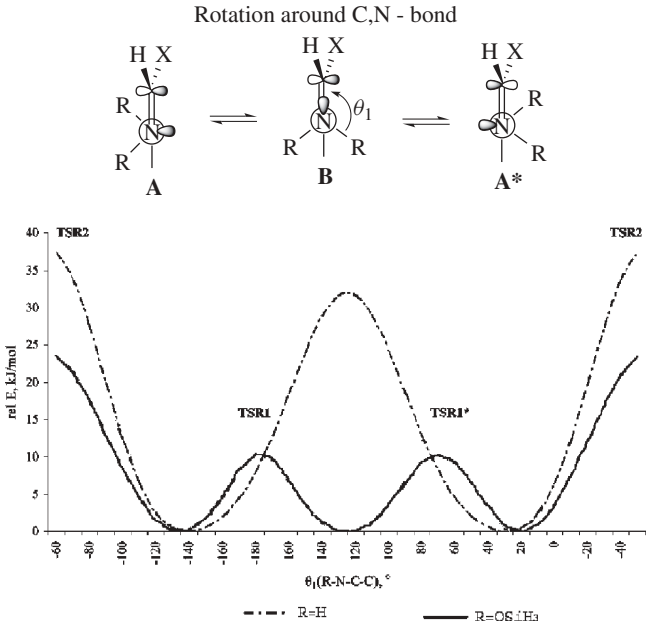


Fig. 3.4 Potential energy curves for internal rotation around C,N bond for enamines $R_2NCH{=}CHX$ (R=X=H (**422**); R = $OSiMe_3$, X=H (**423**))

Table 3.27 Some calculations for model BENA and related compounds

Entry	Compound	R	X	Conform.	rel.E[a] kJ/mol
1	(**422**)	H	H	**A**′[b]	0
2	(**422**)	H	H	**B**	30.3
3	(**422**)	H	H	TSR 2	37.0
4	(**422**)	H	H	TSN	4.5[b]
5	(**423**)	$OSiMe_3$	H	**A**	+0.3
6	(**423**)	$OSiMe_3$	H	**B**	0
7	(**423**)	$OSiMe_3$	H	TSR1	8.8
8	(**423**)	$OSiMe_3$	H	TSR2	23.9
9	(**423**)	$OSiMe_3$	H	TSN	65.3
10	(**424**)	Me	4-NO_2-C_6H_4-	B	45.0[c]
11	(**425**)	Me	EtO_2C	B	51.0[d]

[a]The values were calculated taking into consideration the zero-point vibration energy.
[b]Experimental 4.2 kJ/mol (506a).
[c]By NMR data (see Table 3.25).
[d]Ref. (505)b.

For standard vinylamine (**422**), the change between stable conformations **A**⇄**A**′ through the transition state **B**, caused by rotation about the C,N bond requires more than 30 kJ/mol, whereas both the calculated and experimental nitrogen inversion barriers are not higher than 5 kJ/mol. (The data for compounds (**424**) and (**425**) (entries 10 and 11) demonstrated that the introduction of electron-withdrawing groups at the β-C atom of enamines leads to a substantial increase in the barrier to rotation about the C,N bond in enamines.) The nitrogen atom in vinylamine (**422**) is substantially flattened (the calculated sum of bond angles is 341.4°).

However, a quite different situation is observed for ene nitroso acetal (**423**). First, a stable conformation and, correspondingly, new transition states **TSR1** and **TSR1*** with a low barrier (8.8 kJ/mol) appear on the rotation coordinate about the C,N bond at the place of the transition state of enamine (**422**). Therefore, the barrier to rotation about the C,N bond decreases so that the process is fast on the NMR time scale and cannot be detected by this method.

On the other hand, for compound (**423**) both the nitrogen inversion barrier (65.3 kJ/mol) and pyramidalization at the nitrogen atom are substantially higher (the sum of the bond angles at the nitrogen atom is 309.7° and 321.0° for the conformations **B** and **A**, respectively). A noticeable decrease in the degree of pyramidalization at nitrogen in the conformation **A** is indicative of a certain degree of nπ conjugation.) The nitrogen inversion barrier is suitable for observation on the NMR time scale (see below).

Special calculations for hypothetical nitroso acetal (**426**) demonstrated that the energy minimum for the conformation **B** is due to the partial compensation of the absence of stabilization through nπ conjugation by favorable steric factors (Fig. 3.5).

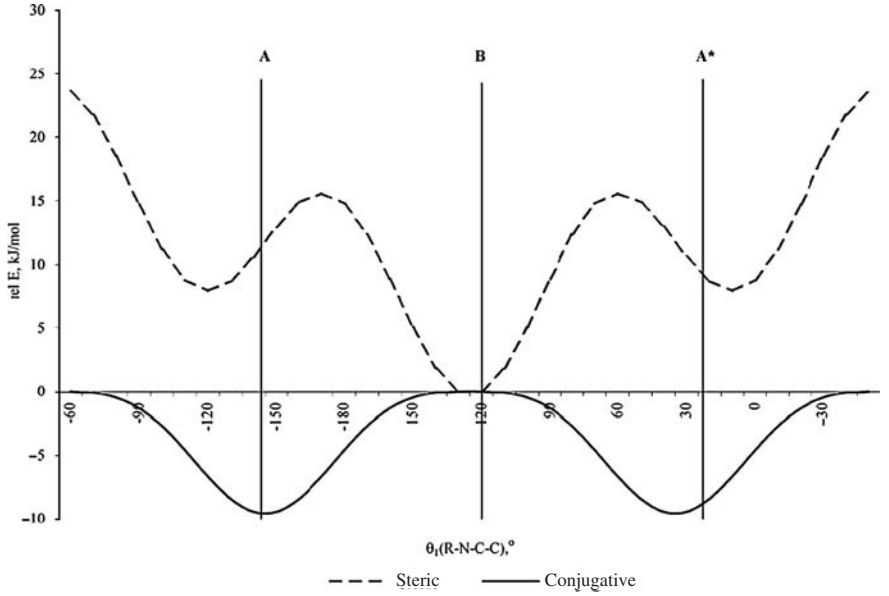


Fig. 3.5 The plots of steric and conjugative constituents of C,N-rotation potential for $CH_2=CHN(OSiH_3)_2$ (**426**)

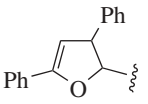
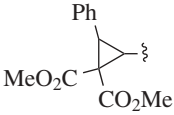
In addition, conformation **B** can be stabilized due to $\pi\sigma^*$ interactions between the π system of nitroso acetal and antibonding orbitals of both N–O bonds.

Table 3.28 presents the results of investigation of the stereodynamics in BENA and related compounds by dynamic NMR spectroscopy (467).

In similar nitroso acetals (**427**) and (**428**) (292, 493), which do not contain a C,C double bond, the nitrogen inversion barrier is so high that it cannot be directly determined by dynamic NMR spectroscopy due to instability of the nitroso acetals at high temperatures. The $n\pi$ conjugation between the nitrogen lone pair and the C,C double bond substantially decreases the barrier and slightly flattens the nitrogen atom, thus increasing its *s* character. (It should be noted that the exchange process in bis-*N,N*-(siloxy)aniline (**429**) (entry 3, Table 3.28) can be interpreted only as nitrogen inversion.) The introduction of electron-withdrawing substituents at the β-C atom of BENA would strengthen the $n\pi$ conjugation, thus resulting in flattening of the nitrogen atom and in a decrease in the inversion barrier. This situation is observed for BENA (cf., for example, entries 4–6 with entries 9 and 14 in Table 3.28).

In contrast, the opposite situation is observed for standard enamines, in which the introduction of electron-withdrawing substituents at the β-C atom leads to an increase in the barrier to rotation about the C,N bond (505). It should be noted that the experimental inversion barrier in BENA (**423b**) (52 kJ/mol, entry 4, Table 3.28) is rather similar to the calculated barrier for its very close analog (**423a**) (65.3 kJ/mol, entry 9, Table 3.27). As can be seen in Table 3.28, steric

Table 3.28 The barriers of nitrogen inversion of BENA and related compounds determined with dynamic NMR

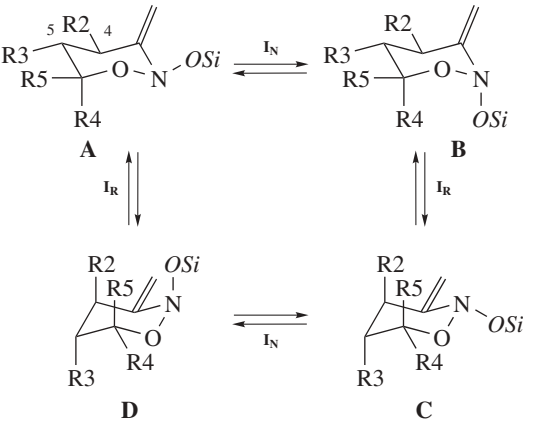
Entry	X	R^1 and R^2	$\Delta G^{\neq}_{298}$, kJ/mol
1	 (**427**)	$OSiMe_3$	$> 80^a$
2		$OSiMe_3$	$> 80^a$
3	C_6H_5 (**429**)	$OSiMe_2Bu$-*t*	52 (471)
4	CH_2=CH ((**423**))	$OSiMe_2Bu$-*t*	49^b
5	MeCH=CH	$OSiMe_2Bu$-*t*	63
6	CH_2=C(Me)	$OSiMe_2Bu$-*t*	56
7	MeO_2CCH=CH	$OSiMe_3$	$-^c$
8	CH_2=C(CO_2Et)	$OSiMe_2Bu$-*t*	58
9	MeO_2CCH=C(Me)	$OSiMe_2Bu$-*t*	$-^d$
10	$CH(OsiMe_3)Pr$-*i*	$OSiMe_3$	59
11	$CH(OsiMe_3)Pr$-*i*	$OSiMe_2Bu$-*t*	56
12	$EtO_2CCH(Me)CH$=CH	$OSiMe_3$	59
13	$EtO_2CCH(Me)CH$=CH	$OSiMe_2Bu$-*t*	52
14	4-$NO_2C_6H_4CH$=CH	$OSiMe_2Bu$-*t*	37
15	4-$NO_2C_6H_4CH$=CH (**424**)	Me	45

[a] Tentative data.
[b] Calculated for (**423**) $\Delta G^{\neq}_{298}$ of nitrogen inversion 52 kJ/mol.
[c] No broadening of signals of ^1H and ^{29}Si over 210 K.
[d] No broadening of signals of ^1H, ^{13}C, and ^{29}Si over 170 K.

hindrances in the trialkylsilyl group have only a slight effect on the nitrogen inversion barrier in BENAs (cf. entries 10 and 11 or entries 12 and 13, Table 3.28), and their influence is ambiguous. In most cases, not only the barriers but also the activation parameters were determined for dynamic processes in BENAs by dynamic NMR spectroscopy (467). As a rule, $\Delta S^{\neq}$ of nitrogen inversion is positive.

The stereodynamics of *N*-siloxy-ene- nitroso acetals related to 3-alkylen-substituted 4*H*-tetrahydro-1,2-oxazines (e.g., see (**416 d**)) differs from that of BENA in that free rotation about the C,N bond in oxazines cannot occur, but the ring inversion should take place (process $\mathbf{I}_R$) (see Scheme 3.228).

Analysis of the published data on the stereodynamics of cyclic nitrogen compounds (510) as well as the results of studies of the stereodynamics of BENA



Scheme 3.228

(467) suggests that both processes, the nitrogen inversion (I_N) and the ring inversion (I_R), could be detected by dynamic NMR spectroscopy and should have close barriers (40–60 kJ/mol). In such a situation, the ratio of the conformers **A–D** at near room temperature is determined by their related thermodynamic preference.

Since the processes can occur at similar rates, analysis of spectroscopic data presents problems. However, the choice between these two types of inversion can be made based on conformational analysis of the observed invertomers (511). The nitrogen inversion (I_N) is not accompanied by changes in the positions of the protons and substituents at the C atoms of the heterocycle, whereas upon ring inversion (I_R) all substituents and protons at the C atoms of the ring change their positions. Hence, analysis of $^3J_{H,H}$ for invertomers unambiguously reveals all I_N processes. Unfortunately, this simple approach does not allow one to distinguish between the simple I_R process and complex inversions $I_N + I_R$. NMR data of a representative group of ene nitroso acetals demonstrated that various dynamic processes can occur in these compounds (511) (Table 3.29).

By this means, $\mathbf{I_N}$ occurs in nitroso acetals **1a–d,i,j**, whereas the ring inversion or the more complex $\mathbf{I_N + I_R}$ process are observed in other derivatives listed in Table 3.29. By contrast, two different processes were distinguished in bicyclic nitroso acetal (**431**)—the fast process (I_N) and the slower process (I_R) (Scheme 3.229).

Evidently, the presence of a bicyclic structure hinders the ring inversion.

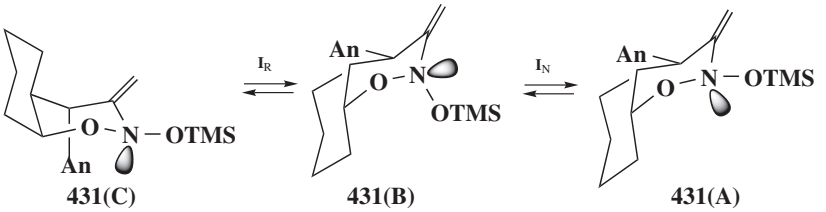
To summarize, all data from physicochemical methods are indicative of a substantial weakening of the $n\pi$ conjugation in ene nitroso acetals (**430**) and (**431**) compared to classical enamines and this should decrease the nucleophilicity of the π system of BENAs and cyclic ene nitroso acetals.

But BENAs could be active in reactions with electrophiles due to stabilization of the resulting carbo-iminium cations (Scheme 3.230, see also Section 3.5.2.6)

Table 3.29 The study of stereodynamic of substituted 3-alkylen-4*H*-tetrahydro-1,2-oxazines with dynamic NMR (Scheme 3.228)

Product	*Si*	R^{2a}	R^4	R^5	Process	Ratio of conformers	$\Delta G^{\#}_{298}$, kJ/mol	$\Delta H^{\#}$, kJ/mol	$\Delta S^{\#}$, J/mol*K
430a	TMS	Ph	Me	Me	$\mathbf{I}_N$	**A/B** 4:1	**A**→**B**: 59.8 ± 2.9	53.2 ± 2.7	−22.3 ± 9.7
							B→**A**: 56.7 ± 2.9	52.4 ± 2.7	−14.3 ± 9.8
430b	TBS	Ph	Me	Me	$\mathbf{I}_N$	**A/B** 4:1	**A**→**B**: 59.5 ± 2.3	48.4 ± 2.0	−37.3 ± 7.7
							B→**A**: 56.4 ± 2.7	45.7 ± 2.4	−35.8 ± 9.1
430c	TMS	An	OMe	Me	$\mathbf{I}_N$	**A/B** 9:1	**A**→**B**: 59.5 ± 3.1	50.2 ± 2.6	−31.3 ± 10.7
							B→**A**: 55.4 ± 3.9	45.9 ± 3.3	−32.0 ± 13.3
430d	TMS	An	H	OEt	$\mathbf{I}_N$	**A/B** 3:1	**A**→**B**: 60.1 ± 2.7	49.4 ± 2.5	−35.7 ± 9.0
							B→**A**: 58.7 ± 2.5	47.6 ± 2.4	−37.1 ± 8.5
430e	TMS	An	OEt	H	$\mathbf{I}_R$ **or** $\mathbf{I}_N + \mathbf{I}_R$	**A/(C** or **D)** = 4:1	**A**→**C**: 61.7 ± 2.8	45.0 ± 2.7	−59.0 ± 10.0
							C→**A**: 58.1 ± 3.5	46.0 ± 2.6	−40.6 ± 9.9
430f	TBS	OBz	Me	Me	$\mathbf{I}_R$ **or** $\mathbf{I}_N + \mathbf{I}_R$	**(C** or **D)/A** 1.1:1	**C**→**A**: 58.7 ± 2.7	50.5 ± 2.5	−27.3 ± 9.1
							A→**C**: 58.4 ± 2.9	52.4 ± 2.6	−19.8 ± 9.8
430g	TMS	OBz	Me	Me	$\mathbf{I}_R$ **or** $\mathbf{I}_N + \mathbf{I}_R$	**A/(C** or **D)** 3:2	**A**→**C**: 60.7 ± 3.0	56.2 ± 2.8	−15.1 ± 10.0
							C→**A**: 59.8 ± 2.9	60.6 ± 2.7	2.5 ± 9.7
430h	TMS	OBz	OMe	Me	$\mathbf{I}_R$ **or** $\mathbf{I}_N + \mathbf{I}_R$	**A/(C** or **D)** 9:1	**A**→**C**: 59.5 ± 3.8	36.7 ± 3.0	−76.4 ± 9.0
							C→**A**: 54.9 ± 2.9	31.7 ± 2.3	−77.7 ± 9.9
430i	TMS	An	Ph	H	$\mathbf{I}_N$	**(C** or **D)/twist** 3:2	**C**→**tw**: 65.6 ± 2.6	83.1 ± 2.7	60.8 ± 8.5
							tw→**C**: 65.0 ± 3	77.5 ± 3.2	39.8 ± 10.2
430j	TMS	An	H	Ph	$\mathbf{I}_N$	**A : B** = 3:2	**A**→**B**: 66.9 ± 1.8	44.7 ± 1.9	74.4 ± 6.2
							B→**A**: 65.6 ± 1.8	53.9 ± 1.9	−39.0 ± 6.0

[a] R^1=R^3=H; TMS−$SiMe_3$; TBS−$SiMe_2Bu^t$; An−4-MeO-C_6H_4.



350K one set signals; at 280K C:B » 1.5:1; at 190K B® B+A (~1:1).

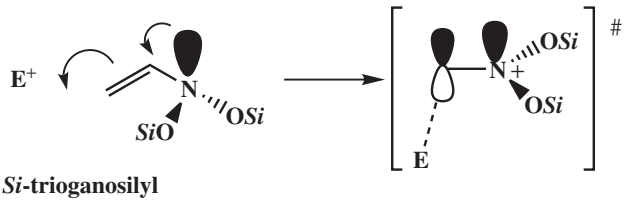
For **B→A** : $\Delta G^{\#}_{298}$ = 45.7 kJ/mol; ΔH = 41.7 kJ/mol; ΔS = −13.2 J/mol·K

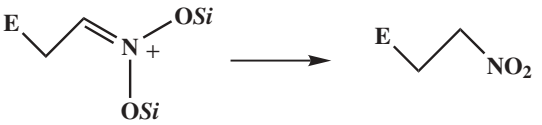
For **A→B** : $\Delta G^{\#}_{298}$ = 45.3 kJ/mol; ΔH = 39.4 kJ/mol; ΔS= −19.7 J/mol·K

For **C→B** : $\Delta G^{\#}_{298}$ = 67.0 kJ/mol; ΔH = 69.3 kJ/mol; ΔS = 7.7 J/mol·K

For **B→C** : $\Delta G^{\#}_{298}$ = 66.5 kJ/mol; ΔH = 63.7 kJ/mol; ΔS = −9.3 J/mol·K

Scheme 3.229



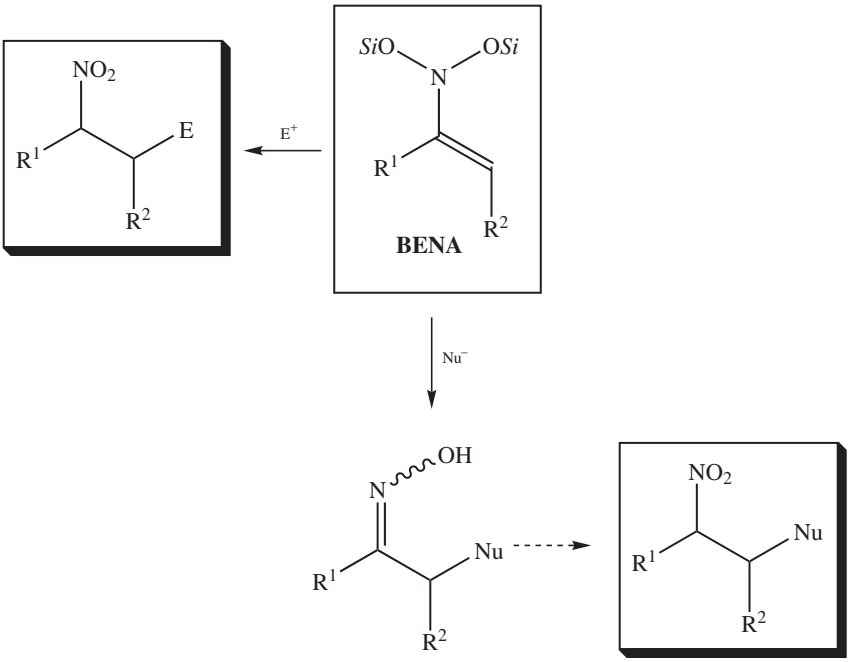


Scheme 3.230

In other words, the reactivity of BENAs depends on the presence of the nitrogen lone pair, which is almost coplanar to the C,C double bond in the transition state for interaction with electrophiles.

3.5.4.2. Main Chemical Transformations of BENA BENAs can be characterized as compounds having "chameleonic" activity. In other words, these compounds depending on the nature of partner can act either as β-C nucleophiles (the attack by an electrophilic agent) or as electrophiles (the attack by a nucleophilic agent) (Scheme 3.231).

Since functionalized oximes generated upon the nucleophilic attack can be oxidized to give the corresponding nitro derivatives according to known methods,



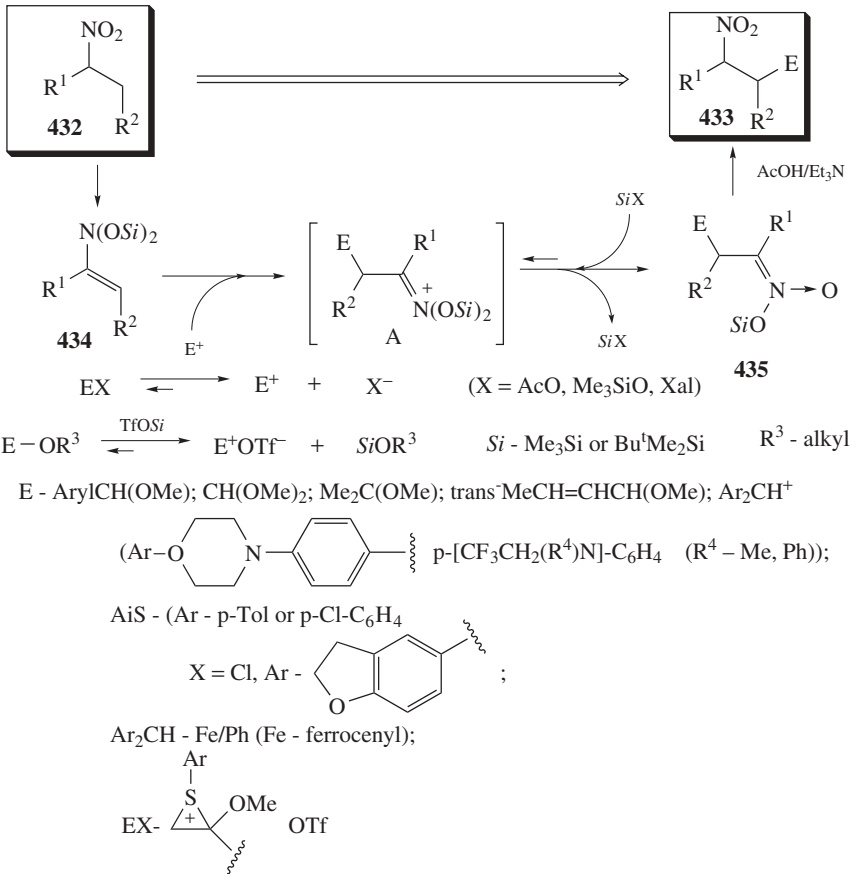
Scheme 3.231

a general conclusion can be drawn that BENAs make it possible to functionalize the β-C atom of AN in the reactions with both nucleophilic and electrophilic agents.

3.5.4.2.1. Reactions of BENA with Electrophiles The reactivity of BENA toward electrophiles was quantitatively estimated on Mayr's scale by kinetic measurements of their C,C-coupling reactions with reference electrophiles 512. The parameter of nucleophilicity N, determined for several terminal BENAs varies in a rather narrow range ($N \approx 4-5$) and depends only slightly on the nature of substituents at the α-C atom and steric hindrance of the trialkylsilyl group. The nucleophilicity of BENA is approximately 9 orders of magnitude lower than the nucleophilicity of standard enamines. It is somewhat lower than the nucleophilicity of silyl enolates. However, in spite of low N, a rather large number of electrophiles of different types can readily be coupled with BENA.

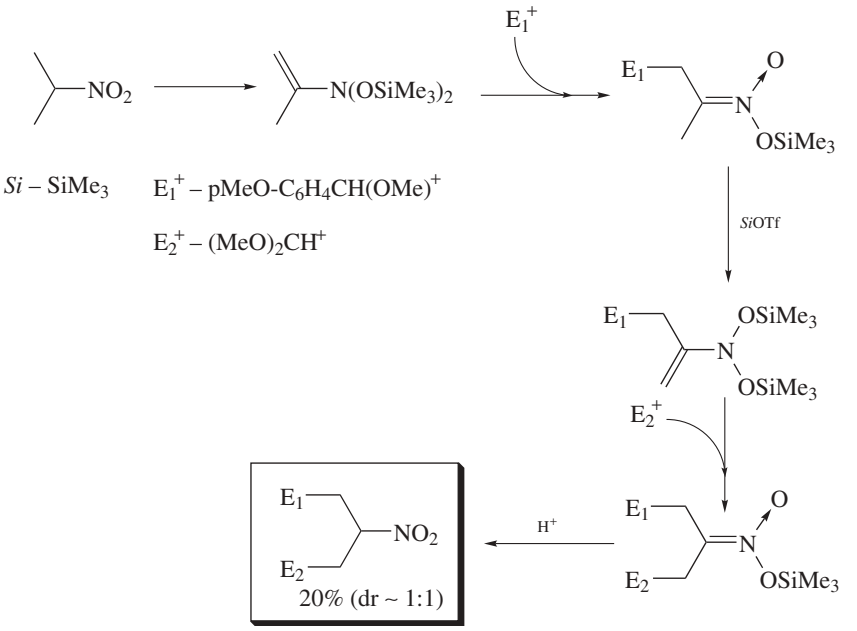
The most interesting reactions are shown in Schemes 3.232 and 3.233 (512–514).

