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# THE NITRO GROUP IN ORGANIC SYNTHESIS

Noboru Ono

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# CONTENTS

**Series Foreword** ix

**Preface** xi

**Acknowledgments** xiii

**Abbreviations** xv

**1. Introduction** 1

**2. Preparation of Nitro Compounds** 3

2.1 Nitration of Hydrocarbons / 3
- 2.1.1 Aromatic Compounds / 3
- 2.1.2 Alkanes / 7
- 2.1.3 Activated C-H Compounds / 10
- 2.1.4 Alkenes / 11
- 2.1.5 Synthesis of α-Nitro Ketones / 16
- 2.1.6 Nitration of Alkyl Halides / 17

2.2 Synthesis of Nitro Compounds by Oxidation / 20
- 2.2.1 Oxidation of Amines / 20
- 2.2.2 Oxidation of Oximes / 21

**3. The Nitro-Aldol (Henry) Reaction** 30

3.1 Preparation of β-Nitro Alcohols / 31
3.2 Derivatives from β-Nitro Alcohols / 38
- 3.2.1 Nitroalkenes / 38
- 3.2.2 Nitroalkanes / 44
- 3.2.3 α-Nitro Ketones / 46
- 3.2.4 β-Amino Alcohols / 48
- 3.2.5 Nitro Sugars and Amino Sugars / 48

3.3 Stereoselective Henry Reactions and Applications to Organic Synthesis / 51

**4. Michael Addition** 70

4.1 Addition to Nitroalkenes / 70

4.1.1 Conjugate Addition of Heteroatom-Centered Nucleophiles / 70
4.1.2 Conjugate Addition of Heteroatom Nucleophiles and Subsequent Nef Reaction / 80
4.1.3 Conjugate Addition of Carbon-Centered Nucleophiles / 85
4.2 Addition and Elimination Reaction of β-Heterosubstituted Nitroalkenes / 100
4.3 Michael Addition of Nitroalkanes / 103
4.3.1 Intermolecular Addition / 103
4.3.2 Intramolecular Addition / 113
4.4 Asymmetric Michael Addition / 115
4.4.1 Chiral Alkenes and Chiral Nitro Compounds / 115
4.4.2 Chiral Catalysts / 118

**5. Alkylation, Acylation, and Halogenation of Nitro Compounds 126**

5.1 Alkylation of Nitro Compounds / 126
5.2 Acylation of Nitroalkanes / 128
5.3 Ring Cleavage of Cyclic α-Nitro Ketones (Retro-Acylation) / 131
5.4 Alkylation of Nitro Compounds via Alkyl Radicals / 133
5.5 Alkylation of Nitro Compounds Using Transition Metal Catalysis / 138
5.5.1 Butadiene Telomerization / 138
5.5.2 Pd-Catalyzed Allylic C-Alkylation of Nitro Compounds / 140
5.6 Arylation of Nitro Compounds / 147
5.7 Introduction of Heteroatoms to Nitroalkanes / 149

**6 . Conversion of Nitro Compounds into Other Compounds 159**

6.1 Nef Reaction (Aldehydes, Ketones, and Carboxylic Acids) / 159
6.1.1 Treatment With Acid (Classical Procedure) / 159
6.1.2 Oxidative Method / 160
6.1.3 Reductive Method / 164
6.1.4 Direct Conversion of Nitroalkenes to Carbonyl Compounds / 165
6.2 Nitrile Oxides and Nitriles / 167
6.3 Reduction of Nitro Compounds into Amines / 170
6.3.1 Ar-$NH_2$ From Ar-$NO_2$ / 170
6.3.2 R-$NH_2$ From R-$NO_2$ / 172
6.3.3 Oximes, Hydroxylamines, and Other Nitrogen Derivatives / 175

**7. Substitution and Elimination of $NO_2$ in R–$NO_2$ 182**

7.1 R–Nu from R–$NO_2$ / 182
7.1.1 Radical Reactions ($S_{RN}1$) / 182
7.1.2 Ionic Process / 185
7.1.3 Intramolecular Nucleophilic Substitution Reaction / 191
7.1.4 Allylic Rearrangement / 192
7.2 R–H from R–$NO_2$ / 193
7.2.1 Radical Denitration / 193
7.2.2 Ionic Denitration / 211
7.3 Alkenes from R–$NO_2$ / 214

7.3.1 Radical Elimination / 214
7.3.2 Ionic Elimination of Nitro Compounds / 218

**8. Cycloaddition Chemistry of Nitro Compounds 231**

8.1 Diels-Alder Reactions / 231
8.1.1 Nitroalkenes Using Dienophiles / 231
8.1.2 Asymmetric Diels-Alder Reaction / 243
8.2 1,3-Dipolar Cycloaddition / 249
8.2.1 Nitrones / 249
8.2.2 Nitrile Oxides / 258
8.2.3 Nitronates / 267
8.3 Nitroalkenes as Heterodienes in Tandem [4+2]/[3+2] Cycloaddition / 274
8.3.1 Nitroalkenes as Heterodienes / 275
8.3.2 Tandem [4+2]/[3+2] Cycloaddition of Nitroalkenes / 279

**9. Nucleophilic Aromatic Displacement 302**

9.1 $S_NAr$ / 302
9.2 Nucleophilic Aromatic Substitution of Hydrogen (NASH) / 309
9.2.1 Carbon Nucleophiles / 310
9.2.2 Nitrogen and Other Heteroatom Nucleophiles / 316
9.2.3 Applications to Synthesis of Heterocyclic Compounds / 318

**10. Synthesis of Heterocyclic Compounds 325**

10.1 Pyrroles / 325
10.2 Synthesis of Indoles / 338
10.3 Synthesis of Other Nitrogen Heterocycles / 346
10.3.1 Three-Membered Ring / 346
10.3.2 Five- and Six-Membered Saturated Rings / 346
10.3.3 Miscellaneous / 355

**Index 365**

# SERIES FOREWORD

In the organic nitro chemistry era of the fifties and early sixties, a great emphasis of the research was directed toward 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.

Henry Feuer
Purdue University

# PREFACE

The purpose of this book is to emphasize recent important advances in organic synthesis using nitro compounds. Historically, it was aromatic nitro compounds that were prominent in organic synthesis. In fact they have been extensively used as precursors of aromatic amines and their derivatives, and their great importance in industrial and laboratory applications has remained.

This book is not intended to be a comprehensive review of established procedures, but it aims to emphasize new important methods of using nitro compounds in organic synthesis.

The most important progress in the chemistry of nitro compounds is the improvement of their preparations; this is discussed in chapter 2. Environmentally friendly methods for nitration are emphasized here.

In recent years, the importance of aliphatic nitro compounds has greatly increased, due to the discovery of new selective transformations. These topics are discussed in the following chapters: Stereoselective Henry reaction (chapter 3.3), Asymmetric Micheal additions (chapter 4.4), use of nitroalkenes as heterodienes in tandem [4+2]/[3+2] cycloadditions (chapter 8) and radical denitration (chapter 7.2). These reactions discovered in recent years constitute important tools in organic synthesis. They are discussed in more detail than the conventional reactions such as the Nef reaction, reduction to amines, synthesis of nitro sugars, alkylation and acylation (chapter 5). Concerning aromatic nitro chemistry, the preparation of substituted aromatic compounds via the $S_NAr$ reaction and nucleophilic aromatic substitution of hydrogen (VNS) are discussed (chapter 9). Preparation of heterocycles such as indoles, are covered (chapter 10).

Noboru Ono
Matsuyama, Ehime

# ACKNOWLEDGMENTS

Mr. Satoshi Ito, a graduate student in my group, has drawn all figures. It would have been impossible to complete the task of writing this book without his assistance. I would like to dedicate this book to the late Dr. Nathan Kornblum whom I met 30 years ago at Purdue University. Since then I have been engaged in the chemistry of nitro compounds.

It is a pleasure to express my gratitude to all persons who contributed directly or indirectly to the accomplishment of the task. Dr. Henry Feuer advised me to write this monograph and also provided many helpful suggestions, for which I thank him. Thanks to professors Node, Vasella, Ballini, Ohno and Ariga, who kindly sent me their papers. I also express my gratitude to Dr. H. Uno for his careful proofreading. Finally, thanks to my wife Yoshiko and daughter Hiroko for their constant encouragement.

Professors Kornblum and Ono.

# ABBREVIATIONS

| | |
|---|---|
| Ac | acetyl |
| AIBN | α,α-azobisisobutyronitrile |
| Ar | aryl |
| 9-BBN | 9-borabicyclo[3.3.1]nonane |
| BINAP | 1,1′-bisnaphthalene-2,2′-diyl-bisdiphenylphosphine |
| BINOL | 1,1′-bi-2-naphthol |
| Boc | *tert*-butoxycarbonyl |
| Bn = Bzl | benzyl |
| Bu | butyl |
| BuLi | *n*-butyllithium |
| Bz | benzoyl |
| CAN | ceric ammonium nitrate |
| CTAB | cetyltrimethylammonium bromide |
| Cbz | benzyloxycarbonyl |
| DBN | 1,8-diazabicyclo[4.3.0]nonene-5 |
| DBU | 1,8-diazabicylo[5.4.0]undecene-7 |
| DCC | dicyclohexylcarbodiimide |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DEAD | diethylazodicarboxylate |
| DMAP | 4-*N*,*N*-dimethylaminopyridine |
| DME | dimethoxyethane |
| DMF | *N*,*N*-dimethylformamide |
| DMI | 1,3-dimethyl-2-imdazolizinone |
| DMSO | dimethyl sulfoxide |
| dba | dibenzylideneacetone |
| d.e. | diastereomeric excess |
| d.s. | diastereoselectivity |
| dppe | 1,2-bis(diphenylphosphino)ethane |
| dppp | 1,3-bis(diphenylphosphino)propane |
| dppb | 1,4-bis(diphenylphosphino)butane |
| dppf | 1,1′-bis(diphenylphosphino)ferrocene |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| E | electrophiles |
| Et | ethyl |
| e.e. | enantiomeric excess |
| HMDS | hexamethyldisilazane |
| Im | 1-imidazolyl |
| LDA | lithium diisopropylamide |
| L-Selectide | lithium tri-*sec*-butyl borohydride |
| MCPBA | *m*-chloroperbenzoic acid |

| | |
|---|---|
| Me | methyl |
| MEM | 2-methoxyethoxymethyl |
| MOM | methoxymethyl |
| NBS | *N*-bromosuccinimide |
| NMO | *N*-methylmorpholine *N*-oxide |
| Nu | nucleophiles |
| PCC | pyridinium chlorochromate |
| Phth | phthaloyl |
| PMB | *p*-methoxybenzyl |
| PNB | *p*-nitrobenzyl |
| TBDMS | *tert*-butyldimethylsilyl |
| TMG | tetramethylguanidine |
| TBAF | tetrabutylammonium fluoride |
| TFA | trifluoroacetic acid |
| TFAA | trifluoroacetic anhydride |
| THF | tetrahydro+furan |
| Tf | trifluoromethanesulfonyl |
| THP | tetrahydropyranyl |
| Tr | trityl |
| TMEDA | tetramethylethylenediamide |
| TMS | trimethylsilyl |
| Tol | *p*-tolyl |
| Ts | *p*-tolenesulfonyl, tosyl |
| SET | single electron transfer reaction |

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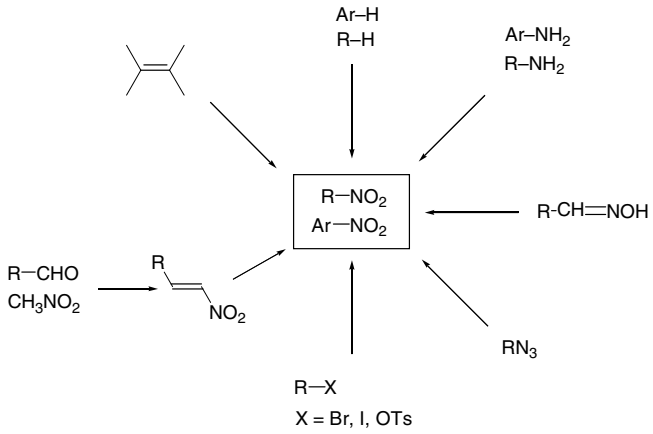
# 1

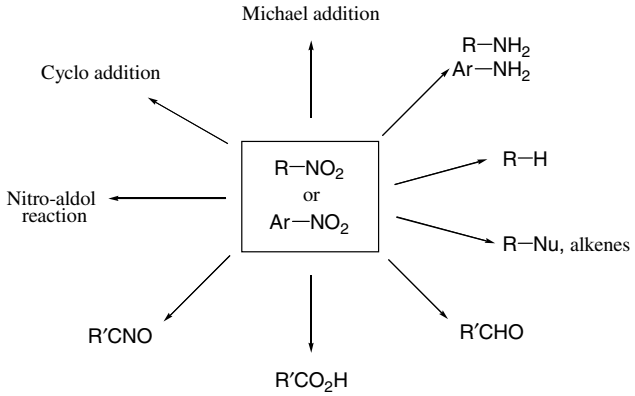
# INTRODUCTION

The remarkable synthetic importance of nitro compounds has ensured long-standing studies of their utilization in organic synthesis. Historically, nitro compounds, especially aromatic nitro compounds, are important for precursors of azo dyes and explosives. Of course, the importance of nitro compounds as materials for dyes and explosives has not been changed; in addition, they have proven to be valuable reagents for synthesis of complex target molecules. The versatility of nitro compounds in organic synthesis is largely due to their easy availability and transformation into a variety of diverse functionalities.

Preparation and reaction of nitro compounds are summarized in Schemes 1.1 and 1.2. Although there are many excellent books and reviews concerning nitro compounds, as listed in the references, the whole aspect of synthetic utility of nitro compounds has not been documented. This book has paid special emphasis to newly developing areas of nitro compounds such as radical reaction of nitro compounds, the stereoselective nitro-aldol reaction, and environmentally friendly chemistry (green chemistry). The control of the stereochemistry of the reactions involving nitro compounds is a quite recent progress. Furthermore, the reactions of nitro compounds have been regarded as non-selective and dangerous processes. However, clean




**Scheme 1.1.** Preparation of nitro compounds




**Scheme 1.2.** Reaction of nitro compounds

synthesis, synthesis in water or without solvents, the use of a fluorous phase, waste minimization, and highly selective reactions have been devised in many cases using nitro compounds. Such recent progresses are described in this book.

General reviews for preparation of nitro compounds[1] and for the reaction of nitro compounds[2–5] are listed in the references.

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# 2

# PREPARATION OF NITRO COMPOUNDS

## 2.1 NITRATION OF HYDROCARBONS

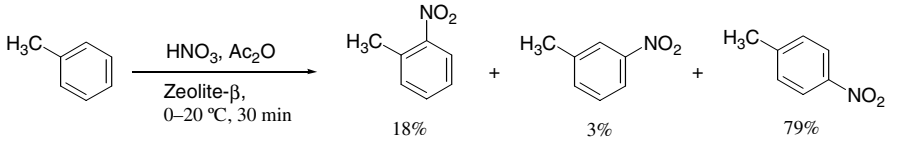
### 2.1.1 Aromatic Compounds

Aromatic nitration is an immensely important industrial process. The nitro aromatic compounds are themselves used as explosives and act as key substrates for the preparation of useful materials such as dyes, pharmaceuticals, perfumes, and plastics. Therefore, nitration of hydrocarbons, particularly of aromatic compounds, is probably one of the most widely studied organic reactions.[1,2] The classical nitration method usually requires the use of an excess of nitric acid and the assistance of strong acids such as concentrated sulfuric acid. Although this process is still in use in industries, nitrations are generally notoriously polluting processes, generating nitrogen oxide (NOx) fumes and large quantities of waste acids. Although many methods to improve the classical nitration method have been reported,[1,2] there is a great need for new nitration methods that can overcome such problems. Nitration has been well documented in the book by Olah, in which the following nitrating agents are discussed:[1] (a) $HNO_3$ + acid catalyst ($H_2SO_4$, $H_2PO_4$, polyphosphoric acid, $HClO_4$, HF, $BF_3$, $CH_3SO_3H$, $CF_3SO_3H$, $FSO_3H$, Nafion-H); (b) $RONO_2$ + acid catalyst ($H_2SO_4$, $AlCl_3$, $SnCl_4$, $BF_3$); (c) $RCO_2NO_2$; (d) $NO_2Cl$ + acid catalyst ($AlCl_3$, $TiCl_4$); (e) $N_2O_5$ or $N_2O_4$ + acid catalyst ($H_2SO_4$, $HNO_3$, $AlCl_3$ et al.); (f) $NO_2^+BF_4^-$, $NO_2^+PF_6^-$; and (g) *N*-nitropyridinum salts.

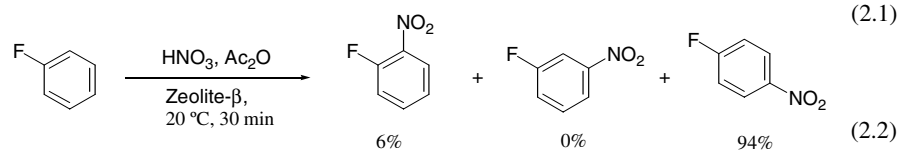
A new nitration process, that is environmentally friendly, has been the focus of recent research. Clark has pointed out that aromatic nitration, a particularly wasteful and hazardous industrial process, has benefited relatively little from the environmentally friendly catalytic methods.[3] An environmentally friendly nitration process requires high regioselectivity (*ortho* to *para*) and avoidance of excess acids to minimize waste. The use of solid acid catalysts is potentially attractive because of the ease of removal and recycling of the catalyst and the possibility that the solid might influence the selectivity.[3] The use of Nafion-H and other polysulfonic acid resins reduces the corrosive nature of the reaction mixture, although it does not improve regioselectivity.[4] A new class of solid acid catalyst systems, a high surface-area Nafion resin entrapped within a porous silica network, has been developed to mono-nitrate benzene in 82% conversion.[5] Copper nitrate supported on montmorillonite K-10 nitrates toluene in the presence of acetic anhydride to produce high *para* selectivity.[6] Nitration of benzocy-

clobutene using acetyl nitrate generated in situ by a continuous process in the presence of montmorillonite K-10 clay gives 3-nitrobicyclo[5.4.0]-1,3,5-triene in 60% yield.[7,8] High *para* selectivity (95%) is reported in the nitration of toluene catalyzed by zeolite ZSM-5 and alkyl nitrate.[9] The selective nitration of 4-hydroxbenzaldehyde to give the 3-nitro derivative has been achieved using iron(III) nitrate and a clay in quantitative yield.[10]

Smith and coworkers have screened the solid catalysts for aromatic nitration, and found that zeolite β gives the best result. Simple aromatic compounds such as benzene, alkylbenzenes, halogenobenzenes, and certain disubstituted benzenes are nitrated in excellent yields with high regioselectivity under mild conditions using zeolite β as a catalyst and a stoichiometric quantity of nitric acid and acetic anhydride.[11] For example, nitration of toluene gives a quantitative yield of mononitrotoluenes, of which 79% is 4-nitrotoluene. Nitration of fluorobenzene under the same conditions gives *p*-fluoronitrobenzene exclusively (Eqs. 2.1 and 2.2)



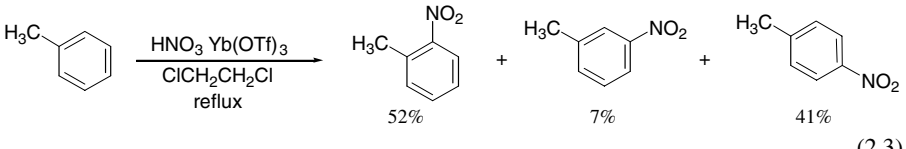

(2.1)



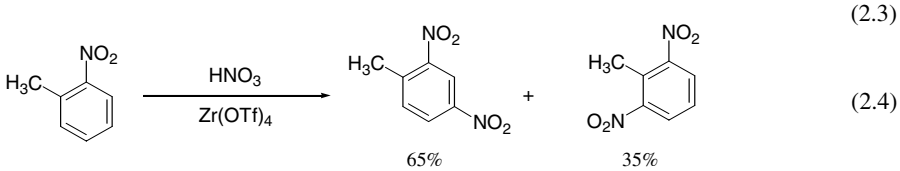

(2.2)

To avoid excessive acid waste, lanthanide(III) triflates are used as recyclable catalysts for economic aromatic nitration. Among a range of lanthanide(III) triflates examined, the ytterbium salt is the most effective. A catalytic quantity (1–10 mol%) of ytterbium(III) triflate catalyzes the nitration of simple aromatics with excellent conversions using an equivalent of 69% nitric acid in refluxing 1,2-dichloromethane for 12 h. The only by-product of the reaction is water, and the catalyst can be recovered by simple evaporation of the separated aqueous phase and reused repeatedly for further nitration.[12]

However, this catalyst is not effective for less reactive aromatics such as *o*-nitrotoluene. In such cases, hafnium(IV) and zirconium(IV) triflates are excellent catalysts (10 mol%) for mononitration of less reactive aromatics. The catalysts are readily recycled from the aqueous phase and reused (Eqs. 2.3 and 2.4).[12]



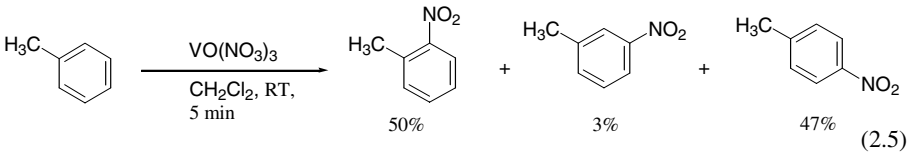

(2.3)




(2.4)

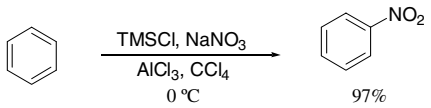
Phenols are easily mononitrated by sodium nitrate in a two-phase system (water-ether) in the presence of HCl and a catalytic amount of $La(NO_3)_3$.[13] Various lanthanide nitrates have been used in the nitration of 3-substituted phenols to give regioselectively the 3-substituted 5-nitrophenols.[14]

Vanadium oxytrinitrate is an easy to handle reagent that can be used to nitrate a range of substituted aromatic compounds in dichloromethane at room temperature, leading to >99% yields of nitration products (Eq. 2.5).[16]




(2.5)

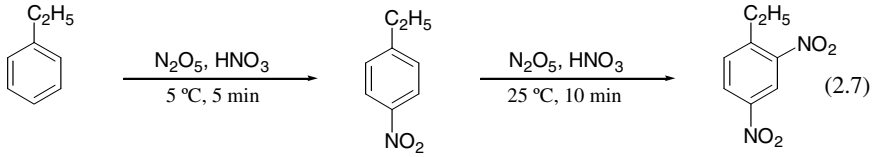
A novel, mild system for the direct nitration of calixarenes has been developed using potassium nitrate and aluminum chloride at low temperature. The side products of decomposition formed under conventional conditions are not observed in this system, and the *p*-nitrocalixarenes are isolated in 75–89% yields.[17] Such Friedel-Crafts-type nitration using nitryl chloride and aluminum chloride affords a convenient system for aromatic nitration.[18] Nitryl chloride was previously prepared either by the oxidation of nitrosyl chloride or by the reaction of chlorosulfonic acid with nitric acid. However, these procedures are inconvenient and dangerous. Recently, a mixture of sodium nitrate and trimethysilyl chloride (TMSCl) has been developed as a convenient method for the in situ generation of nitryl chloride (Eq. 2.6).




(2.6)

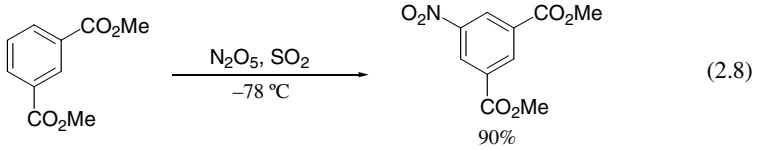
Nitration with dinitrogen pentoxide ($N_2O_5$) has increased in its importance as an environmentally cleaner alternative to conventional procedures. It might become the nitration method of the future. Dinitrogen pentoxide can be produced either by ozone oxidation of dinitrogen tetraoxide ($N_2O_4$) or electrolysis of $N_2O_4$ dissolved in nitric acid.[19]

Dinitrogen pentoxide (prepared by the oxidation of $N_2O_4$ with $O_3$) in nitric acid is a potent nitration system. It can be used for nitrating aromatic compounds at lower temperatures than conventional system. It is also convenient for preparing explosives that are unstable in nitrating media containing sulfuric acid (Eq. 2.7).[20]

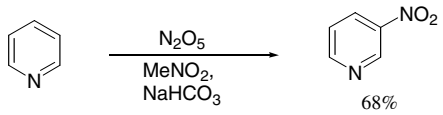



(2.7)

Dinitrogen pentoxide in liquid sulfur dioxide has been developed as a new nitration method with a wide potential for aromatic nitration, including deactivated aromatics, as shown in Eq. 2.8.[21] Electrophilic aromatic substitution of the pyridine ring system takes place under forcing conditions with very low yields of substituted products. Thus, nitration of pyridine with $HNO_3/H_2SO_4$ gives 3-nitropyridine in 3% yield. Bakke has reported a very convenient procedure for the nitration of pyridine using $N_2O_5$. Pyridines are nitrated in the β-position by the reaction with $N_2O_5$ in $MeNO_2$ followed by treatment with an aqueous solution of sodium bisulfate (Eq. 2.9). The reaction proceeds via the *N*-nitropyridinium ion.[22]

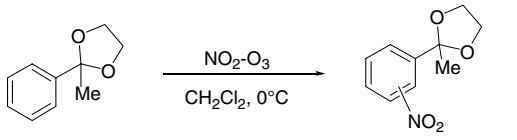



(2.8)



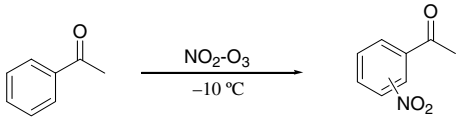

(2.9)

Nitrogen dioxide, in the presence of ozone, is a good nitrating system for various aromatics.[23] Suzuki and coworkers have proposed a mechanism that proceeds in a dual mode, depending on the oxidation potential of the aromatic substrate; nitrogen dioxide reacts with ozone to form nitrogen trioxide, which oxidizes the aromatic substrate to form a radical cation, an intermediate in the ring substitution. In the absence of an appropriate oxidizable substrate, the nitrogen trioxide reacts with another nitrogen dioxide to form dinitrogen pentoxide, which is a powerful nitrating agent in the presence of an acid. The mechanism of this nitration is well discussed in Ref. 27. This method has several merits over the conventional ones. As the reaction proceeds under neutral conditions, acid-sensitive compounds are nitrated without decomposition of acid-sensitive groups.[24a] The regioselectivity of this nitration process differs from that of the conventional nitration process, in that, for example, substrates bearing an electron-withdrawing group are preferentially nitrated in the *ortho*-position (Eqs. 2.10 and 2.11).[25]




58% (*o*:*m*:*p* = 22:19:59)

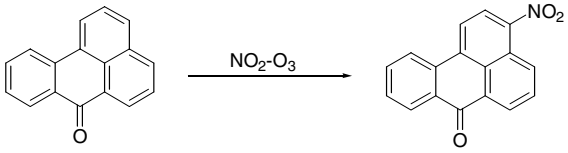
(2.10)




*o*- 52%, *m*- 48%

(2.11)

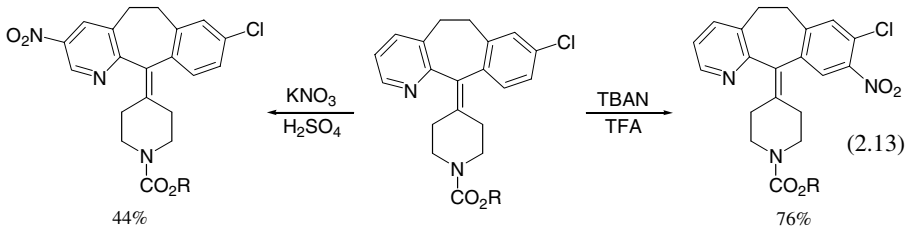
Reaction of benzanthrone with nitrogen dioxide alone or in admixture with ozone gives a mixture of nitrated products including 3-nitrobenzanthrone, which is a new class of powerful direct-acting mutagens of atmospheric origin (Eq. 2.12).[26]




(2.12)

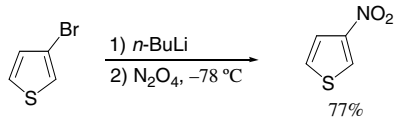
The regioselectivity of aromatic nitration depends on the conditions of nitration. Discussion of the regiochemistry of nitration is voluminous and is beyond the scope of this book; Ref. 1 and other appropriate references should be utilized for this discussion. Some recent interesting related topics are described here. The regiochemistry on the nitration of naphthalenes with various nitrating agents is compared. Unusually high 1-nitro-to-2-nitro isomer ratios are observed in the nitration with $NO_2$ and $O_3$, which proceeds via radical cation intermediates.[27] In a practical synthesis of polycyclic aromatics, regioselectivity of nitration is important. Classical nitration of azatricyclic systems using potassium nitrate and sulfuric acid yield mainly 9-nitro derivatives via the ionic process. However, the use of tetrabutylammonium nitrate (TBAN) and trifluoroacetic anhydride (TFAA) gives exclusively the 3-nitro derivatives. It is

suggested that the nitrating species in this case is the nitrosyl radical, generated from the homolytic decomposition of the TBAN/TFAA adduct (Eq. 2.13).[28] The easily prepared dinitrogen tetroxide complexes of iron and nickel nitrates have been shown to selectively mono- or dinitrate phenolic compounds in high yields.[29] It is well recognized that $NO_2$ is a very reactive radical taking part in atmospheric chemistry. Atmospheric reactions of polycyclic aromatic hydrocarbons forming mutagenic nitro derivatives have also been investigated.[30]

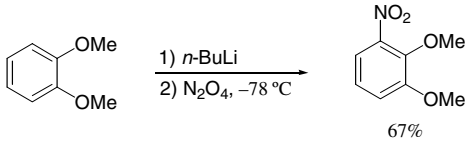



44% 76% (2.13)

Recently, nitration of organolithiums and Grignards with $N_2O_4$ has been developed for the preparation of certain kinds of nitro compounds (Eqs. 2.14 and 2.15).[31] The success of this process depends on the reaction conditions (low temperature) and the structure of substrates. For example, 3-nitrothiophene can be obtained in 70% overall yield from 3-bromothiophene; this is far superior to the older method. 3-Nitroveratrole cannot be prepared usefully by classical electrophilic nitration of veratrole, but it can now be prepared by direct *ortho*-lithiation followed by low-temperature $N_2O_4$ nitration. The mechanism is believed to proceed by dinitrogen tetroxide oxidation of the anion to a radical, followed by the radical's combination.




77% (2.14)




67% (2.15)

Nitration of aromatic compounds published in recent years is summarized in Table 2.1.

### 2.1.2 Alkanes

In contrast to the nitration of aromatic hydrocarbons, saturated aliphatic hydrocarbons are inert toward conventional nitrating agents under ambient conditions. Under forced conditions, they undergo cleavage of the C-C bond to give a complex set of oxidation products and lower nitroalkanes. The nitration in the gas phase has been used in industry since the 1940s, producing nitromethane, nitroethane, 1-nitropropane, 2-nitropropane, 1-nitrobutane and 2-nitrobutane.[1] Although this method is important for the preparation of nitroalkanes in industry, it is not practical for the laboratory preparation of nitroalkanes. Electrophilic nitration of alkanes is a more difficult process than aromatic nitration due to the fast formation of byproducts. Olah has reported nitration of adamantane with nitronium salts in aprotic solvents at ambient temperature, but the yield of 1-nitroadamantane is only 10%.[32] Since then, many attempts of nitration of adamantane have been tried, and the yield has been improved to 60–70% by using purified nitrile-free nitromethane as a solvent.[33] This reaction proceeds by electrophilic substi-

**Table 2.1 Nitration of aromatic compounds**

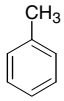
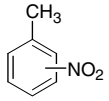
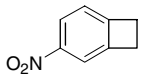
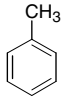
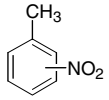
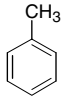
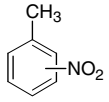
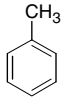
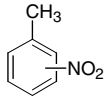
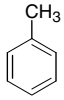
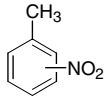
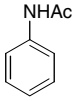
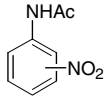
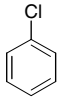
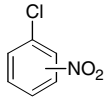
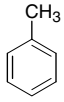
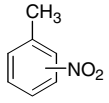
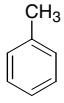
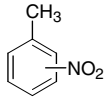
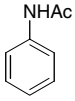
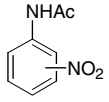
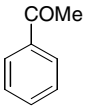
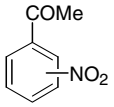
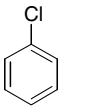
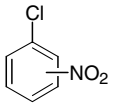
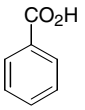
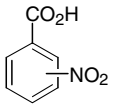
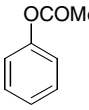
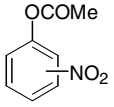
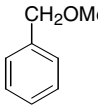
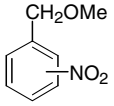
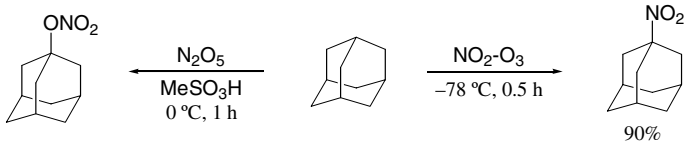
| Substrate | Reagent | Condition | Product | Yield | (%)[a] | Ref. |
|---|---|---|---|---|---|---|
|  | $HNO_3$, $Ac_2O$, K-10 | $CCl_4$ reflux |  | *o*-31 *m*-2 *p*-67 | (75–98) | 6 |
| | $HNO_3$, $Ac_2O$, K-10 | $CCl_4$ reflux |  | | (60) | 8 |
|  | $HNO_3$, $Ac_2O$, Zeolite β | 0–20 °C 30 min |  | *o*-18 *m*-3 *p*-79 | (99) | 11 |
|  | $HNO_3$, $Yb(Otf)_3$ (10 mol%) | $ClCH_2CH_2Cl$ reflux |  | *o*-52 *m*-7 *p*-79 | (95) | 12 |
|  | $HNO_3$, $Me_3SiCl$ $AlCl_3$ | $CCl_4$ 0 °C, 1 h |  | *o*-42 *m*-3 *p*-55 | (90) | 15 |
|  | $VO(NO_3)_3$ | $CH_2Cl_2$ RT, 6 min |  | *o*-50 *m*-3 *p*-47 | (99) | 16 |
|  | $VO(NO_3)_3$ | $CH_2Cl_2$ RT, 15 min |  | *o*-46 *p*-54 | (85) | 16 |
|  | $VO(NO_3)_3$ | $CH_2Cl_2$ RT, 20 min |  | *o*-43 *p*-57 | (99) | 16 |
|  | $NO_2$, $O_3$ | $CH_2Cl_2$ 0 °C, 1 h |  | *o*-51 *m*-6 *p*-43 | (99) | 24b |
|  | $NO_2$, $O_3$ pyridine (3 equiv) | $CH_2Cl_2$ 0 °C, 2 h |  | *o*-22 *m*-66 *p*-13 | (21) | 24b |
|  | $NO_2$, $O_3$ | $CH_2Cl_2$ 0 °C, 2.5 h |  | *o*-81 *p*-19 | (98) | 24c |

**Table 2.1 Continued**

| Substrate | Reagent | Condition | Product | Yield (%)[a] | Ref. |
|---|---|---|---|---|---|
|  | $NO_2$, $O_3$ | $CH_2Cl_2$<br>–10 °C, 4 h |  | *o*-52<br>*m*-48 (99) | 24a |
|  | $NO_2$, $O_3$ | $CH_2Cl_2$<br>0 °C, 3 h |  | *o*-43<br>*m*-1<br>*p*-56 (97) | 27 |
|  | $NO_2$, $O_3$ | $ClCH_2CH_2Cl$<br>0 °C, 1.5 h |  | *o*-29<br>*m*-69<br>*p*-2 (98) | 24d |
|  | $NO_2$, $O_3$ | $CH_2Cl_2$<br>0 °C, 2 h |  | *o*-60<br>*p*-40 (100) | 24e |
|  | $NO_2$, $O_3$ | $CH_2Cl_2$<br>0 °C, 2 h |  | *o*-69<br>*m*-4<br>*p*-27 (99) | 24f |

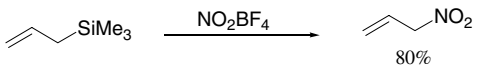
[a] *o*-, *m*-, *p*-ratio and yield.

tution at single bonds. On the other hand, radical nitration of adamantane using $N_2O_5$ gives a mixture of several compounds arising from the N- and O-attacks at the secondary and tertiary positions.[34] Selective N- and O-functionalization of adamantane has been reported. In the presence of ozone at –78 °C, nitrogen dioxide selectively reacts with adamantane at the bridgehead position to give the nitrated product, whereas, in the presence of methanesulfonic acid at 0 °C, $N_2O_5$ reacts with this hydrocarbon at the same position to give the nitrooxylated product (Eq. 2.16).[35]

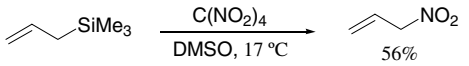



(2.16)

Nitrodesilylation (Eq. 2.17)[36] and nitrodestanylation (Eq. 2.18)[37] are efficient methods for the preparation of some kinds of nitroalkanes from readily available alkylsilanes or allylstannanes. Similar nitration also takes place at the vinylic positions (see Eq. 2.36 in Section 2.1.4).



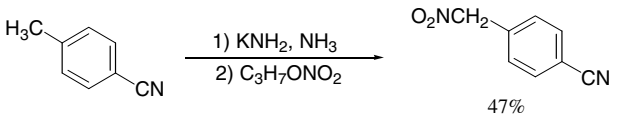

(2.17)



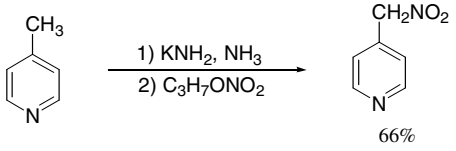

(2.18)

### 2.1.3 Activated C-H Compounds

The nitration of active methylene compounds generally proceeds via the reaction of carbanionic intermediates with an electrophilic nitrating agent such as alkyl nitrate (alkyl nitrate nitration). Details of this process are well documented in the reviews.[38] The alkyl nitrate nitration method has been used extensively for the preparation of arylnitromethanes. The toluene derivatives, which have electron-withdrawing groups are nitrated with alkyl nitrates in the presence of $KNH_2$ in liquid ammonia (Eqs. 2.19 and 2.20).[39]

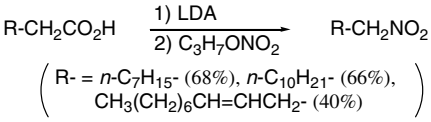



(2.19)

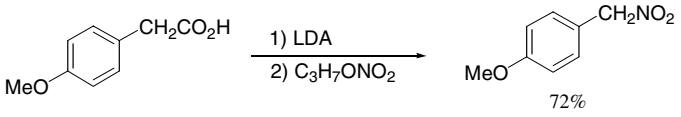



(2.20)

Nitration of delocalized carbanions with alkyl nitrates in the presence of bases provides a useful method for the preparation of nitro compounds. As a typical example, cyclopentanone, cyclohexanone, and cyclooctanone react with amyl nitrate in the presence of potassium *t*-butoxide in THF at a low temperature (–30 °C) to give α,α-dinitrocycloalkanones in 35–72% yield. The products are converted into α,ω-dinitroalkanes. Thus, the potassium salt of 2,6-dinitrocyclohexanone is converted to 1,5-dinitropentane in 78% yield on treatment with acid. In a similar way, 1,5-dinitropentane and 1,4-dinitrobutane are prepared in about 70% yield.[40] Dianions derived from carboxylic acids are nitrated to give nitroalkanes in 45–68% yield (Eq. 2.21).[41] Arylnitromethanes are readily prepared by this method (Eq. 2.22).[42] This method is useful for the preparation of arylnitromethanes with electron-rich aryl groups, which are generally difficult to prepare by nitration of the corresponding halides.

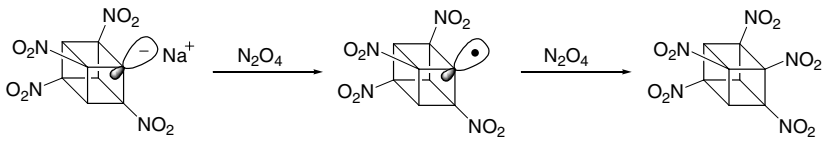



(2.21)



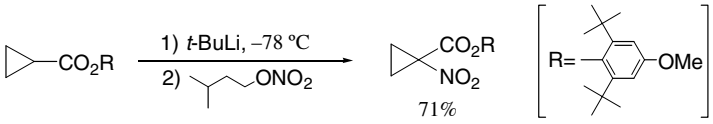

(2.22)

The sodium salts of 1,3,5,7-tetranitrocubane and 1,2,3,5,7-pentanitrocubane can be nitrated successfully with $N_2O_4$ in THF at low temperature. These reactions proceed by $N_2O_4$ oxidation of the anion to the radical and its combination with $NO_2$ (Eq. 2.23).[43] Such highly nitrated cubanes are predicted to be shock-insensitive, very dense, high-energy compounds with great potential as explosives and propellants.




(2.23)

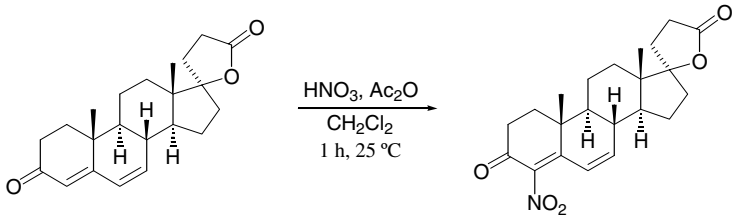
1-Nitrocyclopropane-1-carboxylate is prepared in 71% yield by nitration of the enolate derived from the cyclopropane carboxylate with isoamyl nitrate (Eq. 2.24). It is a precursor of α-amino acid, containing a cyclopropane ring.[44]




(2.24)

### 2.1.4 Alkenes

Nitration of alkenes gives conjugated nitroalkenes, which are useful and versatile intermediates in organic synthesis. Nitroalkenes are generally prepared either by nitration of alkenes or dehydration of 2-nitro alcohols formed via the Henry reaction (see Section 3.2.1). Nitration of alkenes with $HNO_3$ gives nitroalkenes in moderate yields, but this process has not been used for organic synthesis in a laboratory because of the lack of selectivity and decomposition of alkenes. Early references are found in Ref. 1. Nitration of the steroid canrenone using nitric acid and acetic anhydride occurs at the 4-position in 52% yield (Eq. 2.25).[45] This regiochemistry is noteworthy; early papers on nitration of the steroids with $HNO_3$ report the nitration at the 6-position.[46]

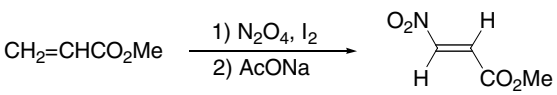



(2.25)

A convenient preparative method for conjugated nitroalkenes has been developed based on the reaction of nitrogen oxides. Nitric oxide (NO) is commercially available and used in the industry for the mass production of nitric acid. Nitric oxide is currently one of the most studied molecules in the fields of biochemistry, medicine, and environmental science.[47] Thus, the reaction of NO with alkenes under aerobic conditions is of a renewed importance.[48]

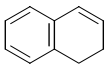
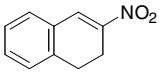
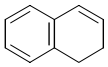
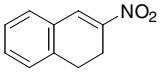
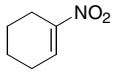
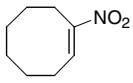
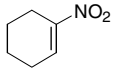
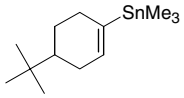
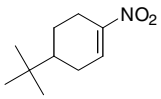
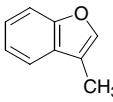
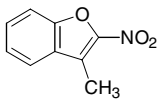
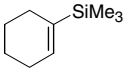
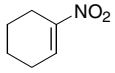
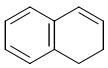
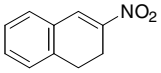
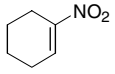
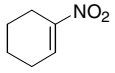
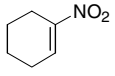
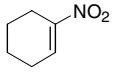
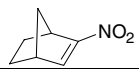
There are many reports for nitration of alkenes using various nitrating agents, which proceeds via an ionic or radical addition process.[49] Nitration of cyclohexene with acetyl nitrate gives a mixture of β-and γ-nitrocyclohexenes, 1,2-nitroacetate, and 1,2-nitronitrate. This reaction is not a simple ionic or radical process; instead, [2+2] cycloaddition of nitryl cation is proposed.[50]

Two important methods for the preparation of nitroalkenes are reported in Collective Volume 6 in Organic Synthesis. Methyl 3-nitroacrylate, which is a very important reagent for organic synthesis, is prepared by the reaction of methyl acrylate with $N_2O_4$ in the presence of iodine, which is followed by the subsequent treatment with sodium acetate (Eq. 2.26).[51] The reaction of alkenes with nitrogen oxides in the presence of oxygen gives a mixture of vicinal nitro nitrates and dinitro compounds, which are precursors of nitroalkenes. Thus, 1-nitrocyclooctene is prepared in 63–64% yield by the reaction of cyclooctene and $N_2O_4$ in the presence of $O_2$ (Table 2.2).[52]

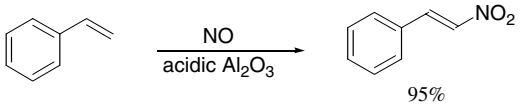



(2.26)

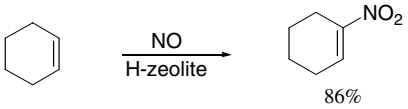
**Table 2.2 Preparation of cyclic nitroalkenes via nitration**

| Cyclic alkenes | Reagent | Product | Yield (%) | Ref. |
|---|---|---|---|---|
|  | NO<br>$Al_2O_3$ |  | 86 | 53 |
|  | NO<br>H-zeolite |  | 76 | 54 |
| | NO<br>H-zeolite |  | 86 | 54 |
| | 1) $N_2O_4$, $O_2$<br>2) $Et_3N$ |  | 63 | 52 |
| | 1) PhSeBr, $AgNO_2$<br>$HgCl_2$<br>2) $H_2O_2$ |  | 81 | 66 |
|  | $C(NO_2)_4$, DMSO |  | 94 | 37 |
|  | 1) *t*-BuLi/THF<br>$Me_3SnCl$<br>2) $C(NO_2)_4$,<br>DMSO |  | 72 | 72 |
|  | $AcONO_2$ |  | 73 | 73 |
|  | 1) $KNO_2$,<br>18-crown-6, $I_2$,<br>THF<br>2) pyridine |  | 90 | 64 |
| | $NaNO_2$<br>$Ce(NH_4)_3(NO_3)_6$<br>AcOH |  | 96 | 56 |
| | $NaNO_2$, $NaNO_3$<br>anodic oxidation |  | 41 | 59 |
| | $NaNO_2$, $I_2$<br>$HOCH_2CH_2OH$ |  | 72 | 63 |
| | 1) $NaNO_2$, $HgCl_2$<br>2) NaOH |  | 92 | 74 |
| | 1) $NaNO_2$, $HgCl_2$<br>2) NaOH |  | 90 | 74 |

A very attractive method for the preparation of nitroalkenes, which is based on the reaction with NO, has been reported. Treatment of alkenes at ambient pressure of nitrogen monoxide (NO) at room temperature gives the corresponding nitroalkenes in fairly good yields along with β-nitroalcohols in a ratio of about 8 to 2. The nitroalcohol by-products are converted into the desired nitroalkenes by dehydration with acidic alumina in high total yield. This simple and convenient nitration procedure is applied successfully to the preparation of nitroalkenes derived from various terminal alkenes or styrenes (Eq. 2.27).[53] This process is modified by the use of HY-zeolites instead of alumina. The lack of corrosiveness and the ability to regenerate and reuse the catalyst make this an attractive system (Eq. 2.28).[54]




(2.27)

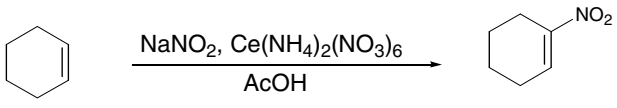



(2.28)

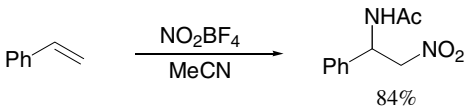
Addition of the $NO_2$ radical to alkenes, followed by oxidation to a carbocation or by halogenation is now widely used for the preparation of nitroalkenes. However, the use of dinitrogen tetroxide is not simple in the laboratory because $N_2O_4$ is very toxic and a small syringe for this gas is rather expensive. To avoid the use of $N_2O_4$, several nitrating systems using liquid or solid reagents have been developed.

The direct conversion of styrene to β-nitrostyrene using clay doped with nitrate salts has been reported. Styrene and clayfen (iron nitrate on clay) or clayan (ammonium nitrate on clay) are mixed well and then heated at 100–110 °C in solid state to give β-nitrostyrene in 68% yield.[55a] A more simple one-pot synthesis of β-nitrostyrene from styrene has been reported; β-nitrostyrene is prepared in 47% yield on treatment of styrene with $CuO{\cdot}HBF_4$, $I_2$, and $NaNO_2$ in MeCN at room temperature.[55b]

Sonication of a chloroform solution containing the alkenes, $NaNO_2$ (10 equiv), $Ce(NH_4)_2(NO_3)_6$ (2.0 equiv), and acetic acid (12 equiv) in a sealed tube at 25–73 °C provides an excellent way to prepare nitroalkenes. For example, cyclohexene is converted into 1-nitrocyclohexene in 96% yield by this method (Eq. 2.29).[56] When the reaction is carried out in acetonitrile, the carbocation intermediates are trapped by acetonitrile to give nitroacetamides in good yield.[57] Analogous nitroacetamidation is possible by using nitronium tetrafluoroborate and acetonitrile (Eq. 2.30).[58]




(2.29)

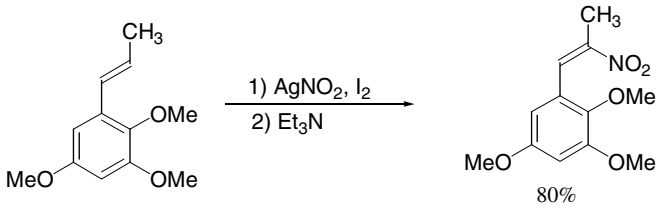



(2.30)

Electrochemical oxidation of a mixture of alkenes, $NaNO_2$ and $NaNO_3$, in water is also a good method for the preparation of nitroalkenes.[59]

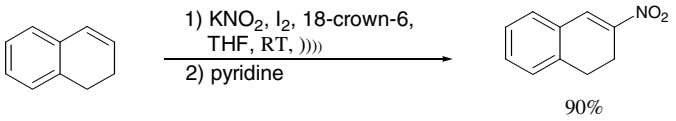
The regioselective addition of nitryl iodide to alkenes, followed by base-induced elimination, gives nitroalkenes. Nitryl iodide is generally prepared by the reaction of $AgNO_2$ and iodine.

The synthetic applications of this reagent to the synthesis of nitroalkenes have been known since the 1960s.[60] Nitration of alkenes with nitryl iodide, generated in situ from iodine and silver nitrite, is convenient for the synthesis of β-nitrostyrenes with various functional groups.[61] This method is applied to the synthesis of *ortho*-methoxylated phenylisopropylamines, which are potent serotonine agonists (Eq. 2.31).[62]



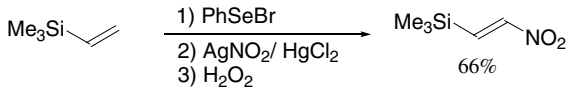

(2.31)

Replacement of silver nitrite by inexpensive sodium or potassium nitrite enhances the utility of this process. Treatment of alkenes with sodium nitrite and iodine in ethyl acetate and water in the presence of ethylene glycol gives conjugated nitroalkenes in 49–82% yield.[63] The method for generation of nitryl iodide is improved by the treatment of iodine with potassium nitrite complexed with 18-crown-6 in THF under sonication, as shown in Eq. 2.32.[64]

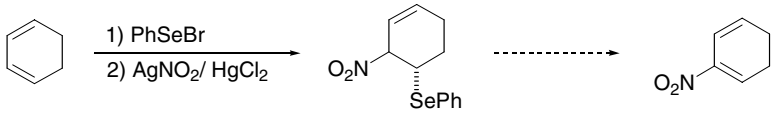



(2.32)

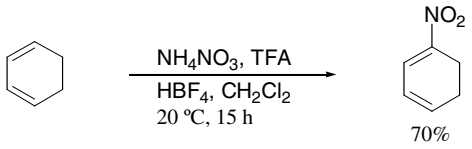
Nitrosulfonylation using sodium nitrite and sulfenyl halides[65] or nitroselenation using phenylselenyl bromide, silver nitrite, and mercuric chloride,[66] as shown in Eq. 2.33 may be useful for the preparation of conjugated nitroalkenes from alkenes. 2-Nitro-1,3-dienes are prepared from the corresponding conjugated 1,3-dienes via a nitroselenation-elimination sequence (Eq. 2.34).[67] Such nitrodienes are of interest synthetically for further reaction with electron-rich alkenes like enol ethers or enamines.[68] They are also transformed into synthetically useful 3,4-epoxy-3-nitro-1-alkenes.[69] On the other hand, the reaction of conjugated dienes with ammonium nitrate in trifluoroacetic anhydride gives 1-nitro-1,3-dienes in good yield (Eq. 2.35).[70]




(2.33)



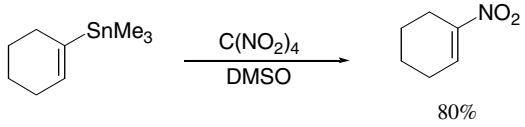

(2.34)




(2.35)

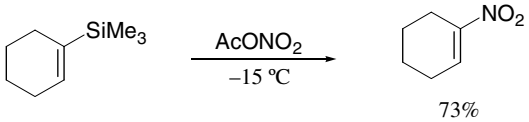
Cyclic nitroalkenes are prepared from cyclic ketones via nitration of vinylstannanes with tetranitromethane in DMSO, as shown in Eq. 2.36, where DMSO is a critical choice of solvent for replacing tin by nitro at the unsaturated carbon. The conversion of ketones to vinylstannanes

can be performed in good yield via arylhydrazone intermediates.[71] Regioselective nitration of 3-alkyl-1-benzofurans at the 2-position is also possible by stannylation and treatment with tetranitromethane in DMSO.[72]

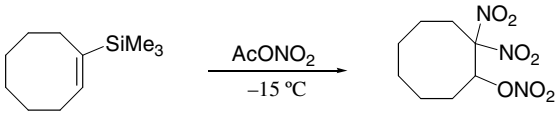



80% (2.36)

The reaction of acetyl nitrate with cyclic vinylsilanes gives 1-nitrocycloalkenes or 1,1-dinitro 2-nitrated cycloalkanes, depending on the ring size, as shown in Eqs. 2.37 and 2.38.[73]




73% (2.37)




70% (2.38)

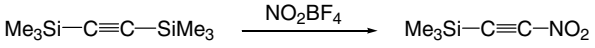
In 1978, Corey reported a general synthetic route for the conversion of alkenes to conjugated nitroalkenes via nitro-mercuration and demercuration.[74] Since then, many chemists have used this method for the preparation of cyclic nitroalkenes such as 1-nitrocyclohexene. However, the use of mercury salts is not recommended even for the small-scale preparation of nitroalkenes. This reaction is not as clean as expected, and formidable efforts are required to remove the mercury in the waste.

The synthesis of cyclic nitroalkenes via nitration of cycloalkenes is summarized in Table 2.2. Acyclic nitroalkenes are more readily prepared via the Henry reaction than by nitration of alkenes (see Section 3.2.1).

Because nitration of alkenes with nitronium salts proceeds via carbocation intermediates, nitration of electron-deficient alkenes with nitronium salts is rare. Only a few cases are reported. The reaction of α,β-unsaturated esters with nitronium salts affords products via highly reactive α-carbonyl cations.[75]

Nitration of aromatics or alkenes with nitronium tetrafluoroborate gives a variety of nitro compounds.[1] However, this process is not always useful because the reagent is expensive and very moisture sensitive. The difficulty is solved by the use of an electrochemically-generated nitronium salt. Anodic oxidation of an acetonitrile solution of nitrogen dioxide at constant current (500 mA/cm$^2$) using a divided H-cell (Pt electrode, $LiBF_4$ as electrolyte) gives a solution of $NO_2BF_4$, which effectively nitrates aromatics, enol silyl ethers, alkenes, and dienes to give, respectively, nitroaromatics, α-nitro ketones, vicinal nitroamides, and nitroacetamides.[76]

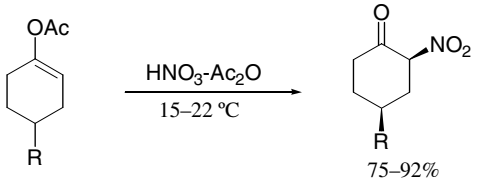
Nitration of acetylenes with nitryl iodide followed by elimination of HI gives nitroacetylenes, but nitroacetylenes are too thermally unstable to be useful for organic synthesis.[77] Recently, nitro-trimethylsilyl-acetylenes are prepared as stable nitroacetylenes by the reaction of bis(trimethylsily)acetylene with nitronium tetrafluoroborate (Eq. 2.39).[78]




70% (2.39)

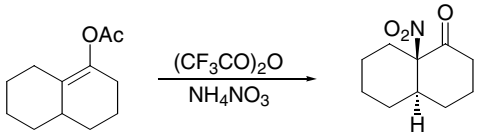
### 2.1.5 Synthesis of α-Nitro Ketones

Nitration of ketones or enol ethers provides a useful method for the preparation of α-nitro ketones. Direct nitration of ketones with $HNO_3$ suffers from the formation of a variety of oxidative by-products. Alternatively, the conversion of ketones into their enolates, enol acetates, or enol ethers, followed by nitration with conventional nitrating agents such as acyl nitrates, gives α-nitro ketones (see Ref. 79, a 1980 review). The nitration of enol acetates of alkylated cyclohexanones with concentrated nitric acid in acetic anhydride at 15–22 °C leads to mixtures of *cis*- and *trans*-substituted 2-nitrocyclohexanones in 75–92% yield. 4-Monoalkylated acetoxycyclohexanes give mainly *cis*-compounds, and 3-monoalkylated ones yield *trans*-compounds (Eq. 2.40).[80]



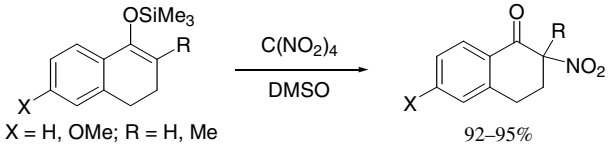

75–92% (2.40)

Nitration of the potassium enolates of cycloalkanones with pentyl nitrate[81] or nitration of silyl enol ethers with nitronium tetrafluoroborate[82] provides a method for the preparation of cyclic α-nitro ketones. Trifluoroacetyl nitrate generated from trifluoroacetic anhydride and ammonium nitrate is a mild and effective nitrating reagent for enol acetates (Eq. 2.41).[83]



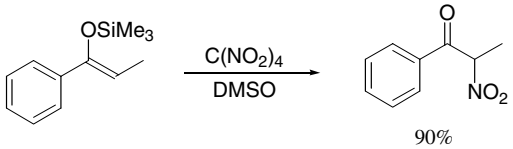

100% (2.41)

Cyclic and acyclic silyl enol ethers can be nitrated with tetranitromethane to give α-nitro ketones in 64–96% yield (Eqs. 2.42 and 2.43).[84] The mechanism involves the electron transfer from the silyl enol ether to tetranitromethane. A fast homolytic coupling of the resultant cation radical of silyl enol ether with $NO_2$ leads to α-nitro ketones. Tetranitromethane is a neutral reagent; it is commercially available or readily prepared.[85]



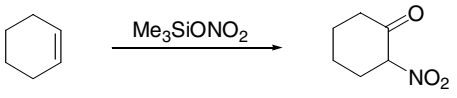

X = H, OMe; R = H, Me

92–95% (2.42)




90% (2.43)

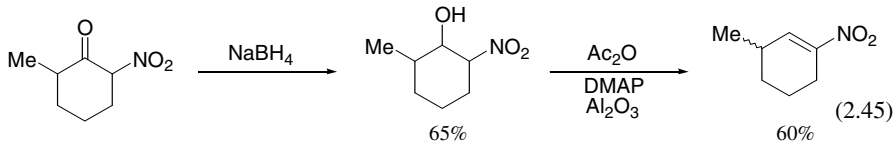
A novel one-pot synthesis of α-nitro ketones from alkenes has been observed on treatment with trimethylsilyl nitrate-chromium trioxide or a trimethylsilyl nitrate-DMSO reagent system (Eq. 2.44).[86]




(2.44)

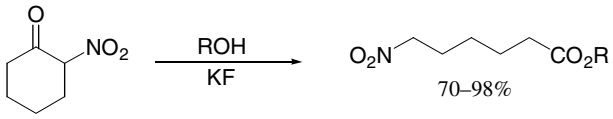
| Reagent | Yield (%) |
|---|---|
| $CrO_3$ | 61 |
| DMSO | 73 |

α-Nitro ketones, which are important intermediates for organic synthesis, are alternatively prepared either by oxidation of 2-nitroalcohols (see Section 3.2.3) or by acylation of nitroalkanes (see Section 5.2). Synthetic application of cyclic α-nitro ketones has been well summarized in recent reviews.[87,88] Because α-nitrocycloalkanones are more readily prepared than nitrocycloalkenes, the former can be used as precursors for nitrocycloalkenes (Eq. 2.45).[89] Sodium borohydride reduction of α-nitro ketones and successive dehydration with $Ac_2O$ N,N-dimethylaminopyridine (DMAP) and basic alumina gives, in a one-pot procedure, conjugated nitrocycloalkenes.




(2.45)

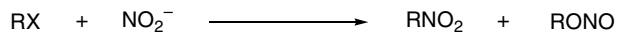
Ring cleavage of cyclic 2-nitro ketones by external nucleophiles gives a variety of functionalized nitro compounds, ketones, or carboxylic acids. The ring cleavage of 2-nitrocycloalkanones with ROH-KF gives ω-nitro esters (Eq. 2.46).[90] A significant improvement of this ring cleavage is obtained by using Amberlyst A-21.[91]




(2.46)

### 2.1.6 Nitration of Alkyl Halides

The reaction of alkyl halides with metal nitrites is one of the most important methods for the preparation of nitroalkanes. As a metal nitrite, silver nitrite (Victor-Meyer reaction), potassium nitrite, or sodium nitrite (Kornblum reaction) have been frequently used. The products are usually a mixture of nitroalkanes and alkyl nitrites, which are readily separated by distillation (Eq. 2.47). The synthesis of nitro compounds by this process is well documented in the reviews, and some typical cases are listed in Table 2.3.[92a] Primary and secondary alkyl iodides and bromides as well as sulfonate esters give the corresponding nitro compounds in 50–70% yields on treatment with $NaNO_2$ in DMF or DMSO. Some of them are described precisely in vol 4 of Organic Synthesis. For example, 1,4-dinitrobutane is prepared in 41–46% yield by the reaction of 1,4-diiodobutane with silver nitrite in diethyl ether.[92b] 1-Nitrooctane is prepared by the reaction with silver nitrite in 75–80% yield. The reaction of silver nitrite with secondary halides gives yields of nitroalkanes of about 15%, whereas with tertiary halides the yields are 0–5%.[92c] Ethyl α-nitrobutyrate is prepared by the reaction of ethyl α-bromobutyrate in 68–75% yield with sodium nitrite in DMF.[92d] Sodium nitrite is considerably more soluble in DMSO than in DMF; as a consequence, with DMSO, much more concentrated solutions can be employed and this makes shorter reaction times possible.[92e]

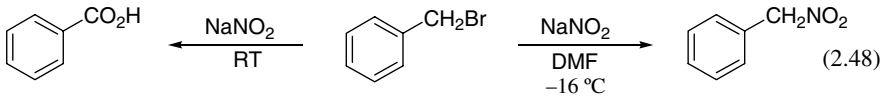



(2.47)

**Table 2.3 Synthesis of nitroalkanes from alkyl halides**

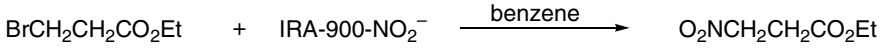
| RX | $NO_2^-$ | Solvent | $RNO_2$ (%) | RONO (%) |
|---|---|---|---|---|
| *n*-$C_4H_9Br$ | $AgNO_2$ | $Et_2O$ | 73 | |
| *n*-$C_8H_{17}Br$ | $AgNO_2$ | $Et_2O$ | 80 | |
| *i*-$C_3H_7Br$ | $AgNO_2$ | $Et_2O$ | 20 | 31 |
| *n*-$C_6H_{13}Br$ | $NaNO_2$ | DMF | 61 | 29 |
| *n*-$C_8H_{17}Br$ | $NaNO_2$ | DMF | 60 | |
| | $NaNO_2$ | DMF | 58 | |
| | $NaNO_2$ | DMF | 57 | 25 |
| | $NaNO_2$ | DMF | 0 | (product: cyclohexane) |
| | $NaNO_2$ | DMF | 55 | |

Thus, the reaction of alkyl halides and α-halo esters with sodium nitrite provides a very useful synthetic method for nitroalkanes and α-nitro esters. However, ethyl bromoacetate is exceptional in that it fails to give ethyl nitroacetate on treatment with sodium nitrite.[93] This is due to the acidic hydrogen of the ethyl nitroacetate, which undergoes a further reaction with sodium nitrite to give the oxidized products (see Section 6.1, which discusses the Nef reaction). In a similar way, the reaction of benzyl bromide with sodium nitrite at 25 °C gives benzoic acid predominantly. To get phenylnitromethane, the reaction must be carried out at low temperature (–16 °C) (Eq. 2.48).[93]



(2.48)

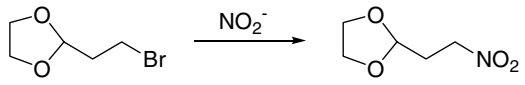
Several improved methods for the nitration of alkyl halides have been reported. For example, the use of $KNO_2$ in the presence of 18-crown-6[94] or nitrite ion bounded to macroporous quaternary ammonium amberlite resin (amberlite IRA 900) improves the yield of nitro compounds (Eq. 2.49).[95]



100% (2.49)

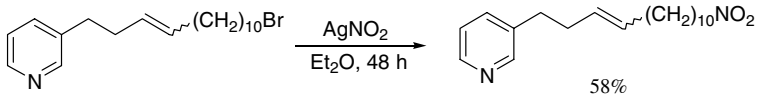
Mosher and coworkers have prepared 2-(2-nitroethyl)-1,3-dioxolane from the corresponding 2-bromo compounds by various procedures (Eq. 2.50).[96] They found that IRA-900-$NO_2^-$ is best for this conversion.

The preparation of nitroalkanes from alkyl halides has been used extensively for organic synthesis. Interestingly, nitroalkylpyridine alkaloids, which have *anti*-macrofouling activity, are isolated from the Okinawan marine sponge *Callyspongia sp*. The synthesis of such compounds has been done by the nitration of the corresponding bromide with silver nitrite (Eq. 2.51). The biogenesis of nitroalkyl compounds is an interesting process, since nitroalkyl compounds are extremely rare metabolites of marine organisms.[97]



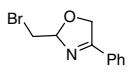
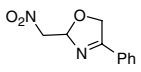
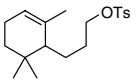
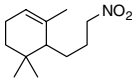
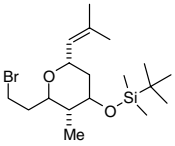
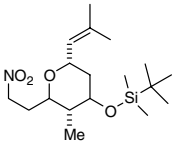
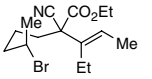
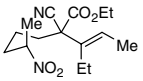
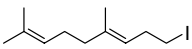
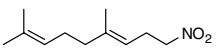
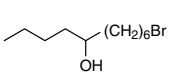
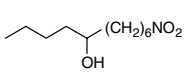
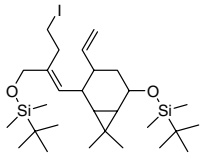
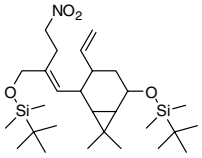

(2.50)

| | Solvent | Condition | Yield (%) |
|---|---|---|---|
| $NaNO_2$ | DMSO | RT, 12 h | 35 |
| $NaNO_2$ | DMSO-urea | RT, 12 h | 36 |
| $KNO_2$ | DMSO 18-crown-6 DMSO | RT, 18 h | 37 |
| $NaNO_2$ | phloroglucinol | RT, 18 h | 51 |
| $AgNO_2$ | $Et_2O$ | 35 °C, 96 h | 47 |
| IRA-900-$NO_2^-$ | Benzene | RT, 36 h | 82 |




(2.51)

**Table 2.4 Synthesis of nitro compounds from halides**

| Halide | Condition | Product | Yield (%) | Ref. |
|---|---|---|---|---|
|  | NaI, acetone $NaNO_2$, DMSO |  | 63 | 98 |
|  | NaI, DMF $NaNO_2$, DMF |  | 67 | 99 |
|  | $AgNO_2$, $Et_2O$ |  | 78 | 100 |
|  | $NaNO_2$, DMF |  | 58 | 101 |
|  | $NaNO_2$, DMSO |  | 60 | 102 |
|  | $NaNO_2$, DMSO |  | 70 | 103 |
|  | $AgNO_2$, $Et_2O$ |  | 67 | 104 |

A number of nitro compounds used in natural product synthesis have been prepared by the nitration of alkyl halides. Some recent examples are summarized in Table 2.4.

β-Nitro carbonyl compounds are important for synthesis of natural products. The reaction of alkyl vinyl ketones with sodium nitrite and acetic acid in THF gives the corresponding β-nitro carbonyl compounds in 42–82%.[105] This method is better for the preparation of β-nitro carbonyl compounds than the nitration of the corresponding halides.

Schneider and Busch have showed that tetraaza[8.1.8.1]paracyclophane catalyzes the nitration of alkyl bromides with sodium nitrite. In dioxane-water (1:1) at 30 °C, the reaction of 2-bromomethylnaphthalene with sodium nitrite is accelerated by a factor of 20 in the presence of the catalyst.[106] Concomitantly, the product ratio of [R-ONO]: [$RNO_2$] changes from 0.50:1 to 0.16:1. Thus, an accumulation of nitrite ions at the positively charged cyclophanes or IRA-900-nitrite form provides a new method for selective nitration of alkyl halides.

## 2.2 SYNTHESIS OF NITRO COMPOUNDS BY OXIDATION

### 2.2.1 Oxidation of Amines

The direct oxidation of primary amines into the corresponding nitro derivatives is very useful for fundamental and industrial applications because it provides nitro compounds, which may otherwise be difficult to synthesize by direct nitration methods. Efficient synthetic methods for the conversion of primary amines into the nitro compounds are described in this section. Saturated primary amines undergo oxidation reactions by ozone to give the corresponding nitroalkanes accompanied by several other compounds depending on the reaction conditions.[107] This drawback is overcome by ozonation on silica gel. Amines are absorbed on the silica gel by mixing with dry silica gel (dried for 24 h at 450 °C). The silica gel (ca 30 g) containing the amine (0.1–0.2 wt/wt%) was cooled to −78 °C and a stream of 3% of ozone in oxygen passed through it. By this procedure, nitro compounds are obtained in 60–70% yield (Eq. 2.52).[108] 1-Nitroadamantane is prepared by oxidation of 1-aminoadamantane with peracetic acid and ozone in 95% yield.[109]

$$R{-}NH_2 \xrightarrow[\text{silica gel}]{O_3} \underset{60\text{–}70\%}{R{-}NO_2} \qquad (2.52)$$

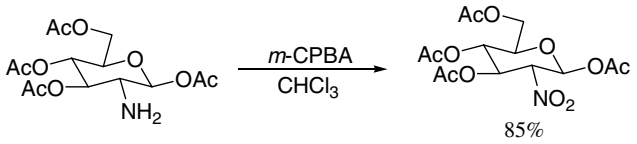
The use of heterogeneous catalysts in the liquid phase offers several advantages compared with homogeneous counterparts, in that it facilitates ease of recovery and recycling. A chromium-containing medium-pore molecular sieve (Si:Cr > 140:1), CrS-2, efficiently catalyzes the direct oxidation of various primary amines to the corresponding nitro compounds using 70% *t*-butylhydroperoxide (TBHP).[110]

Aliphatic and aromatic primary amines are rapidly and efficiently oxidized to nitro compounds by dimethyldioxirane.[111] Dimethyldioxirane is prepared by reaction of OXONE (DuPont trademark)·$2KHSO_5$-$KHSO_4$-$K_2SO_4$ with buffered aqueous acetone.[112]

In a typical reaction, *n*-butylamine (0.052 g, 0.7 mmol) in 5 ml of acetone is treated with 95 ml of dimethyldioxirane in acetone solution (0.05 M). The solution is kept at room temperature for 30 min with the exclusion of light (Eq. 2.53). Aromatic amines are converted into nitro compounds by oxidation using OXONE itself.[113]

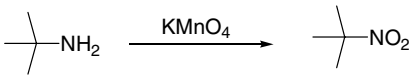
$$R{-}NH_2 \xrightarrow[\text{acetone}]{\text{O–O}} \underset{80\text{–}90\%}{R{-}NO_2} \qquad (2.53)$$

Oxidation of amines to nitro compounds has been carried out with peracids such as peracetic acid or peroxytrifluoroacetic acid.[114] However, the difficulty in handling the hazardous nature of the anhydrous peracids makes these methods less attractive. Gilbert found a general, high-yield synthesis of nitroalkanes from amines using *m*-chloroperbenzoic acid (*m*-CPBA) at elevated temperatures.[115] A simple synthesis of fully saturated 2-nitrosugar derivatives from the corresponding amino derivatives utilizes an *m*-CPBA and sodium sulfate reagent system, giving the product in good yields (Eq. 2.54).[116]



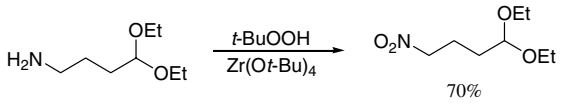

85% (2.54)

Tertiary amines have been oxidized to the corresponding nitro compounds with $KMnO_4$. For example, 2-methyl-2-nitropropane is prepared in 84% yield from *t*-butylamine with $KMnO_4$ (Eq. 2.55).[117] In a similar fashion, 1-aminoadamantane has been oxidized to 1-nitroadamantane in 85% yield with $KMnO_4$ (see Eq. 2.63).[118]

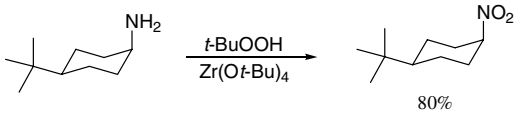



83% (2.55)

Recently, the oxidation of primary aliphatic amines to the corresponding nitro compounds has also been achieved using the catalyst system based on zirconium tetra *tert*-butoxide and *tert*-butyl hydroperoxide in a molecular sieve (50–98% yield) (Eqs. 2.56 and 2.57 and Table 2.5).[119]




70% (2.56)



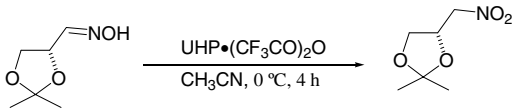

80% (2.57)

### 2.2.2 Oxidation of Oximes

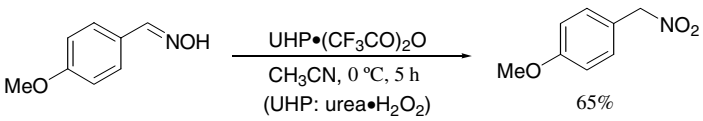
Conversion of carbonyl to nitro groups (retro Nef Reaction) is an important method for the preparation of nitro compounds. Such conversion is generally effected via oximes using strong oxidants such as $CF_3CO_3H$.[120]

Anhydrous peroxytrifluoroacetic acid is not easy to handle, but the procedure has recently been revised.[121] Namely, reaction of urea-hydrogen peroxide complex (UHP) with trifluoroacetic anhydride in acetonitrile at 0 °C gives solutions of peroxytrifluoroacetic acid, which oxidize aldoximes to nitroalkanes in good yields (Eqs. 2.58 and 2.59). Ketoximes fail to react under these conditions, the parent ketone being recovered.

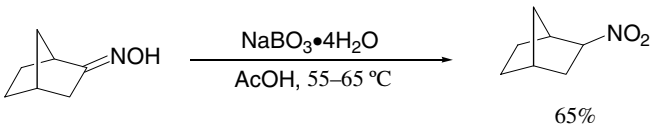
Various convenient methods for the oxidation of oximes to nitro compounds have been developed in recent years. Olah has reported a convenient oxidation of oximes to nitro compounds with sodium perborate in glacial acetic acid (Eq. 2.60).[122]




(2.58)



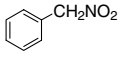
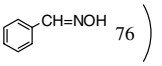

(2.59)

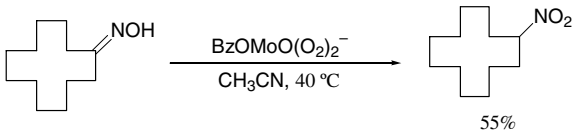



(2.60)

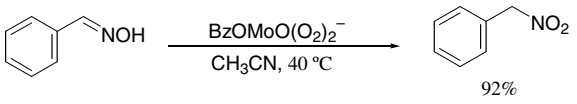
The conversion of oximes to nitroalkanes has been achieved by employing an Mo(IV) oxodiperoxo complex as oxidant in acetonitrile. Both aldoximes and ketoximes are converted into the corresponding nitroalkanes (Eqs. 2.61 and 2.62),[123] representing a complementary synthetic route to the use of the UHP method.

**Table 2.5 Conversion of amines to nitro compounds**

| Amine | Condition | Nitro compound | Yield (%) | Ref |
|---|---|---|---|---|
| | $O_3$, $SiO_2$, –78 °C | | 69 | 108 |
| | , acetone, RT, 30 min | | 95 | 111 |
| | $CrS_2$, TBHP, MeOH, 65 °C, 5 h | | 85 | 110 |
| | *m*-CPBA, $ClCH_2CH_2Cl$, 83 °C, 3 h | | 75 | 115 |
| | TBHP, $Zr(Ot\text{-}Bu)_4$ | | 82 | 119 |
| | *m*-CPBA, $ClCH_2CH_2Cl$, 83 °C, 3 h | | 92 | 110 |
| | $O_3$, $SiO_2$, –78 °C | | 12 | 108 |
| | , acetone, RT | | 97 | 111 |
| | $O_3$, $SiO_2$, –78 °C |  | 66 | 108 |
| | $CrS_2$, TBHP | | 0 | 109 |
| | |  | 76 | |
| $n\text{-}C_4H_9NH_2$ | $O_3$, $SiO_2$, –78 °C | $n\text{-}C_4H_9NO_2$ | 65 | 108 |
| | , acetone, RT | | 84 | 111 |
| | *m*-CPBA, $ClCH_2CH_2Cl$, 83 °C, 3 h | | 63 | 115 |
| $t\text{-}C_4H_9NH_2$ | $KMnO_4$ | $t\text{-}C_4H_9NO_2$ | 83 | 117 |
| | , acetone, RT | | 90 | 111 |
| | $O_3$, $SiO_2$, –78 °C | | 70 | 108 |
| | TBHP, $Zr(Ot\text{-}Bu)_4$ | | 64 | 119 |

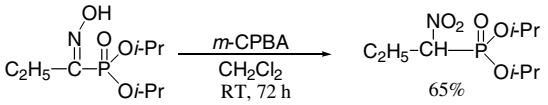



(2.61)




(2.62)

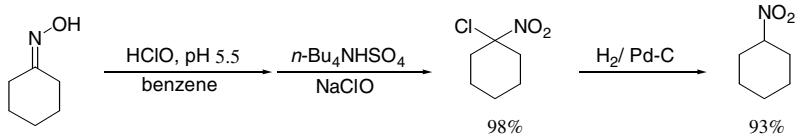
Oxidation of oximes to nitro compounds with *m*-CPBA has been applied to the synthesis of dialkyl 1-nitroalkanephosphonates (Eq. 2.63),[124] which are useful reagents for conversion of carbonyl compounds to nitroalkenes.[125]




(2.63)

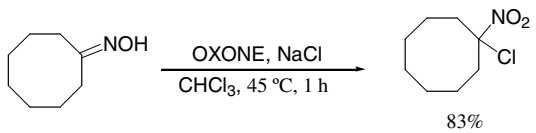
Indirect conversion of oximes to nitro compounds via α-halo nitro compounds has provided a useful method for synthesis of nitro compounds, as shown in Scheme 2.1.

Halogenation of oximes to halonitroso compounds has been achieved by a number of reagents, including chlorine,[126] bromine,[127] aqueous hypochlorous acid,[126], *t*-butyl hypochlorite,[37] and *N*-bromosuccinimide.[128] The resulting halonitroso intermediate is then oxidized to halonitro product with nitric acid,[128] ozone,[129] aqueous sodium hypochlorite,[130] or *n*-butylammonium hypochlorite.[37] The conversion of oximes to α-chloronitro compounds can be carried out by a one-flask operation. For example, 1-chloronitrocyclohexanone is prepared in 98% yield by treatment of cyclohexanone oxime with aqueous hypochlorous acid and by subsequent treatment with a mixture of tetra-*n*-butylammonium hydrogen sulfate and aqueous sodium hypochlorite. The reductive dechlorination of the α-chloronitro compounds is achieved by catalytic hydrogenolysis with 1 atm $H_2$ over 5% Pd/C in methanol-water (4:1). The final step can be replaced by treatment with either Mg or Zn dust (Eq. 2.64).[37]

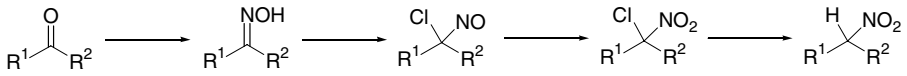



(2.64)

The one-pot conversions of oximes to *gem*-halonitro compounds have been achieved by using *N,N,N*,-trihalo-1,3,5-triazines,[131] chloroperoxidase in the presence of hydrogen peroxide and potassium chloride,[132] or commercial OXONE and sodium chloride.[133] Of these methods, the case of OXONE may be the most convenient (Eq. 2.65).

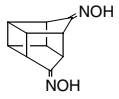
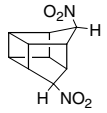
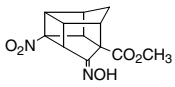
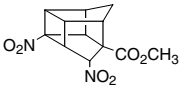
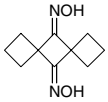
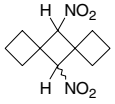
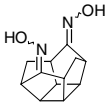
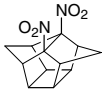



(2.65)



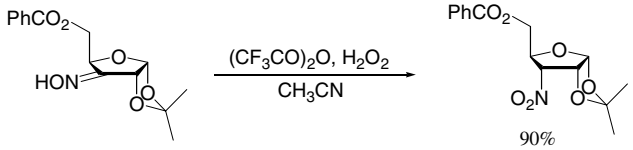

**Scheme 2.1.**

**Table 2.6 Preparation of polycyclic nitro compounds from oximes**

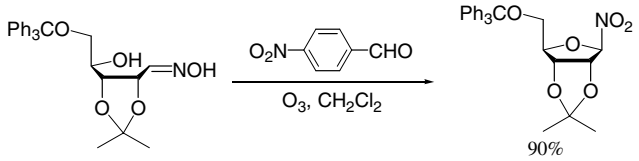
| Oxime | Condition | Nitro compound | Yield (%) | Ref. |
|---|---|---|---|---|
|  | 1) $Br_2$, $NaHCO_3$ aq<br>$(CF_3CO)_2O$, $H_2O_2$<br>2) $NaBH_4$ |  | 17 | 134 |
|  | 1) NBS,<br>dioxane/$H_2O$<br>2) $O_3$, $CH_2Cl_2$ |  | 16 | 141 |
|  | 1) $Na/NH_3$, MeOH<br>2) *m*-CPBA,<br>$ClCH_2CH_2Cl$ |  | 13 | 126 |
|  | $H_2NCONH_2$,<br>$Na_2HPO_4$ *m*-CPBA,<br>MeCN, $\Delta$ |  | 95 | 30 |

Energetically rich polynitro compounds have been prepared from polycyclic ketones by the conversion of oximes to nitro compounds, as shown in Table 2.6.