This approach allows one to functionalize the β-C atom of AN. For this purpose, AN are initially subjected to double silylation to prepare BENAs, which are then coupled with various stabilized carbocations (512, 513), as well as with sulfenyl and episulfonium cations (514). Molecules containing good leaving groups (e.g., arenesulfenyl chlorides (514)) are used as sources (or precursors) of



Scheme 3.232

cations E^+. In this case, Lewis acids are not required for generation of cations. If acetals or related compounds are used as precursors, catalysis by silyl Lewis acids is necessary for generating cations E^+ (512). The main problem is that the coupling reactions produce during the first stage reactive iminium cations **A** (for the chemistry of these compounds, see Section 3.5.2.), and it is necessary to eliminate the trialkylsilyl groups from **A** as rapidly as possible to prepare nitrones (**435**) and then the functionalized nitro compounds (**433**) as target products. The smooth transformation (**435**→**433**) also does not seem to be a easy problem. In other words, the aimed interaction mentioned above is to perform reaction sequences involving cationic intermediates. Secondary AN containing the methyl group at the α-C atom and, consequently, giving terminal BENAs are most readily involved in this process. The easy selective elimination of the trialkylsilyl fragment from the cationic intermediate **A** is favored by the absence of the proton at the α-C atom; this makes it possible to prevent side processes.



Scheme 3.233

The important possibility to introduce two different functional groups into two methyl groups of 2-nitropropane in one step is shown in Scheme 3.233 (513).

It should be noted that the methyl groups 2-nitropropane are generally inert.

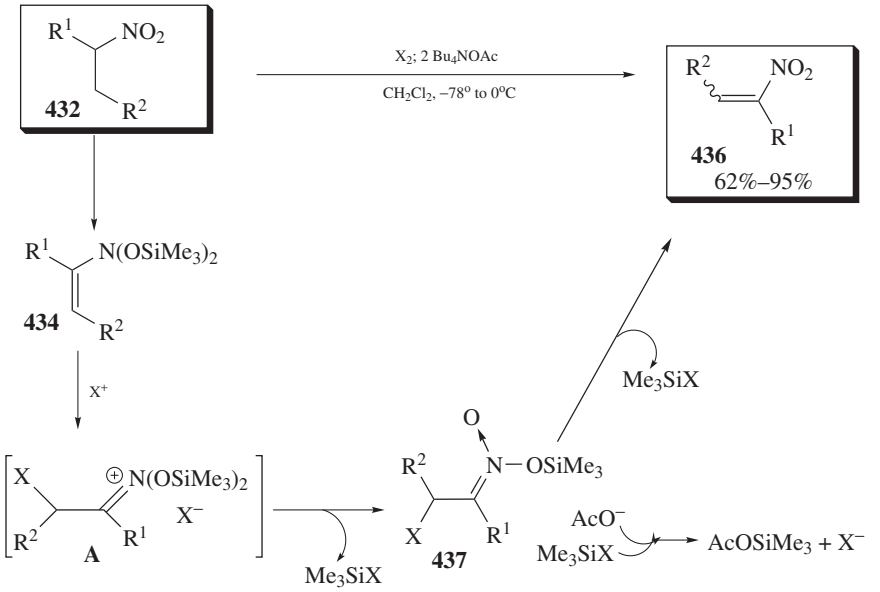
The addition of tetrabutylammonium acetate appeared to be very useful for desilylation of intermediates A (see Scheme 3.232). An efficient procedure was developed for the oxidation of nitroalkanes to nitroalkenes with the use of this reagent (250) (Scheme 3.234).

This sequence involves double silylation of AN (**432**), the addition of the halide cation to BENA (**434**), and the above discussed δ-elimination of halosilane from intermediate SENA (**437**) (see Section 3.5.3.1.3.).

This process can be used with advantage for the preparation of conjugated nitroalkenes from nitroalkanes. It is of interest because the majority of known synthetic methods for generating nitroalkenes, the skeletons of target molecules, are generally assembled from simpler molecules (104).

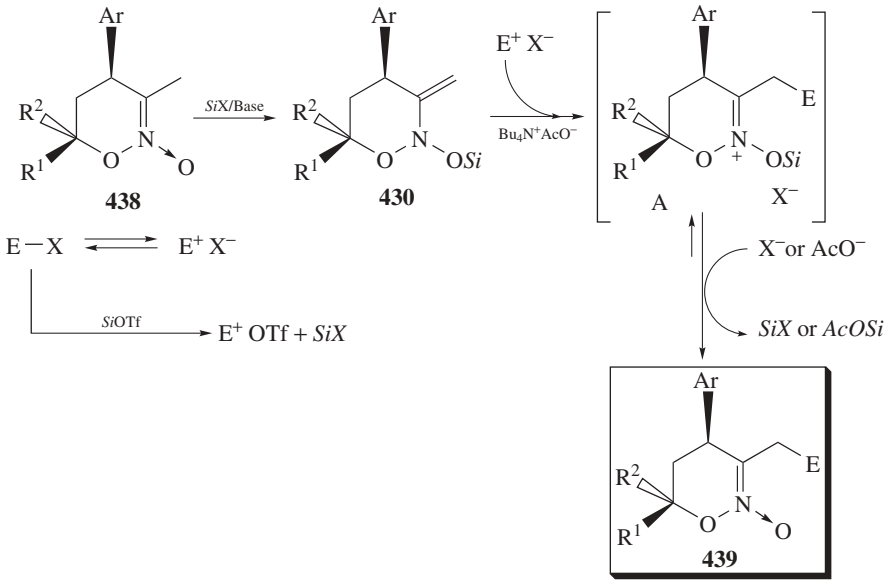
Very interesting results were obtained in studies of the reactions of cyclic ene- nitroso acetals (**430**) with electrophiles E−X (Scheme 3.235, Table 3.30) (264, 515).

Here the bis-oxyiminium cations **A** are also formed as intermediates. The chemistry of these cations was discussed in sufficient detail in Section 3.5.2.3. The trialkylsilyl group can be eliminated from these cations with a good leaving group $\mathbf{X}^-$, but the acetate ion is the reagent of choice for optimization of similar



X_2 - Br_2 or I_2; R^1 = $MeOCO(CH_2)_2$, Bn, $CH_2OSiMe_2Bu^t$, Me, Ph, H; R^2 = H, Me, n-C_5H_{11}.

Scheme 3.234



Scheme 3.235

Table 3.30 The approach to functionalization of substituent at C-3 atom of six-membered cyclic nitronates (see Scheme 3.235)

Entry	Ar	R^1	R^2	Si	X	E	**439**	Yield of **439** %%	dr
1	Ph	Me	Me	$SiMe_3$	OTf	PhCH(OMe)	**a**	71	1.8:1
2	Ph	Me	Me	$SiMe_3$	OTf	p-ClC_6H_4-CH(OMe)	**b**	46	1.3:1
3	Ph	Me	Me	$SiMe_3$	OTf	p-$MeOC_6H_4$-CH(OMe)	**c**	68	1:1
4	Ph	Me	Me	$SiMe_3$	Br[a]	Br	**d**	83	-
5	Ph	Me	Me	$SiMe_3$	I[a]	I	**e**	76	-
6	Ph	MeO	Me	$SiMe_3$	Cl	$4MeC_6H_4S$	**f**	72	-
7	4-MeO-C_6H_4	EtO	H	$SiMe_3$	Cl	$4ClC_6H_4S$	**g**	76	-
8	Ph	H	*n*-BuO	$SiMe_2Bu^t$	OTf	PhCH(OMe)	**h**	45	2:1
9	Ph	*n*-BuO	H	$SiMe_2Bu^t$	OTf	PhCH(OMe)	**i**	55	2.4:1
10	Ph	H	*n*-BuO	$SiMe_2Bu^t$	OTf	4-MeO-C_6H_4 CH(OMe)	**j**	55	2.7:1
11	Ph	H	*n*-BuO	$SiMe_2Bu^t$	OTf	CH_2NMe_2	**k**	89	-

[a] With n-$Bu_4N^+OAc^-$.

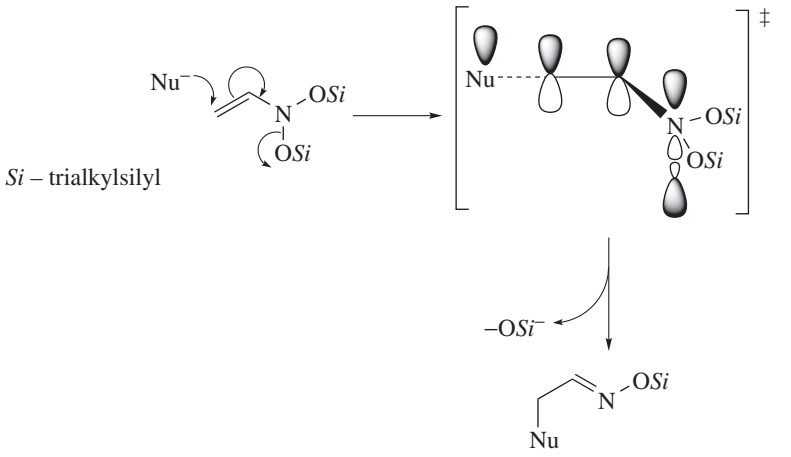
sequences (515). The cations $\boldsymbol{E}^+$ can be generated with the use of substrates $E{-}X$ containing a good nucleofuge $\mathbf{X}^-$. The catalysis with Lewis acids can also be used.

The approach shown in Scheme 3.235 and Table 3.30 makes it possible to functionalize the methyl group at C-3 in various six-membered cyclic nitronates. 3-Halomethyl-substituted nitronates (**439 d,e**) are particularly interesting reagents, which cannot be synthesized by known methods. It should be emphasized that the configurations of the stereocenters at the endocyclic carbon atoms are retained in the transformation (**438**→**439**). Unfortunately, the diastereoselectivity of the generation of a new stereocenter in nitronates (**439**) is low; the resulting stereoisomers can be separated by chromatography.

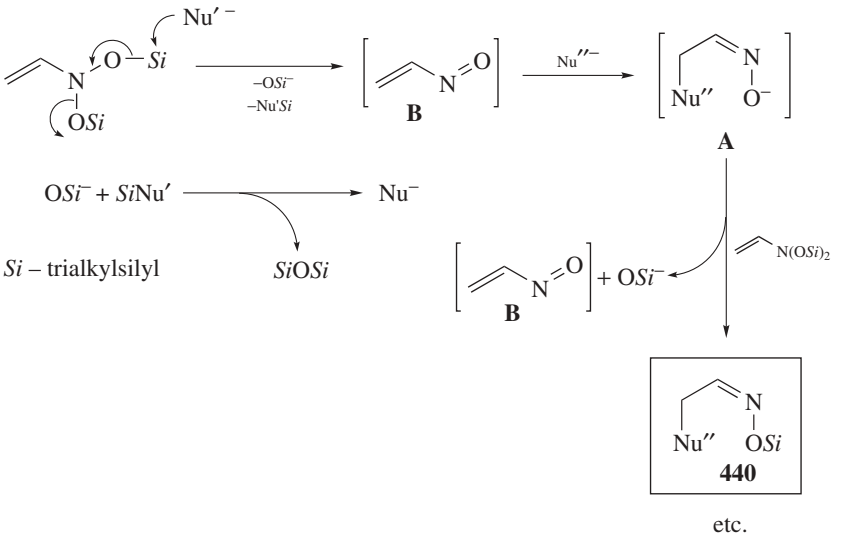
3.5.4.2.2. Reactions of BENA with Nucleophiles The interaction of BENAs with nucleophiles at the β-C atom have been known since the discovery of BENA (188, 464), and these transformations were considered as $S_{N2'}$ processes (Scheme 3.236).

The existence of the stable conformation **B** of BENA (see Section 3.5.4.1. Fig. 3.3), in which the stabilizing $\pi\sigma^*$ interaction is favorable for elimination of the siloxy anion, supports this interpretation.

However, more recent evidence contradicts the above described mechanism of the reaction of BENA with nucleophiles. The mechanistic aspect of the reactions of polyazoles and their *N*-silyl derivatives with BENA has been studied in most



Scheme 3.236



Scheme 3.237

detail (502). According to the interpretation proposed by the authors, nucleophiles (Nu'^-), as well as electrophiles, can induce the transformation of BENAs into conjugated nitrosoalkenes **B** (Scheme 3.237).

The latter as Michael substrates can add a nucleophile at the β-C atom to give the anion of en-oxime **A**. It should be noted that different nucleophiles (Nu'^- and Nu'^-) can be involved in the first and second attacks. Finally, the anion **A** desilylates the next BENA molecule, which leads to the formation of

the silyl derivative of substituted oxime (**440**), as well as to a new nitrosoalkene molecule and the siloxy anion, which either reacts as an initiating nucleophile (Nu') with BENA or reacts with the silyl derivative of azole at the N–Si bond, thus generating the new Nu'^- molecule. Therefore, the reaction of nucleophiles with BENA is considered as a chain process (502) with conjugated nitrosoalkenes **B** as the key intermediates. This interpretation is supported by the following facts: the presence of an evident induction period, instability of BENA toward nitrogen bases, trapping of the nitrosoalkene intermediate by electron-rich dipolarophiles, and finally, visual observation of a blue color of the mixture in some reactions **BENA + nucleophile**.

This complex character of the above mentioned process and the involvement in this interaction of unstable and active intermediates are responsible for the formation of numerous by-products, and therefore, the reaction conditions must be optimized in each particular case.

3.5.4.2.2.1. REACTIONS OF BENA WITH C-NUCLEOPHILES Russian researchers performed comprehensive studies on C,C-coupling reactions of terminal BENAs **A** with anions of nitro compounds (516, 517). This process enables one to assemble β-substituted oximes from two different AN ((**441**) and **442**). It should be noted that compound (**442**) must have the methyl group at the α-C atom necessary for generation of terminal BENA. Both nitroalkanes should be "prepared" for C,C-coupling, that is, AN (**441**) is transformed into the anion **C** by the reaction with DBU, while AN (**442**) is successively transformed into BENA **A** and nitrosoalkene **B**. The C,C-coupling reaction **B + C** is shown in Scheme 3.238.

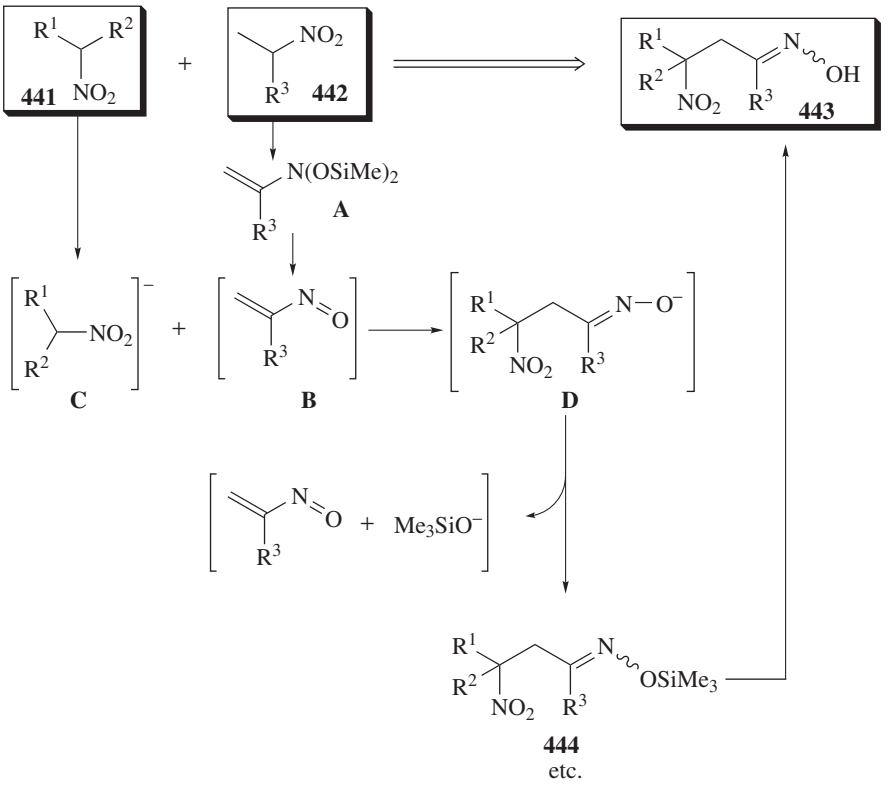
This reaction was interpreted as a chain process. The major reaction is accompanied by two side processes (Scheme 3.239), such as *O*-alkylation of the anion **C** with electrophilic nitrosoalkene (reaction b) giving rise to oximes (**445**) and (**446**) and the addition of the target oxime (**443**) to the second molecule of nitrosoalkene **B** producing dioxime (**447**) (reaction d).

Both processes can be minimized by lowering the C,C-coupling temperature. No evidence for the third possible side reaction, e.g., the addition of the nitro carbanion at the nitroso group of conjugated nitrosoalkene (process c), has been observed in C,C-coupling reactions due apparently to insufficiently high electrophilicity of the nitrogen atom.

After a number of attempts to optimize C,C-coupling, two rather general procedures were developed, which can be performed with anions of both primary and secondary AN (Tables 3.31 and 3.32).

These procedures differ in the nature of the initiating nucleophile (Nu'^-) and the reaction temperature range. For anions derived from secondary AN a lower concentration of active nitroso intermediate **B** is strongly recommended. Therefore, the C,C-coupling of anions obtained from secondary AN is realized at higher temperature (see Table 3.32).

The C,C-coupling reactions of BENAs can also proceed with SENAs (132, 500). However, in this case the part of side reactions is greater and the yields of the target β-nitro oximes are generally lower.



Scheme 3.238

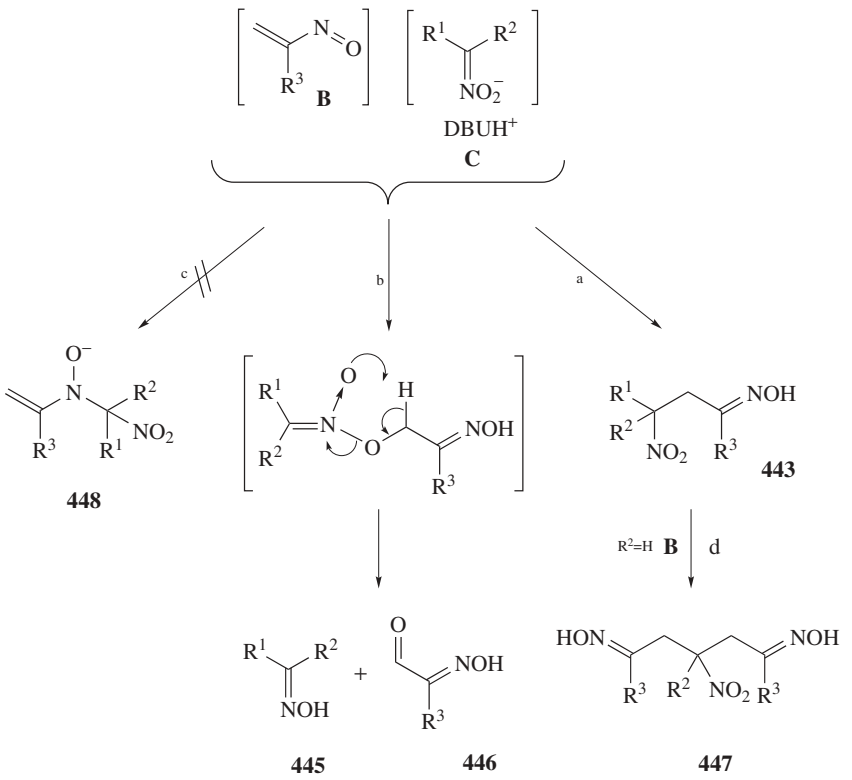
On the basis of the detailed study of C,C-coupling reactions of BENAs with anions of AN, an efficient three-step method was developed for the construction of γ-nitro alcohols (64). It enables one to assemble these difficultly accessible products from two very simple AN molecules (Scheme 3.240).

The first step involves the above considered α,β-C,C-coupling reaction of two different AN molecules; the second step, selective deoximation of the β-nitro oximes obtained the third step, selective reduction of the carbonyl group.

The C,C-coupling reactions of BENA occurs with other stabilized carbanions as well (518) (Scheme 3.241).

This reaction was easily performed with malonic ester derivatives using approaches described above for nitro carbanions. It should be noted that the anion of malonic ester can be prepared not only by the reactions of bases with malonates but also by desilylation of silyl ketene acetal (**449**) with fluoride anion.

For unknown reasons, attempts to perform the C,C-coupling reactions of BENAs with 1,3-diketones (acetylacetone, dimedone, etc.) failed. It is unlikely that this is associated with low nucleophilicity of the resulting carbanions, because



Scheme 3.239

Table 3.31 C,C-coupling BENA with anions of primary AN ($R^2 = H$, catalysis with F^- in CH_2Cl_2)

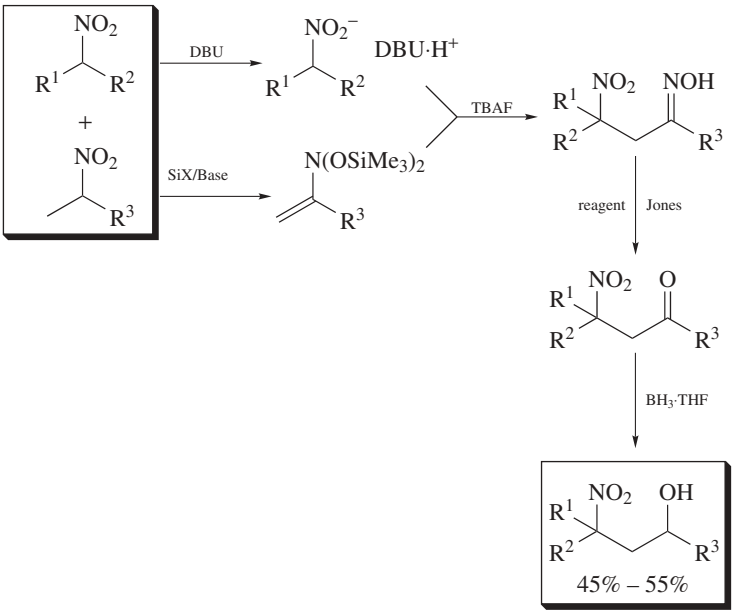
R^1	R^3	Temp., (°C)	Yield of (**443**), %
Et	Me	−78	78
H	Me	−78	64
Me	Me	−78	70
$(CH_2)_2CO_2Me$	Me	−78	90
CO_2Me	Me	−78	64
CH_2CO_2Me	Me	−78	94
CH_2CO_2Me	H	−78	88
$(CH_2)_2CO_2Me$	H	−100	77[a]
Et	$(CH_2)_2CO_2Me$	−100	79[b]
CH_2CO_2Me	$(CH_2)_2CO_2Me$	−100	84
CO_2Me	$(CH_2)_2CO_2Me$	−78	78
Me (R^2 = Me)	Me	−78	52

[a] rel. (**443:447**) = 8:1;
[b] rel. (**443:447**) = 7:1

Table 3.32 C,C-coupling BENA with anions of secondary AN (catalysis with DBU in Et_2O, 0°C)

R^1	R^2	R^3	Yield of (**443**), %
Me	Me	Me	73
Me	$(CH_2)_2CO_2Me$	Me	71
	$-(CH_2)_5-$	Me	54
Me	$(CH_2)_2CO_2Me$	H	62
	$-(CH_2)_5-$	H	47
Me	Me	$(CH_2)_2CO_2Me$	50[a]
Me	$(CH_2)_2CO_2Me$	$(CH_2)_2CO_2Me$	70

[a] rel. (**443:446**)~6:1

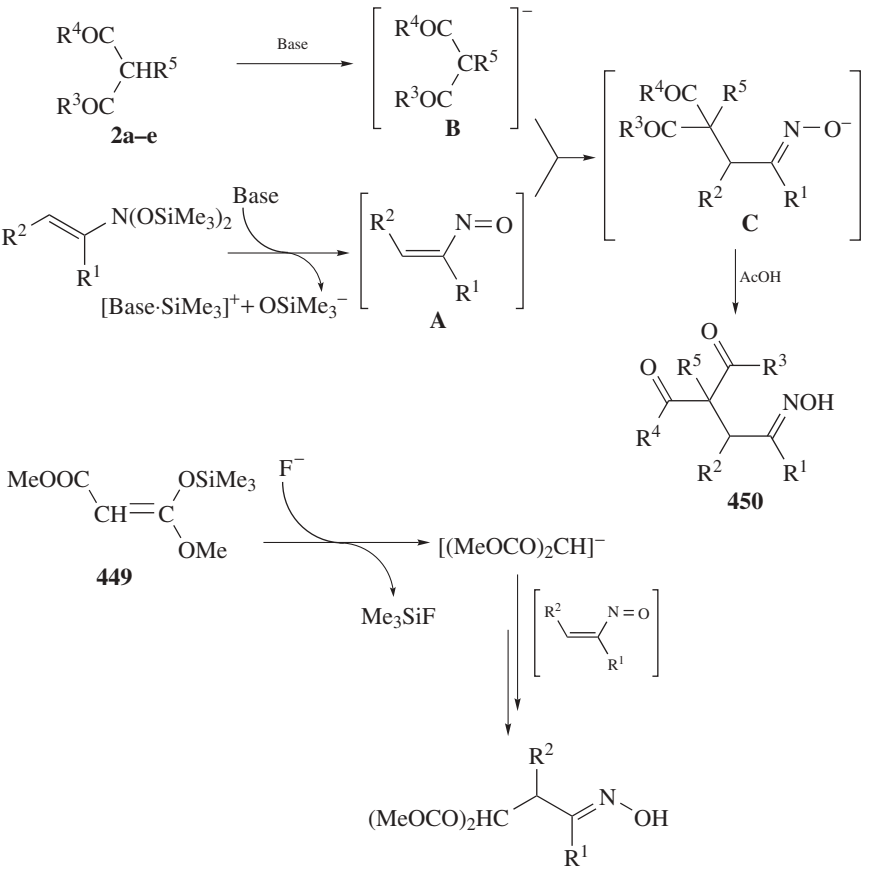


R^1 = Me, Et, $MeO_2C(CH_2)_2$, Ph, H; R^2 = Me, H (instead R^1 and R^2 - $(CH_2)_5$-); R^3 = H, Me, $(CH_2)_2CO_2Me$.