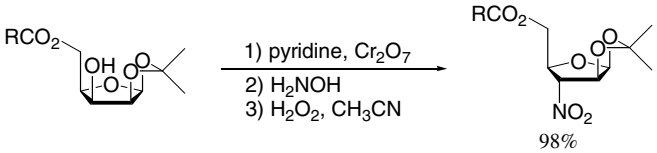
The conversion of oximes to nitro compounds have provided a useful method for the preparation of nitro sugars (see Eqs. 2.66–2.69).[36,136,137,138]



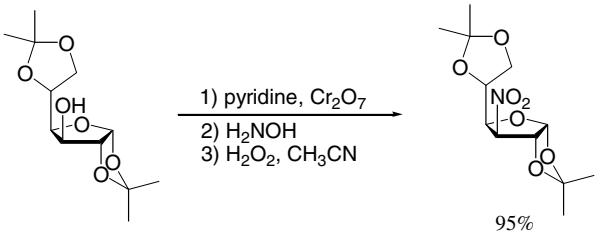

(2.66)




(2.67)

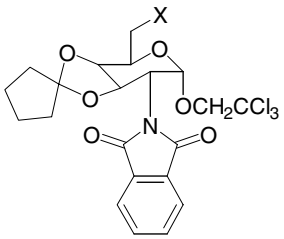



(2.68)




(2.69)

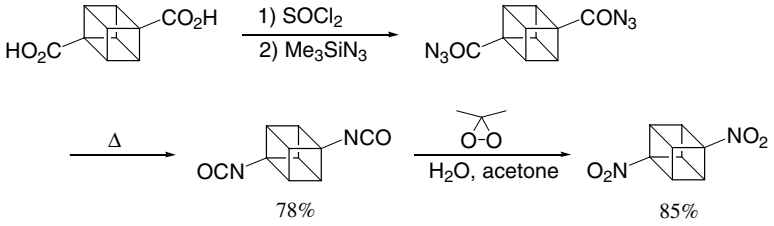
In general, azides are more easily available than nitro compounds by $S_N2$ reaction of the corresponding halides. Thus, the direct conversion of an azide into a nitro group is useful for the synthesis of nitro compounds. Corey and coworkers have reported the easy conversion of azides to nitro compounds via ozonolysis of phosphine imines (Eq. 2.70).[139]




$$X = I \xrightarrow[DMF]{NaN_3} X = N_3 \xrightarrow{Ph_3P} X = N{=}PPh_3 \xrightarrow{O_3} X = NO_2 \quad (2.70)$$

50% (overall)

The standard reaction sequence for transformation of a carboxylic acid into a nitro group is lengthy. Eaton has shortened this conversion via oxidation of isocyanates to nitro compounds with dimethyldioxirane in wet acetone (Eq. 2.71).[140]




78% 85% (2.71)

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*The Nitro Group in Organic Synthesis.* Noboru Ono
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ISBNs: 0-471-31611-3 (Hardback); 0-471-22448-0 (Electronic)

# 3

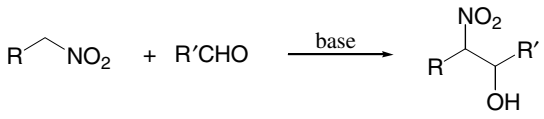
# THE NITRO-ALDOL (HENRY) REACTION

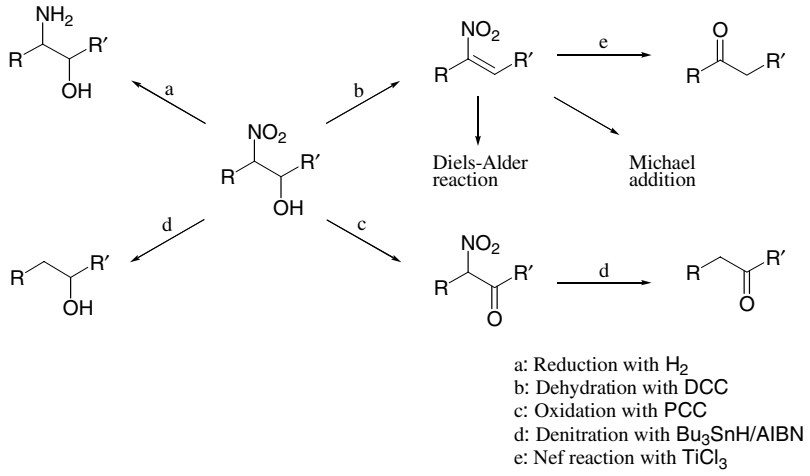
The nitro-aldol reaction between nitroalkanes and carbonyl compounds to yield β-nitro alcohols was discovered in 1895 by Henry.[1] Since then, this reaction has been used extensively in many important syntheses. In view of its significance, there are several reviews on the Henry reaction.[2–5] These reviews cover synthesis of β-nitro alcohols and their applications in organic synthesis. The most comprehensive review is Ref. 3, which summarizes the literature before 1970. More recent reviews are Refs. 4 and 5, which summarize literatures on the Henry reaction published until 1990.

In general, the Henry reaction gives a mixture of diastereomers and enantiomers. The lack of selectivity is due to the reversibility of the reaction and the easy epimerization at the nitro-substituted carbon atom. Existing reviews have hardly mentioned the stereochemistry of the Henry reaction. Recently, Shibasaki has found that the modification of the Henry reaction can control the stereochemistry to give β-nitro alcohols with high diastereo- and enantio-selectivity.[6] In Section 3.3, the progress of the stereoselective Henry reaction and its application to biologically active compounds are discussed.

The β-nitro alcohols are generally obtained in good yield by the reaction of aldehydes with nitroalkanes in the presence of a catalytic amount of base. When aryl aldehydes are used, the β-nitro alcohols formed may undergo elimination of water to give aryl nitroalkenes. Such side reactions are not always disadvantageous, for nitroalkenes are sometimes the ultimate target for the Henry reaction. The choice of reaction conditions is important to stop the reaction at the stage of β-nitro alcohols in aromatic cases.

The synthetic utility of the Henry reaction is shown in Scheme 3.1, where β-nitro alcohols are converted into β-amino alcohols, amino sugars, ketones and other important compounds.

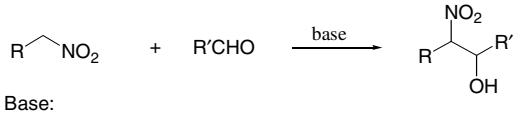




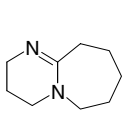

**Scheme 3.1**. Henry reaction and its applications

## 3.1 PREPARATION OF β-NITRO ALCOHOLS

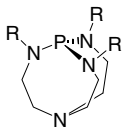
The Henry reaction is catalyzed in homogeneous solution with various catalysts, as shown in Eq. 3.1.




Base:
NaOR, $Et_3N$, DBU, DBN, tetramethylguanidine (TMG),$P(RNCH_2CH_2)_3N$ (PAP), KF, *n*-$Bu_4NF$, $Al_2O_3$, $Al_2O_3$-KF, amberlyst A-21, amberlite IRA-420, NaOH+cetyltrimethylammonium chloride (CTACl)




DBU



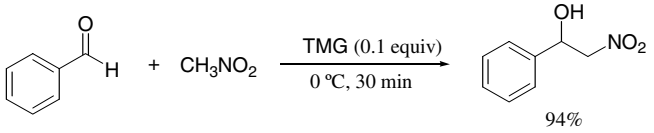

PAP

(3.1)

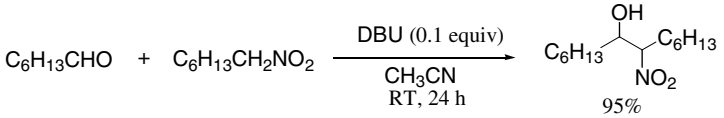
The reaction is generally conducted at room temperature in the presence of about 10 mol% of base to give the desired β-nitro alcohols in good yield. The most popular bases and solvents employed in the Henry reaction are alkali metal hydroxides, carbonates, bicarbonates, and alkoxids in water or ethanol.[7] Recently, powdered KOH in dry medium has been used for this conversion.[7d] This approach is quite simple and inexpensive. It is suitable for the reaction of both aromatic and aliphatic aldehydes with lower nitroalkanes such as nitromethane, nitroethane, and 1-nitropropane. The reaction of aromatic aldehydes with nitromethane using sodium hydroxide (1 equiv) in methanol followed by acidification is a standard method for the preparation of β-nitrostyrenes.[8] Recently, considerable work concerning new reactions mediated by rare earth metal reagents has been reported. The Henry reaction is catalyzed either by rare earth metal alkoxides such as $La_3(O\text{-}t\text{-}Bu)_9$ or rare earth hexamethyldisilazides (HMDS) such as $Sm(HMDS)_3$.[9] Shibasaki and coworkers have developed catalytic asymmetric nitro-aldol reaction using binaphthol (BINOL)-rare earth metal complexes, as discussed in the section of the stereoselective Henry reaction (Section 3.3).

Organic nitrogen bases such as ammonia or various amines are generally effective for the Henry reaction.[10] The reaction between nitromethane and simple aldehydes is particularly simple. Just mixing aldehydes, nitromethane, and amines followed by acidification gives the desired nitro alcohols in good yields. However, the Henry reactions of higher nitroalkanes with aldehydes or ketones proceed very slowly under the conditions using sodium hydroxide or amines. Nonionic strong bases such tetramethylguanidine (TMG),[11] 1,8-diazabicyclo[5.4.0]un-

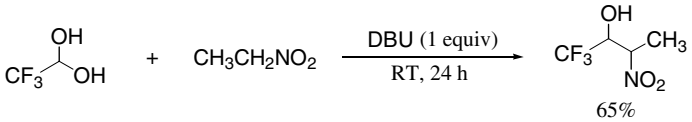
dec-7-ene (DBU), and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN)[12–14] in THF or acetonitrile are more effective catalytic systems than simple amines (see Eqs. 3.2–3.4).




94% (3.2)

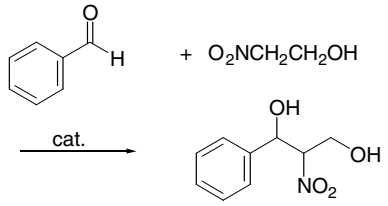


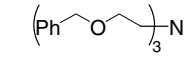

95% (3.3)




65% (3.4)

Dendritic molecules with a single triethylene amine core surrounded by hyperbranched polyether sectors catalyze the nitro-aldol reaction between aromatic aldehydes and nitroalkanes (Eq. 3.5).[15] The activity of the catalysts decreases when the generation number increases. No significant changes in stereo-control are observed on passing from lower- to higher-generation dendrimers.

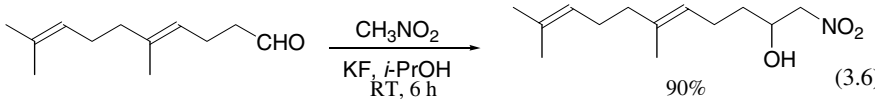



| Catalyst | Time | Yield (%) | *syn:anti* |
|---|---|---|---|
| $Et_3N$ | 0.5 h | 95 | 2:1 |
|  | 4 h | 90 | 2:1 |

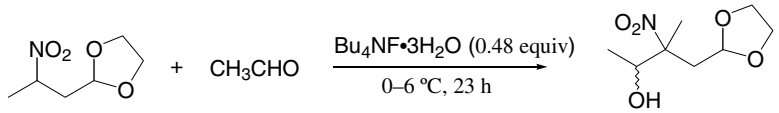


(3.5)

Fluoride ion is effective as a base for the Henry reaction, and potassium fluoride in isopropanol (Eq. 3.6)[16] and tetrabutylammonium fluoride in THF (Eq. 3.7)[17] have been widely used.




90% (3.6)




52% (*anti*/*syn* = 62/38) (3.7)

Thus, various kinds of bases are effective in inducing the Henry reaction. The choice of base and solvent is not crucial to carry out the Henry reaction of simple nitroalkanes with aldehydes, as summarized in Table 3.1. In general, sterically hindered carbonyl or nitro compounds are less reactive not to give the desired nitro-aldol products in good yield. In such cases, self-condensation of the carbonyl compound is a serious side-reaction. Several modified procedures for the Henry reaction have been developed.

**Table 3.1. Preparation of β-nitro alcohol by the Henry reaction**

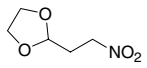
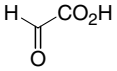
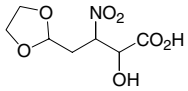
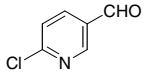
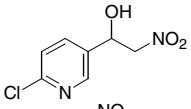
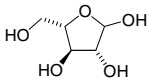
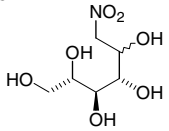
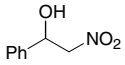
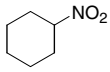
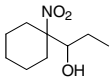
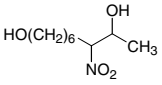
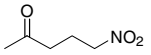
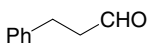
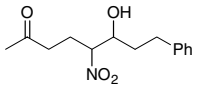
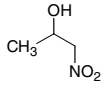
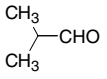
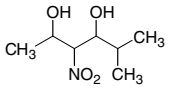
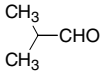
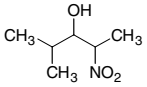
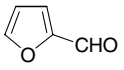
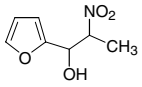
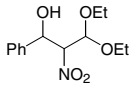
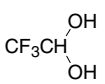
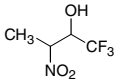
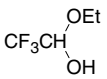
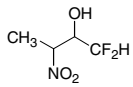
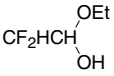
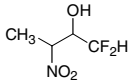
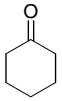
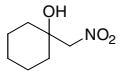
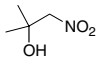
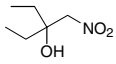
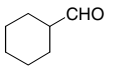
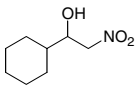
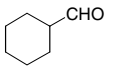
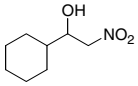
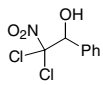
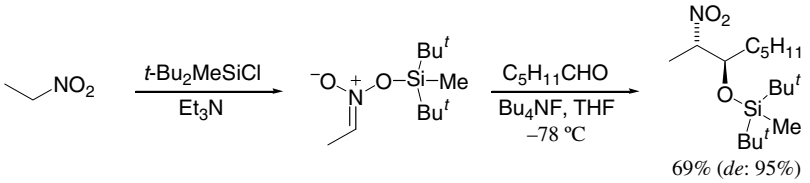
| Nitro compound | Carbonyl compound | Condition | Product | Yield (%) (*syn*/*anti*) | Ref. |
|---|---|---|---|---|---|
|  |  | NaOH EtOH 1 h |  | 100 | 36 |
| $CH_3NO_2$ |  | KF *i*-PrOH |  | 85 | 37 |
| $CH_3NO_2$ |  | $CH_3ONa$ $CH_3OH$ 50 h |  | 61 | 38 |
| $CH_3NO_2$ | PhCHO | TMG 30 min 0 °C |  | 94 | 11 |
| $CH_3CH_2NO_2$ | PhCHO | CTACl NaOH $H_2O$, 2 h | | 71 | 27 |
|  | $CH_3CH_2CHO$ | CTACl NaOH $H_2O$, 3 h |  | 85 | 27 |
| $HO(CH_2)_6CH_2NO_2$ | $CH_3CHO$ | A-21 20 h |  | 70 | 25 |
|  |  | A-21 5 h |  | 95 | 25 |
|  |  | $Al_2O_3$ 24 h |  | 69 | 22 |
| $CH_3CH_2NO_2$ |  | KF-$Al_2O_3$ 5 h |  | 78 | 23 |
| $CH_3CH_2NO_2$ |  | KF-$Al_2O_3$ 15 h |  | 77 | 23 |
| $(EtO)_2CHCH_2NO_2$ | PhCHO | $Et_3N$ $Bu_4NF{\cdot}3H_2O$ *t*-$BuMe_2SiCl$ THF, 2 h |  | 51 (70/30) | 20 |
| $CH_3CH_2NO_2$ | PhCHO | $Et_3N$ $Bu_4NF{\cdot}3H_2O$ *t*-$BuMe_2SiCl$ THF | | 95 (47/53) | 20 |
| $CH_3CH_2NO_2$ |  | DBU 24 h |  | 67 | 13 |
| $CH_3CH_2NO_2$ |  | $K_2CO_3$ |  | 60 | 40 |

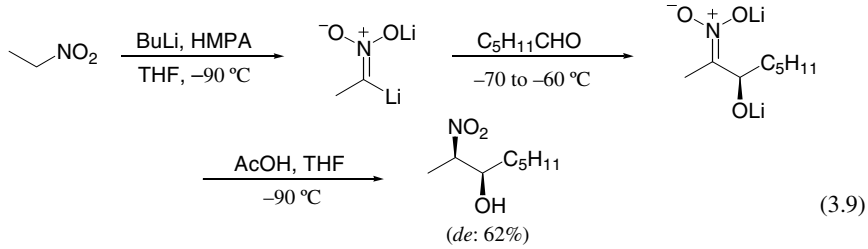
**Table 3.1. Continued**

| Nitro compound | Carbonyl compound | Condition | Product | Yield (%) (*syn*/*anti*) | Ref. |
|---|---|---|---|---|---|
| $CH_3CH_2NO_2$ |  | $K_2CO_3$ |  | 68 (54/46) | 41 |
| $CH_3NO_2$ |  | PAP (see Eq. 3.1, 10 mol%) $MgSO_4$ |  | 95 | 21 |
| $CH_3NO_2$ | | PAP (10 mol%) $MgSO_4$ |  | 91 | 21 |
| $CH_3NO_2$ | | PAP (10 mol%) $MgSO_4$ |  | 60 | 21 |
| $CH_3NO_2$ |  | $La_3(O\text{-}t\text{-}Bu_3)_9$ (3.3 mol%) THF, 0 °C |  | 78 | 9 |
| $CH_3NO_2$ |  | $Sm(HMDS)_3$ (10 mol%) RT, 25 h |  | 100 | 9 |
| $Cl_3CNO_2$ | PhCHO | $SnCl_2$ 0 °C |  | 57 | 39 |

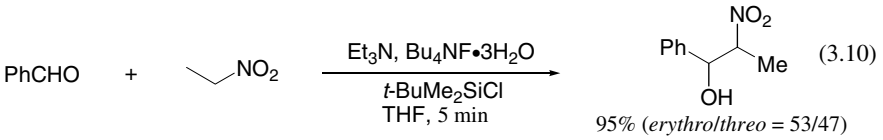
Nitroalkanes are silylated with trialkylsilyl chloride and triethylamine to form stable silyl nitronates, which react with aldehydes to give β-nitro alcohol *O*-silyl ethers in the presence of a catalytic amount of $Bu_4NF{\cdot}3\ H_2O$ at –78 °C in THF. Because the retro nitro-aldol reaction cannot occur, a high diastereoselectivity is observed, as shown in Eq. 3.8.[18] The product is directly reduced to the corresponding β-amino alcohol with retention of the stereochemistry. The dilithium salts of nitroalkanes are formed on treatment with 2 equiv of *n*-butyllithium in THF/HMPA at –90 °C. They react with aldehydes to give β-nitro alcohols with high diastereoselectivity after careful protonation (Eq. 3.9). The dilithium salt is much reactive toward carbonyl compounds than the mono-anion, and this often leads to better yields of β-nitro alcohols than the conventional Henry reaction.[19] The Henry reaction is accelerated by the presence of $Et_3N$, $Bu_4NF{\cdot}3H_2O$ and $^t$BuMe$_2$SiCl (Eq. 3.10).[20] The use of non-ionic strong bases such as the proazaphosphatrane (PAP) is also a good choice for overcoming the low reactivity of the Henry reaction (see Eq. 3.20).[21]




69% (*de*: 95%) (3.8)

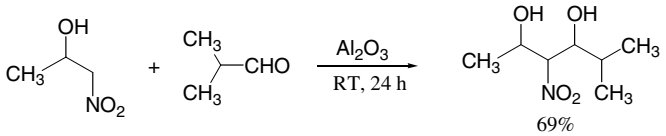



(3.9)

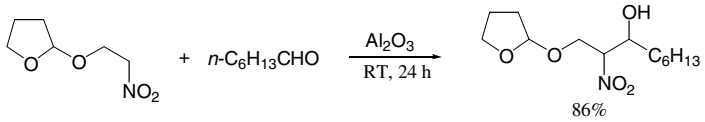



(3.10)

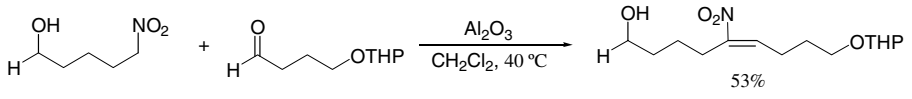
It is inconvenient to remove the base by acidification in the work-up procedure, because acidification may lead to the Nef reaction (Section 6.1). To avoid this inconvenience the reactions catalyzed in heterogeneous systems with $Al_2O_3$, $Al_2O_3$-supported KF, and polymer-supported bases, have been developed. Commercial chromatographic alumina (activity 1 according to Brockmann) is used without solvents for the preparation of functionalized β-nitro alcohols. Acid- or base-sensitive substrates are prepared by this method (Eqs. 3.11 and 3.12).[22] The reactivity is enhanced by a modification using alumina-supported potassium fluoride.[23] Dehydration of β-nitro alcohols is also catalyzed by $Al_2O_3$.[24] One-pot synthesis of nitroalkenes from aldehydes and nitroalkanes using $Al_2O_3$ is convenient (see Section 3.2.1); this process has been applied to a short synthesis of spiro-ethers, (often found in pheromones) involving hydrogenation of the nitroalkene and subsequent Nef reaction (Eq. 3.13).[24b] Importantly, no dehydration is observed when neutral $Al_2O_3$ is employed at room temperature; however, simply warming to 40 °C results in the formation of nitroalkenes.

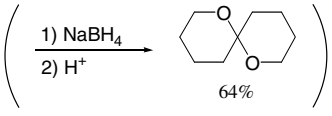



(3.11)




(3.12)

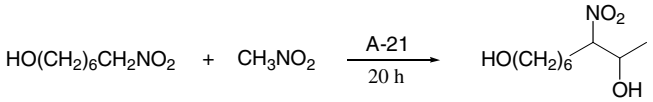


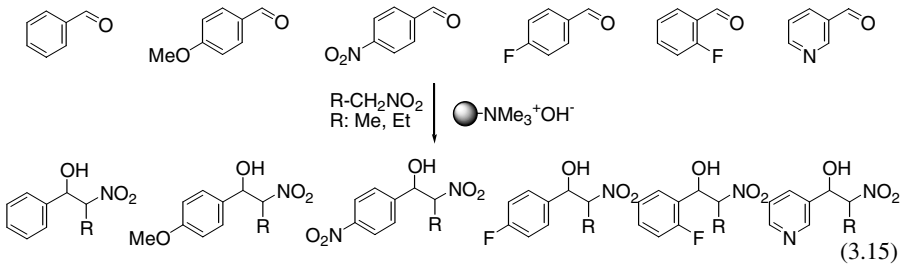

(3.13)

A more effective catalyst for the Henry reaction is a polymer-supported base such as amberlyst A-21. Various β-nitro alcohols can be obtained with the help of amberlyst with or without solvent (Eq. 3.14).[25] A recent report claims that amberlite IRA-420 (OH-form) or DOWEX-1 (OH-form) is more effective for the Henry reaction than amberlyst A-21.[26] Poly-

mer-supported bases are attractive for getting a library of β-nitroalcohols, which are important intermediates for biologically active compounds (Eq. 3.15).

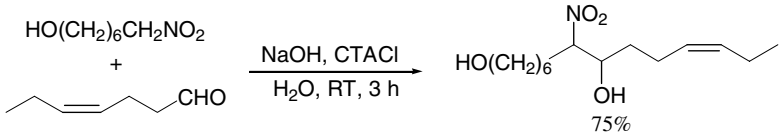



(3.14)



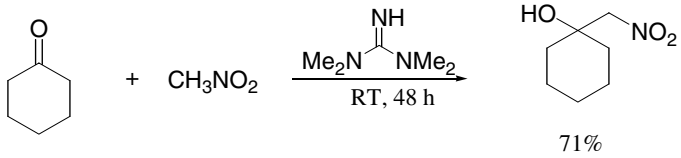

(3.15)

The nitro-aldol reaction can also be carried out in water using NaOH in the presence of cetyltrimethylammonium chloride (CTACl) as a cationic surfactant. CTACl (5 mmol) is added to a mixture of nitroalkane (50 mmol) and aldehyde (50 mmol) in NaOH 0.025 M (150 mL) at room temperature. The mixture is stirred for 2–3 h and worked up to give the product in 70–90% yield. Compared with the classical methods, this procedure has economical and environmental advantages (Eq. 3.16).[27]



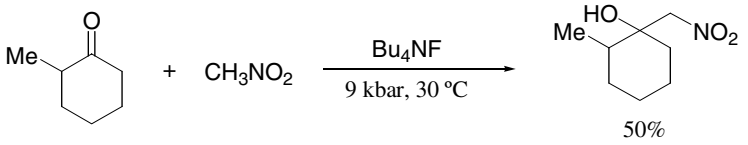

(3.16)

The nitro-aldol reaction with ketones is sensitive to steric factors and generally gives a complex mixture of products depending on the ratio of reactants, base, temperature, and time.[27] Nitromethane is reactive enough toward ketones to give the β-nitro alcohol under various conditions. Cyclohexanone reacts with nitromethane to give 1-(nitromethyl) cyclohexanol in 69–94% yield in the presence of sodium ethoxide in ethanol.[7f] This transformation is more simply carried out using tetramethylguanidine (TMG) as the base (Eq. 3.17).[11] Stronger nonionic bases like proazaphosphatrane (PAP) are more effective in the Henry reaction with ketones (see Eq. 3.20).



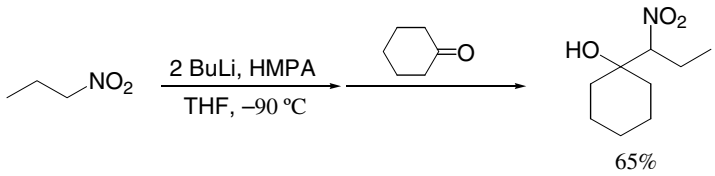

(3.17)

However, 3- or 4-methylcyclohexanone is less reactive to nitromethane than cyclohexanone. Although 2-methylcyclohexanone does not react with nitromethane under the conventional conditions, under high pressure and a fluoride ion catalysis the reaction proceeds to give the β-nitro alcohol in moderate yields (Eq. 3.18).[29]



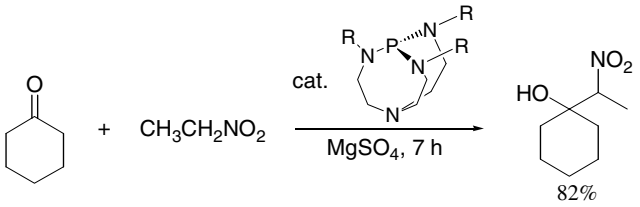

(3.18)

Another method for improving the reactivity of nitro compounds is provided by the double deprotonation of nitroalkanes. In this case, the reaction with ketones affords β-nitro alcohols in 40–60% yield (Eq. 3.19).[30]



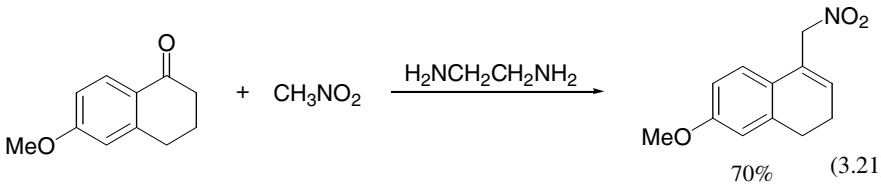

(3.19)

Proazaphosphatrane, $P(RNCH_2CH_2)_3N$, is an efficient catalyst for the Henry reaction, and various ketones give nitro-aldols by the reaction with nitromethane and other nitroalkanes (Eq. 3.20).[21]



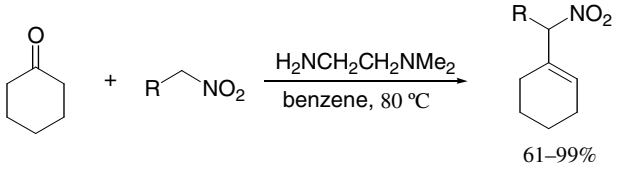

(3.20)

Allylic nitro compounds are obtained by the reaction of cyclic ketones with nitromethane in the presence of 1,2-diaminoethane (1 mol%) as catalyst. Because *exo*-cyclic nitroalkenes are rearranged to the *endo*-cyclic β,γ-nitroalkenes, allylic nitro compounds are selectively produced (Eq. 3.21).[31]

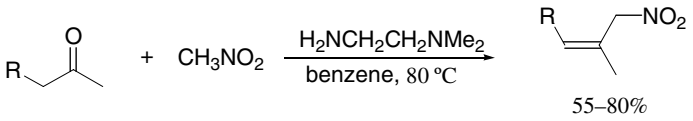



(3.21)

If *N*,*N*-dimethylethylenediamine is used as the base, allylic nitro compounds are obtained in good yields from both acyclic and alicyclic ketones (Eqs. 3.22 and 3.23).[32]

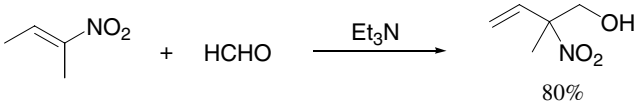



(3.22)



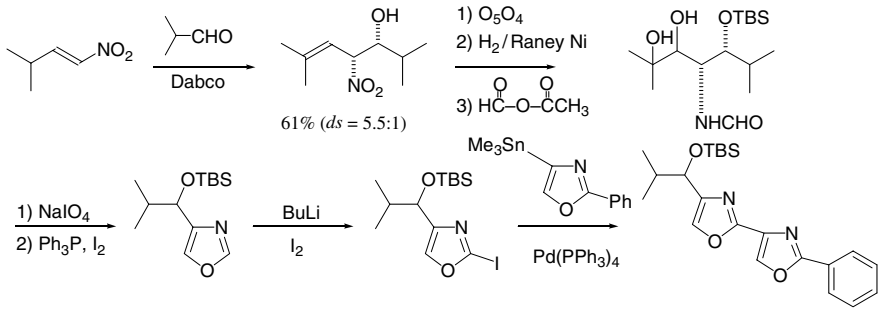

(3.23)

Conjugated nitroalkenes are isomerized to allylic nitro compounds under basic conditions. Reactions of α,β-unsaturated nitro compounds with aldehydes under basic conditions lead directly to γ,δ-unsaturated β-nitro alcohols (Eq. 3.24).[33] This reaction is very useful for preparing allylic nitro compounds.




(3.24)

Barrett and coworkers have used this method for the synthesis of 2,4′-linked bisoxazole, which constitutes a partial structure of hennoxazole A.[34] Condensation of the nitroalkene in Scheme 3.2 with isobutylaldehyde affords the nitro alcohol in 61% yield. Recrystallization gives the pure *syn*-stereoisomer, which is protected as its *tert*-butyldimethylsilyl (TBS) ether and dihydroxylated using osmium tetraoxide as catalyst. Reduction of the nitro group to the amine occurs by hydrogenation over Raney nickel. The subsequent glycol cleavage with $NaIO_4$ followed by cyclization gives the oxazole. Stille coupling of stannyloxazole with iodooxazole using Pd(0) gives the desired bis-oxazole (Scheme 3.2).[35]




**Scheme 3.2.** Model studies on the synthesis of hennoxazole A

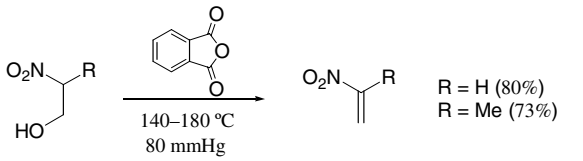
## 3.2 DERIVATIVES FROM β-NITRO ALCOHOLS

### 3.2.1 Nitroalkenes

Dehydration of β-nitro alcohols provides an important method for the preparation of nitroalkenes. Because lower nitroalkenes such as nitroethylene, 1-nitro-1-propene, and 2-nitro-1-propene tend to polymerize, they must be prepared carefully and used immediately after preparation. Dehydration with phthalic anhydride is the most reliable method for such lower nitroalkenes.[42,43] Such lower nitroalkenes have been used as important reagents for Michael acceptors or dienophiles in the Diels-Alder reaction, which will be

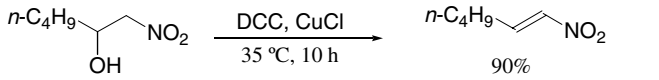
discussed in Chapters 4 and 8. Some typical nitroalkenes which are useful reagents in organic synthesis are presented here.[42]

- **Nitroethylene:** Dehydration of 2-nitroethanol[44] using phthalic anhydride (80%) is the best choice of preparation;[43] bp 38–39 °C/80 mm Hg.
- **1-Nitro-1-propene:** Preparation is accomplished by dehydration of 2-nitro-1-propanol with phthalic anhydride (73%)[45] or acetic anhydride-AcONa[46]; bp 56–57 °C/80 mmHg.
- **2-Nitro-1-propene:** Preparation is accomplished by dehydration of 1-nitro-2-propanol with methanesulfonyl chloride and triethylamine (30% yield),[47] acetic anhydride-AcONa (85% yield),[46] or phthalic anhydride (55%)[45]; bp 58 °C/35 mmHg (Eq. 3.25).

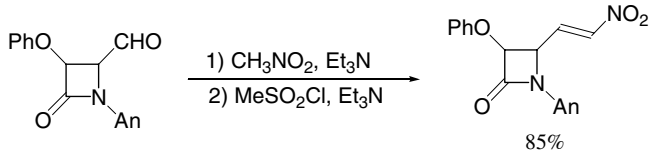



(3.25)

Dehydration of β-nitro alcohols is generally carried out by the following reagents, phthalic anhydride,[44] $CH_3SO_2Cl$-$Et_3N$,[47] dicyclohexylcarbodiimide (DCC),[48] $Ac_2O$-AcONa, $Ph_3P$-$CCl_4$,[49] and TFAA-$Et_3N$,[50] as exemplified in Eqs. 3.26[48] and 3.27[47b].

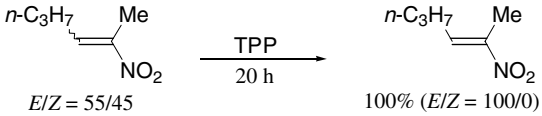



(3.26)

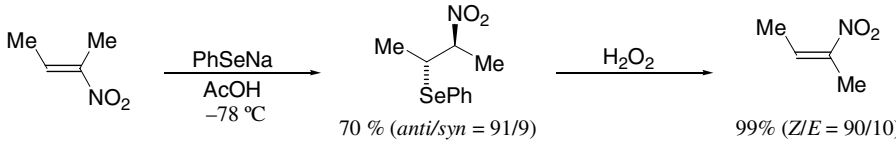



(3.27)

Dehydration of β-nitro alcohols using DCC gives a mixture of *E/Z* nitroalkenes.[48] The pure (*E*)-isomers are obtained on treatment with catalytic amounts of triethylamine or polymer-bound triphenylphosphine (TPP) (Eq. 3.28).[51] When (*Z*) nitroalkenes are desired, the addition of PhSeNa to the *E/Z* mixture and protonation at −78 °C followed by oxidation with $H_2O_2$ gives (*Z*)-nitroalkenes (Eq. 3.29).[52]

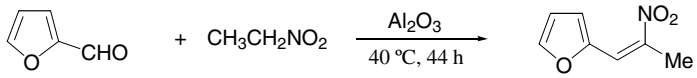



(3.28)



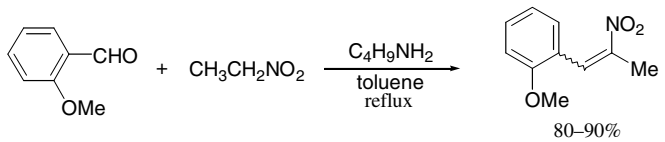

(3.29)

$Al_2O_3$ can be used both as a base for the Henry reaction and as a dehydrating agent. Thus, nitroalkenes are simply prepared by mixing of aldehydes and nitroalkanes with $Al_2O_3$ and subsequent warming at 40 °C (Eq. 3.30).[53]



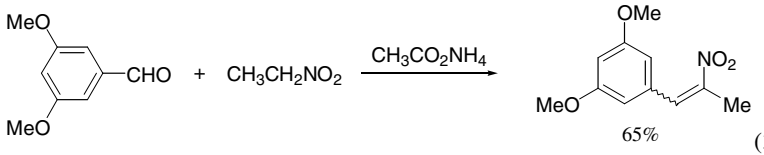

(3.30)

In general, base-catalyzed reactions of aromatic aldehydes with nitroalkanes give nitroalkenes directly (Knoevenagel reaction).[54] The reaction is very simple; heating a mixture of aromatic aldehydes, nitroalkanes, and amines in benzene or toluene for several hours using a Dean-Stark water separator gives the desired nitroalkenes in good yield, as shown in Eqs. 3.31–3.34.[54–58]



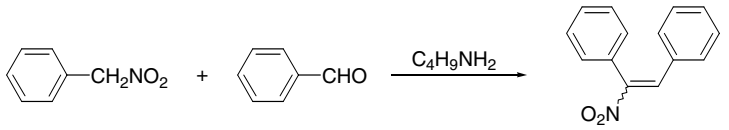

80–90%

(3.31)



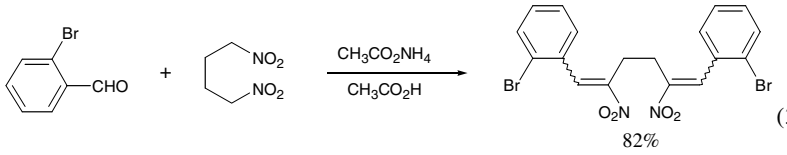

65%

(3.32)




65%

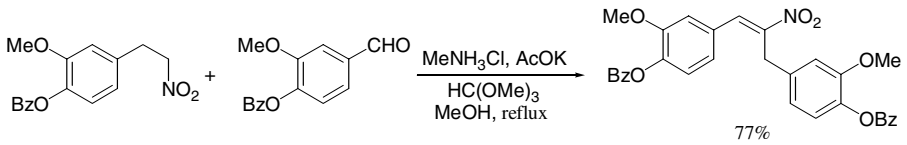
(3.33)




82%

(3.34)

Instead of using the Dean-Stark apparatus, the reaction can be carried out at reflux using $MeNH_3Cl$/AcOK/MeOH with $HC(OMe)_3$ as a water scavenger. A wide variety of nitroalkenes can be prepared in good yields by this method (Eq. 3.35).[59]

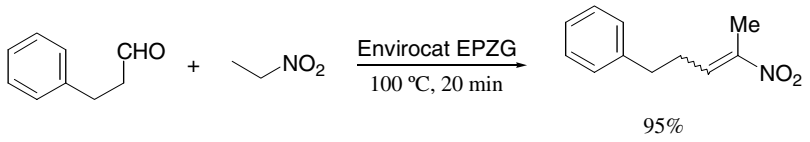



77%

(3.35)

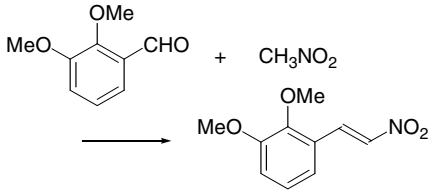
In recent years, there has been a considerable growth of interest in the catalysis of organic reactions by inorganic reagents supported on high surface areas.[60] Envirocat, a new family of supported reagents, which exhibits both Brönstead and Lewis acid character, are ideal for environmentally friendly chemistry. These reagents are non-toxic powders that can be easily

filtered from the reaction mixture and may be reused.[61] With the use of this new heterogeneous catalyst, nitroolefins are prepared directly by heating a mixture of aldehyde and nitroalkane at 100 °C in the absence of solvents (Eq. 3.36).



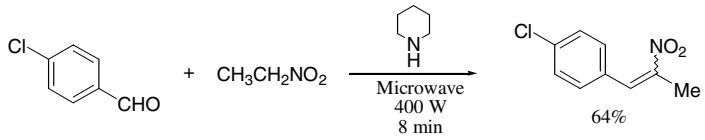

(3.36)

Application of ultrasound[62] or microwave irradiation[63] greatly assists these condensation reactions as shown in Eqs. 3.37 and 3.38, respectively, rendering the use of a Dean-Stark apparatus unnecessary.



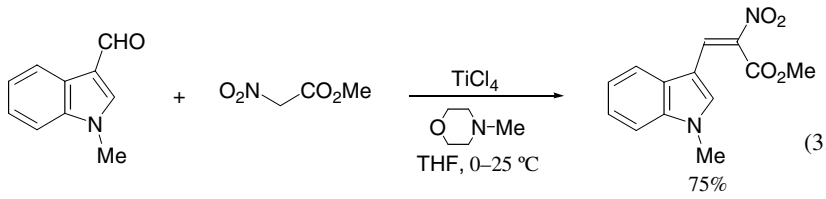

| Condition | Yield (%) |
|---|---|
| $NH_4OAc$/ AcOH 100 ºC, 3 h | 35 |
| $NH_4OAc$/ AcOH 22 ºC, 3 h, ))))) | 99 |

(3.37)




(3.38)

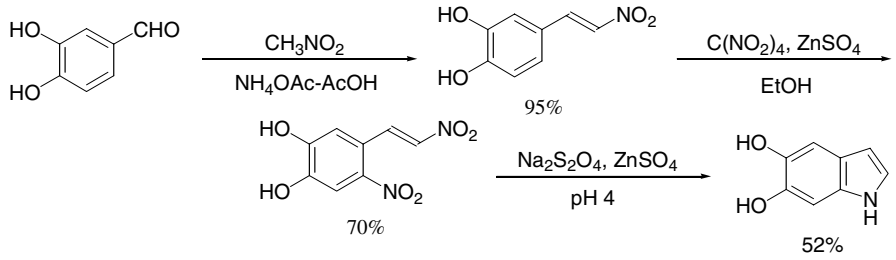
Reactions of methyl nitroacetate with aldehydes are induced by $TiCl_4$ in pyridine. They afford nitroalkenyl-esters,[64] which are used in the preparation of various nonnatural amino acids (Eq. 3.39).[65]



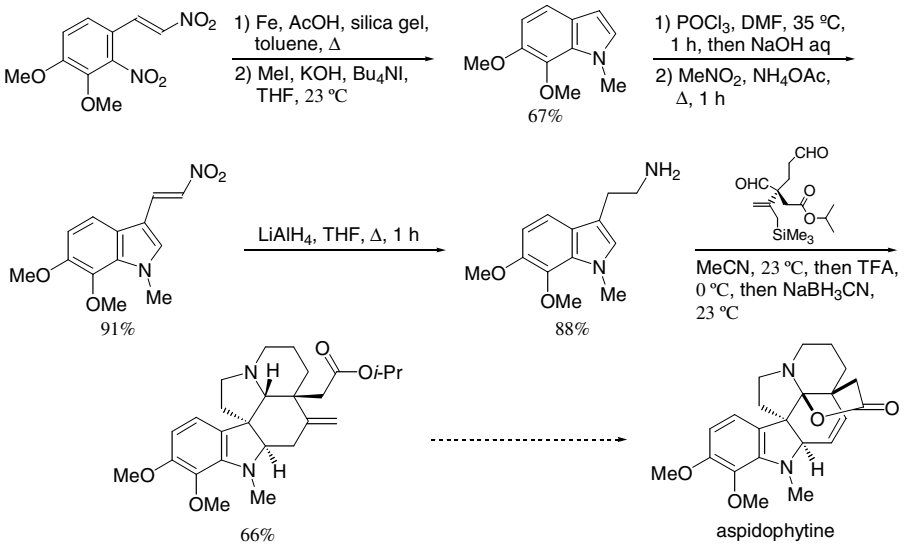

(3.39)

Nitroalkenes prepared from aromatic aldehydes are especially useful for natural product synthesis. For example, the products are directly converted into ketones via the Nef reaction (Section 6.1) or indoles (Section 10.2) via the reduction to phenylethylamines (Section 6.3.2). The application of these transformations are discussed later; here, some examples are presented to emphasize their utility. Schemes 3.3 and 3.4 present a synthesis of 5,6-dihydroxyindole[66] and asperidophytine indole alkaloid,[67] respectively.

Seebach and coworkers have developed the multiple coupling reagent, 2-nitro-2-propenyl 2,2-dimethylpropanoate (NPP). The reaction of nitromethane with formaldehyde gives 1,3-dihydroxy-2-nitropropane in 95% yield. Subsequent acylation with two equivalents of pivaloyl chloride and elimination of pivalic acid affords NPP. The reaction may be run on a 40- to 200-g

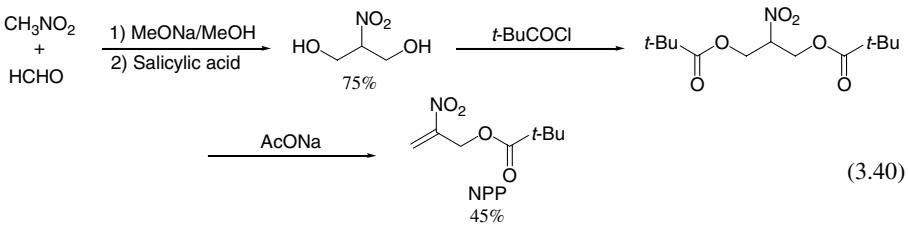



**Scheme 3.3.** Synthesis of 5,6-dihydroxyindole

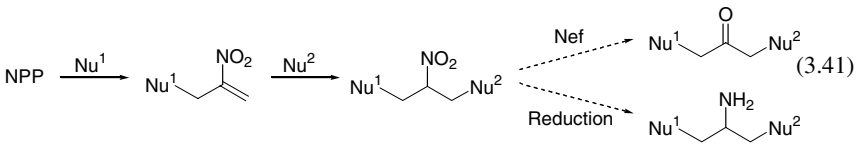



**Scheme 3.4.** Synthesis of aspidophytine

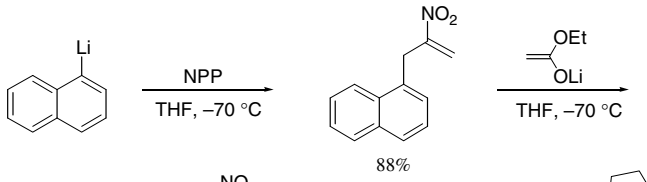
scale without problems (Eq. 3.40).[68] NPP allows successive introduction of two different nucleophiles $Nu^1$ and $Nu^2$ as shown in Eq. 3.41. The conversion of the resulting products via the Nef reaction or reduction into various compounds, makes NPP a useful reagent for convergent syntheses, as demonstrated in Eqs. 3.42 and 3.43.

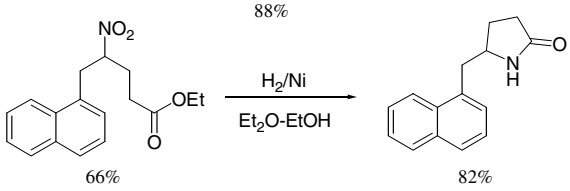



(3.40)

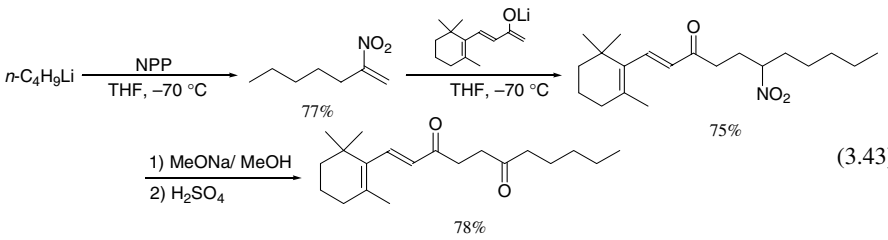



(3.41)



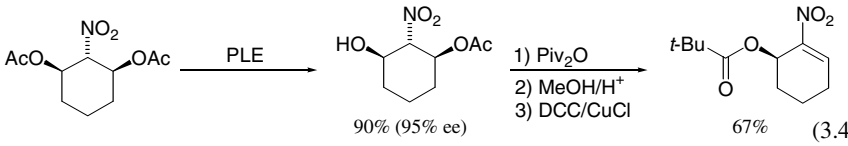




(3.42)



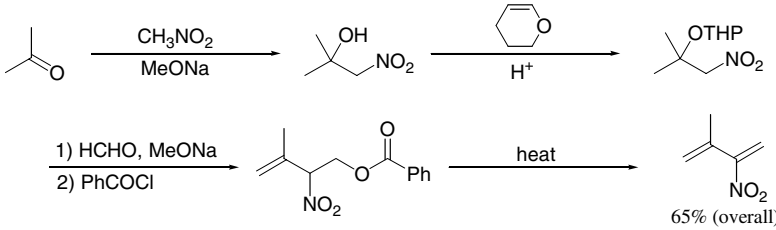

(3.43)

Chiral multiple-coupling reagents have been prepared in enantiomerically pure form by enantio-selective saponification of diesters of meso-2-nitrocyclohexane-1,3-diols (Eq. 3.44) with pig liver esterase (PLE).[69]




(3.44)

The nitro-aldol reaction followed by dehydration gives 2-nitro-1,3-dienes, which are useful reagents for cycloaddition (Eq. 3.45).[70]

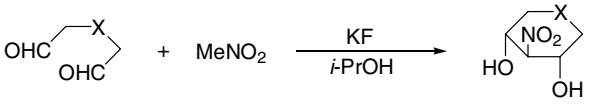



(3.45)

The nitro-aldol approach is impractical for the synthesis of 2,2-disubstituted 1-nitroalkenes due to the reversibility of the reaction when ketones are employed as substrates. Addition-elimination reactions are used for the preparation of such nitroalkenes (see Chapter 4).

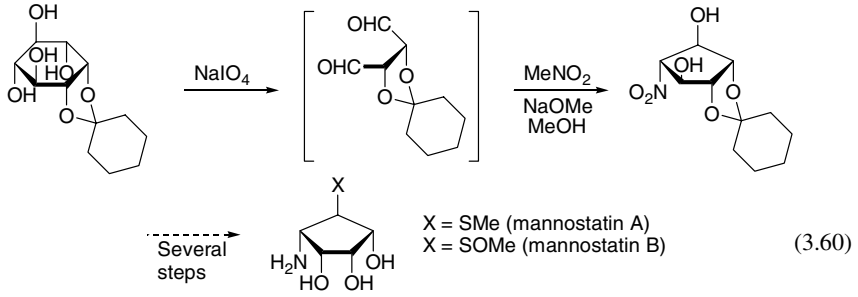
### 3.2.2 Nitroalkanes

activities.[94] Synthesis of nitro and amino sugars is one of the most important applications of nitro-aldol condensation. Synthesis of nitro sugars has been well reviewed by Wade and Giuliano,[95] also there are many other excellent reviews on this topic.[96] Only selected recent papers are described here to show the importance of nitro-aldol reaction in carbohydrate chemistry. The Baer-Fisher procedure is one of the simplest and shortest methods for obtaining 3-deoxy-3-nitrohexopyranosides and 3-amino-3-deoxyhexose derivatives by means of the Henry reaction with sugar dialdehydes. Sugar dialdehydes are obtained by glycol cleavage of glycosides.[95,96] The reaction of nitromethane with sugar dialdehydes as shown in Eq. 3.59 is catalyzed with KF in isopropanol to give one isomer. If this reaction is carried out with sodium methoxide, the stereoselective becomes poor.[97]



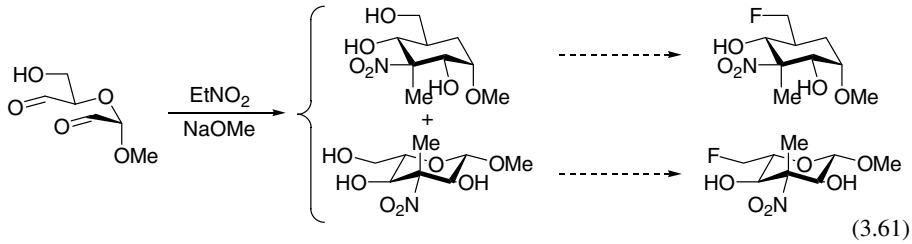

(3.59)

Base-catalyzed nitromethane cyclization of the dialdehyde generated by periodate oxidation of 1,2-*O*-cyclohexylidene-*myo*-inositol affords the nitrodiol with 1,4/2,3,5-configuration. This is converted into the α-mannosidase inhibitor, mannostatin A (Eq. 3.60).[98]



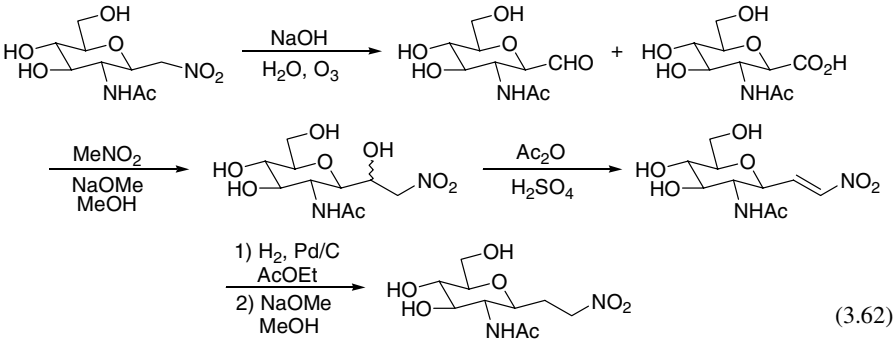

(3.60)

A mixture of methyl 3-deoxy-3-C-methyl-3-nitro-α-D- and β-L-glucopyranosides (1:1) is formed by the reaction of nitroethane with the sugar dialdehyde obtained from D-glucose. The products are separated and converted into branched-chain fluoro nitro D- and L-sugars (Eq. 3.61).[99]



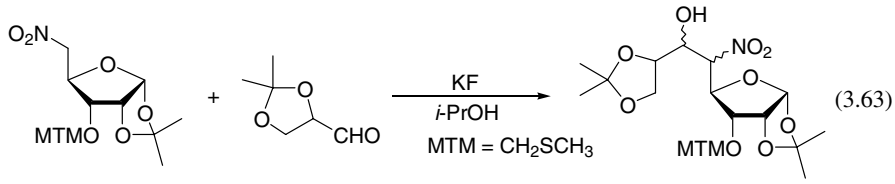

(3.61)

The anion of nitromethane adds easily to the carbonyl functions of sugars. This is a useful strategy for extension of the carbon chain.[100] 2-Acetamido-2-deoxy-β-D-glucose (*N*-acetyl-D-glucosamine) is the carbohydrate unit of glycoproteins that occurs most often. The nitromethylation method provides a straightforward route to a series of *C*-glycosyl compounds with the acetamido functionality (Eq. 3.62).[101]




(3.62)

If a carbohydrate already contains a nitro group, the nitro-bearing carbon atom can become the nucleophilic center for the coupling of two monosaccharide units (see Section 3.2.2). Suami and coworkers have used this method for the synthesis of antibiotics bearing sugars.[102] A typical example is presented in Eq. 3.63.[102b]

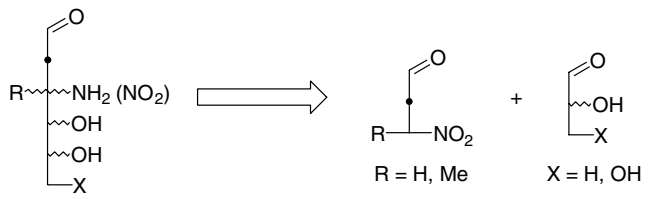



(3.63)

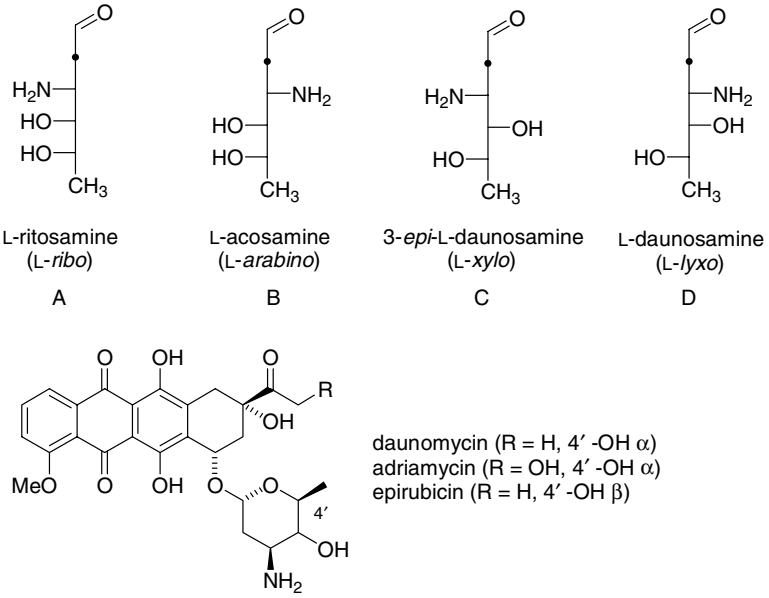
3-Nitro and 3-amino sugars have been prepared via stepwise construction from acyclic precursors by the nitro-aldol strategy as shown in Scheme 3.8.[103]

3-Amino-2,3,6-trideoxy-L-hexoses (A-D in Scheme 3.9) occur naturally, forming the glycone part of anthracyclinone antibiotics, important in anti-tumor treatment.[104]

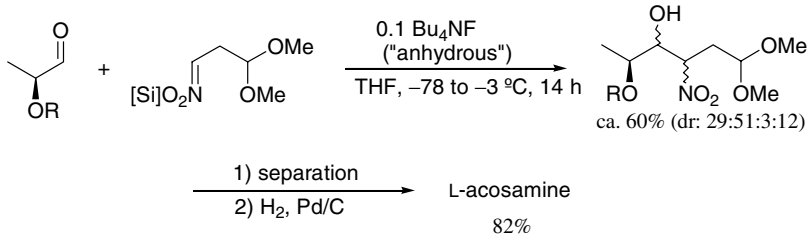
Several approaches based on nitro-aldol for the synthesis of amino sugars have been reported. Alumina-catalyzed reaction of methyl 3-nitropropanoate with *O*-benzyl-D-lactaldehyde gives the D-ribo-nitro-aldol (anti, anti isomer) in 63% yield, which is converted into L-daunosamine[17b,105] (see Section 3.3). Jager and coworkers have reported a short synthesis of L-acosamine based on the stereoselective nitro-aldol reaction of 2-*O*-benzyl-L-lactaldehyde with 3-nitropropanal dimethyl acetal as shown in Scheme 3.10.[106] The stereoselective nitro-aldol reaction is carried out by the silyl nitronate approach as discussed in Section 3.3.




**Scheme 3.8.**




**Scheme 3.9.**

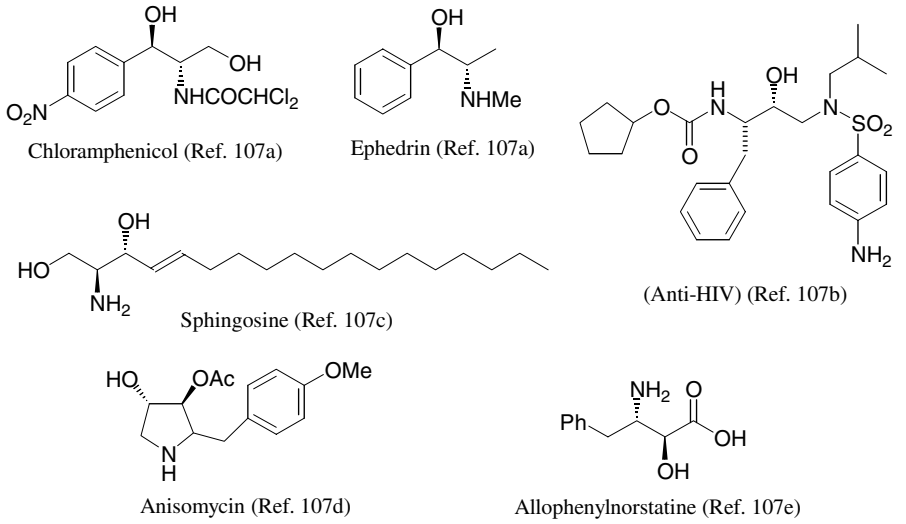



**Scheme 3.10.**

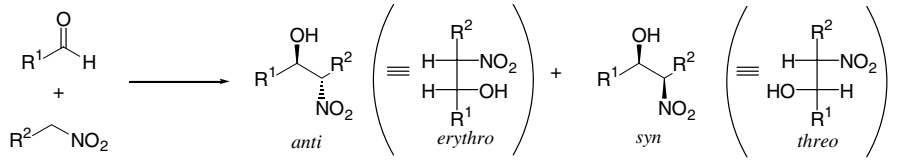
## 3.3 STEREOSELECTIVE HENRY REACTIONS AND APPLICATIONS TO ORGANIC SYNTHESIS

β-Nitro alcohols can be hydrogenated to the corresponding amino alcohols with retention of configuration; the stereoselective Henry reaction is a useful tool in the elaboration of pharmacologically important β-amino alcohol derivatives including chloramphenicol, ephedrine, norephedrine, and others. Some important β-amino alcohols are listed in Scheme 3.11.[107]

In general, the Henry reaction proceeds in a non-selective way to give a mixture of *anti (erythro)* and *syn (threo)* isomers. Ab initio calculations on the Henry reaction suggest that free nitronate anions (not influenced by cations) react with aldehydes via transition states in which the nitro and carbonyl dipoles are antiperiplanar to each other. This kind of reaction yields *anti*-nitro alcohols. The Henry reaction between lithium nitronates and aldehydes is predicted to occur via cyclic transition states yielding *syn*-nitro alcohols as major products (Eq. 3.64).[108]




**Scheme 3.11** Biological active β-amino alcohol derivatives



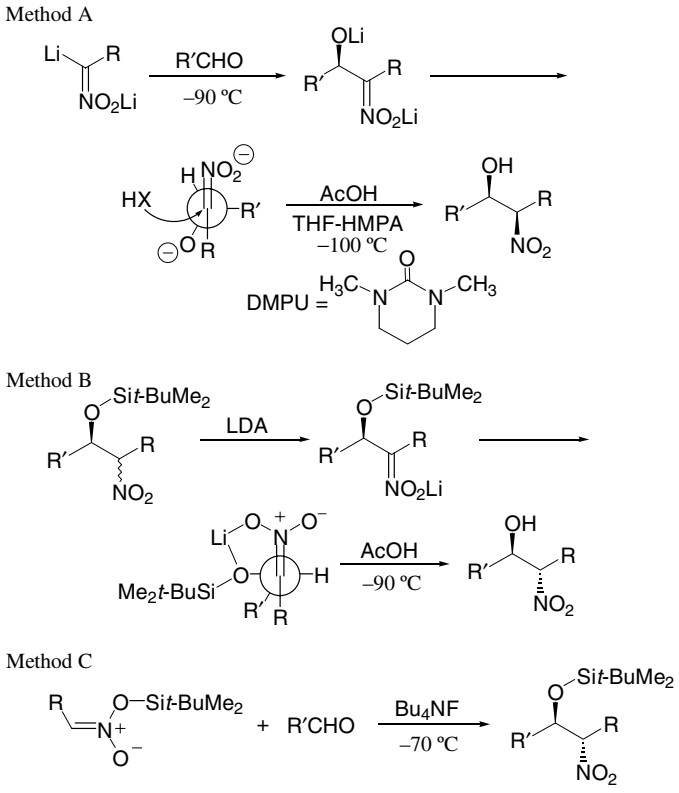

(3.64)

Seebach and co-workers have developed complementary protocols for stereocontrol of the Henry reaction (Scheme 3.12).[18,19]

- Method A: α,α-Doubly deprotonated nitroalkanes react with aldehydes to give intermediate nitronate alkoxides, which afford *syn*-nitroalcohols as major products (18:7–47:3) by kinetic protonation at −100 °C in THF-HMPA. The carcinogenic hexamethylphosphorous triamide (HMPA) can be replaced by the urea derivative (DMPU).
- Method B: In contrast, reprotonation of the *tert*-butyldimethylsilyl-protected nitronate anions gives *anti*-isomers selectively (41:9–19:1).
- Method C: High *anti*-selectivity is also observed in the fluoride-catalyzed reaction of silyl nitronates with aldehydes. Trialkyl silyl nitronates are prepared in good yield from primary nitroalkanes by consecutive treatment with lithium diisopropylamide and trialkylsilyl chloride at −78 °C in THF.

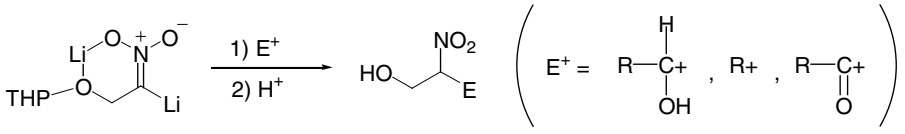
They react with a wide range of aliphatic and aromatic aldehydes in the presence of catalytic amounts of tetrabutylammonium fluoride (TBAF) to give the trialkylsilyl ethers of β-nitro alcohols with high *anti*-selectivity (98%). The diastereoselective Henry reaction is summarized in Table 3.2. The products are reduced to β-amino alcohols using Raney Ni-$H_2$ with retention of the configuration of β-nitro alcohols (Scheme 3.12).

Tetrahydropyranyl (THP)-protected nitroethanol can be doubly deprotonated to lithium α-lithionitronate, which is stable to react with various electrophiles. Higher β-nitro alcohols,

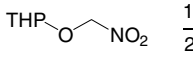



**Scheme 3.12.**

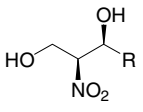
hydroxynitro ketones, and nitrodiols are prepared in good yields after deprotection of THP with an acidic ion-exchange resin in methanol. The nitrodiols are formed with high *syn*-diastereoselectivity (ds 75 to >95%). Because the nitro diols crystallize eventually, pure samples of single diastereomers can easily be prepared (Eqs. 3.65 and 3.66).[109]




(3.65)

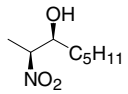
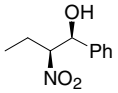
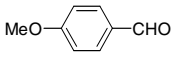
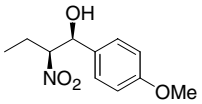
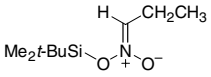
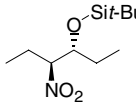
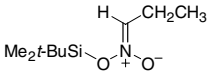
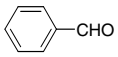
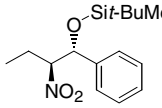
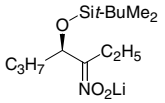
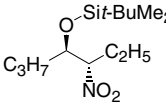
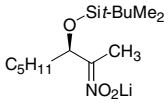
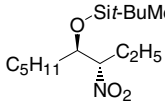
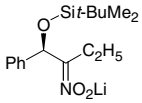
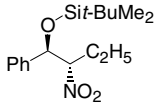



| R | Overall yield (%) | ds (%) |
|---|---|---|
| $Me_2CH$- | 68 | 93 |
| Ph- | 75 | >95 |
| *p*-$MeOC_6H_4$- | 79 | 80 |
| $C_{12}H_{25}$–C≡C– | 74 | 91 |

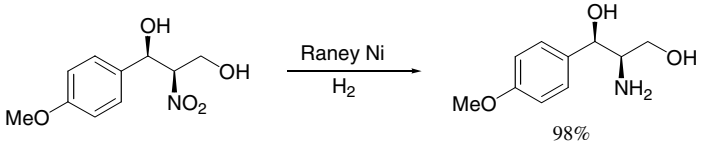


(3.66)

**Table 3.2. Stereoselective Henry reaction**

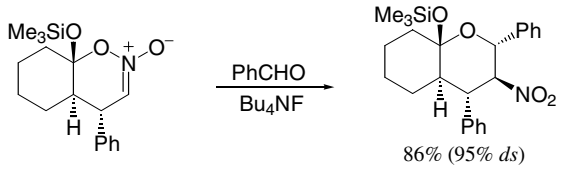
| Nitro compound | Aldehyde | Condition | Product | *syn*/*anti* |
|---|---|---|---|---|
| $CH_3CH_2NO_2$ | $C_5H_{11}CHO$ | 1) 2 *n*-BuLi in THF-HMPA<br>2) AcOH, –100 °C<br>(Method A) |  | 81/19 |
| $CH_3CH_2CH_2NO_2$ | PhCHO | 1) 2 *n*-BuLi in THF-HMPA<br>2) AcOH, –100 °C |  | 90/10 |
| $CH_3CH_2CH_2NO_2$ |  | 1) 2 *n*-BuLi in THF-HMPA<br>2) AcOH, –100 °C |  | 94/6 |
|  | $C_2H_5CHO$ | $Bu_4NF$<br>(Method C) |  | 5/95 |
|  |  | $Bu_4NF$ |  | 22/78 |
|  | | AcOH<br>(Method B) |  | 10/90 |
|  | | AcOH |  | 5/95 |
|  | | AcOH |  | 18/82 |

The products are reduced to amino diols with $H_2$-Raney Ni in ethanol without loss of configurational purity (Eq. 3.67).[109]



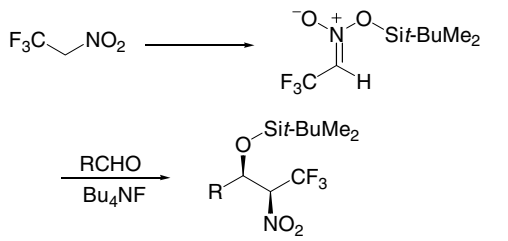

98% (3.67)

Bicyclic trimethylsilyl nitronates undergo stereoselective Henry reactions with benzaldehyde in the presence of fluoride ion to give cyclic hemiacetals in good yield with high diastereo-selectivity (95% ds) (Eq. 3.68).[110]



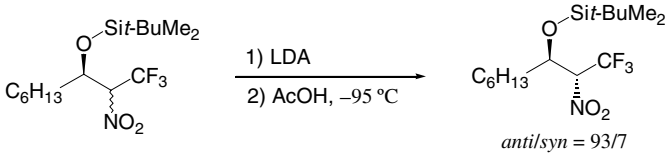

(3.68)

Silyl nitronates of 2,2,2-trifluoronitroethane react with aldehydes in the presence of $Bu_4NF$ in THF to give the *syn*-diastereomers of β-nitro alcohol, as shown in Eq. 3.69. This is in sharp contrast with the results of *anti*-isomers prevailing for non-fluorinated analogues. This is due to the *syn*/*anti* equilibrium of $CF_3$-substituted *O*-silyl nitro aldols. The *anti*-epimer in the trifluoromethyl series can be prepared by diastereoselective protonation of the corresponding *O*-silyl lithium nitronates (Eq. 3.70).[111]



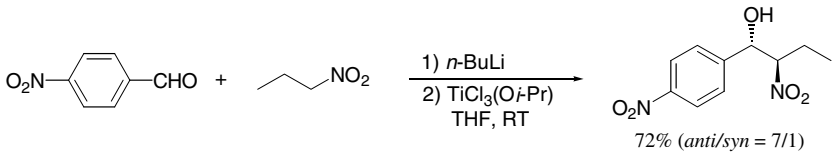

| R | Yield (%) | *syn*/*anti* |
|---|---|---|
| *i*-Pr- | 52 | 76/24 |
| Ph- | 72 | 75/ 25 |
| *p*-$MeOC_6H_4$- | 72 | 73/ 27 |

(3.69)




(3.70)

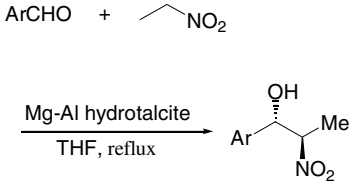
An experimentally simple procedure for stereoselectively preparing β-nitro alcohols has been developed. The alkyl nitronates, formed by the action of *n*-butyllithium on nitroalkanes in THF solution, react with aldehydes in the presence of isopropoxytitanium trichloride at room temperature to give the β-nitro alcohols enriched in the *anti*-diastereoisomers (Eq. 3.71).[112]




(3.71)

This method is particularly useful for electron-deficient aromatic aldehydes, but it is not efficient with aliphatic aldehydes, probably a consequence of competitive aldol reaction.

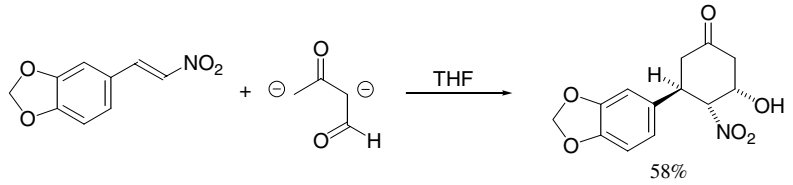
A new heterogeneous catalyst exists that uses Mg-Al hydrotalcites for the diastereoselective synthesis of β-nitro alcohols. The positively charged Mg-Al double hydroxide sheets are charge-balanced by the carbonate anions residing in the interlayer section of the clay structure. Both aromatic and aliphatic aldehydes react with nitroalkanes using this catalyst to give β-nitro alcohols in good yields. Diastereoselectivity depends on the structure of the aldehydes, 4-nitrobenzaldehyde and 2-chlorobenzaldehyde react with nitroethane to give the corresponding nitro alcohols in 100% *anti*-selectivity.[113] However, the reaction with aliphatic aldehydes exhibits low selectivity (Eq. 3.72).



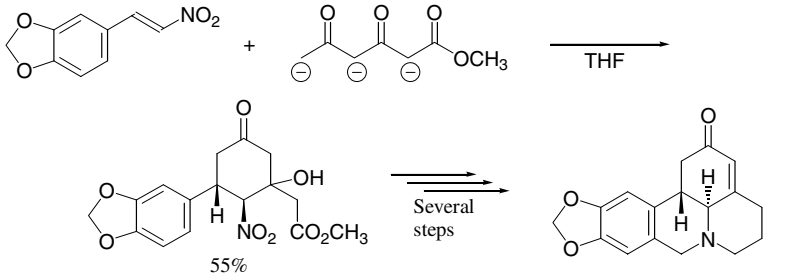

| Ar | Yield (%) | *anti*/*syn* |
|---|---|---|
| Ph- | 87 | 3.75/ 1 |
| *p*-$O_2NC_6H_4$- | 84 | 100/ 0 |
| *p*-$ClC_6H_4$- | 82 | 100/ 0 |
| *p*-$MeOC_6H_4$- | 62 | 1.23/1 |

(3.72)

The stereoselective intramolecular Henry reactions have been reported by Seebach. The Michael addition of doubly deprotonated acetyl acetaldehyde to 1-methylenedioxyphenyl-2-nitroethene followed by subsequent intramolecular nitro-aldol cyclization leads to the diastereomerically pure cyclohexanone derivative, where the nitro and OH groups are *cis* as shown in Eq. 3.73.[114] This reaction is applied to the synthesis of 1-desoxy-2-lycorinone as shown in Eq. 3.74.[115]




(3.73)

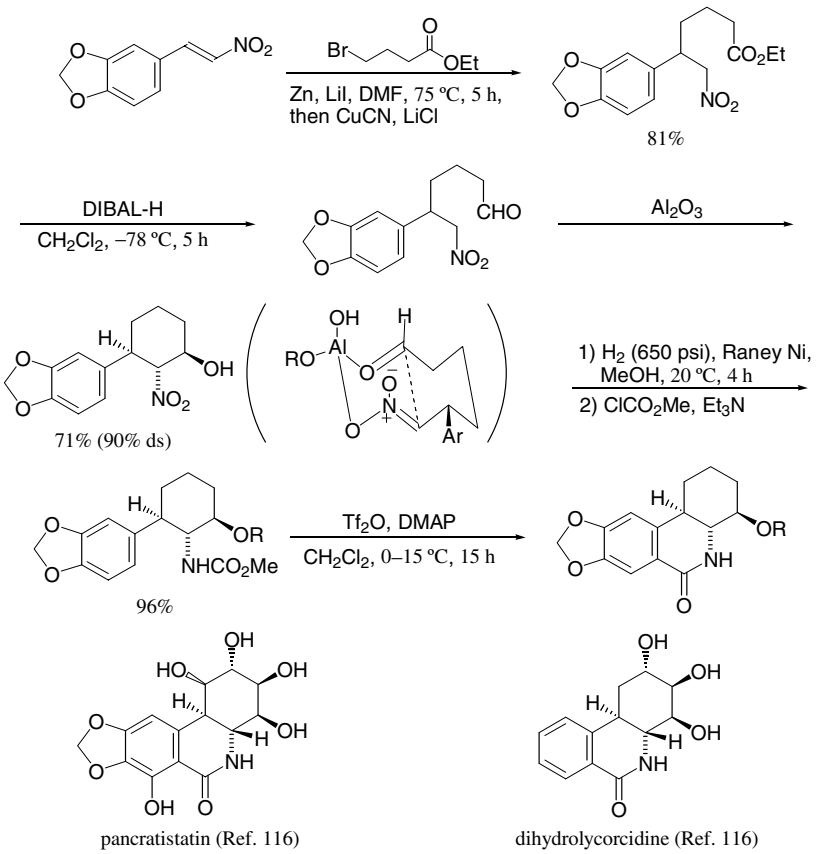



(3.74)

In consideration of the structure of the valuable anticancer alkaloids pancratistatin and *trans*-dihydrolycorcidine,[116] the development of an intramolecular nitro-aldol cyclization exhibiting alternative diastereoselectivity to that of Eq. 3.74 has been achieved. In contrast to cyclization of Eq. 3.74, a neutral alumina-promoted nitro-aldol cyclization provides the desired diastereoselectivity. Scheme 3.13 shows key steps of the total synthesis of lycoricidine alkaloids. Michael addition of the copper-zinc reagent derived from ethyl 4-bromobutanoate to nitroalkene[117] followed by the reduction with diisobutylaluminum hydride (DIBAL-H) gives the requisite nitro-aldehyde, which is the key substrate for the intramolecular nitro-aldol reaction. The alumina-promoted 6-*exo*-trig intramolecular nitro-aldol cyclization proceeds in a highly diastereoselective way via a chelation-controlled chair-like transition state. The major isomer has the correct relative configuration at three stereoisomers, as observed in the pancratistatin series of anti-tumor agents.[118]

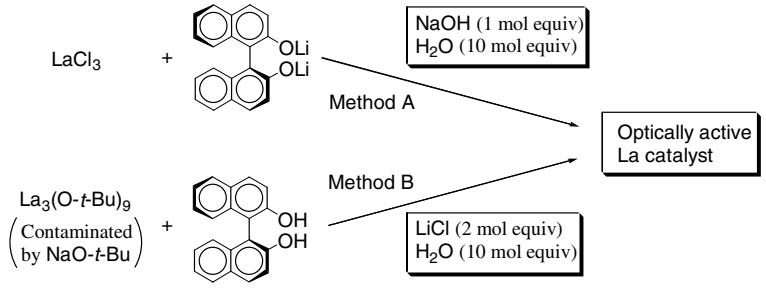
Over the last few years several examples have been reported in the field of asymmetric catalysis that are based on the interaction of two centers.[6,119] Recently, Shibasaki and coworkers have developed an asymmetric two-center catalyst. Scheme 3.14 shows preparation of optically active La binaphthol (BINOL). This catalyst is effective in inducing the asymmetric nitro-aldol reaction, as shown in Scheme 3.15.

These heterobimetallic $M^1$-$M^2$-binol complexes constitute a new class of widely applicable chiral catalysts as shown in Scheme 3.16. The new catalysts consist of a central metal ion (e.g., $La^{3+}$, $Al^{3+}$, $Sm^{3+}$, $Ga^{3+}$), three alkali metal ions (e.g., $Li^+$, $Na^+$, $K^+$), and three chiral diphenol

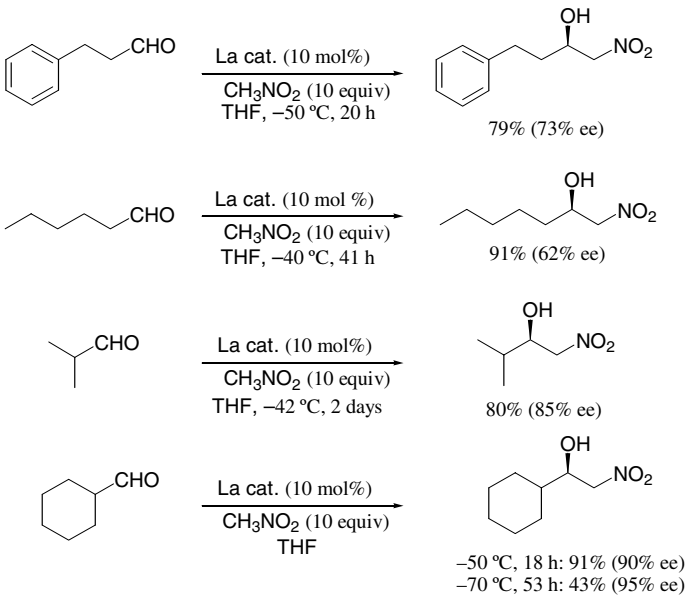



**Scheme 3.13.**

[1,1′-(*R*)- or 1,1′-(*S*)-binaphthol]. These catalysts exhibit basic as well as Lewis acid properties. They are easily prepared, stable to air and moisture, and nontoxic. By careful choice of the metal centers, various types of organic reactions are catalyzed. Asymmetric nitro-aldol reactions are catalyzed by lanthanoid-lithium-BINOL (LLB),[9,120] asymmetric Michael reactions are catalyzed by lanthanoid-sodium BINOL (LSB),[122] asymmetric hydrophosphonylation of imines is catalyzed by lanthanoid-potassium-BINOL (LPB),[121] and asymmetric Michael-aldol reactions




**Scheme 3.14.** Preparation of the optically active La-BINOL complex

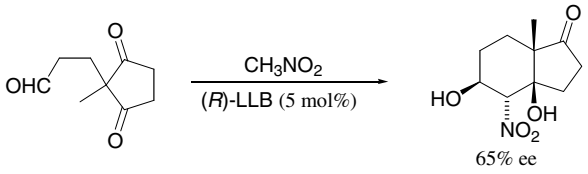



**Scheme 3.15.** La-BINOL complex-catalyzed asymmetric nitro-aldol reactions

and hydrophosphonylation of aldehydes are catalyzed by aluminum-lithium-BINOL (ALB).[122] The nitro-aldol reactions catalyzed by these catalysts are summarized here.

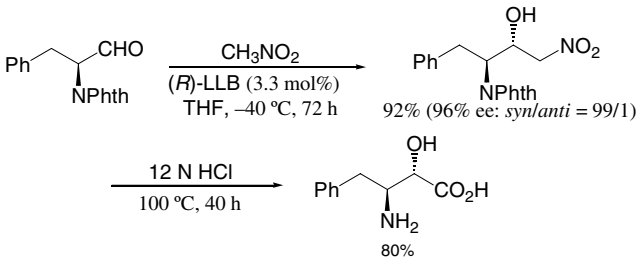
The enantioselective nitro-aldol reaction catalyzed by (*R*)-LLB is effectively applied to the synthesis of three kinds of optically active β-receptor blocking drugs (*S*)-metoprolol,[123a] (*S*)-propanolol,[123b] and (*S*)-pindolol[123c] (Scheme 3.17).

Shibasaki has also extended the use of LLB catalyst to tandem nitro-aldol reactions providing bicyclic adducts with 65% ee (Eq. 3.75).[124]

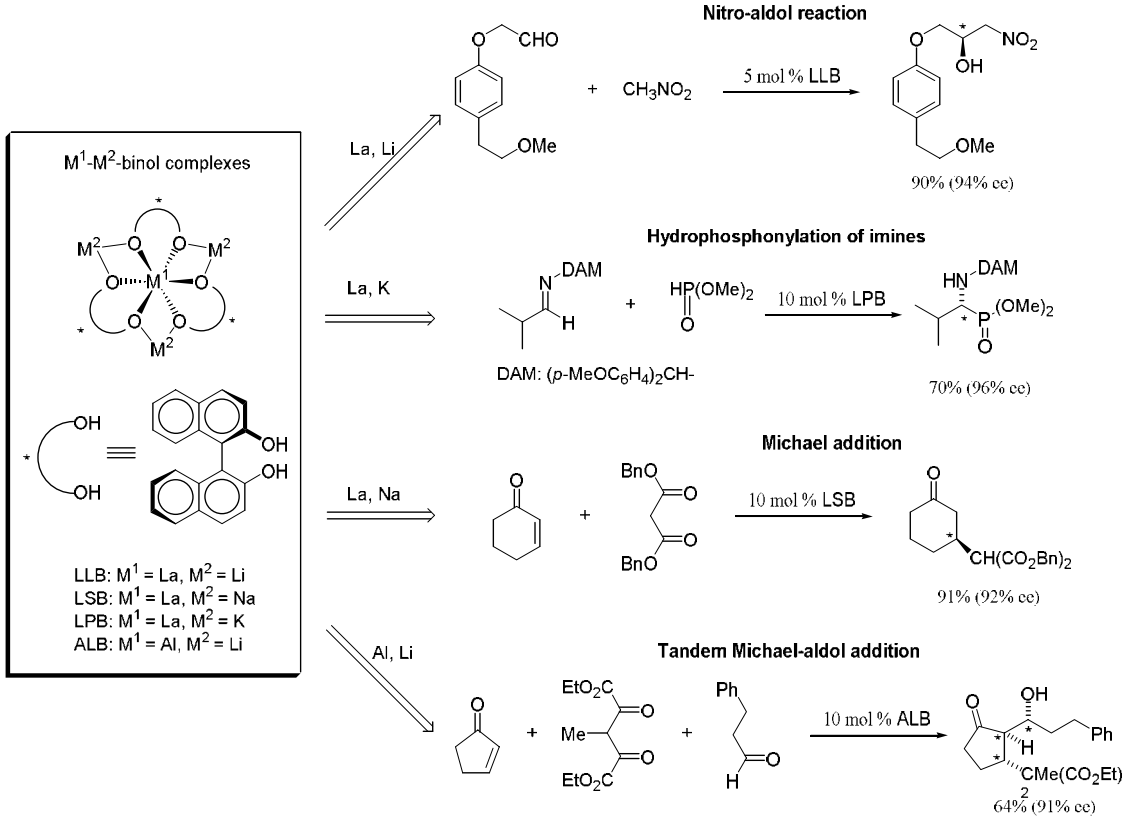



(3.75)

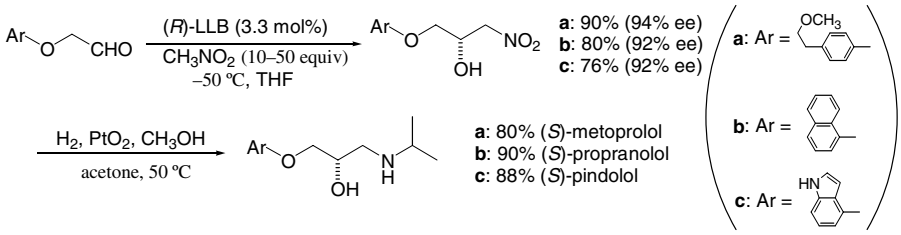
Diastereoselective catalytic nitro-aldol reactions of optically active *N*-phthaloyl-L-phenylalanal with nitromethane in the presence of LLB proceed with high diastereoselectivity (*anti*:*syn* = 99:1) as shown in Eq. 3.76.[125] The product is converted via the Nef reaction into (2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoic acid, which is a subunit of the HIV-protease inhibitor




(3.76)


M1-M2-binol complexes
LLB: M1 = La, M2 = Li
LSB: M1 = La, M2 = Na
LPB: M1 = La, M2 = K
ALB: M1 = Al, M2 = Li
La, Li
Nitro-aldol reaction
5 mol % LLB
90% (94% ee)
La, K
Hydrophosphonylation of imines
DAM: (p-MeOC6H4)2CH-
10 mol % LPB
70% (96% ee)
La, Na
Michael addition
10 mol % LSB
91% (92% ee)
Al, Li
Tandem Michael-aldol addition
10 mol % ALB
64% (91% ee)

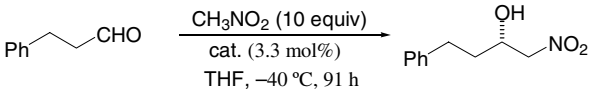
Scheme 3.16.




**Scheme 3.17.** Asymmetric syntheses of β-blockers with (R)-LLB as catalyst

KNI-272. The reaction of the same aldehyde with nitromethane using (*S*)-LLB leads to the reduced diastereoselectivity (74:26).

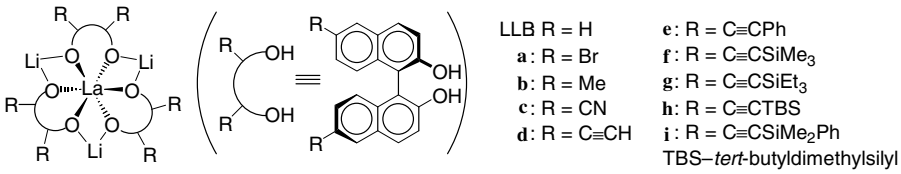
LLB-type catalysts are able to promote diastereo-selective and enantio-selective nitro-aldol reactions from prochiral materials. However, LLB gives unsatisfactory results in terms of both diastereoselectivity (Syn:Anti: 63:37 ~ 77:23) and enantioselectivity (<78% ee) in many cases (Scheme 3.15).[120a] A number of complexes **a**,**b**,**c**,**d**,**e**,**f**,**g**,**h**, and **i** are prepared, as shown in Scheme 3.18, in which BINOL rings are substituted by alkyl, alkenyl, alkynyl, and cyano groups. The effect of substituents on the BINOL rings is tested by the reaction of Eq. 3.77. Thus, stereoselectivity is affected by the substituents of BINOL, and alkynyl-substituted BINOLs, such as **f**–**i**, give the better optical activity of the product than LLB.[126] Another advantage is conferred by introducing 6,6′-substituents to BINOL.




(3.77)

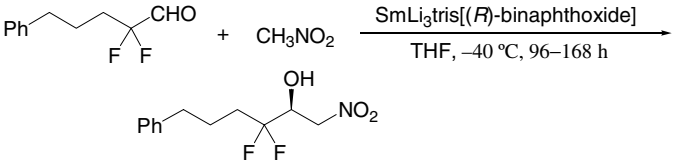
| Entry | Catalyst | Yield (%) | ee (%) |
|---|---|---|---|
| 1 | LLB | 79 | 73 |
| 2 | **a** | 80 | 67 |
| 3 | **b** | 84 | 63 |
| 4 | **c** | 67 | 55[a] |
| 5 | **d** | 69 | 71 |
| 6 | **e** | 74 | 79 |
| 7 | **f** | 85 | 88 |
| 8 | **g** | 84 | 85 |
| 9 | **h** | 59 | 85 |
| 10 | **i** | 54 | 86 |

[a] 6,6′-Dicyano-BINOL with 93% ee was used.



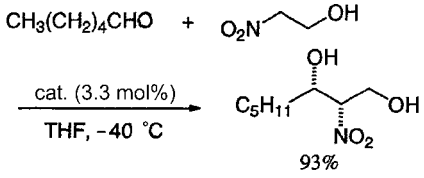

**Scheme 3.18.** Structural modification of LLB

The heterobimetallic asymmetric catalyst, Sm-Li-(*R*)-BINOL, catalyzes the nitro-aldol reaction of α,α-difluoroaldehydes with nitromethane in a good enantioselective manner, as shown in Eq. 3.78. In general, catalytic asymmetric syntheses of fluorine containing compounds have been rather difficult. The *S* configuration of the nitro-aldol adduct of Eq. 3.78 shows that the nitronate reacts preferentially on the *Si* face of aldehydes in the presence of (*R*)-LLB. In general, (*R*)-LLB causes attack on the *Re* face. Thus, enantiotopic face selection for α,α-difluoroaldehydes is opposite to that for nonfluorinated aldehydes. The stereoselectivity for α,α-difluoroaldehydes is identical to that of β-alkoxyaldehydes, as shown in Scheme 3.19, suggesting that the fluorine atoms at the α-position have a great influence on enantioface selection.

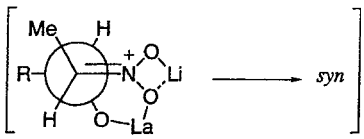


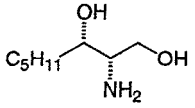

74% (87% ee) (3.78)

A *syn*-selective asymmetric nitro-aldol reaction has been reported for structurally simple aldehydes using a new catalyst generated from 6,6-bis[(triethylsilyl)ethynyl]BINOL (**g** in Scheme 3.18).[126] The *syn* selectivity in the nitro-aldol reaction can be explained by steric hindrance in the bicyclic transition state as can be seen in Newman projection. In the favored transition state, the catalyst acts as a Lewis acid and as a Lewis base at different sites. In contrast, the nonchelation-controlled transition state affords anti product with lower ee. This stereoselective nitro-aldol reaction has been applied to simple synthesis of *threo*-dihydrosphingosine by the reduction of the nitro-aldol product with $H_2$ and Pd-C (Eq. 3.79).




| Catalyst | Yield (%) | *syn*/*anti* | *ee* of *syn* |
|---|---|---|---|
| LLB | 79 | 87/13 | 78 |
| **g** (**Scheme 3.18**) | 96 | 92/8 | 95 |



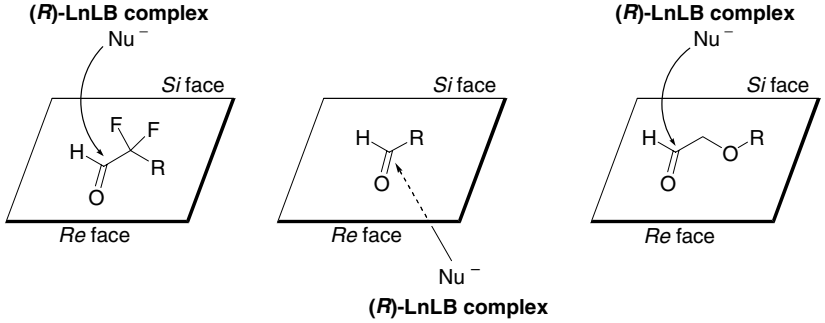




*threo*-dihydrosphingosine

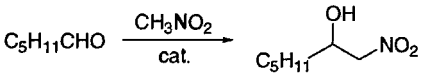
(3.79)

The LLB catalysts requires at least 3.3 mol% of asymmetric catalyst for efficient nitro-aldol reactions, and the reactions are rather slow (first generation). Second-generation LLB catalysts are prepared by addition of 1 equiv of $H_2O$ and 0.9 equiv of *n*-BuLi. The second-generation-catalysts are more reactive than the first generation LLB as shown in Eq. 3.80. The proposed mechanism of asymmetric nitro-aldol reaction using these catalysts is presented in Scheme 3.20.[128]

The diastereoselectivity is observed in the Henry reaction using optical active nitro compounds or α-heteroatom substituted aldehydes. For example, the reaction of O-benzyl-D-lactaldehyde with methyl 3-nitropropionate in the presence of neutral alumina leads to a mixture of three nitro-aldol products from which D-ribo isomer is isolated by direct crystallization. D-Ribo



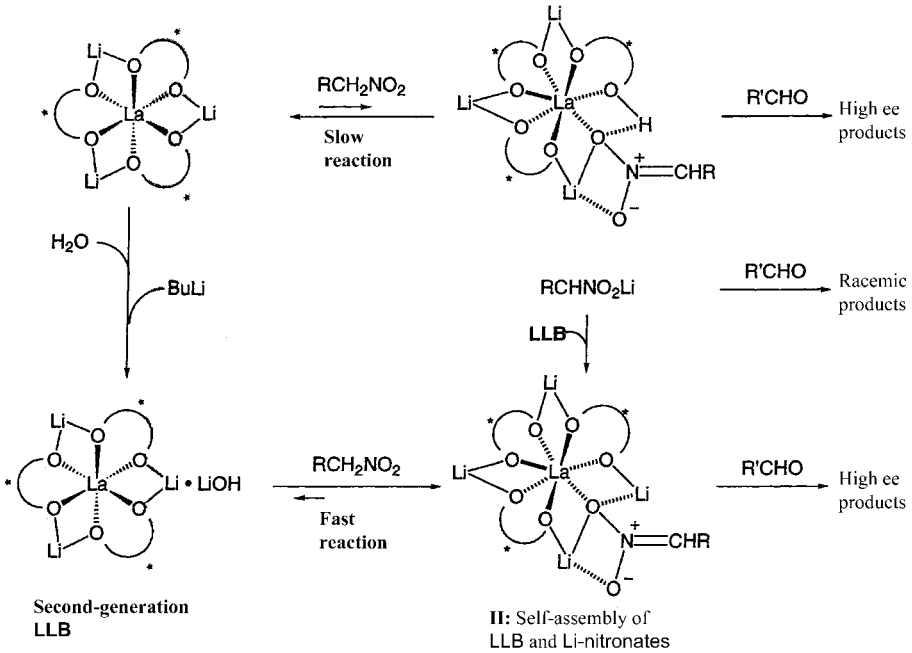

**Scheme 3.19.**




(3.80)

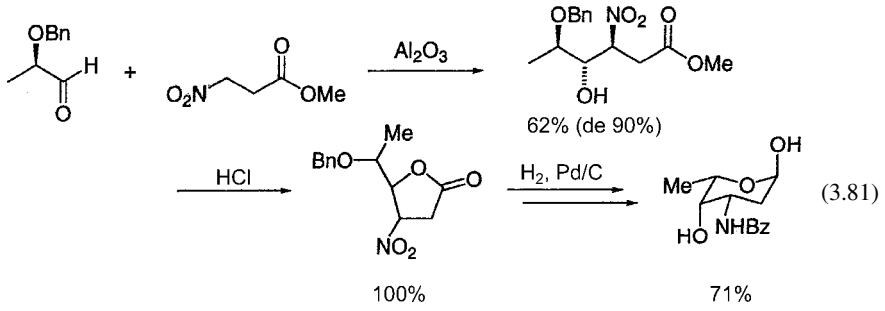
| Catalyst | Condition | Yield(%) | ee (%) |
|---|---|---|---|
| LLB (1 mol%) | −50 °C, 24 h | 56 | 88 |
| | −50 °C, 24 h | 73 | 89 |
| LLB-II | −50 °C, 4 h | 70 | 90 |

LLB-II = LLB + $H_2O$ (1 equiv) + BuLi (0.9 equiv).



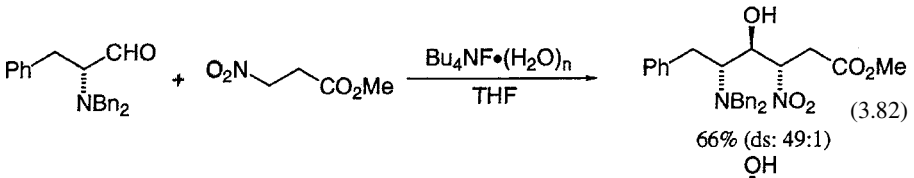

**Scheme 3.20.** Proposed mechanism of asymmetric nitro-aldol reactions catalyzed by LLB, LLB-II, or LLB-Li nitronate

isomer is the thermodynamic product, which is converted into *N*-benzoyl-L-daunosamine, as shown in Eq. 3.81.[129]

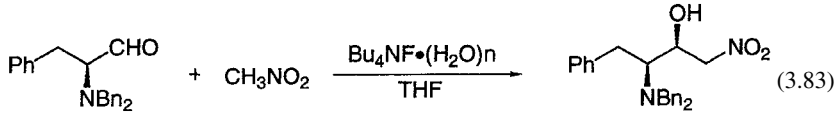


(3.81)

The Henry reactions of *N*,*N*-dibenzyl-L-phenylalaninal with nitroalkanes using 1.2 equiv of tetrabutylammonium fluoride (TBAF) as the catalyst proceed in a highly stereoselective manner, as shown in Eqs. 3.82 and 3.83.[130] This reaction provides rapid and stereoselective access to important molecules containing 1,3-diamino-2-hydroxypropyl segments, which are central structural subunit of the HIV protease inhibitor amprenavir (in Scheme 3.21).



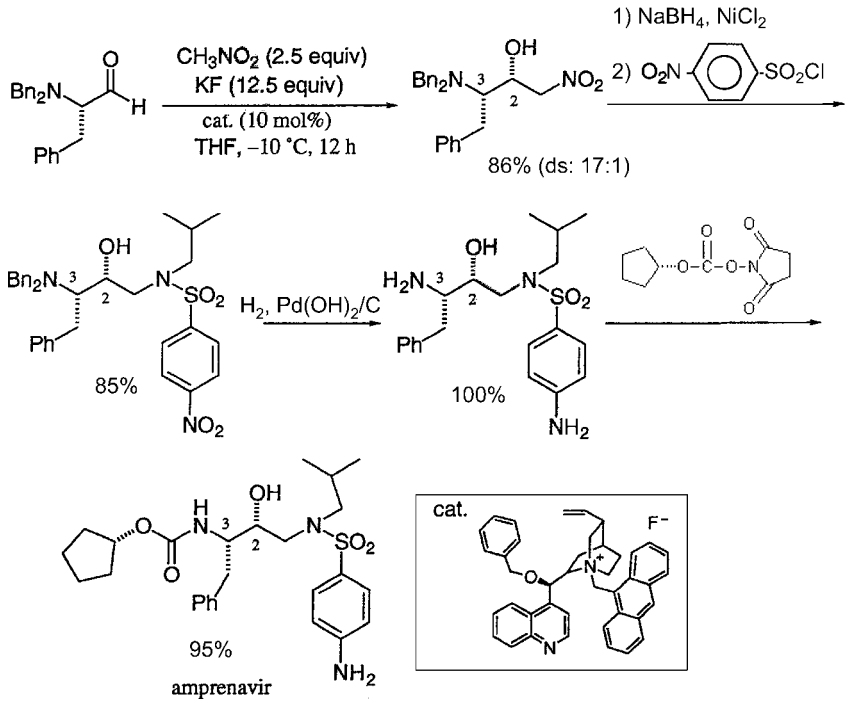
(3.82)
66% (ds: 49:1)



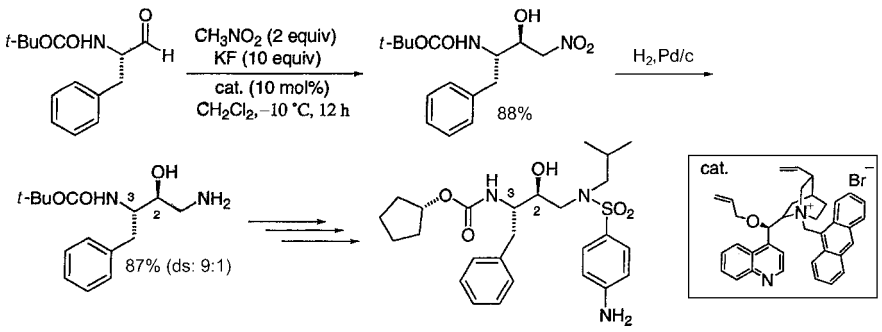
(3.83)
63% (ds: 8:1)

Corey has discovered that chiral quaternary ammonium salts shown in Schemes 3.21 and 3.22 are more effective for inducing *re*- and *si*-face-selective nitro-aldol reactions than TBAF.[131] The sequence utilized for the synthesis of amprenavir is shown in Scheme 3.21. The reaction of *N*,*N*-dibenzyl-(*S*)-phenylalanial with nitromethane gives the desired *syn*-nitro alcohol with a 17:1 diastereoselectivity. The diastereoselectivity is only 4:1 when TBAF is used. This nitro alcohol is reduced to the corresponding amino alcohol with $NaBH_4$ in the presence of $NiCl_2$ in 85% yield. The reductive alkylation with isobutyraldehyde followed by sulfonylation with *p*-nitrobenzenesulfonyl chloride, deprotection with $H_2$-Pd/C, and acylation with (*S*)-3-tetrahydrofuranyl-*N*-oxysuccinimidyl carbonate gives amprenavir in 50% overall yield from the starting amino aldehyde. The (2*S*,3*S*) isomer of amprenavir is prepared from *N*-*tert*-butoxycarbonyl derivative of (*S*)-phenyalaninal as shown in Scheme 3.22. The use of rigid chiral quaternary ammonium cations as shown in Schemes 3.21 and 3.22 control the face selectivity in nucleophilic addition of nitromethyl anion to aldehydes, *re*- or *si*-face selectivity depending on the *N*-protecting group of the *S*-phenylalaninal moiety. This provides a new strategy for stereocontrol of the Henry reaction.

Jager and coworkers have used the TBAF catalyzed-stereoselective nitro-aldol reaction for the synthesis of cyclic amino alcohols such as iminopolyols, imino sugars, and cyclic amino acids. They are important classes of compounds and have the potential utility as *anti*-diabetic,

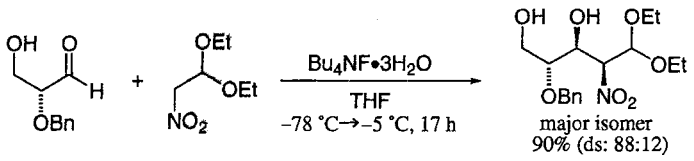



**Scheme 3.21.**



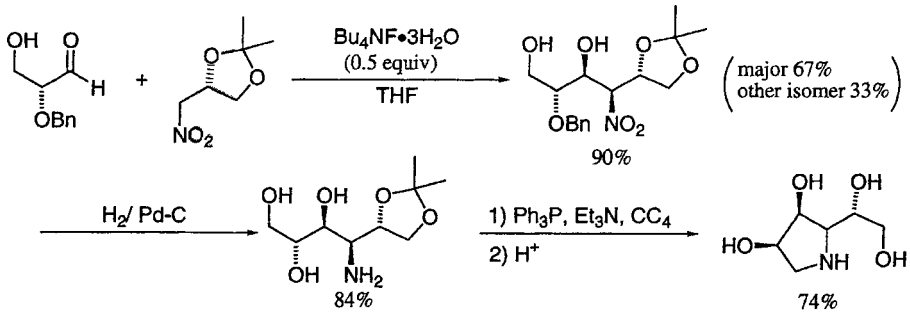

**Scheme 3.22.**

*anti*-viral, or *anti*-tumor agents.[132] TBAF-catalyzed reaction of α-alkoxy aldehydes with nitroacetaldehyde diethylacetal yields *anti-syn* diastereomers as predominant thermodynamic products (Eq. 3.84).[133] The products are good precursors of cyclic amino alcohols.



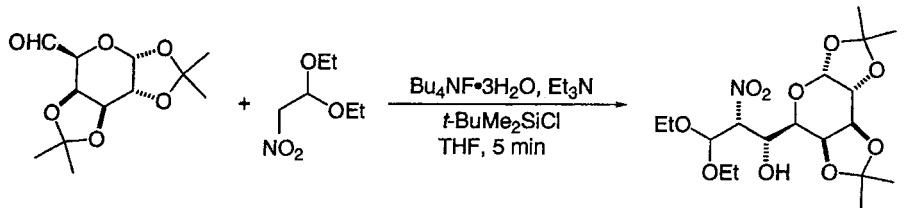

(3.84)

Another application of diastereoselective nitro-aldol reactions catalyzed by $Bu_4NF{\cdot}3H_2O$ is demonstrated in a simple synthesis of 1,4-dideoxy-1,4-imino-D-mannitol (DIM) and amino analogues (Eq. 3.85).[134] The nitro-aldol reaction of nitro compounds bearing α-oxy or α-amino function with glyceraldehyde leads to nitrohexitols, which can be reduced to the corresponding amino compounds. Cyclization gives iminopolyols, as shown in Eq. 3.85.




(3.85)

The nitro-aldol reaction using 1,1-diethoxy-2-nitroethane is useful for lengthening of the carbon chain of carbohydrates. The reaction of Eq. 3.86 proceeds in a stereoselective way (ds 75%) to give the *syn*-nitro alcohol in 58% isolated yield.[135] The product is converted into 2-amino-2-deoxyaldoses by reaction with $H_2$/Raney Ni.




(3.86)

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*The Nitro Group in Organic Synthesis.* Noboru Ono
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ISBNs: 0-471-31611-3 (Hardback); 0-471-22448-0 (Electronic)

# 4

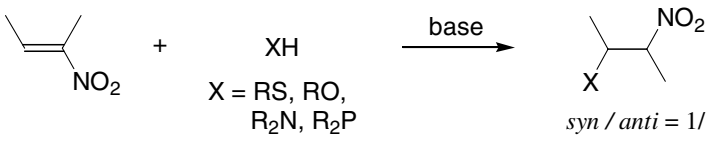
# MICHAEL ADDITION

Conjugate addition of nucleophiles to electron-deficient alkenes is an important tool for the creation of carbon-carbon bond or carbon-heteroatom bond frameworks. This type of reaction is generally called as Michael addition. Because the nitro group is a strong electron-withdrawing group, nitroalkenes serve as good Michael acceptors and the anions of nitroalkanes serve as good Michael donors. These reactions proceed under very mild conditions and tolerate various functional groups. Because the nitro group can be converted into various functional groups as discussed in the Chapters 6 and 7, the Michael addition of nitro compounds has been used extensively in organic synthesis. The synthetic utility of the Michael addition of nitro compounds is shown in Scheme 4.1.

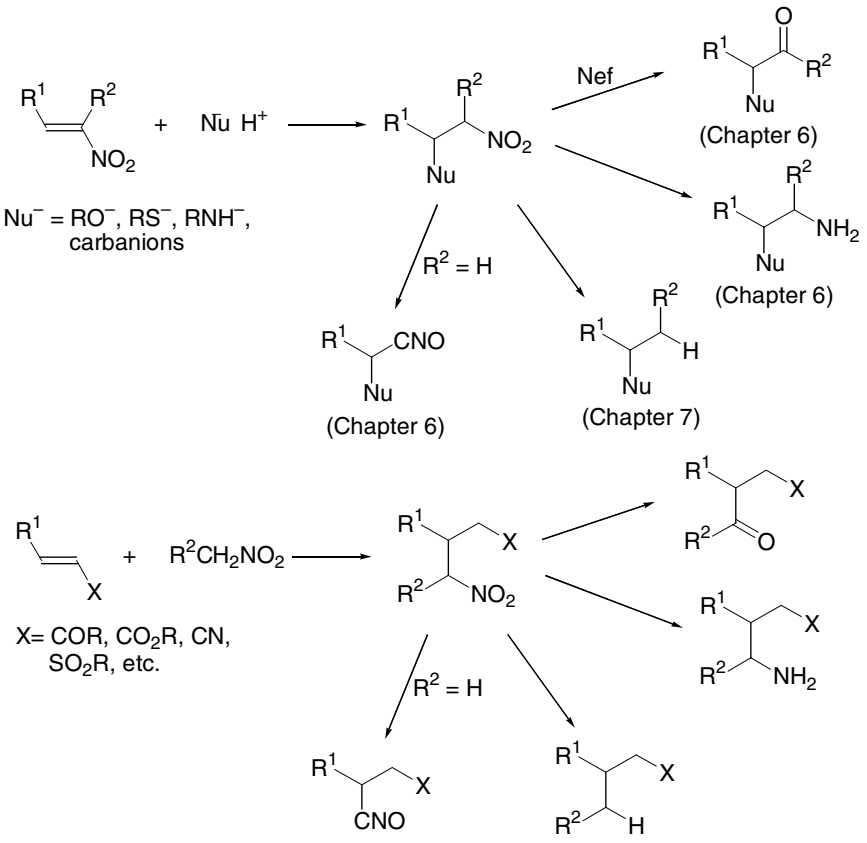
## 4.1 ADDITION TO NITROALKENES

### 4.1.1 Conjugate Addition of Heteroatom-Centered Nucleophiles

Heteroatom-centered nucleophiles such as oxygen, sulfur, nitrogen, and phosphorous anions are good nucleophiles for the Michael addition to nitroalkenes, which provides a useful method for the introduction of two heteroatoms on vicinal positions. Because this type of reaction may undergo a reverse elimination reaction, the addition products of nitrogen nucleophiles are often unstable. Because the addition products of sulfur and oxygen nucleophiles are more stable, the addition of alcohols and thiols has been frequently used for organic synthesis. In general, the experimental procedure for this addition is very simple. For example, the reaction of thiols with nitroalkenes readily proceeds in the presence of catalytic amounts of base to give β-nitro sulfides in quantitative yields.[1] The stereoselectivity of this type of addition is generally low, and two diastereomeric isomers, *syn* and *anti* isomers, are formed in about a 1 to 1 ratio (Eq. 4.1).

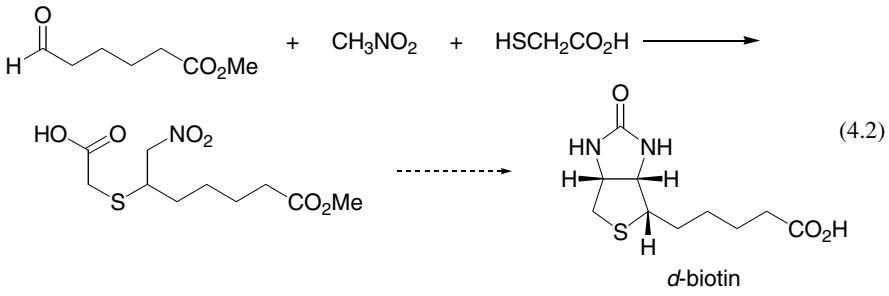



(4.1)



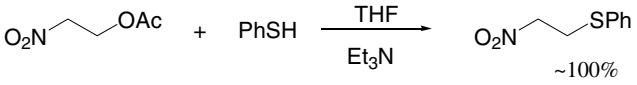

**Scheme 4.1.**

β-Nitro sulfides are conveniently prepared by simply mixing carbonyl compounds, nitroalkanes, and thiols in the presence of triethylamine.[2] β-Nitro sulfide, which is used for synthesis of *d*-biotin, is prepared by this procedure (Eq. 4.2).[3]



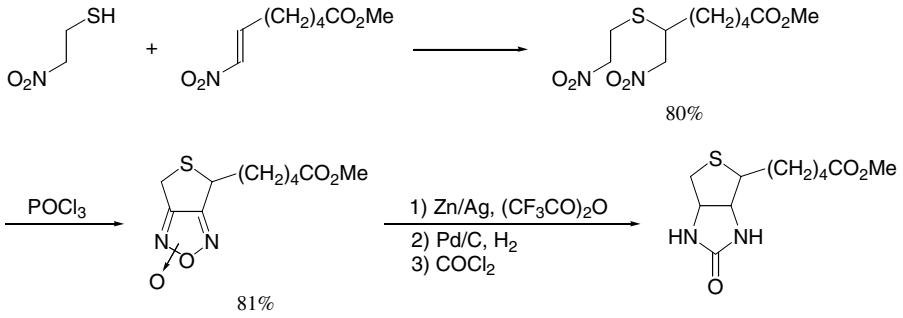

(4.2)

Treatment of β-nitro acetates with thiols in the presence of base is also a simple method for the preparation of β-nitro sulfides (Eq. 4.3).[4]

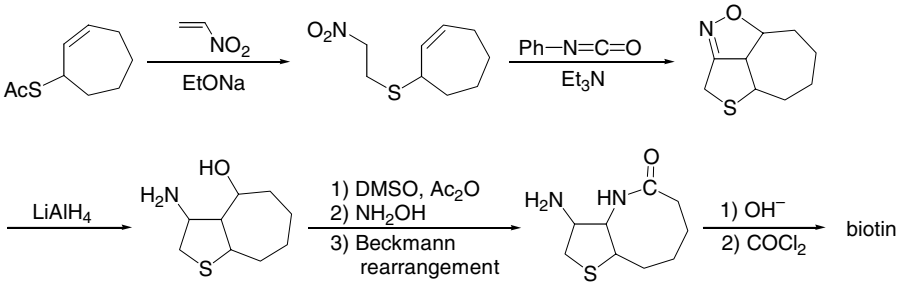



(4.3)

β-Nitro sulfides are useful intermediates for the preparation of various heterocycles containing sulfur atoms. Synthetic applications are demonstrated in Schemes 4.2[5] and 4.3,[6] in which biotin is prepared via cycloaddition of nitrile oxides (see Chapter 8).

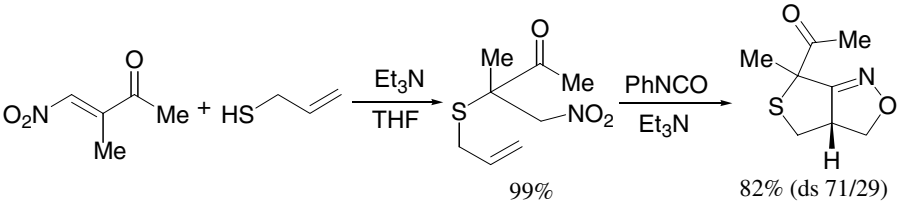



**Scheme 4.2.**




**Scheme 4.3.**

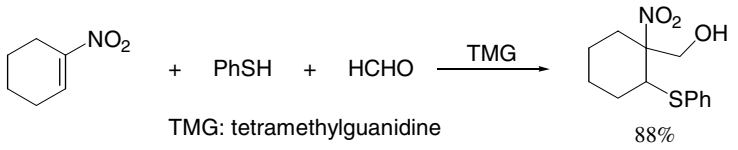
Synthesis of thiopheno[3,4-c]isoxazoline is shown in Eq. 4.4, in which the Michael addition of allyl thiol to β-nitro enones and subsequent nitrile oxide cyclization are involved.[7]



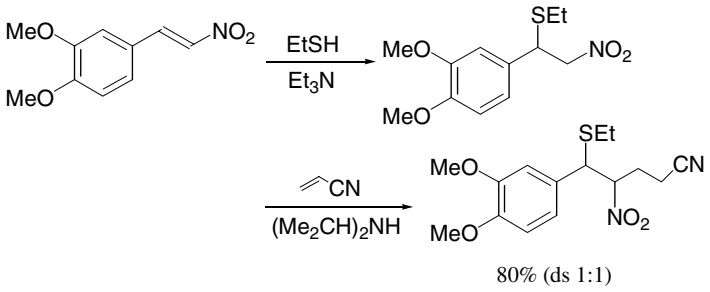

(4.4)

The base-catalyzed joint reaction of nitroalkenes with thiophenol in the presence of aldehydes gives γ-phenylthio-β-nitro alcohols in one pot (Eq. 4.5).[8] The joint reaction of nitroalkenes with thiols and α,β-unsaturated nitriles (or esters) has also been achieved. (Eq. 4.6).[9] β-Nitro sulfides thus prepared show unique reactivity toward nucleophiles or tin radicals. The nitro

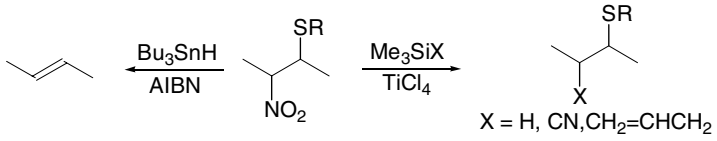
group can be replaced by various nucleophiles in the presence of Lewis acid.[10] The reaction of β-nitro sulfides with tin radical gives alkenes, in which both the nitro and alkylthio groups are eliminated as shown in Eq. 4.7. Details of such substitution and elimination reactions are described in Chapter 7.




(4.5)

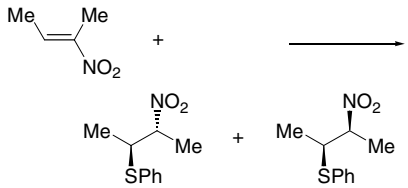



(4.6)



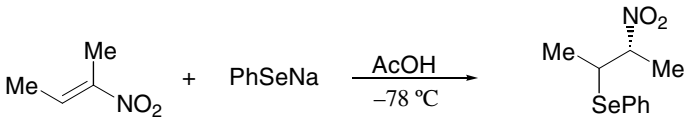

(4.7)

Ono and Kamimura have found a very simple method for the stereo-control of the Michael addition of thiols, selenols, or alcohols. The Michael addition of thiolate anions to nitroalkenes followed by protonation at –78 °C gives *anti*-β-nitro sulfides (Eq. 4.8).[11] This procedure can be extended to the preparation of *anti*-β-nitro selenides (Eq. 4.9)[12] and *anti*-β-nitro ethers (Eq. 4.10).[13] The addition products of benzyl alcohol are converted into β-amino alcohols with the retention of the configuration, which is a useful method for *anti*-β-amino alcohols. This is an alternative method of stereoselective nitro-aldol reactions (Section 3.3). The *anti* selectivity of these reactions is explained on the basis of stereoselective protonation to nitronate anion intermediates. The high stereoselectivity requires heteroatom substituents on the β-position of the nitro group. The computational calculation exhibits that the heteroatom covers one site of the plane of the nitronate anion.[14]

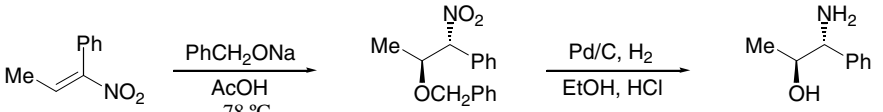



| Reagent and condition | Yield (%) *anti/syn* | |
|---|---|---|
| PhSLi, –78 °C, AcOH | 71 | 91/9 |
| PhSH, $Et_3N$, RT | 88 | 40/60 |

(4.8)

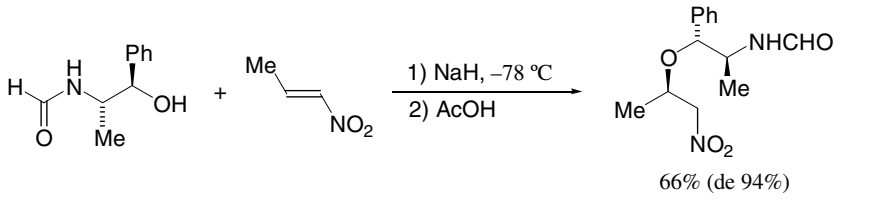



68% (*syn*/*anti* = 91/9) (4.9)




73% (*syn*/*anti* = 91/9) 72% (*syn*/*anti* = 91/9) (4.10)

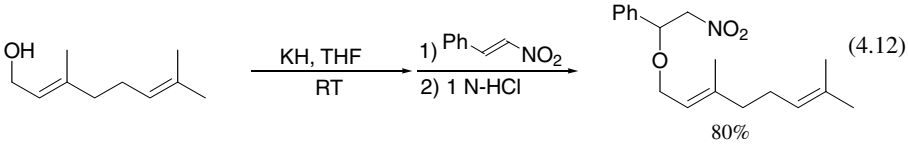
Enantioselective synthesis of β-amino alcohols is also reported by the application of the oxa-Michael addition to nitroalkenes (Eq. 4.11). The sodium salt derived from (1*R*,2*S*)-*N*-formylnorephedrin and NaH reacts with nitroalkenes at –78 °C with high diastereoselectivity (de: 93–98%) in good yields. Virtually diastereomerically pure compounds can be obtained by using column chromatography. After the reduction of the nitro group to the amino group, the cleavage of the ether with sodium in liquid $NH_3$ at –78 °C leads to amino alcohols without racemization.[15]



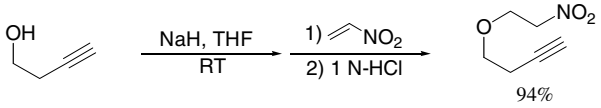

66% (de 94%)

80% ($NO_2 \rightarrow$ NHBoc) 75% (ee 96%) (4.11)

The Michael addition of alkoxides to nitroalkenes gives generally a complex mixture of products due to the polymerization of nitroalkenes.[16] The effect of cations of alkoxides has been examined carefully, and potassium- or sodium-alkoxides give pure β-nitro-ethers in 78–100% isolated yield (Eqs. 4.12 and 4.13).[17] When lithium-alkoxides are employed, the yields are decreased to 20–40%.

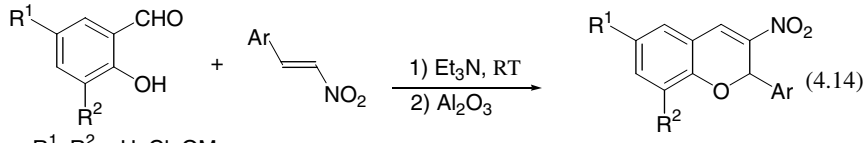



80% (4.12)




94% (4.13)

The Michael addition of oxygen-nucleophiles followed by subsequent cyclization or cycloaddition provides an important method for the preparation of oxygen-heterocycles such as tetrahydrofurans. For example, 3-nitro-2*H*-chromenes bearing various substituents are prepared by the reaction of substituted salicylaldehydes with nitroalkenes (Eq. 4.14).[18a] The reaction with nitroethanol in the presence of di-*n*-butylammmonium chloride in refluxing *iso*pentyl acetate gives 2-unsubstituted 3-nitro-2*H*-chromene in 50% yield.[18b] Some 3-nitro-2*H*-chromenes display efficient optical second harmonic generation for nonlinear optical applications.[19]

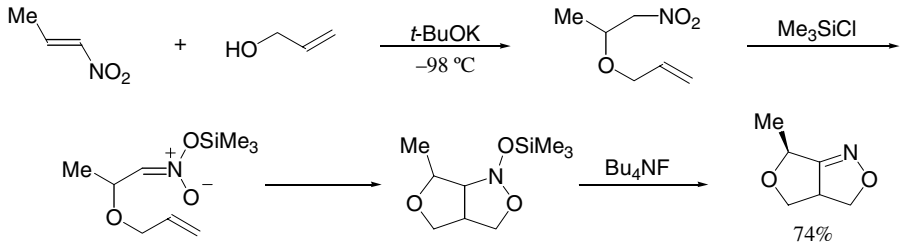



$R^1$, $R^2$ = H, Cl, OMe
Ar = Ph, *p*-$MeOC_6H_4$, 2-thienyl

70–84%

(4.14)

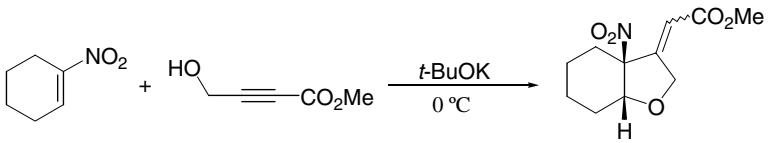
The Michael addition of allyl alcohols to nitroalkenes followed by intramolecular silyl nitronate olefin cycloaddition (Section 8.2) leads to functionalized tetrahydrofurans (Eq. 4.15).[20]




74%
(tandem reaction)

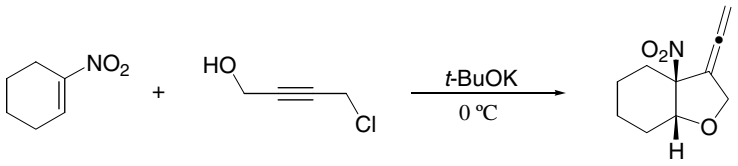
(4.15)

Recently, tandem (domino) Michael addition initiated by oxygen nucleophiles has received much attention for the construction of octahydrobenzo[*b*]furans. The reaction of 1-nitrocyclohexene with 4-hydroxy-2-butynoates, catalyzed by *t*-BuOK at 0 °C, gives the desired furan in 90–100% yield (Eq. 4.16).[21] Similarly, 4-chlorobut-2-yn-1-ols (Eq. 4.17)[22] or prop-2-ynyl alcohols (Eq. 4.18)[23] react with nitroalkenes in the presence of *t*-BuOK to give the furans. Anionic domino transformations induced by the addition of alkoxides to nitroalkenes proceed with high diastereoselectivity due to allylic 1.3-strain.[22] The reduction of the nitro group in the products of Eq. 4.18 with $SmI_2$ affords 3,6-dihydro-1,2-oxazines (Eq. 4.19). The cleavage of the N-O bond of the product generates 1,4-bifunctional groups.[24a] The [2,3]sigmatropic rearrangement of the allylic nitro compounds is also possible.[24b] Such anionic domino transformations have been reviewed.[25]

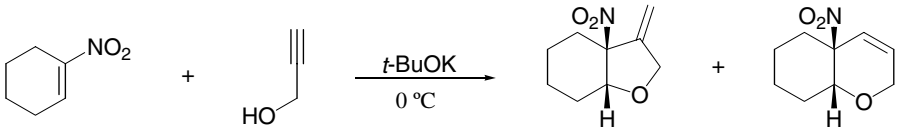



100%

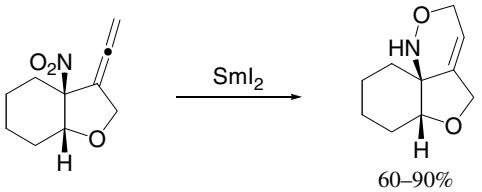
(4.16)




70–78% (4.17)



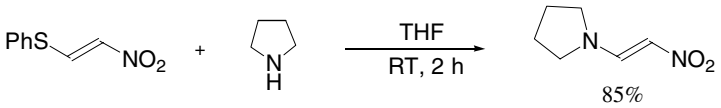

78% (5-*exo*/6-*endo* = 1.7/1) (4.18)



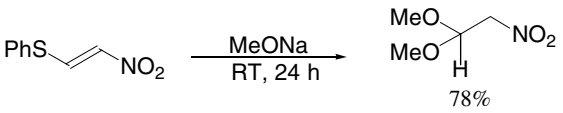

60–90% (4.19)

The addition-elimination reaction of hetero-atom-substituted nitroalkenes provides functionalized derivatives of unsaturated nitro compounds.[26] Nitroenamines are generally prepared from α-nitro ketones and amines (see Chapter 5 regarding acylation of nitro compounds).[26]

The addition of alkoxides to 2-nitro-1-phenylthio-1-alkenes affords β-nitro-aldehyde acetals.[27d] The reaction of the same nitroalkenes with amines gives nitroenamines.[27c] They are important intermediates for organic synthesis and are generally prepared by the reaction of nitroalkanes with triethylorthoformate in the presence of alcohols or secondary amines.[27a–c] The methods of Eqs. 4.20 and 4.21 have some merits over the conventional methods, for variously substituted β-nitro-aldehydes acetals or nitroenamines are readily prepared by these methods.

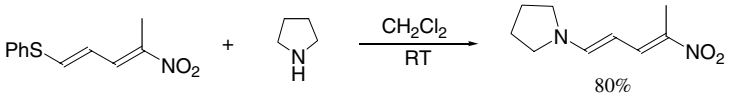



85% (4.20)



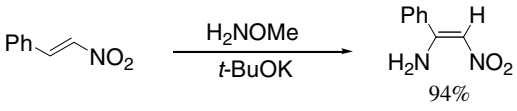

78% (4.21)

Interesting push-pull dienes, 1-dialkylamino-4-nitro-1,3-butadienes, are prepared by the application of this addition-elimination reaction. (Eq. 4.22).[28]



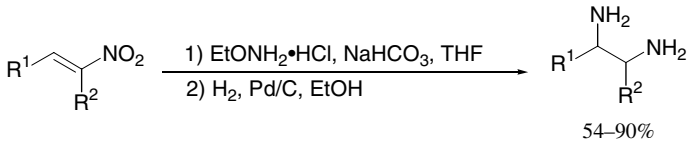

80% (4.22)

A new synthesis of β-nitroenamines by amination of nitroalkenes with methoxyamine in the presence of base is reported (Eq. 4.23).[29]



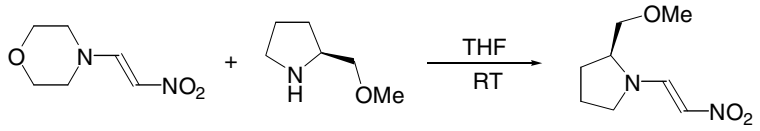

(4.23)

The Michael addition of a nitrogen-centered nucleophile to nitroalkenes affords compounds that may serve as precursors of vicinal diamines, since the nitro group can be reduced to an amino function by reduction. The very convenient method for the preparation of 1,2-diamines is developed by the addition of *O*-ethylhydroxylamines to nitroalkenes followed by reduction with $H_2$ in the presence of Pd/C (Eq. 4.24).[30]



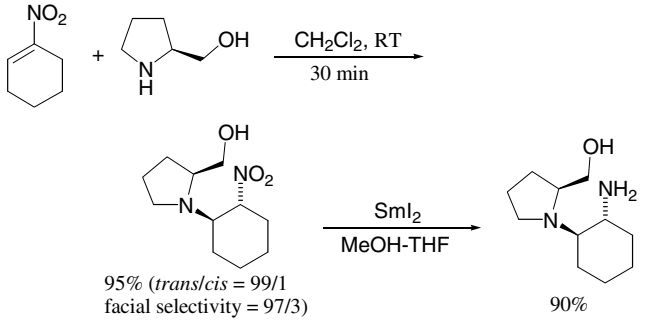

(4.24)

The conjugate addition of chiral-nitrogen nucleophiles to nitroalkenes provides access to chiral compounds having nitrogen functionalities on vicinal carbon atoms. Various natural products belong to this class of compounds such as biotin, penicillin, and several amino acids that are components of the peptide antibiotics. Chiral nitrogen nucleophiles, *(S)*-2-methoxymethylpyrrolidine (SMP) and its enantiomer (RMP) have been used for this process.[30] Fuji and Node developed an elegant method for asymmetric synthesis using (*S*)-2-methoxymethylpyrrolidine and nitro enamines,[118] which is discussed in Section 4.2 (Eq. 4.25).



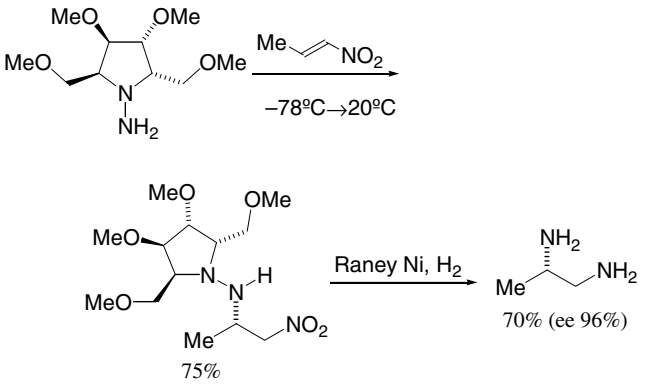

(4.25)

Amino alcohols like (*S*)-prolinol react with nitroalkenes very rapidly with very high facial selectivity.[31] Rapid and stereoselective reduction of the nitro function is essential for the conversion of the products to 1,2-diamine derivatives with the retention of the configuration. Samarium diiodide is recommended in the stereoselective reduction of thermally unstable 2-aminonitroalkanes to give a range of useful 1,2-diamines (Eq. 4.26).[32]



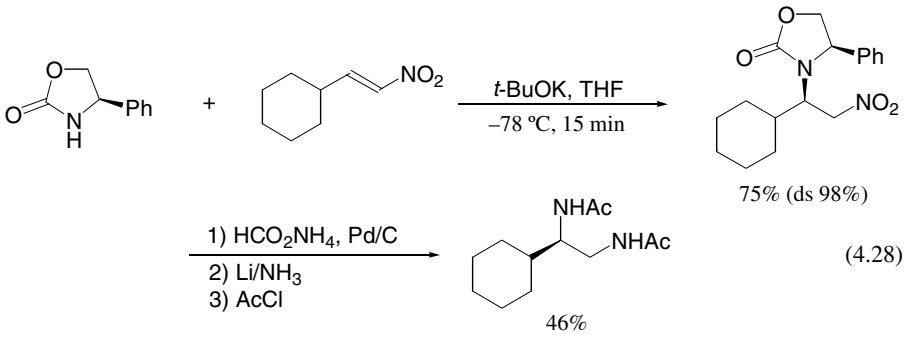

(4.26)

The asymmetric synthesis of 1,2-diamines using (2*S*,3*R*,4*R*,5*S*)-1-amino-3,4-dimethoxy-2,5-bis(methoxymethyl)pyrrolidine with high enantiomeric excess (93–96% ee) has been developed, as in Eq. 4.27.[33]



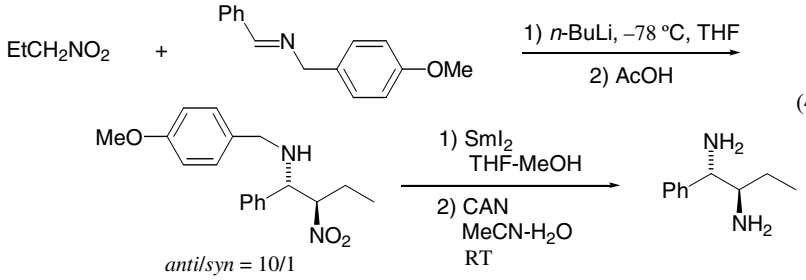

(4.27)

The conjugate addition of *(R)*- or *(S)*-4-phenyl-2-oxazolidinone to nitroalkenes is catalyzed by *t*-BuOK at –78 °C to give the addition product with excellent diastereoselectivity, the products are converted into vicinal diamines (Eq. 4.28).[34]



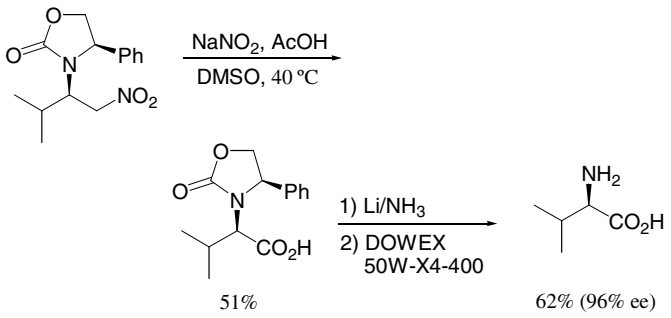

(4.28)

An alternative method for the stereoselective preparation of 1,2-diamines is shown in Eq. 4.29, in which the addition of nitroalkanes to imines is used as a key reaction.[35]



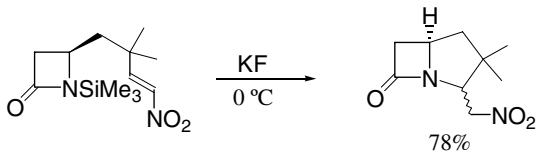

(4.29)

The products of the conjugate addition of (*R*)-4-phenyl-2-oxazolidinone to nitroalkenes are converted into D-α-amino acids with high enantiomeric purity (Eq. 4.30).[36]



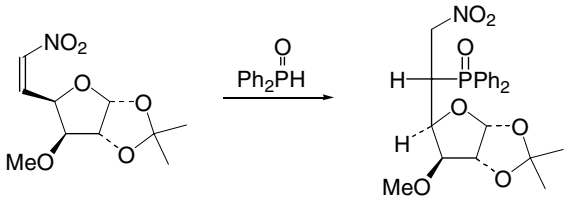

(4.30)

An intramolecular Michael type reaction of a nitrogen nucleophile to nitroalkene, as shown in Eq. 4.31, provides a useful method for the preparation of 2,2-dimethyl-1-carbapenam.[37]



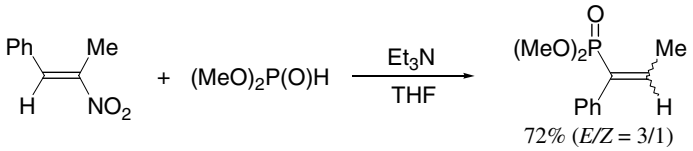

(4.31)

The Michael addition of phosphine nucleophiles to nitroalkenes provides novel β-nitro phosphonates, as in Eq. 4.32.[38] Yamashita and coworkers have shown that the nucleophilic addition of $Ph_2POH$ to chiral nitroalkenes derived from sugars proceeds stereoselectively to the 5-(*S*)-isomer (Eq. 4.32) in high diastereoselectivity (ds 11:1).




(4.32)

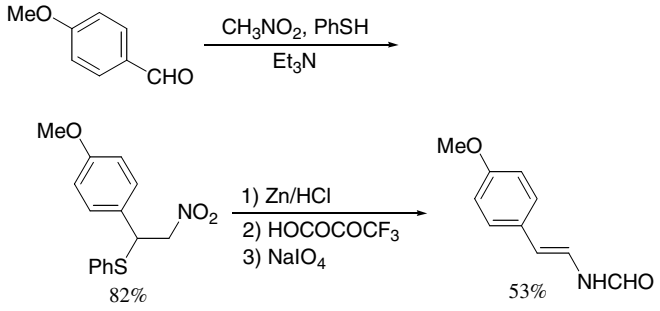
The base-catalyzed reaction of dialkyl phosphite with nitroalkenes results in the formation of alkenyl phosphonates (Eq. 4.33).[39]




(4.33)

Combining, in tandem, the nitro-aldol reaction with the Michael addition using thiophenol is a good method for the preparation of β-nitro sulfides as shown in Eqs. 4.2 and 4.3. This reaction is applied to a total synthesis of tuberine. Tuberine is a simple enamide isolated from *Streptomyces amakusaensis* and has some structural resemblance to erbastatin, an enamide which has received much attention in recent years as an inhibitor of tyrosine-specific kinases. The reaction of *p*-anisaldehyde and nitromethane in the presence of thiophenol yields the requisite β-nitro sulfide, which is converted into tuberine via reduction, formylation, oxidation, and thermal elimination of

the sulfoxide (Eq. 4.34).[40] The selective reduction of β-nitrostyrenes to β-aminostyrene derivatives provides a direct method for the preparation of the same enamides, but the reduction of nitroalkenes leads to a formation of complex products involving carbonyl compounds (see Chapter 6).



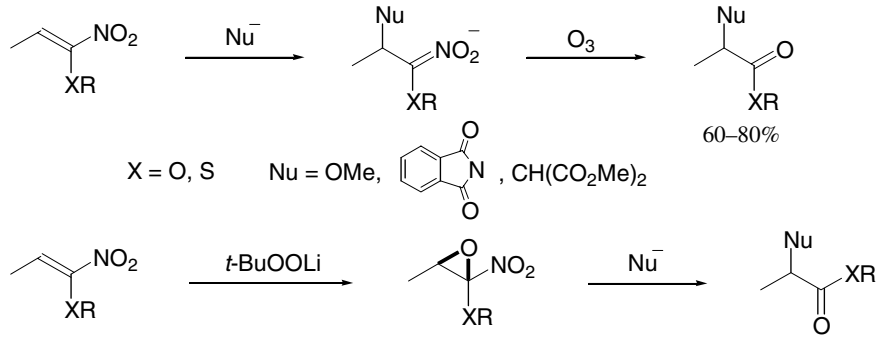

(4.34)

1-Nitro-2,2-bis(methylthio)ethylene is a useful reagent for the preparation of various heterocycles, which is described in Chapter 10.

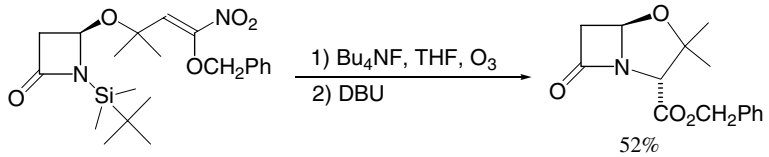
### 4.1.2 Conjugate Addition of Heteroatom Nucleophiles and Subsequent Nef Reaction

Barrett and coworkers have explored hetero-substituted nitroalkenes in organic synthesis. The Michael addition of nucleophiles to 1-alkoxynitroalkenes or 1-phenylthionitroalkenes followed by oxidative Nef reaction (Section 6.1) using ozone gives α-substituted esters or thiol esters, respectively.[41] As an alternative to nucleophilic addition to 1-(phenylthio)-nitroalkenes, Jackson and coworkers have used the reaction of nucleophiles with the corresponding epoxides (Scheme 4.4).[42] Because the requisite nitroalkenes are readily prepared by the Henry reaction (Chapter 3) of aldehydes with phenylthionitromethane, this process provides a convenient tool for the conversion of aldehydes into α-substituted esters or thiol esters.

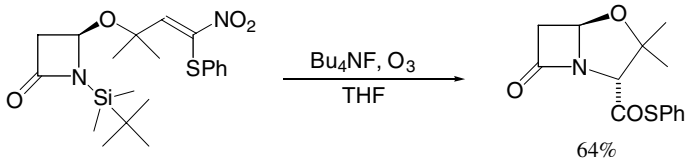
1-(Benzyloxy)nitroalkene is useful for the synthesis of bicyclic β-lactam systems and has been applied for the construction of an oxapenam (Eq. 4.35).[43] Desilylation and cyclization take place on treatment of *N*-silylated nitroalkene with $Bu_4NF$ to give the nitronate of the bicyclic β-lactam, which is treated with ozone in situ to give the benzyl ester of oxapenam. When (phenylthio)nitromethane is used instead of (benzyloxy)nitromethane, the phenylthio ester of oxapenam is obtained (Eq. 4.36).[44]




**Scheme 4.4.**

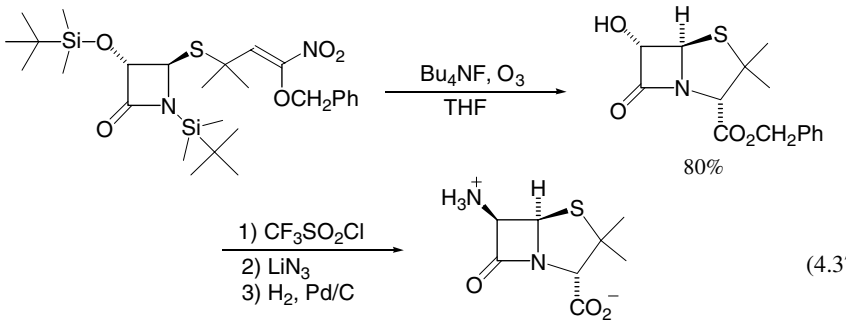



(4.35)




(4.36)

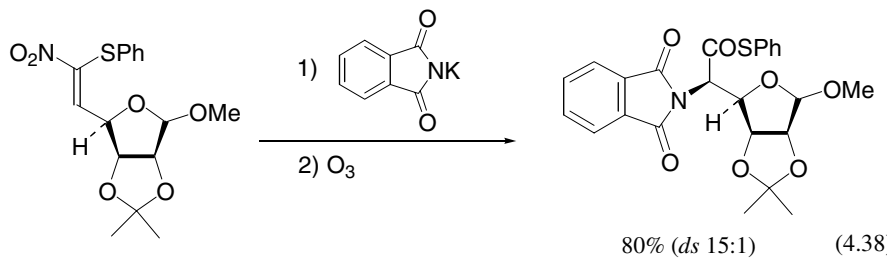
Stereocontrolled total syntheses of penicillanic acid *S,S*-dioxide and 6-aminopenicillanic acid from (*S*)-asparatic acid and (*R,R*)-tartaric acid, respectively, have been reported (Eq. 4.37).[45]



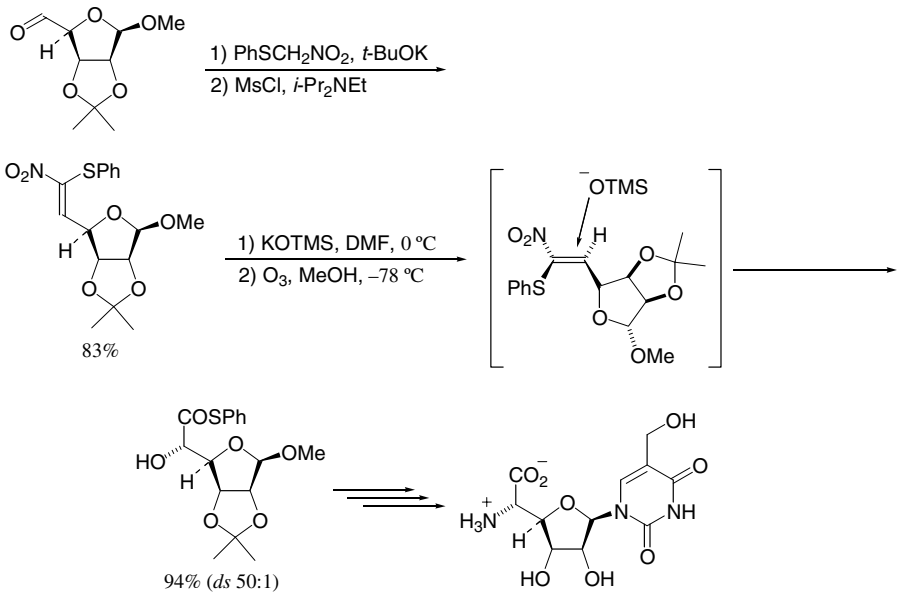

(4.37)

A stereospecific total synthesis of polyoxin C and related nucleosides is reported, in which the reaction of 1-(phenylthio)-1-nitroalkenes with nucleophiles and subsequent ozonolysis are key reactions. Addition of potassium trimethylsilanoate to 1-(phenylthio)-nitroalkenes derived from D-ribose followed by ozonolysis gives the α-hydroxy thioester, which is formed with excellent diastereoselectivity (Scheme 4.5).[46] This conformation meets the stereo-electronic requirements for antiperiplanar addition of the nucleophile with the result of high 5-(*S*) stereochemical bias in the reactions.

However, not all nucleophiles show the same bias as shown in Scheme 4.5 on addition to the nitroalkene. The product of the addition of potassium phthalimide has 5(*R*) stereochemistry (Eq. 4.38).[47] This stereoselective addition is applied for the synthesis of other related antibiotics, such as nikkomycine B.[48]

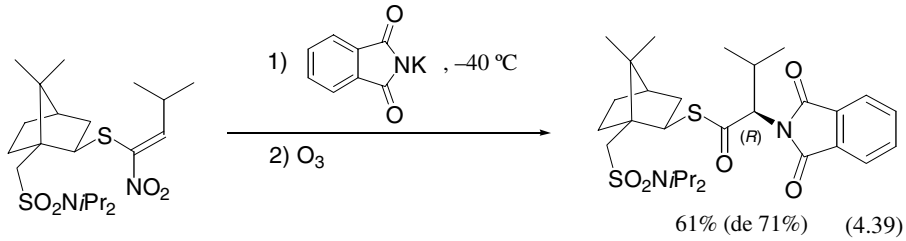



(4.38)



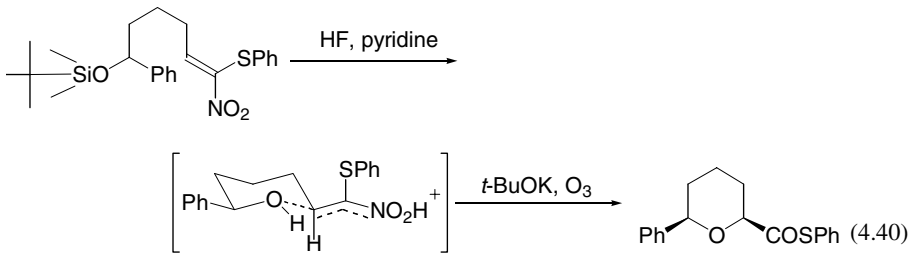

**Scheme 4.5.**

Diastereoselective conjugate addition of oxygen and nitrogen- centered nucleophiles to nitroalkenes derived from (+)-camphorsulfonic acid and ozonolysis give α-hydroxy and α-amino thiol acid derivatives (Eq. 4.39). In all cases, the (*R*)-diasteromer is formed as the major component.[49]

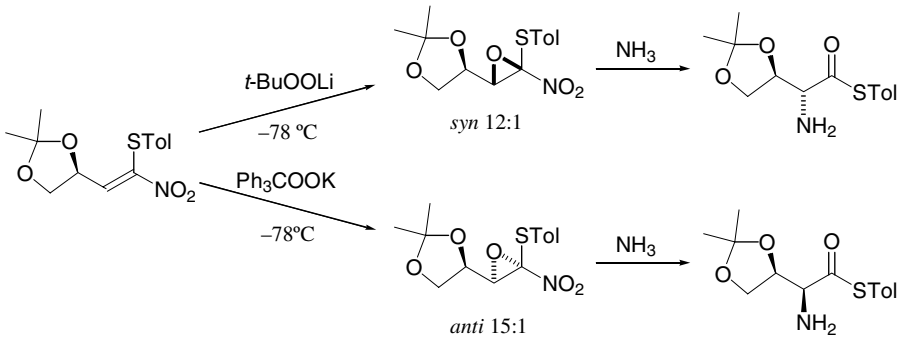



(4.39)

1-(Phenylthio)nitroalkenes are also excellent intermediates for the synthesis of other heterocyclic ring systems. For example, tetrahydropyran carboxylic acid derivatives are formed by the intramolecular addition of oxygen nucleophile to 1-(phenylthio)nitroalkene predominantly as the *cis*-isomer (9.1:1) (see Eq. 4.40). The reaction may proceed via the chair-like transition state with two pseudo-equatorial substituents.[50]




(4.40)



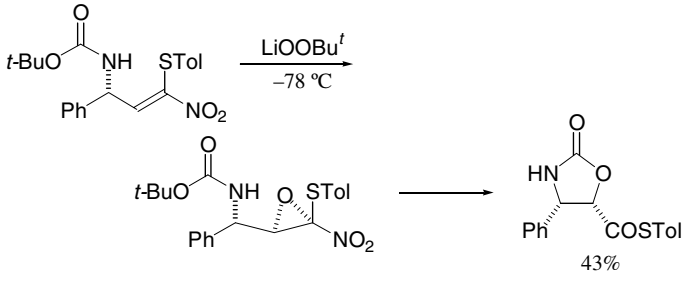

**Scheme 4.6.**

Jackson and coworkers have used a new approach to the synthesis of β-hydroxy-α-amino acids using (arylthio)nitrooxiranes. D-Isopropylideneglyceraldehyde is converted into the corresponding 1-arylthio-1-nitroalkene, which is a key material for stereoselective synthesis of β,γ-dihydroxyamino acids (Scheme 4.6). The key step is stereoselective nucleophilic epoxidation of the 1-arylthio-1-nitroalkene. *Syn* and *anti* epoxides are selectively obtained by appropriate choice of epoxidation reagent.[51]

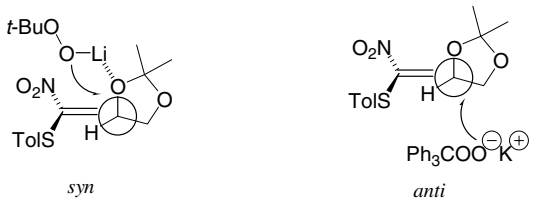
The rationalization of stereoselectivity is based on two assumptions. (1) The 1-arylthio-1-nitroalkenes adopt a reactive conformation in which the allylic hydrogen occupies the inside position, minimizing 1,3-allylic strain. (2) The epoxidation reagent can then either coordinate to the allylic oxygen (in the case of Li), which results in preferential *syn* epoxidation or in the absence of appropriate cation capable of strong coordination (in the case of K); steric and electronic effects play a large part, which results in preferential *anti* epoxidation (Scheme 4.7).[52]

Extension of this strategy enables syntheses of both protected D-threonine and L-allothreonine, in which reagent-controlled stereoselective epoxidation of a common intermediate is the key step (Scheme 4.8).[53]

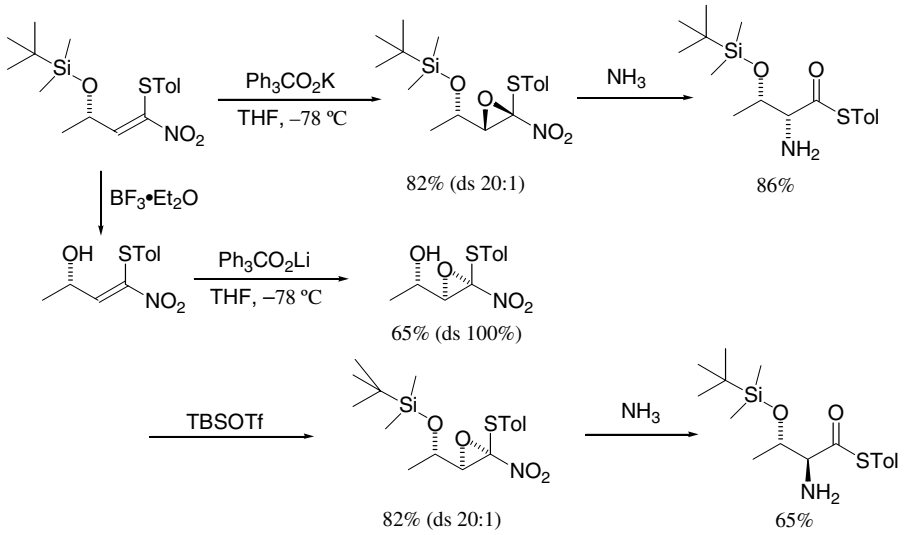
The stereoselective synthesis of *anti*-β-amino-α-hydroxy acid derivatives using nucleophilic epoxidation of 1-arytlthio-1-nitroalkenes has been reported (Eq. 4.41).[54]




(4.41)

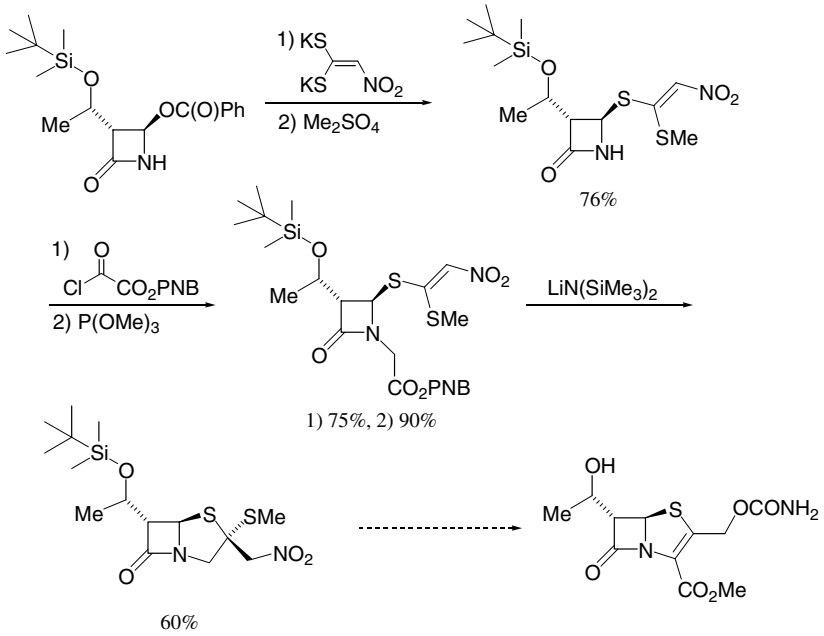



**Scheme 4.7.**




**Scheme 4.8.**

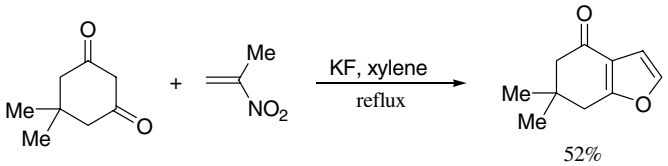
An elegant synthesis of (5*R*, 6*S*, 8*R*)-6-(α-hydroxyethyl)-2-(hydroxymethyl)penem-3-carboxylic acid has been accomplished by the strategy based on the Michael addition and Nef reaction (Scheme 4.9).[55]



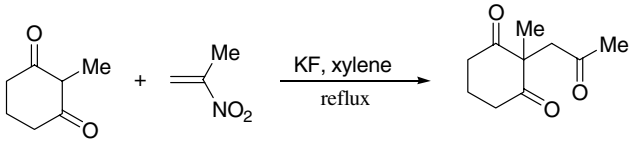

**Scheme 4.9.**

### 4.1.3 Conjugate Addition of Carbon-Centered Nucleophiles

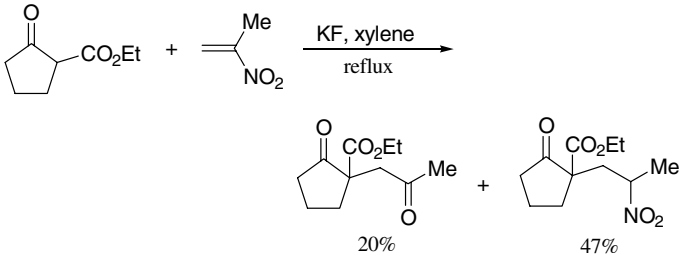
***4.1.3a Active Methylene Compounds*** Nitroalkenes are powerful Michael acceptors that can serve as synthons of the type $^{+}$C-C-$NH_2$ and $^{+}$C-(C=O)R. Classically, the reactions of nitroalkenes with carbon-centered nucleophiles have been limited to reactions carried out under mildly basic conditions using relatively acidic reaction partners such as malonate derivatives and 1,3-diketones.[56] The Michael addition of such active methylene compounds to nitroalkenes is catalyzed by various bases, including ROM (M = metal), triton B, and triethylamine. For example, the reaction of acetyl acetone or ethyl acetate with nitrostyrene proceeds in the presence of catalytic amounts of triethylamine at room temperature to give the adduct in 98% or 78% yield, respectively. The addition products are useful intermediates for the preparation of furans or pyrroles.[57] Metal complex catalysts such as $Ni(acac)_2$ are also effective to induce the Michael addition of acetyl acetone to nitrostyrene.[58] Yoshikoshi and coworkers have found that the potassium fluoride-catalyzed addition of 1,3-dicarbonyl compounds to nitroalkenes leads to the formation of furans (Eq. 4.42) or Michael adducts and their Nef products (Eqs. 4.43 and 4.44), depending on substrates and conditions.[59]




(4.42)

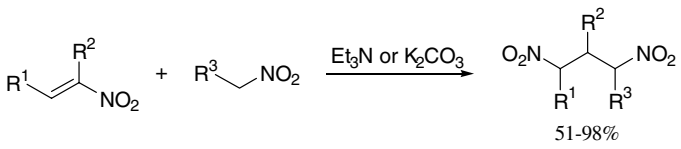



(4.43)

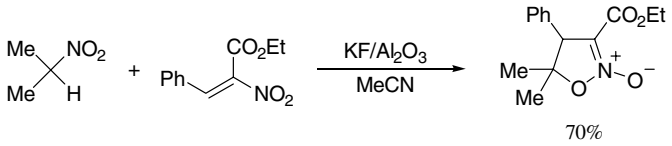



(4.44)

The Michael addition of nitroalkanes to nitroalkenes is catalyzed by triethylamine to give 1,3-dinitro compounds (Eq. 4.45).[60] In some cases, the intramolecular displacement of the nitro group takes place to give cyclic nitronates (Eq. 4.46).[61]

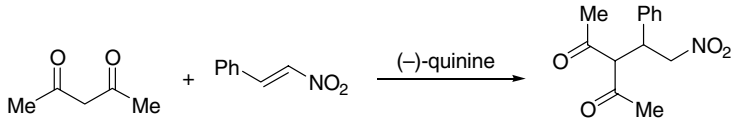



(4.45)



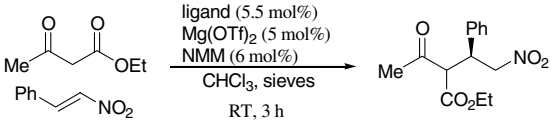

70% (4.46)

The asymmetric Michael addition of 1,3-dicarbonyl compounds to nitrostyrene is promoted by chiral alkaloid catalysts to give the addition products in good chemical yield, but the enantioselectivity is rather low (Eq. 4.47).[62]



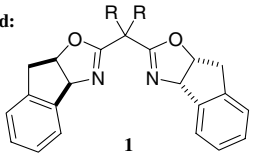

89% (16% ee) (4.47)

Recently, very effective asymmetric conjugate addition of 1,3-dicarbonyl compounds to nitroalkenes has been reported, as shown in Scheme 4.10. The reaction of ethyl acetoacetate with nitrostyrene is carried out in the presence of 5 mol% of the preformed complex of magnesium triflate and chiral bis(oxazoline) ligands and a small amount of *N*-methylmorpholine (NMM) to give the adduct with selectivity of 91%. The selectivity depends on ligands. The effect of ligands is presented in Scheme 4.10.[63]

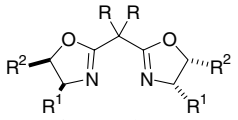



| Entry | Ligand | Selectivity (%) | Conversion (%) |
|---|---|---|---|
| 1 | **1a** | 95 | 96 |
| 2 | **1b** | 65 | 33 |
| 3 | **1c** | 77 | 44 |
| 4 | **2c** | 58 | 9 |
| 5 | **3c** | 0 | 7 |
| 6 | **4c** | 76 | 15 |
| 7 | **4a** | 82 | 99 |

**ligand:**




**1**

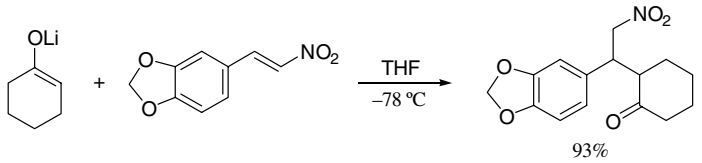



**2**: $R^1$ = Ph, $R^2$ = H
**3**: $R^1$ = $CMe_3$, $R^2$ = H
**4**: $R^1$ = $R^2$ = Ph
**a**: R = -$CH_2CH_2$-; **b**: R = H, **c**: R = Me

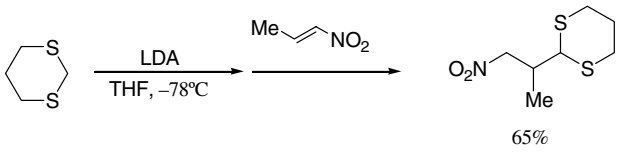
**Scheme 4.10.**

***4.1.3b Enolates Derived From Ketones and Esters and Carbanions Stabilized by Sulfur*** In recent years, a variety of procedures for the successful addition of simple ketones or esters to nitroalkenes have been developed. Seebach and coworkers have reported

the Michael-type addition of lithium enolates, sulfur-substituted organolithium reagents, and other reactive carbanions to nitroalkenes. Some typical examples are presented in Eqs. 4.48 and 4.49.[64a]



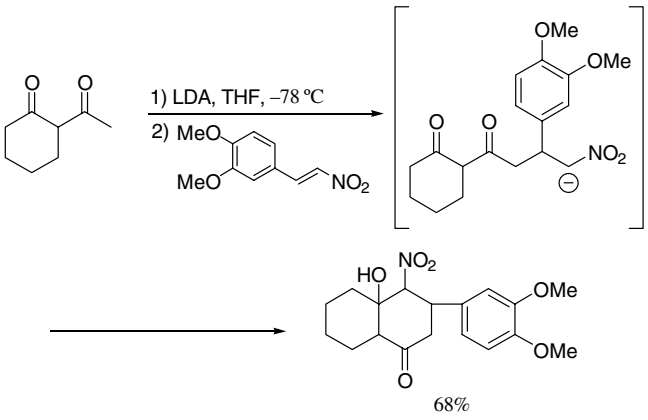

(4.48)



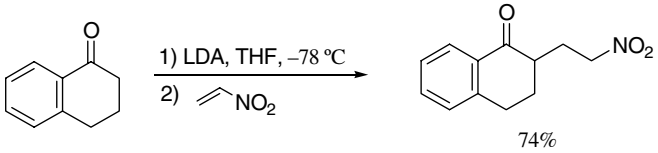

(4.49)

Dianions or trianions derived from 1,3-dicarbonyl compounds react with nitroalkenes at low temperature to give the adduct, which undergoes a nitro-aldol type cyclization (Eq. 4.50).[64c]

Nitroethylene is extremely reactive and sensitive to strong basic conditions, but various ketone and ester enolates undergo alkylation with nitroethylene at low temperature (Eq. 4.51[65] and Table 4.1).




(4.50)




(4.51)

Nitroalkenes react with lithium dianions of carboxylic acids or with lithium enolates at –100 °C, and subsequent treatment of the Michael adducts with aqueous acid gives γ-keto acids or esters in a one-pot operation, respectively (Eq. 4.52).[66] The sequence of Michael addition to nitroalkenes and Nef reaction (Section 6.1) provides a useful tool for organic synthesis. For example, the addition of carbanions derived from sulfones to nitroalkenes followed by the Nef reaction and elimination of the sulfonyl group gives α,β-unsaturated ketones (Eq. 4.53).[67]

**Table 4.1. Michael Addition to Nitroalkenes**

| R-H | Base | Nitroalkene | Product | Yield (%) | Reference |
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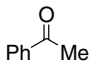
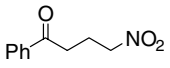
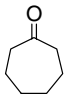
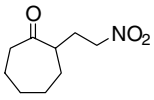
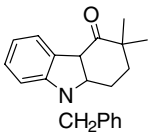
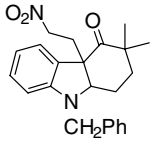
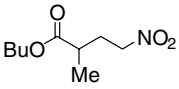
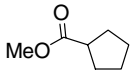
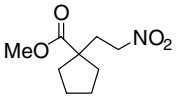
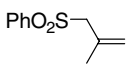
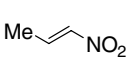
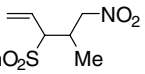
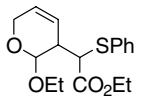
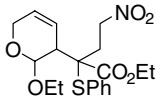
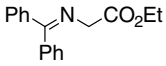
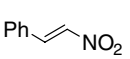
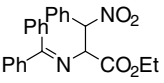
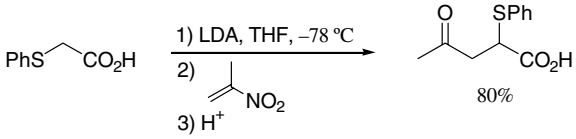
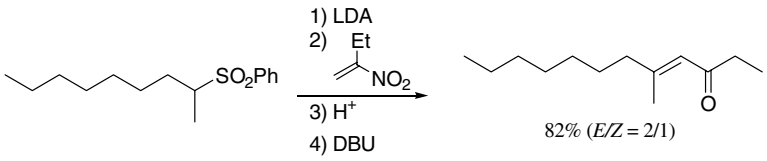
|  | LDA | |  | 81 | 65 |
|  | LDA | |  | 72 | 65 |
|  | LDA | |  | 62 | 71 |
| | LDA | |  | 57 | 65 |
|  | LDA | |  | 94 | 65 |
|  | LDA |  |  | 90 | 72 |
|  | LDA | |  | 85 | 73 |
|  | LDA |  |  | 66 | 74 |

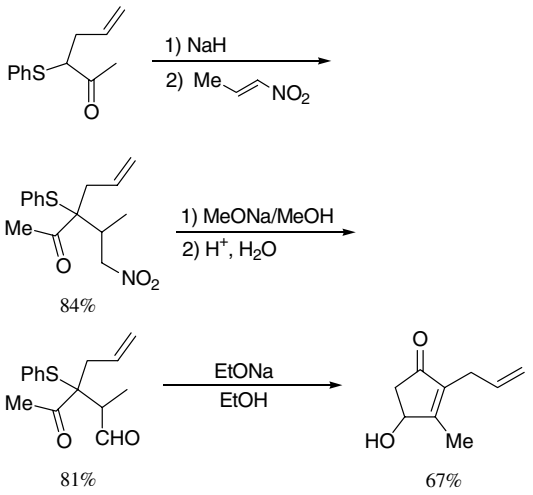



(4.52)



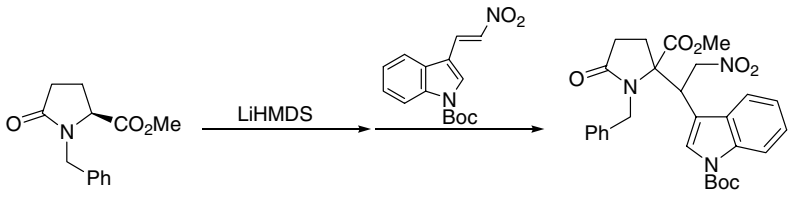

(4.53)

A simple synthesis of allethrolone, the alcohol component of the allethrine (commercially important insecticide), is shown in Scheme 4.11. The conjugated addition of 3-phenylthio-5-hexene-2-one to 1-nitro-1-propene followed by the Nef reaction and aldol condensation gives allethrolone in good yield.[68]

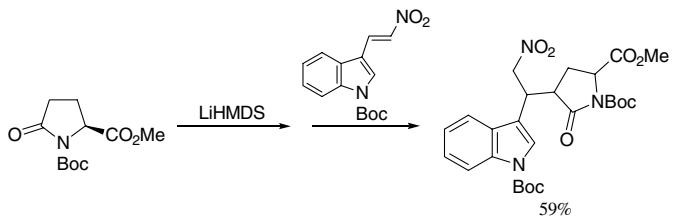



**Scheme 4.11.**

Pyroglutamic acid is a useful starting material for the synthesis of several natural products, such as pyrrolidine alkaloids, kainoids, and other unnatural amino acids. Interesting chemoselective Michael additions of anions derived from pyroglutamates have been reported (see Eqs. 4.54 and 4.55).[69]



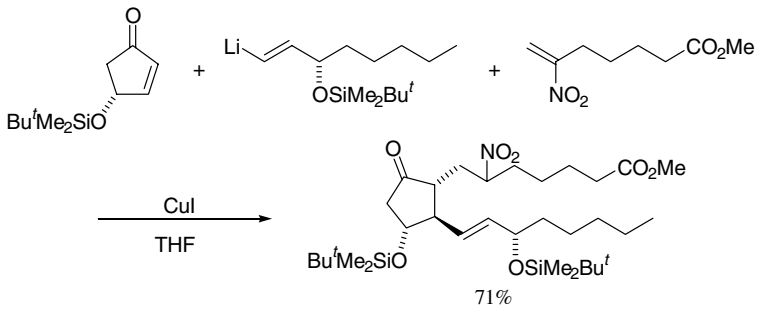

(4.54)




(4.55)

A short synthesis of prostaglandin derivatives via a three component coupling reaction is reported, in which the enolates are trapped with nitroalkenes. The nitro group is removed via

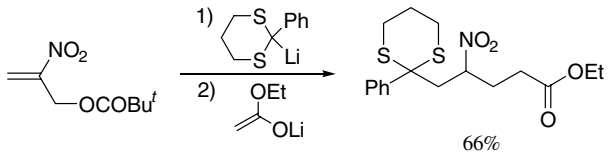
radical denitration (Section 7.2) or is transformed into the carbonyl group by the Nef reaction (Section 6.1) (Eq. 4.56).[70]




71% (4.56)

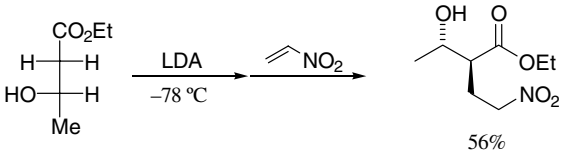
A variety of carbanions have been employed for the conjugate addition to nitroalkenes; recent results are shown in Table 4.1.