Scheme 3.240

the even more stabilized $[(MeO_2C)_2C(NO_2)]^-$ anion gives the corresponding product of C,C-coupling with BENA, although in low yield.

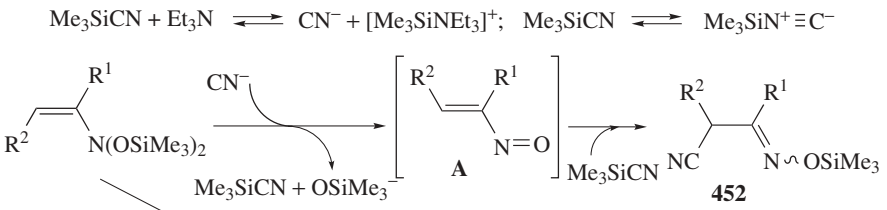
The C,C-coupling reaction of BENAs with the cyanide anion can serve as a convenient procedure for the synthesis of substituted 5-aminoisoxazoles (**451**) from AN (519) (Scheme 3.242). The possible mechanistic scheme of the process



450 c,d

R^1	R^2	R^3	R^4	R^5	**450**	Yield %
Me	H	OMe	OMe	H	**a**	90
H	H	OMe	OMe	H	**b**	55
$MeO_2C(CH_2)_2$	H	OMe	OMe	H	**c**	70 (via **449**)
H	Me	OMe	OMe	H	**d**	59 (via **449**)
— $(CH_2)_4$ —		OMe	OMe	H	**e**	33
Me	H	OMe	OMe	Bn	**f**	74
H	Me	OMe	OMe	Bn	**g**	46
$MeO_2C(CH_2)_2$	H	OMe	OMe	Bn	**h**	54
Me	H	OMe	OMe	$MeO_2C(CH_2)_2$	**i**	50
Me	H	OMe	OMe	NO_2	**j**	17
Me	H	Ph	OEt	H	**k**	38

Scheme 3.241



R^1	R^2	Yield **451** %
H	H	49
Me	H	79
H	Me	70
$MeO_2C(CH_2)_2$	H	61
Ph	H	72
EtO_2C	H	42
MeO_2C	Me	54

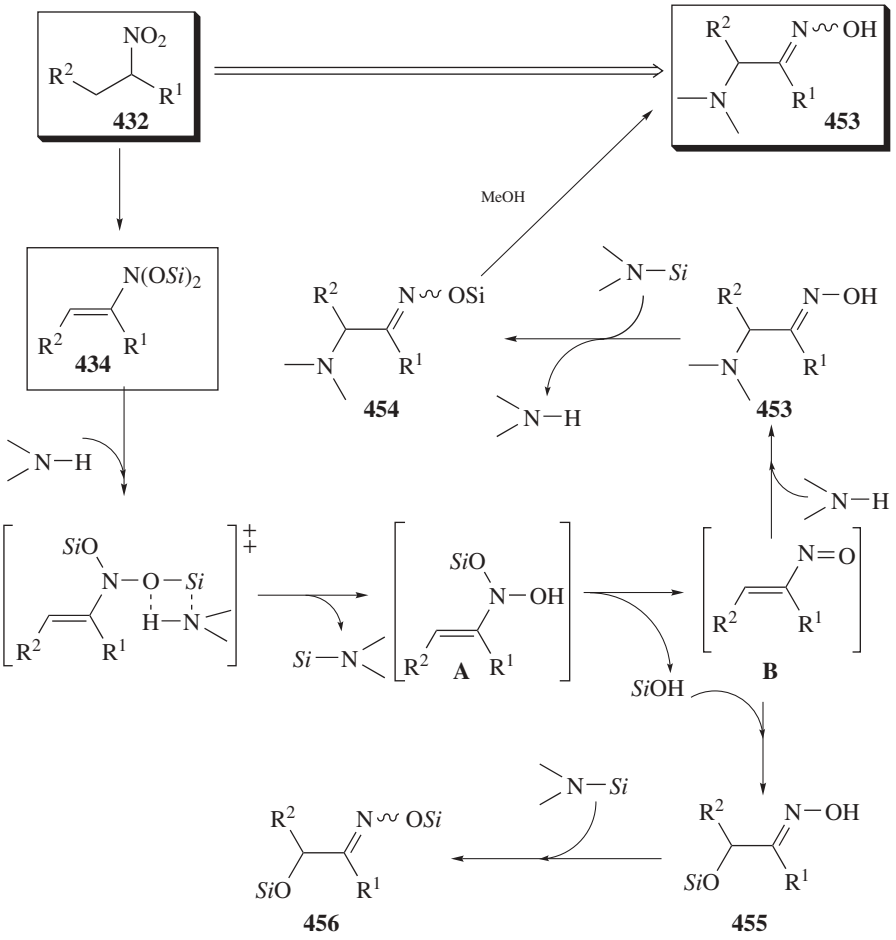
Scheme 3.242

is presented below. It cannot be ruled out that trimethylsilyl isocyanide existing in equilibrium with trimethylsilyl cyanide is the true molecule involved in the reaction (520).

This process affords silyl derivatives of α-cyano oximes (**452**) as the primary products, detected by spectroscopic methods and, in some cases, can be isolated. Their desilylation gives aminooxazoles (**451**). (The synthesis of aminoisoxazoles by the reactions of the cyanide anion with nitrosoalkenes was also documented (503).) The reaction shown in Scheme 3.242 has a general character and can be performed with both terminal and internal BENAs, although special procedures are required for some functionalized BENAs.

3.5.4.2.2.2. REACTIONS OF BENAs WITH *N*-NUCLEOPHILES *N*-Centered nucleophiles, whose reactions with BENA have been studied (291), can be integrated into two large groups: nitrogen bases (various amino derivatives) and amphoteric compounds, which can exhibit both basic and acidic properties (polyazoles, N-nitroamines and HN_3 derivatives). The behavior of these two groups and the conditions of their N,C-coupling reactions with BENA considerably and different therefore are considered separately.

N,C-Coupling Reactions of BENA with Amines. As can be seen from Scheme 3.243, the successful N,C-coupling of BENAs (**434**) with amines allows one to



Scheme 3.243

transform various AN (**432**) into not well known α-amino oximes (**453**), which can be considered as promising building blocks in the design of organic molecules and also as compounds having potential biological activity and other useful properties (e.g., polydentate ligands, chelating agents).

The reactions of amines with BENAs were discussed in several publications (464, 499, 521–523). Although there are no special studies on the reaction mechanism, the available data combined with the results in Reference 502 suggest a mechanistic model for this process (Scheme 3.243).

Apparently, amines act as *Si*-nucleophiles toward BENAs (**434**), and elimination of silylamines (*Si*N <) and silanol (from hemiacetals **A**) affords nitrosoalkenes **B** as key intermediates of this process. According to the published data (503), α-nitrosoalkenes **B** react with amines to give the target oximes (**453**),

which are silylated with $SiN<$ to form a mixture of silylated and free α-amino oximes. The latter can be subjected to desilylation with methanol or analogous agents. This process is accompanied by the side reaction of nitroso intermediate **B** with silanol, which yields oximes (**455**) or its bis-silyl derivatives (**456**) corresponding to the rearrangement product of BENA (see Section **3.5.1.2**).

According to these concepts, the reaction shown in Scheme 3.243 could be characterized by the presence of an induction period. Silyl derivatives of amines ($>N$-*Si*) are not involved in this reaction. The sterically hindered triorganosilyl substituents in BENAs (**434**) also should inhibit the process.

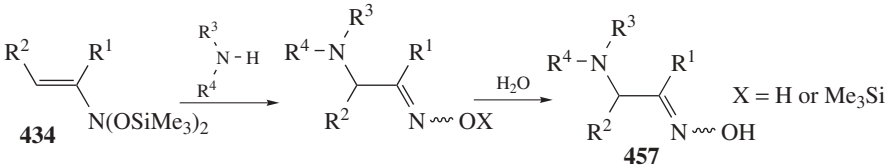
German researchers, who were the first to discover BENAs (464), demonstrated that BENAs (**434**) (both terminal and internal) readily react with secondary amines to give, after aqueous treatment, the corresponding amino oximes (**457**) in yields from moderate to high (Scheme 3.244).

The presence of sterically hindered substituents in amines leads to a decrease in the yield of target products.

The reactions of primary amines with BENAs proceed in a more complex fashion (499, 521). In the absence of steric hindrance in the amine, terminal BENAs are readily and rapidly involved in double β-oximino-alkylation with primary amines (Scheme 3.245, product **A′**). To stop the process at the mono-alkylation step (intermediate **A**), a large excess of amine should be used.

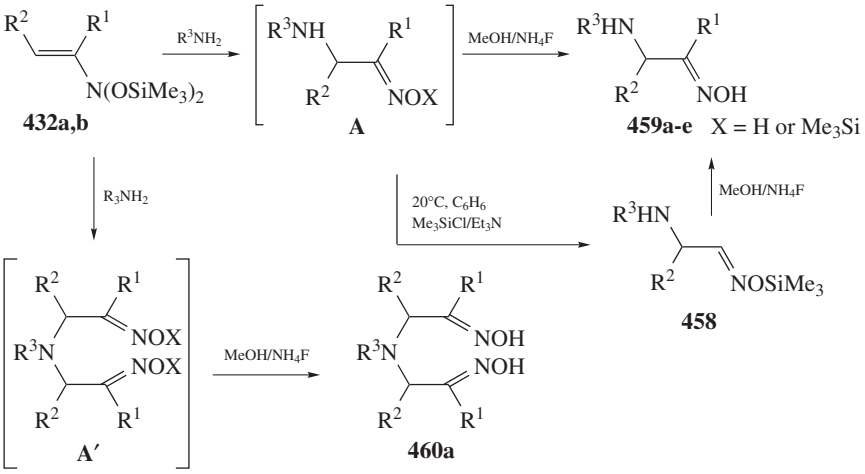
Intermediates **A** and **A′** can be separated by two procedures: complete silylation of these derivatives followed by fractionation of silylated amino oximes (**458**) or by complete desilylation of these intermediates followed by chromatographic purification of the amino oximes (**459**).

The *N,C*-coupling reactions of primary amines with BENAs are very sensitive to steric factors in BENAs. For example, the reactions with terminal BENAs are difficult to stop at the mono-alkylation step, whereas in internal BENAs, it is very difficult to isolate the bis-coupling product. A special procedure, based on this fact, enables one to synthesize bis-oximes (**460**) containing various oximinoalkyl substituents at the nitrogen atom. It should be emphasized that diastereoselectivity of *N,C*-coupling reactions of amines with terminal BENA is very low.

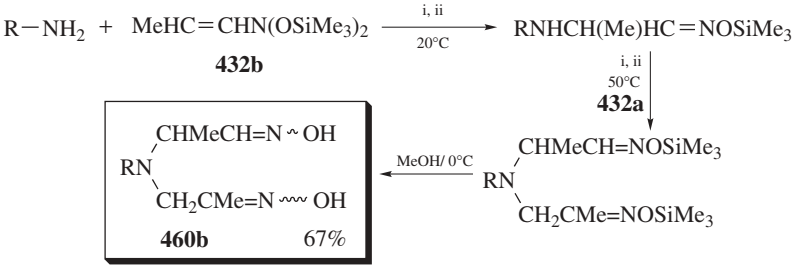


For $R^1 = R^2 = H$: R^3 and R^4 $-(CH_2)_4-$ (64%), $-(CH_2)_5-$ (79%), $-(CH_2)_2-O-(CH_2)_2-$ (68%),
$R^3 = R^4 = Pr^i$ (33%).
For $R^1 = H$; $R^2 = Me$: R^3 and R^4 $-(CH_2)_5-$ (58%).
For $R^1 = Me$; $R^2 = H$: R^3 and R^4 $-(CH_2)_5-$ (81%).

Scheme 3.244



432a (R^1=Me; R^2=H) : R^3 = n –C_6H_{13} **459a** (64%)
R^3 = MeCHPh **459b** (76%)
432b (R^1=H; R^2=Me) : R^3 = n –C_6H_{13} **459c** (57%)
R^3 = MeCHEt **459d** (78%)
R^3 = MeCHPh **459e** (66%)
for **432a** and R^3 = n –C_6H_{13} **460a** (78%)



R = n-C_6H_{13}

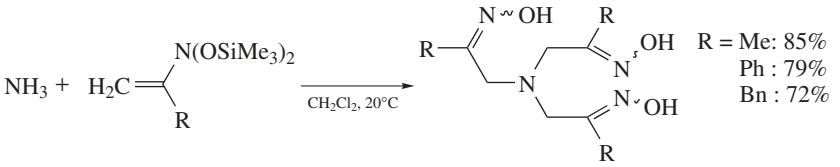
i : 20°C without solvent
ii : C_6H_6, Me_3SiCl/Et_3N

Scheme 3.245

The characteristic features revealed in the coupling reactions of terminal BENAs with primary amines are also true for ammonia (523) (Scheme 3.246).

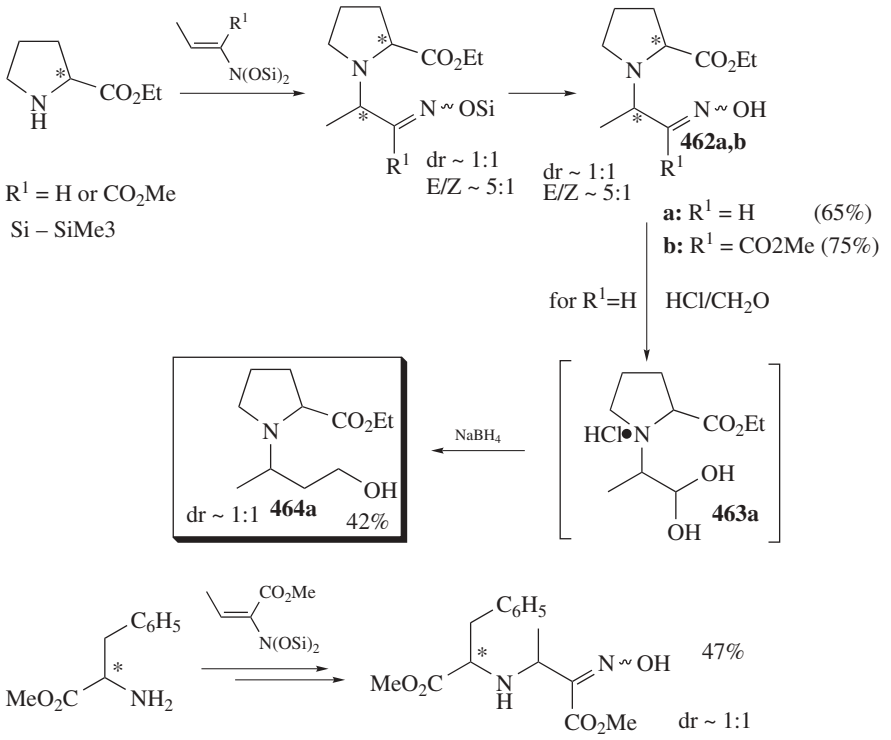
A series of tris -oximes (**461**) were prepared in high yields by the *N,C*-coupling reactions of terminal BENAs with ammonia.

An attempt was made to synthesize optically active non-natural amino acids by the *N,C*-coupling reactions of enantiomerically pure natural amino acids with



461

Scheme 3.246



Scheme 3.247

internal BENAs MeCH=CR'N(OSiMe$_3$)$_2$ (R′=H, CO$_2$Me) (521, 522) (Scheme 3.247). However, not only the low diastereoselectivity of *N,C*-coupling reactions but also low reaction rates of less nucleophilic α-amino acid derivatives, compared to amines, decrease the successful use of this approach.

This reaction was applied to *L*-proline ethyl ester (R′ = H), and two diastereomers were isolated, each diastereomer being a mixture of stereoisomers (*E/Z*) related to the oximino group. Attempts to completely separate these isomers failed. The oximino group of the product (**462a**) was removed by a CH$_2$O/HCl mixture. As a result, hydrated aldehyde hydrochloride (**463a**) was obtained. It

was reduced to form a non-natural amino acid derivative (**464a**), as an equimolar mixture of two diastereoisomers.

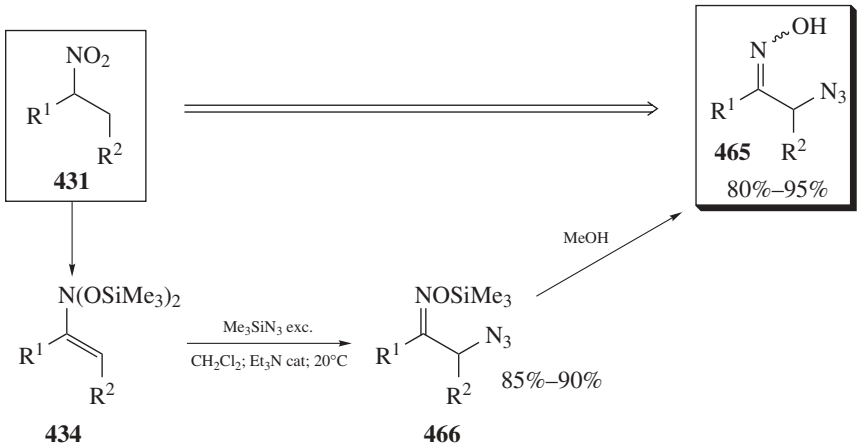
By contrast, *L*-phenylalanine methyl ester does not react with BENA generated from 1-nitropropane (R' = H) due apparently to low nucleophilicity of the amino group. However, the *N,C*-coupling reaction of the ester of this amino acid with another internal BENA (R′ = CO_2Me) proceeds rather readily but is characterized by extremely low diastereoselectivity. Probably, the last N,C-coupling does not occur via an intermediate α-nitroso alkene but by a classical Michael addition to BENA MeCH=C(CO_2Me)N(OSi)$_2$ as to Michael substrate.

N,C-Coupling reactions of BENAs with derivatives of NH-acids. As mentioned above (see Scheme 3.226), *NH*-acids catalyze the rearrangement of BENAs (501, 502), which is the most general process that hinders both the synthesis of BENAs and their desired transformations. Hence, silyl derivatives of *NH*-acids should be used in *N,C-c*oupling reactions with BENAs.

N,C-Coupling reaction of BENA with trimethylsilyl azide is the key step of a very convenient and versatile procedure for the synthesis of otherwise difficultly accessible α-azido oximes (524, 525) (Scheme 3.248).

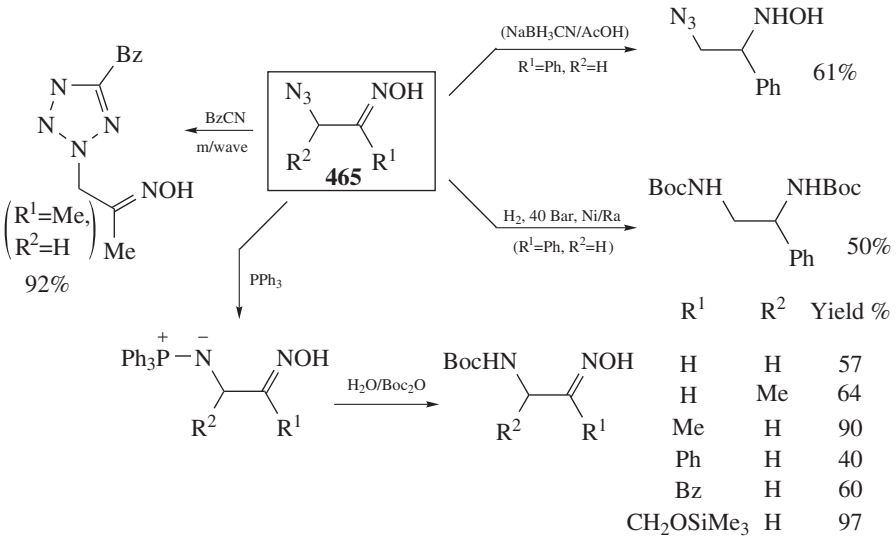
Both terminal and internal BENAs (**434**) are readily subjected to this transformation to give the α-azido oximes (**465**) in very high yields. The improved procedure allows one to prepare compounds (**465**) virtually without by-products. The use of a large excess of silyl azide and the presence of small additives of triethylamine (5%) are of principal importance.

As can be seen in Scheme 3.249, α-azido oximes (**465**) can be involved with advantage in the selective reduction of the azido group in the presence of the oximino fragment and also in the selective or nonselective reduction of the oximino fragment (525).



R^1 = H, Me, $(CH_2)_2CO_2Me$, CH_2OSiMe_3 (OH), Ph, Bn, CO_2Me, CO_2Et; R^2 = H, Me.

Scheme 3.248



Scheme 3.249

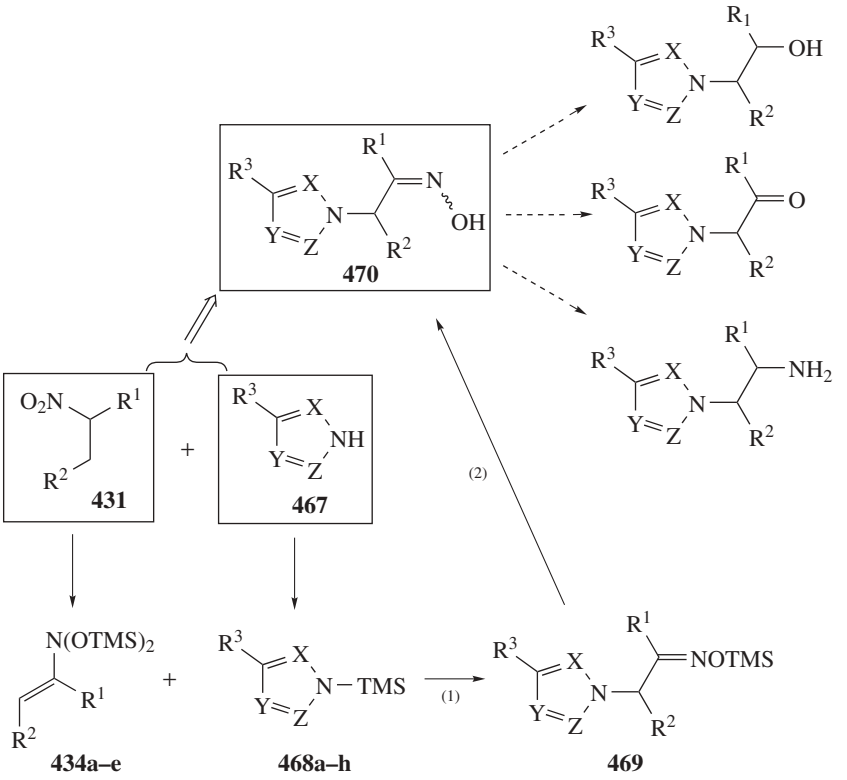
Due to these procedures as well as to some other transformations, the α-azido oximes can be considered as efficient basic reagents in the synthesis of various derivatives of 1,2-disubstituted ethanes using readily available AN (**431**) as starting compounds.

The *N,C*-coupling reaction of BENA with silylated azoles containing at least two nitrogen atoms in the ring was studied in detail (502, 526) (Scheme 3.250, Table 3.32).

Several optimized procedures were developed for the synthesis of various α-azolyl oximes (**470**), including those containing functional groups both in the ring and the alkyl fragment, in high yields. The reaction is performed at near-room temperature without solvent or in dichloromethane in the presence of triethylamine ($\leq 5\%$). The target products are purified by either vacuum fractionation of silyl derivatives (**469**) or chromatography of oximes (**470**).

The *N,C*-coupling reaction of BENAs (**434a–e**) with N-silyl derivatives of asymmetrical azoles (**468**) containing several nitrogen atoms are non-regioselective. Separation of regioisomers of silyl derivatives (**469**) by vacuum distillation can be accompanied by their partial isomerization. Evidently, the reaction of BENA with silyl derivatives of polyazoles occurs through *N,C*-coupling of the above mentioned derivatives (**468**) with intermediate α-nitrosoalkenes **A** (Scheme 3.251) (502).

In this reaction, a new N–C bond is formed with the nitrogen atom more nucleophilic than that bearing the $SiMe_3$ group. Some possible further transformations of intermediates giving rise to the desired oximes and the continuation of the chain are shown in Scheme 3.251 (see Eq. 1).



434	R^1	R^2
a	Me	H
b	H	Me
c	CO_2Me	Me
d	CO_2Et	H
e	$(CH_2)_2CO_2Me$	H

468	X	Y	Z	R^3
a	N	CH	CH	H
b	CH	N	CH	H
c	N	N	CH	H
d	CH	N	N	H
e	C	N	N	*
f	N	N	CH	NHTMS
g	CH	CMe	N	CO_2Et
h	N	CH	CMe	Me

* $-CH=CH-CH=CH-$

Scheme 3.250

Interestingly, the use of free azoles (**471**) instead of their silyl derivatives (**468**) leads to a sharp increase in the contribution of the rearrangement of BENAs (see Eq. (2) in Scheme 3.251; for more details, see Schemes 3.260 and 3.261).