Seebach and coworkers have developed a useful multiple coupling reaction using nitropropenyl pivalate. This opens a possibility of successive introduction of two different nucleophiles, as exemplified in Eq. 4.57 (see also Section 3.2).[75]




66% (4.57)

Asymmetric Michael addition of chiral enolates to nitroalkenes provides a useful method for the preparation of biologically important compounds. The Michael addition of doubly deprotonated, optically active β-hydroxycarboxylates to nitroalkenes proceeds with high diastereoselectivity to give *erythro*-hydroxynitroesters (Eq. 4.58).[76]

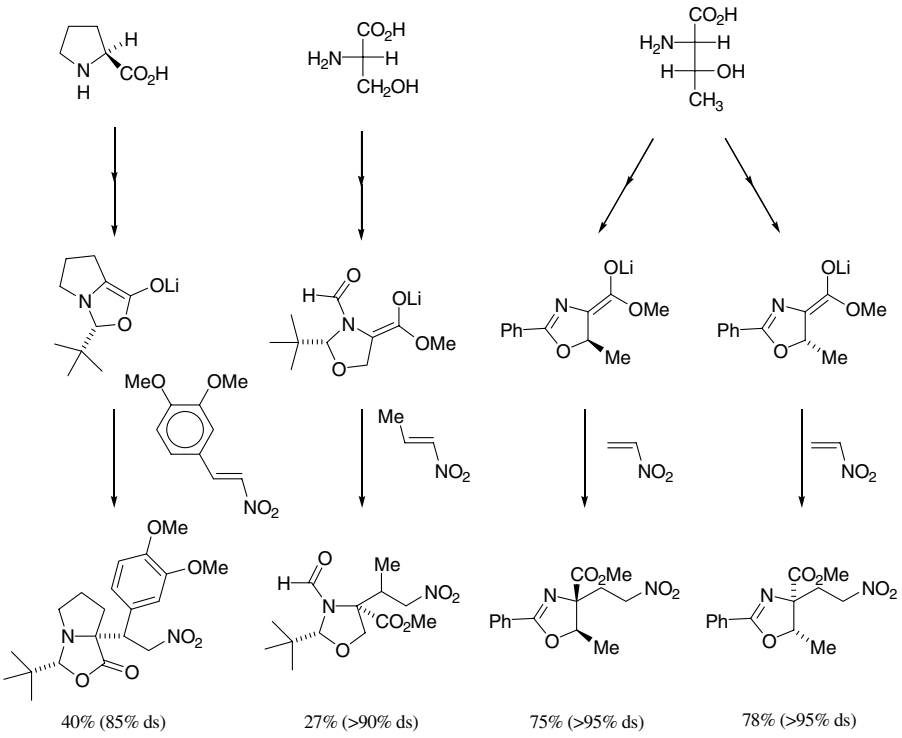



56% (4.58)

Chiral enolates of 1,3-dioxalan-4-ones, methyl 1,3-oxazolidine-4-carboxylates, and 1,3-imidazolidine-4-ones derived from chiral natural sources such as (*S*)-proline, (*S*)-serine, and (*S*)-threonine are added to nitroalkenes in high diastereoselectivity (Scheme 4.12).[77]

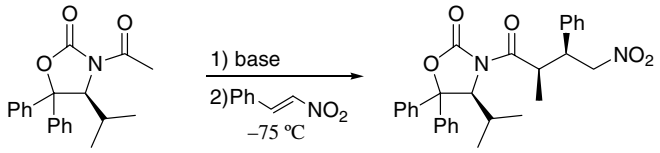
Enantioselective synthesis of the antidepressant rolipram can be done by the asymmetric Michael addition of the enolate of *N*-acetyloxazolidone to nitrostyrene. Chirally branched pyrrolidones like rolipram are highly active antidepressants with novel postsynaptic modes of action. The synthesis is shown in Scheme 4.13.[78]

Seebach and Brenner have found that titanium enolates of acyl-oxazolidinones are added to aliphatic and aromatic nitroalkenes in high diastereoselectivity and in good yield. The effect of bases on diastereoselectivity is shown in Eq. 4.59. Hydrogenation of the nitro products yields γ-lactams, which can be transformed into γ-amino acids. The configuration of the products is assigned by comparison with literature data or X-ray crystal-structure analysis.



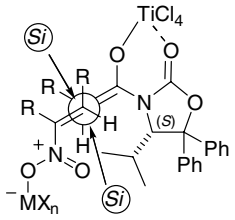

**Scheme 4.12.**

Thus, (*S*)-chiral auxiliary gives rise to combination of the trigonal centers of enolate and nitroalkene with *Si*/*Si* topicity.[79]

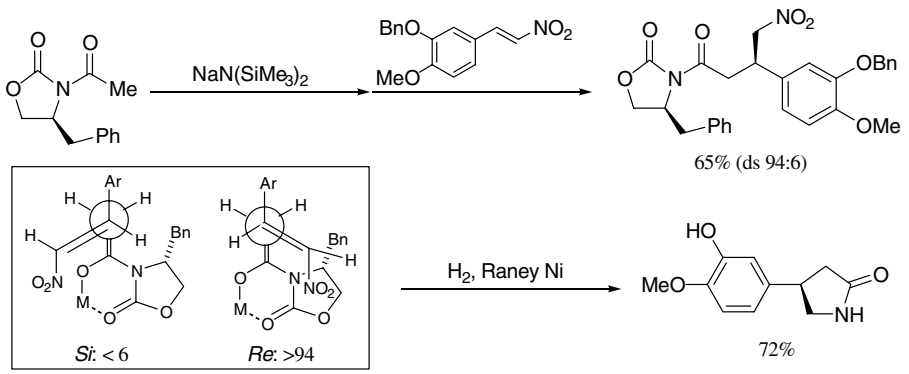



(4.59)

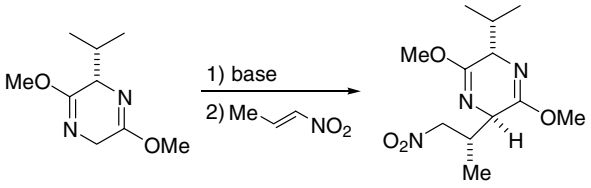
| Base/additive | Solvent | Yield (%) | ds |
|---|---|---|---|
| BuLi | THF | 58 | 90:10 |
| EtN(*i*-Pr)$_2$/2TiCl$_4$ | $CH_2Cl_2$ | 60 | >99:1 |




The titanated bislactim ethers of cyclo(L-Val-Gly-) are added to nitroalkenes with high diastereo-selectivity (Eq. 4.60).[80a] Michael addition of lactam bearing (*S*)-2-(1-ethyl-1-methoxypropyl) pyrrolidine as auxiliary on the lactam nitrogen to nitroalkenes proceeds with high selectivity (de >96%, ee >96%).[80b]



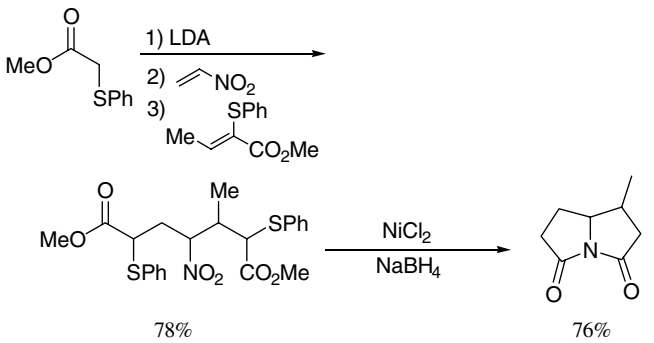

**Scheme 4.13.**




(4.60)

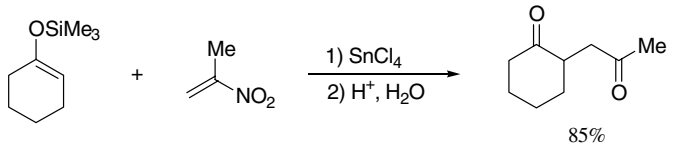
| Base/additive | Yield (%) | ds |
|---|---|---|
| BuLi | 81 | 50:42:5:3 |
| BuLi/ClTi($NEt_2$)$_3$ | 51 | 99:1 |

Nitroalkens are effective Michael acceptor B units for sequential, convenient A + B + C coupling reactions, as shown in Eq. 4.61.[81] This process is very simple and convenient to synthesize nitrogen heterocycles. Reductive cleavage of the PhS group and reduction of the nitro group to amino group can be accomplished with $NiCl_2/NaBH_4$ to give pyrrolizidinones (see Chapter 10).

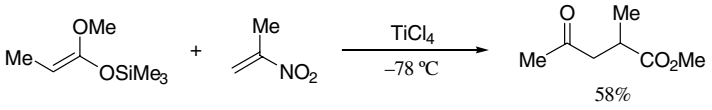



(4.61)

***4.1.3c Silyl Enolates and Enamines*** Yoshikoshi and coworkers have developed the Michael reaction of silyl enol ethers or ketene silyl acetals with nitroalkenes activated by Lewis acids. After hydrolytic treatment, 1,4-diletones and γ-keto esters are obtained (Eqs. 4.62 and 4.63).[82]

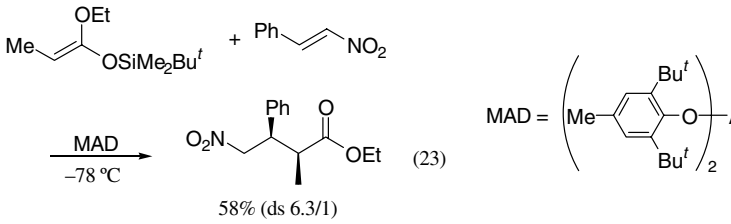



(4.62)



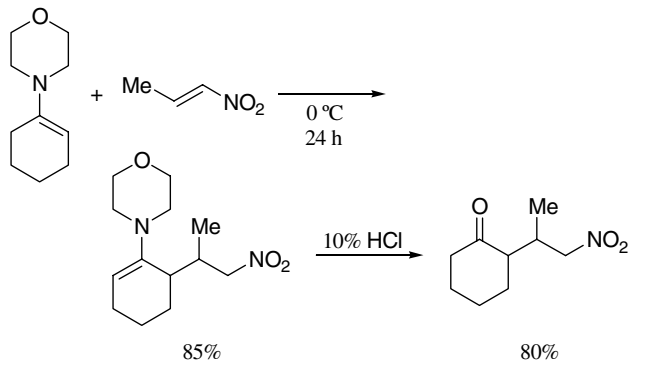

(4.63)

Alkylation of ketene silyl acetals with nitroalkenes has several limitations such as modest yield, lack of generality, and inconveniently low reaction temperatures. Tucker and coworkers have found that sterically encumbered Lewis acids such as MAD give better results than other Lewis acids (Eq. 4.64).[83]



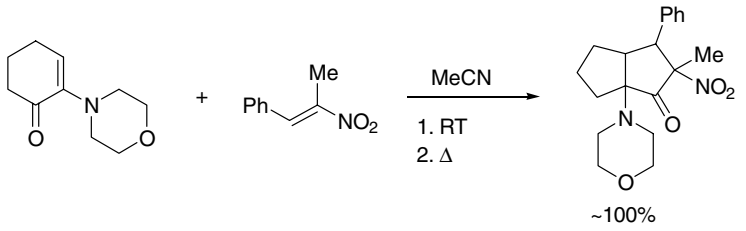

(4.64)

Valentin and coworkers have studied extensively the reaction of enamines with nitroalkenes. The reaction proceeds under mild conditions to give γ-nitroketones, which are converted into 1,4-diketones by the Nef reaction (Eq. 4.65).[84]



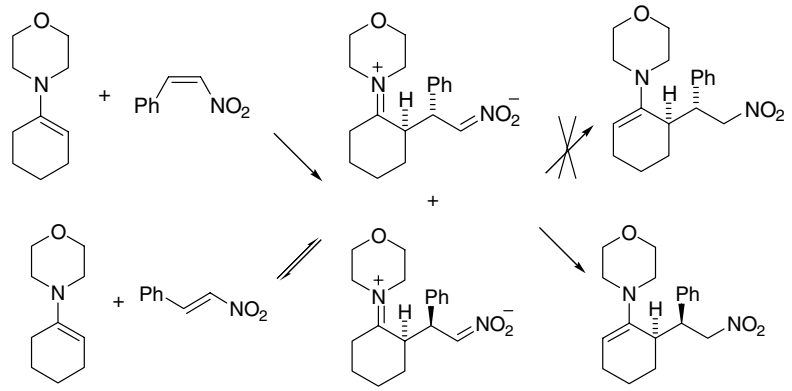

(4.65)

The reaction of enaminones with nitroalkenes gives a pentalenone system via the Michael addition and aldol reaction (Eq. 4.66).[85a] Linear α-keto enamines react with nitroalkenes to afford [3 + 2] carbocyclized products.[85b]



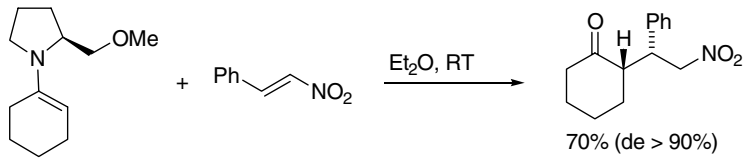

(4.66)

The Michael addition of enamines to nitroalkenes proceeds with high *syn* selectivity. The *syn* selectivity is explained by an acyclic synclinal model, in which there is some favorable interaction between the nitro group and the nitrogen lone pair of the enamine group (Eq. 4.67). [86a–b] Both *Z*- and *E*-nitrostyrenes afford the same product in over 90% diastereoselectivity.



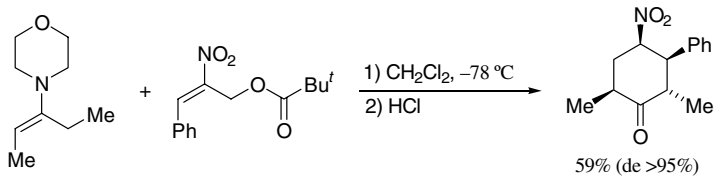

(4.67)

The chiral enamines provide the opportunity for the enantioselective Michael addition to nitroalkenes, as shown in Eq. 4.68, where the ketone is obtained as a single diastereomer with an ee >90%.[87]



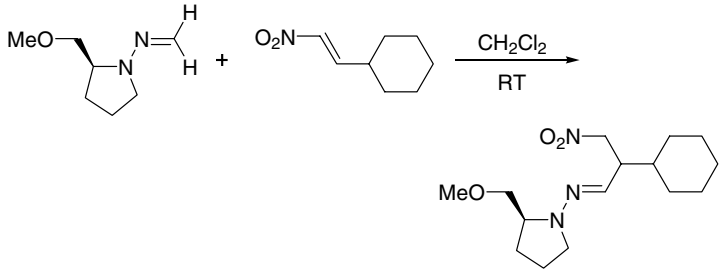

(4.68)

The reaction of enamines with 2-nitro-2-propen-1-yl pivalate gives 4-nitrocyclohexanones, which is regarded as formal [3 + 3] carbocyclization. The reaction proceeds in high diastereoselectivity (60% to >95% selectivity), see Eq. 4.69.[88] If chiral enamines such as that in Eq. 4.68 are employed, the products are obtained with high ee.




(4.69)

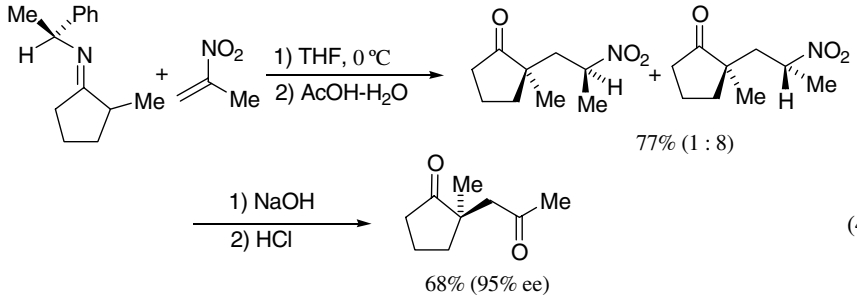
The Michael addition of formaldehyde hydrazone of (*S*)-1-amino-2-(methoxymethyl)pyrrolidine to nitroalkenes gives β-nitrohydrazones in good chemical yield and stereoselectivity (Eq. 4.70).[89]




(4.70)

88% (80% de)

The addition of 2-nitropropene to the chiral imine derived from 2-methylcyclopentanone and (*S*)-1-phenylethylamine gives the adduct in high regio- and stereoselectivity (Eq. 4.71).[90] The product is converted to a chiral 1,4-diketone via the Nef reaction.

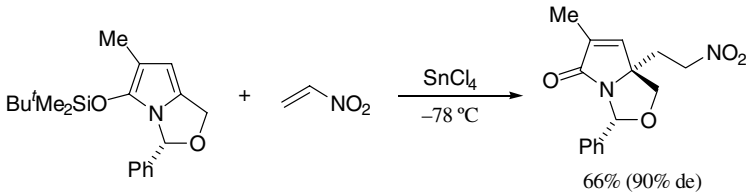



(4.71)

77% (1 : 8)

68% (95% ee)

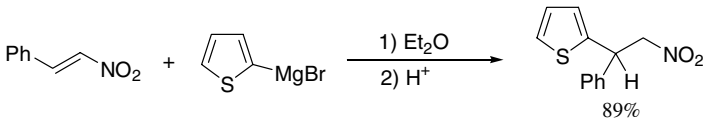
The Michael type reaction of (3*R*)-5-*t*-butyldimethysiloxy-3-phenyl-1*H*-pyrrolo[1,2-c]oxazole with nitroethylene proceeds in the presence of Lewis acid to give the alkylated product in good chemical yield and diastereoselectivity. In the case of nitroethylene, the Diels-Alder type transition state is favored to give the *syn*-adduct selectively (Eq. 4.72).[91]



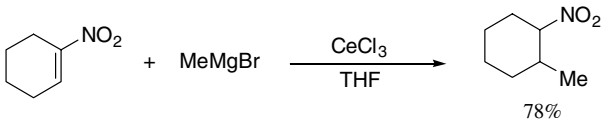

(4.72)

66% (90% de)

***4.1.3d Organometallic Reagents*** The conjugate addition of various organometallic reagents such as RLi, RMgX, $R_2Zn$, $R_2CuLi$, and $R_3Al$ to nitroalkenes provides a useful method for nitro-alkylation. As the nitro group is transformed into various functional groups, this type of addition has been extensively used in organic synthesis. The 1,4-addition of Grignard reagents to β-nitrostyrene gives 1,1-diarylnitroethanes (Eq. 4.73).[92] Addition of cerium chloride improves the yield of addition of RMgX to nitroalkenes (Eq. 4.74).[93]



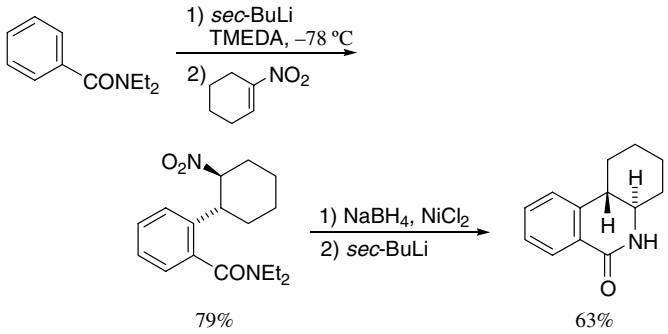

(4.73)




(4.74)

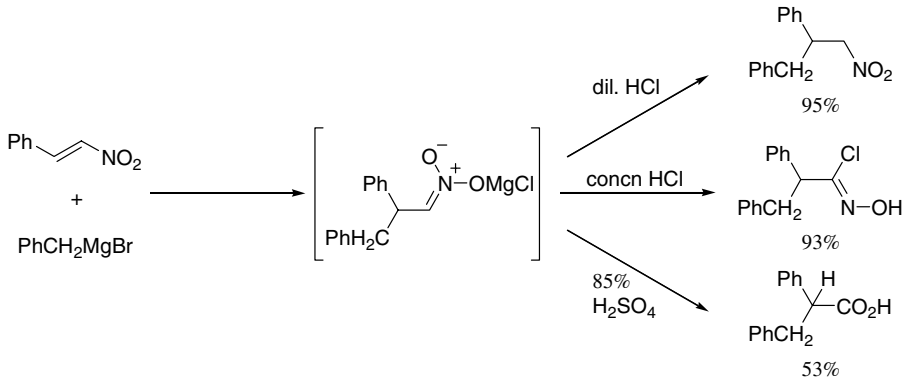
The 1,4-addition of RMgX or RLi to nitroalkenes produces nitronate intermediates, which are converted into nitroalkanes, nitrile oxides (oxime chlorides), or carboxylic acids, depending on the conditions of hydrolysis (Scheme 4.14).[94]

The 1,4- addition of an *ortho*-lithiated benzamide to 1-nitrocyclohexene has been used for synthesis of pancratistatin models (Eq. 4.75).[95]

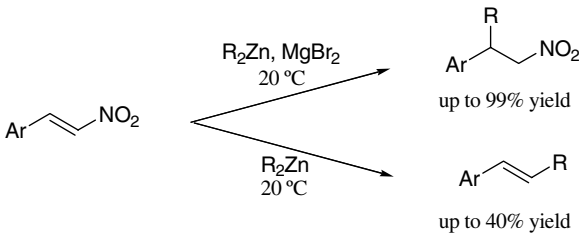



(4.75)

Seebach and coworkers have found that the addition of dialkylzinc to nitroalkenes is catalyzed by Lewis acids such as $MgBr_2$, $MgI_2$, and chlorotitanates.[96] However, the nitro group of nitrostyrene is replaced by alkyl groups in the absence of Lewis acids (Scheme 4.15).[97] Replacement of vinylic nitro groups by alkyl groups is unusual, for nitroalkenes are good

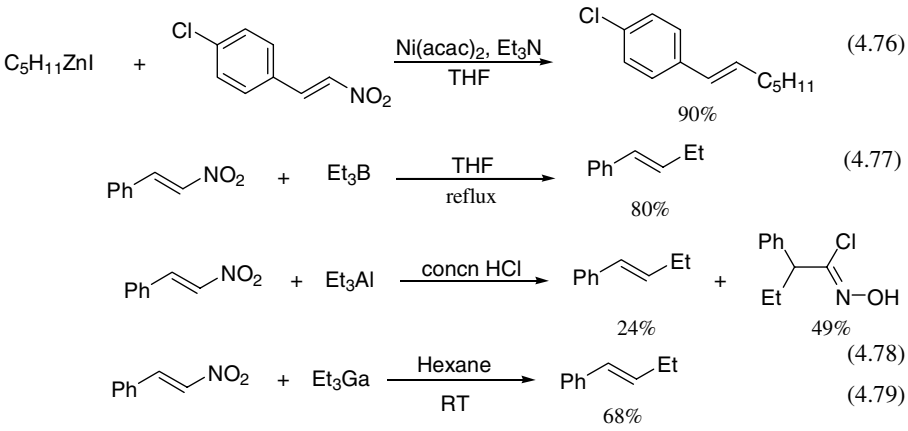



**Scheme 4.14.**

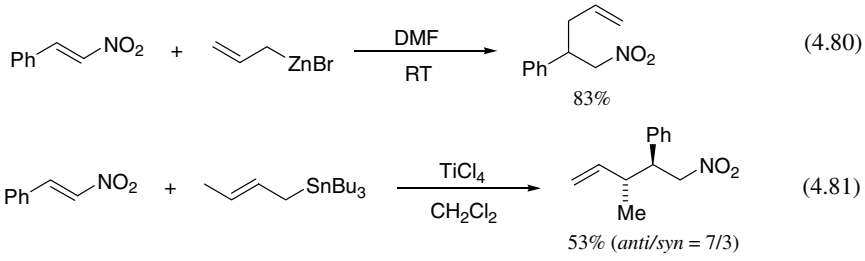



**Scheme 4.15.**

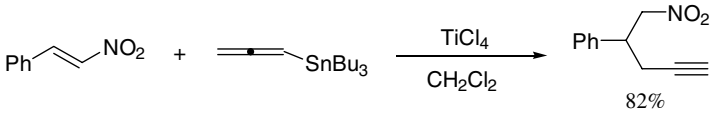
Michael acceptors and 1,4-addition of alkyl group is a normal process. The reaction mechanism is not clear, but the process via addition of alkyl radicals and subsequent elimination of $NO_2$ radical is one of the possible routes. Recently, several related reactions have been reported, as shown in Eq. 4.76[98], Eq. 4.77,[99] and Eq. 4.78,[100] in which alkyl radicals are involved. The reaction of trialkylgallium compounds with nitrostyrene gives also a similar substitution product (Eq. 4.79).[101]




β-Nitrostyrene reacts with allylzinc reagents in dry DMF at room temperature to give the addition products in excellent yield (Eq. 4.80).[102] The reaction of allyl tin compounds or allyl silanes with nitroalkenes requires the assistance of Lewis acids to give the addition products in good yield (Eq. 4.81).[103]

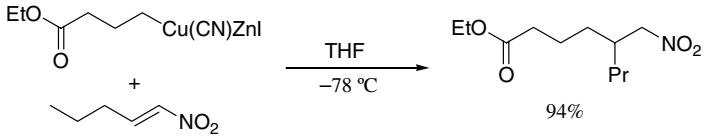



Stannylallenes react with nitroalkenes in the presence of $TiCl_4$ to give the propargylation products (Eq. 4.82).[104]



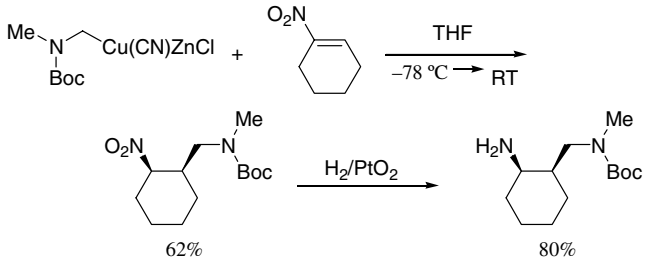

(4.82)

Knochel and coworkers have developed the addition of highly functionalized zinc-copper reagents RCu(CN)ZnI to nitroalkenes. The polyfunctionalized zinc organometallics are readily transmetalated to the copper derivatives by the addition of the THF-soluble copper salt CuCN·2LiCl. These copper reagents add to nitroalkenes in good yields, leading to highly functionalized nitroalkanes (Eq. 4.83).[105]



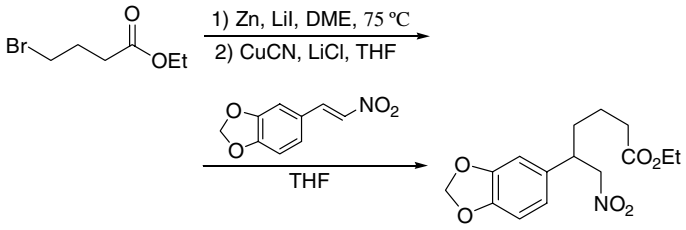

(4.83)

This procedure is applied to synthesis of 1,3-diamines by the addition of metallated *tert*-butyl *N,N*-dimethylcarbamate to nitroalkenes and subsequent reduction (Eq. 4.84).[106]



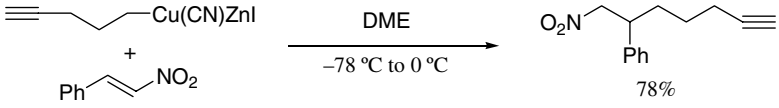

(4.84)

The Michael addition of the copper-zinc reagent derived from ethyl 4-bromobutyrate to the piperonal-derived nitroalkene proceeds cleanly to give the nitro ester, which is an intermediate for the synthesis of lycoricidine alkaloids (Eq. 4.85).[107]

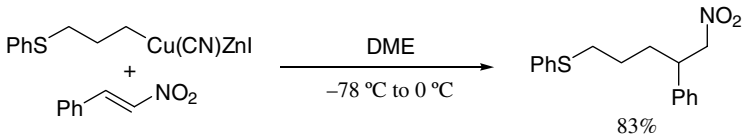



(4.85)

Reactions of zinc-copper reagents bearing acidic hydrogen and sulfur functionalities with various electrophiles, including nitroalkenes, have been reported, as shown in Eq. 4.86[108] and Eq. 4.87,[109] respectively.

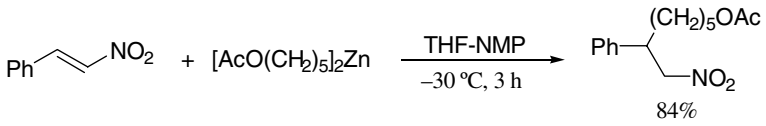



(4.86)



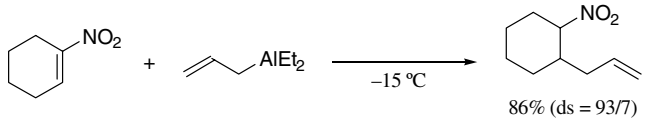

(4.87)

Dialkylzincs react efficiently with nitroalkenes in a mixture of THF and *N*-methylpyrrolidinone (NMP) to give the addition products in good yield (Eq. 4.88).[110]



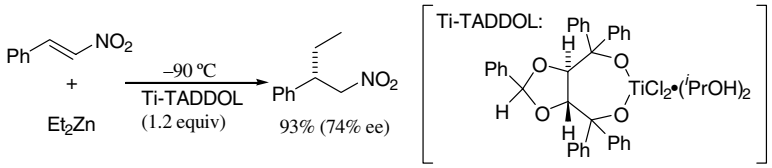

(4.88)

Organoaluminum compounds are also good nucleophiles for 1,4-addition to nitroalkenes as shown in Eq. 4.89.[111]



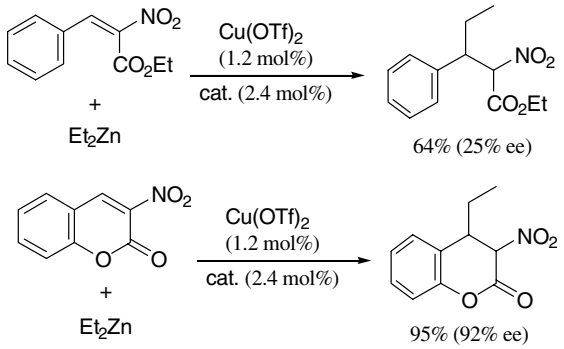

(4.89)

Seebach and coworkers have developed enantioselective conjugate additions of primary dialkylzinc reagents to 2-aryl- and 2-heteroaryl-nitroalkenes mediated by titanium-TADDOLates (Eq. 4.90).[96a] TADDOLs and their derivatives are excellent chiral auxiliaries.[96b]

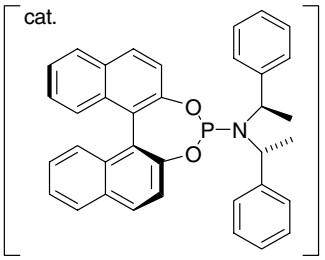



(4.90)

Feringa and coworkers have used copper (I) phosphoramidite as a catalyst for asymmetric conjugate addition of dialkyl zinc reagents to α,β-unsaturated nitroacetates. The reaction of *E,Z*-mixtures of α,β-unsaturated nitroacetates provides 1,4-addition products in excellent yields but with low ee (Eq. 4.91). High enantioselectivities (ee up to 92%) are obtained with structurally rigid 3-nitrocumarins (Eq. 4.92).[112]

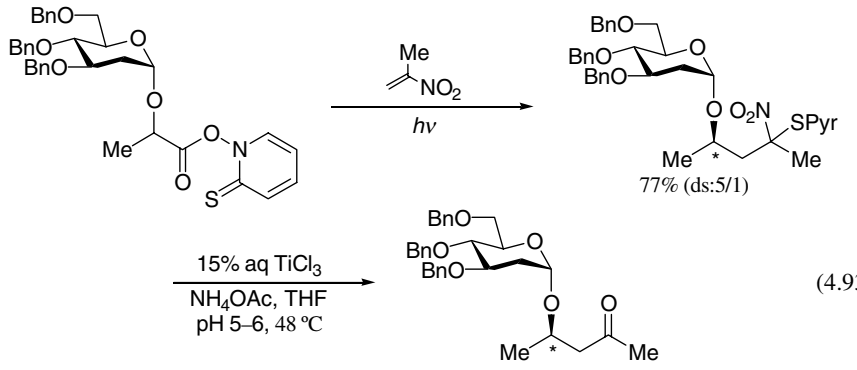



(4.91)




(4.92)

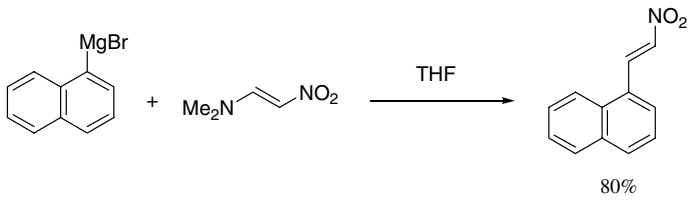
A radical approach to asymmetric aldol synthesis, which is based on the radical addition of a chiral hydroxyalkyl radical equivalent to a nitroalkene, has been reported, as shown in Eq. 4.93.[113] The radical precursor is prepared from the corresponding carboxylic acid by the Barton reaction,[114] which has been used for synthesis of new β-lactams.[115]




(4.93)

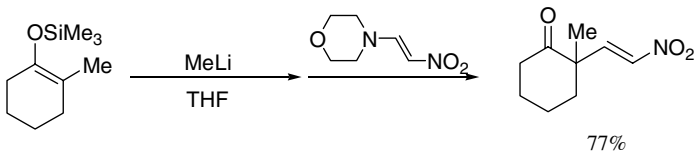
## 4.2 ADDITION AND ELIMINATION REACTION OF β̃-HETEROSUBSTITUTED NITROALKENES

Nitroalkenes with potential leaving groups in β-position such as a dialkylamino, an alkylthio, or a phenylsulfonyl group undergo addition-elimination reactions with nucleophiles. The chemistry of nitroenamines has been extensively investigated, and their potential utility in organic synthesis has been well established.[26b,116] Severin and coworkers have developed the addition of elimination reactions of nitroenamines with carbon nucleophiles in 1960–1970, as exemplified in Eq. 4.94.[117]



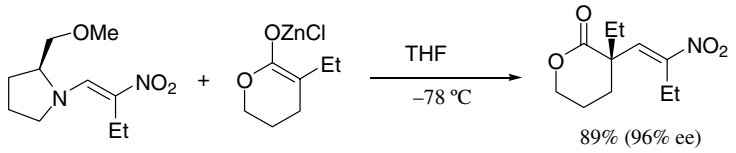

(4.94)

Node and Fuji have developed stereoselective nitroolefination of various carbonyl compounds using β-nitroenamines (Eq. 4.95).[118]



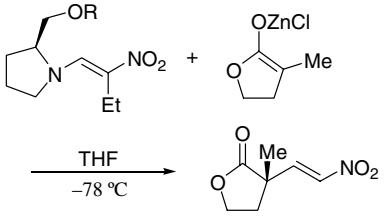

(4.95)

They have developed direct asymmetric synthesis of quaternary carbon centers via addition-elimination process. The reactions of chiral nitroenamines with zinc enolates of α-substituted-δ-lactones afford α,α-disubstituted-δ-lactones with a high ee through addition-elimination process, in which (*S*)-(+)-2-(methoxymethyl)pyrrolidine (SMP) is used as a chiral leaving group (Eq. 4.96).[119] Application of this method to other substrates such as α-substituted ketones, esters, and amides has failed to yield high ee.




89% (96% ee) (4.96)

If the chiral auxiliary in Eq. 4.96 is modified by changing MeO into more bulky groups such as trityl (Tr) or *t*-butyldimethylsilyl (TBS) group, an improved asymmetric nitro-olefination of α-alkyl-γ- and δ-lactones is possible (Eq. 4.97).[120]

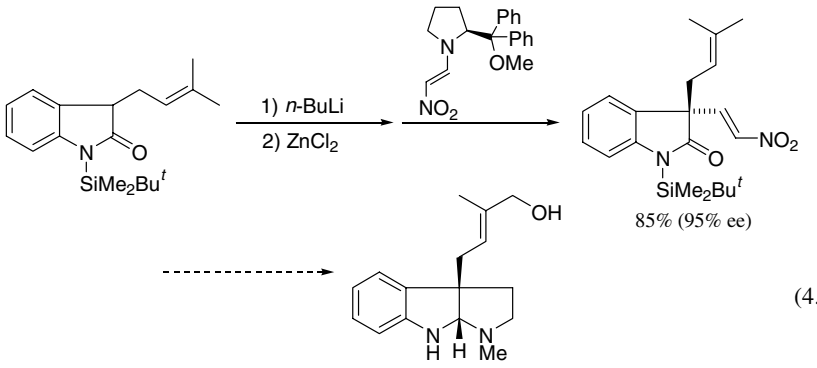



| R | Yield (%) | ee (%) |
|---|---|---|
| Me | 82 | 56 |
| Tr | 75 | 83 |
| TBS | 92 | 88 |

(4.97)

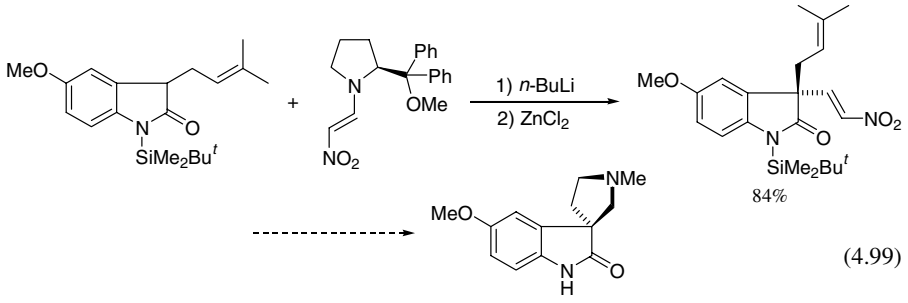
Chiral nitroolefins prepared in Eqs. 4.96 and 4.97 are converted into various natural products as summarized in Scheme 4.16.[121–123]

The modification of chiral enamines enables the asymmetric nitro-olefination of oxyindoles, as shown in Eq. 4.98.[124] An enantioselective synthesis of (–)-psudophyrnaminol is accomplished using this reaction.

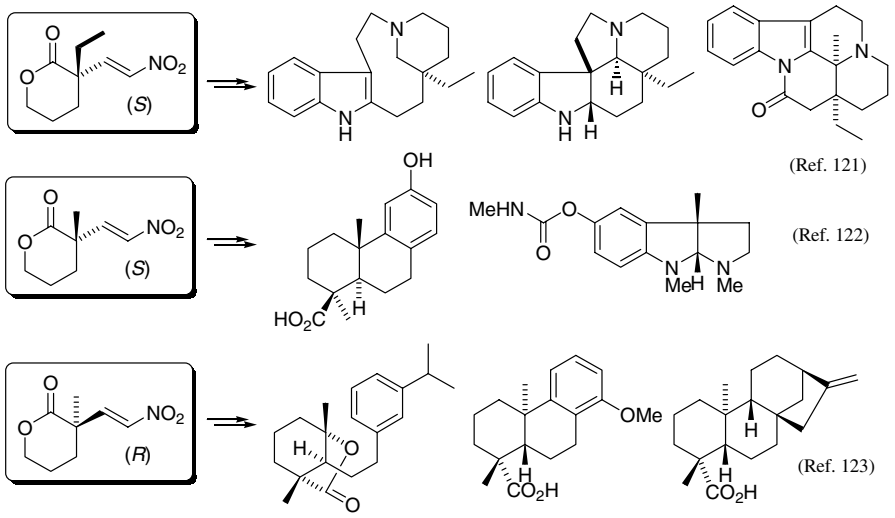



(4.98)

The strategy based on asymmetric nitro-olefination is further applied to a total synthesis of (–)-horsfiline (Eq. 4.99).[125]

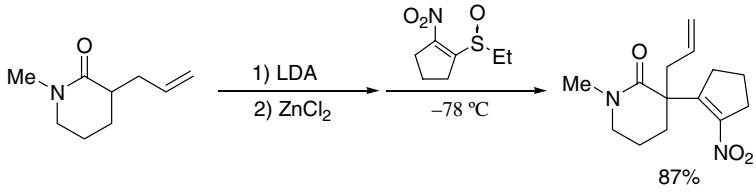



(4.99)



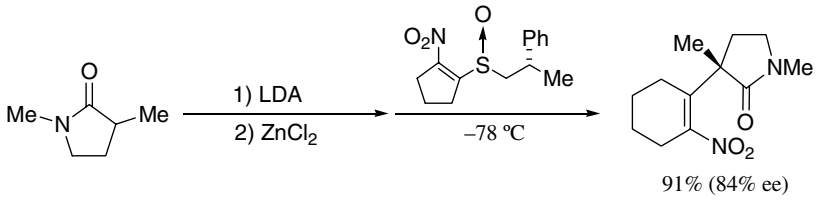

**Scheme 4.16.**

Nitroalkenes are generally prepared by the substitution reaction of β-nitro sulfides and sulfoxides with a variety of carbon nucleophiles via an addition-elimination sequence. This method is particularly useful for the preparation of cyclic nitroalkenes (Eq. 4.100).[126]




(4.100)

A chiral sulfoxide can be used as a leaving group for the asymmetric induction via addition-elimination process. δ-Lactam enolates are converted into the corresponding nitroalkenes substituted with lactams (Eq. 4.101).[127]

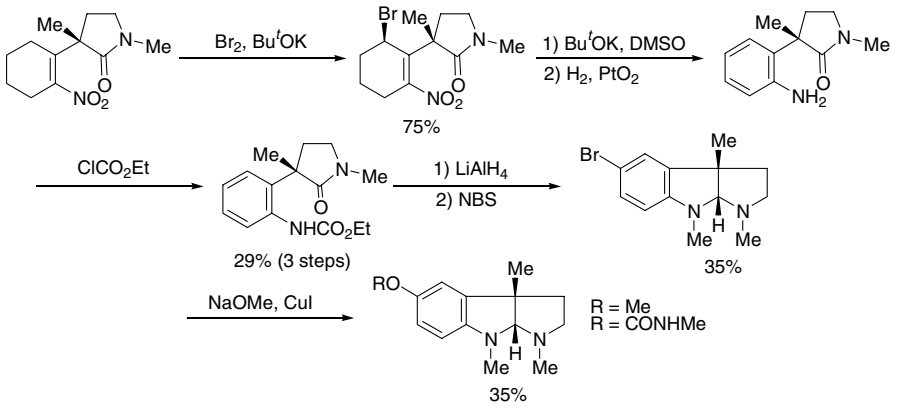



(4.101)

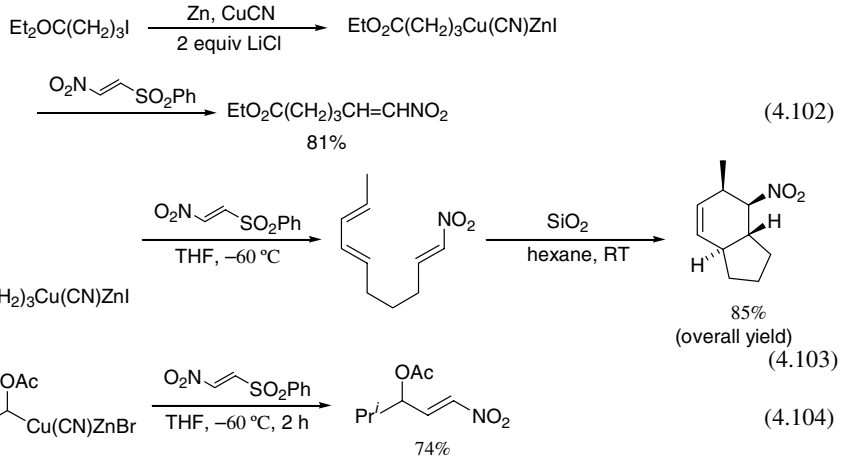
A total synthesis of (–)-physostigmine is accomplished from a chiral nitroolefin of Eq. 4.101 (Scheme 4.17).[128]

The addition-elimination reaction of copper-zinc organometallics RCu(CN)ZnX with (*E*)-1-nitro-2-phenylsulfonylethylene gives highly functionalized (*E*)-nitroalkenes in excellent yields.[129]

Organometallics bearing esters (Eq. 4.102),[13015] dienes (Eq. 4.103),[131] or oxygen functions (Eq. 4.104)[132] give nitroalkenes functionalized by these groups.



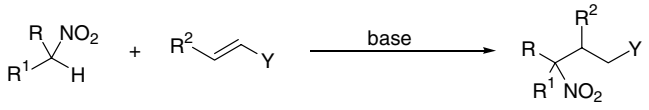

**Scheme 4.17.**




## 4.3 MICHAEL ADDITION OF NITROALKANES

### 4.3.1 Intermolecular Addition

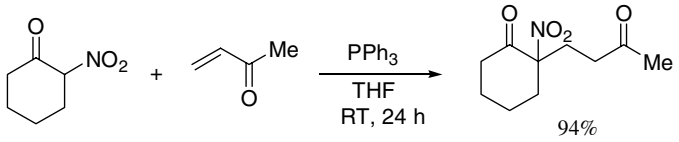
The Michael addition of nitroalkanes to electron-deficient alkenes provides a powerful synthetic tool in which it is perceived that the nitro group can be transformed into various functionalities. Various kinds of bases have been used for this transformation in homogeneous solutions, or, alternatively, some heterogeneous catalysts have been employed. In general, bases used in the Henry reaction are also effective for these additions (Scheme 4.18).[133]




Y = $CO_2Et$, $C(O)R^3$, CN, S(O)Ph, $SO_2Ph$, etc.
base = $RO^-$, $F^-$, $R_3N$, $R_3P$, tetramethylguanidine (TMG), DBU, etc.

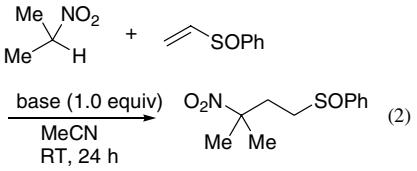
**Scheme 4.18.**

When electron-deficient alkenes are very reactive, weak bases such as triethylamine or triphenylphosphine (Eq. 4.105)[134] are reactive enough as base. On the other hand, stronger bases



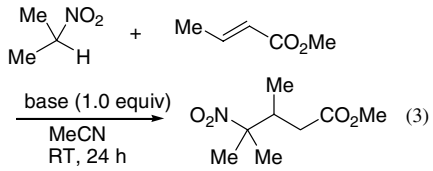

(4.105)

such as DBU or tetramethylguanidine (TMG) are necessary when less reactive alkenes such as vinyl sulfoxides (Eq. 4.106)[135] or α-substituted α,β-unsaturated carbonyl compounds are used (Eq. 4.107).[136] TMG has been widely used for the Michael addition of nitroalkanes to various electron-deficient alkenes since the first report in 1972.[137–140] High-pressure accelerates the reaction to induce the Michael addition with less reactive alkenes.[141]




| Base | Yield (%) |
|---|---|
| $Et_3N$ | 0 |
| TMG | 60 |
| DBU | 95 |

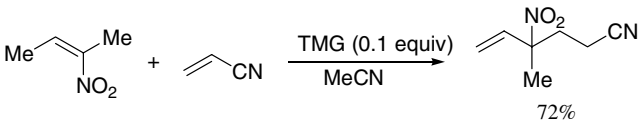
(4.106)




| Base | Yield (%) |
|---|---|
| $Et_3N$ | 0 |
| TMG | 19 |
| DBU | 61 |

(4.107)

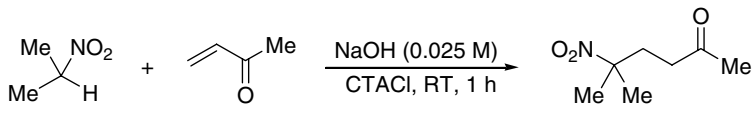
The reaction of conjugated nitroalkenes with α,β-unsaturated esters, ketones, nitriles, and sulfones is catalyzed by TMG to give the Michael adduct of allylic nitro compounds (Eq. 4.108).[142]




(4.108)

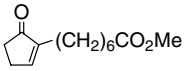
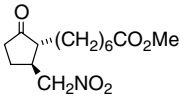
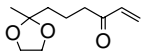
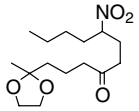
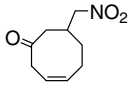
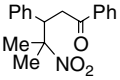
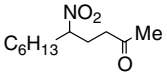
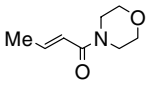
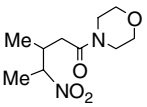
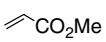
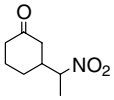
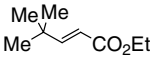
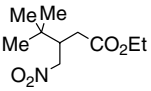
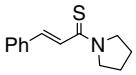
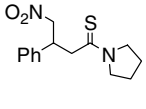
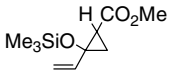
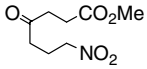
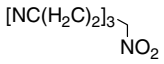
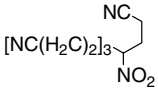
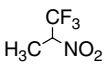
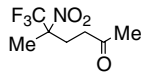
Tetraalkylammonium fluorides or metal fluorides are also effective as catalysts for the Michael addition of nitroalkanes (see, Table 4.2).[143–145]

In recent years, there has been increased recognition that water is an attractive medium for organic reactions from the environmental point of view. The Michael addition of various nitroalkanes to conjugated enones can be performed in NaOH (0.025 M) and in the presence of cetyltrimethylammonium chloride (CTACl) as cationic surfactant in the absence of organic solvents (Eq. 4.109).[146] The Michael addition of nitromethane to methyl acrylate is carried out in water using NaOH as a base to give the mono adduct (Table 4.2).[147]

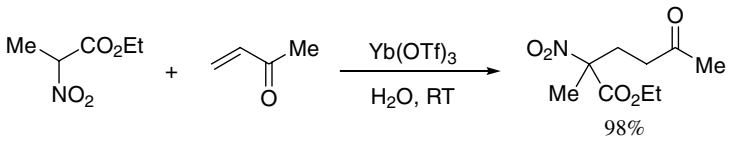



(4.109)

**Table 4.2. Michael Addition to nitro compounds**

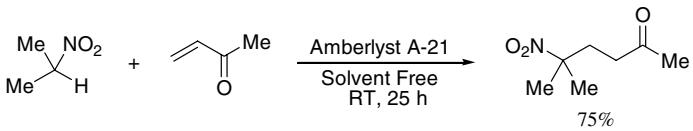
| Nitro compound | Alkenes | Base/conditions | Product (yield, %) | | Ref. |
|---|---|---|---|---|---|
| $CH_3NO_2$ |  | TMG/RT, 2 days |  | (83) | 137 |
| $CH_3(CH_2)_4NO_2$ |  | TMG |  | (64) | 139 |
| $CH_3NO_2$ | | TMG |  | (77) | 140 |
| $(CH_3)_2CHNO_2$ | PhCH=CHC(O)Ph | $Bu_4NF{\cdot}SiO_2$/DMF, 20 °C, 3 h |  | (65) | 143 |
| $C_7H_{13}NO_2$ | | CsF-$Al_2O_3$/20 °C, 1 h |  | (85) | 144 |
| $C_2H_5NO_2$ |  | CsF-$Si(OR)_4$/80 °C, 74 h |  | (74) | 145 |
| $CH_3NO_2$ |  | NaOH, $H_2O$/20 °C | | (57) | 147 |
| $C_2H_5NO_2$ | | KF-basic $Al_2O_3$/THF, RT, 24 h |  | (100) | 148 |
| $CH_3NO_2$ |  | DBU |  | (40) | 180 |
| $CH_3NO_2$ |  | DBU |  | (85) | 181 |
| $CH_3NO_2$ |  | Triton B |  | (75) | 182 |
|  | | DBU |  | (40) | 183 |
|  | | $Al_2O_3$ |  | (85) | 184 |

Ytterbium triflate is an extremely effective catalyst for the Michael addition of α-nitro esters to enones in water (Eq. 4.110).[149]

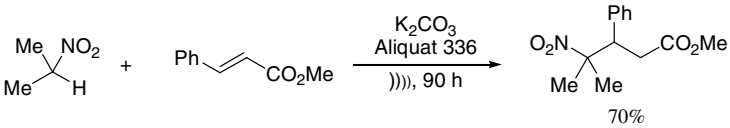



(4.110)

The heterogeneous catalytic systems have some advantages over homogeneous reactions. Chemical transformations under heterogeneous conditions can occur with better efficiencies, higher purity of products, and easier work-up. Ballini and coworkers have found that commercial amberlyst A-27 is the best choice for the Michael addition of nitroalkanes with β-substituted alkene acceptors (Eq. 4.111).[150] The reaction is also carried out by potassium carbonate in the presence of Aliquat 336 under ultrasonic irradiation (Eq. 4.112).[151]

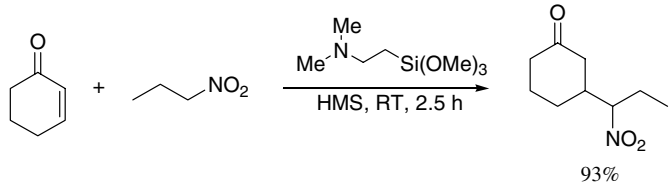



(4.111)




(4.112)

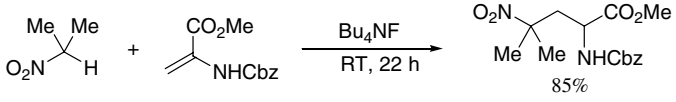
Recently very reactive solid bases have been devised, which are prepared by derivatization of amorphous silica and hexagonal mesoporous silica (HMS) with the dimethylaminopropyl group (Eq. 4.113).[151b]



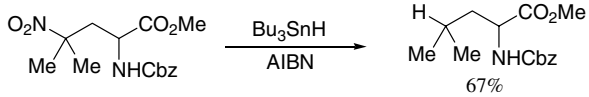

(4.113)

In Table 4.1, the Michael addition of nitro compounds to various electron deficient alkenes is shown.

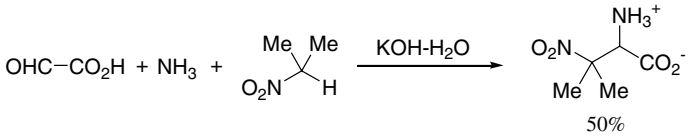
The Michael addition of nitro compounds is a useful method for the preparation of various natural products. The Michael addition of nitroalkanes to dehydroalanines gives γ-nitro-α-amino acids, which provides a convenient synthesis of side-chain modified α-amino acids (Eq. 4.114).[152] Transformations of γ-nitro-α-amino acid derivatives into α-amino acids occur by reductive denitration (see Section 7.2) into γ-oxygenated α-amino acids by the Nef reaction (Eq.




(4.114)



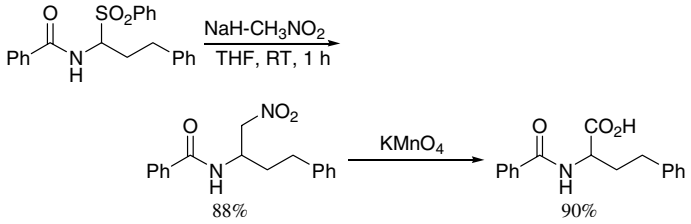

(4.115)




(4.116)

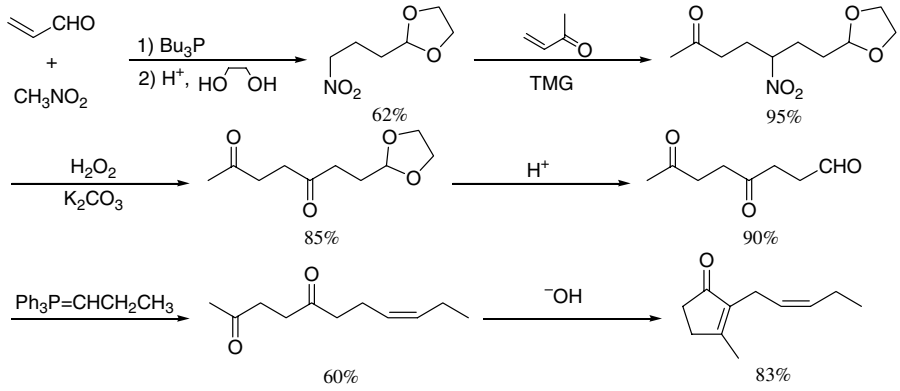
4.115).[153] Condensation of glyoxalic acid, nitroalkanes, and amines provides a simple method for β-nitro-α-amino acids (Eq. 4.116).[154]

The base-catalyzed reaction of nitromethane with α-amidoalkyl sulfones gives the nitro compounds as in Eq. 4.117; the nitromethyl group is converted into a carboxylic group to give α-amino acids by the Nef reaction using $KMnO_4$.[155]

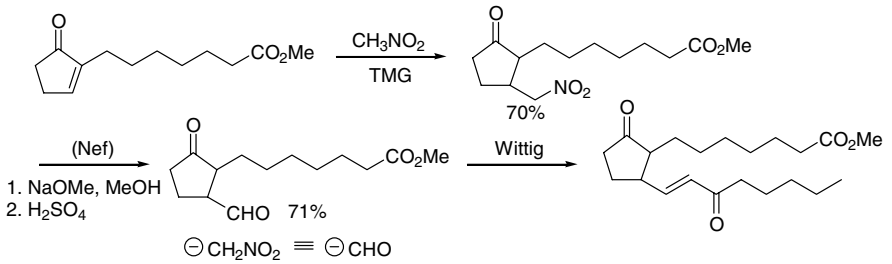



(4.117)

The Michael addition of nitroalkanes to α,β-unsaturated ketones followed by the Nef reaction has been extensively used as a method for the conjugated addition of acyl anions to enones (see Section 6.1, *Nef Reaction*). This strategy is one of the best methods for the preparation of 1,4-dicarbonyl compounds.[156a–h] Various natural products have been prepared via this route.[157] For example, *cis*-jasmone is prepared from readily available materials, as shown in Scheme 4.19.[156f]



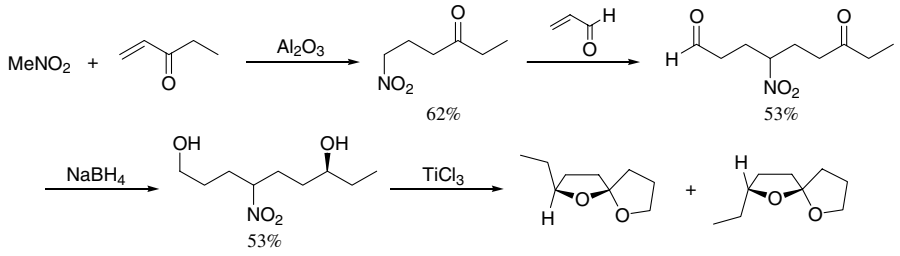

**Scheme 4.19.**




**Scheme 4.20.**

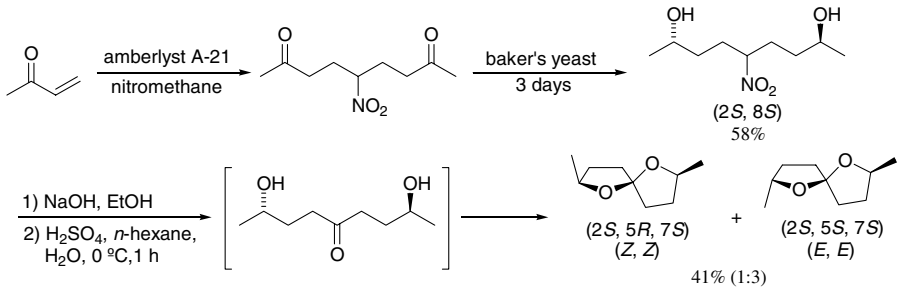
The Michael addition of nitromethane to cyclopentenone derivatives is used for synthesis of prostaglandins (Scheme 4.20).[158] Here, the anion of nitromethane is used as a formyl anion synthon.

Ballini and coworkers have used the Michael addition of nitro compounds followed by the Nef reaction for the synthesis of various spiroketalic pheromones (Scheme 4.21).[159]



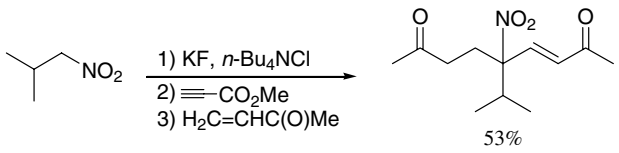

**Scheme 4.21.**

Asymmetric synthesis of spiroketalic pheromones is also reported, in which the asymmetric reduction of carbonyl group is carried out with baker's yeast (Scheme 4.22).[160]



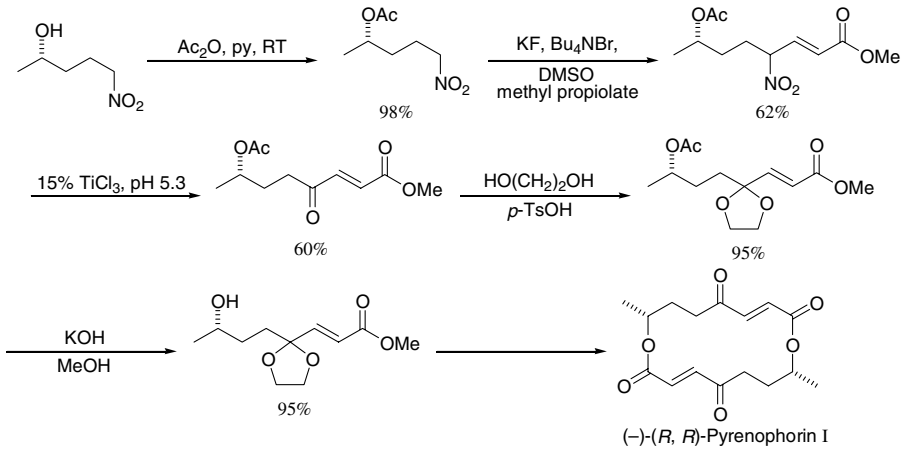

**Scheme 4.22.**

The Michael addition of nitro compounds to electron-deficient alkynes affords allylic nitro compounds in good yields, in which KF-*n*-$Bu_4NCl$ in DMSO is used as a base and solvent (Eq. 4.118).[161]



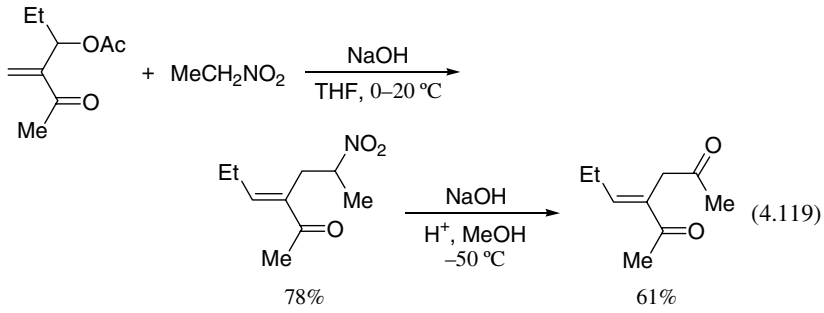

(4.118)

A short enantioselective synthesis of (–)-(*R,R*)-pyrenophorin, a naturally occurring anti-fungal 16-membered macrolide dilactone, is prepared from (*S*)-5-nitropentan-2-ol via the Michael addition and Nef reaction (Scheme 4.23).[162] The choice of base is important to get the *E*-alkene in the Michael addition, for other bases give a mixture of *E* and *Z*-alkenes. The requisite chiral (*S*)-5-nitropentan-2-ol is prepared by enantioselective reduction of 5-nitropentan-2-one with baker's yeast.[163]



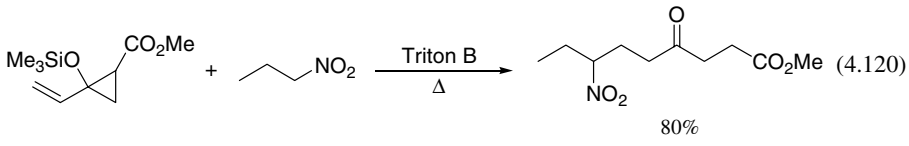

**Scheme 4.23.**

Conjugate addition of nitroalkanes to allyl Baylis-Hillman acetates in the presence of NaOH (0.6 N) in THF gives 2-alkylidene-4-nitro ketones with high stereoselectivity; these are converted via the Nef reaction into the corresponding 1,4-diketones (Eq. 4.119).[164]




(4.119)

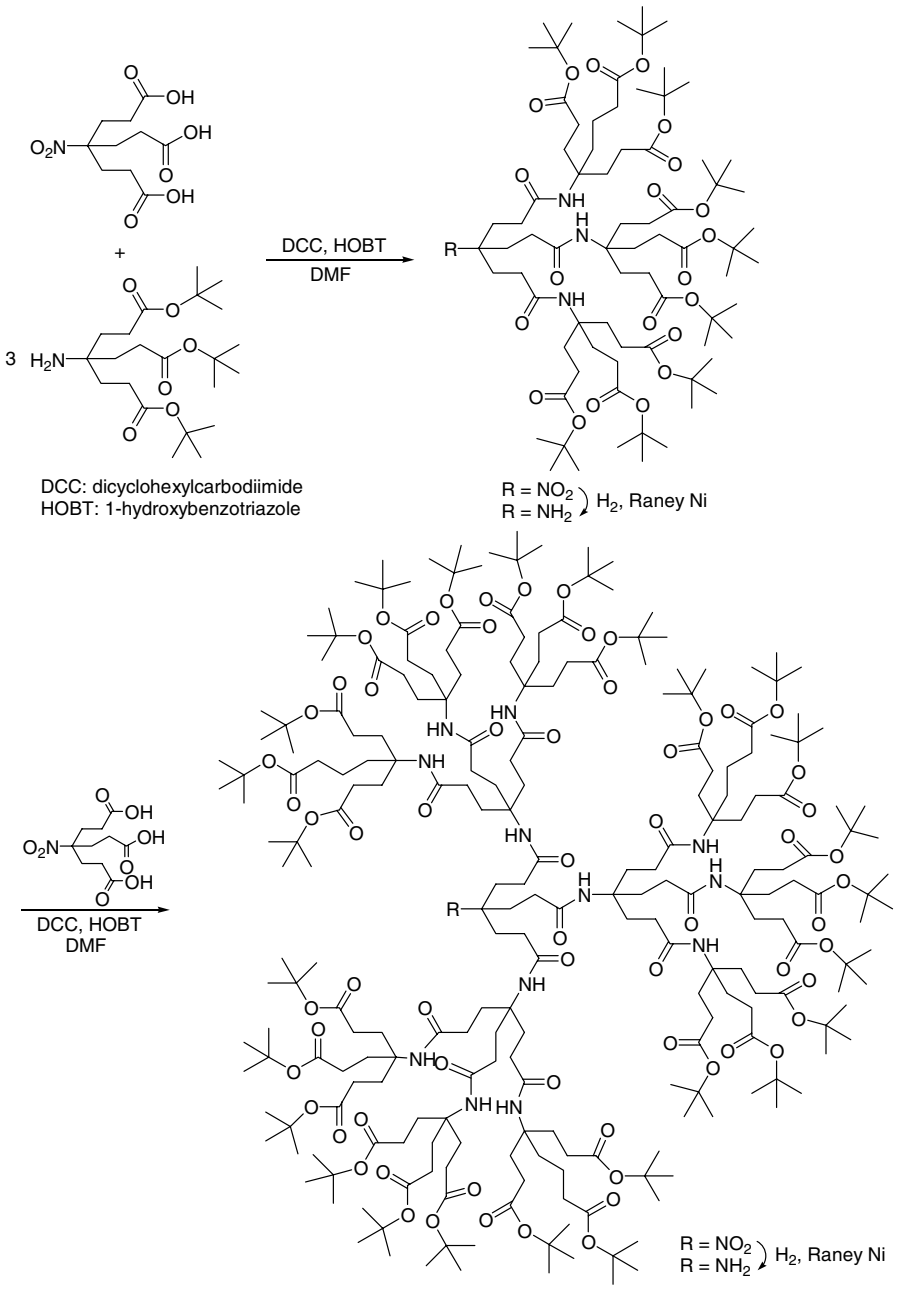
Polyfunctionalized nitro compounds are prepared by the Michael addition using 2-alkenyl-substituted 2-siloxycyclopropanecarboxylates as Michael acceptors (Eq. 4.120).[165]



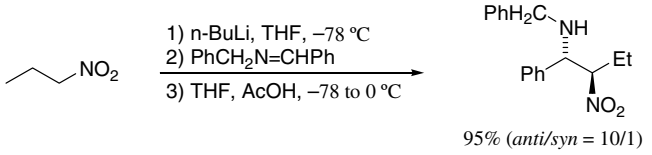

(4.120)

Newkome and coworkers have developed synthesis of dendritic molecules using the Michael addition of nitromethane to α,β-unsaturated esters as a key reaction (Scheme 4.24).[166]

The addition of alkyl nitronate anions to imines in the presence of a Lewis acid proceeds in high yield with up to 10:1 diastereoselection favoring the *anti* isomer. This reaction is used for the stereoselective synthesis of 1,2-diamines (Eq. 4.121).[167] Scandium triflate catalyzes the addition of 1-trimethylsilyl nitropropanoate to imines with a similar selectivity.[35]

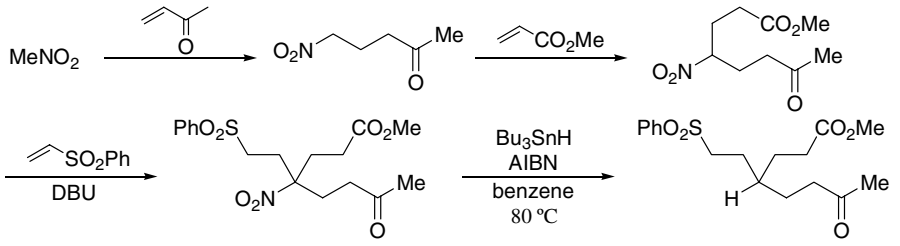



**Scheme 4.24.**

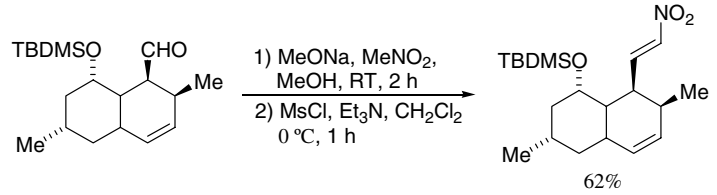


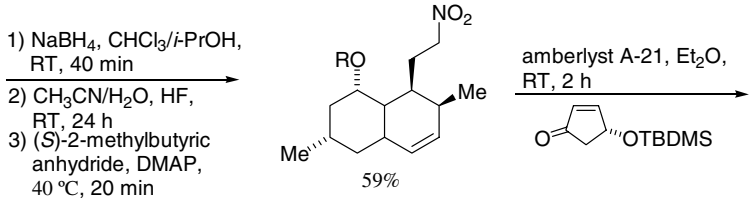

95% (*anti/syn* = 10/1) (4.121)

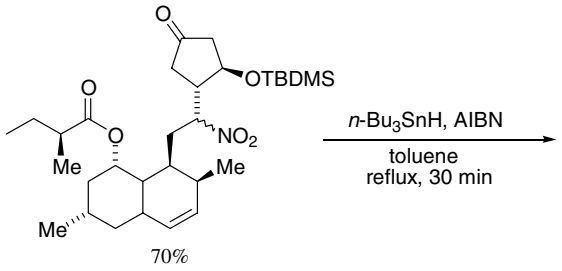
The sequence of the Michael addition of nitroalkanes and denitration provides a general method for conjugate addition of primary and secondary alkyl groups to electron deficient alkenes (Eq. 4.122).[168]

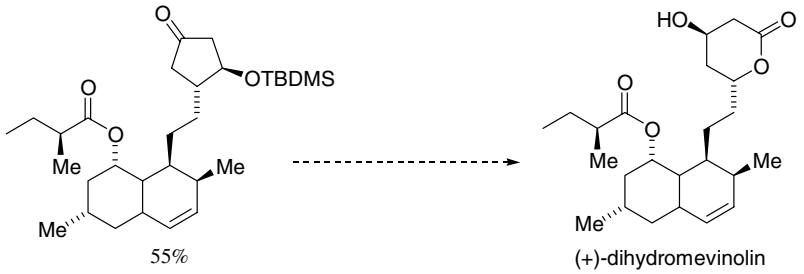



(4.122)



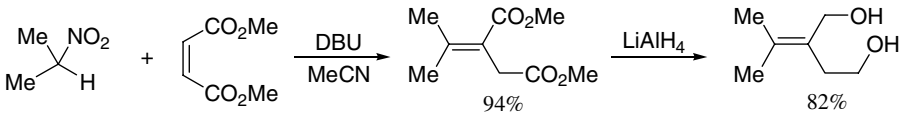




**Scheme 4.25.**

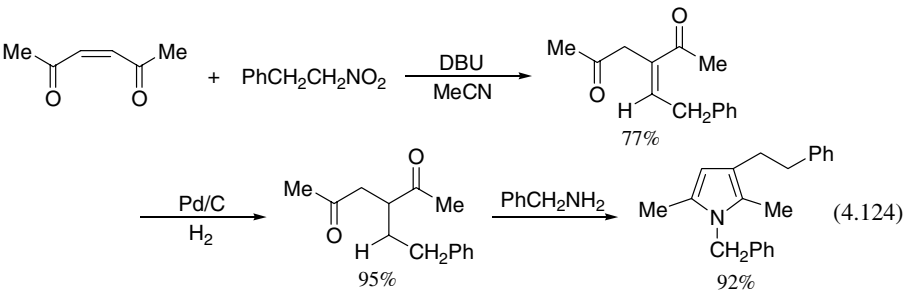
Hanessian and coworkers have used this strategy for a total synthesis of (+)-dihydromevinolin (Scheme 4.25).[169]

Ballini and coworkers have developed a new strategy for alkenylation of carbonyl compounds based on the Michael addition followed by elimination of $HNO_2$ (see Section 7.3). A variety of 2-alkylidene 1,4-dioles have been conveniently prepared, in two steps, by the Michael addition of a nitroalkane to the appropriate enedione derivatives under basic conditions, followed by chemoselective reduction with $LiAlH_4$ (Eq. 4.123).[170]



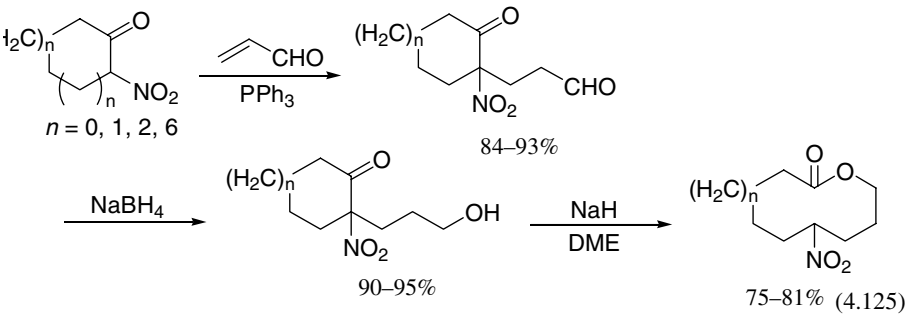

(4.123)

The synthesis of 2,3,5-trialkylpyrroles can be easily achieved by conjugate addition of nitroalkanes to 2-alken-1,4-dione (prepared by oxidative cleavage of 2,5-dialkylfuran) with DBU in acetonitrile, followed by chemoselective hydrogenation (10% Pd/C as catalyst) of the C-C- double bond of the enones obtained by elimination of $HNO_2$ from the Michael adduct. The Paal-Knorr reaction (Chapter 10) gives 2,3,5-trialkylpyrroles (Eq. 4.124).[171]

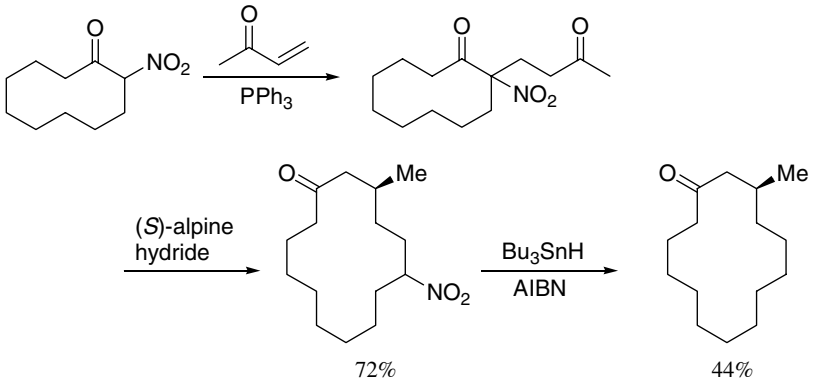



(4.124)

The Michael addition of cyclic α-nitro ketones to acrolein or methyl vinyl ketone followed by reduction of the carbonyl group and treatment with base results in the ring expansion (Eq. 4.125).[172] Hesse and coworkers have used this strategy for the preparation of various macrolides.[173] For example, Michael addition of 2-nitrocyclodecanone methyl vinyl ketone followed by reduction with (*S*)-alpine-hydride gives the nitrolactone in 72% yield. Radical denitration of the nitrolactone with $Bu_3SnH$ gives (+)-(*S*)-tetradecan-13-olide in 44% yield (Eq. 4.126).[173c]

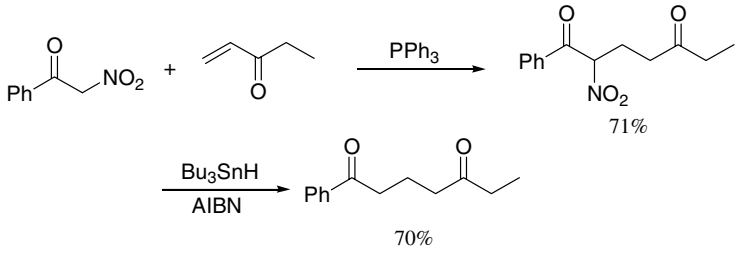



(4.125)




(4.126)

The Michael addition of α-nitro ketones to α,β-unsaturated ketones followed by radical denitration provides a useful strategy for the preparation of 1,4-diketones.[134b] 1-Phenylheptane-1,5-dione, isolated from the decayed heart wood of aspens, is prepared by this strategy (Eq. 4.127).[174]

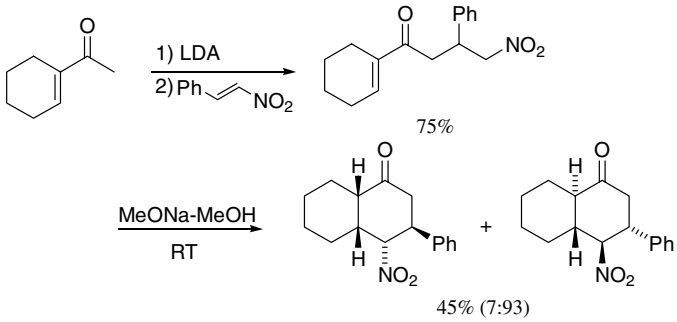



(4.127)

The Michael addition of nitro compounds to α,β-unsaturated ketones or esters followed by reduction of the nitro to amino group is useful for the preparation of various heterocycles. This is presented in Chapter 10 (*Synthesis of Heterocycles*).

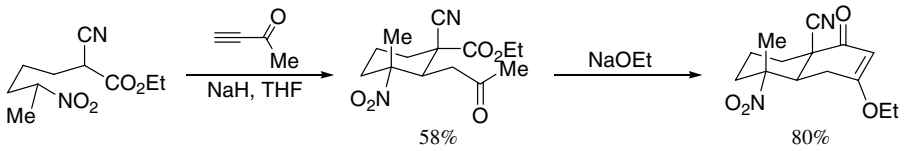
### 4.3.2 Intramolecular Addition

Intramolecular Michael addition of nitro compounds proceeds in a stereoselective way to give various types of cyclic nitro compounds with high stereoselectivity. The Michael addition of 1-acetylcyclohexene to nitrostyrene followed by treatment with MeONa in MeOH gives 4-nitro-3-phenyldecalone with high stereoselectivity (Eq. 4.128).[175]



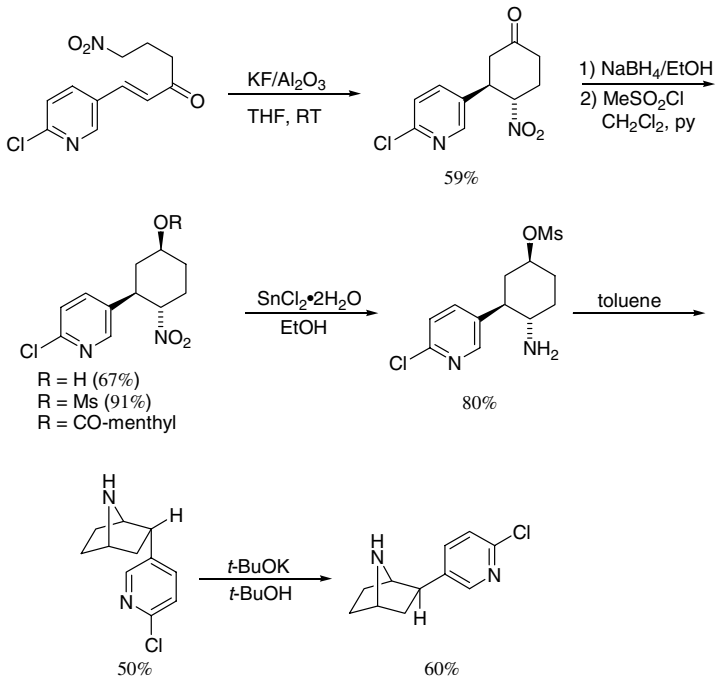

(4.128)

Double Michael additions of nitro compounds bearing tethered acidic carbons to 3-butyn-2-one under NaH catalysis give nitrocyclohexanes with high stereoselectivity. The products are transformed into *trans*-fused bicyclic compounds via the Dickmann reaction on treatment with base. (Eq. 4.129).[176]



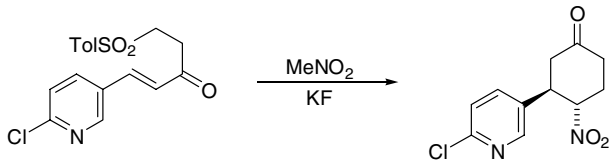

(4.129)

The intramolecular Michael addition is used as a key step for synthesis of epibatidine (Scheme 4.26).[177] Epibatidine is an analgesic, operating by a nonopioid mechanism, it is several hundred times more potent than morphine.