The necessity of the presence of two nitrogen atoms in the azole molecule for *N,C*-coupling reactions is exemplified by indole (see Eq. (3)). Neither indole nor

Table 3.33 Synthesis of silyl derivatives (469) (see Scheme 3.250)

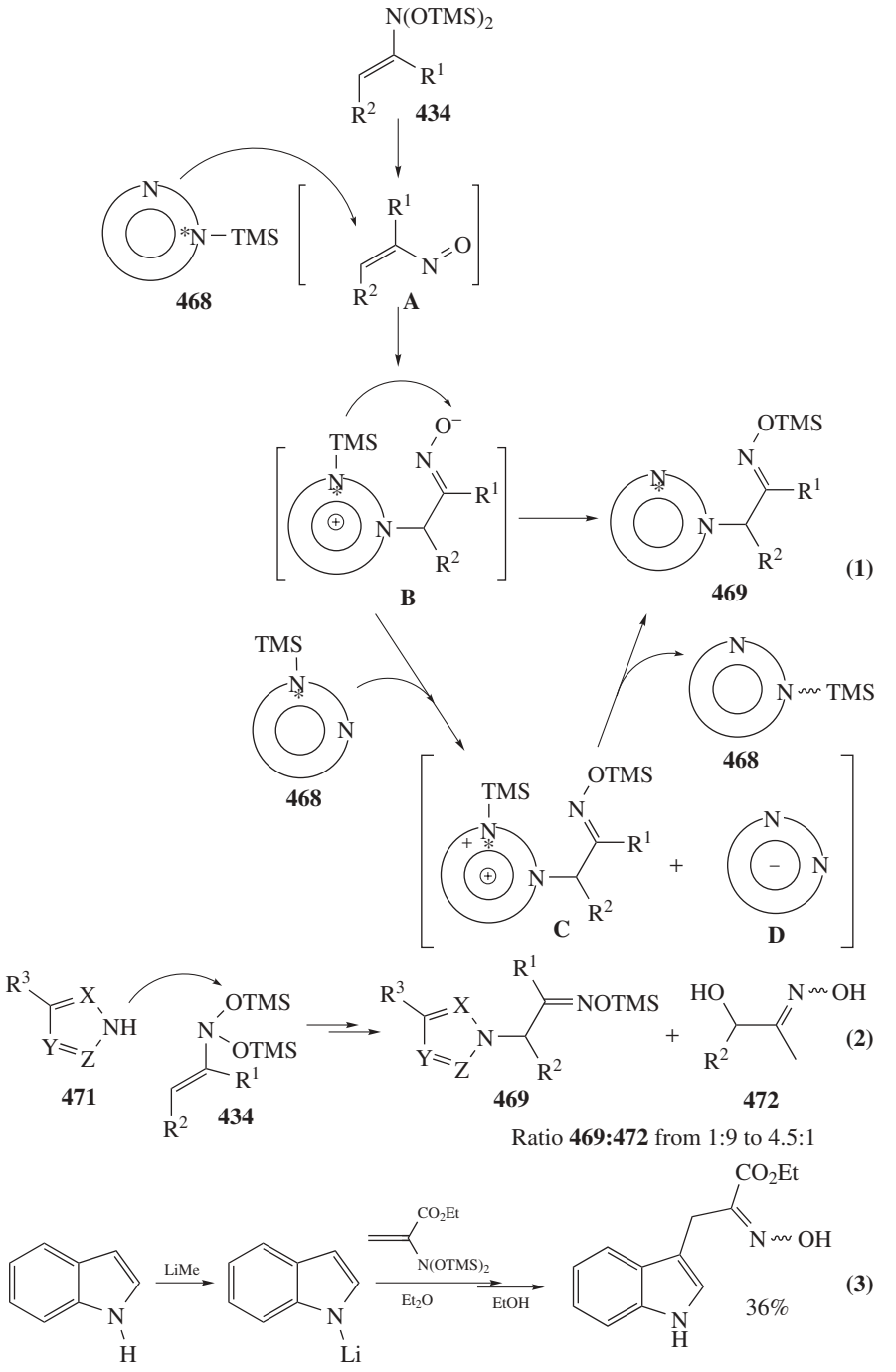
469	X	Y	Z	R^1	R^2	R^3	Yield%
a	N	CH	CH	Me	H	H	95
b	N	CH	CH	H	Me	H	78
c	N	CH	CH	CO_2Me	Me	H	59
d	N	CH	CH	CO_2Et	H	H	88
e	N	CH	CH	$(CH_2)_2CO_2Me$	H	H	92
f	CH	CMe	N	Me	H	CO_2Et	30
g	N	CH	N	Me	H	H	92
h	CH	N	CMe	CO_2Et	H	Me	97
i	CH	N	CH	Me	Me	H	97
k	CH	N	CH	H	Me	H	84
l	N	N	CH	CO_2Me	H	H	92
l'	CH	N	CH	Me	H	H	83
m	N	N	N	Me	Me	H	12
m'	CH	N	CH	H	Me	H	71
n	N	N	CH	H	Me	H	17
n'	CH	N	CH	CO_2Me	Me	H	78
o	N	N	CH	CO_2Me	H	[b]	18
o'	CH	N	CH	$(CH_2)_2CO_2Me$	H	H	64
p	CH	N	CH	$(CH_2)_2CO_2Me$	H	H	33
p'	N	CH	N	Me	H	H	38
q	N	N	N	Me	Me	H	57
q'	N	CH	N	H	Me	H	72
r	CH	N	N	H	H	H	18
s	CH	N	N	$(CH_2)_2CO_2Me$	H	H	98
s'	N	[a]	N	Me	H	[a]	75
t	CH	N	N	Me	Me	[b]	12
t'	N	[a]	N	H	Me	[a]	25
u	[a]	N	N	H	Me	[a]	71
u'	N	[a]	N	CO_2Me	Me	[a]	78
v	[a]	N	N	CO_2Me	H	[a]	19
v'	N	[a]	N	$(CH_2)_2CO_2Me$	H	[a]	65
w	N	N	N	$(CH_2)_2CO_2Me$	H	H	33
w'	N	N	CH	Me	H	NHTMS	69

[a] –CH=CH–CH=CH– attached to X (Y) and instead of R^3;
[b] N instead of CR^3

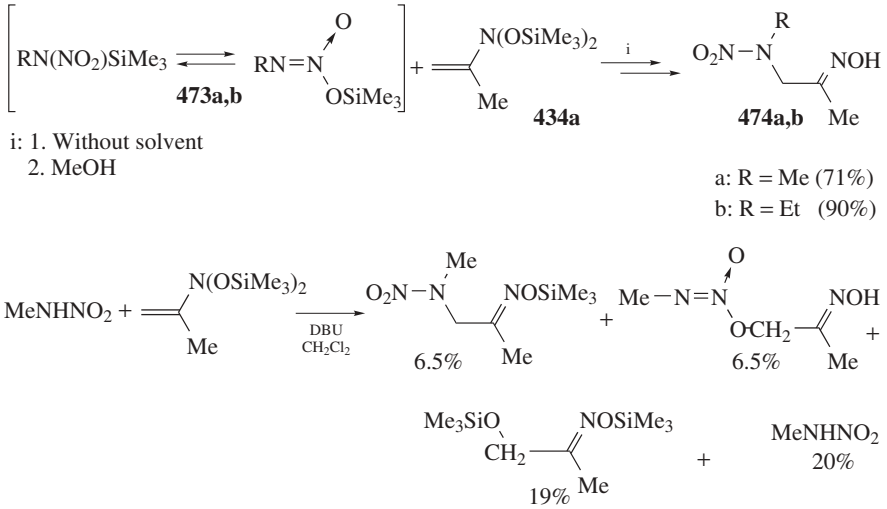
its Li- or trimethylsilyl derivatives are involved in *N,C*-coupling reactions with most of BENAs. The exception is BENA $CH_2=C(CO_2Et)N(OSiMe_3)_2$ containing an EWG group activating the α-C-atom, which, apparently, can react with indole as the Michael substrate.

Similar features were found for *N,C*-coupling reactions of silyl derivatives of N-nitroamines (**473a,b**) and BENA (**434a**) (Scheme 3.252) (501).

Satisfactory yields of the target oximes (**474**) and high chemoselectivity of the process are achieved only with the use of silyl derivatives (**473**). Attempts to


N(OTMS)2
R1
R2
434
N
*N – TMS
468
R1
N
O
R2
A
TMS
O–
N
R1
N
R2
B
OTMS
N
R1
N
R2
469
(1)
TMS
N
N
468
N
N TMS
468
TMS
N
OTMS
N
R1
N
R2
C
+
N
N
D
R3
X
NH
Y
Z
OTMS
N
OTMS
R1
R2
471
434
R1
NOTMS
R3
X
N
Y
Z
R2
469
+
HO
N OH
R2
472
(2)
Ratio 469:472 from 1:9 to 4.5:1
LiMe
N
H
N
Li
CO2Et
N(OTMS)2
Et2O
EtOH
CO2Et
N OH
N
H
36%
(3)

Scheme 3.251



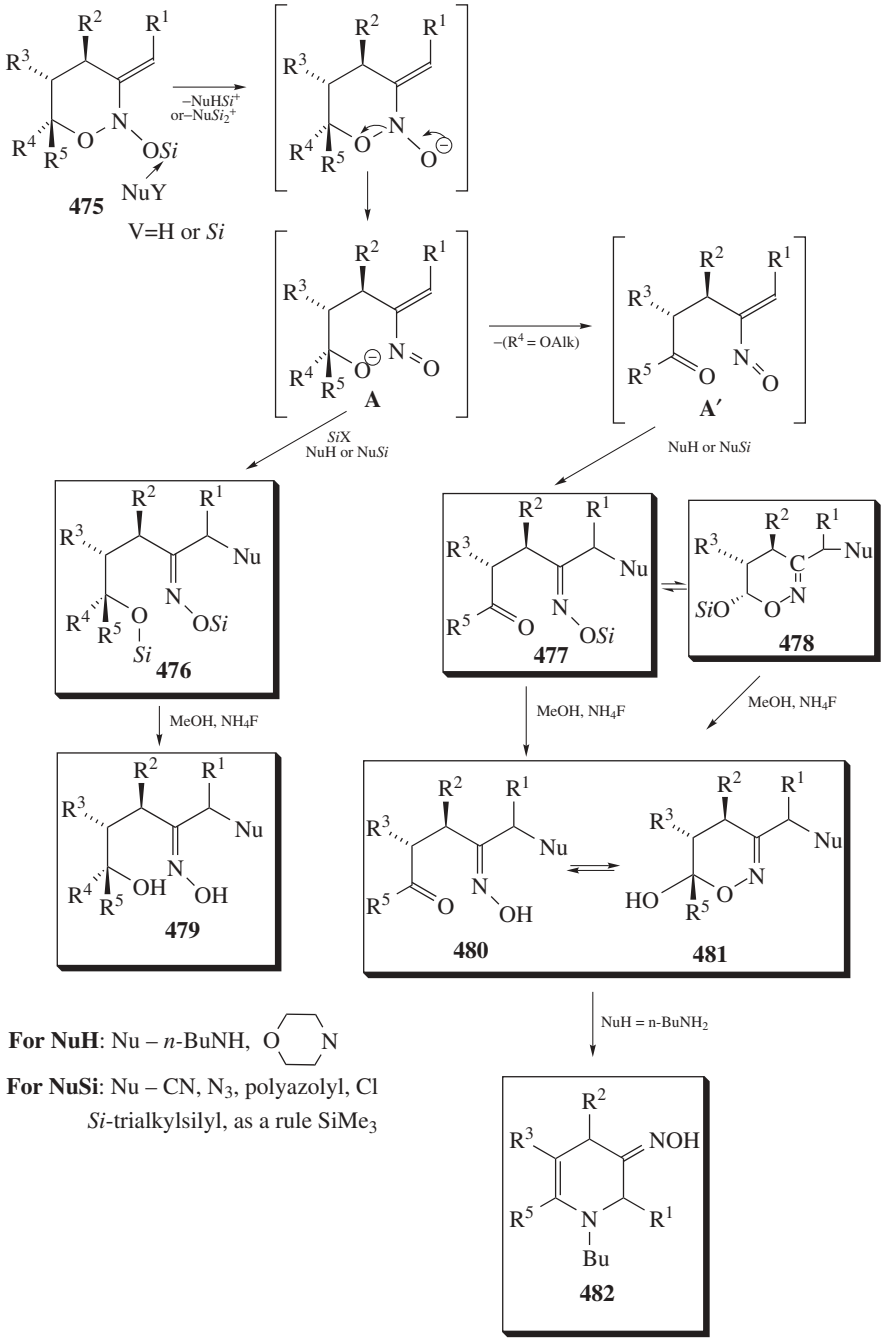
Scheme 3.252

involve free nitroamines in *N,C*-coupling reactions led, first, to a sharp decrease in the rate of the main reaction and, second, to complications of this reaction not only by the rearrangement of BENA but also by *O,C*-coupling of the reagents in side reactions.

3.5.4.2.3. Reactions of Cyclic Conjugated Ene Nitroso Acetals with Nucleophiles
The reaction of six-membered cyclic ene nitroso acetals (**475**) with nucleophiles has a high potential and will probably provide the basis for a promising procedure for the synthesis of polyfunctional compounds from very simple precursors, the more so that the configurations of stereocenters in the starting nitronate (**475**) can be retained in particular transformations (Scheme 3.253). Unfortunately, the available data (264) are insufficient to elucidate the complete mechanism of this process.

Although the reactions of cyclic nitroso acetals with nucleophiles need to be studied in more detail, important known tendencies are in good agreement with mechanistic models considered in the previous section. Initially, nucleophiles **NuY** (*n*-$BuNH_2$, Me_3SiCN, Me_3SiN_3, Me_3SiCl and *N*-TMS derivatives of polyazoles) react with the silicon atom of ene nitrosoacetals (**475**). (This interpretation is supported by the fact that the N,C-coupling reaction does not proceed in the presence of a sterically more hindered trialkylsilyl fragment ($Si = Me_2Bu^tSi$)).

Then the trialkylsilyl fragment is eliminated and the resulting anion is rearranged into the anion **A** through the cleavage of the weak endocyclic N–O bond. Then, if the substituent R^4 is the alkoxy group, it is eliminated to form functionalized nitrosoalkene **A′**. The reaction of the latter with nucleophiles in the presence of silylating agents produces silyl derivatives of oximes (**477**) or six-membered cyclic ethers (**478**). Both intermediates can be detected by NMR


475
V=H or Si
A
A′
476
477
478
479
480
481
482
MeOH, NH4F
NuH = n-BuNH2
For NuH: Nu – n-BuNH,
For NuSi: Nu – CN, N3, polyazolyl, Cl
Si-trialkylsilyl, as a rule SiMe3

Scheme 3.253

monitoring. Methanolysis of these intermediates affords oximes (**480**) containing the carbonyl group or their respective cyclic ethers **481**. The tautomeric equilibria (**477**)⇄(**478**) and (**480**)⇄(**481**) were observed by NMR. If NuH is *n*-$BuNH_2$, oximes (**480**) can be cyclized into derivatives of tetrahydropyridine (**482**).

If the alkoxy group at the C-6 atom in nitroso acetals (**475**) is absent, silyl derivatives (**476**) are generated instead of nitroso ketones A′, and methanolysis of compounds (**476**) gives rise to γ-hydroxy oximes (**479**).

Generally, the N,C-coupling reactions of compounds (**475**) with nucleophiles are performed at 20°C in dichloromethane in the presence of 5% triethylamine or N-methylimidazole.

Hence, oximes (**476**) to (**482**) are the major products of this reaction sequence (Table 3.34).

In many cases, the yields of these products are high. However, the use of *N*-silylated triazoles as nucleophiles or the use of cyclic nitroso acetals (**475**) substituted at the C-3 atom leads to a noticeable decrease in the yield of the oximes. Therefore, steric hindrance in nitroso acetals and a decrease in nucleophilicity of *N*-centered nucleophiles result in an increase in the contribution of side reactions. It should be emphasized that *C*-nucleophiles, such as anions of nitro compounds, are not involved in coupling reactions with cyclic nitroso acetals (**475**). However, the products, which formally correspond to the C,C-coupling mechanism, can be prepared by the nucleophilic substitution of chlorine in compound (**476 d**) by a S_{N2} mechanism (Scheme 3.254, product (**483c**), the yield was 79%).

The nucleophilic substitution of halogen by the CN^- or N_3^- anions in product (**476 d**) provides an alternative route to bis-silyl derivatives of oximes (**476a**) and (**477a**) (cf. entries 7 and 10, Table 3.34). Interestingly, desilylation of these products can be performed in steps by removing silyl protecting groups from the oximino and hydroxyl groups successively.

An efficient procedure for the synthesis of 5-aminoisoxazoles starting from BENAs (Scheme 3.242) was described in Section 3.5.4.2.2.1. An analogous approach to the synthesis of aminooxazoles can be successfully used in the case of silyl derivatives of α-cyano-substituted oximes (**476a,b**) (Scheme 3.255).

It should be noted that one of the N,C-coupling reactions, involving cyclic nitroso acetals, cannot be explained by a traditional explanation involving intermediate conjugated nitrosoalkenes (Scheme 3.256).

It cannot be ruled out that this reaction occurs by an $S_{N2'}$ mechanism, which has been proposed many times earlier for the interpretating the reactions of nucleophiles with BENA (see, e.g., Scheme 3.236). The removal of the Me_3Si group from nitroso acetals is facilitated by the contribution of the $\pi \rightarrow \sigma^*$ interaction. The reaction shown in Scheme 3.256 is highly diastereoselective.

3.5.4.2.4. Behavior of BENA in Radical Reactions Until recently, data on the behavior of BENAs in radical reactions have been lacking in the literature. However, several successive approaches to radical alkylation of BENA at the β-C atom have been recently developed by Korean researchers (527).

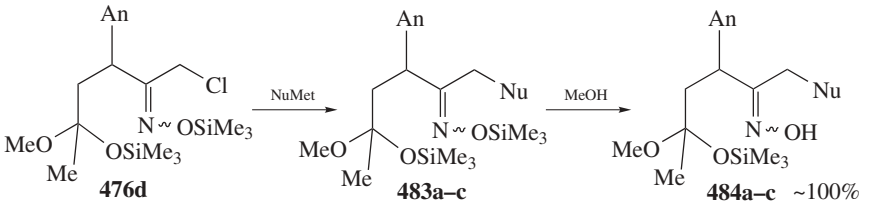
Table 3.34 The coupling of nitroso acetals 475 with nucleophiles (20°C, CH_2Cl_2) (528)

Entry	Nu-Y (Y−H or $SiMe_3$)	R^1	R^2	R^3	R^4	R^5	Product	Yield %
1	Morpholine	H	An	H	OMe	Me	(**480a + 481a**)	70
2	Morpholine	H	An	H	OEt	H	(**481b**)	71
3	Morpholine	H	Ph	H	OMe	Me	(**480c + 481c**)	60
4	Morpholine	H	Ph	H	Me	Me	(**479a**)	69
5	n-$BuNH_2$	H	Ph	H	Me	Me	(**479b**)	76
6	n-$BuNH_2$	H	An	H	OMe	Me	(**482a**)	91
7	Me_3SiCN[a]	H	An	H	OMe	Me	(**476a**)	95
8	n-$BuNH_2$	H	An	H	OEt	H	(**482b**)	92
9	Me_3SiCN[a]	H	Ph	H	Me	Me	(**476b**)	98
10	Me_3SiN_3[a]	H	An	H	OMe	Me	(**477a**)	84
11	Me_3SiN_3[a]	H	Ph	H	Me	Me	(**476c**)	92
12	Me_3SiCl[b]	H	An	H	OMe	Me	(**476d**)	87
13	Bu^tMe_2SiCl[b]	H	An	H	OMe	Me	(**477b**)	56
14	Me_3Si-N-pyrazol[a]	H	An	H	OMe	Me	(**477c**)	74
15	Me_3Si-N-pyrazol[a]	H	An	H	OEt	H	(**478a**)	73
16	Me_3Si-N-pyrazol[a]	H	Pr	H	Me	Me	(**476e**)	92
17	Me_3Si-N-imidazole[a]	H	An	H	OMe	Me	(**478b**)	87
18	Me_3Si-N-imidazole[a]	H	An	H	OEt	H	(**478c**)	85
19	Me_3Si-N-imidazole[a]	H	An	-$(CH_2)_4$-		H	(**476f**)	67
20	Me_3SiCl[b]	H	Ph	H	OMe	Me	(**476g**)	92
21	Me_3Si-N-imidazole[a]	H	Ph	H	Me	Me	(**476h**)	74
22	Me_3Si-N-imidazole[a]	Me	An	H	OMe	Me	(**478d**)	32
23	1-Me_3Si-triazole-1,2,3[a]	H	An	H	OMe	Me	(**477d**)	42
24	1-Me_3Si-triazole-1,2,3	H	An	H	OMe	Me	(**478e**)	47
25	1-Me_3Si-triazole-1,2,3[a]	H	Ph	H	OMe	Me	(**477e**)	41
26	1-Me_3Si-triazole-1,2,3[a]	H	Ph	H	Me	Me	(**476i**)	41
27	1-Me_3Si-triazole-1,2,3[a]	H	An	H	OMe	Me	(**477f**)	35
28	1-Me_3Si-triazole-1,2,3	H	An	H	OMe	Me	(**478f**)	38
29	1-Me_3Si-triazole-1,2,3	H	Ph	H	OMe	Me	(**477g**)	39
30	1-Me_3Si-triazole-1,2,3	H	Ph	H	Me	Me	(**476j**)	45

[a] 5% Et_3N.
[b] N-methyl-imidazole.

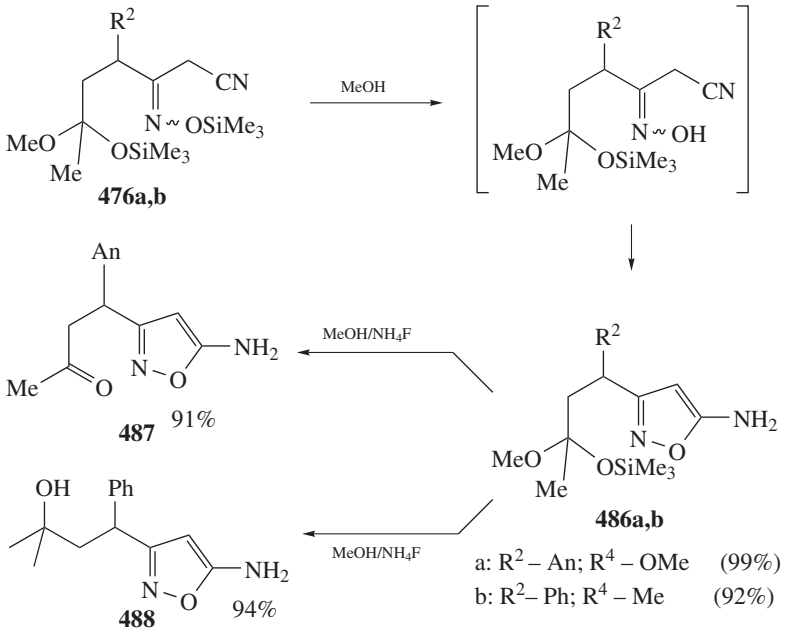
One approach is based on the generation of radicals R′ by UV irradiation of alkyl halides R′I together with hexaalkyldistannanes (Scheme 3.257).

The resulting radicals R′ efficiently alkylate BENAs (**495**) at the β-C atom to give silyl derivatives of oximes (**496**) in good yields. The latter readily undergo deoximation in the presence of 1 M hydrochloric acid to give the corresponding carbonyl compounds (**494**). Thus, a convenient procedure was developed for the synthesis of carbonyl compounds (**494**) from secondary AN (**493**) through the intermediate terminal BENA (**495**) (527).

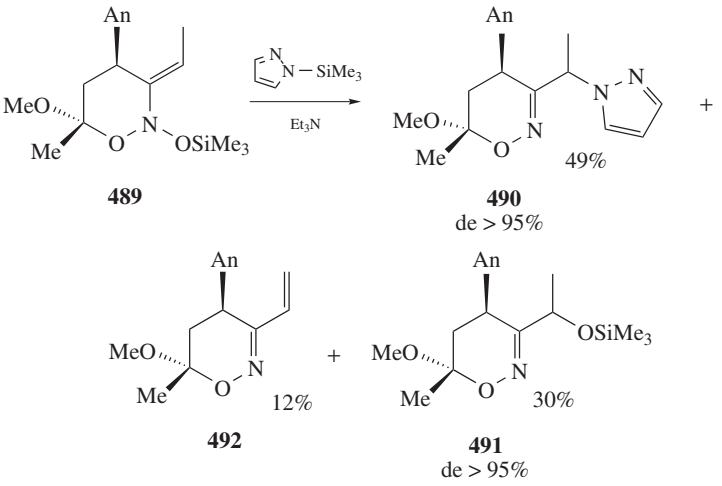


Nu	Met	Conditions	Product	Yield %
CN	K	DMF, 100°C	**483a**	91
N_3	Na	DMF, 100°C	**483b**	92
$[HC(CO_2Me)_2]^-$	K	DMF, 20°C	**483c**	79

Scheme 3.254



Scheme 3.255



Scheme 3.256

Special experiments demonstrated that, under similar conditions, BENA (**497**) containing the terminal C,C double bond conjugated with the enamine fragment is regioselectively alkylated at the terminal double bond to give (**498a–d**), which are silyl derivatives of conjugated ene oximes. The oximino groups in these products can be subjected to desoximation giving rise to conjugated unsaturated aldehydes containing remote functional groups (see, e.g., (**499c**) Scheme 3.258).