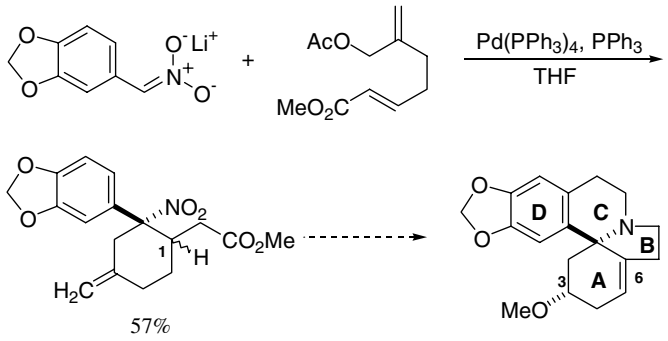

**Scheme 4.26.**

Barco and coworkers have reported a more elegant synthesis of the nitrocyclohexanone via the double Michael addition of nitromethane with enones. (Eq. 4.130).[178]




(4.130)

The sequential process consisting of palladium-catalyzed alkylation and the intramolecular Michael addition of nitro compound provides a nitrocyclohaxane derivative, which is a good precursor for synthesis of Erythrina alkaloids (Eq. 4.131).[179]



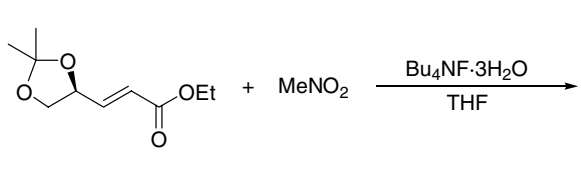

(4.131)

## 4.4 ASYMMETRIC MICHAEL ADDITION

### 4.4.1 Chiral Alkenes and Chiral Nitro Compounds

Diastereoselective conjugate addition of nucleophiles to enones, enals, and enoates occurs with high stereocontrol and constitutes a powerful method in stereoselective synthesis.[185]

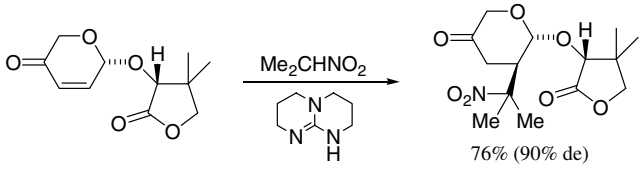
The conjugate addition of nucleophiles to optically pure γ-oxygenated substrates is of special interest in the enantioselective synthesis of natural products. Highly *syn*-selectivity is observed in the conjugate addition of ammonia,[186] alkoxides,[187] and alkyllithium derivatives.[188] High *anti*-selective addition is observed in the addition of metal enolates and cuprates.[189] The Michael addition of nitromethane to enoates derived from glyceraldehyde acetonide leads to *syn*-adducts with high diastereoselectivity (de 76–90%) (Eq. 4.132).[190] Primary and secondary nitroalkanes afford *syn*-adducts diastereoselectively in the $Bu_4NF$- or DBU-catalyzed Michael addition to the same enoates of Eq. 4.132.[191]



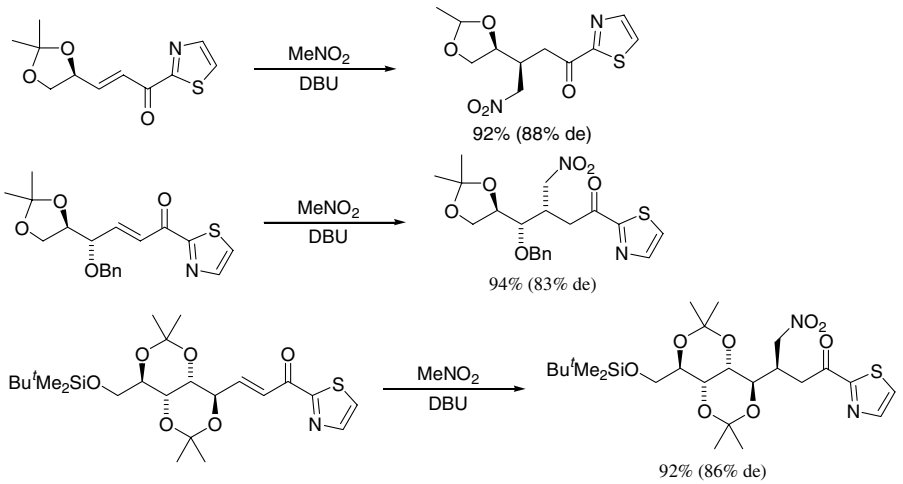

(4.132)

*Syn*-selectivity of the DBU-catalyzed Michael addition of nitromethane to chiral γ-oxygenated enones is quite general, as shown in Scheme 4.27.[192]

Feringa and coworkers have used the optical active furanone or pyranone as an acceptor for the diastereoselective Michael reactions (Eq. 4.133).[193]

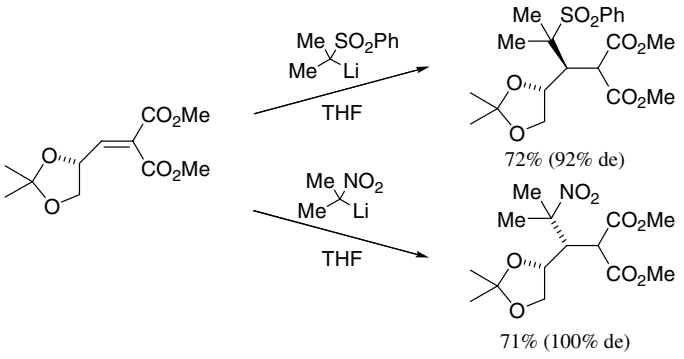



(4.133)



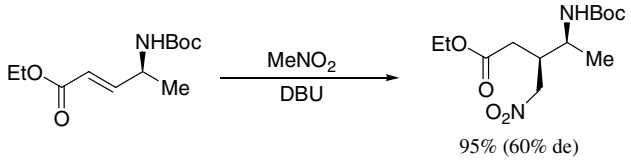

**Scheme 4.27.**

Krief and coworkers have found that 2-lithio-2-sulfonylpropane and 2-lithio-2-nitropropane behave differently in the addition to dimethyl alkylidenemalonate. Thus, 2-lithio-2-sulfonylpropane reacts with it almost exclusively on the (*Si*)-face and leads to the *anti*-adduct, whereas 2-lithio-2-nitropropane reacts under similar reaction conditions, exclusively on the (*Re*)-face, providing the *syn*-product (Eq. 4.134).[194]




(4.134)

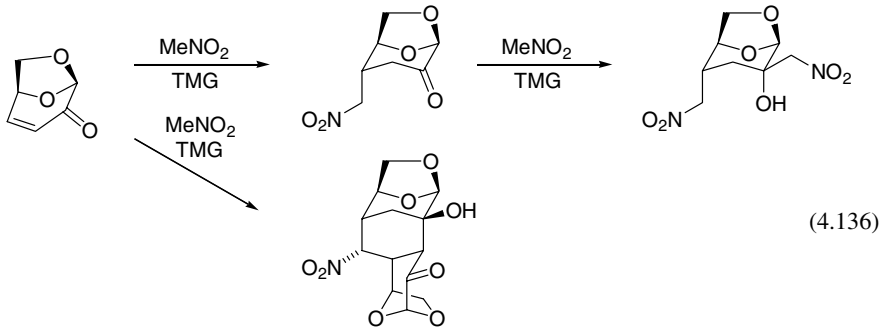
The Michael addition of nitromethane to vinylogous esters of *N*-protected amino acids proceeds with good yields and with good diastereoselectivity (Eq. 4.135).[195]




(4.135)

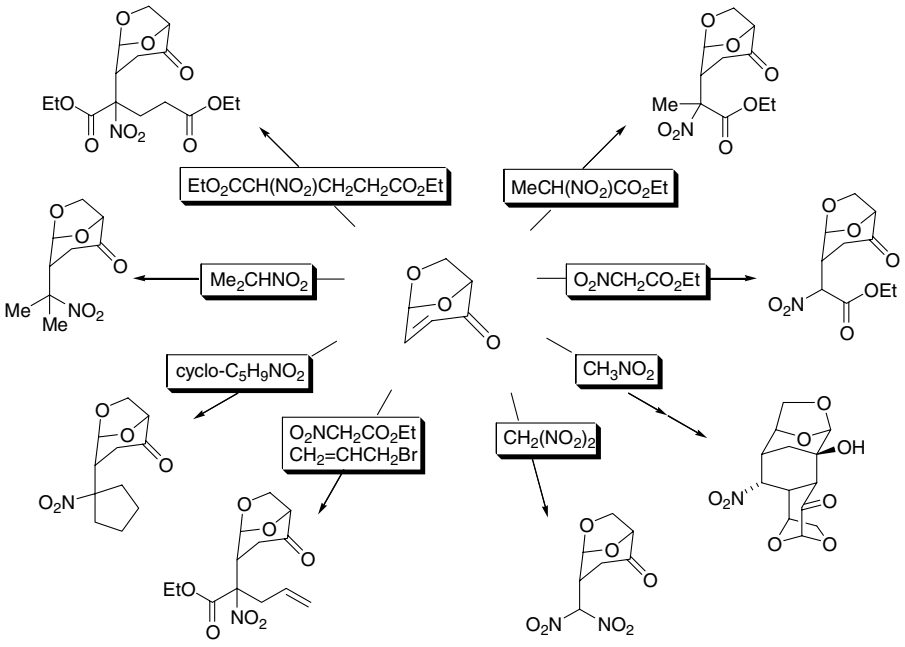
Levoglucosenone, a cellulose-derived α,β-unsaturated ketone, is an interesting material because it is both chiral and contains an activated double bond. This compound has been used

as a chiral starting material for synthesis of a variety of natural compounds such as alkaloids or antibiotics.[196] The Michael addition of nitro compounds to levoglucosenone provides a useful tool for the synthesis of various chiral compounds. Nitromethane undergoes TMG-catalyzed addition to levoglucosenone, affording 2:1 and 1:2 adducts in high yield (95%); the products result from initial Michel addition exclusively at the *exo*-face of the alkene *anti* to the 1,6-anhydro bridge (Eq. 4.136).[197] If nitromethane is used as a solvent, the 2:1 adduct is obtained. A reaction is carried out by stirring a mixture of nitromethane and levoglucosenone (2:1 ratio) in $CH_2Cl_2$ in the presence of catalytic amounts of TMG to give a 1:2 adduct.




(4.136)

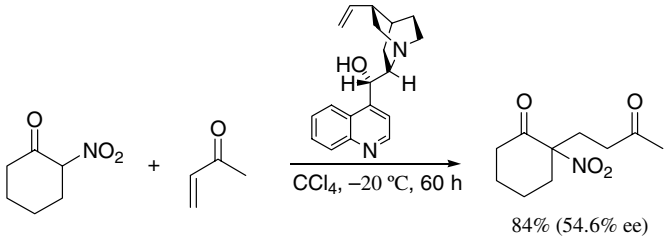
A variety of important synthetic reactions can be promoted by electrogenerated bases (EGB). The Michael addition and alkylation of compounds with activated hydrogen atoms are two examples in which using EGB has been very successful. The electrochemical method is very successful for functionalization of levoglucosenone as shown in Scheme 4.28.[198]




**Scheme 4.28.**

### 4.4.2 Chiral Catalysts

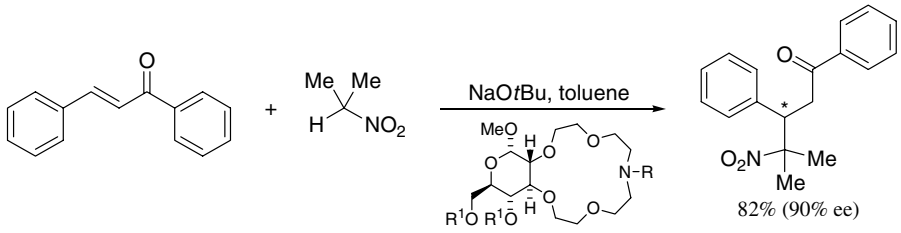
Catalytic enantioselective nucleophilic addition of nitroalkanes to electron-deficient alkenes is a challenging area in organic synthesis. The use of cinchona alkaloids as chiral catalysts has been studied for many years. Asymmetric induction in the Michael addition of nitroalkanes to enones has been carried out with various chiral bases. Wynberg and coworkers have used various alkaloids and their derivatives, but the enantiomeric excess (ee) is generally low (up to 20%).[199] The Michael addition of methyl vinyl ketone to 2-nitrocycloalkanes catalyzed by the cinchona alkaloid cinchonine affords adducts in high yields in up to 60% ee (Eq. 4.137).[200]




84% (54.6% ee) (4.137)

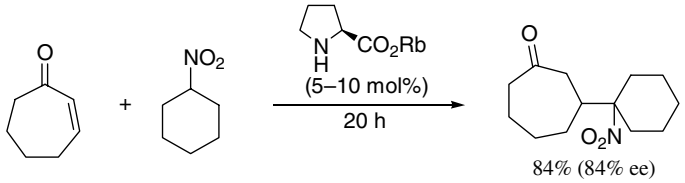
Matsumoto and coworkers have introduced a new strategy for asymmetric induction under high pressure. The Michael addition of nitromethane to chalcone is performed at 10 kbar in the presence of a catalytic amount of chiral alkaloids. The extent of asymmetric induction reaches up to 50% ee with quinidine in toluene.[201]

Chiral monoaza-crown ethers containing glucose units have been applied as phase-transfer catalysts in the Michael addition of 2-nitropropane to a chalcone to give the corresponding adduct in up to 90% ee. (Eq. 4.138).[202]



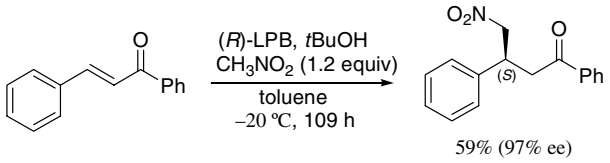

82% (90% ee) (4.138)

Yamaguchi and coworkers have found that proline rubidium salts catalyze the asymmetric Michael addition of nitroalkanes to prochiral acceptors. When (2*S*)-L-prolines are used, acyclic (*E*)-enones give (*S*)-adducts. Cyclic (*Z*)-enones give (*R*)-adducts predominantly (Eq. 4.139).[203] Recently, Hanessian has reported that L-proline (3 ~ 7% mol equiv) and 2,5-dimethylpiperazine are more effective to induce catalytic asymmetric conjugate addition of nitroalkanes to cycloalkanones.[204]



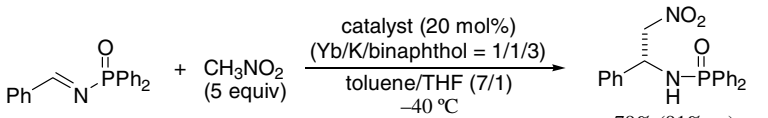

84% (84% ee) (4.139)

Heterobimetallic asymmetric complexes contain both Bronsted basic and Lewis acidic functionalities. These complexes have been developed by Shibasaki and coworkers and have proved to be highly efficient catalysts for many types of asymmetric reactions, including catalytic asymmetric nitro-aldol reaction (see Section 3.3) and Michael reaction. They have reported that the multifunctional catalyst (*R*)-LPB [$LaK_3$tris(*R*)-binaphthoxide] controls the Michael addition of nitromethane to chalcones with >95% ee (Eq. 4.140).[205]




59% (97% ee) (4.140)

The catalytic asymmetric nitro Mannich-type reaction using the complex Yb, K, and binaphthol gives the best result (see Eq. 4.141).[206] The reaction conditions are important to get a good ee, where nitromethane is added very slowly over 27 h.




79% (91% ee) (4.141)

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*The Nitro Group in Organic Synthesis.* Noboru Ono
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ISBNs: 0-471-31611-3 (Hardback); 0-471-22448-0 (Electronic)

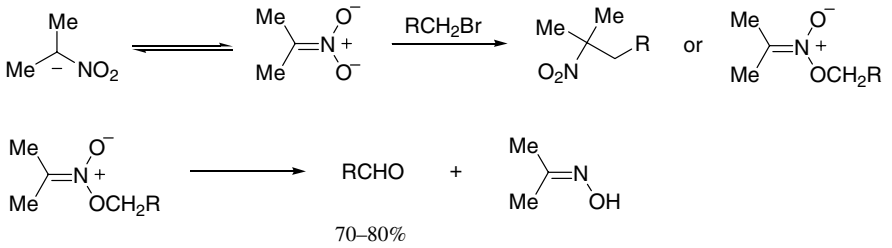
# 5

# ALKYLATION, ACYLATION, AND HALOGENATION OF NITRO COMPOUNDS

The carbon-carbon bond forming reactions of nitro compounds by alkylation with alkyl halides or acylation with acyl halides have been encountered with difficulties of the competing O-alkylation or O-acylation, respectively. In this chapter, the recent developments of C-alkylations and C-acylations of nitro compounds are summarized. The O-alkylated compounds undergo cycloaddition reactions, which are discussed in the chapter of cycloaddition (Chapter 8).

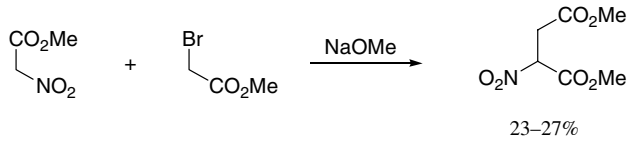
## 5.1 ALKYLATION OF NITRO COMPOUNDS

Anions derived from aliphatic nitro compounds are capable of covalency formation at either carbon or oxygen. Although the carbon alkylate is stable, and is isolated without difficulty, the oxygen alkylate is unstable and the carbonyl compounds corresponding to the alkyl halides are obtained. In general, nitroparaffin salts undergo oxygen alkylaton with little, if any, concomitant carbon alkylation; indeed, this is the basis of a useful synthesis of aldehydes and ketones (Scheme 5.1).[1] However, there are some exceptions to give the C-alkylation, the reaction of *p*-nitrobenzyl chloride with the salt of 2-nitropropane give the C-alkylation exclusively [see the section of 7.1.1 radical substitution ($S_{RN}1$)].




**Scheme 5.1.**

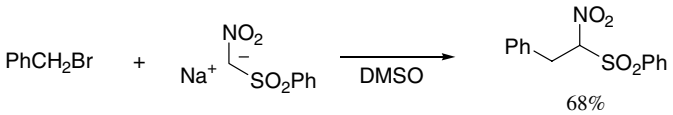
C-Alkylation takes place in the reaction of methyl nitroacetate with alkyl halides; the products are useful intermediates for preparing amino acids (Eq. 5.1).[2] The requisite nitro acetate is prepared by self condensation of nitromethane.[3]



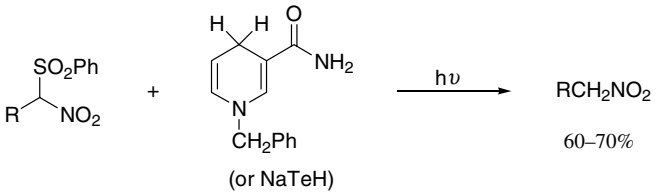

(5.1)

Preparation of Merrifield resin-bound nitro acetates, which is a suitable building block for the development of combinatorial solid phase synthesis, is reported.[4] The anion of ethyl nitro acetate is generated in DMF by an electrochemical method using Pt cathode, magnesium rod anode, and tetrabutylammonium bromide as an electrolyte. Alkylaton of this anion with alkyl halides gives mono-alkylated products in 80% yield.[5]

Arylsulfonylnitromethane easily undergoes C-alkylation to form α-nitro sulfones, which are useful intermediates in organic synthesis (Eq. 5.2).[6] The sulfonyl group may be replaced by other groups via $S_{RN}1$ reactions,[7] including by hydrogen with various reducing reagents; for example, see Eq. 5.3, which shows reduction with *N*-benzyl-1,4-dihydronicotinamide.[8a] More convenient desulfonylation of α-nitro sulfones can be carried out with sodium dithionite by using octylviologen as an electron-transfer catalyst.[8d] The overall reaction is regarded as alkylation of nitromethane, which is rather difficult by any other methods. In contrast to the mono-anion of nitromethane, the α,α-dianion gives predominant C-alkylation; however, the yield is low.[9]

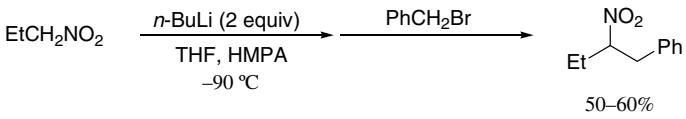



(5.2)



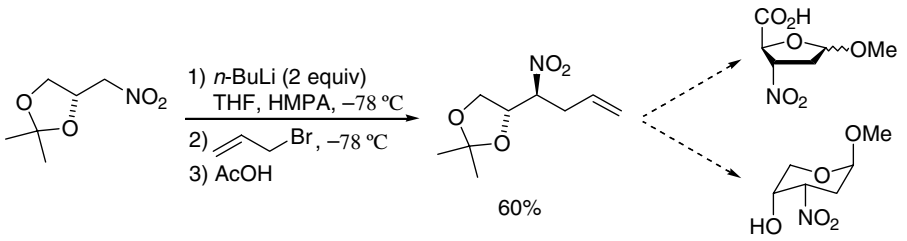

(5.3)

The reactivity of carbon is much enhanced by the double deprotonated intermediates of nitro compounds. Except for nitromethane, other nitroalkanes are alkylated to give the C-alkylated products in 50–60% yield by this procedure (see Eq. 5.4).[9,10]



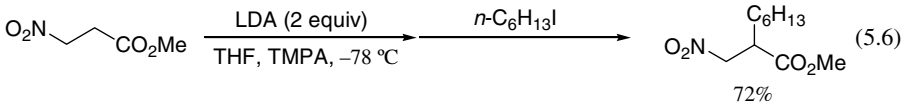

(5.4)

Mosher and coworkers have adopted this strategy for the enantioselective synthesis of 2,3-dideoxy-3-nitro-furanosides and pyranosides using chiral nitronate dianions, as shown in Eq. 5.5.[11]




(5.5)

The dianion derived from methyl 3-nitropropanoate is formed on treatment with LDA, and it is alkylated by alkyl halides exclusively at the 2-position (Eq. 5.6). Elimination of $HNO_2$ with DBU in THF furnishes methyl α-methylenealkanoate (see Section 7.3, which discusses alkene formation).[12]



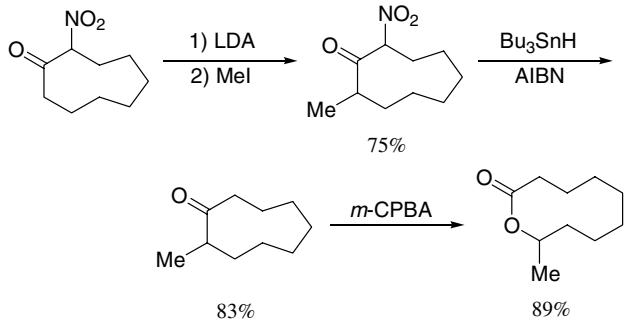

(5.6)

Dianions derived from cyclic α-nitro ketones have been used for the preparation of the natural product phoracanthlide and related macrocyclic lactones (see Scheme 5.2).[13] Alkylation of dianion of α-nitro cyclic ketones is followed by radical denitration with $Bu_3SnH$ (see Section 7.2).

Thus, the direct alkylation of the anions derived from nitroalkanes with alkyl halides has some difficulties, and such difficulties are partially overcome by the radical reaction or transition metal catalyzed reactions, as discussed in Sections 5.4 and 5.5.

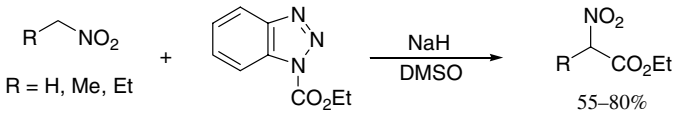
## 5.2 ACYLATION OF NITROALKANES

The carboxylation of nitroalkanes with magnesium methyl carbonate followed by esterification gives α-nitro esters in 40–58% yield.[14] Magnesium methyl carbonate is prepared by the saturation of a magnesium methoxide suspension in DMF with $CO_2$. More elegantly, sodium salt of nitroalkanes can be carboxylated by means of 1-ethoxycarbonylbenzotriazole to give α-nitro esters in 55–80% yield (Eq. 5.7).[15] Nitroacetic acids and its esters can serve as useful



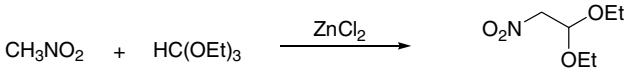

**Scheme 5.2.**

starting materials for the synthesis of many kinds of substances, including amino acids, oxazolines, and amino alcohols.[16]



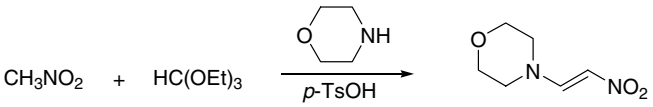

(5.7)

Nitroacetaldehyde diethyl acetal is prepared by the reaction of nitromethane with triethyl orthoformate in the presence of $ZnCl_2$ (Eq. 5.8).[17] Jager and coworkers have used this reagent for the synthesis of amino sugars via nitro-aldol reaction.[18] Preparation of this useful reagent is now described in volume 74 of Organic Synthesis.[19]




(5.8)

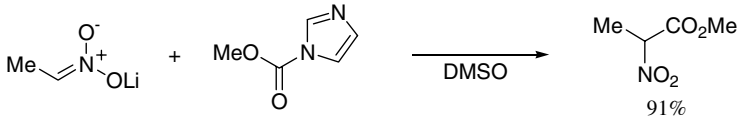
Nitromethane reacts with triethyl orthoformate in the presence of secondary amines to give nitroenamines (Eq. 5.9).[20]



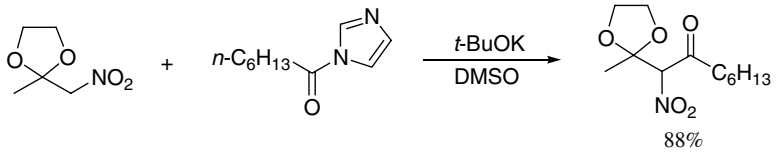

(5.9)

α-Nitro ketones are versatile compounds in the synthesis of ketones or related compounds. They can be prepared either by nitration of enol nitrates (see Section 2.1.5, which discusses nitration) or oxidation of nitro aldols (see Section 3.2.3, which discusses Henry reaction). Furthermore, direct acylation of nitroalkanes with suitable acylating agents also provides a reliable method.

The acylation of the carbanions derived from nitroalkanes with acyl imidazoles or alkoxycarbonylimidazoles takes place at the carbon atom to yield α-nitro ketones or α-nitro esters, respectively (Eq. 5.10).[21] The lithium salts of nitroalkanes were isolated and used in THF or DMSO in the original procedure. Later, potassium salts generated in situ on treatment with *t*-BuOK in DMSO are reactive enough to give α-nitro ketones in good yield (Eq. 5.11).[22]



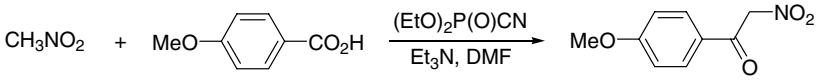

(5.10)




(5.11)

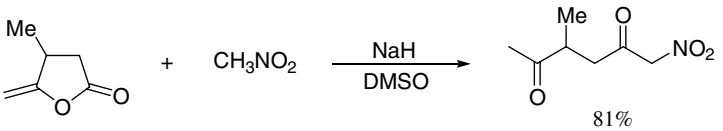
Although acyl imidazoles can be replaced by phenyl esters in some cases,[23] acyl imidazoles are more effective for the acylation of nitroalkanes. A combination of diethyl phosphorcyanidates and triethylamime allows the direct C-acylation of nitromethane by aromatic carboxylic

acids. The procedure is very simple, and the use of hazardous alkali nitronates is avoided (see Eq. 5.12).[24]



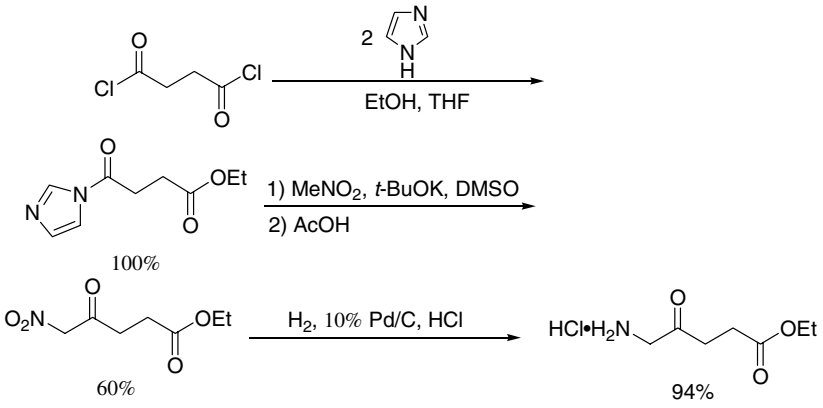

81% (5.12)

In summary, reactions of nitronates with acid anhydrides or acyl chlorides give the O-acylated products, and reactions with acyl imidazoles, phenyl esters, acyl nitriles, and enol-lactones gives the C-acylated products. (see Eq. 5.13).[25] The C/O selectivity of nitronate acylation by RCOX is qualitatively correlated with strength ($pK_a$) of the acid HX conjugated to the leaving group $X^-$.[25]



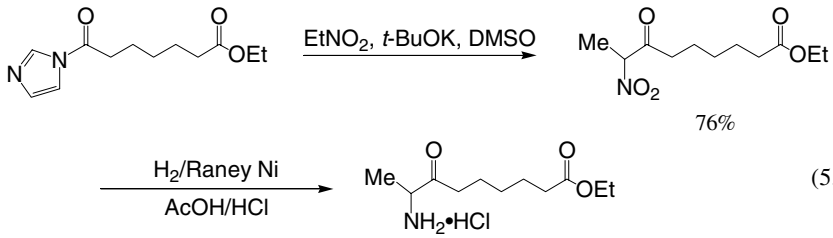

81% (5.13)

α-Nitro ketones are useful intermediates for synthesis of α-amino ketones such as α-aminolevulinic acid (5-ALA), which is a precursor for the preparation of protoporphyrin IX (see Scheme 5.3).[26] Selective reduction of the nitro group and concomitant hydrolysis are carried out under acidic catalytic hydrogenation conditions to give 5-ALA·HCl in 94% yield.




**Scheme 5.3.** Synthesis of δ-aminolevulinic acid (5-ALA).

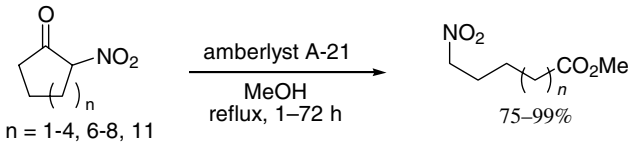
A precursor for biotin, 7-keto-8-aminopelargonic acid, is also prepared by acylation of nitromethane, followed by the selective reduction of the nitro group, as shown in Eq. 5.14.[27]




(5.14)

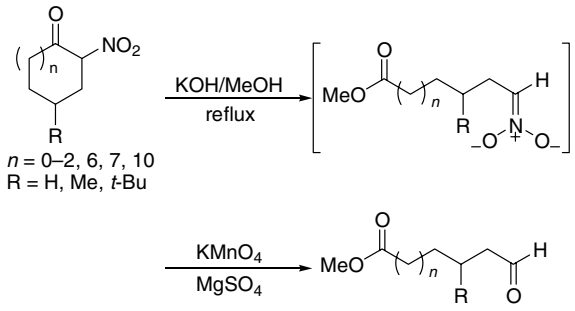
## 5.3 RING CLEAVAGE OF CYCLIC α-NITRO KETONES (RETRO-ACYLATION)

Because the anions of nitroalkanes are stable, retro-acylation of α-nitro ketones proceeds smoothly in the presence of a base catalyst. This type of reaction provides an important tool in organic synthesis.[28] Nucleophilic attack of water or alcohol to α-nitro cycloalkanones produces the ring cleavage with the formation of ω-nitro acids and ω-nitro esters. This type of cleavage is a well-known reaction,[29] but it has not been used in organic synthesis until quite recently. Ballini and coworkers have studied the effect of base and solvent for this reaction. They have found a significant improvement of the ring cleavage of cyclic α-nitro ketones using a weakly basic ion-exchange resin (amberlyst A-21) (Eq. 5.15).[30] α-Nitro cycloalkanones are cleaved to ω-nitro acids (71–97%) in aqueous media (0.05 M sodium hydroxide) and in the presence of a catalytic amount of cetyltrimethylammonium chloride (CTACl) as cationic surfactant.[28]



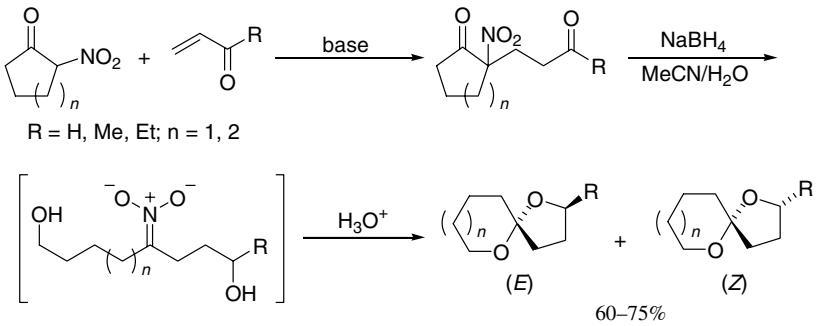

(5.15)

One-pot syntheses of 1,4-diketones, γ-oxoaldehydes, γ-ketoesters, and ω-oxoalkanoates have been reported by bond cleavage of cyclic α-nitroketones with KOH in methanol and subsequent Nef reaction (Section 6.1) with $KMnO_4$ (Eq. 5.16).[31]



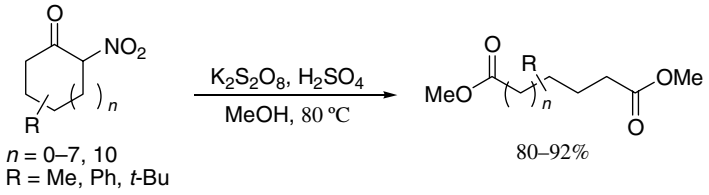

(5.16)

Regioselective reduction of 2-nitrocycloalkanones with sodium borohydride affords ω-nitro alcohols. This reaction is applied to the synthesis of spiroketals as shown in Eq. 5.17, in which spiro[4,5]- and spiro[4,6]ketal systems are obtained in good yields.[32]



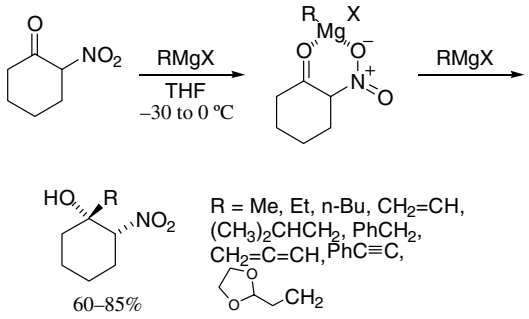

(5.17)

Oxidative cleavage of 2-nitrocyclohexanones gives α,ω-dicarboxylic acids or their esters, as shown in Eq. 5.18.[33]

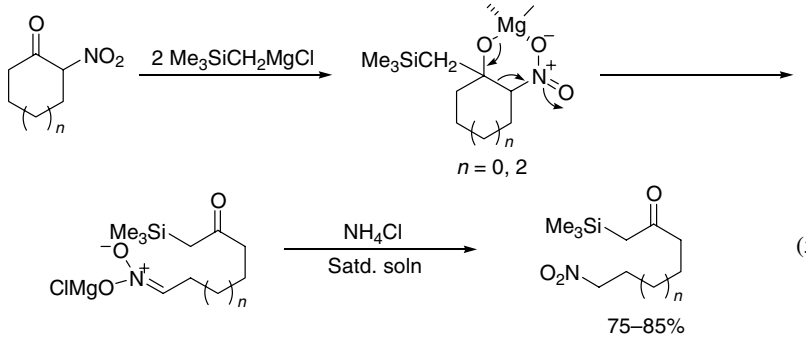



(5.18)

The reaction of organometallic reagents with cyclic α-nitroketones gives tertiary β-nitroalkanols (Eq. 5.19).[34] However, the reaction of the same nitro ketone with trimethylsilylmethylmagnesium gives ring cleavage products (Eq. 5.20).[35] Ballini postulates that the silicon β effect assists the cleavage of the C-C bond in the sense of the arrows.

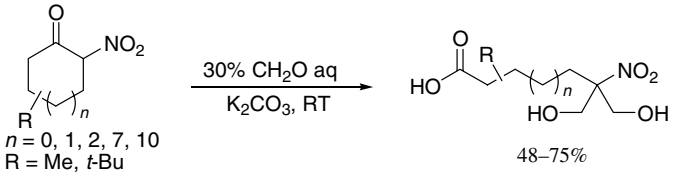



(5.19)



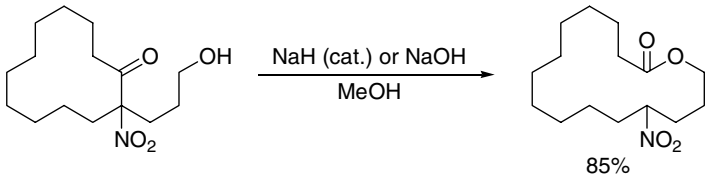

(5.20)

The reaction of α-nitrocycloalkanones with an aqueous solution of formaldehyde in the presence of potassium carbonate affords 2-nitro-1,3-diol-ω-alkanoic acids (Eq. 5.21).[36]



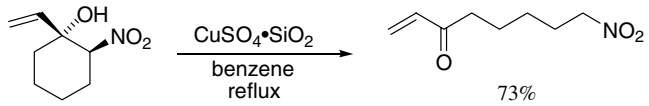

(5.21)

Ring enlargement of α-nitrocycloalkanones has been extensively used for the synthesis of macrocyclic compounds, as exemplified in Eq. 5.22.[37]




(5.22)

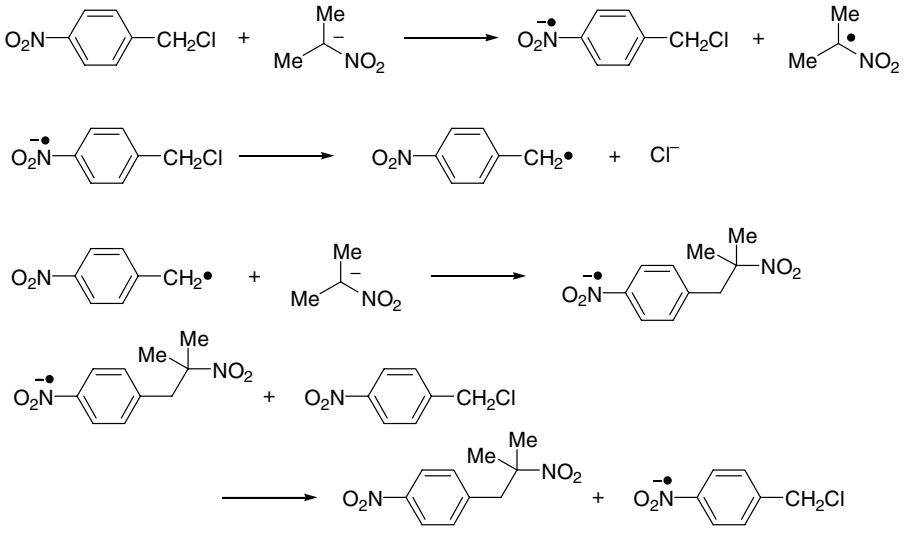
The retro-Henry reaction of 2-nitrocycloalkanols gives ω-nitro ketones, as shown in Eq. 5.23.[38]



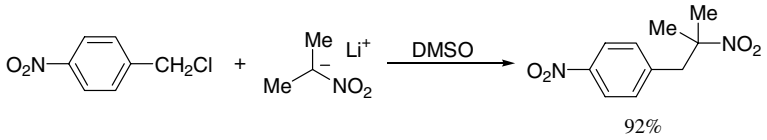

(5.23)

## 5.4 ALKYLATION OF NITRO COMPOUNDS VIA ALKYL RADICALS

The ability of a nitro group in the substrate to bring about electron-transfer free radical chain nucleophilic substitution ($S_{RN}1$) at a saturated carbon atom is well documented.[39] Such electron transfer reactions are one of the characteristic features of nitro compounds. Kornblum and Russell have established the $S_{RN}1$ reaction independently; the details of the early history have been well reviewed by them.[39] The reaction of *p*-nitrobenzyl chloride with a salt of nitroalkane is in sharp contrast to the general behavior of the alkylation of the carbanions derived from nitroalkanes; here, carbon alkylation is predominant. The carbon alkylation process proceeds via a chain reaction involving anion radicals and free radicals, as shown in Eq. 5.24 and Scheme 5.4 ($S_{RN}1$ reaction).[40]

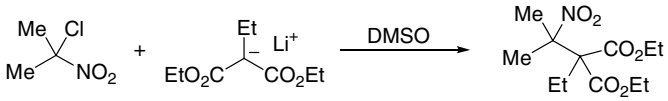



**Scheme 5.4.** $S_{RN}1$ reaction.



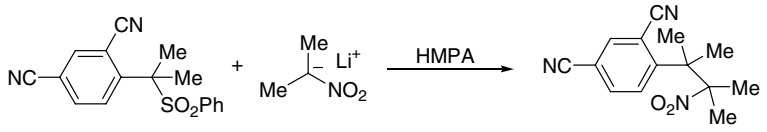

92% (5.24)

$S_{RN}1$ reactions using related *p*-nitrophenyl or *p*-nitrocumyl systems[41] as reductive alkylating agents have been studied by Kornblum and co-workers; these are well summarized in the reviews.[39] At the same time, Russell discovered the $S_{RN}1$ reaction of geminal halonitroalkanes with stabilized carbanions (see Eq. 5.25).[42] The products are readily converted into alkenes via elimination of nitro groups (see Section 7.3).

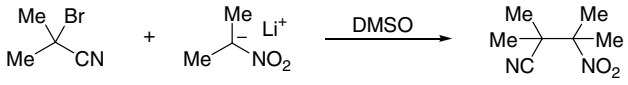



68% (5.25)

The cyano group is also a good electron acceptor for $S_{RN}1$ substrates, as shown in Eq. 5.26[43] and Eq. 5.27,[44] but a nitro group is a better electron acceptor than a cyano group.

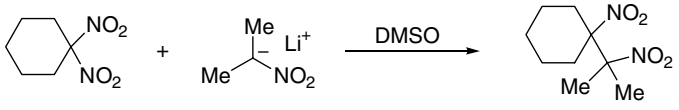



84% (5.26)

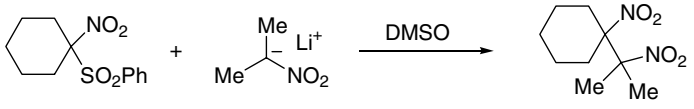



82% (5.27)

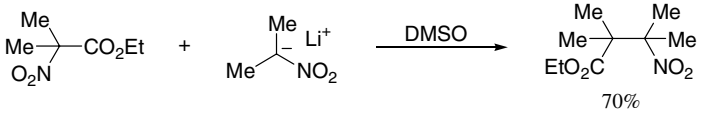
Geminal dinitro compounds,[45] α-nitro sulfones,[46] α-nitro esters,[47] or α-nitro nitriles[48] react with anions derived from nitroalkanes to give the $S_{RN}1$ products, as shown in Eqs. 5.28, 5.29, 5.30 and 5.31, respectively (Section 7.1).



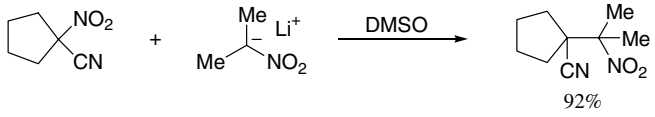

91% (5.28)




85% (5.29)

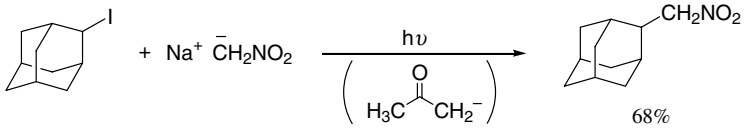



70% (5.30)



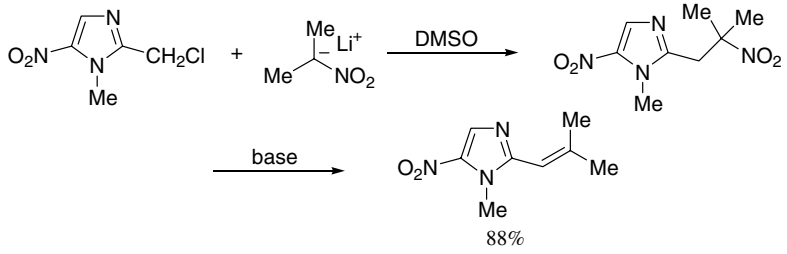

(5.31)

The anion of nitromethane is particularly reactive in $S_{RN}1$ reactions. Various kinds of tertiary nitro groups are replaced by a nitromethyl group on treatment with the anion of nitromethane (Section 7.1).[49] 2-Iodoadamantane reacts with the anion of nitromethane in the presence of acetone enolate (entrainment reaction) under irradiation of a 400-W UV lamp to give 2-nitromethyladamantane in 68% yield, (see Eq. 5.32).[50a] 1-Iodoadamantane also reacts with the anion of nitromethane in a similar way.[50b]



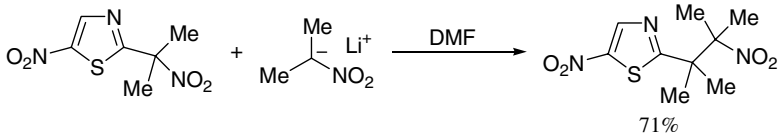

(5.32)

Crozet and co-workers have used $S_{RN}1$ reactions for synthesis of new heterocycles, which are expected to be biologically active (see also Section 7.3, which discusses synthesis of alkenes). For example, 2-chloromethyl-5-nitroimidazole reacts with the anion of 2-nitropropane to give 2-isopropylidene-5-nitroimidazole. It is formed via C-alkylation of the nitronate ion followed by elimination of $HNO_2$ (Eq. 5.33).[51a] Other derivatives of nitroimidazoles are also good substrates for $S_{RN}1$ reactions.[51b,c]



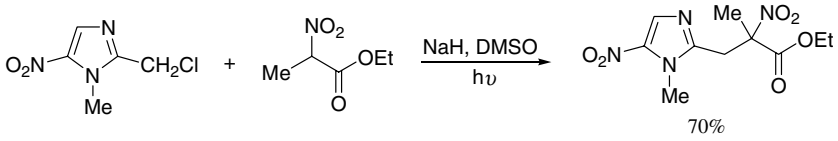

(5.33)

Reactions of nitrothiazole derivatives with anions of nitroalkanes, such as shown in Eq. 5.34, proceed via a $S_{RN}1$ mechanism.[52]



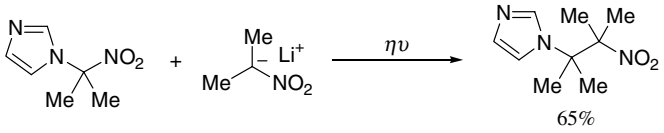

(5.34)

The anion derived from ethyl 2-nitropropionate reacts with various reductive alkylating agents ($S_{RN}1$ substrates) to give new unsymmetrically disubstituted nitro esters (Eq. 5.35), which are interesting precursors for unusual amino acids.[53]



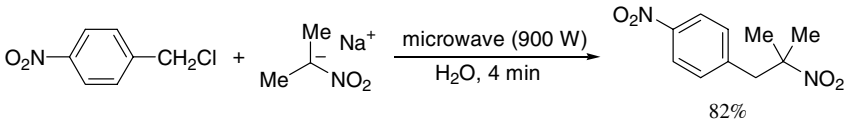

(5.35)

Gem-nitro imidazolyl alkanes undergo $S_{RN}1$ reactions with the anion of various nitroalkanes, as shown in Eq. 5.36.[54] The nitro group is replaced by hydrogen in 80–90% yield on treatment with $Bu_3SnH$ (see Chapter 7, which discusses radical denitration).



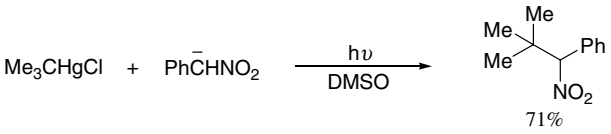

(5.36)

$S_{RN}1$ reactions are generally accelerated by irradiation with tungsten lamps (200–500 W) or fluorescent lamps. They are retarded in the presence of oxygen or other radical inhibitors. Recently, microwave irradiation has been shown to be effective in inducing $S_{RN}1$ reactions; the reaction of Eq. 5.37 proceeds under microwave irradiation (900 W, 5 min) in the presence of trace amounts of water.[55]



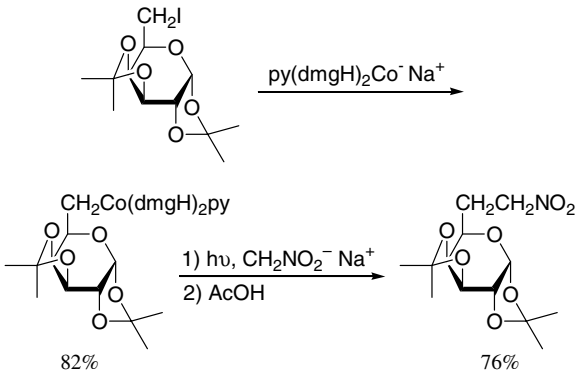

(5.37)

Alkyl mercury halides participate in a photo-stimulated radical chain reaction of the anion of nitroalkanes (see Eq. 5.38) in which a 275-W sun lamp is used.[56a–c] Primary, secondary, and tertiary alkyl radicals generated from alkyl mercury halides react with the anion of nitroalkanes to form new C-C bonds.



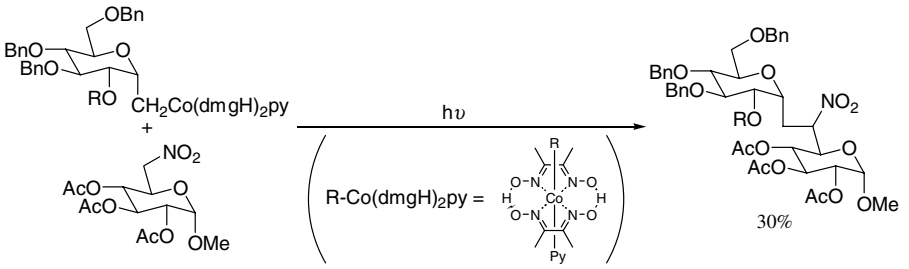

(5.38)

Branchaud and coworkers have used cobaloximes as alkyl radical precursors for the cross-coupling reaction with nitronates.[57] This method is very useful for producing branched-chain monosaccharides, as shown in Eq. 5.39.[57b]



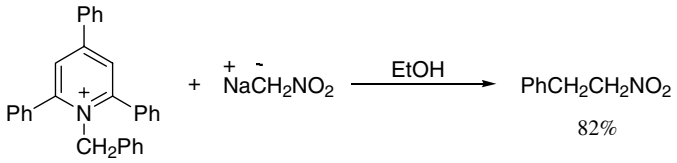

(5.39)

Martin and coworkers have used this strategy for synthesis of α- and β-(1,6)-linked C-disaccharides (Eq. 5.40).[58]



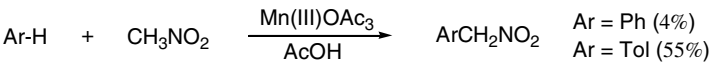

(5.40)

Carbon alkylation of simple nitronate anions is also possible by the reaction with *N*-substituted pyridiniums, as exemplified in Eq. 5.41. Such types of reactions are classified as $S_{RN}2$ reactions, in which electron transfer reactions from nitronate anions to pyridiniums are involved as key steps.[59]



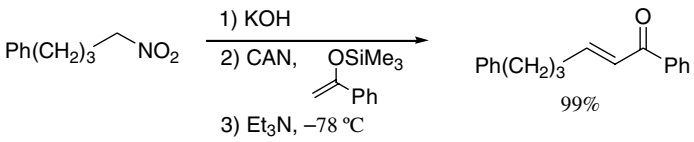

(5.41)

The anions derived from nitroalkanes are converted into the corresponding radicals on treatment with various oxidizing agents. The C-C bond-forming reactions using nitroalkyl radicals generated by this procedure are also important in organic synthesis. For example, aromatic nitromethylation can be carried out by heating a mixture of an aromatic compounds and Mn(III)$OAc_3$ in acetic acid (see Eq. 5.42).[60]



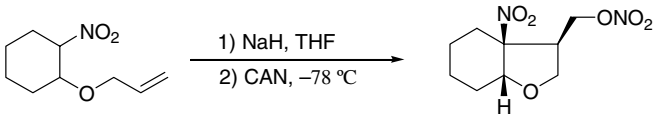

(5.42)

Recently, Narasaka and co-workers have found that 1-nitroalkyl radicals are generated by oxidation of *aci*-nitroanions with CAN, and they undergo the intermolecular addition to electron-rich olefins.[61] For example, when oxidation is carried out in the presence of silylenol ethers, β-nitroketones are formed in good yield. β-Nitroketones are readily converted into enones on treatment with base (see Section 7.3), as shown in Eq. 5.43.



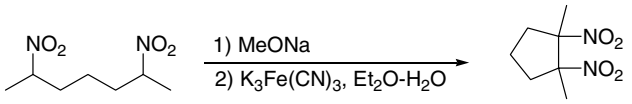

(5.43)

Interesting intramolecular cyclization of 1-nitroalkyl radicals generated by one-electron oxidation of *aci*-nitro anions with CAN is reported. As shown in Eq. 5.44, stereoselective formation of 3,4-functionalized tetrahydrofurans is observed.[62] 1-Nitro-6-heptenyl radicals generated by one electron oxidation of aci-nitroanions with CAN afford 2,3,4-trisubstituted tetrahydropyrans.[63] The requisite nitro compounds are prepared by the Michael addition of 3-buten-1-al to nitroalkenes.



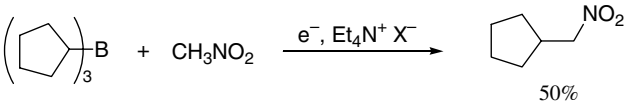

58% (5.44)

Radical cyclization of α,ω-dinitroalkanes is reported, as shown in Eq. 5.45. Oxidation of the dinitronate derived from 2,6-dinitroheptane with $K_3Fe(CN)_6$ in a two-phase system (water-ether) yields the cyclized vicinal dinitrocyclopentane in 71–85% yield in a *cis*-to-*trans* ratio of 60:40.[64]




71–85% (5.45)

Couplings of nitroalkyl radicals with nucleophiles such as $CN^-$, $N_3^-$, $NO_2^-$, and other nitrogen nucleophiles provides a useful method for the preparation of nitro compounds with such groups at the α-position.[49,65] The alkylation of nitromethane with trialkylborane is possible by electrolysis, in which alkyl radicals may be involved (Eq. 5.46).[66]




50% (5.46)

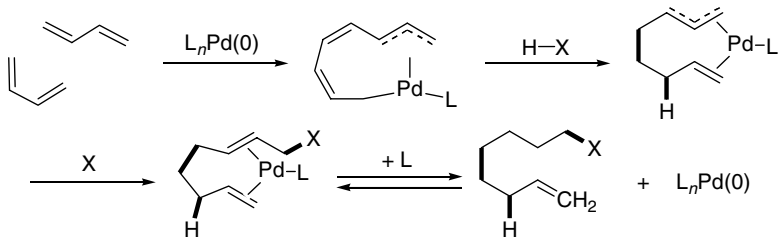
Oxidative cross-coupling reactions of alkylated derivatives of activated CH compounds, such as malonic esters, acetylacetone, cyanoacetates, and certain ketones, with nitroalkanes promoted by silver nitrate or iodine lead to the formation of the nitroalkylated products.[67] This is an alternative way of performing $S_{RN}1$ reactions using α-halo-nitroalkanes.

## 5.5 ALKYLATION OF NITRO COMPOUNDS USING TRANSITION METAL CATALYSIS

Monoanions derived from nitroalkanes are more prone to alkylate on oxygen rather than on carbon in reactions with alkyl halides, as discussed in Section 5.1. Methods to circumvent O-alkylation of nitro compounds are presented in Sections 5.1 and 5.4, in which alkylation of the α,α-dianions of primary nitro compounds and radial reactions are described. Palladium-catalyzed alkylation of nitro compounds offers another useful method for C-alkylation of nitro compounds. Tsuji and Trost have developed the carbon-carbon bond forming reactions using π-allyl Pd complexes. Various nucleophiles such as the anions derived from diethyl malonate or ethyl acetoacetate are employed for this transformation, as shown in Scheme 5.7. This process is now one of the most important tools for synthesis of complex compounds.[68a–b] Nitro compounds can participate in palladium-catalyzed alkylation, both as alkylating agents (see Section 7.1.2) and nucleophiles. This section summarizes the C-alkylation of nitro compounds using transition metals.

### 5.5.1 Butadiene Telomerization

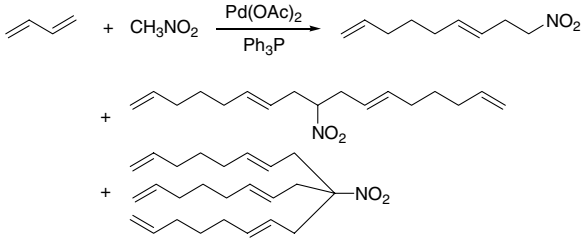
The palladium-catalyzed linear telomerization of 1,3-butadienes provides a useful method for the preparation of functionalized alkenes. A proposed catalytic cycle for the palladium-catalyzed




**Scheme 5.5.** Catalytic cycle in the palladium-catalyzed telomerization of 1,3-butadiene

telomerization of 1,3-butadiene is shown in Scheme 5.5; a wide range of H-X trapping reagents (X = nucleophilic carbon, oxygen, nitrogen, or sulfur) are used.[69]

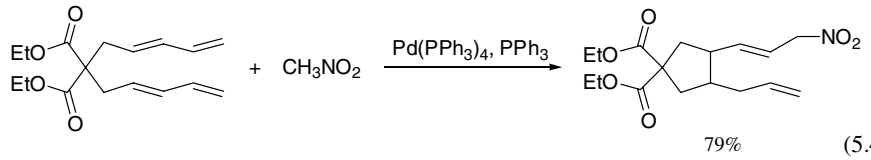
When nitromethane is used as a trapping reagent in the telomerization of butadiene using $Pd(OAc)_2$ and $Ph_3P$, mono-, di- and trialkylated compounds of nitromethane are formed (Eq. 5.47).[70] They are selectively formed by changing the ratio of nitromethane and butadiene. As the nitro groups are transformed into various functional groups, the reaction of Eq. 5.47 is very useful in organic synthesis.



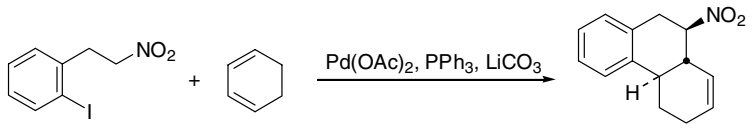

(5.47)

Butadiene telomerization using nitroethane as a trapping reagent is applied to the total synthesis of the natural product, recifeiolide, where the secondary nitro group is converted into the ketogroup by the Nef reaction, and the terminal double bond is converted into the iodide via hydro alumination (Scheme 5.6).[71]

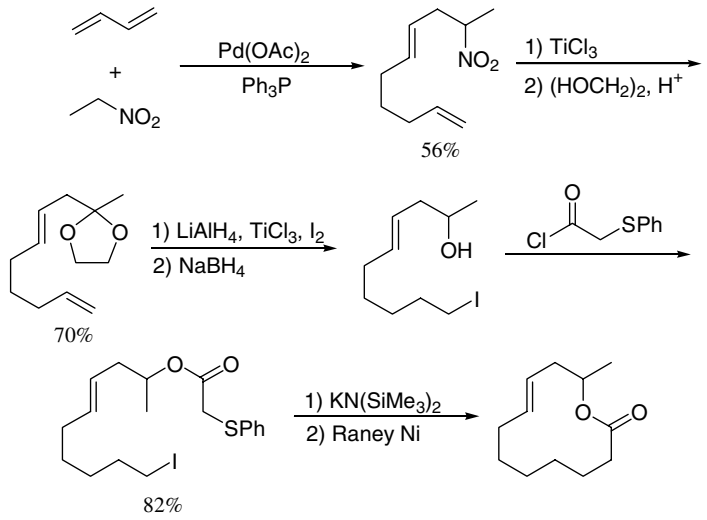
Extension to carbocyclization of butadiene telomerization using nitromethane as a trapping reagent is reported (Eq. 5.48).[72] Palladium-catalyzed carbo-annulation of 1,3-dienes by aryl halides is also reported (Eq. 5.49).[73] The nitro group is removed by radical denitration (see Section 7.2), or the nitroalkyl group is transformed into the carbonyl group via the Nef reaction (see Section 6.1).




(5.48)

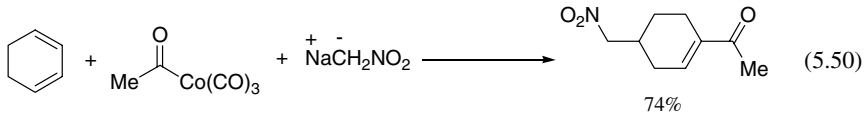



(5.49)




**Scheme 5.6.** Synthesis of recifeiolide

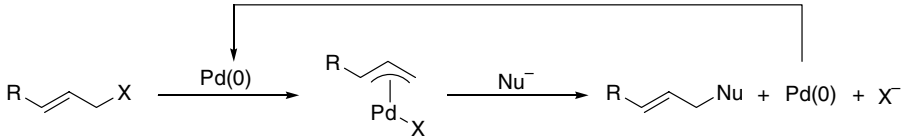
Nitronate anions react with (π-allyl)cobalt complexes prepared from acylation of 1,3-dienes by acetylcobalt tetracarbonyl to produce nitro enones (Eq. 5.50).[74]




(5.50)

### 5.5.2 Pd-Catalyzed Allylic C-Alkylation of Nitro Compounds

The palladium-catalyzed allylic alkylation of soft nucleophiles (Tsuji-Trost reaction) represents one of the most useful organic transformations. Various allylating reagents and nucleophiles can participate in this reaction, as summarized in Scheme 5.7. Although allyl acetates, allyl carbonates, or 1,3-dienemonoepoxides are generally used as alkylating reagents, allylic nitro compounds also can be used as alkylating reagents (see Section 7.1). Active methylene compounds are generally used as nucleophiles in Tsuji-Trost reaction. Nitroalkanes, α-nitro ketones, α-nitro esters, and α-nitro sulfones can be also used as nucleophiles for this transformation.

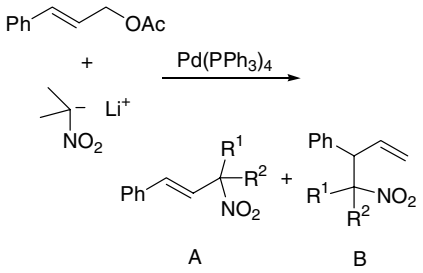



X = OAc , OC(O)OR, $SO_2Ph$, $NO_2$, $OP(O)(OR)_2$, $NR_2$, SR, etc.

NuH = $CH_2(CO_2R)_2$, $CH_2(CN)CO_2R$, $CH_2(SO_2Ph)CO_2R$, $CH_2(NO_2)CO_2R$, $CH_2(NO_2)SO_2Ph$, $CH_2(SO_2Ph)_2$, etc.

**Scheme 5.7.** Pd(0) catalyzed allylic alkylation

The monoanions of primary nitroalkanes, phenylnitromethane, and α-nitro esters are all preferentially C-alkylated by cinnamyl acetate and 2-butenyl acetate in 50–89% yield in the presence of Pd catalyst (Eq. 5.51).[75] The α-nitro ester gives the C-alkylate in 89% yield, but 2-nitropropane gives the C-alkylate in only 29% yield. The main product is cinnamaldehyde, which is derived from O-alkylation.[75a]

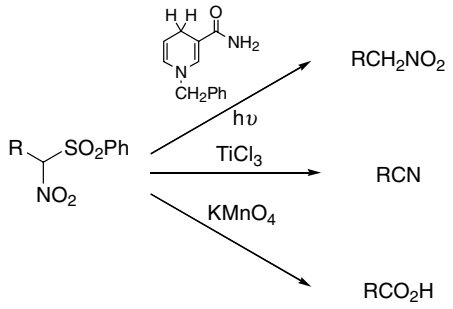



| $R^1$ | $R^2$ | Yield | A/B |
|---|---|---|---|
| $CO_2Et$ | Et | 89% | 97/3 |
| Me | Me | 29% | 93/7 |

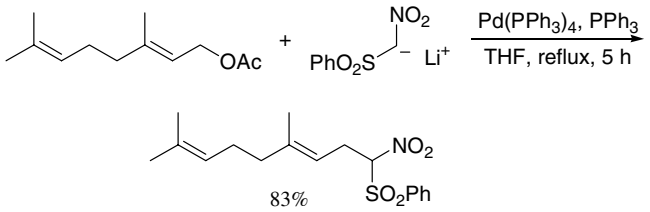
(5.51)

Wade and coworkers have found that α-nitro sulfones are useful reagents in organic synthesis because they are converted into nitroalkanes, nitriles, or carboxylic acids (see Eq. 5.52).[76]

(Phenylsulfonyl)nitromethane is preferentially C-alkylated by allylic acetates in the presence of $Pd(PPh_3)_4$ (5 mol%) to give various α-nitro sulfones as shown in Eq. 5.53.[76]

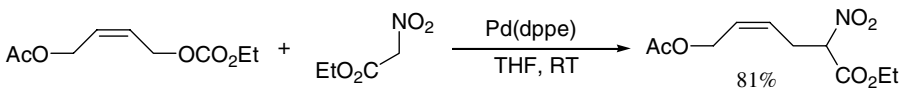



(5.52)



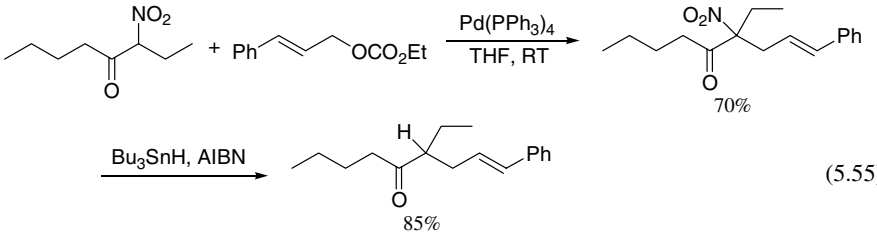

(5.53)

Allylic carbonates are better electrophiles than allylic acetates for the palladium-catalyzed allylic alkylation.[77] Reaction of Eq. 5.54 shows the selective allylic alkylation of α-nitro ester with allylic carbonates without affecting allylic acetates.[78]



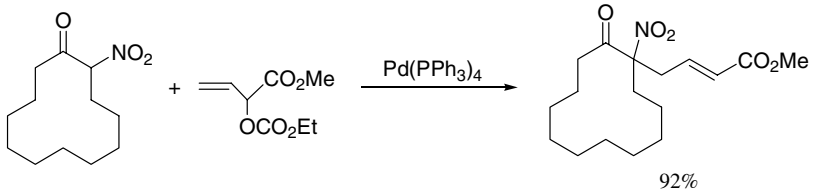

(5.54)

As the nitro group is removed by radical denitration with $Bu_3SnH$, allylic alkylation of α-nitro ketones with allyl carbonates in the presence of Pd(0) followed by denitration with $Bu_3SnH$ provides a new regio-selective allylation of ketones under neutral conditions (Eq. 5.55).[79]

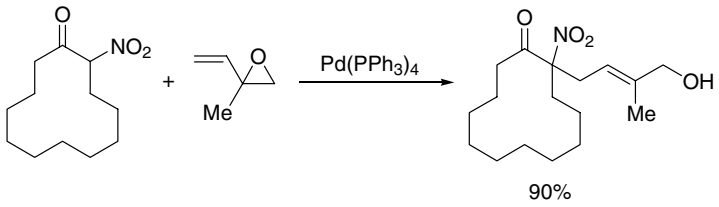



(5.55)

2-Nitrocycloalkanones can be successfully C-allylated by Pd(0)-catalyzed reaction with various allyl carbonates and 1,3-dienemonoepoxides under neutral conditions, as shown in Eqs. 5.56 and 5.57, respectively.[80a] The product of Eq. 5.56 is converted into cyclic nitrone via the reduction of nitro group with $H_2$-Pd/C followed by hydrolysis and cyclization.[80b]

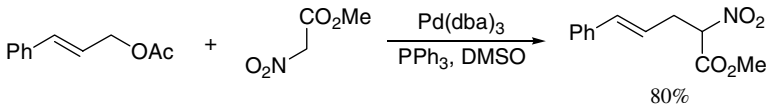



(5.56)



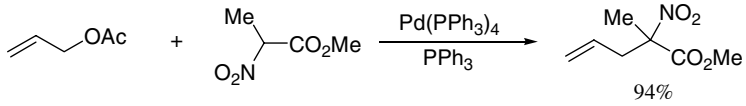

(5.57)

Recent papers have disclosed that Pd(0) catalyzed allylic alkylations under neutral conditions are not limited to allylic carbonates or epoxides but also can be extended in many cases to the more popular allylic acetates (Eq. 5.58).[81a]



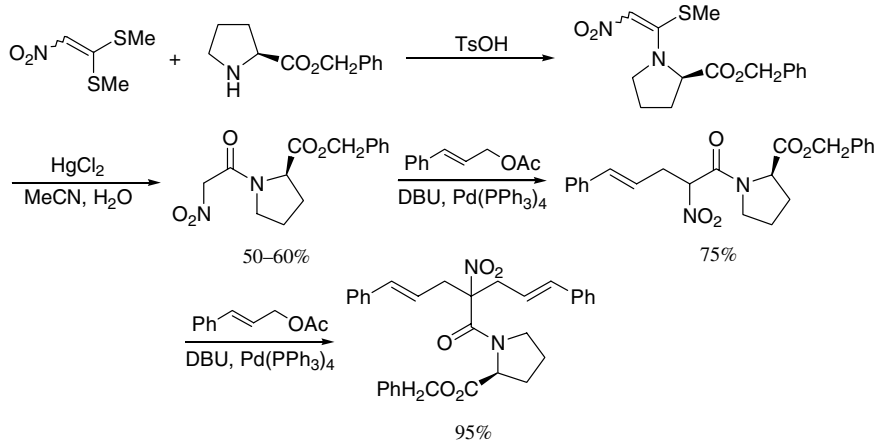

(5.58)

Wong and co-workers have prepared various quaternary α-nitro-α-methyl carboxylic acid esters by the palladium-catalyzed allylic alkylation of α-nitropropionate ester (Eq. 5.59). The products can be kinetically resolved by using α-chymotrypsin and are converted into optical active α-methyl α-amino acids. Such amino acids are important due to the unique biological activity of these nonproteinogenic α-amino acids.[82]



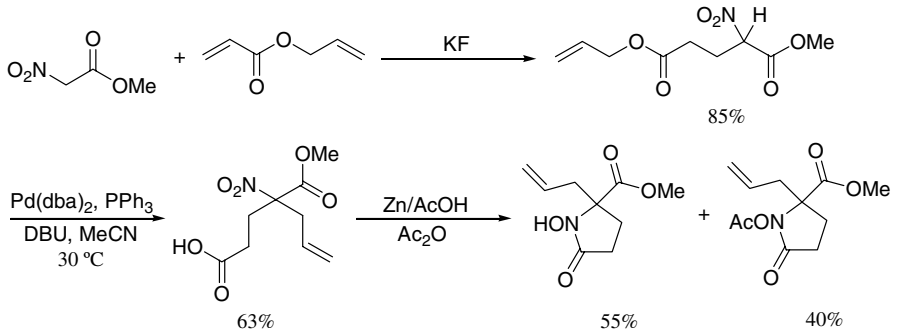

(5.59)

Rajappa and co-workers have reported synthesis of dipeptides with an α,α-bisallylglycine residue at the $NH_2$-terminal, which are biologically important.[83] Their strategy is based on (1) nitroacetylation of an amino acid derivative, (2) regioselective bisallylation by Pd-catalyzed reaction, and (3) generation of the free terminal $NH_2$ from the $NO_2$ group as shown in Scheme 5.8. Esters of L-proline, L-valine, and L-phenylalanine are converted into the corresponding *N*-nitroacetyl derivatives using 1,1-bis(methylthio)-2-nitroethylene[84] (see Section 4.2, Michael addition). Subsequent palladium-catalyzed allylation followed by reduction with Zn in AcOH gives the desired dipeptides.

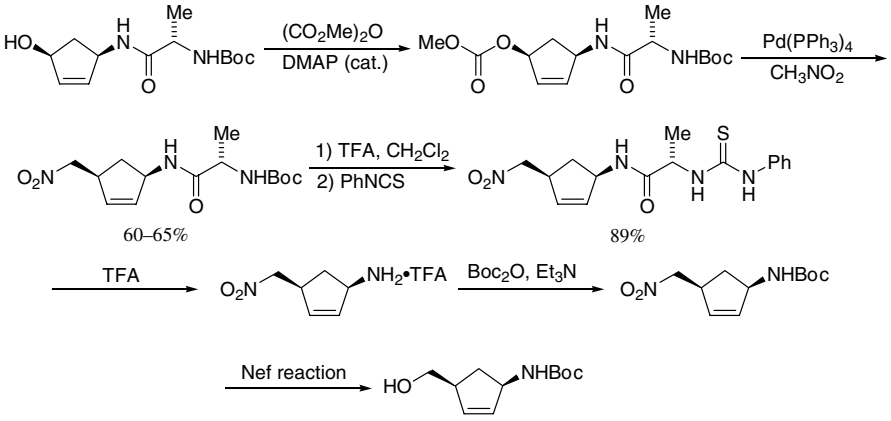



**Scheme 5.8.**

Hydroxamic acids constitute an important class of siderophores, which play a major role in iron solubilization and transport. Some of them are important as therapeutic agents. The Michael addition of nitroacetyl proline esters to allyl acrylate followed by Pd(0)-catalyzed intramolecular allyl transfer and subsequent reduction of the nitro group yields a novel class of cyclic hydroxamic acids related to pyroglutamic acid (Scheme 5.9).[85]



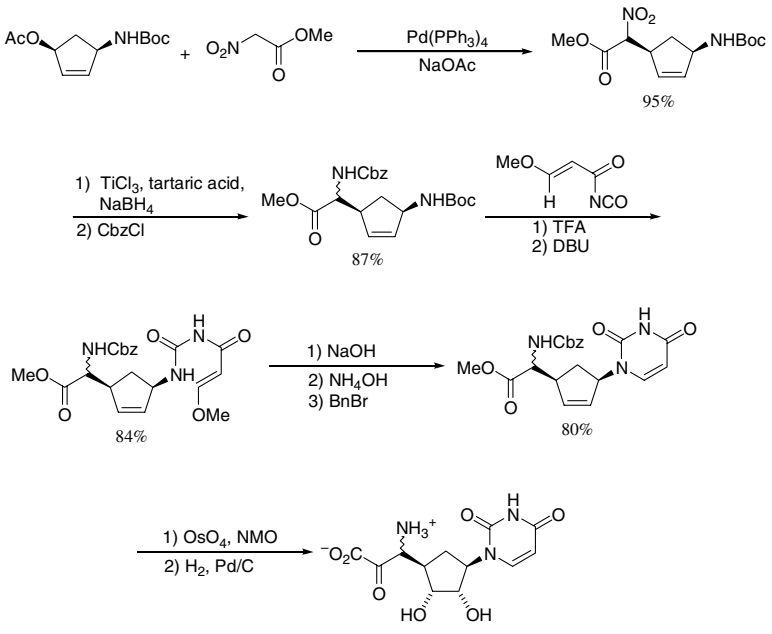

**Scheme 5.9.**



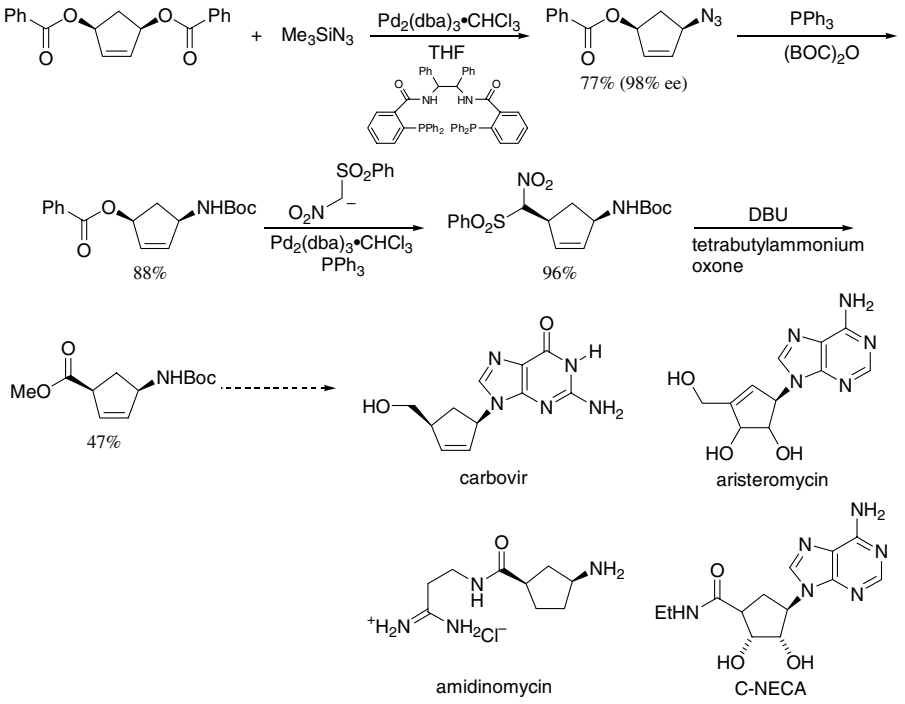

**Scheme 5.10.**

1,4-*cis*-Disubstituted cyclopentene precursors of carbocyclic nucleosides are prepared by acyl-nitroso hetero Diels-Alder reaction and subsequent Pd(0)-catalyzed allylic alkylation. Acylnitroso dienophiles derived from amino acids are used for asymmetric hetero Diels-Alder reaction. The alcohol in Scheme 5.10, prepared by this route,[86] is converted into the corresponding nitromethyl group by Pd(0)-mediated alkylation.[87] Removal of the L-alanine side chain followed by the Nef reaction leads to an important intermediate for the preparation of carbovir, aristermycin, and related analogs, which show potent and selective anti-HIV activity.[88a] A short, enantioselective synthesis of the carbocyclic nucleoside carbovir is also reported, in which the reaction of Pd catalyzed allylation of nitro compounds is used in a key step.

Miller and coworker report a total synthesis of carbocyclic polyoxin C from *cis*-(*N*-*tert*-butylcarbamoyl)cyclopent-2-en-1-ol, as shown in Scheme 5.11.[89] This synthesis features a




**Scheme 5.11.**



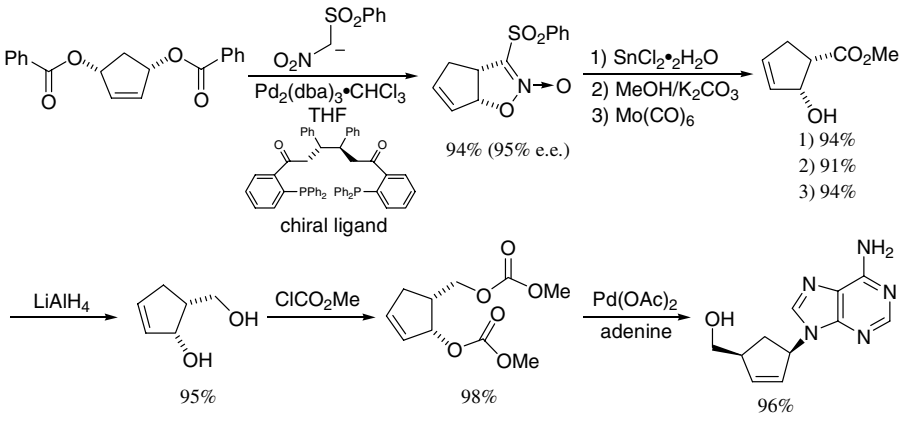

**Scheme 5.12.**

Pd(0)-catalyzed substitution reaction, a novel, mild reduction of α-nitro ester to an amino acid ester with $TiCl_3$, and an improved procedure for uracil ring formation.

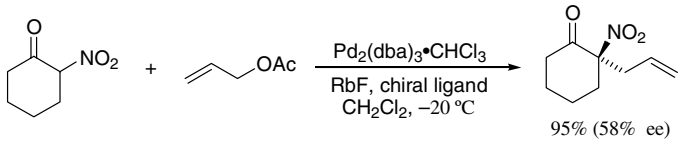
Trost and co-workers have explored asymmetric transition metal-catalyzed allylic alkylations. Details on this subject have been well reviewed by Trost and others.[90] With the use of asymmetric palladium-catalyzed desymmetrization of meso-2-ene-1,4-diols, *cis*-1,4-dibenzoyloxy-2-cyclopentene can be converted to the enantiometrically pure *cis*-4-*tert*-butoxycarbamoyl-1-methoxycarbonyl-2-cyclopentene.[91] The product is a useful and general building block for synthesis of carbocyclic analogs of nucleosides as presented in Scheme 5.12.

Another approach to asymmetric syntheses of carbonucleosides is presented in Scheme 5.13. The reaction of *cis*-1,4-dibenzoyloxy-2-cyclopentene with the lithium salt of (phenylsulfonyl)nitromethane in the presence of Pd catalyst and a chiral ligand gives a chiral isoxazoline *N*-oxide, in which C-alkylation and O-alkylation of nitronates take place simultaneously. Deoxygenation with $SnCl_2{\cdot}2H_2O$ in MeCN gives the isoxazoline in 94% yield, which is converted into the corresponding hydroxy ester on treatment with MeOH in the presence of $K_2CO_3$ followed by reduction with $Mo(CO)_6$. Thus, diastereo- and enantio- selective hydroxyalkoxycabonylation of cyclopentene ring provides useful building blocks for the synthesis of important antiviral carbanucleosides, as shown in Scheme 5.13.[92]

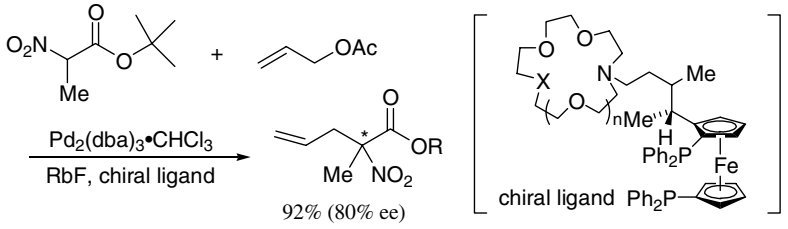
Enantioselective allylations of α-nitro ketones and α-nitro esters with allyl acetates are carried out in the presence of 2 equiv of alkali metal fluorides (KF, RbF, CsF) and 1 mol% palladium catalysts prepared in situ from $Pd_2(dba)_3{\cdot}CHCl_3$ and chiral phosphine ligands. Moderate enantio-selectivity (ca 50% ee) is reported for allylation of α-nitroketones (Eq. 5.60). The highest selectivity (80% ee) is observed for allylation of the reaction of *tert*-butyl ester (Eq. 5.61).[93]




**Scheme 5.13.**

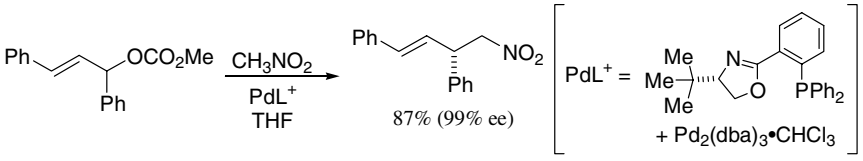



(5.60)

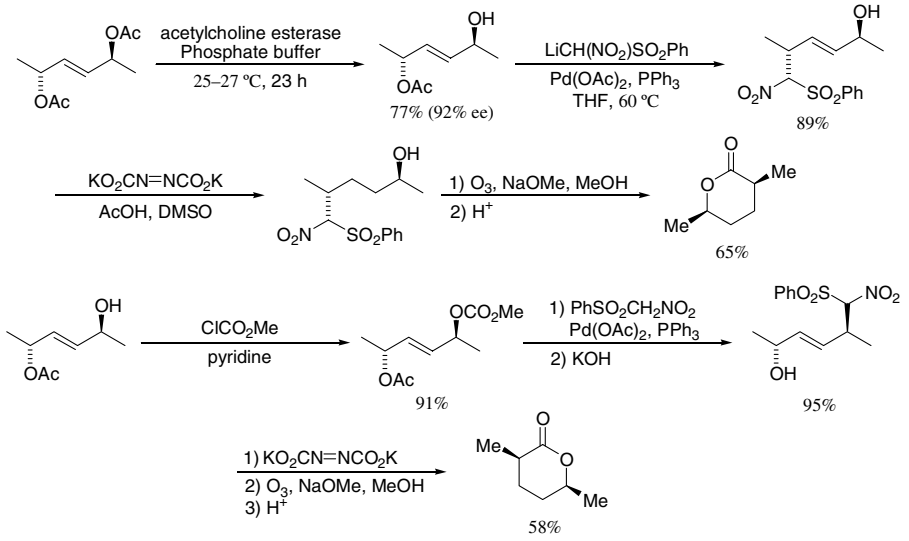



(5.61)

Asymmetric synthesis of tricyclic nitro ergoline synthon (up to 70% ee) is accomplished by intramolecular cyclization of nitro compound Pd(0)-catalyzed complexes with classical $C_2$ symmetry diphosphanes.[94] Palladium complexes of 4,5-dihydrooxazoles are better chiral ligands to promote asymmetric allylic alkylation than classical catalysts. For example, allylic substitution with nitromethane gives enantioselectivity exceeding 99% ee (Eq. 5.62).[95] Phosphinoxazolines can induce very high enatioselectivity in other transition metal-catalyzed reactions.[96] Diastereo- and enantioselective allylation of substituted nitroalkanes has also been reported.[95b]




(5.62)



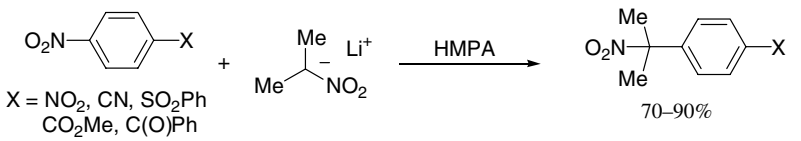

**Scheme 5.14.**

An enantio-selective enzymatic hydrolysis of *meso*-(*E*)-2,5-diacetoxy-3-hexene gives (+)-(*E*)-(2*S*,5*R*)-5-acetoxy-3-hexen-2-ol in 77% yield (92% ee).[97] The monoacetate with its two allylic groups offers possibilities for stereo-controlled introduction of nucleophiles via Pd(0) catalysis. Synthesis of both enantiomers of the Carpenter bee pheromone based on this strategy is presented in Scheme 5.14.[98]

Tamura and coworkers have reported a novel C-C-bond formation reaction using organotellurium chlorides and lithium nitronates. A combination of the bis(organo)tellurium dichlorides [$(R^1COCH_2)_2TeCl_2$] and $LiC(NO_2)R^2R^3$ leads to the coupling products $R^1COCH = CR^2R^3$ in good yields. The reaction proceeds by a polar mechanism that is initiated by coordination of the nitronate oxygen atom to the tellurium followed by intramolecular C-C bond formation and subsequent elimination of nitro and tellurium moieties.[99]

## 5.6 ARYLATION OF NITRO COMPOUNDS

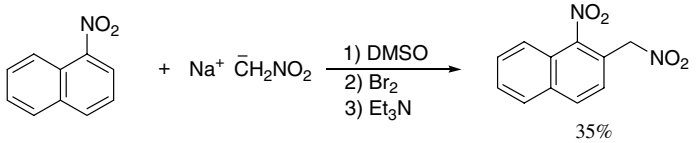
Arylations of nitro compounds can be achieved by aromatic nucleophilic substitution using aromatic nitro compounds, as discussed in Chapter 9.[100] Kornblum and coworkers reported displacement of the nitro group of nitrobenzenes by the anion of nitroalkanes. The reactions are usually carried out in dipolar aprotic solvents such as DMSO or HMPA, and nitroaromatic rings are substituted by a variety of electron-withdrawing groups (see Eq. 5.63).[101]



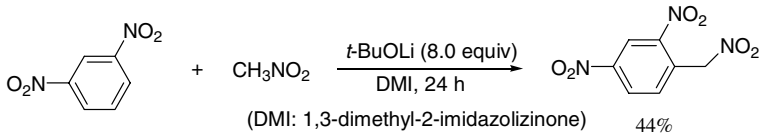

(5.63)

There are many cine substitution reactions of aromatic nitro compounds using various nucleophiles.[100] In this chapter, the cine-substitution reactions using the anion of nitroalkanes

are summarized. 1-Nitronaphthalene reacts with the anion of nitromethane to give the nitromethylated product, as shown in Eq. 5.64.[102] Suzuki and coworkers have extended this reaction to *m*-dinitrobenzene (Eq. 5.65). Although the reaction proceeds slowly, this is the first example of nitromethylation of monocyclic nitrobenzenes. The reaction of Eq. 5.64 requires additional oxidizing agents to complete the reaction, but that of Eq. 5.65 does not need the external oxidizing agents.[103]

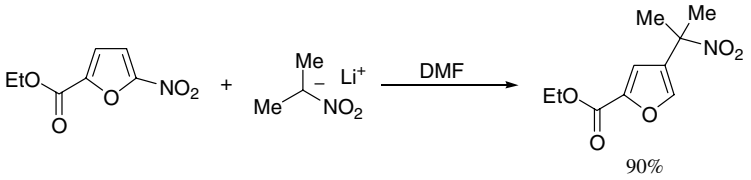



(5.64)



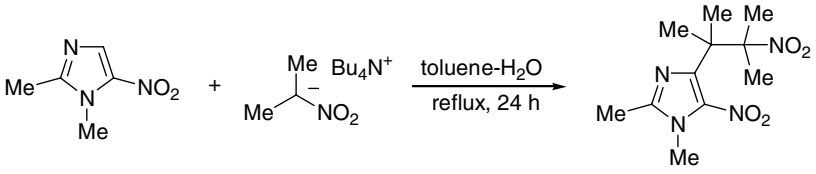

(5.65)

In general, heterocyclic nitro compounds undergo cine substitution reactions more readily than nitrobenzenes. For example, the reaction of 5-acyl- or 5-alkoxycarbonyl-2-nitrofurans with the anion of nitroalkanes gives cine substitution products in excellent yields (Eq. 5.66).[104]



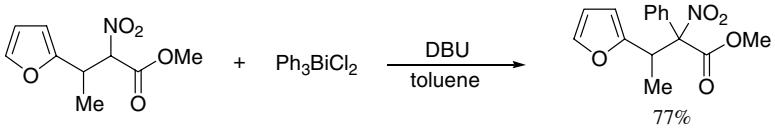

(5.66)

The reaction of 1,2-dimethyl-5-nitroimidazole with 2-nitropropane anion gives the new highly branched imidazole derivative, which is formed via cine-substitution and $S_{RN}1$ substitution (Eq. 5.67).[51b]



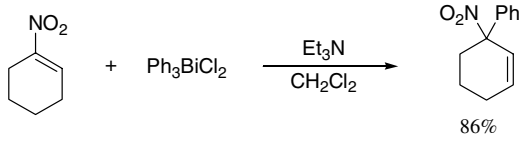

(5.67)

Barton and coworkers have explored the arylation of various nucleophiles including nitroalkanes using bismuth reagents.[105] Reaction of 2-nitropropane with triphenylbismuth carbonate gives 2-nitro-2-phenylpropane in 80% yield.[106] Recently, this arylation has been used for the synthesis of unusual amino acids. Arylation of α-nitro esters with triphenylbismuth dichloride followed by reduction gives unique α-amino acids (Eq. 5.68).[107]



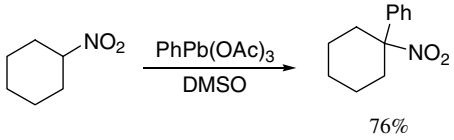

(5.68)

The reaction of 1-nitrocyclohexene with triphenylbismuth dichloride in the presence of triethylamine gives the deconjugated arylated product, as shown in Eq. 5.69.[108]




(5.69)

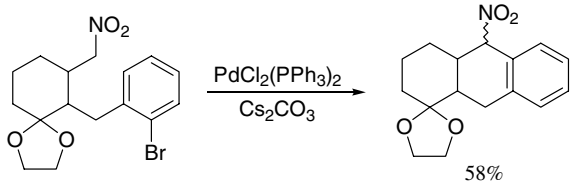
Aryllead triacetates are also good reagents for arylation of stabilized carbanions, including the anion of nitroalkanes (Eq. 5.70).[109] As a related reaction, α-vinylation[110] or α-acetylation[111] of nitro compounds is possible using vinyllead triacetates or alkynyllead triacetates.




(5.70)

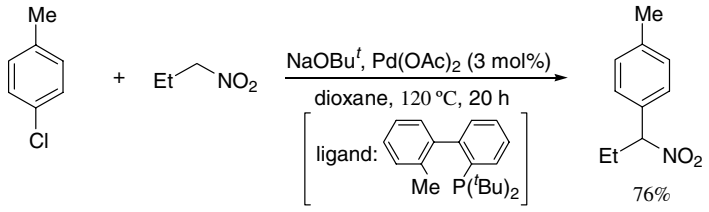
In recent years, a variety of hypervalent iodine reagents have been available. The versatility of these hypervalent organoiodine reagents in organic synthesis has been well recognized. Diaryliodonium salts constitute an important reagent class for the transfer of aryl groups. These iodonium ion salts have been used effectively in C-arylation of a variety of nucleopohiles.[112] The arylation of the anion of nitroalkanes with diaryliodonium salts was already reported in 1963.[113]

Intramolecular cyclization using palladium-catalyzed arylation of nitro compounds has been reported recently (Eq. 5.71).[114]




(5.71)

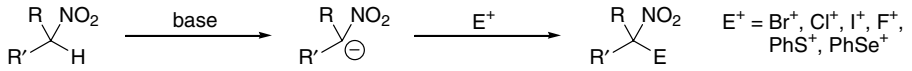
Buchwald and co-workers have developed highly active catalysts consisting of bulky, electron-rich phosphine ligands with a biphenyl backbone combined with $Pd(OAc)_2$ for the arylation of ketones or nitroalkanes (Eq. 5.72).[115]




(5.72)

## 5.7 INTRODUCTION OF HETEROATOMS TO NITROALKANES

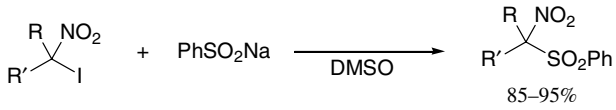
The anion derived from nitroalkanes react with various electrophiles to give α-hetero-substituted nitroalkanes (Scheme 5.15).[116] Halogenation of nitroalkanes is especially well known and very




**Scheme 5.15.**

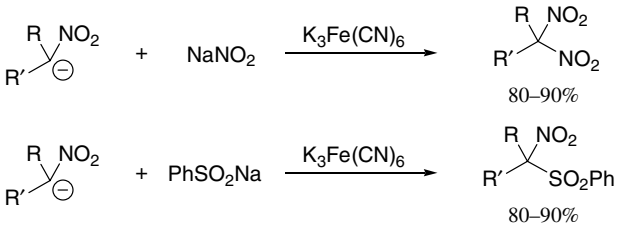
simple, except for fluorination. The widespread interest in halogenated nitro compounds mainly stems from their antimicrobial and insecticide activities.[116b]

The reaction of α-bromo or α-iodonitroalkanes with sodium benzenesulfinate gives α-nitro sulfones in 85–95% yields (Eq. 5.73), which proceeds via $S_{RN}1$ reaction (Section 5.4).[117]




(5.73)

α-Nitrosulfones react with various nucleophiles to give the $S_{RN}1$-alkylated products, as discussed in Section 5.4. α,α-Dinitro compounds, α-nitrosulfones, and α-nitronitriles are prepared in excellent yields when nitroalkane salts are coupled to nitrite, benzensulfinate, and cyanide ions in the presence of potassium ferricyanide (Eqs. 5.74 and 5.75) (see Section 5.4).

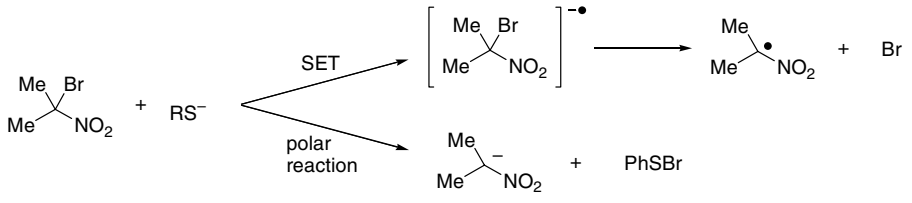



(5.74)

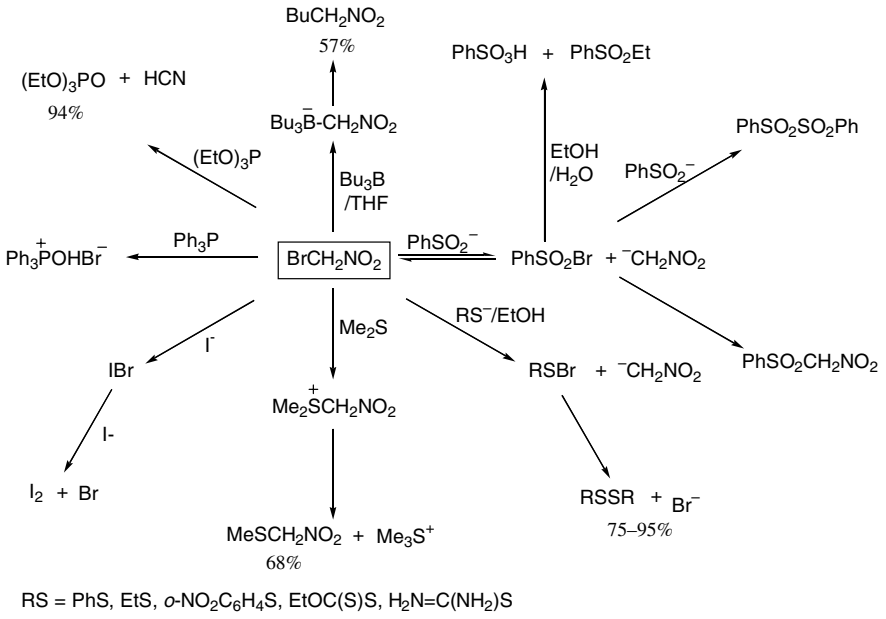
(5.75)

Bowman has surveyed the reactions of α-substituted aliphatic nitro compounds with nucleophiles, which undergo either $S_{RN}1$ substitution or polar reaction (Scheme 5.16).[118] The reactions between a wide variety of nucleophiles and $BrCH_2NO_2$ are shown in Scheme 5.17.[119a–b] All the thiolates, $PhSO_2^-$ and $I^-$ attack Br to liberate the anion of nitromethane. The hard nucleophiles, $MeO^-$, $OH^-$, and $BH_4^-$ attack the hard $H^+$ electrophilic center. Phosphorous nucleophiles attack the oxygen electrophilic center, and only $Me_2S$ attacks the carbon electrophilic center.

Bromonitromethane is used for the preparation of nitrocyclopropane. The reaction of *N*-benzylmaleimide and bromonitromethane in the presence of base gives the azabicyclo[3.1.0] hexane ring system. Many bases have been tried to improve the yield; however, amidine base, particularly 1,2-dimethyl-1, 4, 5, 6-tetrahydropyrimidine (DMTHP), gives the best yield



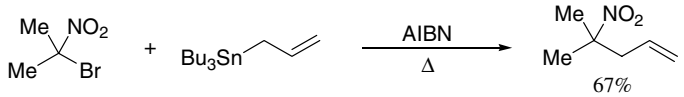

**Scheme 5.16.**



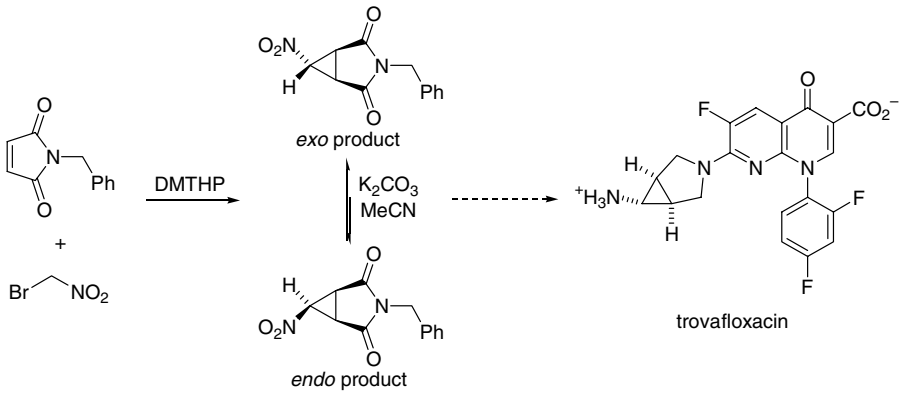

**Scheme 5.17.**

(30–35%). This reaction is used for a total synthesis of trovafloxacin (Scheme 5.18).[120] Trovafloxacin is a new and powerful antibiotic that is active against a wide variety of microorganisms.[121]

α-Bromonitro compounds yield α-nitro radicals on treatment with allyltin compounds to give allyl coupling products (Eq. 5.76).[122]



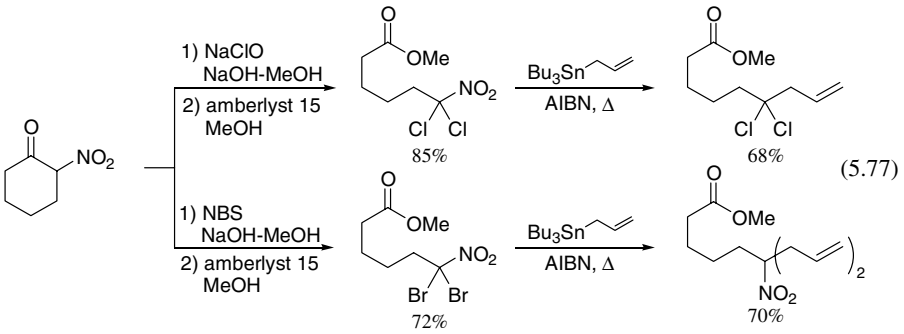

(5.76)




**Scheme 5.18.**

Ring cleavage often represents a particularly effective route to α,ω-difunctionalized frameworks. As discussed in Section 5.4, 2-nitrocyclocycloalkanones are able to produce a consistent array of functionalized molecules through an easy nucleophilic retro-Claisen condensation. Treatment of 2-nitrocycloalkanones with basic solution of sodium hypochlorite leads to the formation of ω,ω-dichloro-ω-nitroalkanoic acids. The ring cleavage-bromination with NBS and MeONa in MeOH leads to the formation of the corresponding bromides. The reaction of these halides with allylstannane in the presence of AIBN gives the denitro-allylated or debromo-allylated products, depending on the halides, as shown in Eq. 5.77.[123]

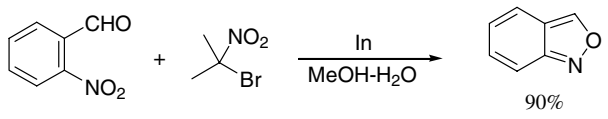
Indium-mediated reductive cyclization of 2-nitroacylbenzenes into 2,1-benzisoxazoles in




(5.77)

aqueous media is catalyzed by the presence of 2-bromo-2-nitropropane (Eq. 5.78).[124] The mechanism is not clear yet; the electron transfer to 2-bromo-2-nitropropane may induce the reduction.

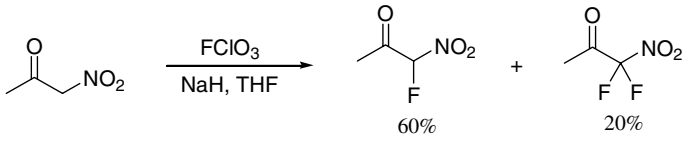
The potassium salts of nitro compounds are fluorinated on treatment with $FClO_3$, but it is




(5.78)

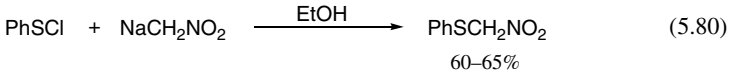
still troublesome to handle the fluorinating agents. Safer methods are highly desired (Eq. 5.79).[125,126]

α-Nitrosulfides have been often used in organic synthesis, especially (phenylthio)ni-



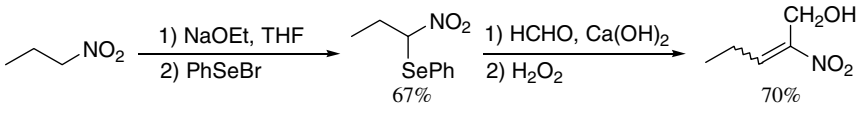

(5.79)

tromethane, which is a convenient reagent for synthesis of furan, for preparation of α-substituted thiol esters via the Michael addition followed by the Nef reaction and for the preparation of β-lactam.[127] This useful reagent is prepared by sulfenylation of nitromethane with phenysulfenyl chloride (Eq. 5.80).[128] Alternatively, this reagent may be prepared from the nitration of the dianion derived from (phenylthio)acetic acid.[129]



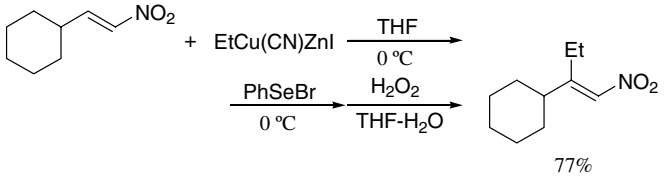

(5.80)

In a similar way, α-nitroselenides are prepared via the reaction of nitronates with phenylselenyl bromide, which gives a new synthetic method of 1-nitroalkenes from nitroalkanes.[130] The sequence of α-selenation, nitro-aldol reaction, and oxidation provides a useful method for the preparation of nitroalkenes with a hydroxymethyl group (Eq. 5.81).[131]



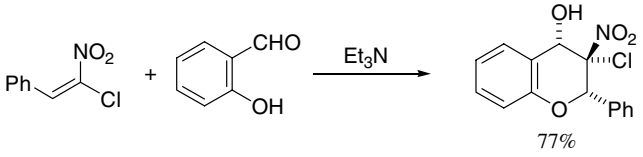

(5.81)

This strategy is applied to a general method for the preparation of 2,2-disubstituted 1-nitroalkenes. Conjugate 1,4-addition of complex zinc cuprates to 1-nitroalkenes, followed by trapping with phenylselenyl bromide and subsequent oxidative elimination, affords the corresponding 2,2-disubstituted 1-nitroalkenes in good yields (Eq. 5.82).[132]



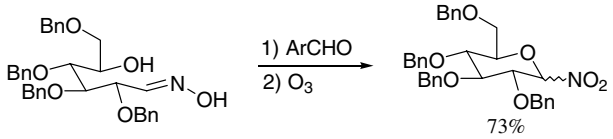

(5.82)

The review by Barrett (Ref. 127) documents synthetic application of hetero-substituted nitroalkenes (see also Chapter 4). 1-Chloro-1-nitroalkenes are readily obtained either by the Henry reaction of chloronitromethane with aldehydes or chlorination of 1-nitroalkenes. Dauzonne and coworkers have used 1-chloro-1-nitroalkenes for construction of dihydrobenzofuran or dihydrobenzopyran frameworks. (Eq. 5.83).[133]

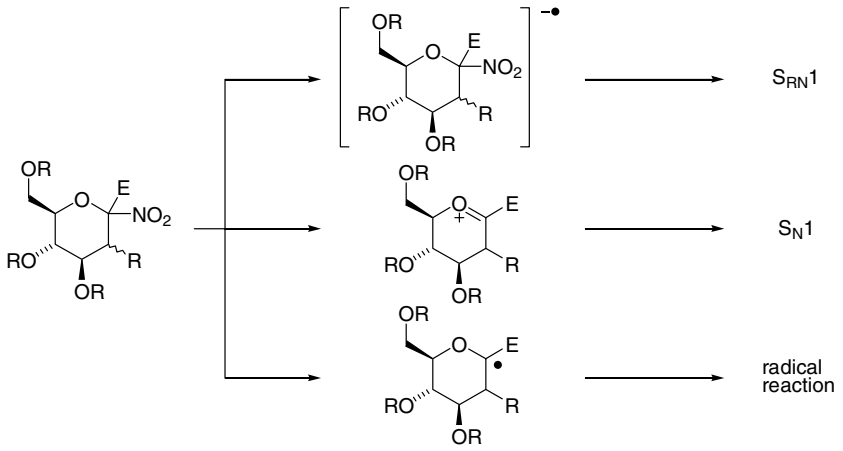



(5.83)

α-Nitro ethers are difficult to prepare due to their instability. However, Vassella and co-workers have succeeded in preparation of deoxy-nitrosugars. Ozonolysis of *N*-glycosylnitrones obtained from the corresponding oximes affords 1-deoxy-1-nitroaldose (Eq. 5.84).[134] They have developed new reactions and intermediates using 1-deoxy-1-nitroaldose, as summarized in Scheme 5.19.[135] α-Nitroethers are good precursors of alkyl radicals or carbenium ions stabilized by the oxygen atom. Details of the reactions in Scheme 5.19 are discussed in Chapter 7.




(5.84)




**Scheme 5.19.**

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*The Nitro Group in Organic Synthesis.* Noboru Ono
Copyright © 2001 Wiley-VCH
ISBNs: 0-471-31611-3 (Hardback); 0-471-22448-0 (Electronic)

# 6

# CONVERSION OF NITRO COMPOUNDS INTO OTHER COMPOUNDS

Nitro compounds are versatile precursors for diverse functionalities. Their conversion into carbonyl compounds by the Nef reaction and into amines by reduction are the most widely used processes in organic synthesis using nitro compounds. In addition, dehydration of primary nitro compounds leads to nitrile oxides, a class of reactive 1,3-dipolar reagents. Nitro compounds are also good precursors for various nitrogen derivatives such as nitriles, oximes, hydroxylamines, and imines. These transformations of nitro compounds are well established and are used routinely in organic synthesis.

## 6.1 NEF REACTION (ALDEHYDES, KETONES, AND CARBOXYLIC ACIDS)

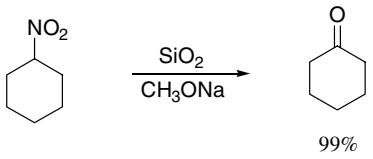
The conversion of primary or secondary nitro compounds into aldehydes or ketones is normally accomplished by use of the Nef reaction, which is one of the most important transformations of nitro compounds. Various methods have been introduced for this transformation: (1) treatment of nitronates with acid, (2) oxidation of nitronates, and (3) reduction of nitroalkenes. Although a comprehensive review is available,[3] important procedures and improved methods published after this review are presented in this chapter. The Nef reaction after the nitro-aldol (Henry reaction), Michael addition, or Diels-Alder reaction using nitroalkanes or nitroalkenes has been used extensively in organic synthesis of various substrates, including complicated natural products. Some of them are presented in this chapter; other examples are presented in the chapters discussing the Henry reaction (Chapter 3), Michael addition (Chapter 4), and Diels-Alder reaction (Chapter 8).

### 6.1.1 Treatment With Acid (Classical Procedure)

The Nef reaction was originally carried out under acidic conditions using strong acid such as aqueous HCl.[1–3] However, the use of base followed by acid is incompatible with polyfunctional substrates; in addition, some compounds are prone to undergo side reactions or fail to react, as discussed in the references.[1–3] Thus, various modified methods have been developed, and they

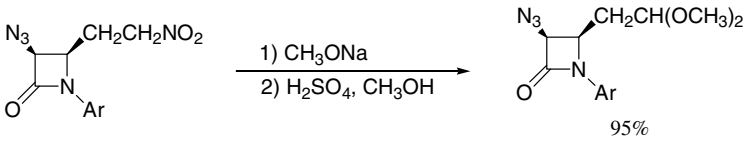
are well summarized in the review by Pinnick.[3] Duplication of this review is minimized here; the recent progress of the Nef reaction is described.

Silica gel can be used as an acid for the Nef reaction. The basic silica gel impregnated with sodium methoxide has been used very conveniently for the Nef reaction (Eq. 6.1).[4]



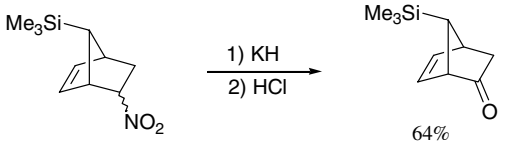

(6.1)

In general, the acid-catalyzed Nef reaction is carried out in water or water-containing solvents. If the reaction is carried out in methanol, nitro compounds are converted into the corresponding dimethylacetals. This process has merits over the conventional one due to the wider applicability of the Nef reaction (Eq. 6.2).[5]




(6.2)

The Nef reaction is accelerated by the presence of silicon atom at γ-position of nitro functions, as shown in Eq. 6.3. The presence of the γ-silicon is essential for such smooth reaction.[6] The conversion of 5-nitrobicyclo[2.2.1]heptenes to the corresponding ketones via the Nef reaction is very complicated by the degradation of the product. Thus, β-trimethylsilyl ketones can be prepared by a one-flask method via the addition of Grignard reagents containing trimethylsilyl groups to nitroalkenes and the subsequent hydrolysis, as shown in Eq. 6.4.



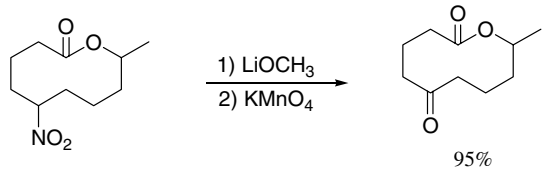

(6.3)

(6.4)

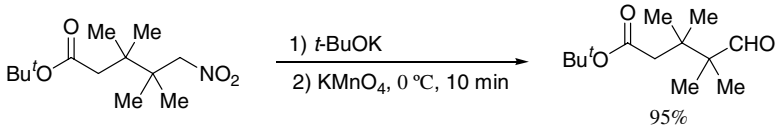
### 6.1.2 Oxidative Method

Various oxidizing agents such as $KMnO_4$,[7] *m*-chloroperbenzoic acid,[8] $MoO_5$-pyridine-HMPA complex,[9] ceric ammonium nitrate,[10] hydrogen peroxide,[11] ozone,[12] singlet oxygen,[13] *t*-BuOOH/$VO(acac)_2$,[14] Oxone™,[15] sodium chlorite,[16] dimethyldioxirane,[17] tetrapropylammonium perruthenate,[18] and *m*-iodoxbenzoic acid[19] are typical oxidizing agents for the Nef-type reaction.

The use of $KMnO_4$ provides a simple and effective method for converting various nitro compounds to aldehydes and ketones in 80–96% yield,[7] and even quaternary aldehydes are prepared despite their instability by this method, as shown in Eq. 6.6.[7b]

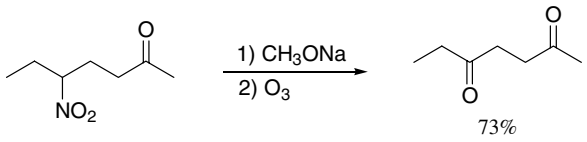



(6.5)



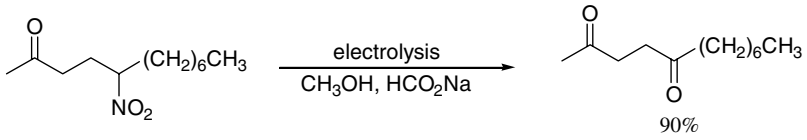

(6.6)

When the substrate does not contain a reactive carbon–carbon double bond, the ozonolysis procedure appears to provide a convenient and efficient method for the conversion of primary and secondary nitro compounds into carbonyl compounds (Eq. 6.7).[12]



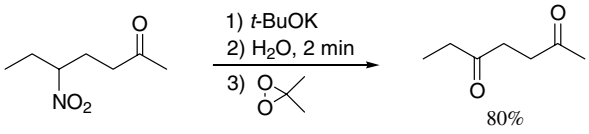

(6.7)

Anodic oxidation of nitronate anions provides an attractive method for the Nef reaction (Eq. 6.8).[20]



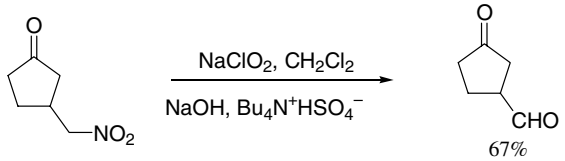

(6.8)

Dimethyldioxirane oxidation of nitronates anions affords the corresponding carbonyl products. Highest yields are obtained when one equivalent of water is added before the oxidation (Eq. 6.9).[17]



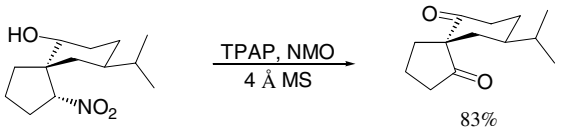

(6.9)

Sodium chlorite under phase-transfer catalysis conditions ($CH_2Cl_2$-NaOH-$Bu_4NHSO_4$) is also a good choice for the Nef reaction of primary and secondary nitro compounds (Eq. 6.10).[16]

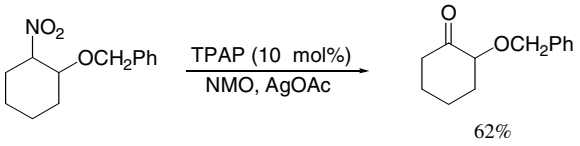



(6.10)

A very mild oxidative transformation of nitro compounds into ketones using tetrapropylammonium perruthenate (TPAP) has been developed. A stoichiometric amount of TPAP in the presence of *N*-methylmorpholine *N*-oxide (NMO) and 4 A molecular sieves (MS).[18a] As the reaction conditions are neutral and mild, this method is compatible with the presence of other sensitive functionalities (Eq. 6.11). This transformation can be carried out with 10 mol% of TPAP and 1.5 equiv of NMO in the presence of potassium carbonate, 4 A MS, and silver acetate (Eq. 6.12).[18b]




(6.11)



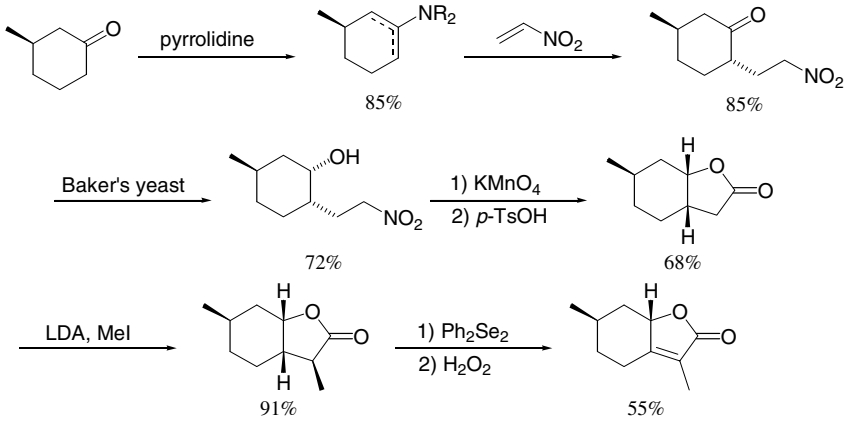

(6.12)

Secondary nitro compounds are converted into ketones under very mild conditions using *n*-propyl nitrite and sodium nitrite in DMSO.[21]

The Nef reaction of primary nitro compounds gives aldehydes or carboxylic acids, depending on the reaction conditions. Each transformation provides an important tool in organic synthesis. Primary nitro compounds are converted into carboxylic acids with concentrated mineral acids.[22] Because such harsh conditions also lead to side reactions, a milder method is required in organic synthesis. Basic phosphate-buffered $KMnO_4$ rapidly converts primary nitroalkanes into carboxylic acids in 90–99% yield (Eq. 6.13).[23]

$$HO(CH_2)_{11}CH_2NO_2 \xrightarrow[K_2HPO_4,\ t\text{-BuOH}]{KMnO_4,\ KOH} HO(CH_2)_{11}CO_2H \qquad (6.13)$$

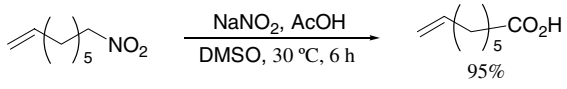
Scheme 6.1 shows a simple preparation of (+)-isomintlactone, isolated from a sample of peppermint oil. The addition of pyrrolidino enamine of (*R*)-3-methylcyclohexanone to ni-



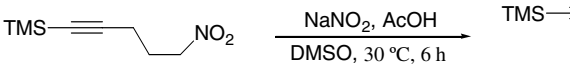

**Scheme 6.1.**

troethylene followed by reduction with baker's yeast and the Nef reaction gives the condensed lactone. Methylation followed by olefination using α-phenylselenation and oxidation yields the desired lactone (Scheme 6.1).[24]

Strong oxidizing agents such as $KMnO_4$ are not always useful for synthesis of highly sensitive compounds. In 1956, Kornblum found that a mixture of nitrite ester and sodium nitrite oxidizes primary nitro paraffins to the corresponding carboxylic acids.[25] However, the reaction was prone to poor yields and long reaction time. Forty years later, a very efficient related reaction using a mixture of sodium nitrite and acetic acid in DMSO has been reported (Eqs. 6.14 and 6.15).[26] Because carbon–carbon double and triple bonds and other various functional groups are compatible with this reaction condition, this method is useful for natural product synthesis. For example, one-synthesis of alkaloid, (–)-horsfiline is shown in Scheme 6.2, in which the creation of chiral quaternary carbon centers via an addition-elimination process is used as the key reactions.[27] This strategy has been used very effectively for the synthesis of various natural products; this is discussed in Chapter 4 on the Michael addition to nitroalkenes.

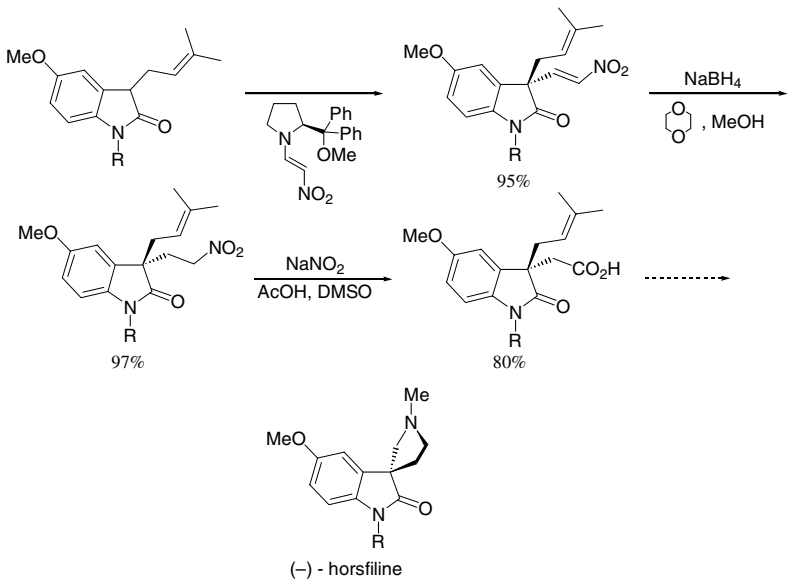



(6.14)

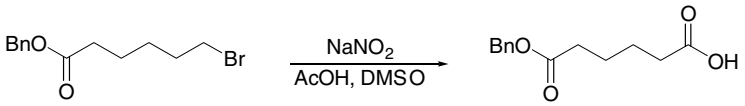



(6.15)

Because primary alkyl bromides can be converted into the corresponding nitro compounds by the action of $NaNO_2$ in DMSO, primary alkyl bromides are converted directly into the corresponding carboxylic acids by the reaction with an excess of sodium nitrite in acetic acid (Eq. 6.16).[26]



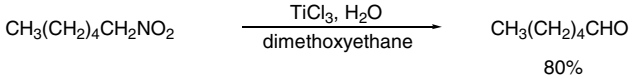

**Scheme 6.2.**



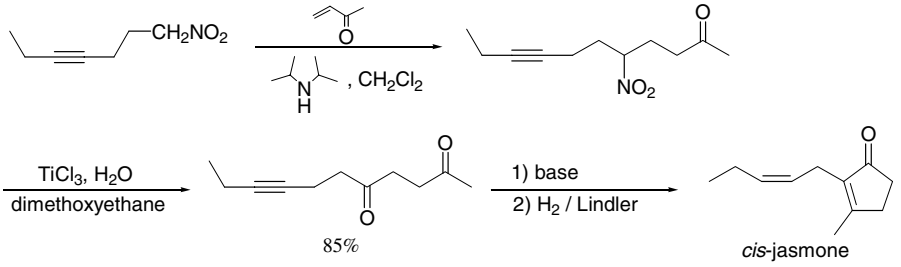

(6.16)

### 6.1.3 Reductive Method

The Nef reaction can also be carried out with reducing agents. Aqueous titanium chloride reduces nitro compounds to imines, which are readily hydrolyzed to carbonyl compounds (Eq. 6.17).[28] The Michael addition of nitroalkanes to enones followed by reaction with $TiCl_3$ provides an excellent route to 1,4-diketones and hence to cyclopentenones. For example, *cis*-jasmone is readily obtained,[28] as shown in Eq. 6.18.

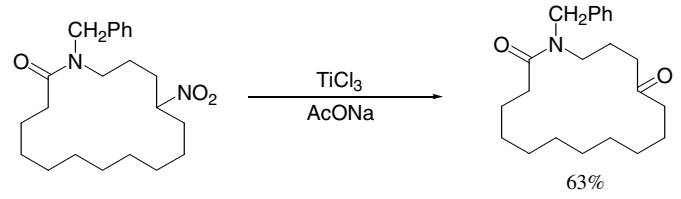



(6.17)

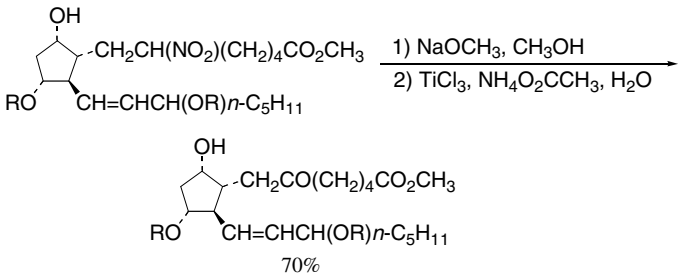



(6.18)

The $TiCl_3$ solution is very acidic such that acid-sensitive compounds do not survive. In such cases, sodium acetate or ammonium acetate is added to the reaction mixture to control pH at 5–6.[29] Highly functionalized substrates are synthesized by the Nef reaction using $TiCl_3$ and sodium acetate, as shown in Eq. 6.19,[30] and Eq. 6.20.[31]




(6.19)

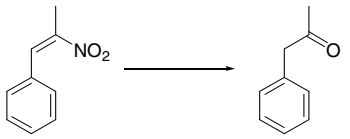



(6.20)

Vanadium chloride,[32] chromium chloride,[33] and the combined use of tributylphosphine and diphenyldisulfide[34] are also effective in promoting the reductive Nef reaction.

### 6.1.4 Direct Conversion of Nitroalkenes to Carbonyl Compounds

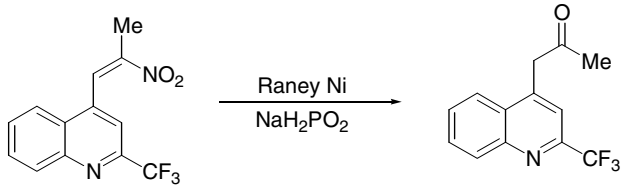
Because nitroalkenes are directly prepared by the condensation of aldehydes with nitroalkanes, the conversion of nitroalkenes into carbonyl compounds provides a powerful tool in organic synthesis. In general, the reduction of nitroalkenes followed by the hydrolysis or oxidation gives carbonyl compounds. Old procedures for this transformation involve the reduction with Fe-HCl[35] or Zn-AcOH.[36] There are many modified procedures for the conversion of 1-phenyl-2-nitropropene into phenylacetone (Eq. 6.21); method A[37]: Raney Ni-$NaH_2PO_2$, method B[38]: Cr(2)Cl, method C[39]: $LiBHR_3$/HCl, method D[40]: $CdCl_2$-Mg-$H_2O$, method E[41]: electrochemical reduction using Pb as an electrode.



| Method | | Yield (%) |
|---|---|---|
| A | Raney Ni/$NaH_2PO_2$ | 88 |
| B | $CrCl_2$ | 80 |
| C | $LiBHR_3$, HCl | 80 |
| D | $CdCl_2$ -Mg-$H_2O$ | 80 |
| E | Electrochemical reduction, Pb | 80 |

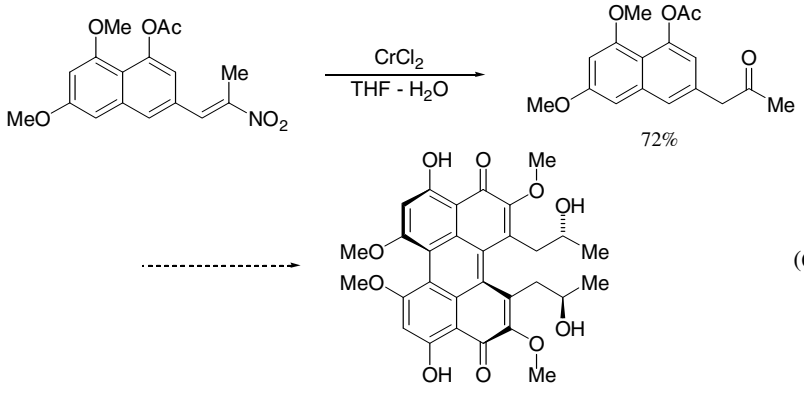
(6.21)

The direct conversion of nitroalkenes into ketones is especially useful for the preparation of arylacetones. They are readily prepared by the condensation of aromatic aldehydes with nitroethane and by the subsequent Nef reaction.[42] Typical examples are presented in Eq. 6.22[37] and Eq. 6.23; the product of Eq. 6.23 is used for total synthesis of perylenequinone, calphostin D, which is a potent inhibitor of protein kinase C.[42b]



86%

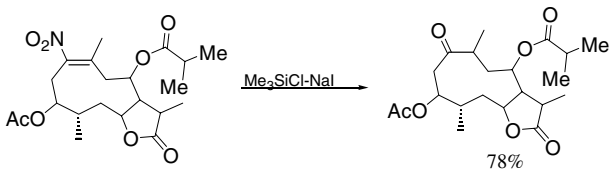
(6.22)



72%

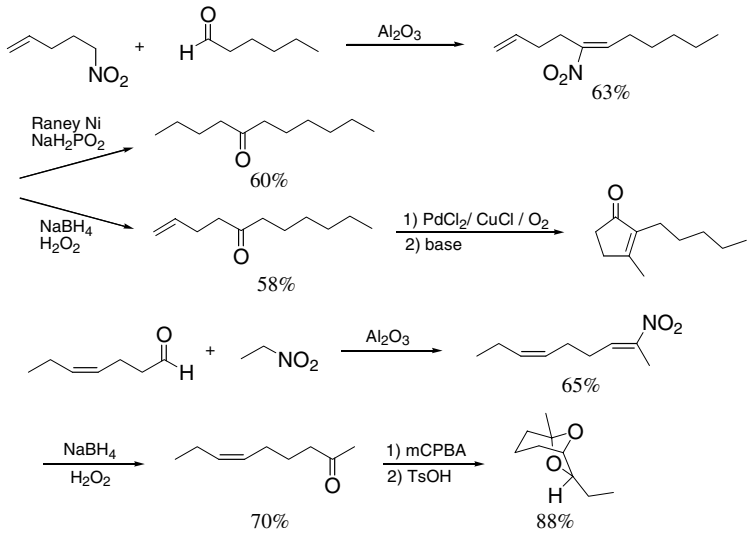
(6.23)

Iodotrimethylsilane generated in situ from chlorotrimetylsilane and sodium iodide effects the reduction of nitroalkenes into ketones at 0 °C. This method is useful for the conversion of nitro steroids or nitro terpenoids to the corresponding ketones (Eq. 6.24).[43]



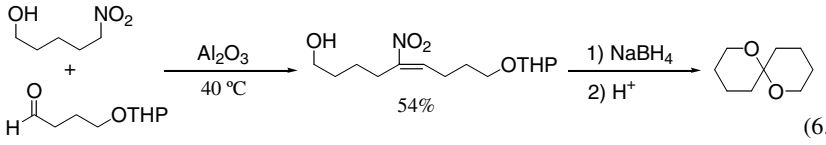

(6.24)

Ballini and his coworkers have used the strategy based on the Nef reaction after the carbon–carbon bond formation for the synthesis of various natural products.[44] The requisite nitroalkenes are simply prepared by the nitro-aldol condensation using $Al_2O_3$. When double bonds are present in nitroalkenes, the reductive Nef reaction gives saturated compounds, as shown in Eq. 6.25.[45] A new simple, cheap, and practical procedure for the direct transformation of nitroalkenes into ketones has been obtained by the $NaBH_4/H_2O_2$ system. By this method, other functional groups such as double bonds, acetals, or aromatic nitro groups are preserved. A convenient synthesis of dihydrojasmone and brevicomine using this transformation is presented in Eqs. 6.25 and 6.26, respectively.[46] Other applications of the Nef reaction to the synthesis of natural products such as spiroketalic pheromones and lactonic pheromones are demonstrated in Eqs. 6.27 and 6.28.[47]

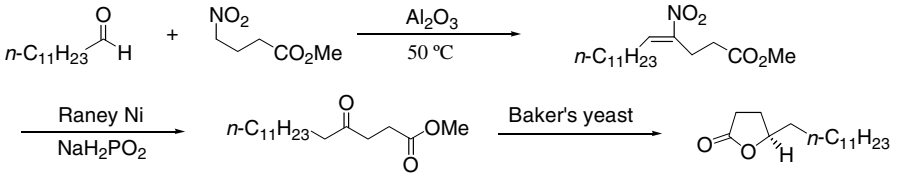



(6.25)

(6.26)

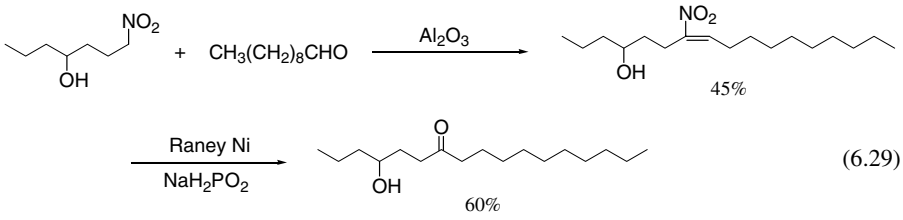



(6.27)



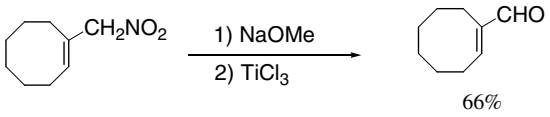

(6.28)

The 4-hydroxyheptadecan-7-one, isolated from the root of *Chiococca alba*, is simply prepared using hydroxy-functionalized nitroalkenes, as shown in Eq. 6.29.[48]




(6.29)

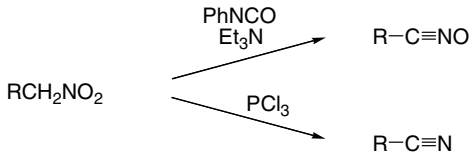
The Henry reaction of ketones with nitroalkanes in the presence of ethylenediamine gives allylic nitro compounds, which give α,β-unsaturated carbonyl compounds via the Nef reaction (Eq. 6.30).[49]




(6.30)

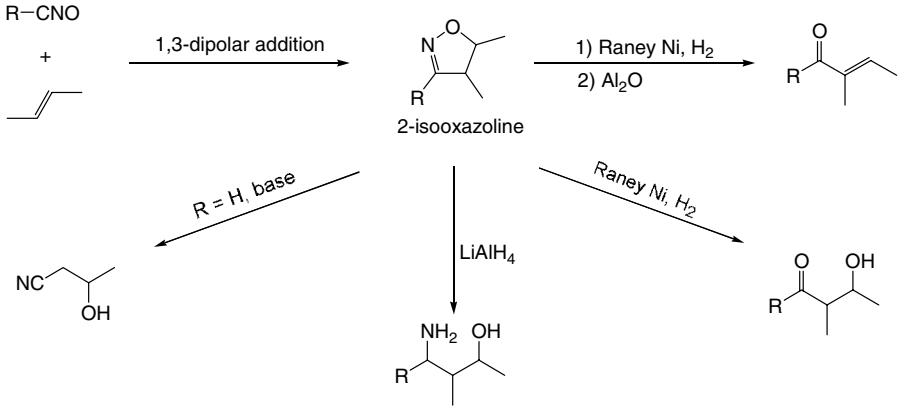
## 6.2 NITRILE OXIDES AND NITRILES

Primary nitro compounds are good precursors for preparing nitriles and nitrile oxides (Eq. 6.31). The conversion of nitro compounds into nitrile oxides affords an important tool for the synthesis of complex natural products. Nitrile oxides are reactive 1,3-dipoles that form isoxazolines or isoxazoles by the reaction with alkenes or alkynes, respectively. The products are also important precursors for various substrates such as β-amino alcohols, β-hydroxy ketones, β-hydroxy nitriles, and β-hydroxy acids (Scheme 6.3). Many good reviews concerning nitrile oxides in organic synthesis exist; some of them are listed here.[50–56] Applications of organic synthesis using nitrile oxides are discussed in Section 8.2.2.



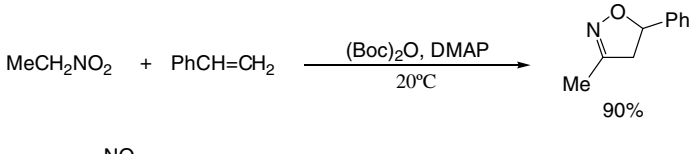

(6.31)

The dehydration of primary nitro compounds with phenyl isocyanate (PhNCO) and triethylamine has been widely used for generating nitrile oxides (Mukaiyama-Hoshino method).[57a] Polymer-bounded nitrile oxide cycloaddition reactions employing phenyl isocyanate have experimental advantage of removing the urea by-product by simply washing the resin with solvent.[57b] The use of diisocyanates for in situ preparation of nitrile oxides from primary nitroalkanes is of similar advantage, in which the by-product urea polymer is simply removed by filtration.[57c] An alternative method for generating nitrile oxides is based on the chlorination of oximes. However, the former method is better, because the use of chlorinating agents can be avoided. Recently, some new preparing methods of nitrile oxides from nitro compounds have been achieved, as shown in Eqs. 6.32–6.35; however, the Mukaiyama-Hoshino method is still the most widely used in organic synthesis.

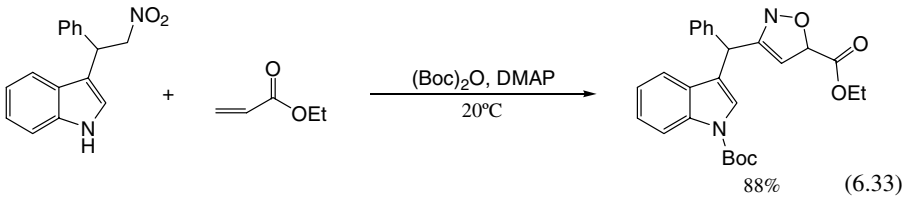



**Scheme 6.3.**

For example, the reaction of nitroalkanes with di-*tert*-butyl dicarbonate, $(BOC)_2O$, and 4-dimethylaminopyridine (DMAP) as catalysts in the presence of dipolarophiles at room temperature affords cycloadducts in improved yields compared with the Mukaiyama-Hosino method.[58] The conversion of Eq. 6.32 gives a 90% yield by this procedure, whereas the conventional method using PhNCO gives a 79% yield of the same product. An additional advantage of this new method is that the use of $(BOC)_2O$ allows the reaction to be carried out with substrates that contain NH or OH groups without prior protection. The cycloaddition leads directly to protected *N*- or *O*-Boc products (see Eq. 6.33).

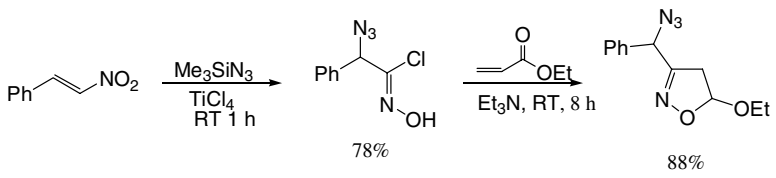



(6.32)




(6.33)

The reaction of nitroalkenes or nitroalkanes with $TiCl_4$ and $Me_3SiN_3$ gives α-azido functionalized hydroxamoyl chlorides, which act as precursors of nitrile oxides (Eq. 6.34).[59]



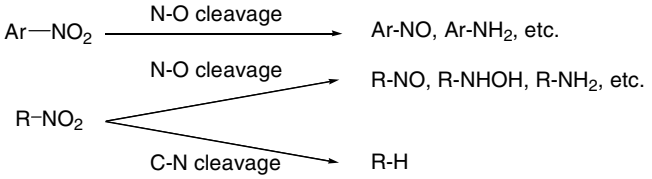

(6.34)

A new route to nitrile oxides based on the reaction of primary alkyl bromides with $NaNO_2$ in the presence of acetic acid, is also reported (Eq. 6.35).[60] This reaction is used for the direct

conversion of alkyl bromides or nitroalkanes to carboxylic acids on treatment with $NaNO_2$ and acetic acid, if the alkenes are absent. The reaction proceeds via nitrolic acids, which can be isolated when the reaction is carried out at 20 °C. When heated in THF, they allow corresponding nitrile oxides to be obtained under neutral conditions.[60b]

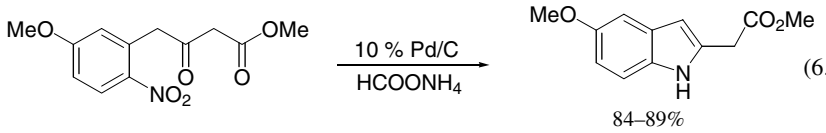
Primary nitro ketones, ethyl nitroacetate, and (phenylsulfonyl)nitromethane react with alkenes in the presence of Lewis acids to give nitrile oxide cycloaddition.[61a] Similarly, the reaction of α-nitro ketones with $TeCl_4$ generates the corresponding nitrile oxides, as shown in Eq. 6.36.[61b]

The conversions of nitro compounds into nitrile oxides have been used extensively in organic synthesis (see Section 8.2.2). On the other hand, nitro compounds have rarely been used as precursors of nitriles in organic synthesis. Some recent procedures for conversion of nitro compounds into nitriles are presented in Eqs. 6.37–6.40. The oxygen transfer from nitrile oxides by isocyanide gives nitriles; thus, treatment of nitro compounds with *t*-butylisocyanide, *n*-butylisocyanate, and triethylamine gives nitriles in 70–80% yield (Eq. 6.37).[62]



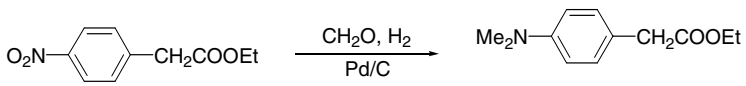

**Scheme 6.4.**

Procedures for the reduction of nitro compounds to amines are described precisely in the series of books; Organic Synthesis, namely, Fe + AcOH,[72] Zn + NaOH,[73] Fe + HCl,[74] Sn + HCl,[75] $H_2$-Raney Ni,[76a–c] $H_2$-$PtO_2$,[77] $H_2$-Pd/C,[78] and $N_2H_4$-Pd/C[79] are presented there. Sodium sulfide and polysulfides are also effective for this transformation.[80] The combination of sodium borohydride with cobalt(II), copper(II), and rhodium (III) halides has been used to reduce functional groups such as nitro, nitriles, amides, and olefins, which are inert to $NaBH_4$ itself.[81] Aromatic nitro compounds are reduced to amines with formic acid and triethylamine with Pd/C.[82a] Ammonium formate in the presence of Pd/C is a very convenient method for the reduction of both aromatic and aliphatic nitro compounds. For example, this method is applied for the preparation of indoles, as in Eq. 6.42.[82b] Synthesis of indoles via the reduction of the nitro group is presented in Section 10.2 (synthesis of heterocycles).



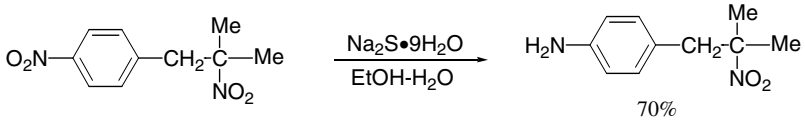

84–89% (6.42)

The reductive alkylation of aromatic nitro compounds using $H_2$+Pd/C in the presence of 40% aqueous formaldehyde gives directly dimethylamino derivatives in good yield (Eq. 6.43).[83]




67–77% (6.43)

Electrochemically generated nickel is very selective for the reduction of aromatic nitro compounds into anilines, in which alkenyl, alkynyl, halo, cyano, formyl, and benzyloxy groups are not affected.[84] Sodium sulfide has been used for the selective reduction of aromatic nitro group in the presence of aliphatic nitro groups (Eq. 6.44).[85]



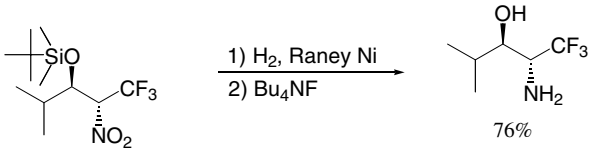

70% (6.44)

Treatment of aromatic nitro compounds with indium powder in aqueous ethanolic ammonium chloride results in selective reduction of nitro groups; ester, nitrile, amide, and halide substituents are unaffected.[86] This method is more selective than the method of catalytic hydrogenation. For example, catalytic hydrogenation of 4-chloro-3-nitroacetophenone over Pd/C results in hydrogenolysis of the halide and reduction of the ketone as well as of the nitro group.[87] Samarium iodide is a good reducing agent of both aromatic and aliphatic nitro

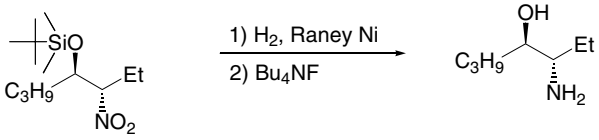
compounds. Because the nitro group is a better electron acceptor than other functional groups, the reduction of nitro compounds with $SmI_2$ proceeds selectively. Thus, *p*-nitrobenzonitrile is reduced to *p*-cyanoaniline selectively.[88] Ultrasound-promoted, highly efficient reduction of aromatic nitro compounds to the aromatic amines has been achieved by samarium ammonium chloride mediated reaction.[88c] Intermolecular and intramolecular reductive coupling reactions between aromatic nitro compounds and nitriles are induced by $SmI_2$ to give amidines and 2-aminoqunolines.[89]

### 6.3.2 R-$NH_2$ From R-$NO_2$

In general, the reduction of aliphatic nitro compounds gives amines, in which various reducing agents are as effective as they are in the reduction of aromatic nitro compounds.[70] The reduction of β-nitro alcohols to the corresponding amino alcohols is the most important application of this process in organic synthesis. Hydrogenation catalyzed by Raney Ni under high pressure has been widely used for this conversion,[90] and some recent examples are presented in Eq. 6.45,[91] and Eq. 6.46.[92] The stereochemistry of the nitro alcohol is retained by the Raney Ni-catalyzed hydrogenation.

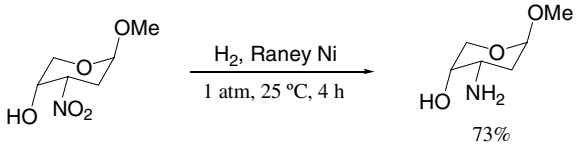



(6.45)



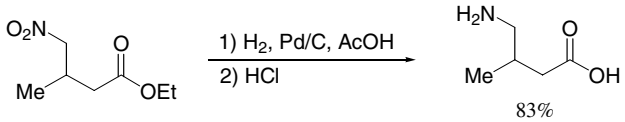

(6.46)

The reduction of nitro sugars with $H_2$ in the presence of Raney Ni is one of the standard methods for the preparation of amino sugars (Eq. 6.47).[93]



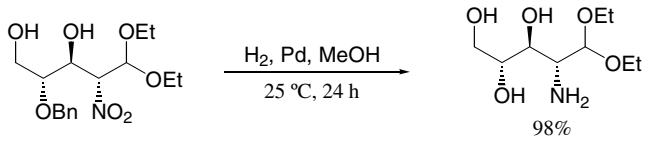

(6.47)

The hydrogenation in the presence of Pd/C is also effective for the conversion of nitro compounds to amines.[94] The Michael addition of nitromethane to 2-alkenoic esters followed by catalytic hydrogenation using 10% Pd/C in acetic acid and hydrolysis is a convenient method for the preparation of 3-alkyl-4-aminobutanoic acids, which are important γ-amino acids for biological study (Eq. 6.48).[94b] The reduction can be carried out at room temperature and atmospheric pressure.




(6.48)

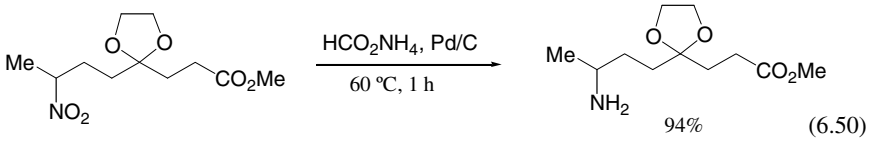
Jager and co-workers have prepared various amino sugars by the reduction of the corresponding β-nitro alcohols with $H_2$ and Pd/C, as exemplified in Eq. 6.49 (see Chapter 3).[95]



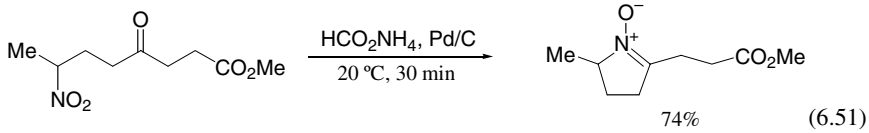

(6.49)

Hydrogen gas can be replaced by ammonium formate for the reduction of nitro compounds to amines. The ammonium formate method is efficient, and the rapid workup procedure by simple filtration makes it widely used for converting the $NO_2$ to the $NH_2$.[96] For example, α-nitro esters are reduced to α-amino esters in excellent yields on treatment with $HCO_2NH_4$ and Pd/C in methanol.[96]

The reduction of γ-nitroketone acetals as in Eq. 6.50 with ammonium formate in the presence of Pd/C gives the corresponding amines in good yields. However, the reduction of γ-nitro ketones are reduced to cyclic nitrones (Eq. 6.51).[97] This reduction is far superior to the classical method using $Zn/NH_4Cl$ due to improved yield and simple workup.

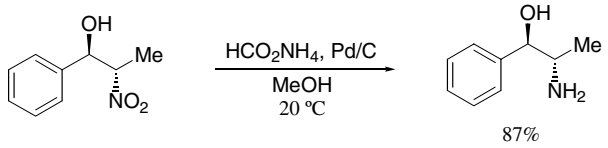



(6.50)



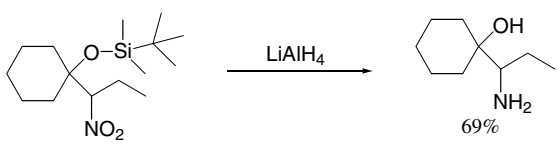

(6.51)

The reduction of β-nitro alcohols with ammonium formate in the presence of Pd/C also proceeds with retention of their configurations (Eq. 6.52).[98]




(6.52)

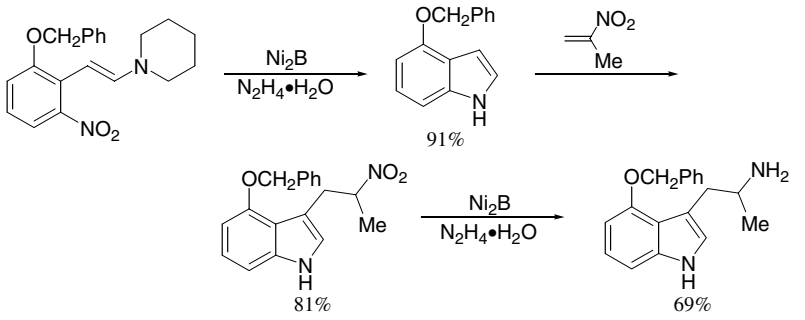
The reduction of β-nitro alcohols with $LiAlH_4$ results in low yields of β-amino alcohols due to the occurrence of a retro-aldol reaction. This problem is resolved by protecting of OH of β-nitro alcohols, as shown in Eq. 6.53.[99]




(6.53)

A reagent of nickel boride/hydrazine hydrate reduces both aromatic and aliphatic nitro compounds. For example, it has been used for synthesis of 4-(benzyloxy)indole and –alkyltryp-

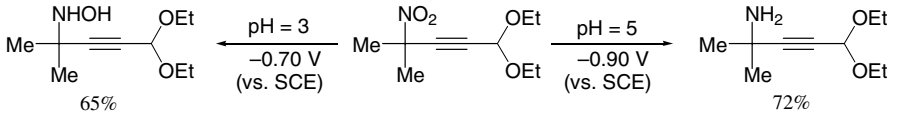
tamines, as shown in Eq. 6.54.[100] This reducing agent has advantages over the method using $H_2$ and Raney Ni because double bonds are inert to $Ni_2B/N_2H_4$.




(6.54)

Sodium borohydride is activated in the presence of Pd/C,[101] $CoCl_26H_2O$,[102] $Ni(OAc)_2$,[103] $CuSO_4$,[104] and $NiCl_2$.[105] Aromatic and aliphatic nitro compounds are reduced to the corresponding amines, by these reagents as summarized in Table 6.1. The active hydrogenation catalyst is formed by the reaction of $NaBH_4$ with metal catalysts in such reductions.[106] Because reaction proceeds rapidly under mild conditions, the method using activated $NaBH_4$ is very convenient for the reduction of a variety of nitro compounds as shown in Table 6.1.

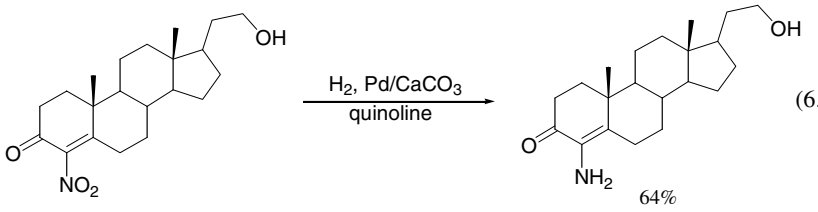
Various other reducing methods are employed for the conversion of β-nitro alcohols to amino alcohols, namely, electrochemical reduction.[107] The selective electrohydrogenation of nitroaliphatic and nitroaromatic groups in molecules containing other groups that are easy to hydrogenate (triple bond, nitrile, C-I) are carried out in methanol-water solutions at Devarda copper and Raney cobalt electrodes (Eq. 6.55).[107]




(6.55)

The sonochemical-promoted aluminum amalgam reduction of β-nitro alcohols provides an improved yield and accelerated conversion to the corresponding amino alcohols.[108]

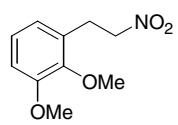
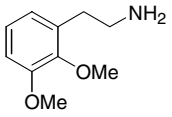
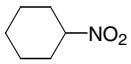
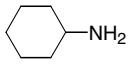
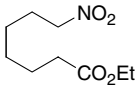
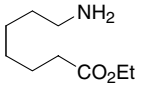
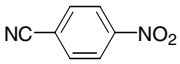
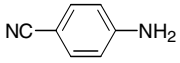
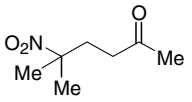
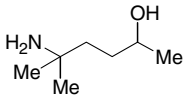
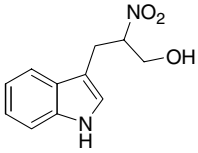
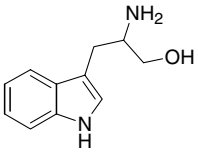
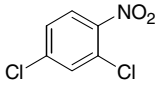
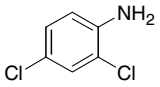
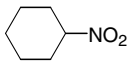
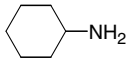
The selective reduction of 4-nitrosteroid to the corresponding aminosteroid has been carried out by $Pd/CaCO_3$ and quinoline (5 mol wt%) under $H_2$ atmosphere (Eq. 6.56).[109] This is the first reported catalytic reduction of an α-nitro enone to an α-amino enone. Other hydrogenation catalysts as well as the use of $Na_2S$, Fe/AcOH, or $Na_2S_2O_4$ fails to provide the aminosteroid. Reduction with $SnCl_2$ in EtOH gives the aminosteroid in 46% yield.




(6.56)

A variety of Group VIII transition metal phosphine complexes are shown to be active catalysts for hydrogenation of aliphatic nitro compounds. However, chiral phosphines have been found to be noneffective to induce asymmetric induction.[110]

**Table 6.1.**

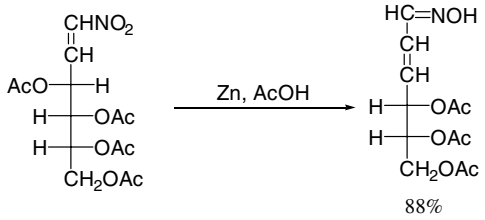
| Nitro compound | Reducing reagent | Product | Yield (%) | Ref. |
|---|---|---|---|---|
|  | $NaBH_4$-$CuSO_4$ EtOH, reflux, 30 min |  | 80 | 104 |
|  | $NaBH_4$-exchange Resin-$Ni(OAc)_2$, RT, 1 h |  | 94 | 103 |
|  | $NaBH_4$-10% Pd/C THF, 40 min |  | 75 | 103 |
|  | $NaBH_4$-10% Pd/C THF, 30 min |  | 90 | 103 |
|  | $NaBH_4$-$NiCl_2$ MeOH, RT, 30 min |  | 76 | 105 |
|  | $NaBH_4$-$CoCl_2{\cdot}6H_2O$ MeOH, 0 °C |  | 73 | 102 |
|  | $NaBH_4$-$ZrCl_4$ THF, reflux |  | 84 | 129 |
|  | $NaBH_4$-$ZrCl_4$ THF, RT |  | 80 | 129 |

### 6.3.3 Oximes, Hydroxylamines, and Other Nitrogen Derivatives

The final reduction products of nitro compounds are amines, but reduction intermediate products such as oximes and hydroxylamines have been also isolated on reduction of nitro compounds, as shown in Eq. 6.57, where the reaction is controlled by the applied reduction potentials. The partial reduction of nitroalkanes gives either oximes or alkyl-substituted hydroxylamines, depending on reaction conditions. Samarium diiodide is a good single electron-transfer reagent and it is very easy to control the reaction. Primary, secondary, or tertiary nitroalkanes can be reduced with $SmI_2$ and $CH_3OH$ as the proton source to either alkyl hydroxylamines or amines, depending on the amount of $SmI_2$. Reaction with 4 equiv of $SmI_2$ in THF/MeOH for less than 5 min provides hydroxylamines in 60–90% yields. Reaction with 6 equiv of $SmI_2$ for 8 h provides amines in 50–80% yields.[111]

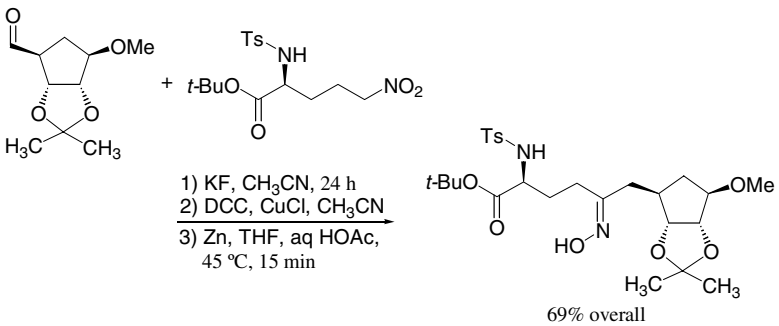
$$\text{R-NHOH} \xleftarrow[\text{THF-MeOH (2:1)}]{\text{4 equiv } SmI_2} \text{R–NO}_2 \xrightarrow[\text{THF-MeOH (2:1)}]{\text{6 equiv } SmI_2} \text{R-NH}_2 \quad (6.57)$$

The conversion of nitroalkanes to ketoximes can be achieved by the reduction with Zn in acetic acid,[112] or Fe in acetic acid.[113] Nitroalkenes are directly reduced into saturated ketoximes by these reagents, which are precursors for ketones (see Section 6.1.4 Nef reaction). Reduction of 3-*O*-acetylated sugar 1-nitro-1-alkenes with Zn in acetic acid gives the corresponding 2,3-unsaturated sugar oximes in high yield, which is a versatile route to 2,3-unsaturated sugar derivatives (Eq. 6.58).[114]



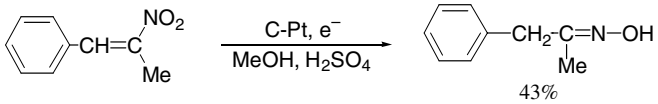

88% (6.58)

As shown in Eq. 6.59, Rapoport has prepared sinefungin, nucleoside antibiotics, via nitro-aldol reaction, dehydration, and reduction with Zn in acetic acid.[115a] β-Nitrostyrenes are selectivity reduced to the corresponding oximes by indium metal in aqueous methanol under neutral conditions.[115b]



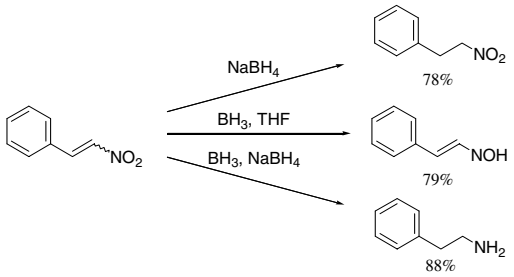

69% overall (6.59)

The conversion of nitroalkenes into the oximes can be achieved by electrochemical reduction (Eq. 6.60).[116]



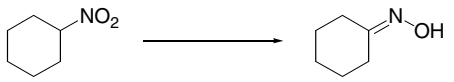

43% (6.60)

Reaction of the salts of primary and secondary alkylnitro compounds with diborane in THF solution at 25 °C yields the corresponding hydroxylamines.[117] Kabalka has reported the reduction of nitroalkenes to hydroxylamines or amines with a variety of borane and borohydride reagents (Eq. 6.61).[118]




(6.61)

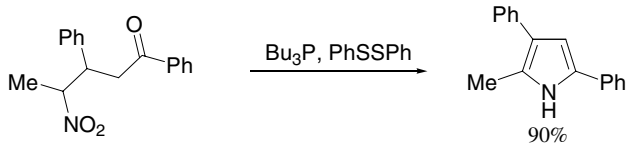
Deoxygenation from nitroalkanes is possible by other various reagents, including $TiCl_3$,[119] $Me_3SiI$,[63] carbon disulfide in the presence of base,[120] $Me_3SiSiMe_3$,[121] and $Sn(SPh)_2$-PhSH-$Et_3N$ (Eq. 6.62).[122]




| Reagent | Yield (%) |
|---|---|
| $Me_3SiI$ | 84 |
| BuLi + $Me_3SiSiMe_3$ | 69 |

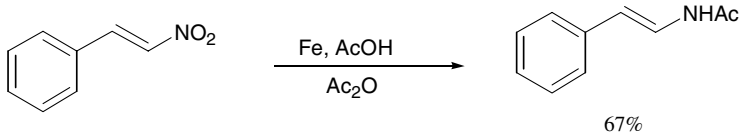
(6.62)

A combination of tributylphosphine-diphenyldisulfide reduces secondary nitro compounds to imines, which is applied to pyrrole synthesis (Eq. 6.63).[34]



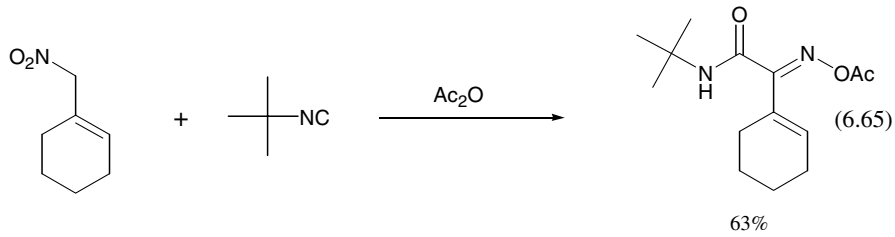

(6.63)

A new selective reduction of nitroalkenes into enamides has been carried out by a combination of iron powder, a carboxylic acid, and the corresponding anhydride (Eq. 6.64).[123]



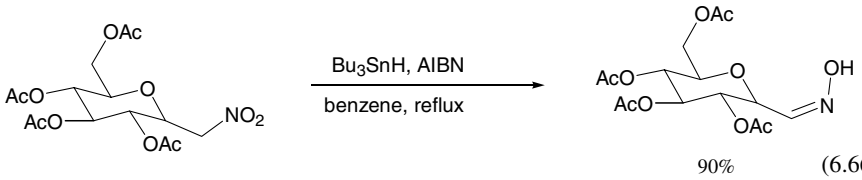

(6.64)

A new multicomponent reaction of nitro compounds with isocyanides gives α-oxyiminoamides, which are important for drug synthesis such as cephalosporin and β-lactamase inhibitor (Eq. 6.65).[124a] Multicomponent reactions using isocyanides (Ugi reaction) is reviewed.[124b]




(6.65)

Photoreduction of aromatic and aliphatic nitro compounds gives hydroxylamines or amines, which is well reviewed.[125] The radical reaction of primary nitro compounds with tin hydride does not give the denitrated product (see Chapter 7), but give the corresponding oximes (Eq.




(6.66)

6.66).[126a] This reaction is useful in carbohydrate chemistry and a nitromethylene linked disaccharide is prepared via this reaction.[126b]

Nitroxides are *N,N*-disubstituted nitric oxide radicals, the unpaired electron being delocalized between the nitrogen and oxygen. The reduction of 2-methyl-2-nitropropane with sodium or electrochemically yields di-*t*-butyl nitroxide as the final product.[127] Such nitroxide radicals are important for the study of a organic ferromagnet.[128]

Phosphorous reagents are well established as deoxygenating agents of nitro compounds. Cadogan and others have reported the abstraction of oxygen from aromatic nitro compounds by triethyl phosphite to form various heterocycles.[130] These reactions proceed via nitrene intermediates to give heterocycles (Section 10.2). Diethyl chlorophosphite is more reactive than triethyl phosphite, and it reduces both aromatic and aliphatic nitro groups to the corresponding amino groups in the presence of tertiary amines.[131]

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ISBNs: 0-471-31611-3 (Hardback); 0-471-22448-0 (Electronic)

# 7

# SUBSTITUTION AND ELIMINATION OF $NO_2$ IN R–$NO_2$

The aliphatic nitro groups can be displaced by various nucleophiles via one electron transfer reactions ($S_{RN}1$)[1] or ionic reactions[2] using palladium-catalyzed reactions of allylic nitro compounds, Lewis acid-catalyzed reactions, or intramolecular nucleophilic substitution reactions. These reactions have been well summarized by Kornblum[1] and Ono;[2] therefore, duplication of these is minimized here. The $S_{RN}1$ reaction has also been applied to the direct replacement of the nitro group by hydrogen. This transformation is relatively new compared with the Nef reaction of nitro compounds or the reduction of the nitro group to the amino group, but it has already been widely accepted as a useful transformation in organic synthesis (Section 7.2). Elimination of the nitro group to afford alkenes proceeds either via radical or ionic processes, which provides a useful strategy for olefin synthesis (Section 7.3).

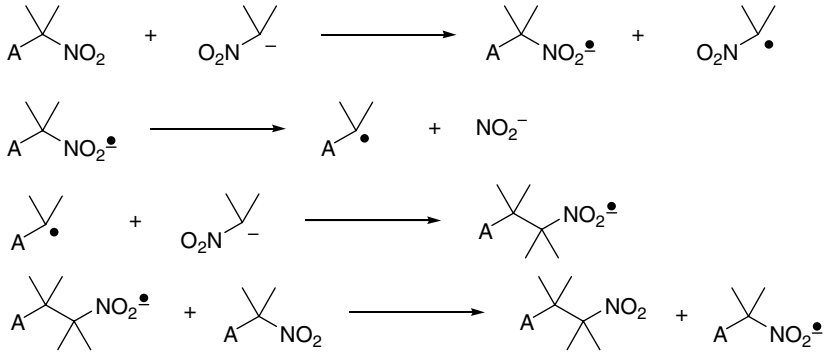
## 7.1 R–Nu FROM R–$NO_2$

### 7.1.1 Radical Reactions ($S_{RN}1$)

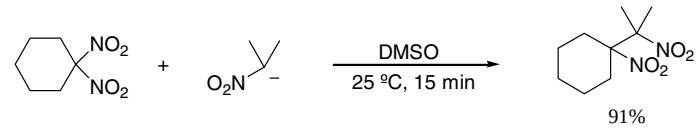
In 1970, a new reaction, the displacement of a nitro group from α-nitro esters, α-nitro nitriles, α-nitro ketones, and α,α-dinitro compounds by nitroalkane salts, was described.[3] These displacements, which are exemplified by the reaction presented in Eq. 7.1, take place at room temperature and give excellent yields of pure products. The reaction proceeds via a radical chain mechanism involving one electron-transfer processes as shown in Scheme 7.1; the details of the mechanism are described in a review.[1]

(7.1)

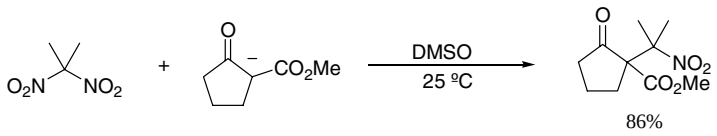
When α,α-dinitro compounds are employed, the nitro group is displaced by various stabilized carbanions as shown in Eqs. 7.2–7.5.[4]



**Scheme 7.1.** $S_{RN}1$ mechanism



91% (7.2)



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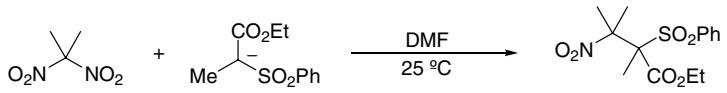
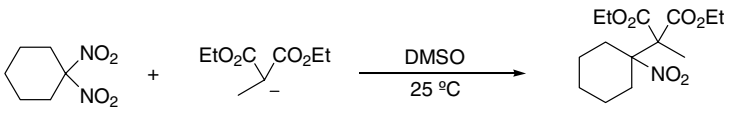
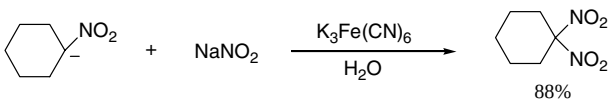


80% (7.4)

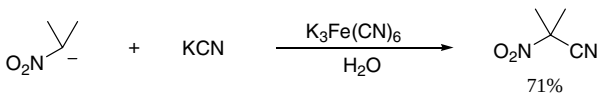


80% (7.5)

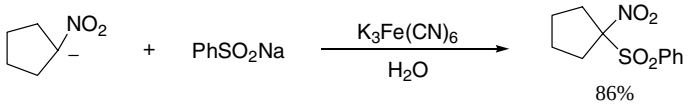
α,α-Dinitro compounds are very reactive substrates for $S_{RN}1$ reactions. They are readily prepared by oxidation of nitroalkane salts in the presence of nitrite ion with potassium ferricyanide.[5] In a similar way, α-nitrosulfones and α-nitronitriles are prepared in excellent yields (see Eqs. 7.6–7.8).[5] The modified procedure using persulfate and a catalytic amount of ferricyanide is very effective for the preparation of these compounds.[6]



88% (7.6)

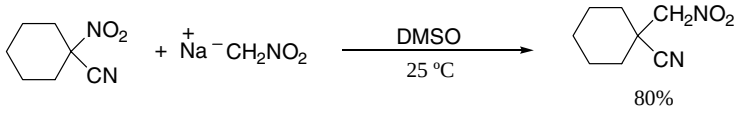


71% (7.7)



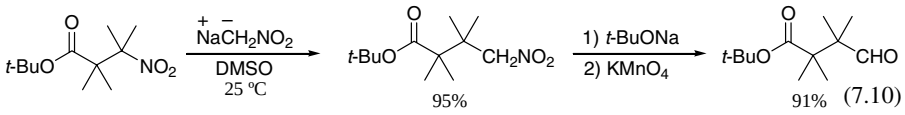

(7.8)

Various α-nitronitriles are readily prepared by the reaction of Eq. 7.7; the reaction of α-nitronitriles with nitroalkane salts provides an excellent method for the preparation of β-nitronitriles (Eq. 7.9).[7]

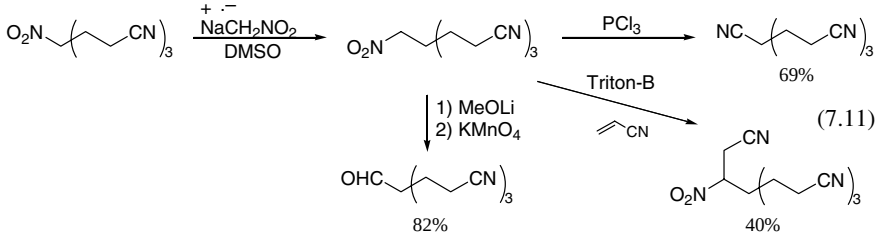



(7.9)

The reaction of tertiary nitro compounds with the sodium salt of nitromethane followed by the Nef reaction provides a good method for the preparation of quaternary aldehydes (Eq. 7.10).[8] Because the nitromethyl group can be transformed into other groups such as CN, $CO_2H$, or $CH_2NH_2$, the $S_{RN}1$ reaction of tertiary nitro compounds with the anion of nitromethane is a synthetically useful method (Kornblum reaction).[10] For example, the nitromethylation of tertiary nitro compounds has been applied for preparing starting materials for cascade polymers (Eq. 7.11).[9]




(7.10)

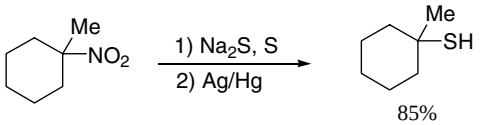



(7.11)

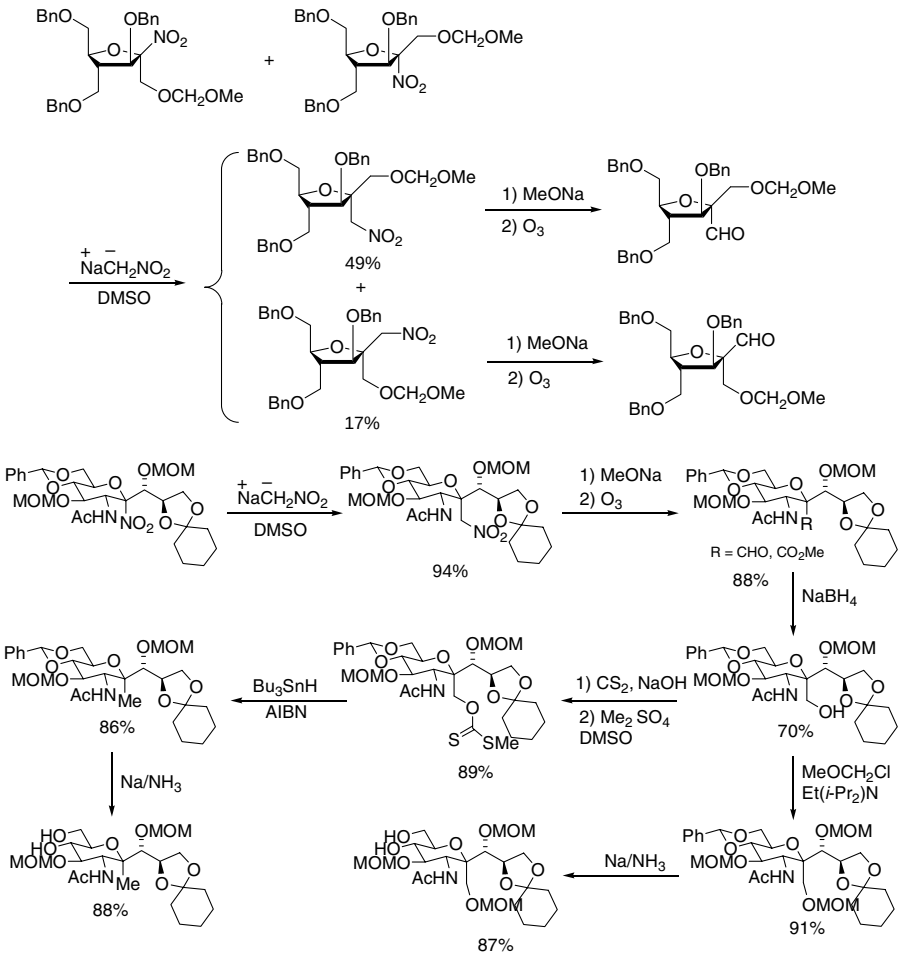
Vasella has used deoxy-nitro sugars for the synthesis of various biologically important carbohydrates,[10] and the radical nitromethylation of deoxy-nitro sugars has been used for synthesis of fructose 6-phosphate[11] and 6-C-methyl and 6-C-(hydroxymethyl)analogues of *N*-acetylneuraminic acid (see Scheme 7.2).[12]

The key step in the synthesis of the branched sugars presented in Scheme 7.2 is a Kornblum reaction of the nitropyranose. A mixture of anomers is obtained in the reaction of nitrofuranose, but the reaction with nitropyranose proceeds diastereoselectively to give a single product with an equatorially oriented side chain.