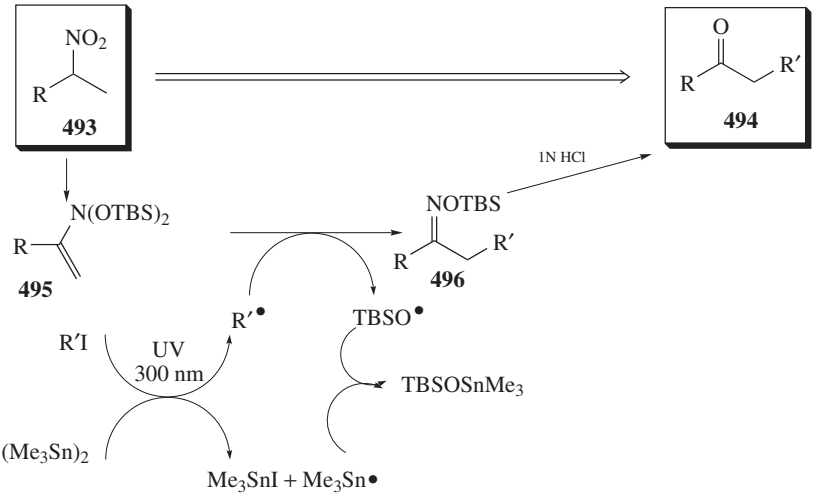
It was demonstrated (527) that radical alkylation of BENAs can be performed in the absence of totic organotin compounds (Scheme 3.259).

In this modification, the radical C,C-coupling reaction is initiated by the addition of the initiator V-70, which evidently generates the $OSiPh_2Bu^t$ radical from the specially prepared BENA (**500**). Under the reaction conditions, the latter radical is rearranged into the $Si(OPh)PhBu^t$ radical (529), which can cause growth of the chain as shown in Scheme 3.259. The product of this C,C-coupling is a functionalized conjugated ene oxime (**501**).

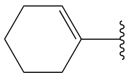
A representative group of oximes (**502**) were prepared according to this approach.

3.5.4.3. Main Side Reactions Occurring During the Synthesis and Transformations of BENA

3.5.4.3.1. Main Rearrangements of BENA In previous Sections (3.5.4.1. and 3.5.4.2.), α-hydroxy oximes (**503**) and their bis-silyl derivatives (**504**) were considered as undesired by-products, formed in the synthesis and chemical transformations of BENA. The aim was to minimize the amount of these impurities. On the other hand, oximes (**503**) are convenient precursors of various useful products, such as β-amino alcohols (530), amino acids (531), α-hydroxycarbonyl compounds (532) and various heterocyclic systems (533).



TBS − $SiMe_2Bu^t$

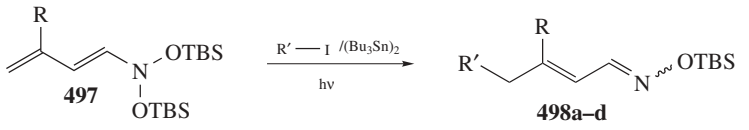
R	R′	Yield **496** %,%	Yield **494** %,%
H	CH_2SO_2Ph	85	86
Me	CH_2SO_2Ph	71	91
n-C_3H_7	CH_2SO_2Et	70	85
Ph	CH_2SO_2Et	82	93
	CH_2SO_2Ph	79	85
	CH_2SO_2Et	72	
SPh	CH_2SO_2Et	76	73
	CH_2SO_2Ph	79	
CO_2Et	CH_2SO_2Et	70	88
Br	CH_2SO_2Ph		93

Scheme 3.257

Hence, it is worthwhile to make an attempt to develop a convenient procedure for the synthesis of oximes (**503**) from available AN by rearrangements of the corresponding BENAs.

There are two main approaches to the generation of derivatives (**504**) from BENA (534) (Scheme 3.260).

One approach is based on the reaction of BENAs with electrophiles *E*–*X* (path (a)) giving rise to cationic intermediates **A**, which react with the anionic intermediate [X–E–O*Si*]$^-$ without leaving the cell. As a result, the O*Si*$^-$ fragment is "transferred" by the electrophile (LA) to the β-carbon atom to give bis-silyl derivative (**504**). If the O*Si*$^-$ anions leaves the cell, it can react with the starting BENA as the nucleophile through the pathway (b) (see below).



TBS – $SiMe_2Bu^t$

$EtO_2CCH_2CH_2CH{=}CHCHO$

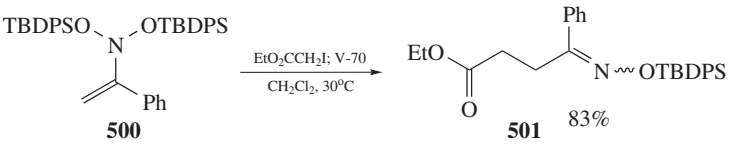
499c 93%

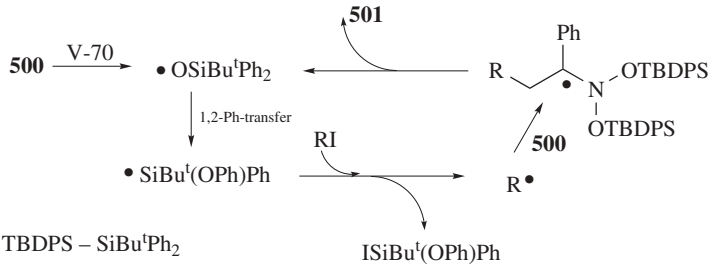
498	R	R′	Yield%
a	OTBS	$PhSO_2$*	50
b	OTBS	CH_2CO_2Me	58
c	H**	CH_2CO_2Et	65
d	H	CH_2SO_2Ph	62

* $PhSO_2Br$ as precursor

** $(Me_3Sn)_2$ instead $(Bu_3Sn)_2$

Scheme 3.258

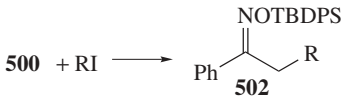




TBDPS – $SiBu^tPh_2$

$ISiBu^t(OPh)Ph$

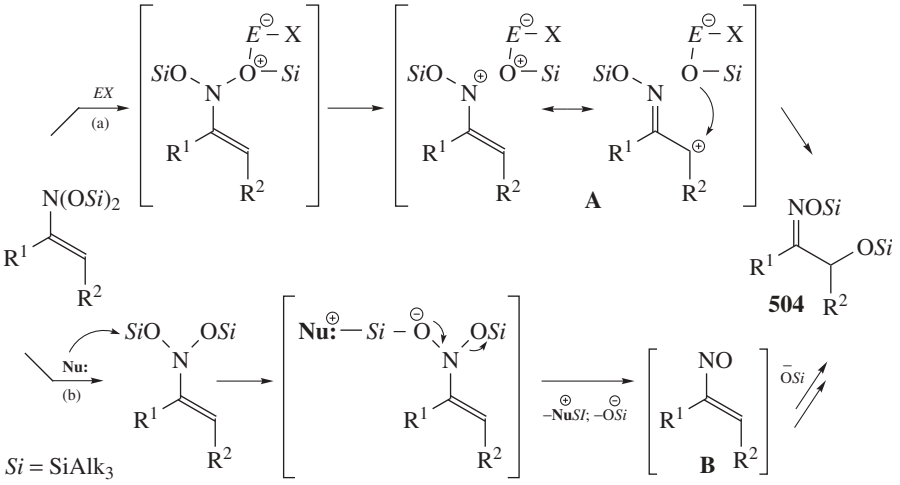
V-70 – 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile)



R	Yield **502** %
$PhSO_2CH_2$	61
Et_2NCOCH_2	63
$NCCH_2$	68
EtOCOCH(Me)	72
$(EtOCO)_2CH$*	75

* $(EtOCO)_2CHBr$ as precurssor

Scheme 3.259

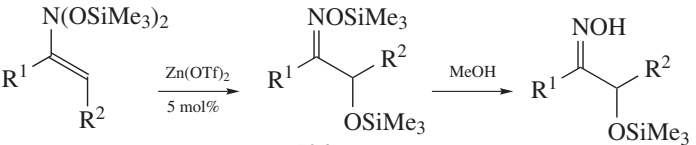


Scheme 3.260

Another approach is based on the reaction of nucleophiles with BENA at the silicon atom (path (b)) generating nitrosoalkene **B** as the key intermediate. After the addition of the O*Si*$^-$ anion and the reaction of the resulting anion with the next BENA molecule in the chain process, this nitrosoalkene gives the target derivative (**504**) (for more details, see the study (502)). Nitrosoalkenes **B** tend to be involved in various side reactions, such as polymerization, rearrangements, and so on (for more details, see Ref. 503). In addition, the reactivity of these compounds toward the O*Si*$^-$ anion would be much lower than that of the cationic intermediate **A**. Hence, the approach (a) seems to be a preferred strategy for the rearrangement BENA→(**504**). Lewis acid *E*–*X* used for the rearrangement must not passivate the O*Si*$^-$ anion, and the X$^-$ fragment involved in the LA must not be nucleophilic toward the cation **A**, lest the acid be competitive with the O*Si*$^-$ anion for this cation.

A priori, derivatives of triflic acid (silyl triflates, salts of triflic acid, etc.) correspond to the above conditions. After a series of experiments, $Zn(OTf)_2$ was chosen as the most efficient LA for the rearrangement BENA→(**504**) (Scheme 3.261) (534). (It should be noted that the rearrangement BENA→(**504**) under the action of silyl LA has been observed earlier (188, 465, 466), but the yields of derivatives (**504**) have been disappointing.)

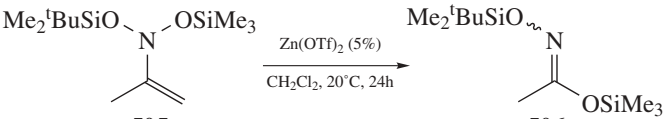
The rearrangement of BENA (**505**) containing various silyl fragments afforded exclusively a derivative of oxime (**506**) containing various triorganosilyl fragments in the oximino and hydroxy groups, that is, only the sterically least hindered trimethylsilyl fragment (Scheme 3.262) migrated. These data rule out the formation of nitrosoalkene **A** as the intermediate, which indicates that the rearrangement occurs through the pathway (a).



434 **504** **503**

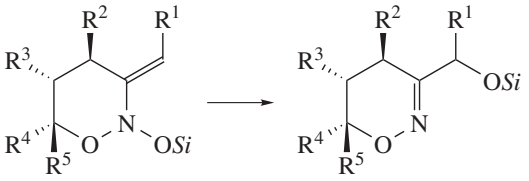
R^1	R^2	Yield 504 %	Yield 503 % (on BENA)
Me	H	88	83
H	H	91	87
H	Me	90	89
$-(CH_2)_4-$		86	80
Ph	H	95	93
$PhCH_2$	H	83	81
CO_2Et	H	75	63
CO_2Me	Me	83	78
$CH_2CH_2CO_2Me$	H	80	71

Scheme 3.261



505 **506**

Scheme 3.262



507a-g **508a-g**

Scheme 3.263

Interestingly, $Zn(OTf)_2$ is of little use for the rearrangement of cyclic six-membered *N*-siloxynitroso acetals (**507a–g**) into the corresponding 5,6-dihydro-4*H*–oxazines (**508a–g**) (Scheme 3.263, Table 3.35) (264, 535).

For products (**507**), the choice of reaction conditions is governed by the nature of the C,C double bond. For terminal enamines (**507a,b**), trialkylsilyl triflates with a pyridine additive is the reagent of choice (535) (Table 3.35, entries 1,2). By

Table 3.35 Rearrangement of cyclic six-membered *N*-siloxynitroso acetals 507a–g.

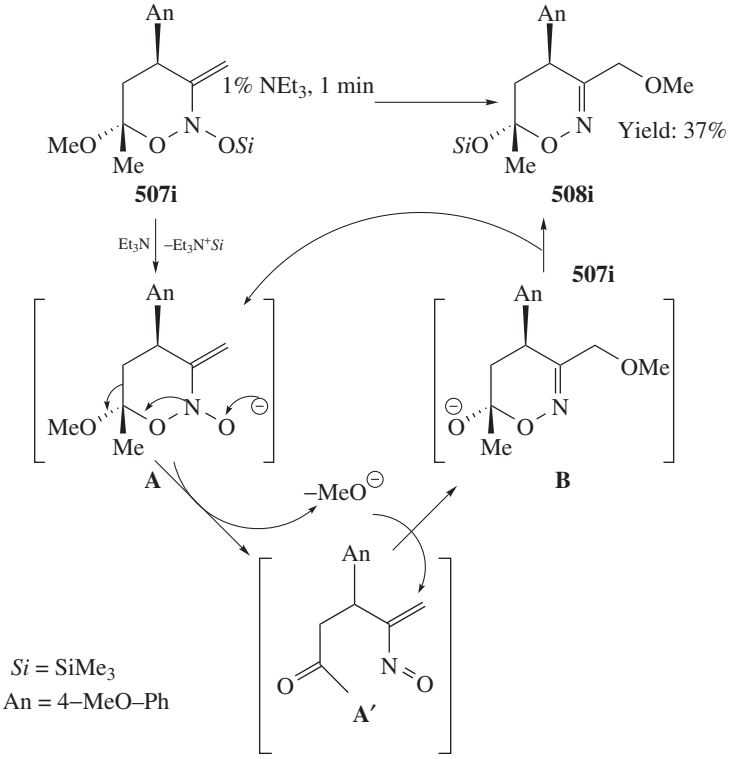
Entry	Product (**508**)(**507**)	R^1	R^2	R^3	R^4	R^5	*Si*	Conditions	Yield, (**508**) %
1	**a**	H	Ph	H	Me	Me	TMS	TMSOTf, Py, −78°C, 1 h	92
2	**b**	H	An	$-(CH_2)_4-$		H	TMS	TMSOTf, Py, −78°C, 1 h	66
3	**c**	Me	An	H	OMe	Me	TMS	$CHCl_3$, 20°C, 24 h	95[a]
4	**d**	Me	An	H	OEt	H	TBS	$CHCl_3$, 20°C, 24 h	74[a]
5	**e**	Me	Ph	H	OMe	Me	TMS	$CHCl_3$, 20°C, 24 h	92[a]
6	**f**	4-Cl-Ph	An	H	OMe	Me	TBS	TBSOTf, Et_3N, −78°C, 1 h	88[a]
7	**g**	An	An	H	OMe	Me	TMS	TMSOTf, Et_3N, −78°C, 24 h	88[a]
8	**h**	CO_2Me	An	H	OMe	Me	TMS	No reaction	

TMS–$SiMe_3$, TBS–$SiMe_2Bu^t$, An–4-MeO-C_6H_4; [a]de > 95%

contrast, internal nitroso acetals **507c–e** most readily undergo rearrangements at ambient temperature in the absence of Lewis acids after storage in chloroform to give a new stereocenter with very high diastereoselectivity (Table 3.35, entries 3–5). Interestingly, other solvents (hexane or ethyl acetate) do not facilitate the rearrangement under these conditions. If R^1 is an electron-donating aryl fragment (see e.g., in product (**507 g**)), the rearrangement (**507**→**508**) can also occur in the absence of LA. However, to increase the chemoselectivity of the reaction, it is worthwhile to perform this reaction at lower temperature (see entry 7, Table 3.35).

Entry 8 (Table 3.35) indicates that nitroso acetals (**507**) containing electron-withdrawing substituents at the end of the double bond, that is, those having no considerable $\pi \rightarrow \sigma^*$ effect and destabilizing the cationic intermediate **A** (Scheme 3.260), do not undergo rearrangements into respective α-hydroxy oxime derivatives at all. It should be noted that the reaction of nitroso acetal (**507a**) in the presence of trifluoroacetic anhydride produces 5,6-dimethyl-4-phenyl-3-trifluoroacetoxymethylene-5,6-dihydro-4*H*-oxazine in 85% yield (535).

The reactions of six-membered cyclic nitroso acetals containing an alkoxy group at C-6 with nucleophiles leads to a very interesting rearrangement (237b) (Scheme 3.264). Initially, the $SiMe_3$ group is eliminated from nitroso acetal (**507i**) to give the anion **A**, which is stabilized to form nitrosoalkene **A′** by elimination of the methoxy anion. The **A′** immediately adds MeO^- to give anion **B** which is silylated by the next nitroso acetal molecule (**507i**) to give rearrangement product (**508i**).



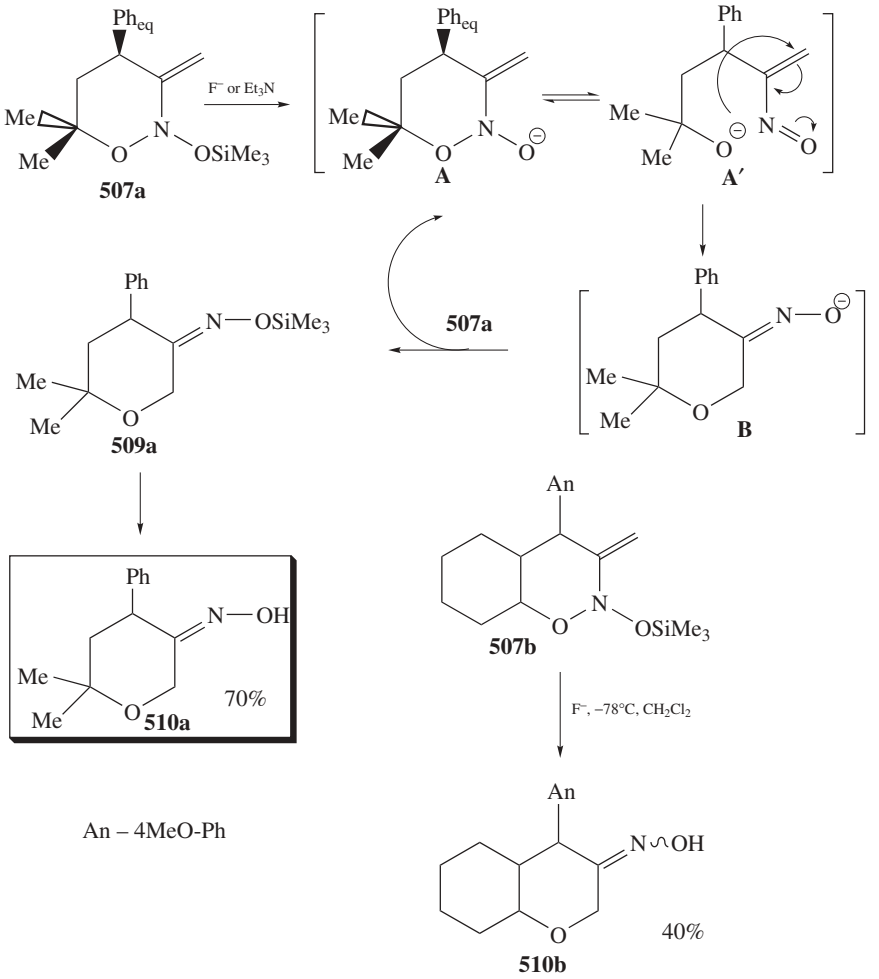
Scheme 3.264

If a good leaving group is absent at C-6 in cyclic nitroso acetal (**507**), the reaction induced by certain nucleophiles (F^- or Et_3N) proceeds through another pathway (Scheme 3.265).

After the formation of tautomeric anions $\mathbf{A} \rightleftarrows \mathbf{A}'$, the anion $\mathbf{A}'$ a rearranges to give the anion **B**, which reacts with the second nitroso acetal molecule to form a mixture of stereoisomers of silyl derivative **509a**. After desilylation of **509a**, oxime **510a** is isolated. The reaction with the fluoride anion proceeds at low temperature, whereas the use of triethylamine is efficient only at room temperature. The yield of oxime (**510a**) is virtually independent of the reaction conditions, whereas the diastereomeric ratio varies substantially.

The process shown in Scheme 3.265 substantially complicates the reaction of cyclic nitroso acetals with nucleophiles at the β-C atom of the enamine fragment.

3.5.4.3.2. Quaternization of Tertiary Amines and Nitrogen-Containing Heterocycles with N,N-Bis(siloxy)Enamines Ammonium salts $[HON{=}CR'CHR''NEt_3]^+ X^-$ were found for the first time as by-products in studies of double silylation of AN (465, 466). To optimize the reaction, efforts were made to reduce the



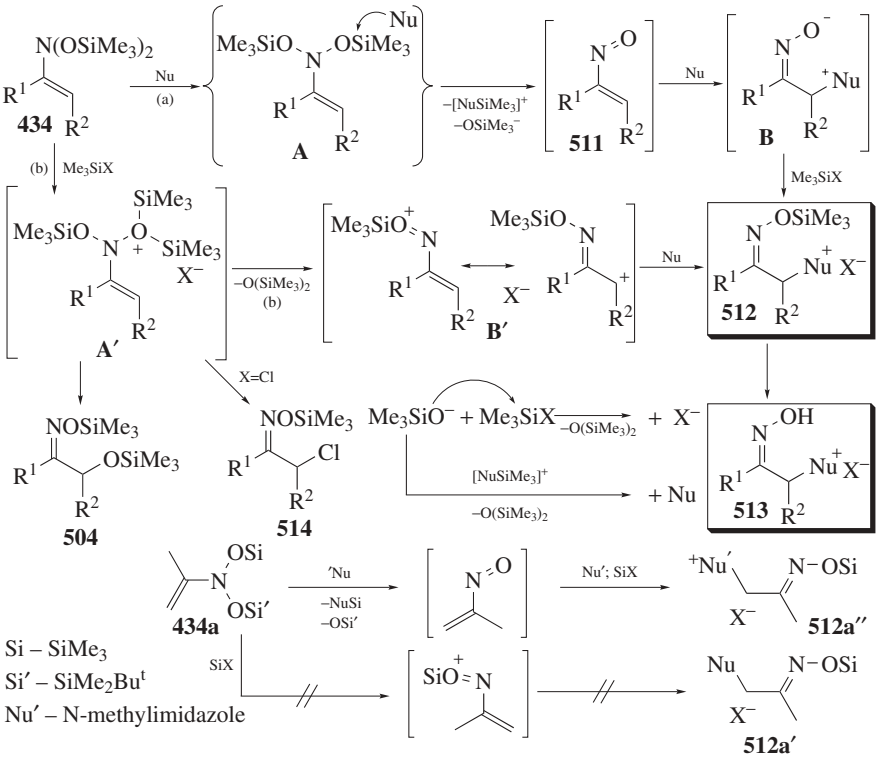
Scheme 3.265

formation of these and other by-products. However, these products are of interest as convenient precursors of α-functionalized oximes and certain heterocyclic systems. In addition, liquid salts could be used for modifying ionic liquids.

BENAs can be considered as precursors of the above mentioned salts (465). Two approaches to the synthesis of ammonium salts from BENAs by modified silylation are presented in Scheme 3.266 (536).

Both approaches include the reaction of BENA with ternary amines or the −C=N−C− fragment of a nitrogen heterocycle (Nu) in the presence of a silylating agent (Me_3SiX).

If Nu is sufficiently nucleophilic toward the silicon atom in BENA (**434**), intermediate (**511**) (a conjugated nitroso alkene) is generated, and the latter reacts



Scheme 3.266

with the second Nu molecule to give the silyl derivative of ammonium salt (**512**), whose desilylation affords the target salt (**513**) (path (a)). The role of the silylating agent is to trap the reactive Me_3SiO^- anion.

Another transformation of BENA is observed in the reactions of Nu having a lower nucleophilicity toward silicon (path (b)). This reaction produces the cation **B′** as the key intermediate, which is more reactive than nitrosoalkene (**511**). As a result, two by-products, viz., α-siloxy oxime (**504**) and α-halo oxime (**514**), are generated along with the target salt (**512**).‡

The formation of product (**514**) can be prevented by using non-nucleophilic trimethylsilyl triflate instead of trimethylhalosilane.

It can easily be seen that Scheme 3.266 has many features in common with Scheme 3.260, which describes the improved procedure for the rearrangement of BENAs. However, the path (b) in Scheme 3.260 is, on the contrary, more efficient.

‡Only in one case (498), α- chloro-substituted oxime was isolated as the only product of silylation of secondary β-functionalized AN.

The reactions of most of known Nu (tertiary amines, N-alkylated azoles, etc.) with BENA proceed through the pathway (a). This interpretation is additionally confirmed by the fact that the reaction of N-methylimidazole with unsymmetrical BENA (**434a**) produces exclusively trimethylsilyl salt (**512″**), whereas the pathway (b) would afford salt (**512′**).

Earlier, another scheme was suggested for the generation of salts (**513**) based on oximino-alkylation of Nu with halo-oximes (**504**) (453). However, special experiments demonstrated that this reaction requires more severe conditions (536) and does not proceed during the real generation of salts (**513**).

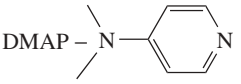
A representative group of salts (**513**) was prepared (Scheme 3.267) by the reactions presented in Scheme 3.266.

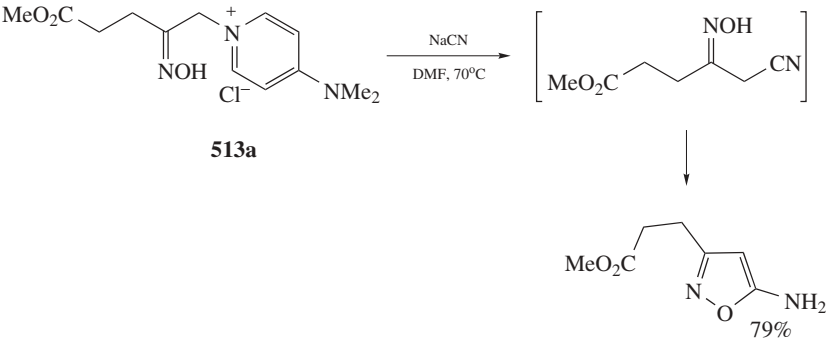
In addition to the salts shown in Scheme 3.267, several quaternary ammonium salts were detected by NMR spectroscopy among the products of the reactions of BENAs with DBU and $HCONMe_2$. However, attempts to crystallize these salts failed, while other methods of purification of these products are lacking.