Tertiary nitro compounds are converted into the corresponding thiols by the reaction with sodium sulfide and sulfur ($S_8$) in DMSO followed by the reduction with Al-Hg. (Eq. 7.12). Secondary and primary nitro compounds do not give thiols in these reactions; instead, a complex set of product is formed.[13]



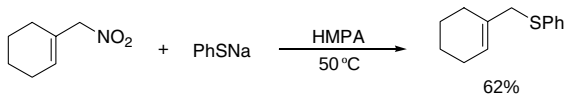

(7.12)



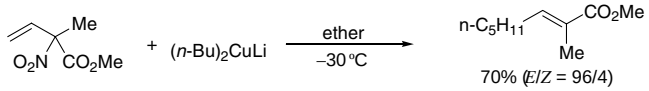

**Scheme 7.2.**

### 7.1.2 Ionic Process

Simple nitroalkanes such as nitroethane, 1-nitropropane, or 2-nitropropane are generally bad electrophiles for the $S_N2$ reactions.[14] In contrast, nitro groups at allylic positions are readily displaced by thiolate ions (Eq. 7.13)[15] or lithium dialkylcuprates (Eq. 7.14).[16]

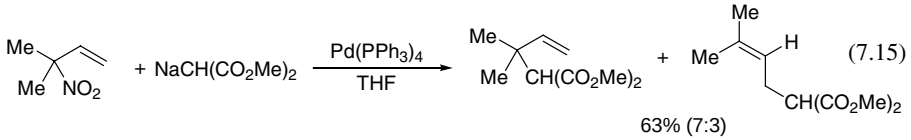



(7.13)




(7.14)

In 1982, a new reaction was reported by Tamura and Ono; namely, allylic nitro compounds undergo replacement of the nitro group by various nucleophiles in the presence of a palladium (0) catalyst.[17a–b, 18a–b] The details of these reactions are discussed in Ref. 2b; here, only some typical examples are presented. Carbon, sulfur, nitrogen, and phosphorous centered nucleophiles replace the nitro groups at the allylic positions. The reaction of allylic nitro compounds with triphenylphosphine is applied to the highly stereoselective olefination of aldehydes (Eqs. 7.15–7.18).[19]

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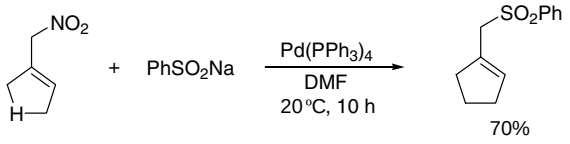
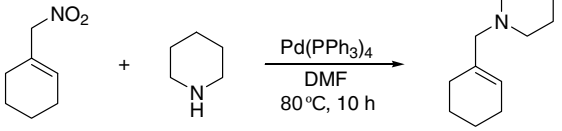
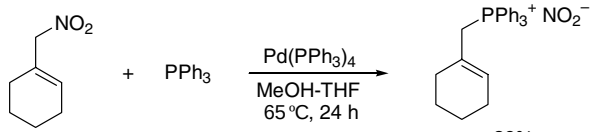



70% (7.16)

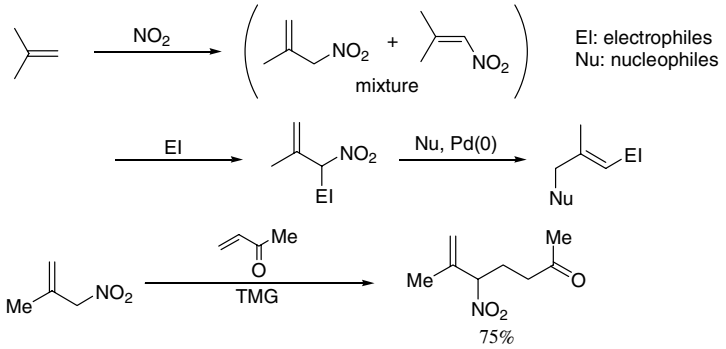


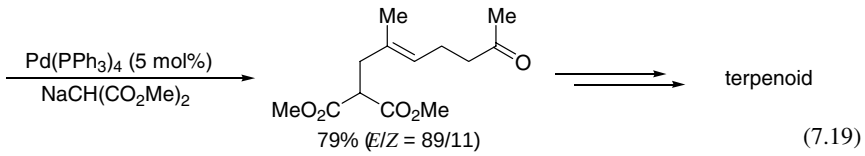

87% (7.17)




80% (7.18)

Allyl acetates are more commonly used as electrophiles for the palladium-catalyzed allylic alkylation than allylic nitro compounds.[20] However, the reaction of allylic nitro compounds has found wider applications. Allylic nitro compounds are readily available by nitration of alkenes. The regio- and stereoselective introduction of electrophiles and nucleophiles into alkenes is possible as outlined in Eq. 7.19. In fact, this strategy is applied to the synthesis of terpenoids.[21]

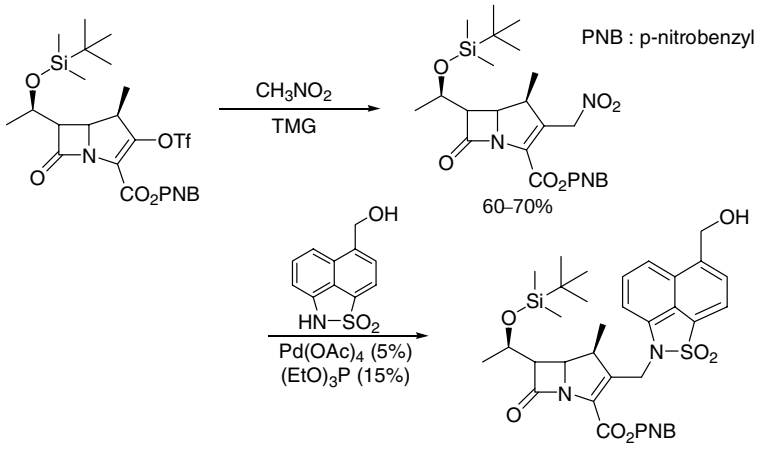





(7.19)

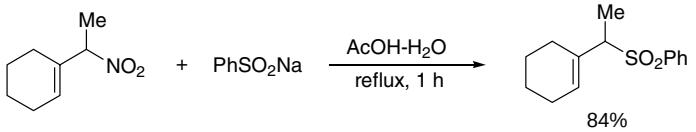
The starting allylic nitro compound is obtained by nitration of 2-methylpropene with $NO_2$. Subsequent Michael addition to methyl vinyl ketone followed by Pd-catalyzed allylic alkylation affords terpenoids.

Recently, elegant synthesis of *anti*-MRS carbapenum has been reported. Sequential reaction of nitromethane via conjugate addition-elimination to α,β-unsaturated esters followed by Pd-catalyzed substitution of the resulting allyl nitro compound with the naphthosultam affords the allylation product which is an anti (Eq. 7.20).[22]

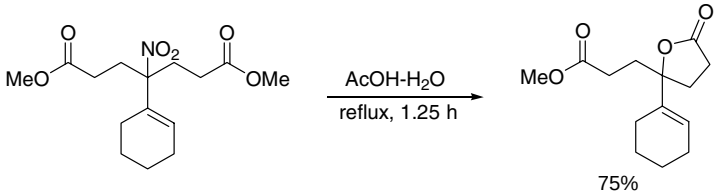



(7.20)

Allylic nitro derivatives undergo the $S_N1$ reaction in aqueous acetic acid. Allylic sulfones in the presence of a sulfinate salt (Eq. 7.21) or allylic lactones if the substrate contains a suitably located ester group are formed in these reactions (Eq. 7.22).[22]



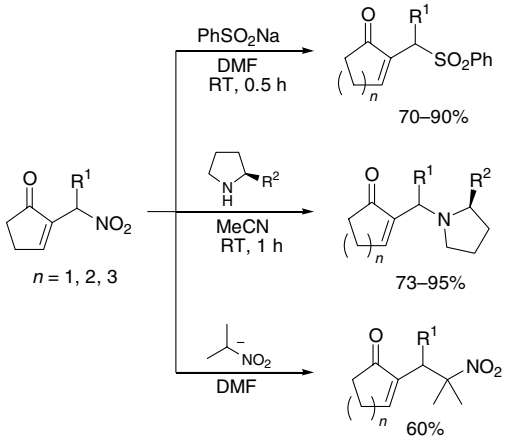

(7.21)




(7.22)

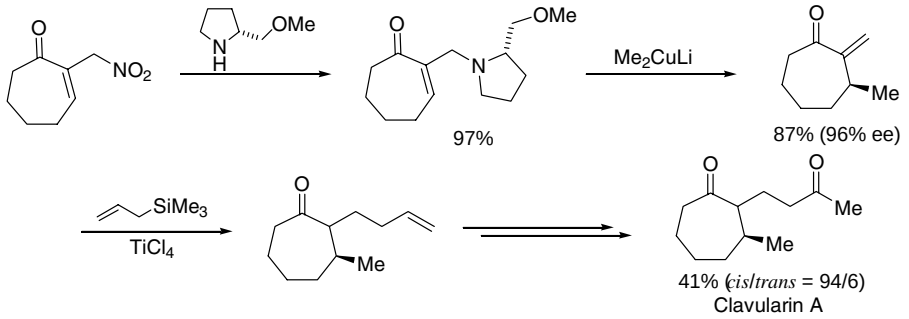
Tamura and coworkers have reported a related substitution reaction; cyclic α-(nitroalkyl) enones undergo regioselective substitution of the nitro group by sulfinate ion, amino, and carbon nucleophiles (Eq. 7.23).[24] Several reaction pathways are envisioned for this useful

transformation involving electron-transfer mechanisms, such as $S_{RN}1$,[25] or a simple addition-elimination process.[24]



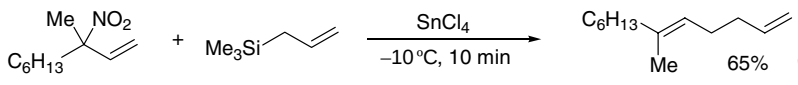

(7.23)

This reaction is nicely applied to total synthesis of Clavularin A[26b] as shown in Scheme 7.3. The key reactions involve a high enantioselective addition-elimination process[26a] and stereoselective synthesis of *cis*-2,3-disubstituted cycloheptanones.[27]

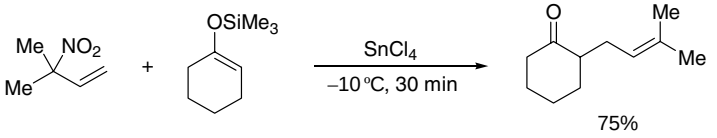



**Scheme 7.3.**

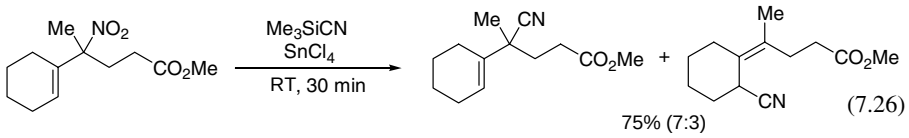
Lewis acids are also effective to induce the nucleophilic substitution of allylic nitro compounds. These compounds react with allyltrimethylsilane,[28] silyl enolates,[28] or cyanotrimethylsilane[29] in the presence of $SnCl_4$ to give substitution products, respectively (see Eqs. 7.24–7.26).




(7.24)



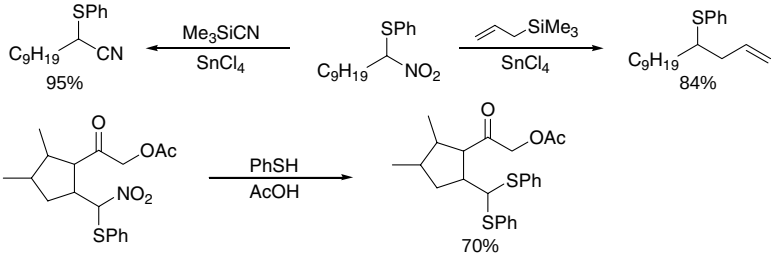

(7.25)




(7.26)

Thus, the nitro group at the allylic position is replaced by nucleophiles in the following three ways: (1) assistance by transition metal, (2) assistance by Lewis acids, and (3) assistance by proton. Zard and coworkers have reported a short total synthesis of estrone derivatives, where acid catalyzed allylic 1,3-shift of nitro group is used as a key step as shown in Scheme 7.4.[30] The Knoevnagel reaction of 6-methoxytetralone with nitromethane in the presence of ethylenediamine followed by the nitro-aldol reaction and the Michael addition gives the required allylic nitro compounds. Subsequent treatment with acetic acid induces 1,3-shift of the nitro group. Base catalyzed cyclization gives the estrone derivative. Finally the nitro group is removed by radical denitration (see Section 7.2).

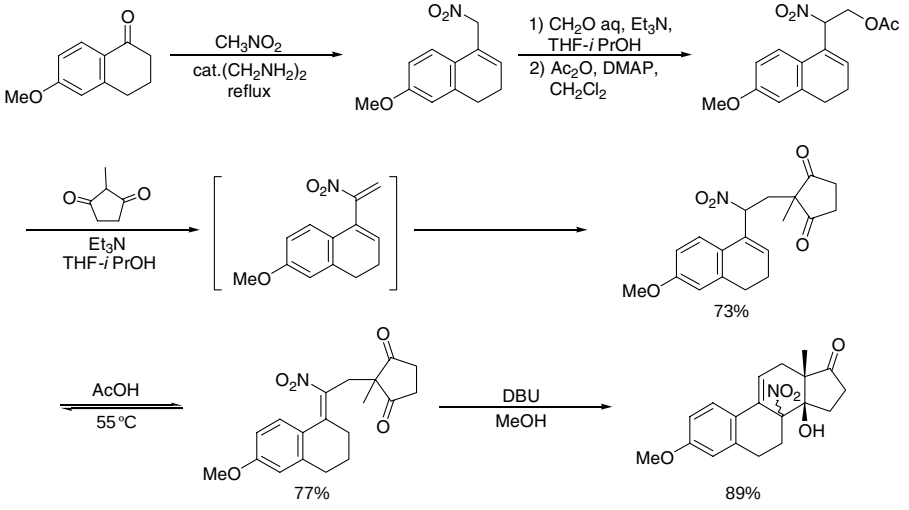
Allylic nitro groups are readily displaced by nucleophiles via an $S_N1$-type mechanism. Thus, nitro groups with heteroatoms at the α- or β-positions (for example, α- or β-nitrosulfides) are expected to be cleaved in a similar way. In fact, the nitro group in α-nitrosulfides is replaced by nucleophiles in the presence of a Lewis acid[31] or acetic acid.[32] The nitro groups in the reaction of Eqs. 7.27 and 7.28 are cleanly replaced by CN, allyl, or PhS group on treatment with $Me_3SiY$ (Y = CN, allyl) in the presence of $SnCl_4$ or simple treatment with PhSH in AcOH.




(7.27)

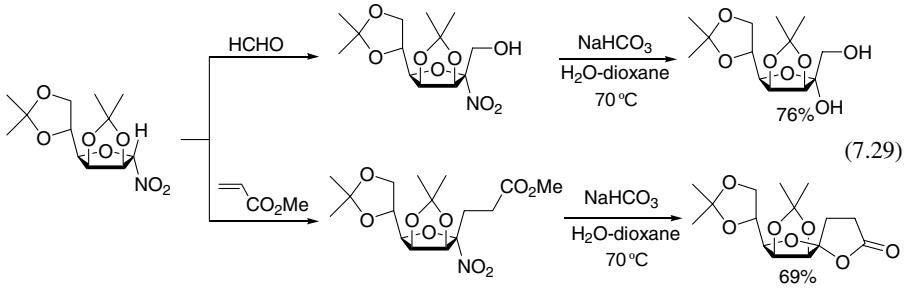



(7.28)



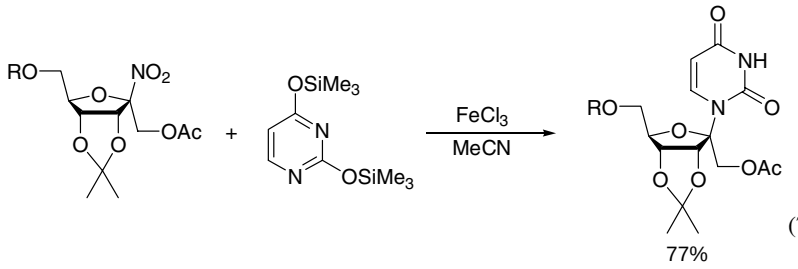

**Scheme 7.4.**

α-Nitro ethers effect a similar $S_N1$-type substitution under solvolytic conditions; tertiary nitro compounds derived from 1-deoxy-1-nitroaldose and formaldehyde or methyl acrylate undergo denitro-hydroxylation or intramolecular lactonization, respectively (Eq. 7.29).[33]



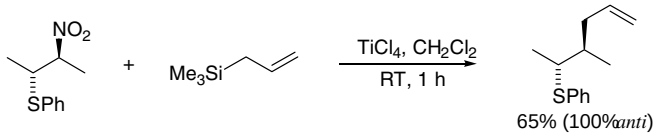

(7.29)

This type of substitution reaction is useful for the synthesis of biologically active nucleosides. 1-Deoxy-1-nitroribose reacts with 2,4-bis(trimethylsilyloxy)pyrimidine in the presence of $FeCl_3$ in MeCN to give the nucleoside in 77% yield (Eq. 7.30).[34]

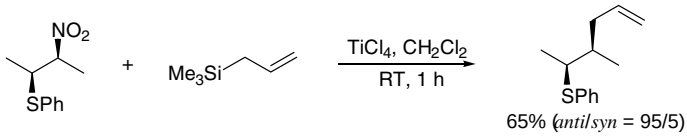



(7.30)

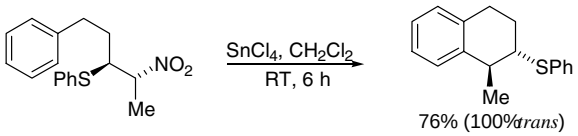
Furthermore, a neighboring group participation of a phenylthio function is observed in the Lewis acid-catalyzed nucleophilic substitution reaction of various β-nitrosulfides. Because the β-nitrosulfides are readily available, by the Michael addition of thiols to nitroalkenes (see Michael addition Chapter 4), this reaction is very useful. The β-nitrosulfides are prepared stereoselectively, and the reaction proceeds in a stereo-specific way (retention of configuration) as shown in Eqs. 31–34.[35]




(7.31)




(7.32)

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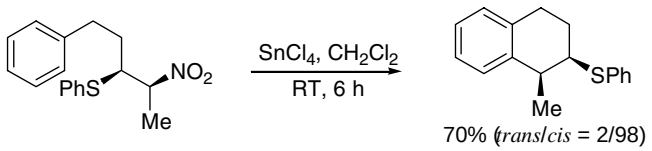
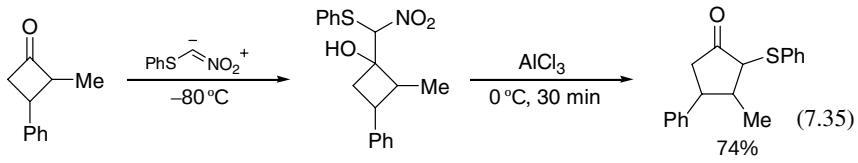



(7.34)

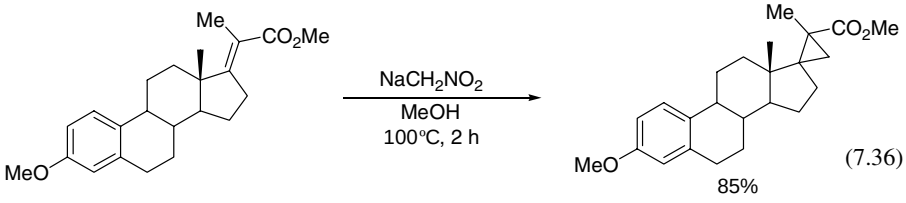
Ring expansion of cyclic ketones via nitro-aldol reaction of α-nitrosulfides followed by treatment with $AlCl_3$ has been reported (Eq. 7.35).[36]



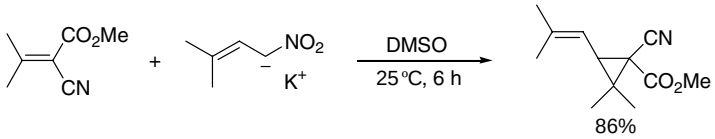

(7.35)

### 7.1.3 Intramolecular Nucleophilic Substitution Reaction

Although the base-catalyzed addition of nitroalkanes to electron-deficient olefins has been extensively used in organic synthesis (see Michael addition Chapter 4), it is only recently that the reaction has been extended to the cyclopropanation reaction. In 1978, it was reported that the anion of nitromethane reacts with certain highly electron-deficient olefins to produce cyclopropanes in good yield (Eq. 7.36).[36] More recently, this reaction has been extended to more general cyclopropanations, as shown in Eqs. 7.37 and 7.38, in which potassium salts of nitroalkanes are employed in DMSO as alkylidene transfer reagents.[37–39]




(7.36)

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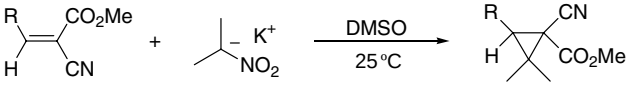
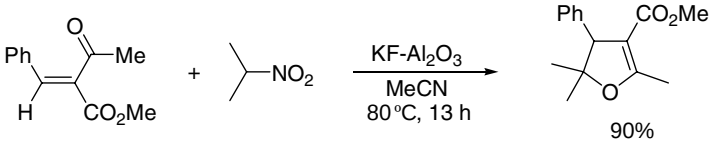


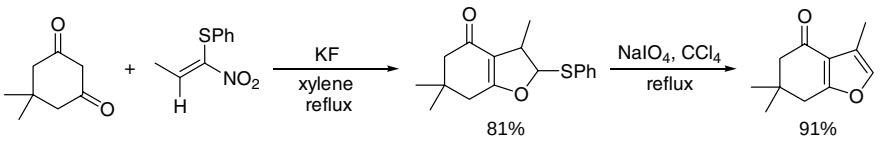

(7.38)

Alumina-supported KF is an effective reagent for Michael addition of nitroalkanes to electron-deficient olefins. Subsequent cycloalkylations afford cyclopropanes.[37] However, the reaction of α,β-unsaturated ketones with nitroalkanes in the presence of KF-$Al_2O_3$ in acetonitrile gives 4,5-dihydrofuranes (Eq. 7.39).[40]



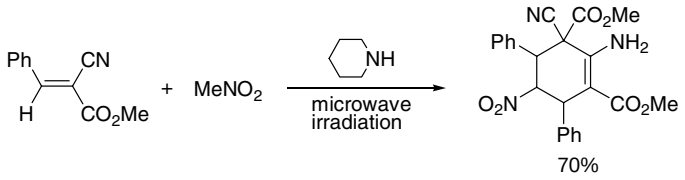

(7.39)

Yosikoshi reported the synthesis of furan derivatives by the reaction of 1,3-diketones with nitroalkenes, in which the Michael addition of the anions of 1,3-diketones and the subsequent intramolecular displacement of the nitro group by enolate oxygen are involved as key steps (Eq. 7.40).[42]



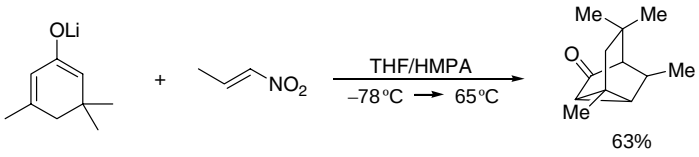

(7.40)

In some cases, no cycloalkylation is observed by the reaction of nitromethane with electron-deficient olefins with cyano and methoxycarbonyl groups. The reaction affords new, highly functionalized cyclohexenes in the presence of catalytic amount of piperidine under solvent-free conditions with focused microwave irradiation (Eq. 7.41).[42]




(7.41)

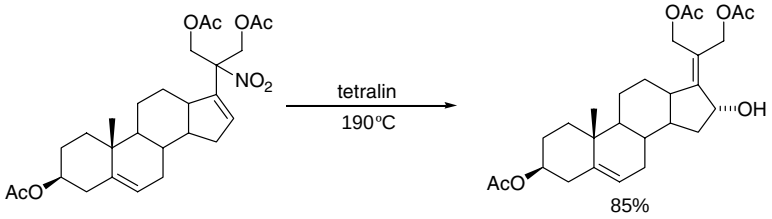
The tandem Michael and cyclopropanation reaction of lithium enolates with nitroalkenes gives tricyclic ketones in one pot, as shown in Eq. 7.42.[43]



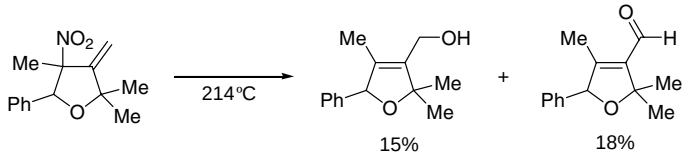

(7.42)

### 7.1.4 Allylic Rearrangement

Allylic nitro compounds undergo [2.3]sigmatropic rearrangement to afford rearranged alcohols, as shown in Eq. 7.43[46] and Eq. 7.44.[47] Because the allylic nitro compounds used in these reactions are readily prepared either by the Henry reaction or the Michael addition, these reactions may be useful in organic synthesis.




(7.43)



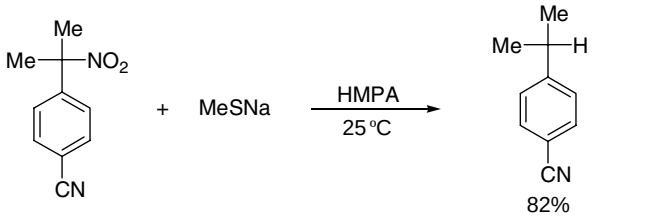

(7.44)

## 7.2 R–H FROM R–NO$_2$

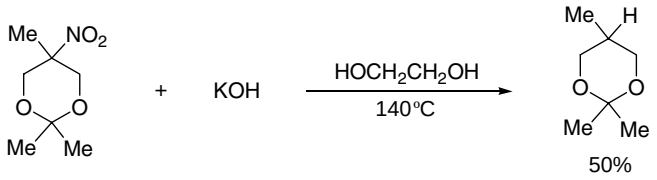
The replacement of the nitro group by hydrogen is a relatively new reaction as compared with other traditional functional transformations. Good reviews are available for this transformation.[48] The removal of the nitro group after the construction of the carbon frameworks using the activating property of the nitro group is a recent strategy in organic synthesis. Thus, anions derived from nitroalkanes can be regarded as equivalent of alkyl anions. Alkyl anions are generally difficult to generate (p$K_a$ = ca. 50 for R-H) and hence unstable at room temperature, but the anions of nitroalkanes are generated readily (p$K_a$ = ca. 10 for $RCH_2NO_2$), stable, and selective in the presence of other electron-withdrawing groups. The denitration reaction is now widely used for the synthesis of complex natural products with various functional groups.

### 7.2.1 Radical Denitration

Denitrohydrogenation can be achieved either by radical or ionic processes. The first radical denitration was done with MeSNa in DMSO or HMPA (Eq. 7.45)[49] followed by heating with KOH in ethylene glycol (Eq. 7.46).[50] The reaction using MeSNa has played a pioneering role in this area. An electron-transfer chain mechanism has been proposed for these reactions, in which radical anions and free radicals are involved. The nitro groups, which are replaced by hydrogen using MeSNa, are limited to tertiary ones. Some of them are listed in Table 7.1.

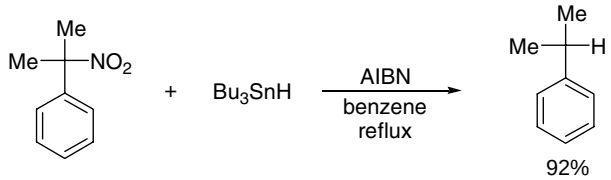



(7.45)

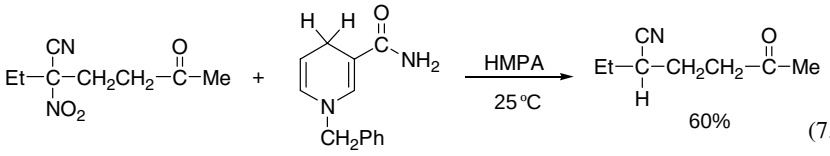



(7.46)

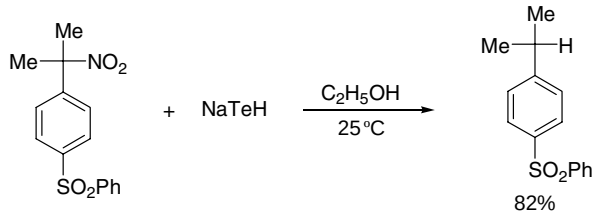
In 1981, Ono[51] and Tanner[52] reported independently that $Bu_3SnH$ is a more versatile reagent for denitrohydrogenation than MeSNa. A radical initiator, 2,2-azobisisobutyronitrile (AIBN)[51] or benzoylperoxide,[52] was used (see Table 7.1). α-Nitrocumene is converted into cumene in 92% yield on treatment with $Bu_3SnH$ (Eq. 7.47), whereas the yield is only 29% if the same conversion is carried out using MeSNa. Although several other radical denitration reagents such as 1,4-dihydronicotinamide (Eq. 7.48),[53] NaTeH (Eq. 7.49),[54] and $Na_2S_2O_4$-$Et_3SiH$ (Eq. 7.50)[55] have been used, tin hydride is most widely employed for effecting this useful transformation.




(7.47)

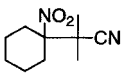
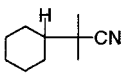
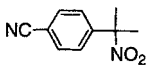
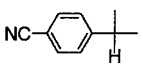
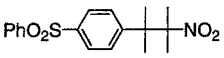
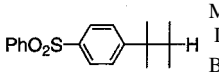
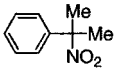
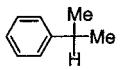
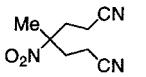
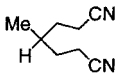
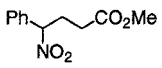
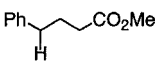
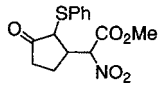
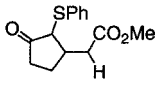
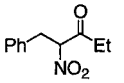
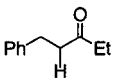
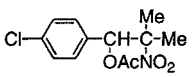
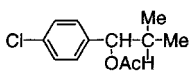


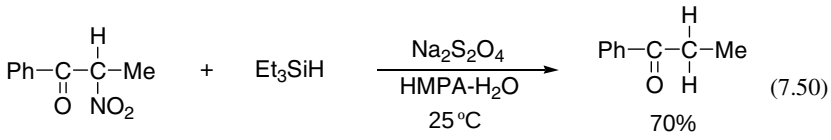

(7.48)




(7.49)

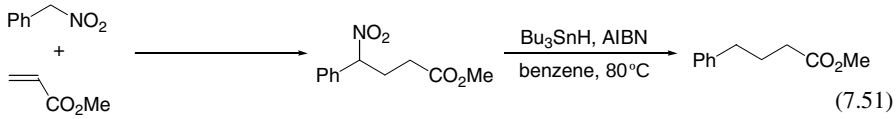
**Table 7.1. Denitration of nitro compounds with MeSNa or $Bu_3SnH$**

| R-$NO_2$ | Product | Reagent | Yield (%) | Ref. |
|---|---|---|---|---|
|  |  | MeSNa DMSO, 3 h | 95 | 49 |
| | | $Bu_3SnH$, $(PhCO)_2O_2$ benzene, 18 h | 95 | 52 |
|  |  | MeSNa HMPA, 16 h | 82 | 49 |
| | | $Bu_3SnH$, $(PhCO)_2O_2$ benzene, 18 h | 90 | 52 |
|  |  | MeSNa DMF, 8 h | 83 | 49 |
| | | $Bu_3SnH$, $(PhCO)_2O_2$ benzene, 18 h | 85 | 52 |
|  |  | $Bu_3SnH$, AIBN benzene (80 °C) 1.5 h | 92 | 51 |
|  |  | $Bu_3SnH$, AIBN benzene, 1.5 h | 92 | 51 |
|  |  | $Bu_3SnH$, AIBN benzene, 1.5 h | 64 | 51 |
|  |  | $Bu_3SnH$, AIBN benzene, 1.5 h | 75 | 51 |
|  |  | $Bu_3SnH$, AIBN benzene, 1.5 h | 78 | 51 |
|  |  | $Bu_3SnH$, AIBN benzene, 1.5 h | 83 | 51 |

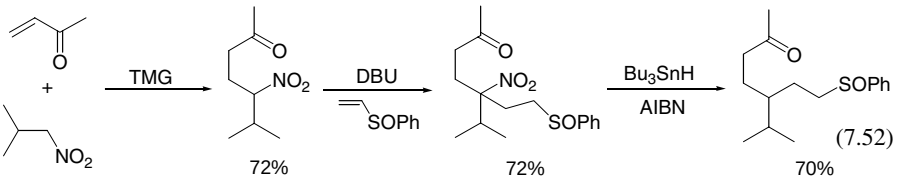


(7.50)

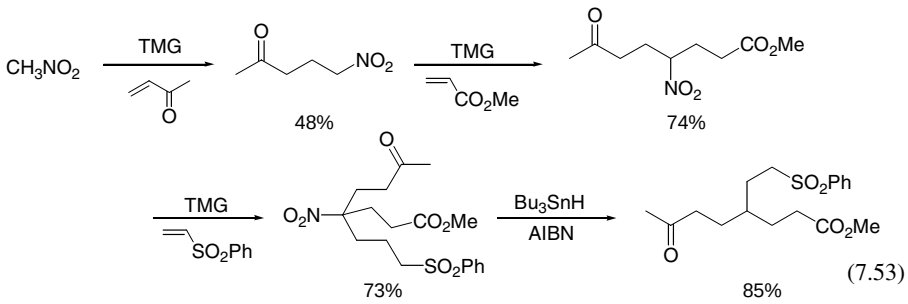
Tanner and coworkers investigated the denitrohydrogenation reaction and proposed an electron-transfer mechanism, which is analogous to the denitration mechanism using MeSNa.[52]. These nitro compounds are all tertiary and rather special. The results are summarized in Table 7.1. On the other hand, Ono and coworkers have selected the more general nitro compounds which are formed by the conventional reactions such as the Henry reaction or the Michael reaction, for denitration with tin radical. They have found that such nitro groups are cleanly denitrated with $Bu_3SnH$. Now, the sequence of the Henry reaction or Michael reaction and denitration provides a very useful strategy for organic synthesis. The regio-controlled carbon-carbon bond formation and functional selective denitration are very attractive, as exemplified in Eqs. 7.51–7.53. The nitro group is selectively removed from the compounds, which contain other functional groups such as Cl, OH, C=O, CN, SO, and $SO_2$ groups. The sequence of the Michael addition of nitroalkanes and denitration provides a new and general method for conjugate additions of primary and secondary alkyl groups.[56]



(7.51)

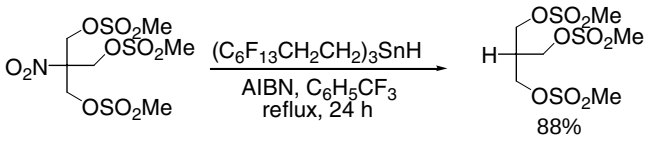


(7.52)



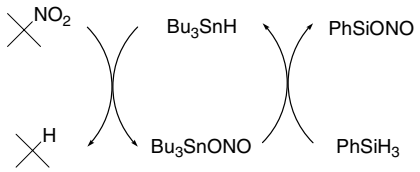
(7.53)

Synthetic chemists have long lauded the radical reactivity profile of $Bu_3SnH$, but bemoaned its separation of organic tin compounds from the product and toxicity problems. To overcome these drawbacks of tin reagents, several alternatives to $Bu_3SnH$ have been devised: such as polymeric tin hydrides,[57] acid soluble tin hydrides,[58] water-soluble tin hydrides,[59] and tris(2-(perfluorohexyl)ethyl)tin hydride.[60] The last reagent is used in $C_6H_5CF_3$. Tin reagents and the denitrated products are separated by liquid-liquid extraction using perfluoromethylcyclohexane and $CH_2Cl_2$. This is a new technique for the purification and separation of organic compounds using organic fluorine compounds (Eq. 7.54).



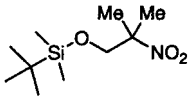
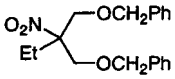
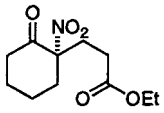
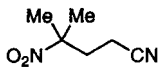
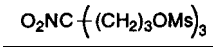

(7.54)

Silicon hydrides, in particular $(Me_3Si)_3SiH$, can serve as substituents for $Bu_3SnH$ in a number of radical-mediated processes.[61] However, silicon hydrides cannot promote the reduction of tertiary nitroalkanes to alkanes.[62] In 1998, Fu reported the catalytic cycle for the $Bu_3SnH$-catalyzed reduction of nitroalkanes to alkanes, using 10% $Bu_3SnH$ as the catalyst and $PhSiH_3$ as the reducing agent (see Eq. 7.55 and Scheme 7.5). The new catalytic reaction proceeds with efficiency, comparable to the stoichiometric $Bu_3SnH$ method (Table 7.2).[63] Like the stoichiometric method, the catalytic reaction is effective for the reduction of tertiary nitroalkanes and activated secondary nitroalkanes and is compatible with functionality, such as ethers, acetals, ketones, esters, nitriles, and mesylates. The conversion of nitroalkanes to alkanes is currently most often accomplished with stoichiometric $Bu_3SnH$, but the environmentally friendlier $Bu_3SnH$-catalyzed variant may become the method of choice for effecting these important transformations.



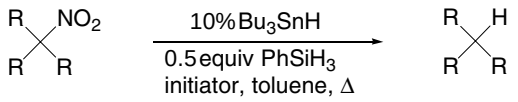

**Scheme 7.5.** $Bu_3SnH$-catalyzed reduction of nitroalkanes to alkanes

**Table 7.2. $Bu_3SnH$-catalyzed reduction of nitroalkane to alkanes**

| | Yield (%) | |
|---|---|---|
| Substrate | Catalyzed[a] | Stoich[b] |
|  | 76 | 77 |
|  | 71 | 74 |
|  | 75 | 78 |
|  | 70 | 67 |
|  | 61 | 58 |

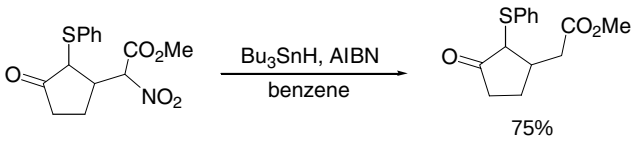
[a] 10% $Bu_3SnH$, $PhSiH_3$ (0.5 equiv), ACHN (0.2 equiv), toluene, 110 °C, 5 h.

[b] $Bu_3SnH$ (1.5 equiv), ACHN (0.2 equiv), toluene, 110 °C, 5 h.



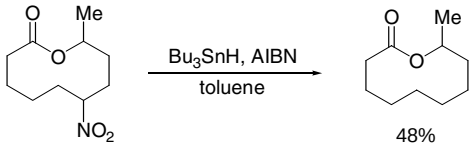

(7.55)

Although the nitro compounds, which can be denitrated, are mostly tertiary ones, the radial denitration using $Bu_3SnH$ can also be applied to secondary nitro compounds. The nitro groups at benzylic and allylic positions are readily denitrated with $Bu_3SnH$ by the procedure that is used for the denitration of tertiary nitro compounds (60–80% yield). The secondary nitro groups of α-nitro ketones or α-nitro esters are also cleanly replaced by hydrogen on treatment with $Bu_3SnH$ (Eq. 7.56).[56]

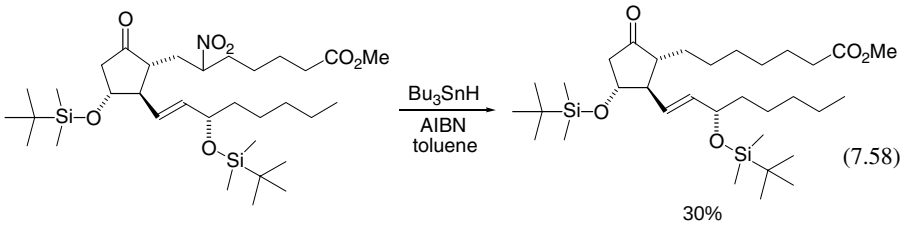



(7.56)

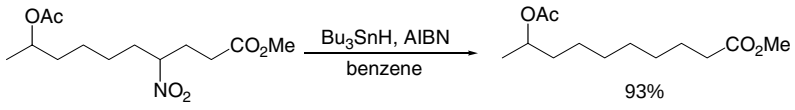
The unactivated secondary nitro groups are rather difficult to be replaced by hydrogen. Rather drastic conditions using a large excess of $Bu_3SnH$ in refluxing toluene are required for the denitration of simple secondary nitro groups.[64] Although the yield is moderate (40–60%), the direct removal of the secondary nitro groups is synthetically useful. Some examples are presented in Eq. 7.57,[64] Eq. 7.58,[65] and Eq. 7.59.[66] The high yield reported in Eq. 7.59 is exceptional. Any other methods without using $Bu_3SnH$ fail in denitrating secondary nitro groups.




(7.57)



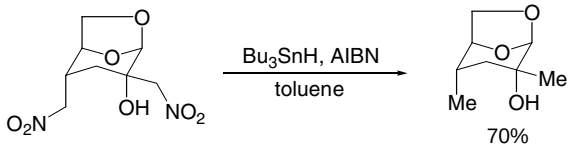

(7.58)




(7.59)

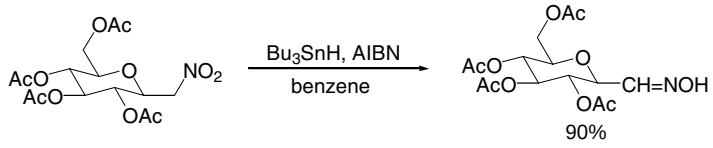
Primary nitro groups are much more difficult to be replaced by hydrogen. Indirect methods are required for the conversion of a nitromethyl group to a methyl group. The Nef reaction and subsequent reduction via the hydroxymethyl group and radical deoxygenation may be the method of choice for this conversion (see Scheme 7.2). However, in 1995, Witczak and Li reported the removal of primary nitro groups by reaction with $Bu_3SnH$ in the presence of 1,1′-azobis(cyclohexanecarbonitrile)(ABCN) (Eq. 7.60).[67] This is the only report of the radical

denitration of a primary nitro group. The mechanism of denitration is shown in Scheme 7.6. When R is tertiary or secondary, alkyl radicals are formed. However, the scission of N–O bond to give nitroso (oxime) is the more favored process for the reaction of primary nitro compounds with tin radicals.

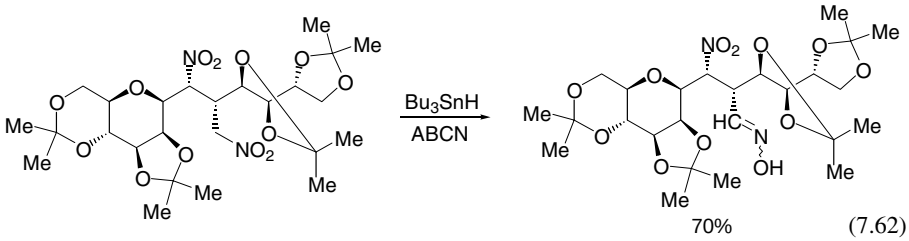



(7.60)

Recently, it was reported that a nitromethyl group was reduced to the corresponding oxime by reaction with $Bu_3SnH$ in the presence of radical initiator (Eq. 7.61).[68] Interestingly, primary nitro groups are selectively reduced to oximes in the reaction of the compounds containing both primary and secondary nitro groups (Eq. 7.62).[69] The product of Eq. 7.60 may not be correct, but may be the oxime.




(7.61)

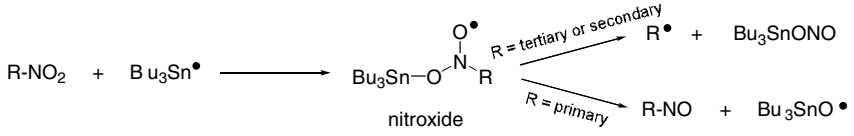



(7.62)

The mechanism for the reduction of nitro compounds with $Bu_3SnH$ has been established as shown in Scheme 7.6. The key propagation steps are the addition of $Bu_3Sn^-$ to the nitro group and the subsequent elimination of an alkyl radical. Cleavage at the carbon-nitrogen bond is characteristic to tin adducts of nitro compounds, whereas fragmentation takes place preferentially at the nitrogen-oxygen bond in the analogous adducts of other radicals. The mechanism of radical denitration with tin hydride and related reactions has been well studied.[70]

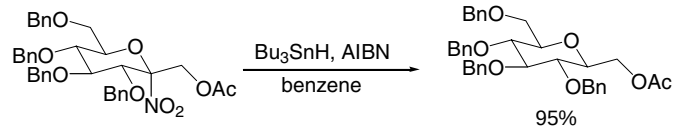
Because the radical denitration using $Bu_3SnH$ proceeds under neutral conditions with high-functional selectivity, it has been widely used in organic synthesis. It is noteworthy that the nitro group is selectively replaced by hydrogen without affecting other reducible groups, such as Cl, $CF_3$, CHO, and PhSO groups.

The Henry reaction of nitroalkanes followed by denitration is a good method for the preparation of alcohols. This methodology has been applied in carbohydrate chemistry. For

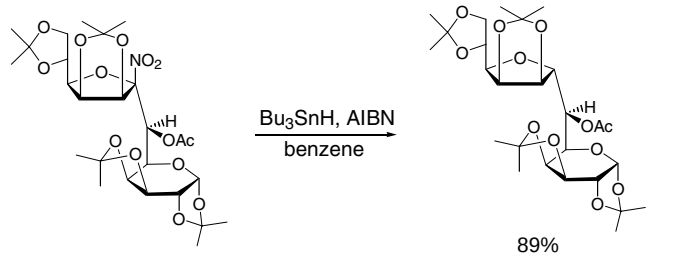



**Scheme 7.6.**

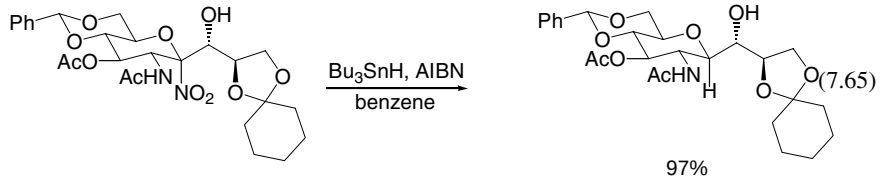
example, the reaction of 1-deoxy-1-nitroaldoses with formaldehyde followed by denitration opens a new way to C-glycoside (see Eq. 7.63,[71] Eq. 7.64,[71] and Eq. 7.65.[72]




(7.63)

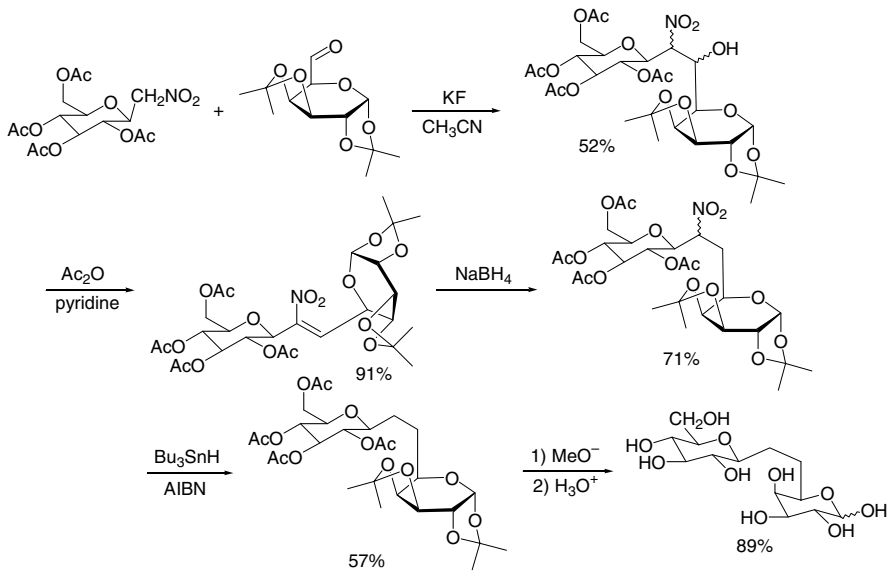



(7.64)

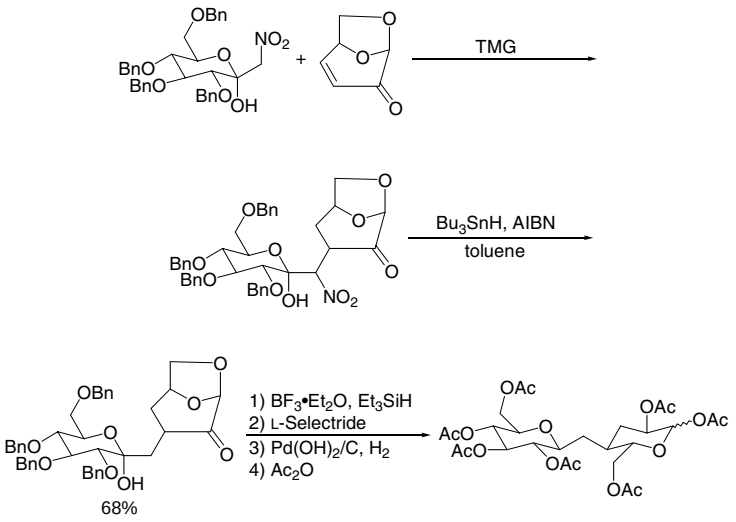



(7.65)

Martin has used this strategy for the preparation of β-(1,6) and β,β-(1,1) linked C-disaccharides, as shown in Scheme 7.7.[73] Such C-disaccharides are a class of nonhydrolyzable mimics of disaccharide and potential glycosidase inhibitors in the treatment of metabolic diseases (Scheme 7.7).



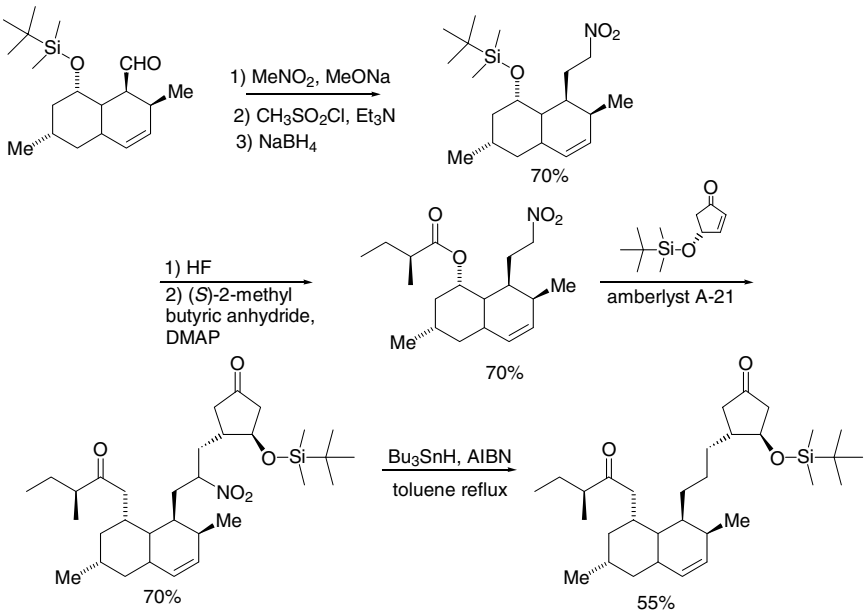

**Scheme 7.7.**




**Scheme 7.8.**

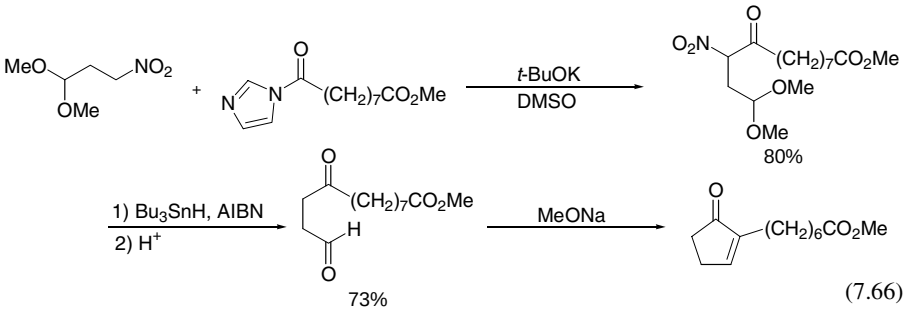
The Michael addition of nitroalkanes followed by denitration is also a useful method for the preparation of C-disaccharide. The Michael addition of glucosyl nitromethane to the levoglucosenone proceeds stereoselectively, and subsequent denitration gives the C-disaccharide in 68% yield (Scheme 7.8).[74]

Elegant application of the Michael addition of nitroalkanes to enones followed by denitration is demonstrated in the synthesis of (+) dihydromevinol, (see Scheme 7.9).[75]




**Scheme 7.9.**

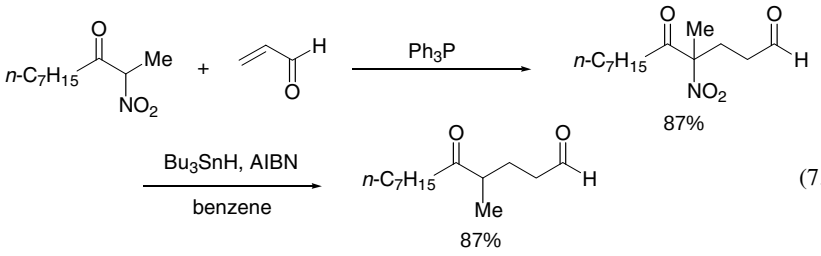
Because the α-nitroketones are prepared by the acylation of nitroalkanes (see Section 5.2), by the oxidation of β-nitro alcohols (Section 3.2.3), or by the nitration of enol acetates (Section 2.2.5), denitration of α-nitro ketones provides a useful method for the preparation of ketones (Scheme 7.10). A simple synthesis of cyclopentenone derivatives is shown in Eq. 7.66.[76]



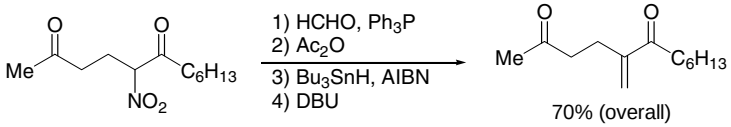

(7.66)

Magnus and coworker have presented a new strategy for the preparation of taxane diterpenes by using nitro-aldol reaction and denitration as key steps (see Scheme 7.11).[77]

The high acidity of α-nitroketones makes it possible to perform the Henry reactions or Michael additions under extremely mild conditions. The reaction proceeds in the presence of catalytic amounts of $Ph_3P$ to give the C–C bond formation products under nearly neutral conditions. Thus, 1,5-dicarbonyl compounds[78] and α-methylenecarbonyl compounds[79] are prepared by the denitration of α-nitroketones, as shown in Eqs. 7.67 and 7.68, respectively.

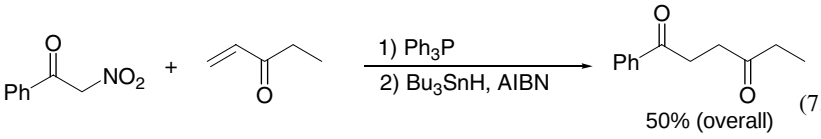



(7.67)

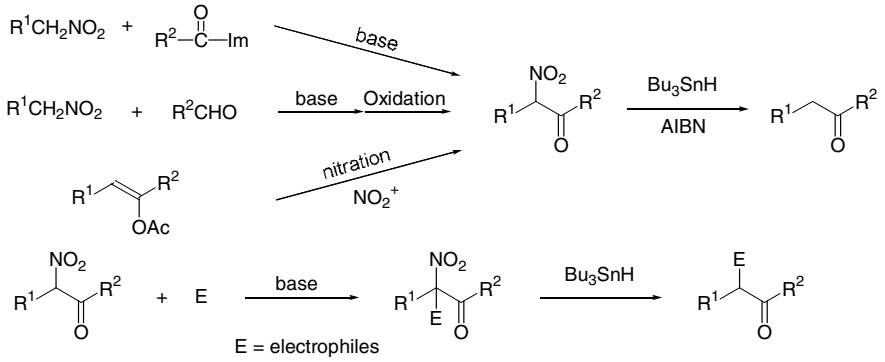



(7.68)

Ballini and coworkers have reported a simple synthesis of 1-phenylheptane-1,5-dione based on the strategy of the Michael addition and denitration as shown in Eq. 7.69).[80] The product is a natural product that is isolated from fungus.

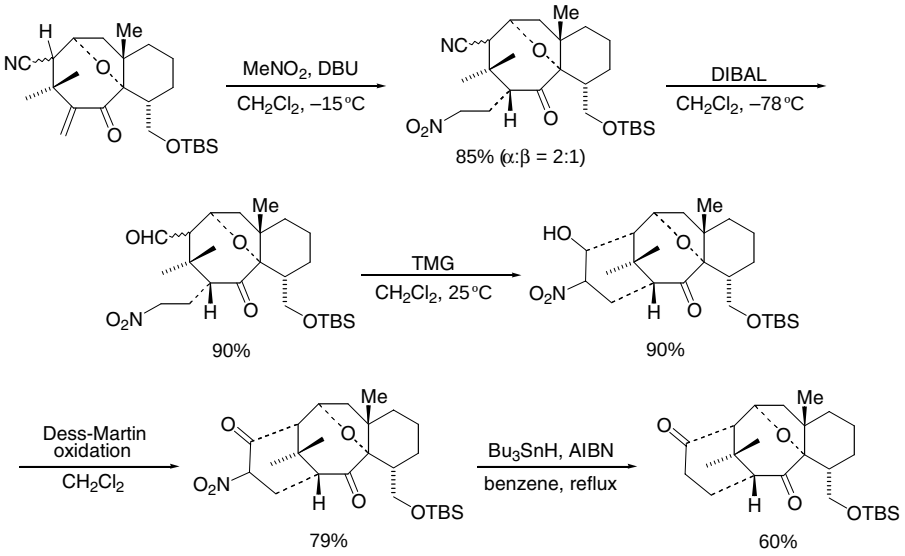



(7.69)

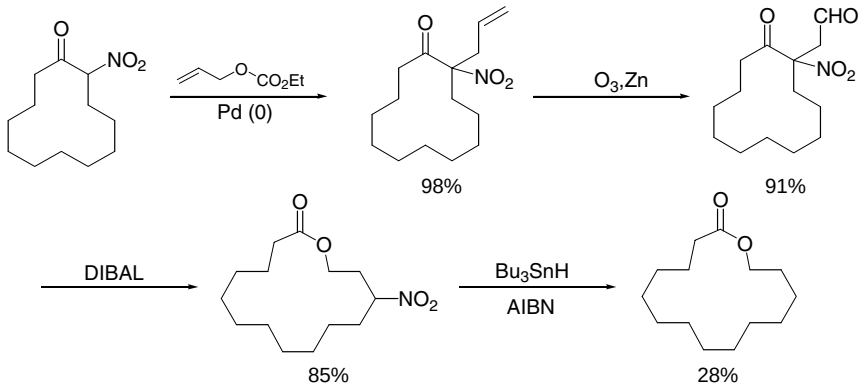



**Scheme 7.10.**

Biologically active natural products frequently contain medium or large rings, and many methods have been used in preparing of such compounds.[81] Hesse and coworkers have exploited an elegant ring expansion reaction of α-nitroketones using the ability of the nitro group to stabilize a carbanion (retro-acylation of nitro compounds). Various macro cyclic compounds are now prepared by this route (see Section 5.3).[82] The carbon-carbon bond-forming reactions of α-nitroketones followed by an intramolecular addition of the alkoxide to the carbonyl group give the ring-expanded products. The nitro groups are finally removed on treatment with $Bu_3SnH$. For example, tetradecano-14-lactone is prepared via palladium-catalyzed allylation (Section 5.5) of 2-nitrocyclodecanone followed by ozonolysis, reduction, ring expansion, and denitration, as shown in Scheme 7.12.[83] In a similar way, (−)-15-hexadodecanolide (Scheme 7.13)[84], (+)-13-tetradodecanolide (Scheme 7.14),[85] and muscone (Scheme 7.15)[86] are prepared.

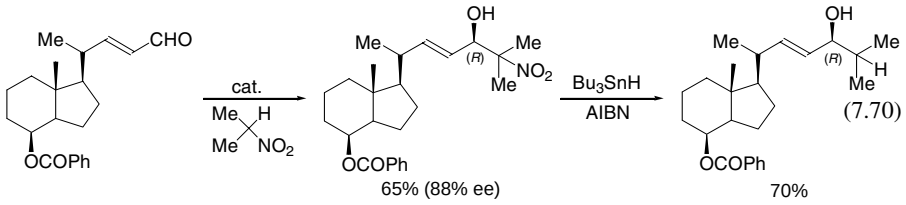



**Scheme 7.11.**

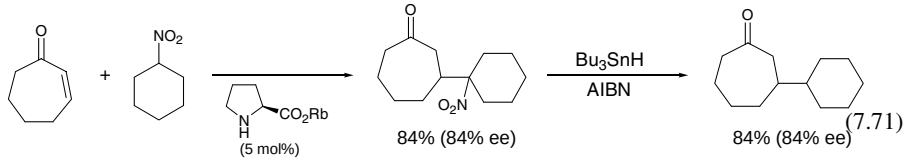


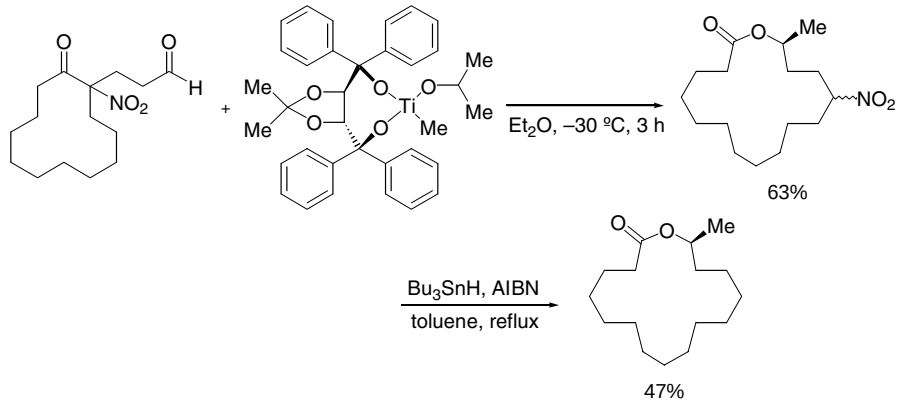

**Scheme 7.12.**

Enantioselective nitro-aldol reaction (see Section 3.3) or Michael reaction (see Section 4.4) followed by radical denitration is useful as an alternative indirect method of enantioselective 1,2- or 1,4-addition of alkyl anions (see Eq. 7.70[87] and Eq. 7.71[88]).

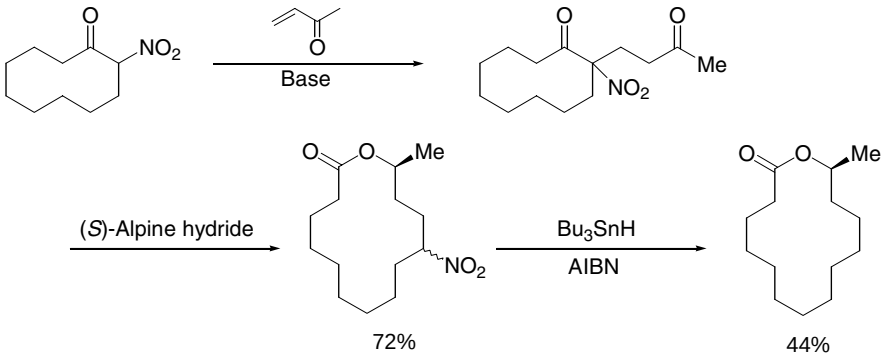



cat.: La-K-(*S*)-6,6-bis(triethylsilyl)ethynyl BINOL (see Section 3.3)



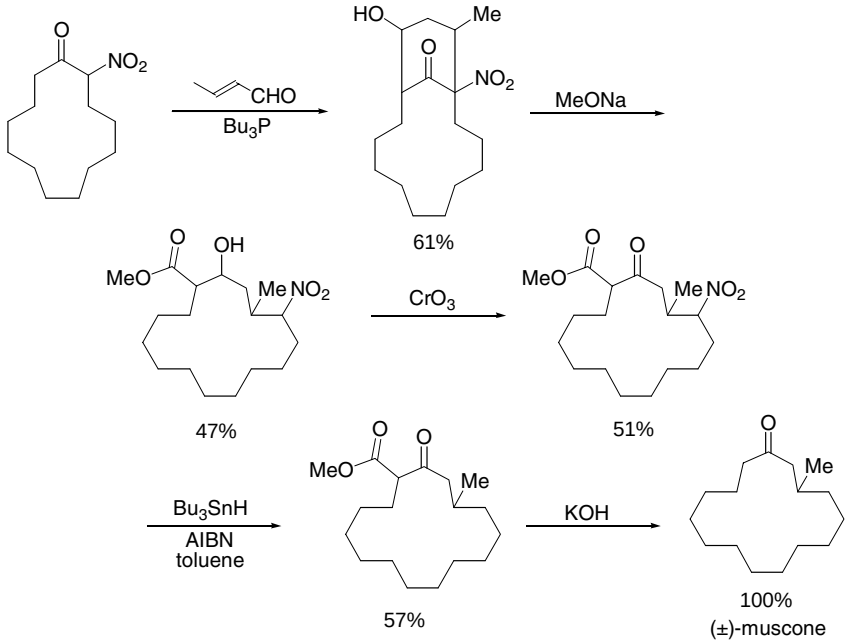

**Scheme 7.13.**



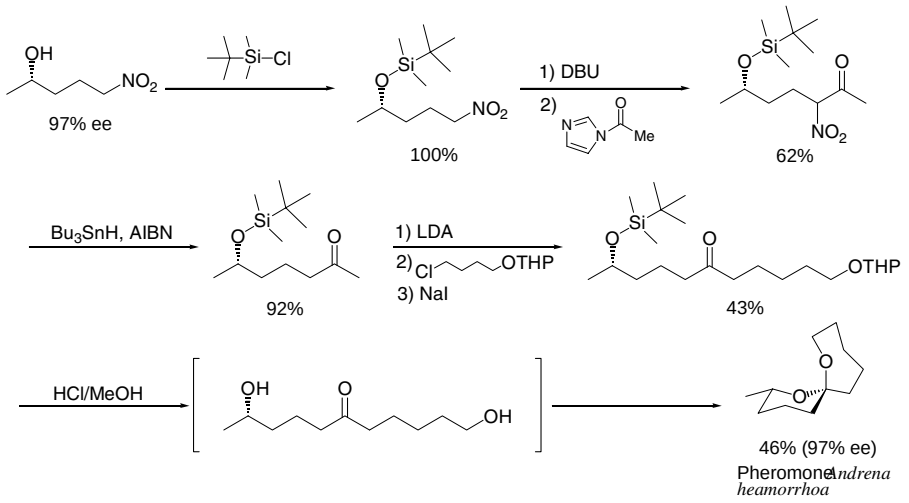

**Scheme 7.14.**

The reduction of nitro ketones with baker's yeast is a good method for the preparation of chiral nitro alcohols.[89] The reduction of 5-nitro-2-pentanone with baker's yeast gives the corresponding (*S*)-alcohol, which is an important chiral building block. Various chiral natural products are prepared from it. In Scheme 7.16, the synthesis of the pheromone of *Andrena haemorrhoa* is described, where the acylation of the chiral nitro alcohol followed by radical denitration is involved as key steps.[89a]

The Michael addition of heteroatom nucleophiles to nitroalkenes (Section 4.1.1) followed by denitration provides a useful method for the preparation of various natural products.



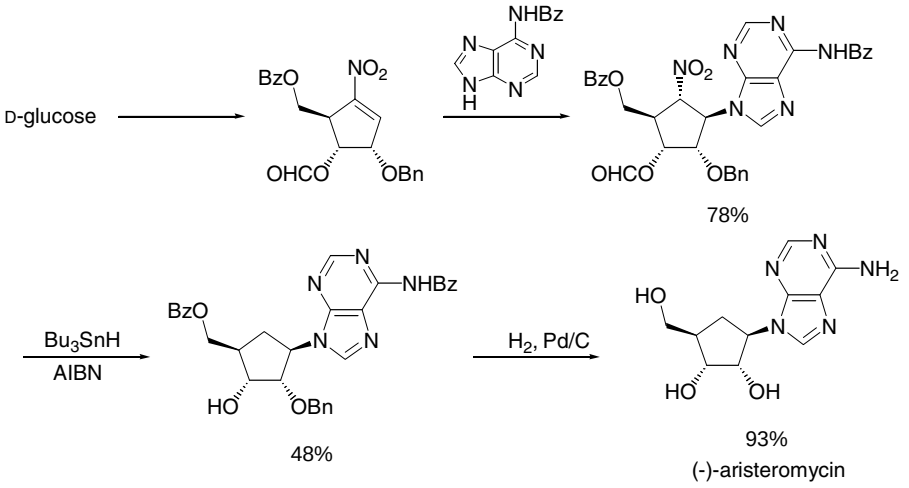

**Scheme 7.15.**



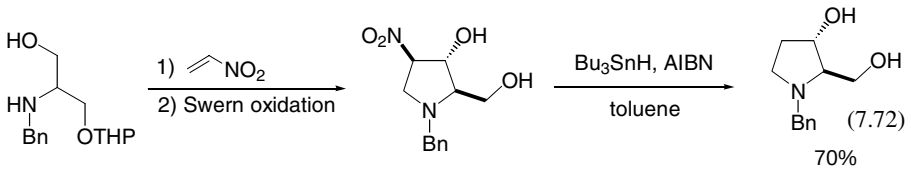

**Scheme 7.16.**

Kitagawa and coworkers have used this strategy for the preparation of pseudo-nucleosides exhibiting various biological activities. The synthesis of (–)-aristeromycin from D-glucose is demonstrated in Scheme 7.17.[90]

Naturally occurring and synthetic polyhydroxylated pyrrolidine and piperidines have recently received considerable attention due to their biological activities. Barco has used tandem Michael-Henry reactions to synthesize 2-hydroxymethyl-3-hydroxy-4-nitro-pyrrolidines, from which the nitro group is removed to give the natural product, *trans* 2-hydroxymethyl-3-hydroxypyrrolidine (Eq. 7.72).[91]

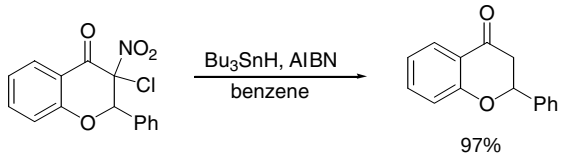



**Scheme 7.17.**



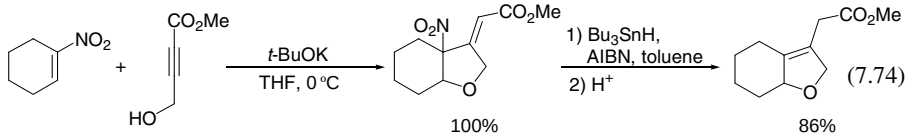

(7.72)

Dauzonne has reported a simple synthesis of flavanones by radical denitration and dehalogenation of 3-chloro-2,3-dihydro-3-nitro-2-aryl-4*H*-1-benzopyran-4-ones,[92] which are readily prepared by the reaction of salicylaldehydes with 1-chloro-1-nitro-2-arylethenes (Eq. 7.73).[93]



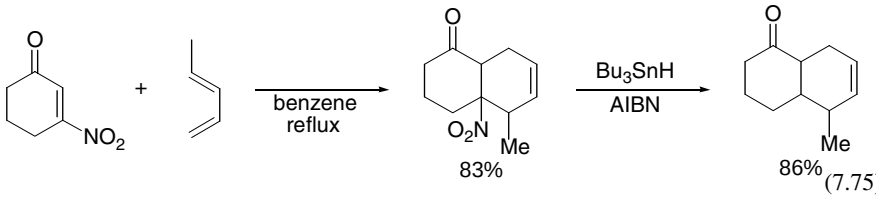

(7.73)

Sequential Michael additions are versatile methods for the construction of cyclic compounds. Although a variety of these reactions have been developed, the use of alcohols as nucleophiles for the Michael addition to nitroalkenes has been little studied. Recently, Ikeda and coworkers have reported an elegant synthesis of octahydrobenzo[*b*]furans via the sequential Michael addition of 1-nitro-cyclohexene with methyl 4-hydroxy-2-butynoate in the presence of *t*-BuOK followed by radical denitration (Eq. 7.74).[94]



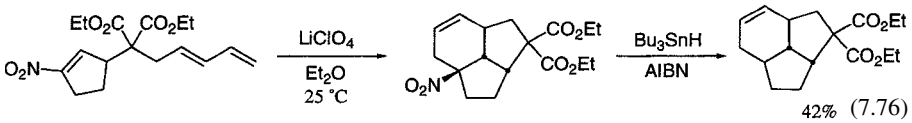

(7.74)

The Diels-Alder reaction followed by radical denitration provides a useful strategy for construction of six-membered compounds, in which the nitro group accelerates the reaction and also controls the regio-chemistry of the addition (Eq. 7.75).[95]




(7.75)

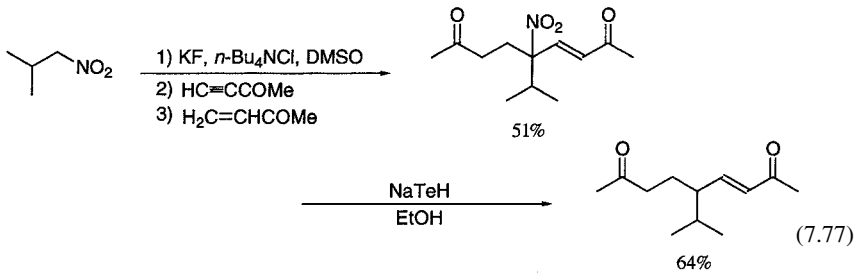
The intramolecular Diels-Alder reaction of nitrotrienes proceeds stereoselectively in the presence of $LiClO_4$ in diethyl ether to give one stereoisomer from *endo* selectivity. The nitro group is removed from the adduct with $Bu_3SnH$ (Eq. 7.76).[96]




(7.76)

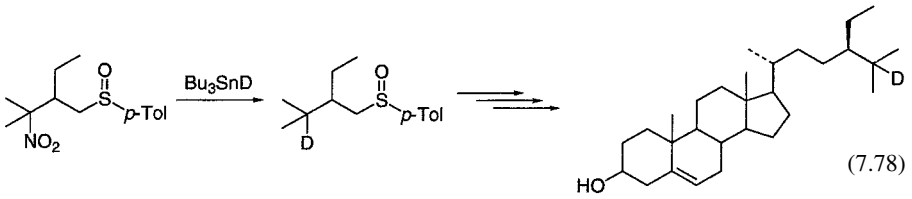
Thus, radical denitration has developed as a reliable tool in organic synthesis and has been mainly carried out using tin hydride in total syntheses of natural products. There is one report in which NaTeH was used for removing the nitro group. Norslanadione, a biologically active

terpenoid is prepared by the double Michael addition and subsequent denitration with NaTeH, as shown in Eq. 7.77.[97]




(7.77)

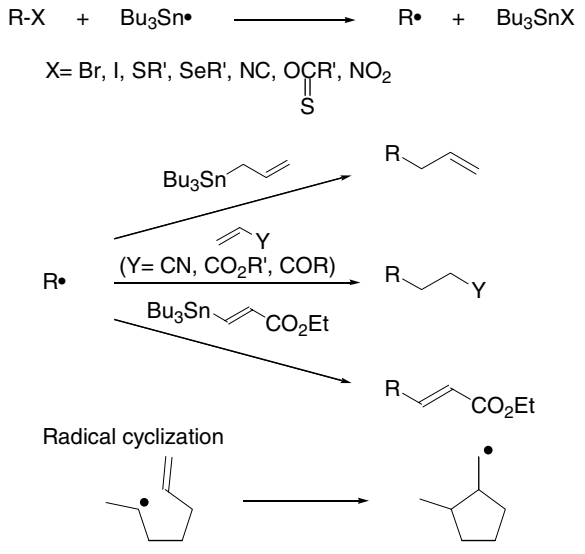
Denitration of nitro compounds with $Bu_3SnD$ provides an elegant method for the synthesis of deuterated compounds.[98] Recently, the synthesis of deuterium labeled plant sterols has been reported (see Eq. 7.78).[99]




(7.78)

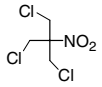
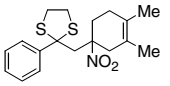
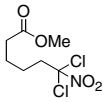
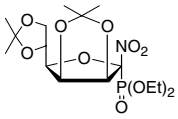
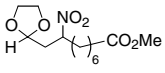
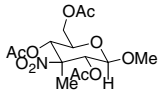
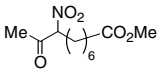
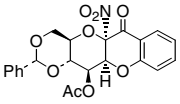
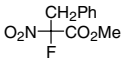
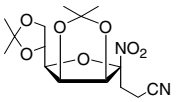
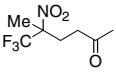
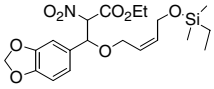
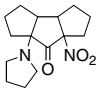
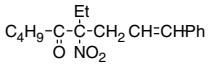
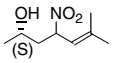
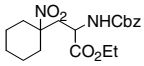
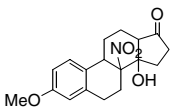
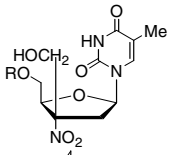
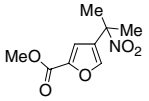
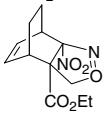
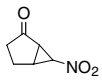
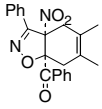
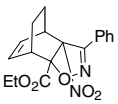
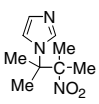
Other applications of radical denitration in organic synthesis are summarized in Table 7.3.