The preparation of salts 513 with BENA (see Scheme 3,266)

Pathway a: R^1=R^2=H; X=Cl,N-methylimidazole (80%), DMAP (49%), Et_3N (54%).
R^1=Me, R^2=H; X=Cl, N-methylimidazole (87%), DMAP (70%).
R^1=H, R^2=Me; X=Cl, N-methylimidazole (60%).
R^1=$(CH_2)_2CO_2Me$, R^2=H; X=Cl, N-methylimidazole (94%), DMAP (84%), Et_3N (72%).
R^1=CO_2Et, R^2=H; X=Cl, N-methylimidazole (54%).
R^1=CO_2Et, R^2=H; X=Br, Et_3N (72%).
R^1=Me, R^2=H; X=Cl, Me_3N (72%).

Pathway b: R^1=R^2=H; X=Cl, Pyridine (32%, impurities **504** and **514**).
R^1=R^2=H; X=OTf, Pyridine (60%, impurity **504**).





513a

515

Scheme 3.267

The possibility of using these salts (**513**) in organic synthesis was exemplified by the synthesis of amino oxazole (**515**) through ammonium salt (**513a**) (Scheme 3.267).

3.5.4.3.3. Synthesis of 5,6-Dihydro-4H-Oxazines Containing Functionalized Substituents at the C-3 Atom Unlike BENAs, six-membered cyclic nitroso acetals do not form quaternary ammonium salts in the reactions with ***Si*X/Nu**.[§]

The reactions of enamines (**516**) with trialkylsilyl halides in the presence of triethylamine (or other nitrogen bases) produce 3-halomethyl-substituted oxazines (**517**) (or **517′**) in good yields (Scheme 3.268) (472).

It is very likely, that this reaction occurs due to the equilibrium between trimethylsilyl halide and a nitrogen-containing nucleophile, which increases the electrophilicity of silyl Lewis acids. It should be noted that the configuration of stereocenters at the carbon atoms of the oxazine ring is partially distorted. Hence, it is assumed that the reaction proceeds through the intermediate cation **B**, which is partially isomerized into the stereoisomeric cation **B′** through the "open chain" cation **B″**.

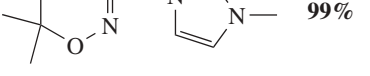
Oxazines (**517**) can be prepared in somewhat lower yields directly from six-membered cyclic nitronates (**518**) without isolation of the corresponding nitroso acetals (**516**) (see Table 3.36).

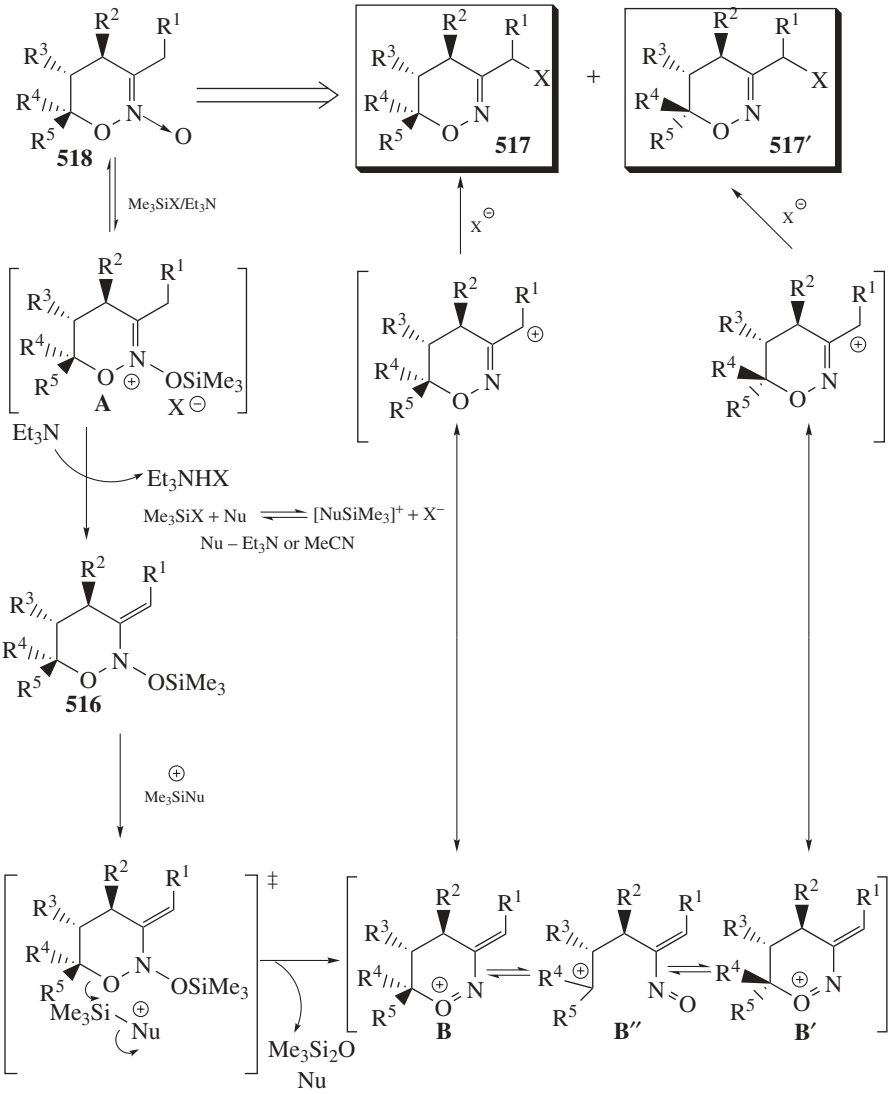
The reactions (**518**→**517** + **517′**) or (**518**→**516**→**517** + **517′**) are complex processes and require optimization and the use of special procedures in each particular case. If the starting nitronates or nitroso acetals are unsubstituted at the C-3 atom, the target 3-halomethyl-oxazines can be synthesized in satisfactory yields, although diastereomers (**517**) and (**517′**) are unseparable in some cases. In the presence of a substituent R′ (see entry 14), the yield of the product is substantially lower, whereas the reaction is diastereoselective.

Halomethyl-substituted oxazines (**517**) can be considered as the key intermediates in many strategies for organic synthesis. However, the lack of a convenient procedure for generating these compounds undoubtedly delayed studies on their possible use. Actually, very unstable α-halomethylnitroso alkenes could serve as the only source of such products (537). The approach developed by Russian chemists (472, 473) enables the synthesis of these products from stable and available AN.

The advantages of this approach were provided by nitroethane (473) (Scheme 3.269). A series of stereoisomerically pure six-membered cyclic nitronates (**519**) were synthesized from nitroethane and other available AN, and

[§]The only salt of this type was prepared by refluxing of *N*-methylimidazole with 3-bromomethyl-6,6-dimethyl-4-phenyl-5,6-dihydro-4*H*-oxazine in toluene for 5 h (473).





Scheme 3.268

these products were used for the synthesis of the corresponding bromo derivatives (**520**) according to the procedure described in the study (472).

Functionalized oxazines (**521**) and (**522**) were synthesized from these key intermediates by the nucleophilic substitution of bromine (in 55%–100% yields based on derivatives (**520**) or 20%–30% yields based on the starting nitroethane). Besides, bromo derivatives (**520**) are convenient starting reagents for the synthesis of functionalized oxazines (**523**) and (**524**).

Table 3.36 The synthesis of 3-halomethyl substituted 5,6-dihydro-4*H*-oxazines (517).

Entry	(**516**, **517**)	(**518**)	R^1	R^2	R^3	R^4	R^5	X	**518**→ **517**+**517'** Yield %	**518**→**516**→ **517**+**517'** Yield %	Ratio (**517:517"**)
1	**a**	**a**	H	An[a]	H	OMe	Me	Br	54	69	12:1
2	**a**	**b**	H	An	H	OMe	Me	Cl	66	75	9:1
3	**b**	**c**	H	An	H	OEt	H	Br	65	75	17:1
4	**b**	**d**	H	An	H	OEt	H	Cl	68	79	only 517d
5	**c**	**e**	H	An	H	H	OEt	Br	58	64	6:1
6	**d**	**f**	H	An	H	Ph	H	Cl	65	68	15:1
7	**e**	**g**	H	An	H	H	Ph	Cl	67	67	10:1
8	**f**	**h**	H	An	$-(CH_2)_4-$		H	Br	60	59	only 517h
9	**f**	**i**	H	An	$-(CH_2)_4-$		H	Cl	51	53	only 517i
10	**g**	**j**	H	An	H	OMe	Me	Br	63	78	11:1
11	**h**	**k**	H	Ph	H	Me	Me	Br	53	61	-
12	**h**	**l**	H	Ph	H	Me	Me	Cl	45	48	-
13	**i**	**m**	H	OBz	H	Me	Me	Cl	63	72	-
14	**j**	**n**	Me	An	H	OMe	Me	Cl	21	34	only 517j

[a] An 4-$MeOC_6H_4$.

A convenient procedure for catalytic carbonylation of bromooxazines (**520**) giving rise to previously unknown methoxycarbonylmethyl-substituted oxazines (**525**) in good yields (538) deserves note, all the more because this is the first example of catalytic C,C-coupling reactions of ethers of α-halo substituted oximes.

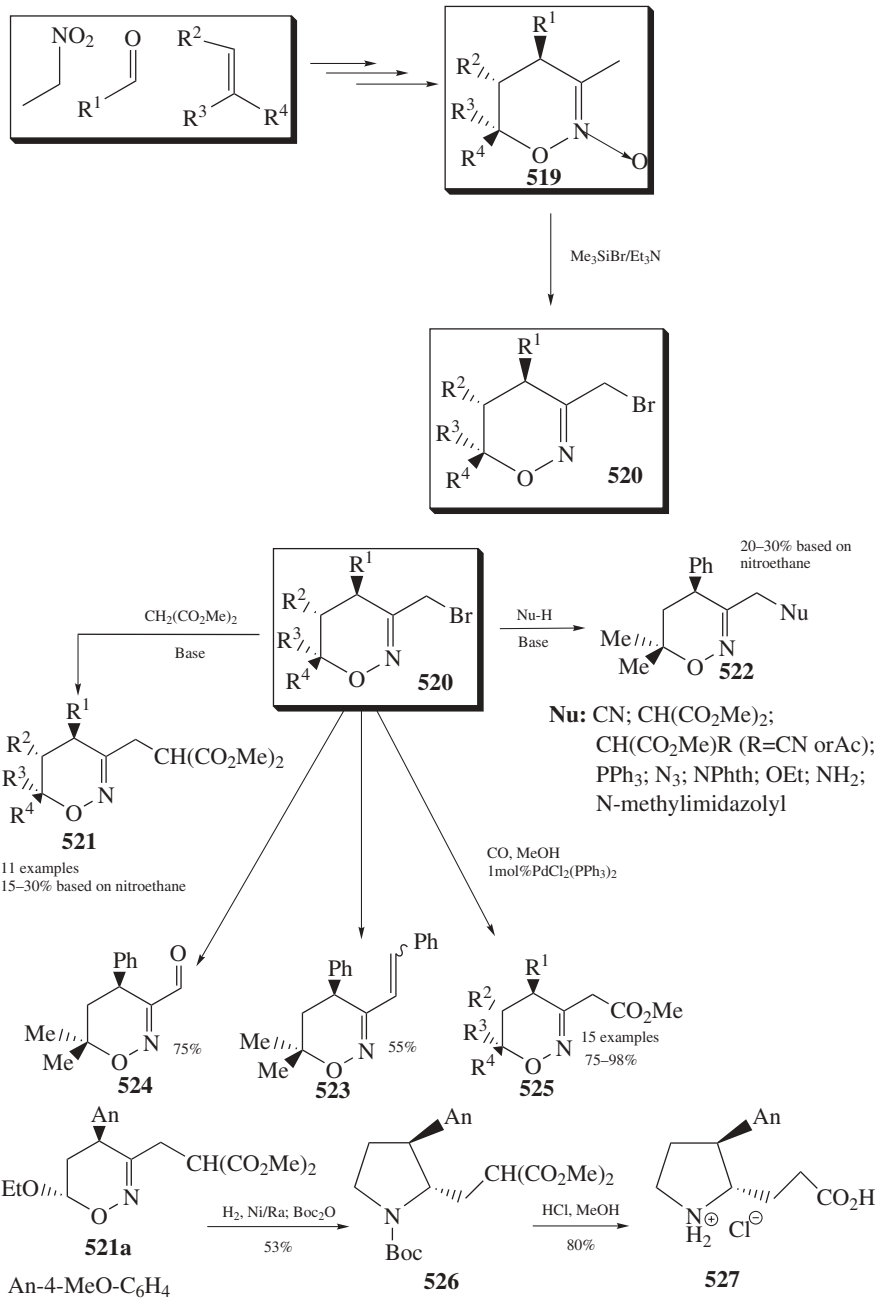
Functionalized 5,6-dihydro-4*H*-oxazines are direct precursors of a series of useful products, for example, of proline derivatives (539), unnatural amino acids (540), and some alkaloids (541).

The possibility of synthesizing unnatural amino acids from the resulting functionalized oxazines was exemplified by the selective reduction of product (**521a**) to amino acid (**527**) (473).

3.5.5. Silylation of β-Functionalized Aliphatic Nitro Compounds as a Procedure for the Synthesis of β-Functionalized α-Nitrosoalkenes

In Sections 3.5.3. and 3.5.4, it was demonstrated that silylation of **AN** sometimes afford conjugated nitrosoalkenes as unstable intermediates with various reactivities (503). The generation of scarcely known α-nitroso alkenes, containing *EWG* groups in the β position, by elimination of trimethylsilanol from the corresponding SENAs is of particular interest (see Scheme 3.224).

3.5.5.1. Selected Transformations of β-Functionalized α-Nitroso Alkenes The reactivity of β-*EWG*-substituted α-nitrosoalkenes is similar to that of nitroso


519
Me3SiBr/Et3N
520
CH2(CO2Me)2
Base
Nu-H
Base
20–30% based on nitroethane
522
Nu: CN; CH(CO2Me)2; CH(CO2Me)R (R=CN orAc); PPh3; N3; NPhth; OEt; NH2; N-methylimidazolyl
521
11 examples
15–30% based on nitroethane
CO, MeOH
1mol%PdCl2(PPh3)2
524
75%
523
55%
525
15 examples
75–98%
521a
An-4-MeO-C6H4
H2, Ni/Ra; Boc2O
53%
526
HCl, MeOH
80%
527

Scheme 3.269

compounds containing *EWG* groups in the α-position. In particular, these compounds are active *N*-electrophiles. At the same time, the electrophilic center can be transferred to the β-C atom. It is in these in which the transformations of *EWG*-substituted α-nitrosoalkenes, generated by silylation of β-functionalized AN, are interpreted (491) (Schemes 3.270 and 3.271).

Silylation of primary AN of the general formula $R^1CHXCH_2NO_2$ (**528a–e**) with BSA affords trimethylsilyl derivatives of divinylhydroxylamines (**531a–e**) in moderate to good yields. This reaction is regio- and stereospecific. Both vinyl fragments in products (**531a,b,e**) adopt a *trans* configuration. The corresponding divinylhydroxylamine (**532a**) was obtained after removal of the silyl protecting group from derivative (**531a**).

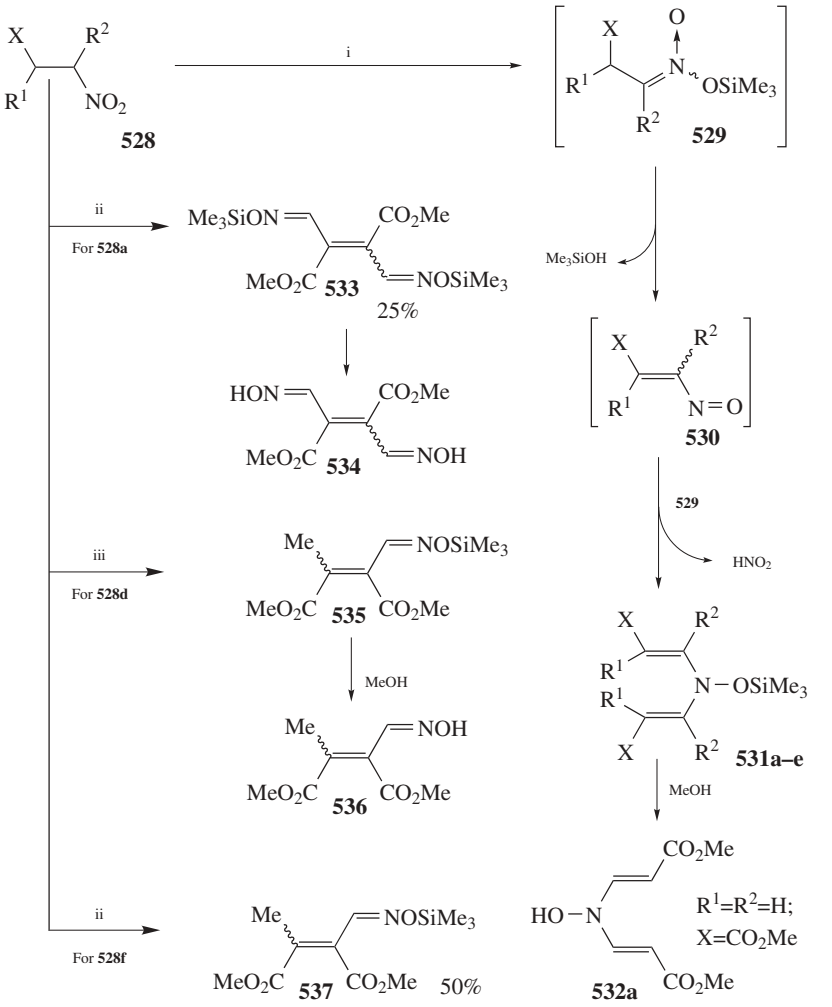
Silylation of AN (**528b,c,e**) with another silylating agent (Me_3SiCl/Et_3N) gives poorly separable mixtures of unidentified products. However, the reaction of AN (**528a**) under these conditions produces the silyl derivative of bis-oxime (**533**), which can be subjected to desilylation to prepare free bis-oxime (**534**) (491, 497). The stereoselectivity of the reaction with respect to the new C,C double bond is low (*E/Z* ≈ 1.3:1). Silylation of sterically more hindered nitroalkane (**528 d**) with Me_3SiCl/Et_3N affords derivative (**535**), which can be desilylated to form en-oxime (**536**) (216, 491). As mentioned above, secondary nitroalkane (**528f**) gives chloro oxime (**537**). The latter is the only product of this type, which was isolated upon silylation of acyclic AN (216, 491, 498).

Silylation of AN with BSA involves N,C-coupling of two intermediates, nitronate (**529**) and nitrosoalkene (**530**), as the key step, which apparently proceeds through the cyclic transition state **A** (Scheme 3.271). (Here, it should be noted that intermediates (**529a**) and (**530a**) were detected with by trapping agents.(491) Nitronate (**529d**) was found in the reaction mixture by NMR monitoring (491). Evidently, elimination of nitrous acid is only one of possible pathways for the transformation **B**→(**531**).

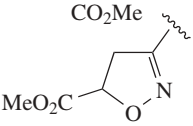
From this it follows that it is necessary to maintain a high concentration of nitronate (**529**) but a low current concentration of nitrosoalkene (**530**) for the successful N,C-coupling reaction (**528**→**531**). The highest yield of the target derivative (**531 d**) was achieved in the reaction with (**529d**), because nitronate is relatively slowly transformed into the corresponding nitrosoalkene (**530 d**). Steric hindrance in nitrosoalkene (**530f**) prevents its coupling with nitronate (**529f**).

An increase in nucleophilicity of the silylating agent apparently leads to reversible ionization of nitronate (**529**) (see **529a**⇄**529a′** in Scheme 3.271). Evidently, anion (**529a′**) reacts with nitrosoalkene (**530a**) in a Michael-type fashion to give, after a series of transformations, derivative (**533**). (These transformations are described in more detail in Section 3.5.6.)

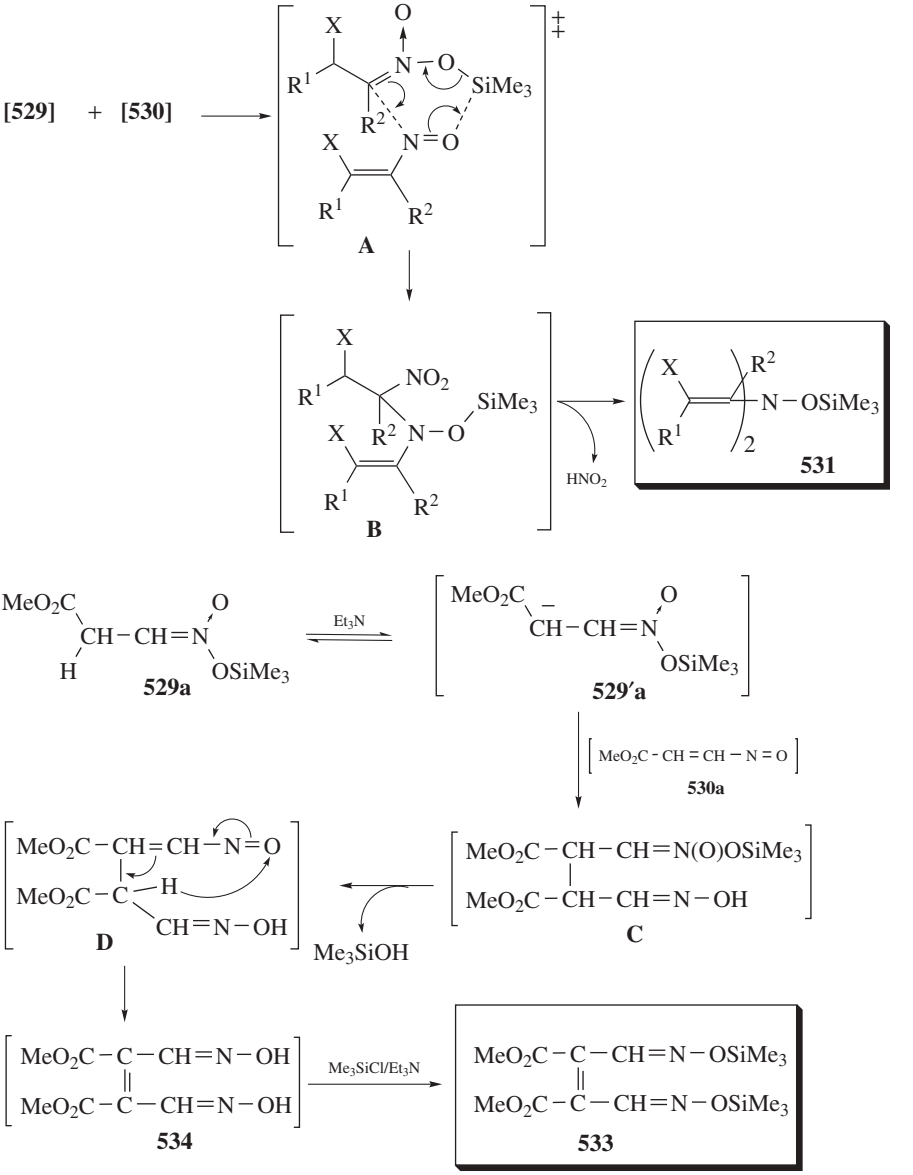
3.5.5.2. Reactions of β-Functionalized α-Nitrosoalkenes with the C,C Double Bond The reactivity of α-nitrosoalkenes toward double bonds depends drastically on the structure and configuration of the reagents. The characteristic features of the behavior of β-functionalized α-nitrosoalkenes were studied using readily available methyl β-nitrosoacrylate (**530a**). It appeared that this derivative is readily involved in the ene reactions with electron-donating and neutral olefins either



i : BSA ex. (20°), CH_2Cl_2
ii : Me_3SiCl/Et_3N, CH_2Cl_2
iii : Me_3SiCl/Et_3N, C_6H_6

	X	R^1	R^2	Yield **531**%
a	CO_2Me	H	H	32
b	CN	H	H	29
c	CO_2Me	Me	H	47
d	CO_2Me	$MeCHCO_2Me$	H	72
e		H	H	56
f	CO_2Me	H	Me	–

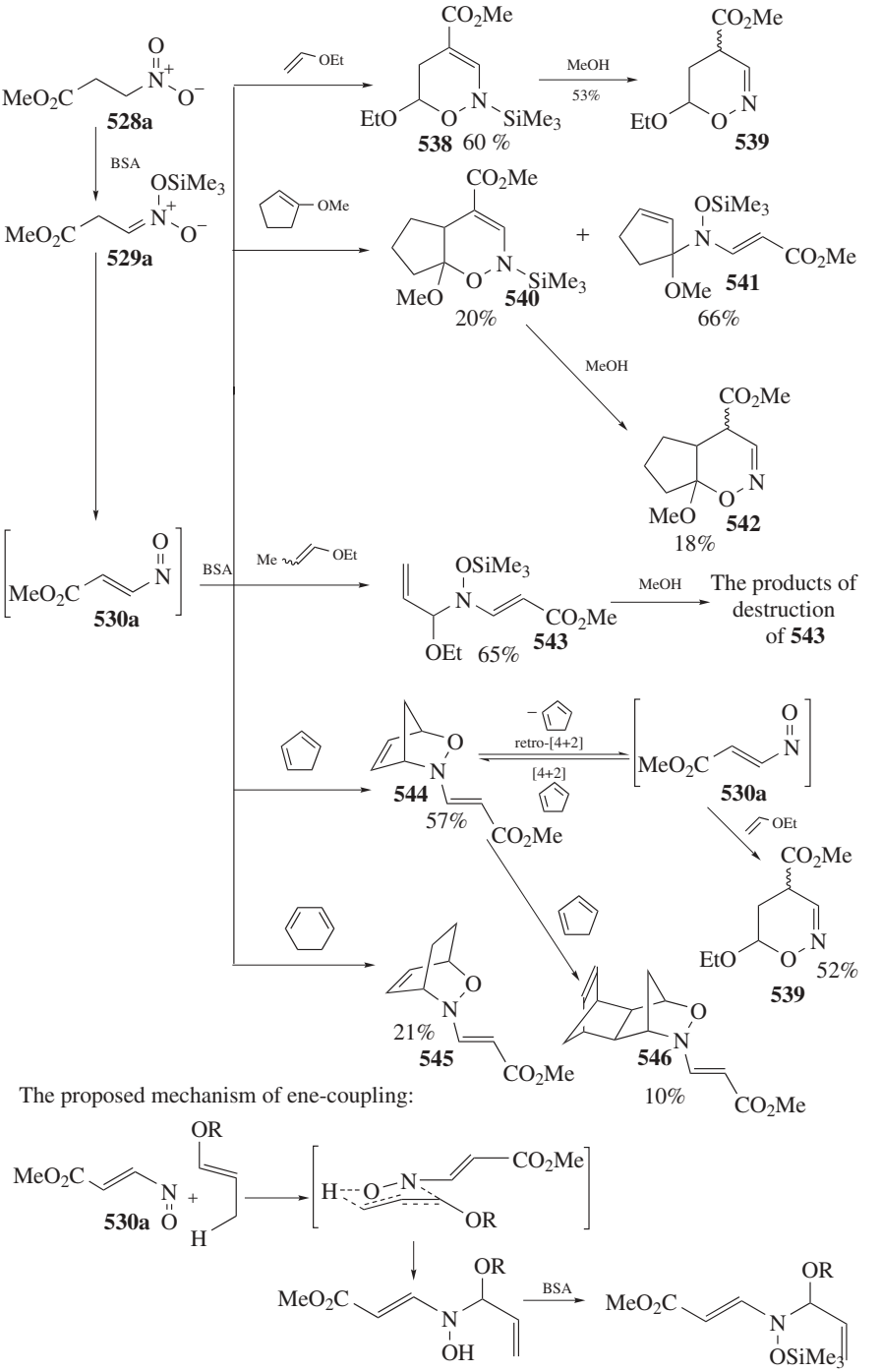
Scheme 3.270



Scheme 3.271

as heterodiene or as heteroalkene (491, 541, 542) (Scheme 3.272). For example, ethyl vinyl ether, which cannot be involved in the ene reaction, undergoes "normal" [4 + 2]-cycloaddition to give product (**539**).

Under these reaction conditions, the latter undergoes silylation to form dihydrooxazine (**538**), which can be again easily desilylated with methanol to form



The proposed mechanism of ene-coupling:

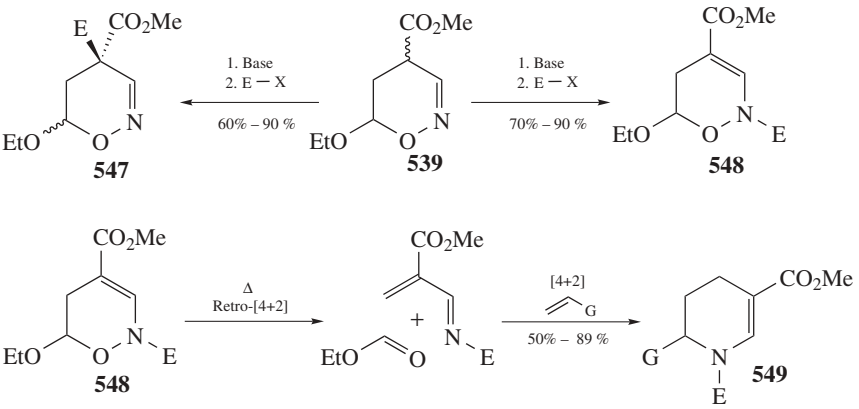
Scheme 3.272

(**539**). However, α-methoxycyclopentene reacts with nitrosoalkene (**530a**) to give primarily the product of the ene reaction, viz., silylated vinylhydroxylamine (**541**), whereas the normal adduct of the diene synthesis (**540**) is generated only as an impurity. The reaction of (**530a**) with EtOCH=CHMe produces only ene adduct (**543**), which undergoes complete resinification in attempting to perform desilylation. Therefore, the behavior of nitrosoalkene (**530a**) in reactions with olefins is similar to that of nitroso derivatives > C(*EWG*)N=O, which are generally involved in ene reactions with olefins (543). (The mechanistic interpretations of ene reactions of nitrosoalkene (**530a**) are presented in the lower part of Scheme 3.272.)

At the same time, nitrosoalkene (**530a**) reacts with conjugated cyclic dienes exclusively as a heterodienophile (542) (see products (**544–546**) in Scheme 3.272). These reactions are chemo- and stereoselective, and products (**544**) and (**545**) were isolated as endo-(*E*) isomers. Prolonged storage of monoadduct (**544**) with an excess of cyclopentadiene leads to the addition of a second cyclopentadiene molecule to give bis -adduct (**546**) in low yields. Adduct (**544**) is of particular interest because the preparation of this compound is reversible and, therefore, dihydrooxazine (**544**) can be considered as a "reservoir" for storage of unstable nitrosoalkene (**530a**). In any case, the reaction of (**544**) with an excess of $EtOCH{=}CH_2$ affords oxazine (**539**) in good yield.

Therefore, the ability of (**530a**) to be involved in [4 + 2]-cycloaddition reactions with some olefins and dienes is very important in dihydrooxazines chemistry, although the ene reactions limit the use of this nitrosoalkene in organic synthesis.

3.5.5.3. Development of the Chemistry of 5,6-Dihydro-4H-Oxazines Main approaches to the development of the chemistry of 5,6-dihydro-*4H*-oxazines with the use of product (**539**) are presented in Scheme 3.273 (541).



E − X = R-Hal, RCOCl; G = OR, Alk; Base = LiHMDS, Et_3N or Na_2CO_3

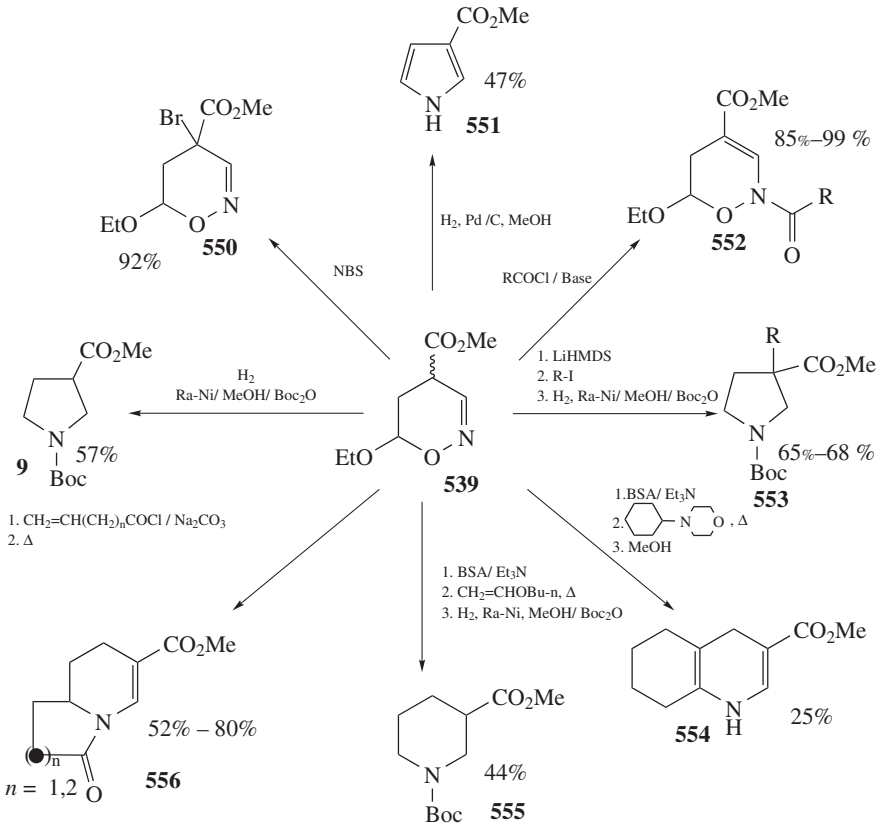
Scheme 3.273

These methods involve the modification of the C-4 atom in (**539**) by its alkylation products (**547**) and *N*-acylation of (**539**) in the presence of bases, which is accompanied by the double-bond transfer in heterocyclic system (products (**548**)).

On heating, dihydrooxazines (**548**) undergo the known [4 + 2]-cycloreversion to give the previously unknown conjugated en-imines $CH_2{=}C(CO_2Me)CH{=}N{-}E$ as intermediates. The latter can be trapped in a Diels–Alder reaction at the terminal or internal electron-rich double bond.

Enamines (**549**), which are generated by [4 + 2]-cycloaddition of the above mentioned en-imine with olefins > = –G are shown in Scheme 3.273.

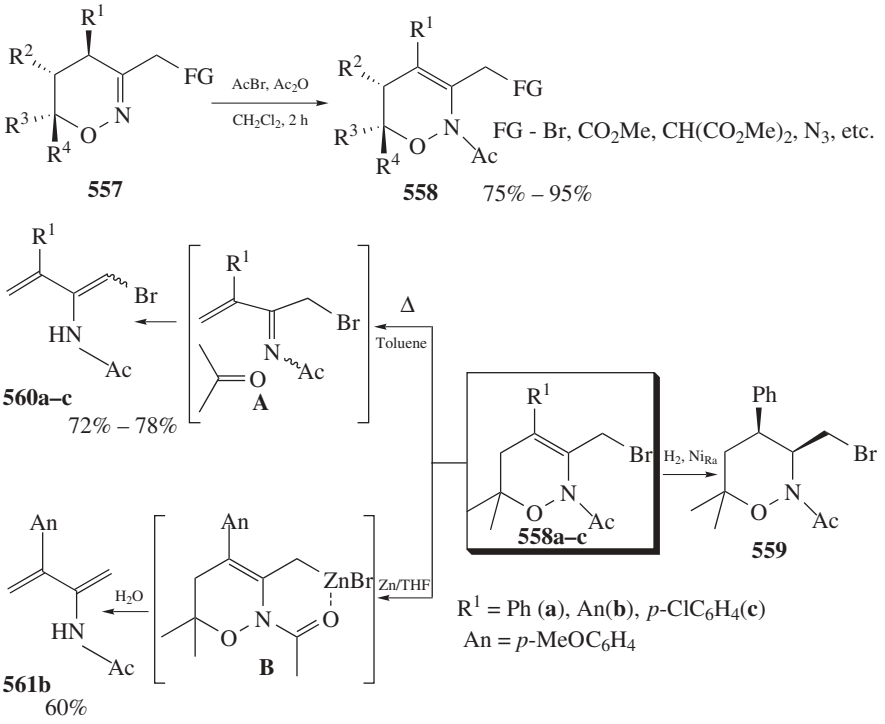
Additional data on the use of oxazine (**539**) and products of its modifications in syntheses of compounds having potential biological activity and their precursors are presented in Scheme 3.274 (541). Catalytic hydrogenation of the imino and oximino fragments is primarily used for this purpose. This approach made it possible to prepare a representative series of nitrogen-containing heterocycles and of other previously unknown compounds.



Scheme 3.274

Thus, the synthesis of dihydrooxazine (**539**), the double-bond transfer in this derivative, and the subsequent controlled fragmentation of N-acylated dihydrooxazines is a interesting new strategy for preparing direct precursors of biologically active products. The application of this approach to a series of 5,6-dihydro-4*H*-oxazines containing a functionalized substituent at the C-3 atom (see Section 3.5.4.3.3.) (473) opens up additional possibilities (544) (Scheme 3.275). In this context, a very efficient procedure was developed for *N*-acylation of dihydrooxazines (**557**) in the absence of bases. The C,C double bond in the resulting products can be chemo- and stereoselectively reduced (544) (see the transformation (**558a**→**559**), Scheme 3.275). However, the [4 + 2]-cycloreversion of derivatives (**558**) is of most interest. This process enables the detection of the resulting enimino intermediates in the absence of trapping agents. In particular, heating of bromides (**558a–c**) in toluene affords 2-acylamino-1-bromodienes (**560a–c**) in good yield.

These products are apparently generated through isomerization of the starting enimines **A**. Treatment of bromide (**558b**) with zinc in THF is also apparently accompanied by the fragmentation of the intermediate **B** to form *N*-acylaminodiene (**561b**) (544). Upto this time, dienes analogous to products (**560**) and (**561**) have not been described in the literature.



Scheme 3.275

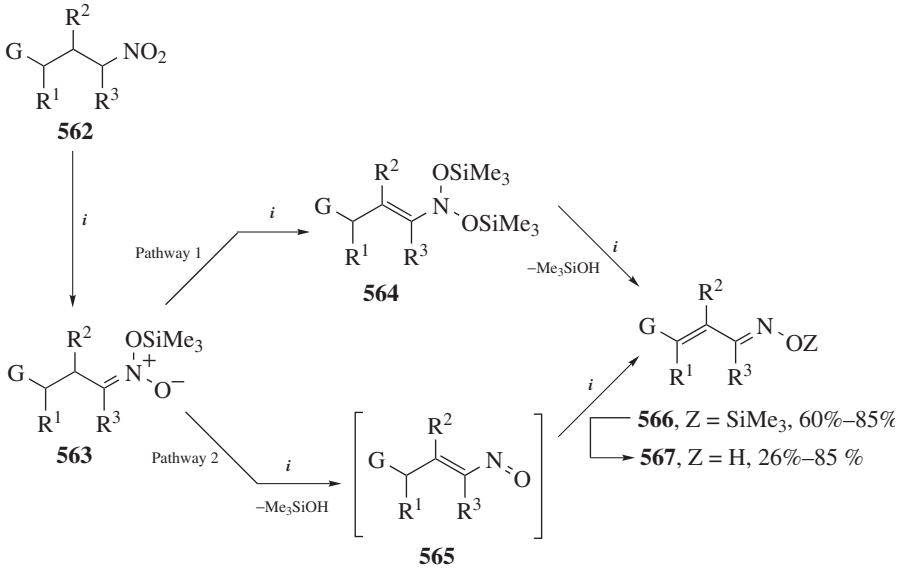
3.5.6. Silylation of Functionalized Aliphatic Nitro Compounds as a Procedure for the Synthesis of Functionalized Conjugated Enoximes

As can be seen from Sections 3.5.2 to 3.5.5, silylation of AN affords silyl derivatives of conjugated enoximes. Conjugated enoximes can serve as convenient precursors of α,β-unsaturated carbonyl compounds and nitriles, as well as of aziridines, pyridines, isoxazoles, and pyrazole *N*-oxides. In addition, the α,β-unsaturated oximino fragment is involved in a series of highly biologically active compounds (see Reference 545). However, general procedures for the synthesis of conjugated enoximes are lacking (several approaches were documented (546)).

3.5.6.1. Procedure for the Synthesis of β-Functionalized Conjugated Enoximes

Silylation of γ-functionalized AN (**562**) can generate silyl derivatives of enoximes (**566**) via two pathways: either through BENA (**564**), the products of double silylation (pathway 1), or through SENA (**563**) and α-nitrosoalkenes (**565**) (pathway 2) (545) (Scheme 3.276).

The reactions of AN without electron-withdrawing groups at the β-C atom proceed through the pathway 1. In this case, trimethylsilanol is eliminated from intermediate BENA to give silyl derivatives (**566**), which can easily be transformed into oximes (**567**) (504, 545). Evidently, the presence of bases would accelerate elimination of trimethylsilanol.



R^1 = H, Me, CO_2Me; R^2 = H, Me, Ph, CO_2Me; R^3 = H, $CH_2CH_2CO_2Me$, Ph, CO_2Me; G = CN, NO_2, CO_2Me, Ac, Bz

i: Me_3SiX (Et_3N), X = Cl, Br, OTf, N=C(OSiMe$_3$)Me

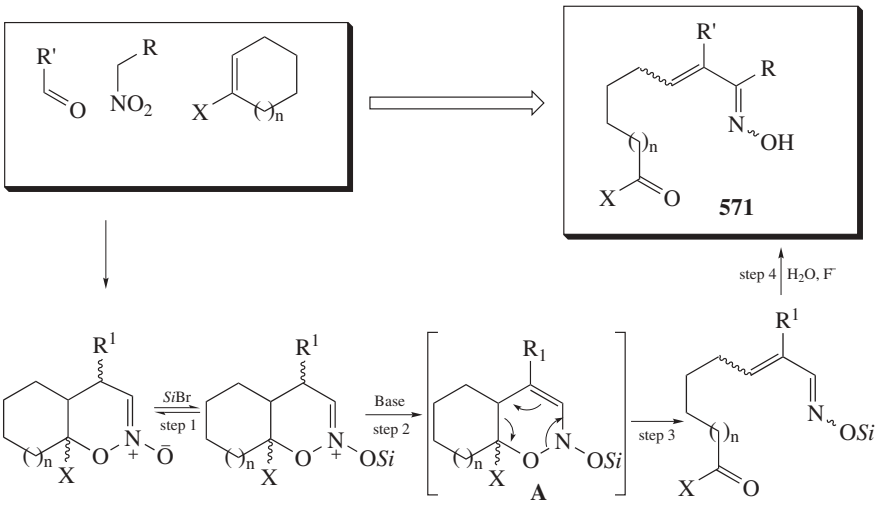
Scheme 3.276

However, if AN (**562**) contain electron-withdrawing groups at the β-C atom, SENA (**563**) generated after the first silylation can eliminate trimethylsilanol to give unstable α-nitrosoalkenes (**565**) rather than the corresponding BENA (pathway 2). It is known (503) that conjugated nitrosoalkenes (**565**) can undergo rearrangements into the corresponding enoximes (**567**). The presence of an *EWG* group in the γ-position of nitrosoalkene, as well as the presence of bases in the reaction mixture, accelerate elimination (496, 545). In the presence of silylating agents, free enoximes (**567**) are transformed into silyl derivatives (**566**). (Analogous isomerization reactions are suggested for the intermediate **D** in the synthesis of dioxime (**534**) (497); see Scheme 3.271).

Unfortunately, the stereoselectivity of the generation of enoximes (**567**) toward the newly formed C,C bond is often low, and, in some cases, this reaction is complicated by the formation of by-products due the to reactivity of bis-oxyiminium cationic intermediates (for more details, see Section 3.5.2).

3.5.6.2. Method for the Synthesis of Conjugated Enoximes with a Remote Functional Group In Section 3.5.2.5, where the ring-chain tautomerism of bicyclic nitronates was considered (Scheme 3.218), the transformation of these nitronates into conjugated enoximes, containing a remote carbonyl-containing group, (153, 293, 547) was mentioned. This transformation is based on the above considered [4 + 2]-cycloreversion of 5,6-dihydro-2*H* -N-siloxyoxazines. This reaction is presented in detail in Scheme 3.277.

At first glance, this transformation is very attractive because it enables the synthesis of conjugated enoximes (**571**) from very simple precursors in several



R^1 = C_6H_5; X = $OSiMe_3$, OMe; *n* = 1,2; base – Et_3N; *Si* – $SiMe_3$; Yield of (**571**) 15%–95%

Scheme 3.277

steps. For this purpose, cyclic nitronates (**568**) are synthesized initially, and their silylation through cations (**569**) and oxazines **A** afford silyl derivatives (**570**) whose desilylation produces the target oximes. However, the desired reaction is complicated by a side reaction associated with the ring-chain tautomerism of cations (**569**) (for more details, see Section 3.5.2.5).

An increase in the size of the carbocycle and steric hindrance of the base leads to a decrease in the contribution of the target enoxime in the reaction products. Hence, in each particular case it is necessary to perform special experiments to elucidate whether the scheme is applicable for the synthesis of conjugated enoximes containing a remote functional group and to find optimal conditions.

3.5.6.3. Approaches to the Synthesis of Unfunctionalized Conjugated Enoximes

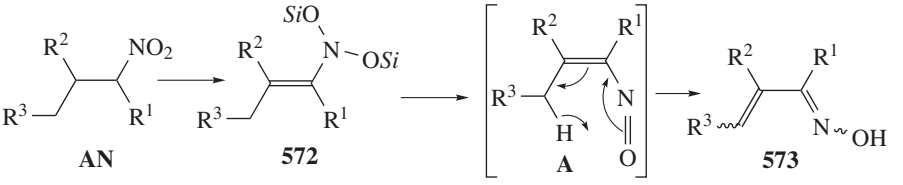
The role of conjugated enoximes as biologically active compounds and as valuable reagents and intermediates in organic synthesis was considered in the beginning of Section 3.5.6.

Therefore, it is important to develop special procedures for the synthesis of enoximes (**573**) from available AN through relatively stable intermediate BENA (**572**) and unstable α-nitrosoalkenes **A** (Scheme 3.278).

Such procedures are presently lacking, although uncontrolled transformations of selected BENA into silyl derivatives of enoximes were documented (469).

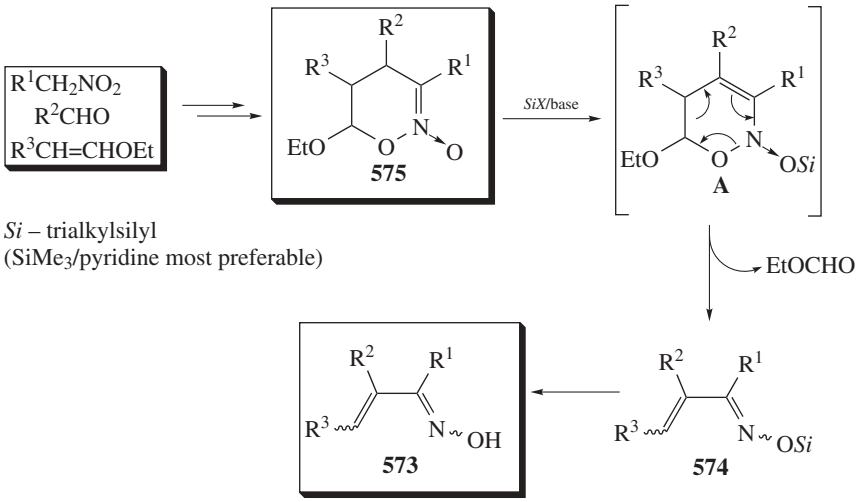
Another possible route to the synthesis of conjugated enoximes (**573**) is based on the sequence presented in Scheme 3.279.

Here, six-membered cyclic nitronate (**575**) is initially assembled from the simple reagents according to known procedures, and this nitronate is silylated to give the intermediate **A**, whose [4 + 2]-cycloreversion affords silyl derivative of enoxime (**574**). Finally, desilylation of the latter compound gives rise to enoxime (**573**). This chain of transformations was repeatedly documented in the literature (see, e.g., Refs (153, 264)). However, this sequence was not optimized as a method for the synthesis of conjugated enoximes. It can be concluded that the absence of an alkyl substituent at the C-3 atom (R^1=H) and the use of sterically unhindered bases (e.g., of pyridine) is favorable for realizing the desired pathway.

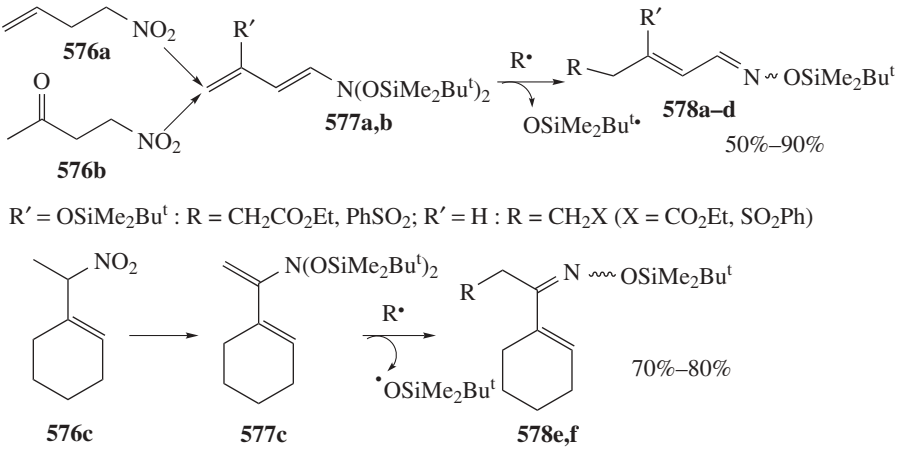


Si – trialkylsilyl ($SiMe_3$ most preferable)

Scheme 3.278



Scheme 3.279



Scheme 3.280

Finally, conjugated enoximes can be synthesized by the reactions of radical reagents with specially synthesized BENA containing a system of conjugated double bonds (527) (see Scheme 3.280, for more details, see Section 3.5.4.2.3). The advantage of this method is that it does not afford unstable intermediate α-nitrosoalkenes.

However, the necessity of using rather rare AN (**576**) for the construction of BENA (**577**) substantially limits its preparative value.

In any case, the data considered in Section 3.5.6 lead to the conclusion that AN can be considered in the context of silylation as preparatively valuable precursors of conjugated enoximes.

3.5.7. Exhaustive Silylation of Aliphatic Nitro Compounds

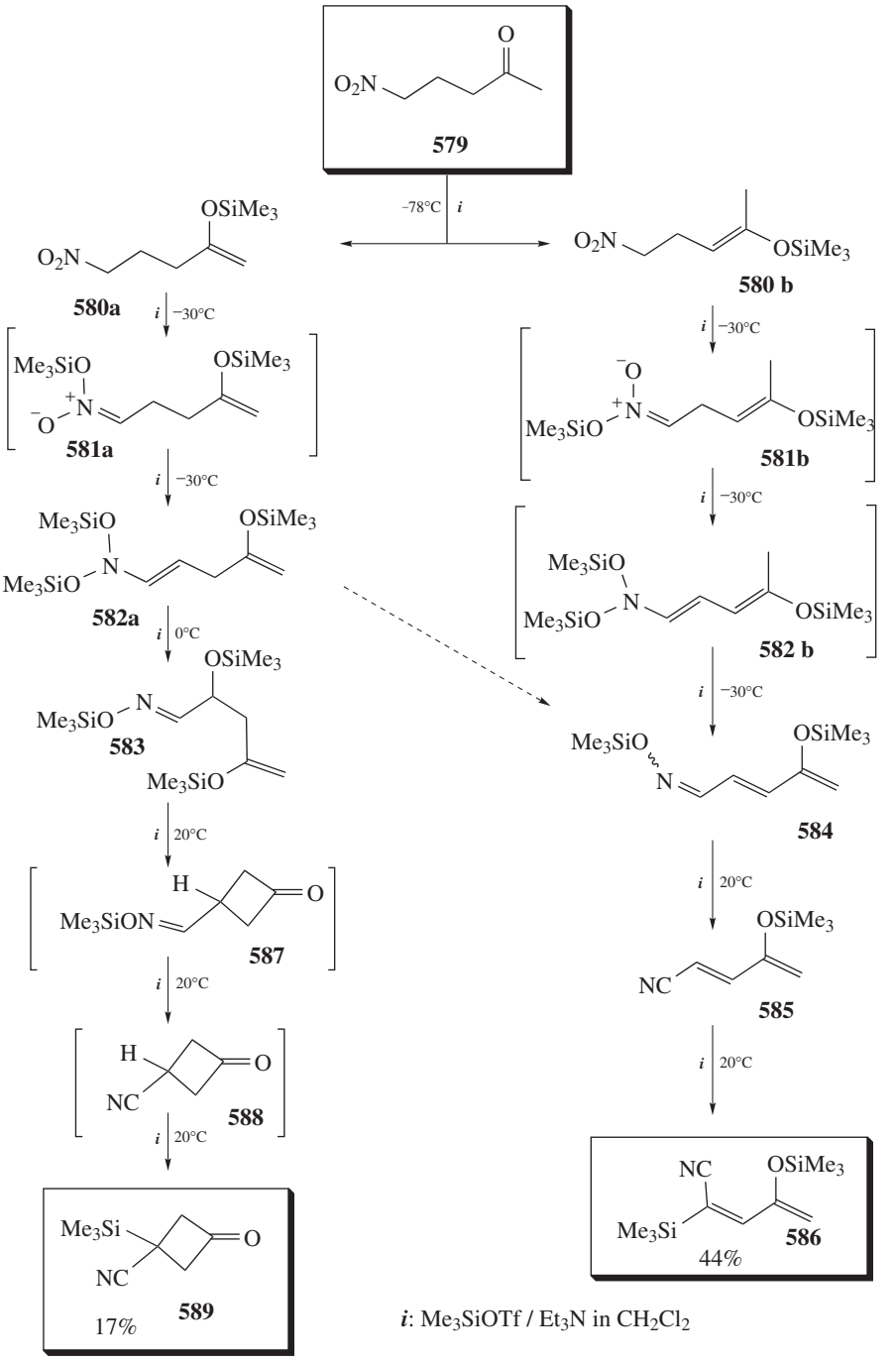
A standard procedure for the silylation of AN affords silyl derivatives of conjugated enoximes as the final products. However, the reactions with primary AN can proceed further (see Scheme 3.185). The reaction of 1-nitropentan-4-one (**579**) with a large excess of the powerful silylating agent Me_3SiOTf/Et_3N was monitored by NMR (548) (Scheme 3.281, all products and intermediates, which are not enclosed in square brackets, were detected by NMR). At $-78^{\circ}C$, exclusive silylation of the more nucleophilic carbonyl group giving rise to two isomeric silyl enolates (**580a**) and (**580b**) in a *ca* 1:1 ratio was observed, only the *E* isomer being detected for (**580b**). At higher temperature ($-30^{\circ}C$), both silyl enolates undergo double silylation of the nitro fragment to give, respectively, BENA (**582a**) and the silyl derivative of enoxime (**584**) in a ratio of 1:1. (After quenching of the reaction mixture, the *E* isomer of enoxime MeCOCH=CHCH=NOH can be isolated in 56% yield.) Most likely, the silyl derivative of oxime (**584**) is generated as a result of the elimination of silanol from BENA (**582b**) which is unstable under these conditions.

The cleavage of the weak N–O bond promoted by the $\pi\sigma^*$ interaction in BENA (**582b**) is the driving force of the reaction (**582b**→**584**). The rise of the monitoring temperature to $0^{\circ}C$ and an increase in the exposure time enable the detection of silylated enoxime (**583**) as the rearrangement product of BENA (**582a**). Since the (**583:584**) ratio is substantially lower than the (**580a:580b**) ratio, the partial transformation (**582a**→**584**), involving apparently the corresponding α-nitroso alkene cannot be ruled out.

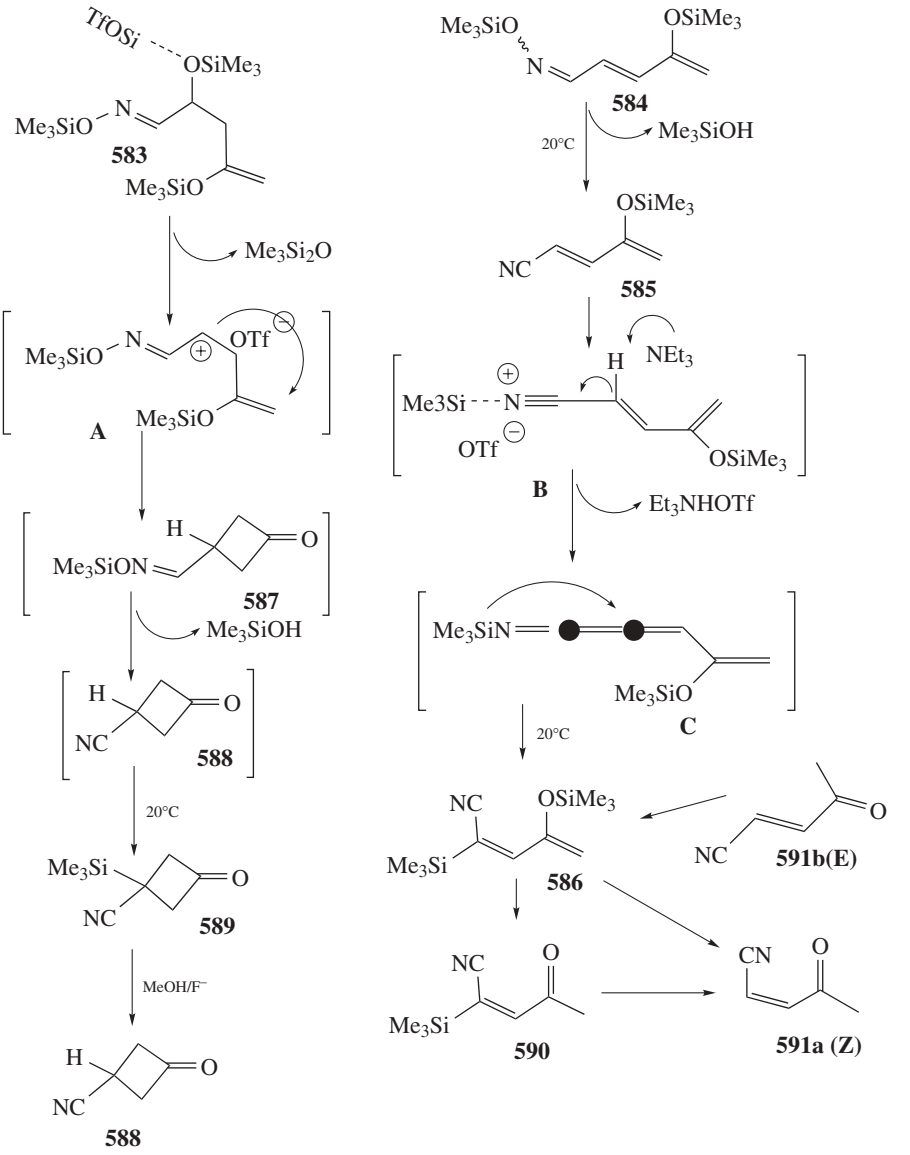
At room temperature, silylation of nitro ketone (**579**) affords nitriles (**585**) and (**589**) or (**586**) and (**589**) as the final products depending on the exposure time and the excess of the silylating agent (Scheme 3.281) (548).

The probable pathway giving rise to silylated cyclic nitrile (**589**), which is the most unusual reaction product, is shown on the left of Scheme 3.282. Apparently, this compound is generated through the cationic intermediate **A**. It undergoes cyclization at the terminal electron-rich C,C-double bond to form silylated oxime (**587**), which is transformed into nitrile (**588**). After silylation of the latter, nitrile (**589**) can be isolated. Desilylation of (**589**) according to standard procedures affords nitrile (**588**).

The probable pathway resulting in the stereoselective formation of silylated ene nitrile (**586**) from enoxime (**584**) is presented on the right of Scheme 3.282. At higher temperature, the latter eliminates trimethylsilanol to give ene-nitrile (**586**) under the action of silyl Lewis acid ($TfOSiMe_3$). Evidently, the reaction of compound (**585**) with $TfOSiMe_3$ at room temperature involves initial silylation of the nitrogen atom to form the cationic intermediate **B**, which is deprotonated with triethylamine, followed by the thermodynamically favorable 1,3-N,C-shift


579
−78°C i
580a
580 b
i −30°C
581a
581b
582a
582 b
i 0°C
583
584
i 20°C
587
585
588
589
17%
586
44%
i: Me3SiOTf / Et3N in CH2Cl2

Scheme 3.281



Scheme 3.282

of the trialkylsilyl fragment in the resulting unstable derivative **C**. Apparently, this rearrangement is very sensitive to steric factors due to which the *Z* isomer of silylated nitrile (**586**) is formed stereoselectively. This product can undergo desilylation with retention of the-*cis* configuration of the C,C double bond. For example, the carbonyl group can be selectively desilylated (nitrile (**590**)) by

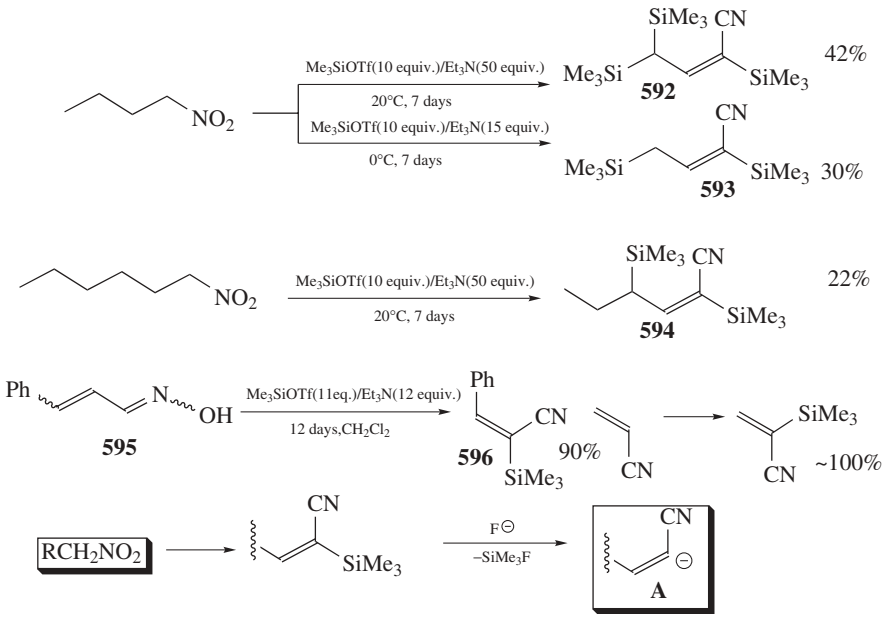
bubbling a solution of nitrile (**586**) through a layer of silica gel. Catalysis by the fluoride ion leads to complete removal of the silyl protecting group to form the *Z* isomer of β-acetylacrylonitrile (**591a**).

Probably, silylation will be a convenient procedure for the **trans→cis isomerization** of β-functionalized ene nitriles. Special experiments demonstrated that silylation of *E* isomer (**591b**) with an excess of Et_3N/Me_3SiOTf in CH_2Cl_2, followed by the removal of the silyl protecting group, gives the thermodynamically unfavorable *Z* isomer (**591a**) in a total yield of 75%.

Several examples of exhaustive silylation of primary AN, conjugated enoximes, and ene nitriles (470, 554) are presented in Scheme 3.283. As can be seen from these data, silylation of the C,C double bond is accompanied by the introduction of trimethylsilyl groups at the allylic position with respect to this bond. In the presence of a substituent in the β-position, the reaction is stereoselective at the C,C double bond.

It should be noted that total silylation of AN remains to be optimized. However, a convenient and simple procedure is expected to be developed for the synthesis of anionic intermediates **A** from the corresponding primary AN (see the lower line in Scheme 3.283).

The latter can be involved in coupling reactions with various electrophiles to give interesting products (550). The development of this strategy is hindered by the lack of convenient procedures for the synthesis of α-silylated conjugated ene nitriles (see, e.g., Ref. 551).

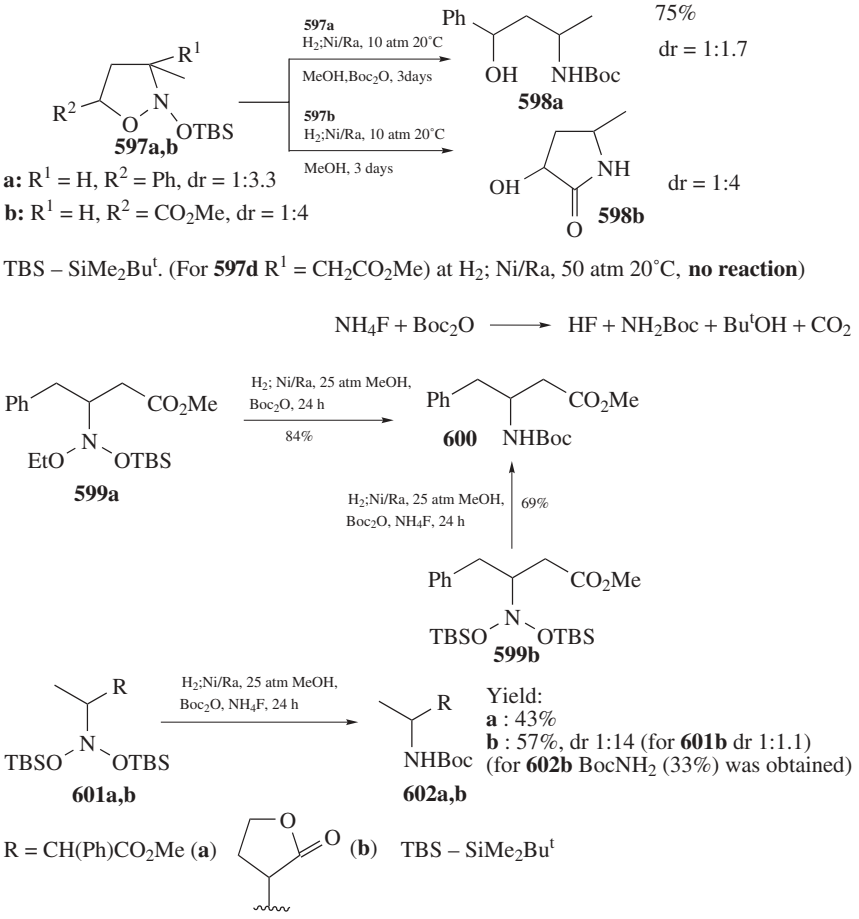


Scheme 3.283

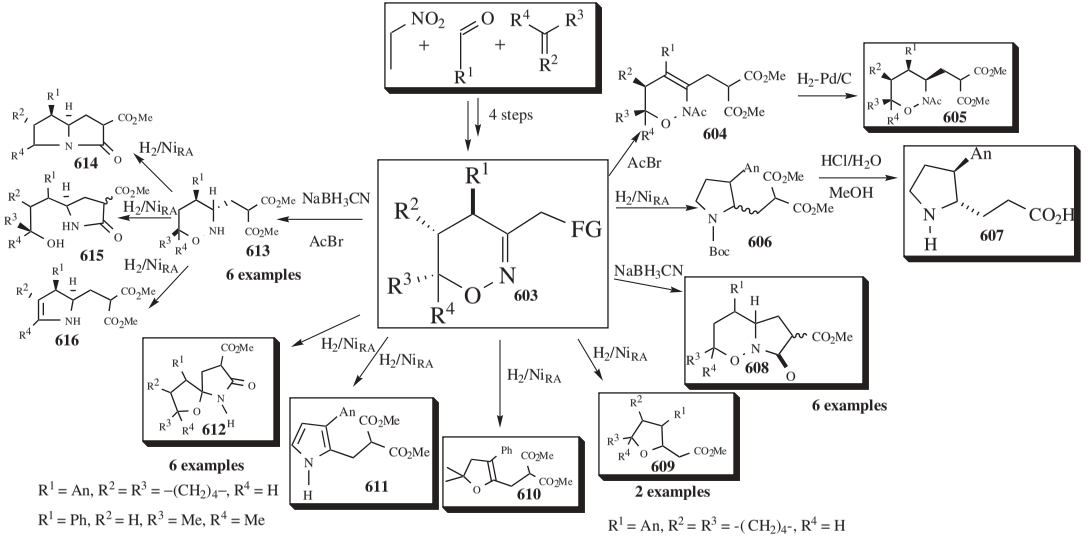
3.5.8. Selective Reduction of the Nitroso Acetal and Oximino Fragments in Products of AN Silylation

In some cases, silylation of AN and their derivatives produces nitroso acetals containing the *N*-siloxy fragment or cyclic ethers of oximes (predominantly substituted 5,6-dihydro-4*H*-oxazines). To use these products in strategies for synthesis, it is worthwhile to develop convenient procedures for selective reductions of the above derivatives to the corresponding amines.

3.5.8.1. New Procedures for Reduction of Nitroso Acetals Containing the N–OSiMe$_2$Bu^t Fragment Selective reduction of cyclic nitroso acetals was briefly considered in Section 3.4.3.4.3. The latest data on catalytic hydrogenation of cyclic and NOSiMe$_2$Bu^t-containing acyclic nitroso acetals (including



Scheme 3.284


4 steps
603
604
605
606
607
608
609
610
611
612
613
614
615
616
AcBr
NaBH3CN
H2/NiRA
H2-Pd/C
HCl/H2O
MeOH
6 examples
2 examples
FG – functional group

Scheme 3.285

those containing functional groups) over Raney nickel are shown in Scheme 3.284 (402).

Evidently, an increase in steric hindrance around the reduced fragment requires the presence of ammonium fluoride in the reaction mixture. It should be noted that potassium fluoride has no effect. It is highly probable that ammonium fluoride is required for slow elimination of HF, which gradually desilylates the nitroso acetal fragment thus facilitating its reduction. As can be seen from Scheme 3.284, many reduction products are derivatives of unnatural amino acids. Since the initial nitroso acetals can be prepared by silylation of simple acyclic AN, possibilities have been opened for the synthesis of unnatural amino acids from available AN.

3.5.8.2. Reduction of the Oximino Fragment in Substituted 5,6-Dihydro-4H-Oxazines Catalytic hydrogenation of substituted dihydro-4*H*-oxazines (552), as well as their reduction with sodium cyanoborohydride (553), were studied in sufficient detail and were used in several total syntheses. However, the use of silylation of six-membered cyclic nitronates enables the synthesis of previously unknown dihydrooxazines containing functionalized substituents at the C-3 and C-4 atoms from easily available precursors.

New selected possibilities created by reduction of new types of oxazines (**603**) in the synthesis of polyfunctional products (473, 554) are presented in Scheme 3.285. Coupling the reduction of the C=N bond with $NaBH_3CN$ followed by hydrogenation of the N–O bond or a one-step catalytic hydrogenation, and the double-bond transfer from the C(3) to the C(4) position, enables the synthesis and detection of 14 types of reduction products. In some cases, reduction is stereoselective.

3.6. CONCLUSION

To conclude, silylation of AN and their derivatives made it possible to substantially extend the reactivity of AN. The reactions of AN with nucleophilic, electrophilic, and radical reagents at both the α- and β-carbon atoms are summarized in Chart 3.24.

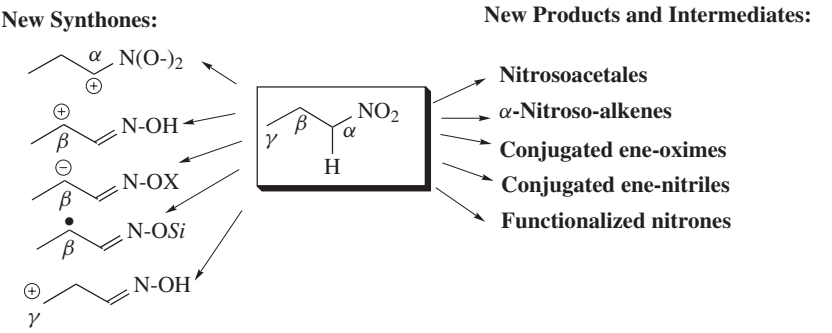
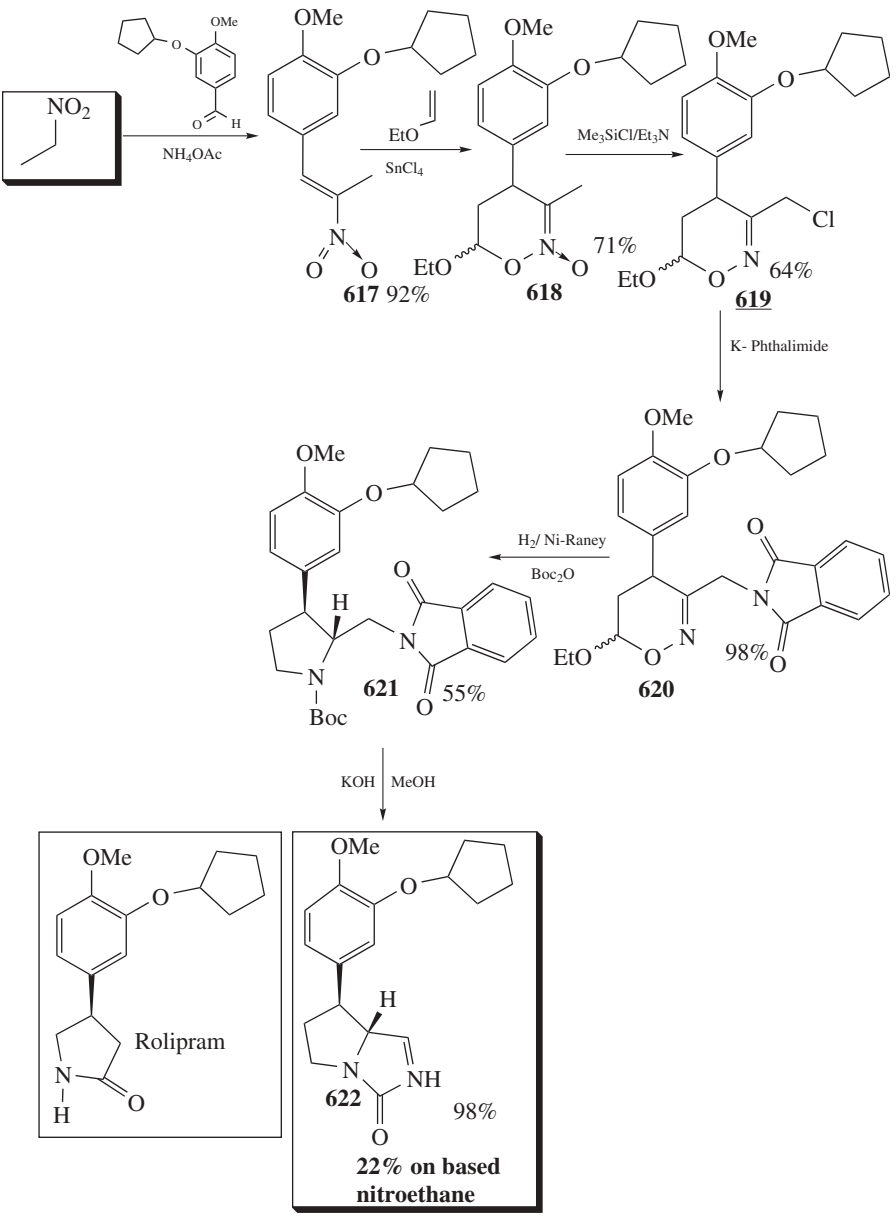


Chart 3.24 New reactivities of aliphatic nitro compounds realized via their silylation.


NO2
NH4OAc
OMe
EtO
SnCl4
Me3SiCl/Et3N
Cl
71%
64%
617 92%
618
619
K- Phthalimide
H2/ Ni-Raney
Boc2O
620
98%
621
55%
Boc
KOH
MeOH
Rolipram
622
98%
22% on based nitroethane

Scheme 3.286

Due to the silylation of AN, the latter can be considered as promising precursors of various nitroso acetals (primarily of ene nitroso acetals), conjugated en-oximes, α-nitrosoalkenes, and some other products. Convenient alternative methods for the synthesis of most of the above mentioned compounds are lacking.

All of these facts substantially extend the possibilities of using AN in organic synthesis. There are prerequisites for the development of new strategies for the organic synthesis involving silylation of AN as the key step. Of course, these aims will be realized in future.

But now, a strategy, used for the synthesis of derivative (**622**) (lit. synthesis (**622**) see in Ref. 555), which is the most efficient analog of the commercial drug rolipram with a broad spectrum of action (in particular, anti-inflammatory, antidepressant, neuroprotective, and immunodepressing effects), is presented in Scheme 3.286. (The principle action of rolipram is based on selective inhibition of adenosine monophosphate (AMP)-specific phosphodiesterase.) Derivative (**622**) is almost 10 times more efficient than rolipram, but the biological activity of (**622**) was determined only for the racemate (555).

An original approach to the synthesis of (**622**) from nitroethane was silylation of the key step (**618**→**619**) (556). This approach involves a smaller number of steps and gives the products in a higher yield. The obvious advantage of this approach is that it can be performed enantioselectively.

The synthesis nitroethane→(**622**) provides a good example of the potential of using silylation of AN in organic synthesis.

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Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis: Novel Strategies in Synthesis, Second Edition, By Henry Feuer

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