Application of radical reactions to organic synthesis has recently received much attention, and various important reactions have been discovered in this field. Alkyl halides, sulfides, selenides, and thiocarbonyl compounds have been used as precursors to alkyl radicals. Some examples are illustrated in Scheme 7.18.[125]




**Scheme 7.18.**

**Table 7.3. Radical denitration with $Bu_3SnH$**

| $RNO_2$ | Yield (%) RH | Ref. | $RNO_2$ | Yield (%) RH | Ref. |
|---|---|---|---|---|---|
|  | 87 | 100 |  | 95 | 112 |
|  | 78 | 104 |  | 78 | 107 |
|  | 78 | 103 |  | 83 | 106 |
|  | 75 | 103 |  | 63 | 108 |
|  | 80 | 102 |  | 58 | 72 |
|  | 31 | 101 |  | 87 | 116 |
|  | 80 | 105 |  | 85 | 115 |
|  | 64 | 109 |  | 65 | 117 |
|  | 59 | 30 |  | 82 | 118 |
|  | 85 | 114 |  | 91 | 120 |
|  | 26 | 111 |  | 90 | 121 |
|  | 91 | 113 |  | 85 | 122 |

(*continues*)

**Table 7.3. Continued**

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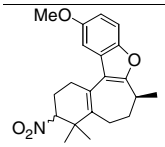
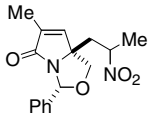
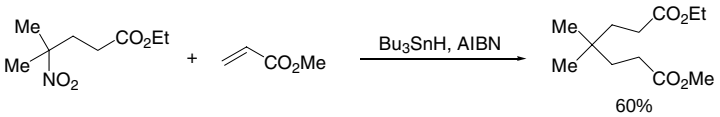
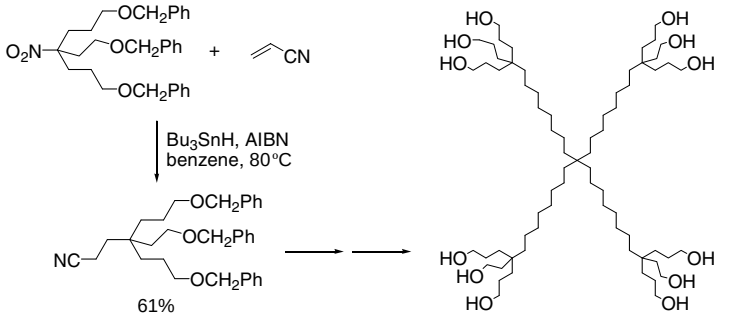
|  | 58 | 123 |  | 83 | 124 |

Because reductive cleavage of aliphatic nitro compounds with $Bu_3SnH$ proceeds via alkyl radicals, nitro compounds are also used as precursors to alkyl radicals. Reactions using nitro compounds may have some advantages over other ones, since aliphatic nitro compounds are available from various sources. For example, the sequence of the Michael additions of nitro compounds provides an excellent method for the construction of quaternary carbon compounds (Eq. 7.79).[126] Newkome has used this strategy for the construction of dendritic polymers (Eq. 7.80).[127]

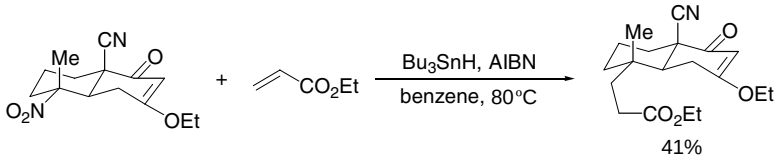



(7.79)



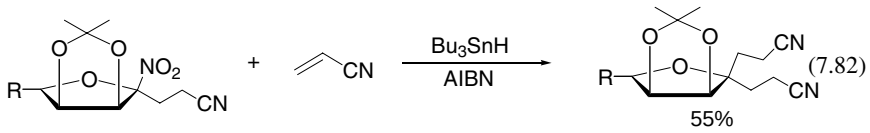

(7.80)

*Trans*-fused bicyclic compounds are prepared by the double Michael reactions of nitro compounds; the nitro group is further alkylated by the radical reaction (Eq. 7.81).[128]



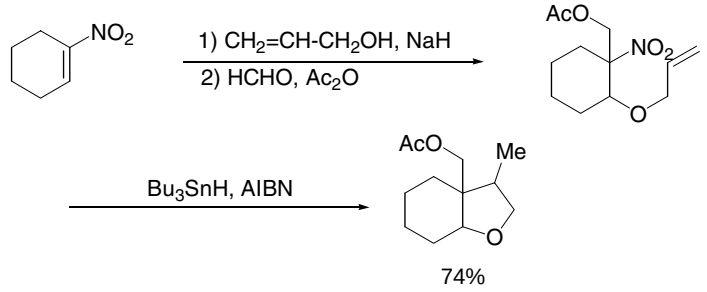

(7.81)

Giese has used this strategy for the synthesis of sugar derivatives, as shown in Eq. 7.82.[129]

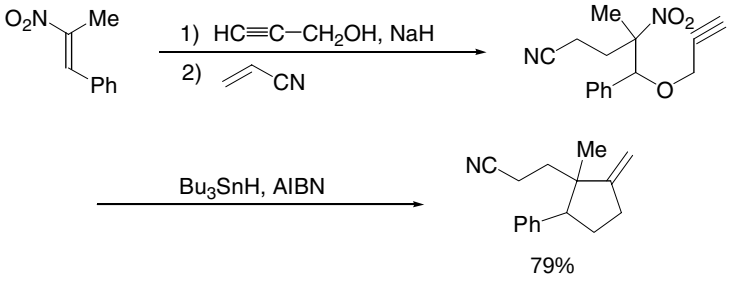



(7.82)

An intramolecular radical cyclization gives the *exo*-cyclic compounds, which has been extensively used in the synthesis of cyclic compounds. Michael additions of allyl alcohols or propargyl alcohols to nitroalkenes and the subsequent treatment with tin radicals provide a useful method for the preparation of substituted furans (Eqs. 7.83 and 7.84).[126]

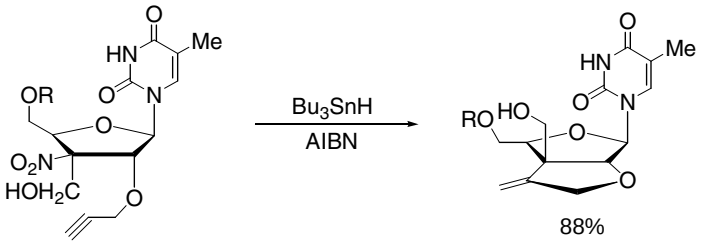



(7.83)




(7.84)

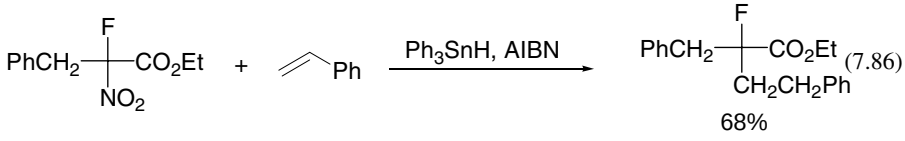
This methodology has also been applied to the synthesis of nucleoside derivatives, which are used in the preparation of drugs against AIDS (Eq. 7.85).[130]



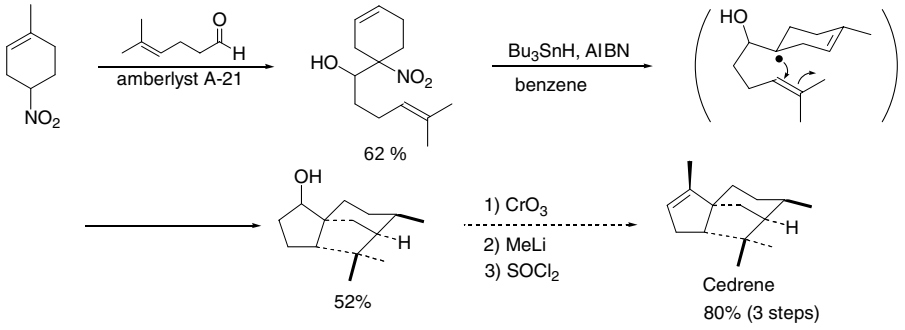

(7.85)

The tandem radial cyclization using the nitro compounds has been used for synthesis of the tricyclic sesequiterpenes, cedrene,[131] and biotol[132] and their derivatives, as shown in Schemes 7.19 and 7.20. The merits using nitro compounds are nicely demonstrated in these cases, in which the nitro group controls the reaction and it acts as a radical-leaving group at the final step.

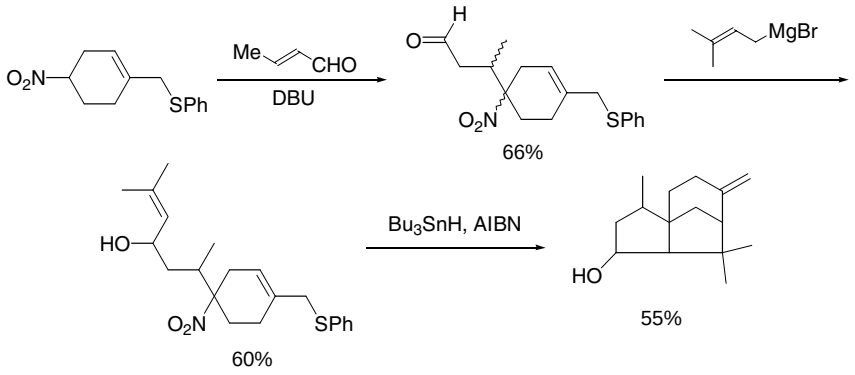
Carbon radicals bearing a single fluorine atom are produced via denitration. They react with styrene to give the adduct in good yield (Eq. 7.86), but with electron-deficient alkenes yields are very low.[133]




(7.86)



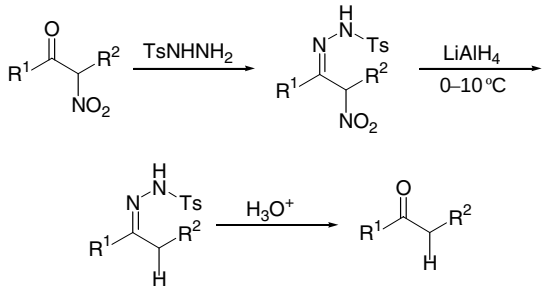

**Scheme 7.19.**




**Scheme 7.20.**

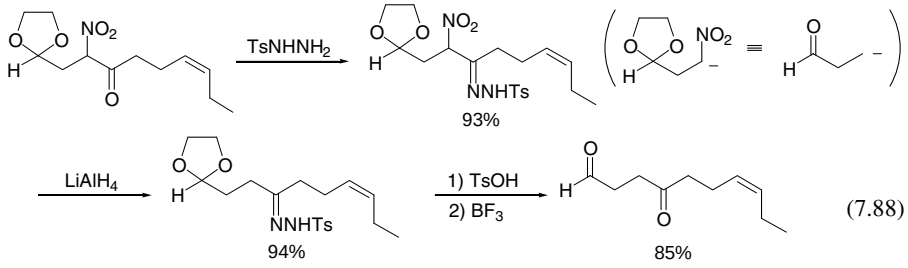
### 7.2.2 Ionic Denitration

Denitration is generally carried out via a radical process using tin hydride, but some nitro groups are replaced by hydrogen via an ionic process. Rosini and coworkers have developed an indirect denitration method of α-nitroketones by the treatment of the corresponding tosylhydrazones with $LiAlH_4$, in which 1,4-elimination of $HNO_2$ and the reduction of tosylazoalkanes to tosylhydrazones occur (Eq. 7.87).[134]



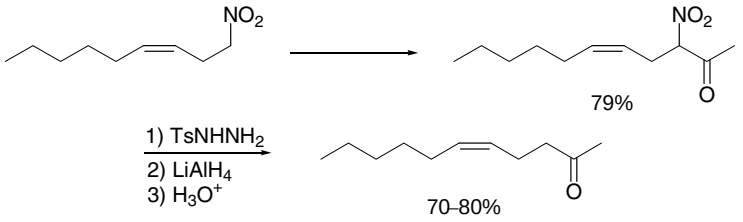

(7.87)

Although this method is not a general procedure, being specific for α-nitroketones, it has several merits to avoid the use of toxic reagents such as organotin compounds. Functionalized ketones have been prepared by this denitration reaction, in which functionalized nitroalkanes are used as alkyl anion synthons. For example, 3-nitropropanal ethylene acetal can be used as synthon of the 3-oxo-propyl anion and 1,4-dicarbonyl compounds are prepared, as shown in Eq. 7.88.[135]



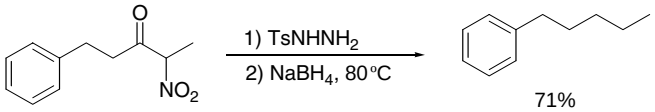

(7.88)

(*Z*)-1-Nitro-3-nonene is converted into a pheromone, (*Z*)-5-undecen-2-one, via nitro-aldol reaction (see Section 3.2.3), followed by oxidation, and denitration, as shown in Eq. 7.89.[136]



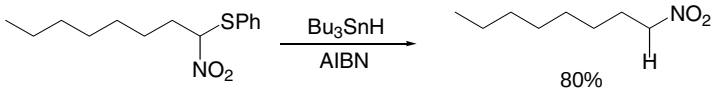

(7.89)

The simultaneous denitration-deoxygenation of α-nitroketones is performed on treatment with $TsNHNH_2$ and $NaBH_4$ at 80 °C to give alkanes (Eq. 7.90).[137]

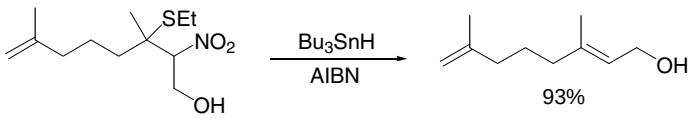



(7.90)

The nitro groups in Eqs. 7.88–7.90 are readily replaced by hydrogen with tin hydride under radical conditions as discussed already. However, the nitro groups in the α-nitrosulfides or β-nitrosulfides are not replaced by hydrogen on treatment with tin hydride but the reaction affords desulfonated products (Eq. 7.51) and alkenes (Eq. 7.97) such radical elimination reactions are discussed in Section 7.3.1. (see Eqs. 7.91 and 7.92).[138]

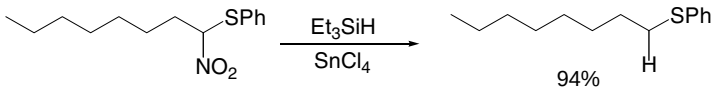



(7.91)

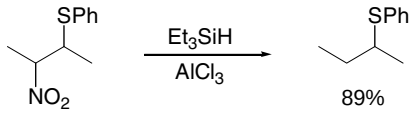



(7.92)

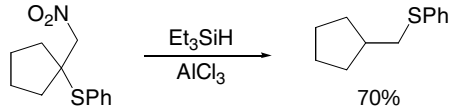
The nitro groups of α- or β-nitrosulfides are cleanly replaced by hydrogen via ionic hydrogenation to give sulfides, as shown in Eqs. 7.93–7.95. The attack of hydride takes place at the more substituted carbon.[139]




(7.93)

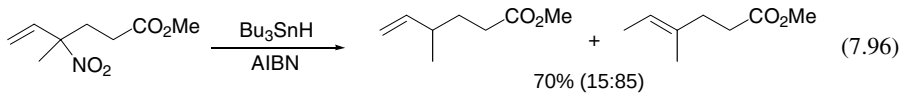



(7.94)

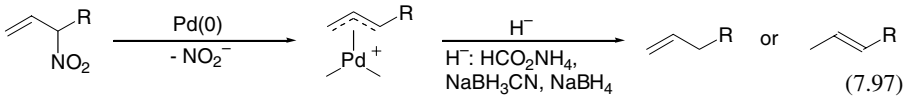



(7.95)

The difficulty in controlling the regiochemistry during radical-denitration of allylic nitro compounds is well known. The migration of the double bond is a serious problem, as shown in Eq. 7.96. This problem is overcome by a hydride transfer reaction in the presence of a palladium catalyst (Eq. 7.97).[140]

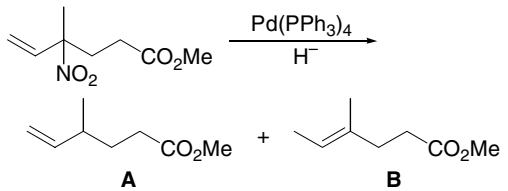



(7.96)



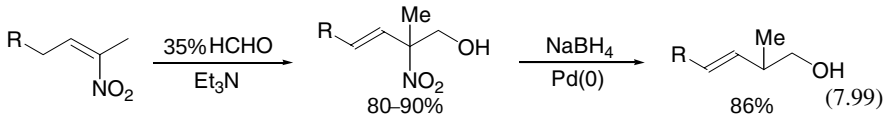

(7.97)

The regiochemical control of Pd-catalyzed hydride transfer reaction is much more effective than that of the radical denitration, as shown in Eq. 7.98. The base-catalyzed reaction of nitroolefins with aldehydes followed by denitration provides a new synthetic method of homoallyl alcohols (Eq. 7.99).[140] Exomethylene compounds are obtained by denitration of cyclic allylic nitro compounds with Pd(0), $HCO_2H$ and $Et_3N$ (Eq. 7.100).[140b]

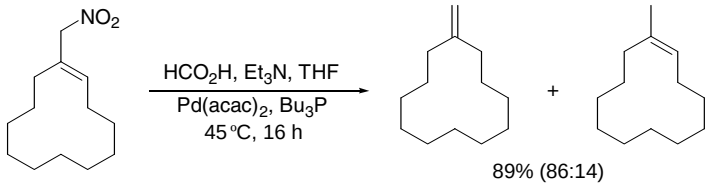



| $H^-$ | Yield (A/B) |
|---|---|
| $NaBH_4$ | 70% (3/97) |
| $HCO_2NH_4$ | 60% (90/10) |

(7.98)

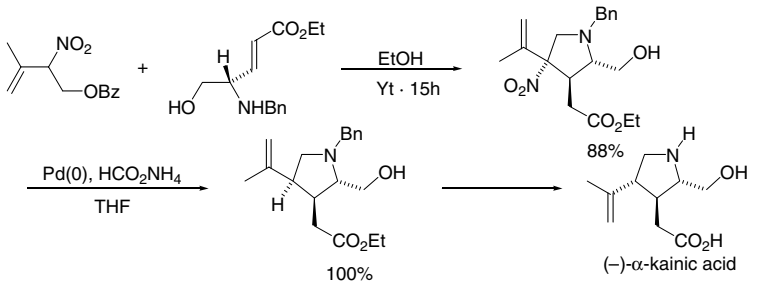



(7.99)

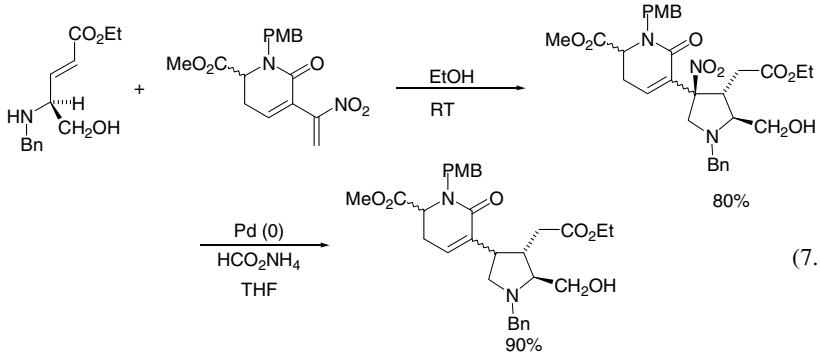



(7.100)

This denitration of allylic nitro compounds catalyzed by Pd(0) is applied to total synthesis of kainic acid, as shown in Eq. 7.101. The tandem Michael addition of a nitrogen nucleophile to nitrodiene gives the requisite framework. The radical denitration does not give the desired product, but it gives a mixture of regio- and stereoisomer. On the other hand, the Pd(0)-mediated denitration proceeds with high regio- and stereoselectivity.[141] In a similar way, other proteinogenic amino acids having a pyrrolidine dicarboxylic acid ring are prepared (Eq. 7.102).[142]




(7.101)



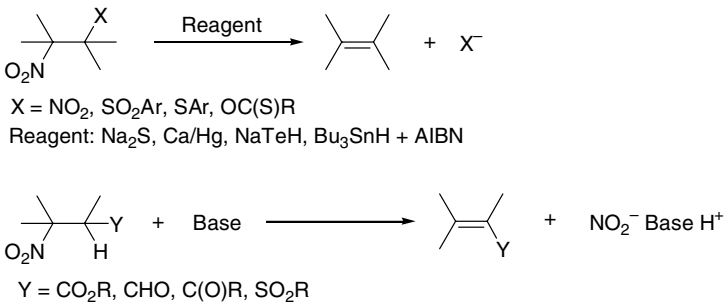

(7.102)

## 7.3 ALKENES FROM R–$NO_2$

Elimination of the $NO_2$ group via radical process or via ionic process from aliphatic nitro compounds affords a useful method for the preparation of olefins. Nitro compounds, with two radical leaving groups at vicinal positions, are prone to undergo radical elimination to give olefins. The nitro group at a β-position with respect to an electron-withdrawing group is readily eliminated to give α,β-unsaturated compounds on treatment with a base (Scheme 7.21).

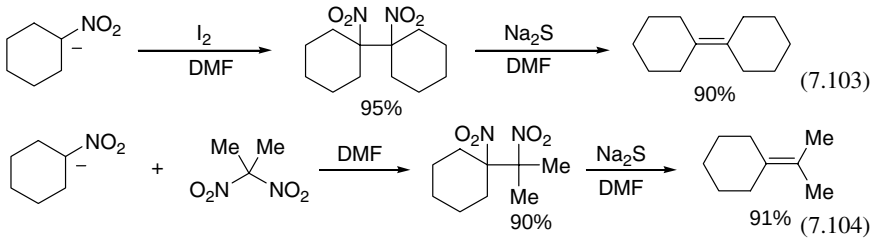
### 7.3.1 Radical Elimination

In 1971, Kornblum and coworkers reported a new synthesis of *tetra*-substituted alkenes from vicinal dinitro compounds.[143] The requisite vicinal dinitro compounds are prepared by the

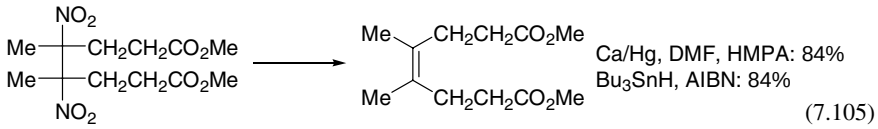



**Scheme 7.21.**

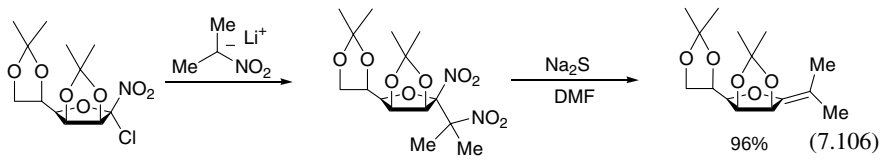
oxidation of the anion derived from nitroalkanes. Unsymmetrical dinitro compounds are prepared by the reaction of geminal dinitro compounds with nitroalkane salts (see Eqs. 7.103 and 7.104).[143]




Because sodium sulfide is a strong nucleophile, other non nucleophilic reagents such as Ca/Hg [144] or $Bu_3SnH$[145] are more suitable than $Na_2S$ in the synthesis of functionalized olefins (see Eq. 7.105). NaTeH is also effective to induce the elimination reaction presented in Eqs. 7.103 and 7.104.[146]

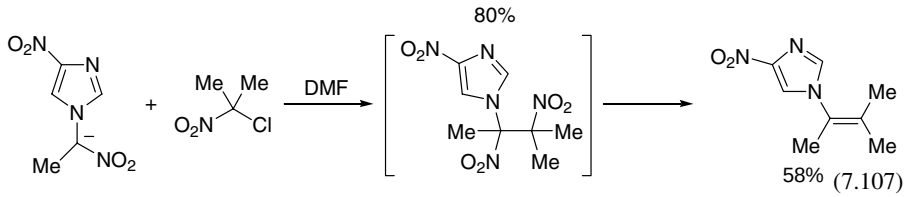



Vasella and coworkers have used this radical elimination for the chain elongation of 1-C-nitroglycosyl halides.[147] The requisite 1-C-nitroglycosyl chlorides and bromides are easily available from sugar oximes.[148] Treatment of 1-C-nitromannosyl chloride with the potassium salt of 2-nitropropane gives the vicinal dinitro sugar in 81% yield. Reduction of this dinitro sugar with $Na_2S$ gives the enol ether in 96% yield (see Eq. 7.106).

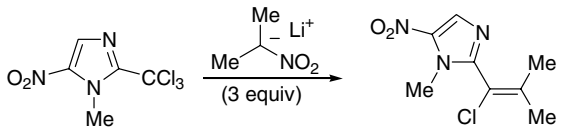



Because anions of nitro compounds are good electron-transfer reagents, they can serve as reducing agents in radical type eliminations of vicinal dinitro compounds. In fact, *N*-azolyl-sub-

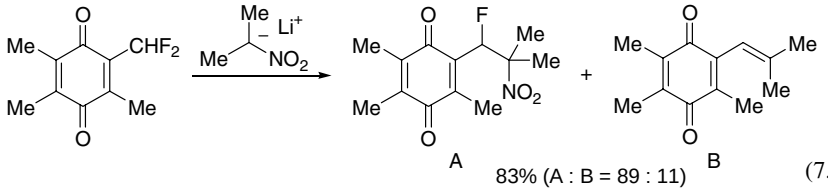
stituted olefin is spontaneously formed by an $S_{RN}1$ reaction of the anion derived from *gem*-nitroimidazolylethane with *gem*-chloronitropropane (Eq. 7.107).[149] Similar sequential $S_N1$ reaction followed by radical elimination is observed in the reaction of 1-methyl-2-trichloromethyl-5-nitroimidazole with the anion of 2-nitropropane (see Eq. 7.108),[150a] or difluoromethyl quinone (see Eq. 7.109).[150b] The main product of Eq. 7.109 is substitution product, but it can be converted to 2,3,5-trimethyl-6-(2-methyl-1-propenyl)benzo-1,4-quinone on treatment with the anion of 2-nitropropane.




(7.107)

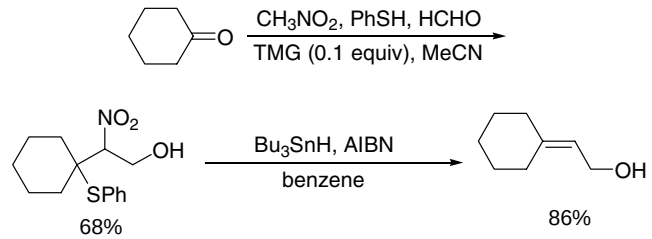



(7.108)




(7.109)

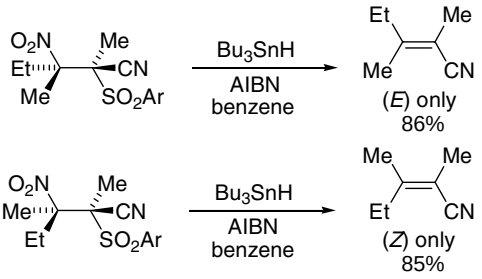
Ono and coworkers have extended the radical elimination of *vic*-dinitro compounds to β-nitro sulfones[151] and β-nitro sulfides.[138,152] As β-nitro sulfides are readily prepared by the Michael addition of thiols to nitroalkenes, radical elimination of β-nitrosulfides provides a useful method for olefin synthesis. For example, cyclohexanone is converted into allyl alcohol by the reaction shown in Eq. 7.110. Treatment of cyclohexanone with a mixture of nitromethane, PhSH, 35%-HCHO, TMG (0.1 equiv) in acetonitrile gives a hydroxymethylated-β-nitro sulfide in 68% yield, which is converted into the corresponding allyl alcohol in 86% yield by the reaction with $Bu_3SnH$.[138] Nitro-aldol and the Michael addition reactions take place sequentially to give the required β-nitro sulfides in one pot.




(7.110)

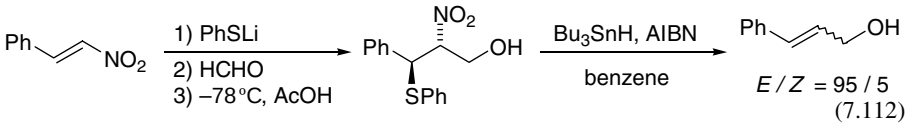
Tin radical-induced elimination from β-nitro sulfones or β-nitro sulfides proceeds in a stereoselective way to give *anti* elimination products.[153] When diastereomers of β-nitro sulfones can be separated, each diastereomer gives (*E*)- and (*Z*)-alkenes selectively (Eq. 7.111). Such

stereo-specific radical elimination is rather unusual because usually radical reactions proceed in a nonspecific way.



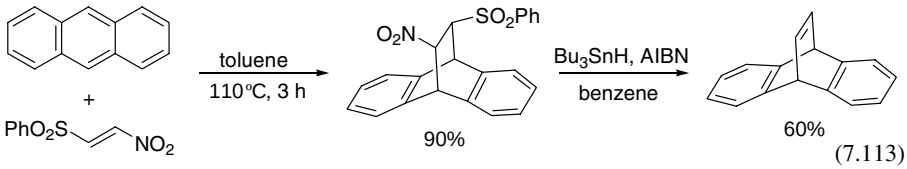

(7.111)

Stereoselective preparation of (*E*)-allyl alcohols via radical elimination from *anti*-γ-phenylthio-β-nitro alcohols has been reported.[154] The requisite *anti*-β-nitro sulfides are prepared by protonation of nitronates at low temperature (see Chapter 4), and subsequent treatment with $Bu_3SnH$ induces anti elimination to give (*E*)-alkenes selectively (see Eq. 7.112). Unfortunately, it is difficult to get the pure *syn*-β-nitro sulfides. Treatment of a mixture of *syn*- and *anti*-β-nitrosulfides with $Bu_3SnH$ results in formation of a mixture of (*E*)- and (*Z*)-alkenes.



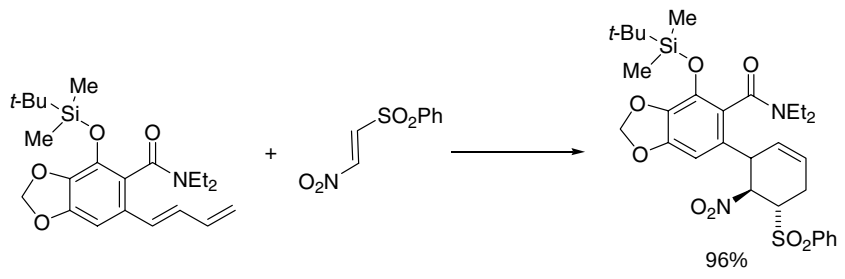

(7.112)

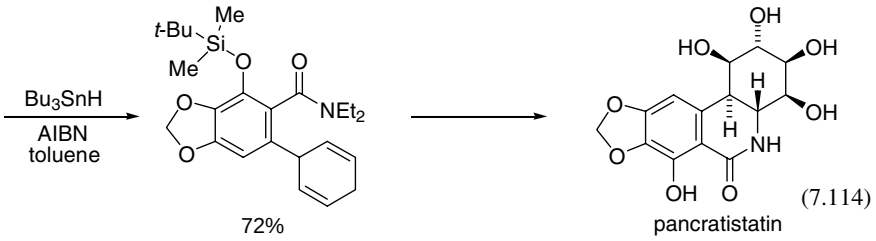
Ono and coworkers have devised a new acetylene equivalent for the Diels-Alder reaction; namely, 1-phenylsulfony-2-nitroethylene is a very reactive dienophile, and the radical elimination from the adduct gives the Diels-Alder adduct of acetylene, as exemplified in Eq. 7.113.[155] Other acetylene equivalents are summarized in a review.[156]




(7.113)

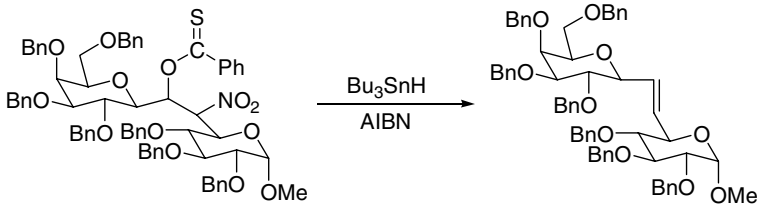
Acetylene equivalent of β-sulfonylnitroalkene in the Diels-Alder reaction is used in part for total synthesis of pancratistatin (Eq. 7.114). Pancratistatin is isolated from the root of the plant *Pancratium littorale* Jacq., native to Hawaii, which exhibits anti-cancer activity.[157]





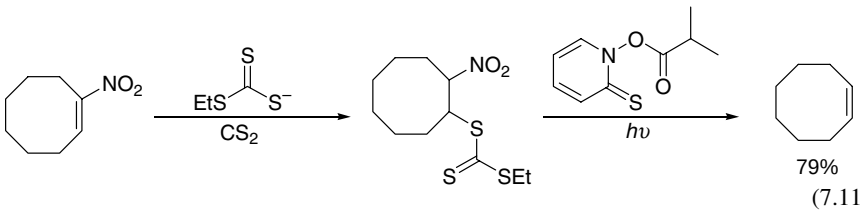

(7.114)

Nitro-aldols, which are readily available (see Henry reaction Section 3.1), are converted into olefins via conversion of the hydroxyl group to the corresponding phenyl thiocarbonate ester and treatment with tin radical.[158] The yield was not reported. Because the radical deoxygenation via thiocarbonate (Barton reaction) proceeds in good yield, the elimination of Eq. 7.115 might be good choice for olefin synthesis.[159]




(7.115)

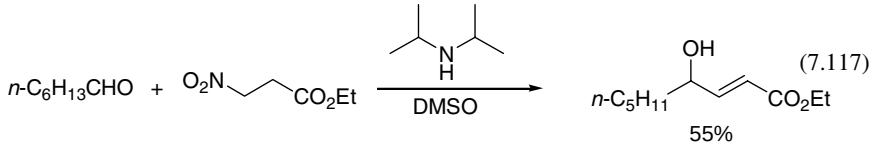
Due to the toxicity of tin reagents, a new radical elimination without using $Bu_3SnH$ is highly desirable. Barton has reported that nitro olefins are converted into olefins via radical elimination of β-nitro trithiocarbonates (Eq. 7.116).[160] The Michael addition of trithiocarbonate to nitroalkenes is carried out in $CS_2$ to avoid the addition of EtSH.



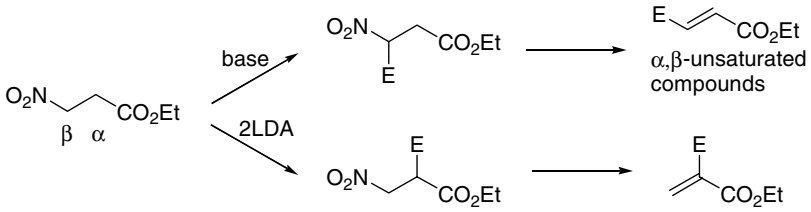

(7.116)

### 7.3.2 Ionic Elimination of Nitro Compounds

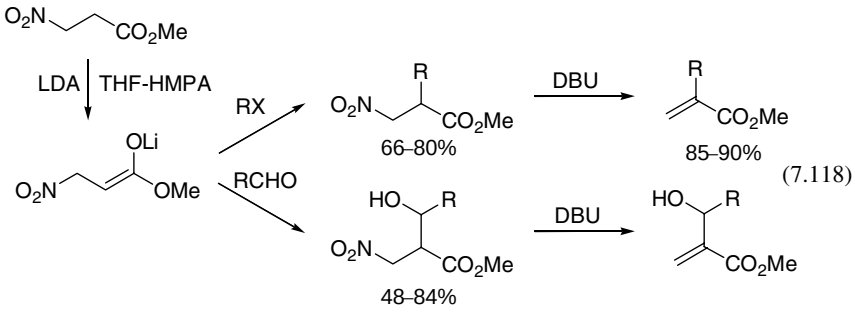
In a previous review dealing with β-elimination reactions of nitrous acid, the literature is covered up to 1985.[161] The basic concept is very simple: the nitro group at the β-position of the electron-withdrawing groups is eliminated to give alkenes on treatment with base. A typical example is shown in Scheme 7.22; electrophiles can be introduced to ethyl β-nitropropionate at both α- and β-positions, and subsequent elimination of $HNO_2$ gives various alkenes. The Henry reaction or Michael reaction of ethyl β-nitropropionate followed by elimination of $HNO_2$ gives β-substituted acrylate.[162] On the other hand, alkylation of the dianion derived from the same compound followed by elimination of $HNO_2$ gives α-substituted acrylate (Eqs. 7.117 and 7.118).[163]




(7.117)

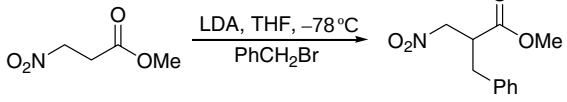



**Scheme 7.22.**




(7.118)

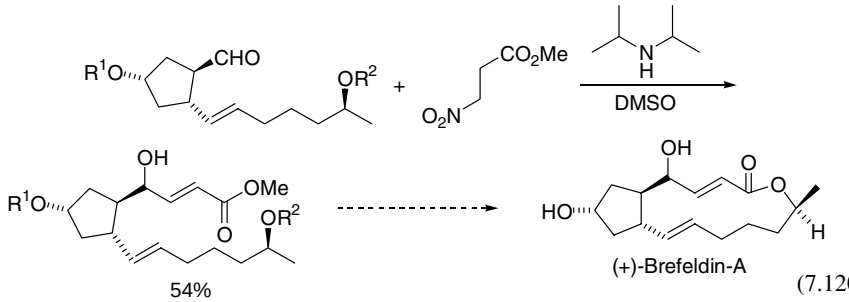
The alkylation of dianion of methyl 3-nitropropionate requires 5 equiv of HMPA. HMPA is a listed mutagen and should not be used in industry or in academia. 1,3-Dimethyl-3,4,5,6-tetrahydropyrimidine (DMPU)[164] and quinuclidine *N*-oxide (QNO)[165] are recommended as replacements of HMPA (Eq. 7.119).




| Additive (equiv) | Yield (%) |
|---|---|
| None | 8 |
| HMPA (5) | 85 |
| DMPU (10) | 85 |
| QNO (5) | 78 |

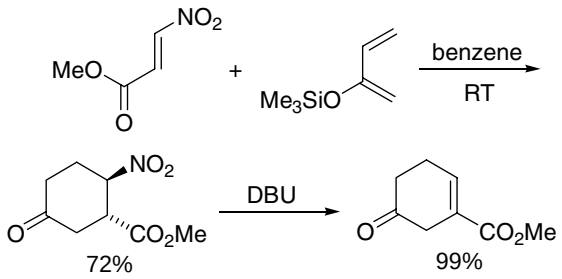
(7.119)

The reaction shown in Eq. 7.120 has been applied to a total synthesis of (+)-brefeldin-A.[166]

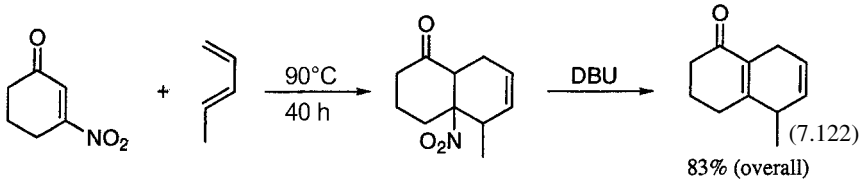



(7.120)

Esters and ketones bearing β-nitro groups can be prepared in many ways. For example, the Diels-Alder reaction of methyl β-nitroacrylate is one typical case. Various cyclic dienes are prepared by this route, and the reactions of Eq. 7.121[167] and Eq. 7.122[168] are exemplified.

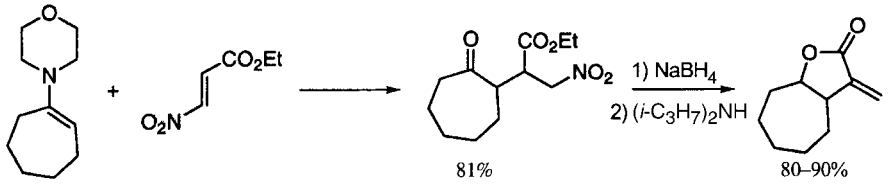



(7.121)



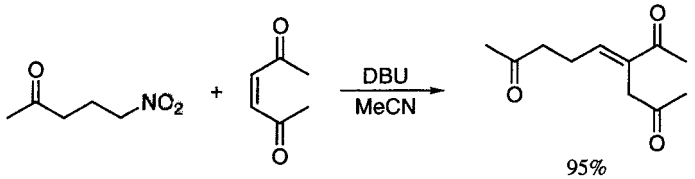

(7.122)

Another approach is the Michael addition to ethyl β-nitroacrylate, as shown in Eq. 7.123, which has been used in the synthesis of α-methylenebutyrolactone, a moiety characteristic of many sesquiterpenes.[169]

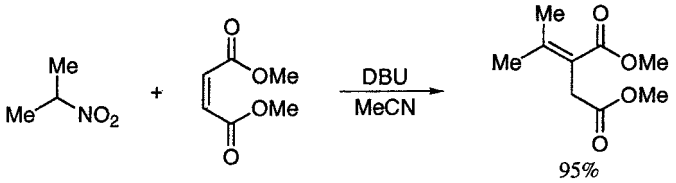



(7.123)

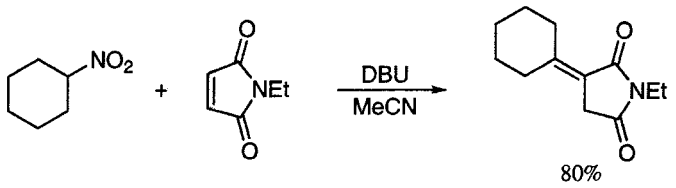
The Michael addition of nitroalkanes to alkenes substituted with two electron-withdrawing groups at the α- and β-positions provides a new method for the preparation of functionalized alkenes. Although reactions are not new,[170] Ballini and coworkers have used this strategy in the synthesis of polyfunctionalized unsaturated carbonyl derivatives by Michael addition of nitroalkanes to enediones as shown in Eqs. 7.124–7.126.[171] Success of this type of reaction depends on the base and solvent. They have found that DBU in acetonitrile is the method of choice for this purpose. This base-solvent system has been used widely in Michael additions of nitroalkanes to electron-deficient alkenes (see Section 4.3, which discusses the Michael addition).[172]




(7.124)

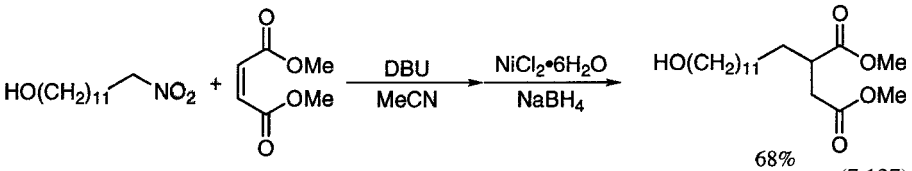



(7.125)



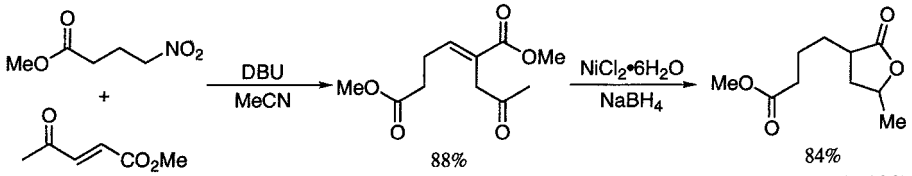

(7.126)

Alkenylation using nitroalkanes followed by the selective reduction of the double bonds with $NiCl_2$ and $NaBH_4$ can be regarded as the addition of alkyl anions to electron-deficient alkenes (Eq. 7.127).[173]



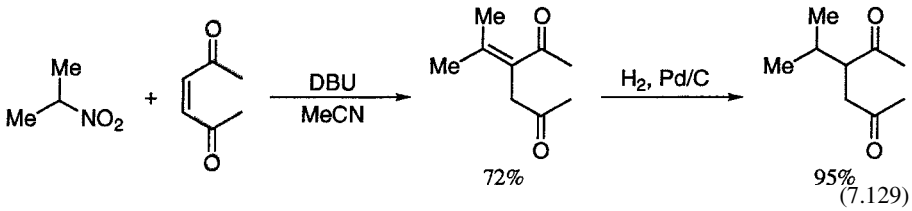

(7.127)

Very simple synthesis of α-substituted γ-methyl-γ-lactones is also possible by olefination using nitroalkanes followed by reduction, as shown in Eq. 7.128.[174]



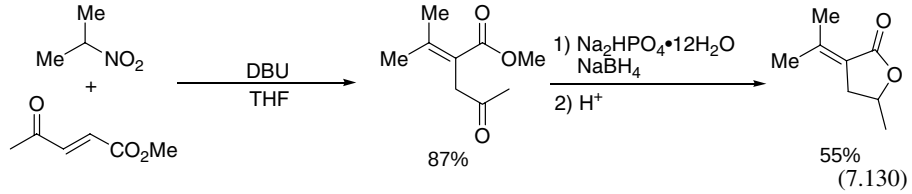

(7.128)

When the reduction of the double bond in the olefination product is carried out using $H_2$ and Pd/C, 1-alkylated-1,4-diketone is obtained in good yield (Eq. 7.129).[175]




(7.129)

The selective reduction of the carbonyl group in the olefination product of keto-esters using $Na_2HPO_4$ and $NaBH_4$ leads to the synthesis of α-alkylmethylene-γ-butyrolactones (see Eq. 7.130).[176]




(7.130)

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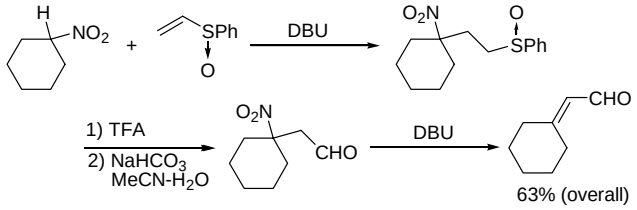


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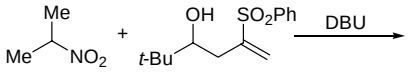


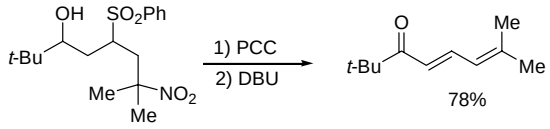


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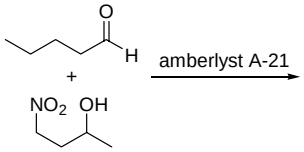
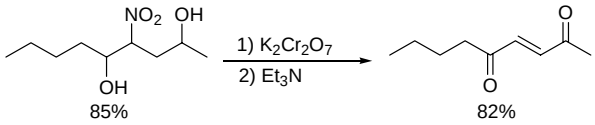



amberlyst A-21

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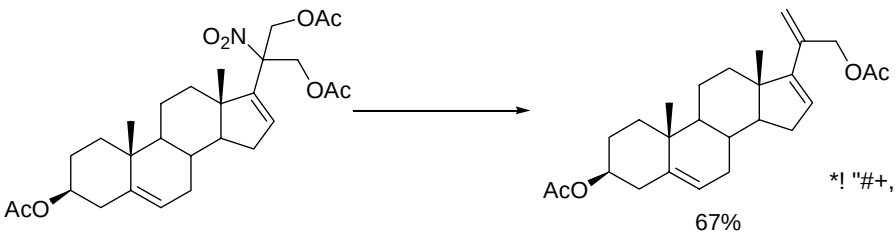


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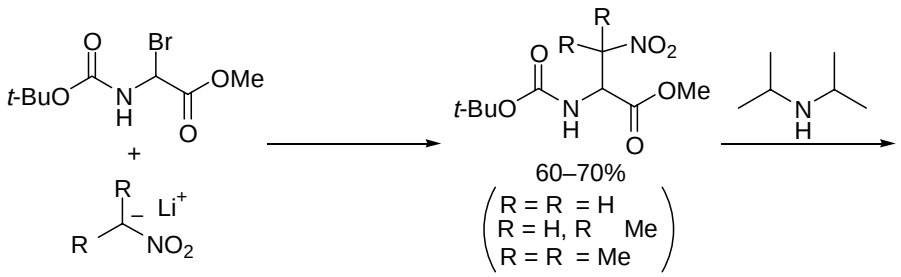


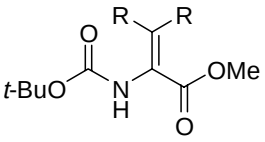


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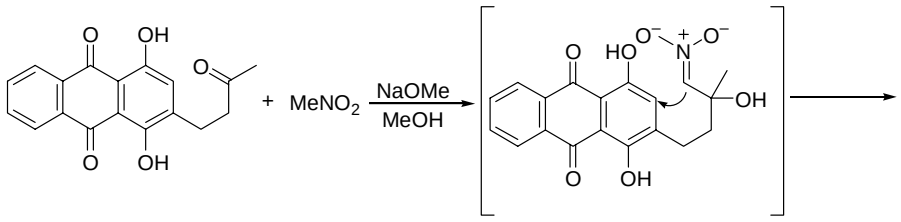


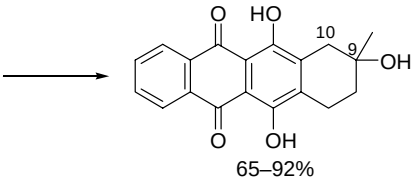


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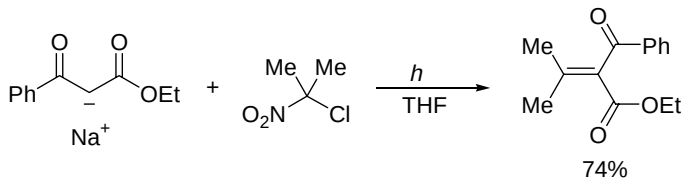


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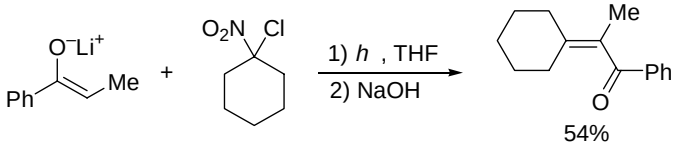


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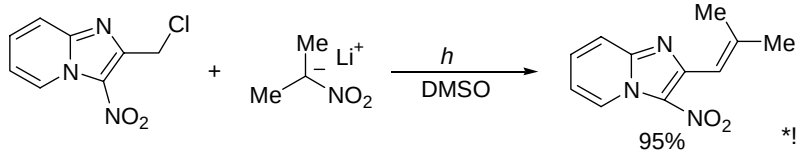


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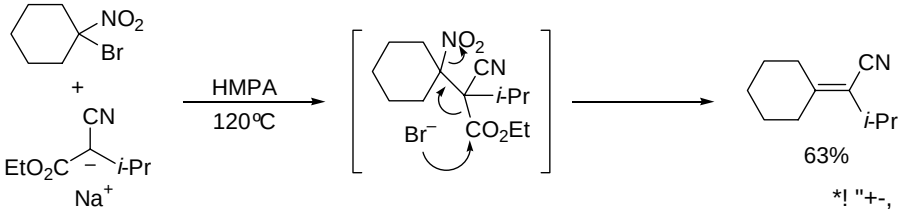


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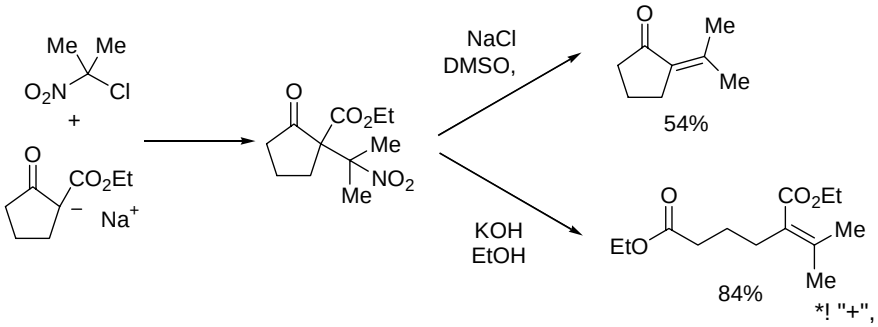


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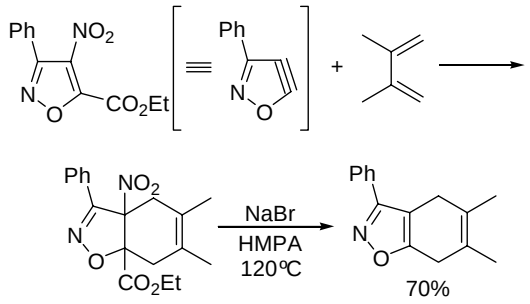


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## REFERENCES


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5 C @ D C C B ) C : *Organic Letters* **1** "!$# *'"%%%,
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6- = ) F *Tetrahedron Lett* " +# *'"%!%,
6" 1 : . = / *Tetrahedron Lett* **22** "!-6 *'"%$",
6 . 0 0 A ; B 0 8 *J. Am. Chem. Soc* **103** "66! *'"%$",
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9- 5 0 ) 7 *J. Am. Chem. Soc* **118** 6#" *'"%%9,
9- 5 0 ) *Angew. Chem. Int. Ed. Engl.* **37** ""!+ *'"%%$,
9" 5 5 *Acc. Chem. Res* **25** "$$ *'"%% ,
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$ 7 ( 7 ; 1 ( 1 *Tetrahedron Lett* **34** 9"-! *'"%%#,
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$+ 7 ( 7 1 *Helv. Chim. Acta* **73** +9- *"%%-,

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$9 ; 8 7 1 *Helv. Chim. Acta* **70** "+9 *"%$!,

$! C 1 7 8 . . *Tetrahedron Asymmetry* **8** 6!% *"%%!,

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"- . @ = . = 8 *J. Org. Chem* **54** 6+6# *"%$%,

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""" 7 = . & . 7 *Tetrahedron Lett* **40** + "6 *"%%%,

"" 7 0 ) = *Helv. Chim. Acta,* **69** 9" *"%$+,

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" 6 B ; *Radicals in Organic Synthesis>Formation of Carbon-Carbon Bonds* ) ) ' "%$9

" 6 B ; *Angew. Chem. Int. Ed. Engl* **22** !6# *"%$#,

" 6 1 ? ; 0 5 *Free Radical Chain Reactions in Organic Synthesis* ) D "%%

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" 9 1 = / *Chem. Lett* 9#6 *'"%$6,

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"+# = 7 0 ; ? ) : B 7 *J. Am. Chem. Soc* **93** +#"9 *'"%!",

"++ = D 5 *J. Org. Chem* **42** %++ *'"%!!,

"+6 1 : . & = / *Chem. Lett* ""#% *'"%$",

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"9" & *Nitro Compounds Recent Advances in Synthesis and Chemistry* 2 . A5 "%%- $93""-

"9 ; 8 ) 1 D 2 ; 8 . 2 ? *Tetrahedron Lett* **19** #!" *'"%!$,

"9# 7 0 : . 1 *Chem. Ber* **115** "!-6 *'"%$ ,

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"9! 0 7 1 ) ) 7 *J. Am. Chem. Soc* **100** %"$ *'"%!$,

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"$" 5 ) 5 C *Tetrahedron Lett* **40** +!+6 *"%%%,
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*The Nitro Group in Organic Synthesis.* Noboru Ono
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ISBNs: 0-471-31611-3 (Hardback); 0-471-22448-0 (Electronic)

# 8

# CYCLOADDITION CHEMISTRY OF NITRO COMPOUNDS

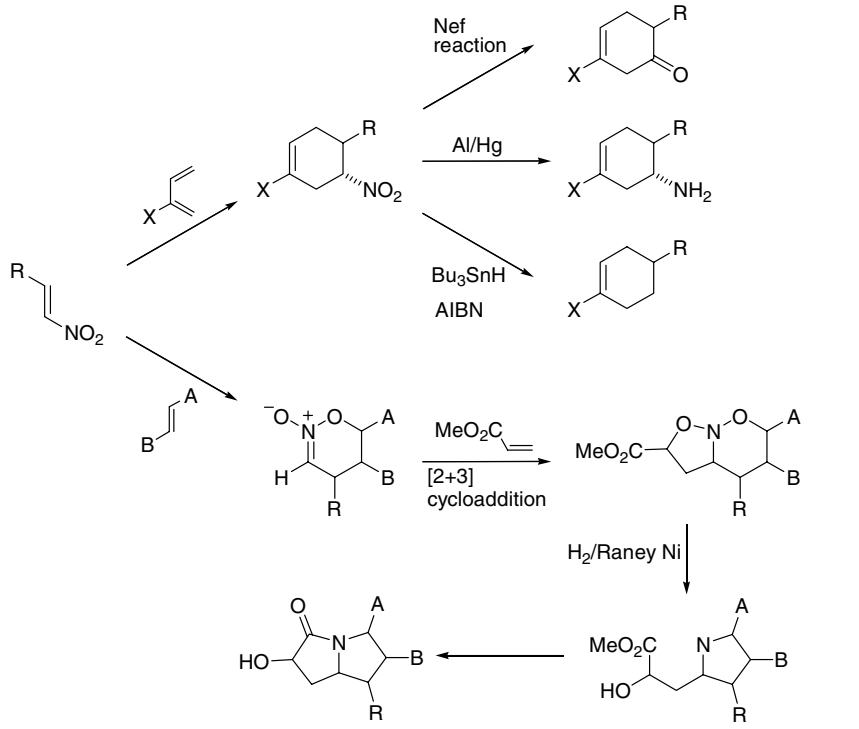
Nitro compounds have been converted into various cyclic compounds via cycloaddition reactions. In particular, nitroalkenes have proved to be useful in Diels-Alder reactions. Under thermal conditions, they behave as electron-deficient alkenes and react with dienes to yield 3-nitrocyclohexenes. Nitroalkenes can also act as heterodienes and react with olefins in the presence of Lewis acids to yield cyclic alkyl nitronates, which undergo [3+2] cycloaddition. Nitro compounds are precursors for nitrile oxides, alkyl nitronates, and trialkylsilyl nitronates, which undergo [3+2]cycloaddition reactions. Thus, nitro compounds play important roles in the chemistry of cycloaddition reactions. In this chapter, recent developments of cycloaddition chemistry of nitro compounds and their derivatives are summarized.

## 8.1 DIELS-ALDER REACTIONS

Diels-Alder reactions are one of the most fundamental and useful reactions in synthetic organic chemistry. Various dienes and dienophiles have been employed for this useful reaction.[1] Nitroalkenes take part in a host of Diels-Alder reactions in various ways, as outlined in Scheme 8.1. Various substituted nitroalkenes and dienes have been employed for this reaction without any substantial improvement in the original discovery of Alder and coworkers.[2] Nitrodienes can also serve as $4\pi$-components for reverse electron demand in Diels-Alder reactions. Because the nitro group is converted into various functional groups, as discussed in Chapters 6 and 7, the Diels-Alder reaction of nitroalkenes has been frequently used in synthesis of complex natural products. Recently, Denmark and coworkers have developed [4+2] cycloaddition using nitroalkenes as heterodienes; it provides an excellent method for the preparation of heterocyclic compounds, including pyrrolizidine alkaloids. This is discussed in Section 8.3.

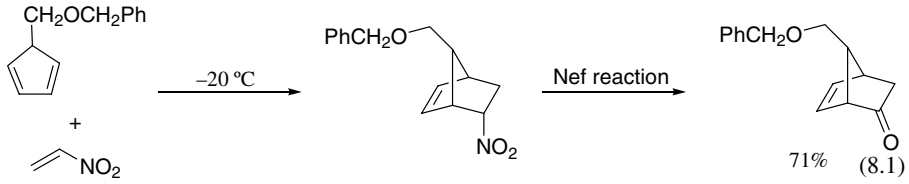
### 8.1.1 Nitroalkenes Using Dienophiles

Nitroethene undergoes rapid cycloaddition to 1,3-dienes; the subsequent Nef reaction gives cyclohexenones, which are formally produced by the Diels-Alder reaction of ketene with




**Scheme 8.1.**

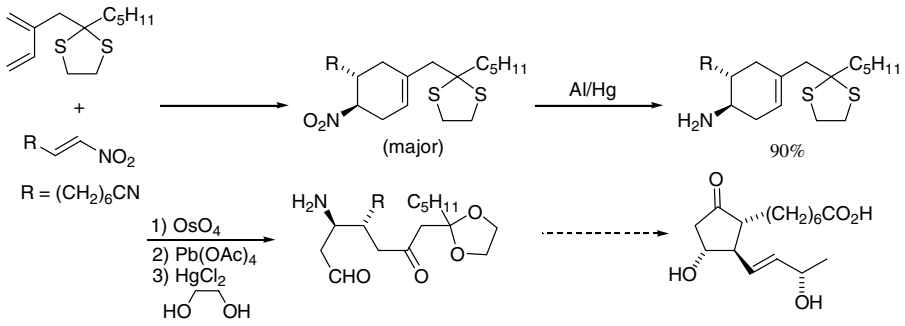
1,3-dienes (Eq. 8.1).[3] This strategy has been used for the synthesis of prostaglandins by Corey and coworkers.[4] Another synthesis of prostaglandin based on the Diels-Alder reaction of nitroalkenes is presented in Scheme 8.2, in which the nitro group is reduced to an amino group.[5] A total synthesis of antheridium-inducing factor of the fern *Anemia phyllitidis* uses the Diels-Alder reaction of nitroethylene followed by the Nef reaction.[6]



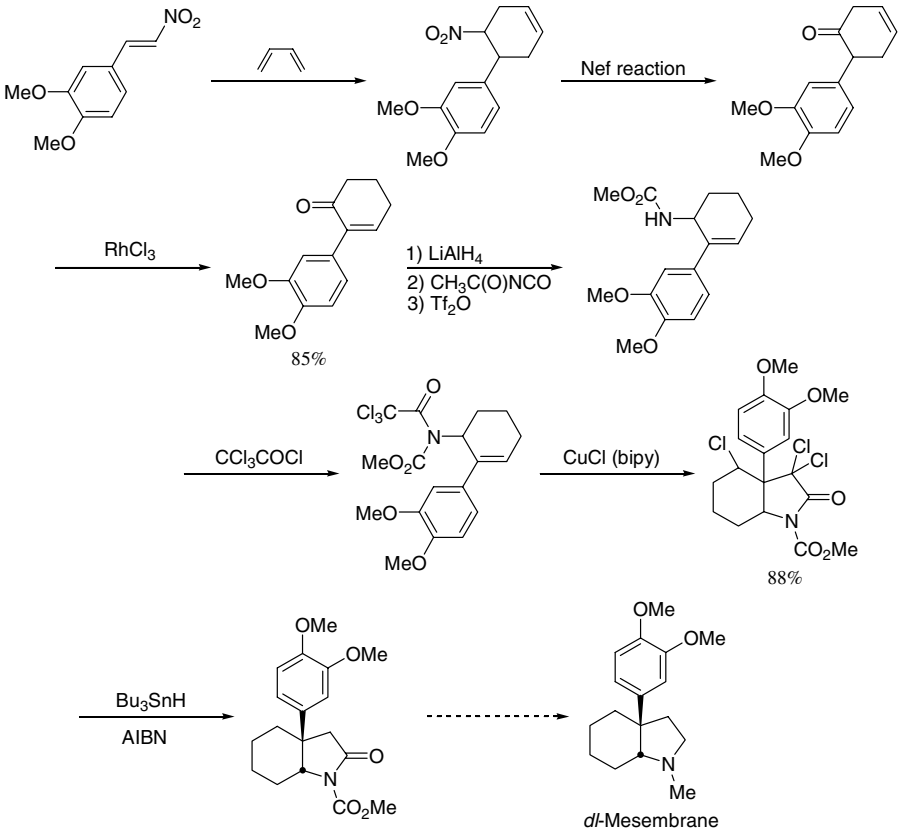

(8.1)

The Diels-Alder reaction of nitroalkenes followed by the Nef reaction is frequently used in natural product synthesis.[7] For example, Scheme 8.3 shows an elegant synthesis of *dl*-mesembrane starting from the Diels-Alder reaction of 1-arylnitroethene with 1,3-butadiene.[7a]

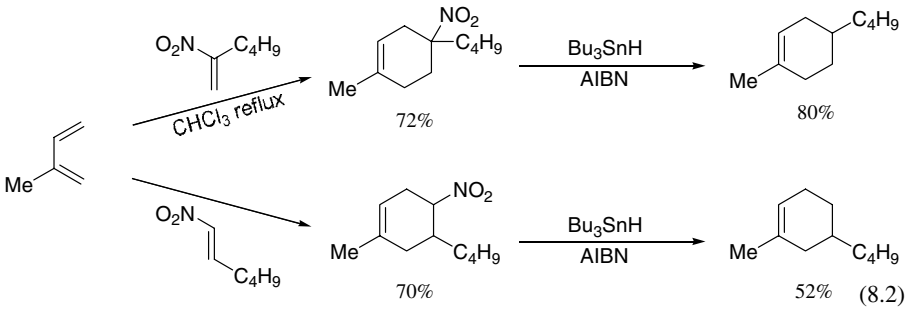
Ono and coworkers have developed a new strategy using nitroalkenes as alkene equivalents in Diels-Alder reactions. When unsymmetrical dienes are used, the nitro group controls the regiochemistry of the Diels-Alder reaction, as shown in Eq. 8.2. The nitro group in cycloadducts is removed by radical denitration (see Chapter 7); therefore, nitroalkenes can be regarded as reactive dienophilic alkene equivalents.[8] Vinyl sulfones have similar utility in organic synthesis.[9] In general, nitroalkenes are more reactive and selective than the corresponding sulfones, but the latter are more readily available than nitroalkenes.




**Scheme 8.2.**

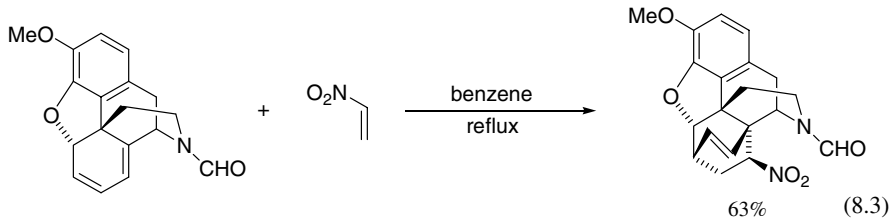



**Scheme 8.3.**



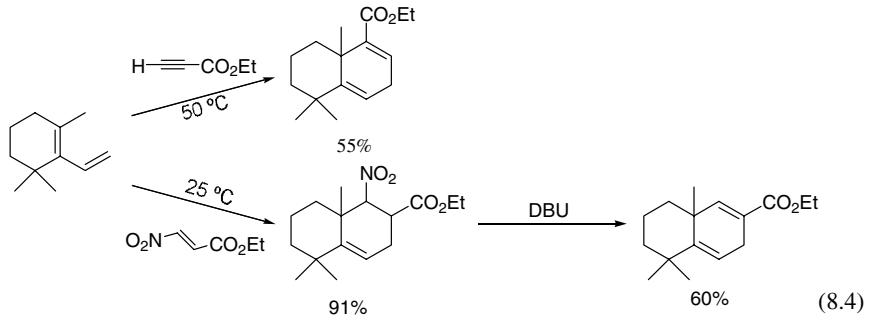
(8.2)

The Diels-Alder reaction of morphinan-6,8-dienes with nitroethene affords a novel type of opium alkaloids (Eq. 8.3).[10a] High reactivity of nitroethylene is demonstrated for the Diels-Alder reaction with thermally unstable dienes, and this is used for synthesis of polycyclic kopsane-like alkaloids.[10b]



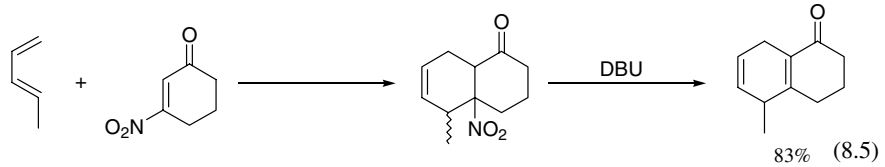
(8.3)

Functionalized nitroalkenes are important dienophiles in the Diels-Alder reaction. For example, (*E*)-methyl β-nitroacrylate is an important reagent in organic synthesis. The nitro group can be readily eliminated; the Diels-Alder reaction of β-nitroacrylate is equivalent to that of ethyl propiolate with an inverse regiochemistry (Eq. 8.4).[11]



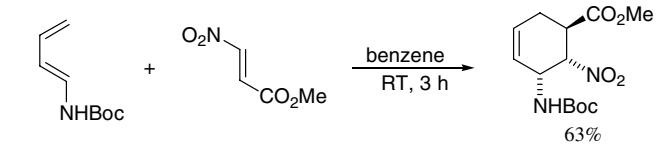
(8.4)

Another example is presented in Eq. 8.5, in which the nitro group is more effective in controlling the direction of addition than the carbonyl group.[12]

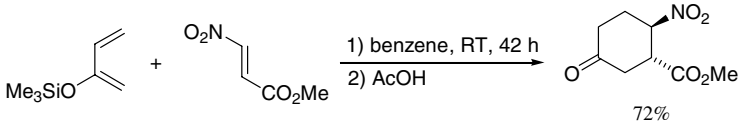


(8.5)

Various dienes substituted with heteroatoms such as 1-oxabuta-1,3-dienes have been used in organic synthesis, as shown in Eq. 8.6[13] and Eq. 8.7.[14]

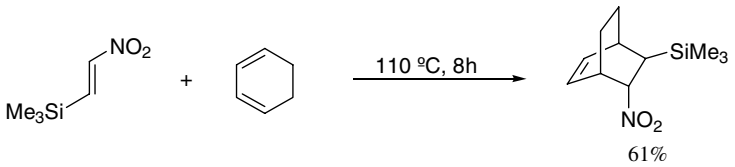



(8.6)



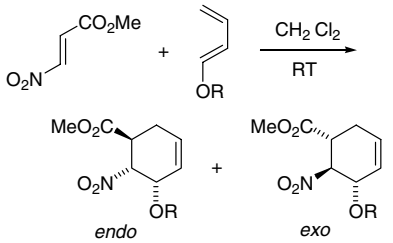

(8.7)

Nitroethene substituted with the $Me_3Si$ group is used in a Diels-Alder reaction (Eq. 8.8).[15a] An example of the reaction with 1-nitro-2-(trialkylsilyl)acetylenes has also been published.[15b]




(8.8)

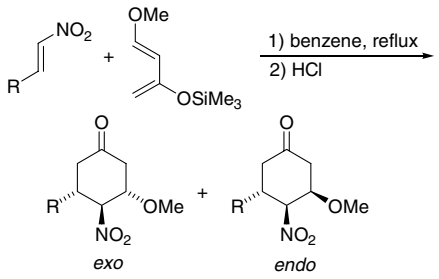
Recently, enhanced *endo* selectivity has been reported in the Diels-Alder reaction of *(E)*-1-acetoxybuta-1,3-dienes with methyl β-nitroacrylate. The selectivity is compared with that of the reaction using 1-methoxybuta-1,3-dienes and 1-trimethylsilyloxybuta-1,3-dienes.[16] The degree of electron richness of a diene is an important consideration in *endo*:*exo* selectivity issues. In particular, electron-rich dienes favor the formation of *exo*-nitrocycloadducts (Eq. 8.9).




| R | *endo* | *exo* | Yield (%) |
|---|---|---|---|
| Me | 67 | 33 | 67 |
| $SiMe_3$ | 68 | 32 | — |
| COMe | 95 | 5 | 71 |

(8.9)

Node and co-workers have found that the Diels-Alder reaction of nitroalkenes with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's dienes) exhibit abnormal *exo*-selectivity. Electrostatic repulsion between the nitro and the silyloxy group of the diene induces this abnormal *exo*-selectivity (Eq. 8.10).[17] This selective reaction has been used for the asymmetric synthesis of various natural products as shown in Scheme 8.6.

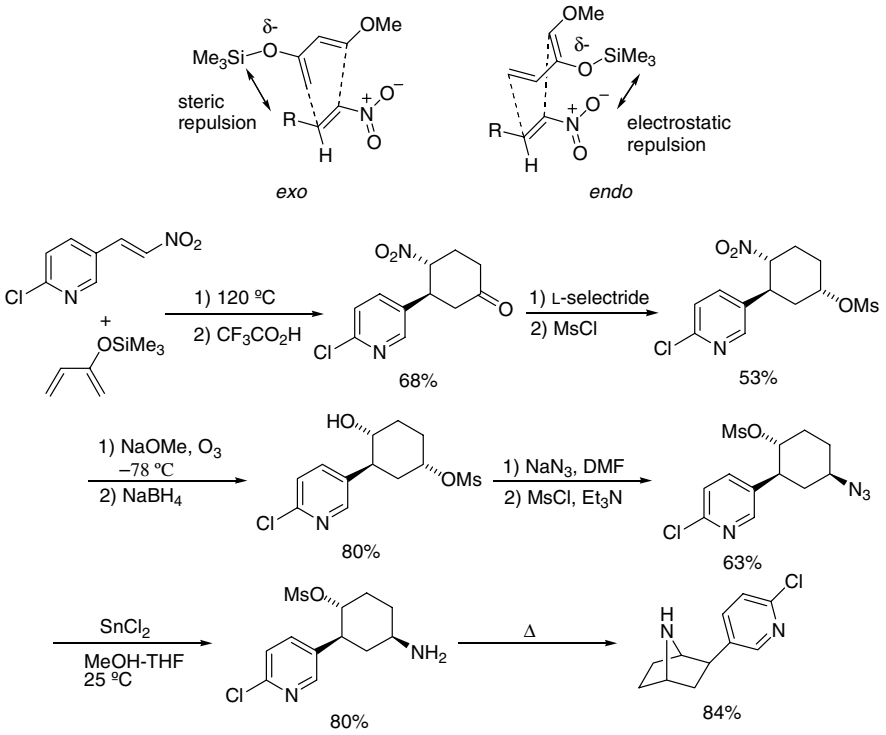



| R | *exo* | *endo* | Yield (%) |
|---|---|---|---|
| Ph | 87 | 13 | 60 |
| *n*-$C_5H_{11}$ | 66 | 34 | 71 |

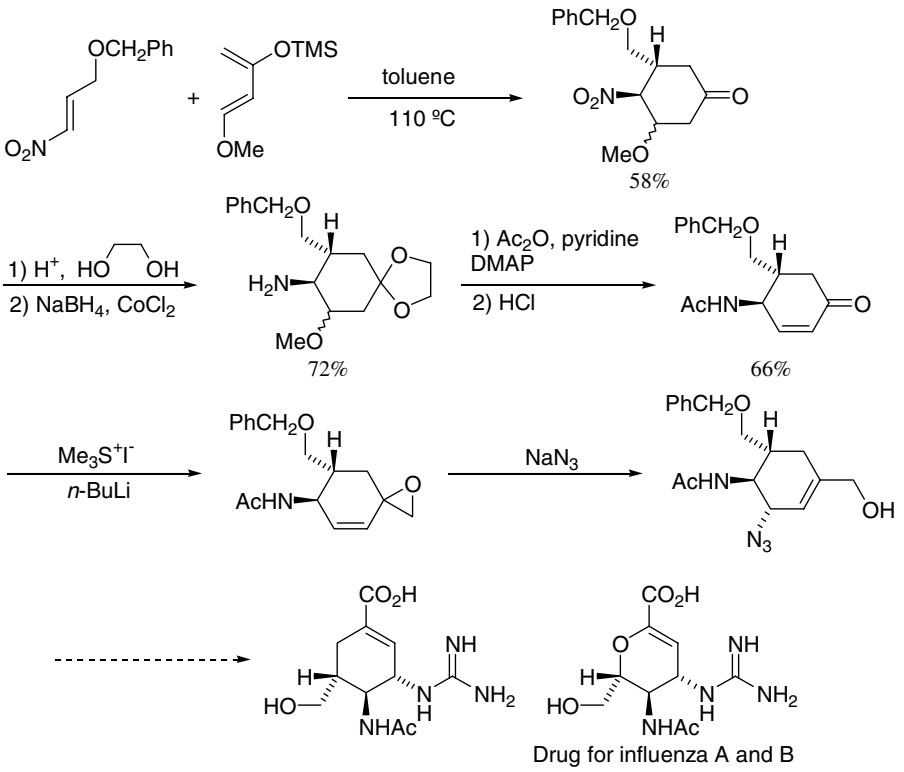
(8.10)

Total synthesis of epibatidine, a potent analgesic compound isolated from the Ecuadorian poison frog *Epopedibates tricolor* has been accomplished as shown in Scheme 8.4. Here the Diels-Alder reaction of 5-(2-nitrovinyl)-2-chloropyridine with 2-trimethylsilyloxy-1,3-butadiene is used as a key step.[18] This alkaloid is prepared by using polymer-supported reagents and sequencing agents in a successive manner. The key steps are similar to those in Scheme 8.4, but no chromatographic purification steps are required to afford the product in >90% purity.[19]

The Diels-Alder reaction of nitroalkenes with Danishefsky's dienes is applied to synthesis of truncated carbocyclic analogues of a potent neuraminidase inhibitor 4-guanidino-$Neu_4Ac_2en$ (see Scheme 8.5).[20] Carbocyclic analogs are found to retain interesting levels of antiviral activity comparable to those shown by their oxygen-containing compounds in Scheme 8.5.

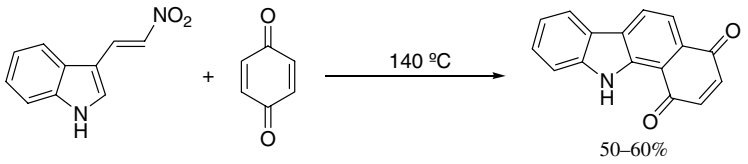



**Scheme 8.4.**

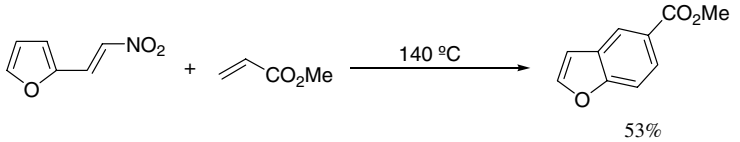



**Scheme 8.5.**

1-Nitrodiene systems such as 3-(2-nitrovinyl)indoles[21] and 2-(2-nitrovinyl)furans[22] are reactive enough as dienes for the Diels-Alder reaction, as shown in Eqs. 8.11 and 8.12. Elimination of $HNO_2$ and dehydrogenation take place spontaneously to give aromatized products, respectively.

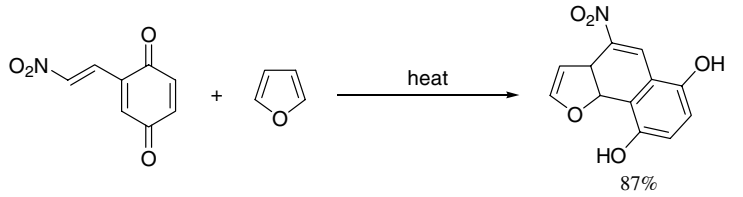



(8.11)



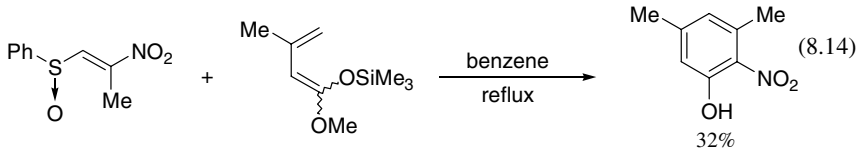

(8.12)

Reactions of 2-(2-nitrovinyl)-1,4-benzoquinone with furans, indoles, and endocyclic enol ethers form angular, fused heterocyclic quinoid ring systems (see Eq. 8.13).[23]

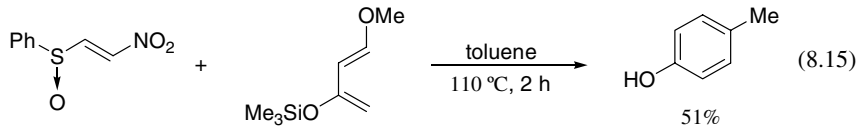



(8.13)

Aromatization is often observed during the Diels-Alder reaction using nitroalkenes. Jung[24] and Ono[25] have reported that 2-phenylsulfinyl-1-nitroalkenes act as nitroacetylene equivalents in Diels-Alder reactions to give aromatic compounds, as shown in Eqs. 8.14 and 8.15, respectively.

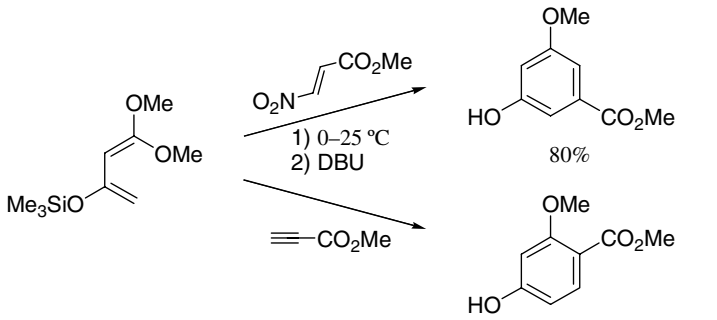



(8.14)




(8.15)

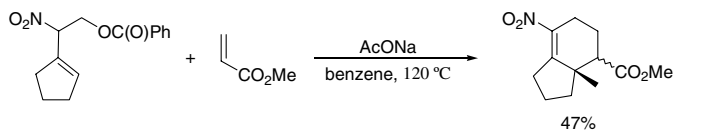
Another example of the preparing of aromatic compounds via the Diels-Alder reaction of nitroalkenes is presented in Eq. 8.16.[26] Cycloaddition of methyl propiolate affords a high yield of the isomeric product.



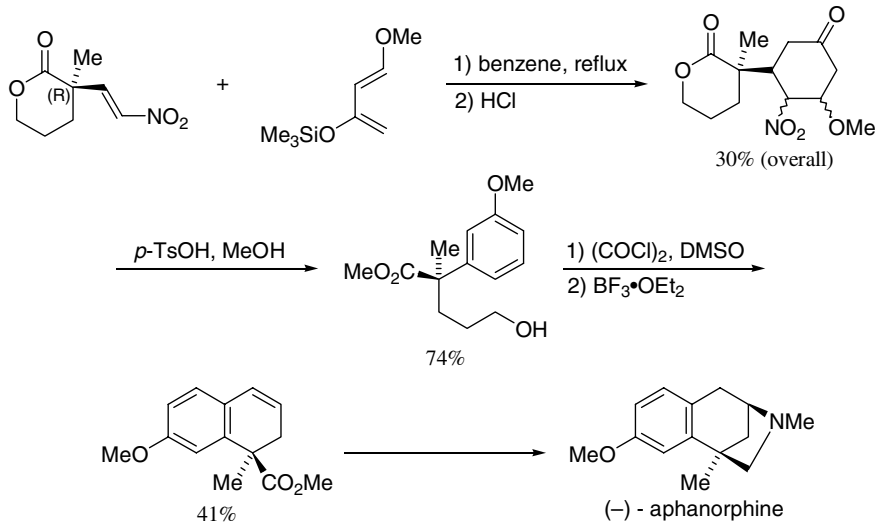

(8.16)

Node and coworkers have used this aromatization strategy for the synthesis of (–) aphanorphine.[27] The Diels-Alder reaction of chiral nitroalkene, prepared by the asymmetric nitroolefination reaction of α-methyl-δ-valerolactone, with the Danishefsky's diene followed by aromatization is used as a key step for this total synthesis, as shown in Scheme 8.6.

Nitrodienes are conveniently prepared by elimination of benzoic acid from β-nitro-β-1-cyclopentenyl-α-benzoyloxyethane. They undergo the Diels-Alder reaction with methyl acrylate (Eq. 8.17).[28]

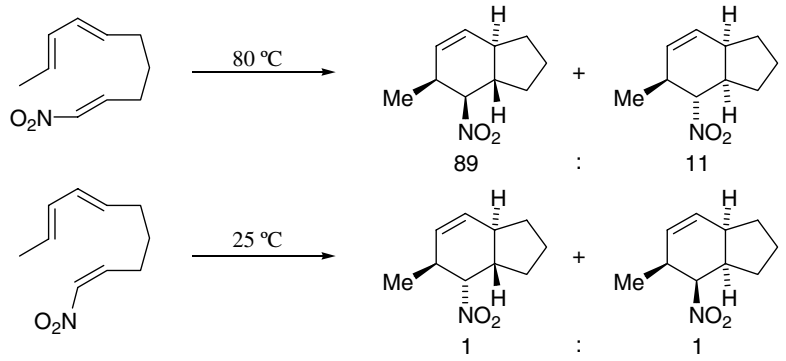



(8.17)



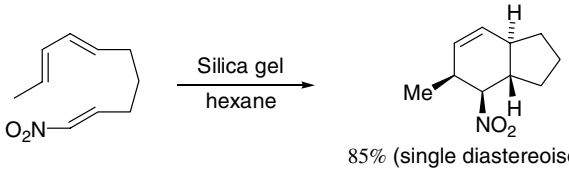

**Scheme 8.6.**

In intramolecular Diels-Alder reactions, two rings are formed in one step. The reaction has been used to synthesize a number of interesting ring systems.[29] The intramolecular cyclization of (*E*)-1-nitrodeca-1,6,8-triene at 80 °C affords an *endo* cycloadduct with the *trans* ring fusion preferentially, as shown in Eq. 8.18. In contrast, (*Z*)-nitroalkenes produce a nearly 1:1 mixture of *cis*- and *trans*-fused cycloadducts.[30]



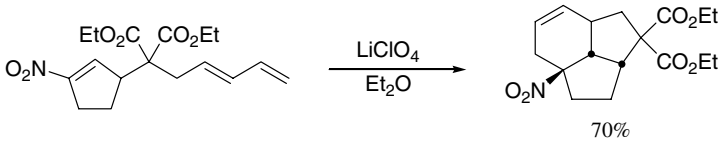

(8.18)

Although Lewis acid-catalyzed-Diels-Alder reactions of enones are common, there are few reports on the catalysis of Diels-Alder reaction of nitroalkenes. The reaction of nitroalkenes with alkenes in the presence of Lewis acids undergoes a different course of reaction to give cyclic nitronates (see Section 8.3). Knochel reported an enhanced reactivity and selectivity of the intramolecular Diels-Alder reaction using silica gel as Lewis acid in hexane (Eq. 8.19).[31]



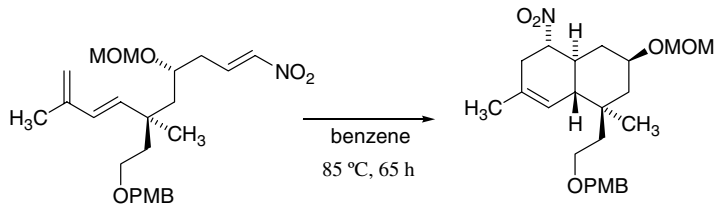

(8.19)

A concentrated solution of $LiClO_4$ in diethyl ether has also been shown to activate the intramolecular Diels-Alder reactions (Eq. 8.20).[32] The reaction proceeds at room temperature to give the adduct in good yield, whereas noncatalyzed reaction proceeds very slowly even at 80 °C (yield was 22% for 65 h).




(8.20)

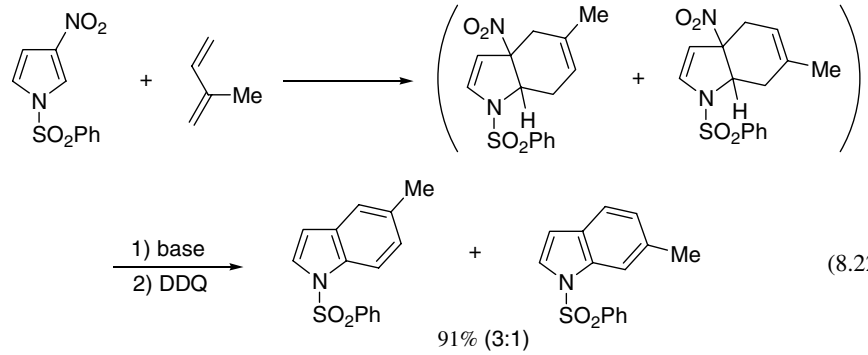
Intramolecular Diels-Alder cyclizations of (*E*)-1-nitro-1,7,9-decatrienes under thermal conditions and Lewis acid conditions lead to the formation of decalin ring systems with excellent *endo* selectivity (Eq. 8.21). This strategy is used for preparing of the AB ring system of norzoanthamine.[33]




(8.21)

Oppolzer and Robbiani have reported highly stereoselective total syntheses of alkaloids such as chelidonine by an intramolecular *o*-quinodimethene/nitrostyrene-cycloaddition (Scheme 8.7).[34] (Benzocyclobutane is used as a source of quinodimethene). The high regio- and stereoselectivity in the intramolecular cycloaddition is remarkable; a strong preference for transition state, *exo*-$NO_2$, over transition state, *endo*-$NO_2$, is responsible for the stereoselectivity.

It has been known that aromatic heterocycles such as furan, thiophene, and pyrrole undergo Diels-Alder reactions despite their aromaticity and hence expected inertness. Furans have been especially used efficiently as dienes due to their electron-rich properties. Thiophenes and pyrroles are less reactive as dienes than furans. But pyrroles with *N*-electron-withdrawing substituents are efficient dienes. There exists a limited number of examples of five-membered, aromatic heterocycles acting as dienophiles in Diels-Alder reactions. Some nitro heteroaromatics serve as dienophiles in the Diels-Alder reactions. Heating a mixture of 1-(phenylsulfonyl)-3-nitropyrrole and isoprene at 175 °C followed by oxidation results in the formation of indoles (see Eq. 8.22).[35a] *N*-Tosyl-3-nitroindole undergoes high-yielding Diels-Alder reactions with

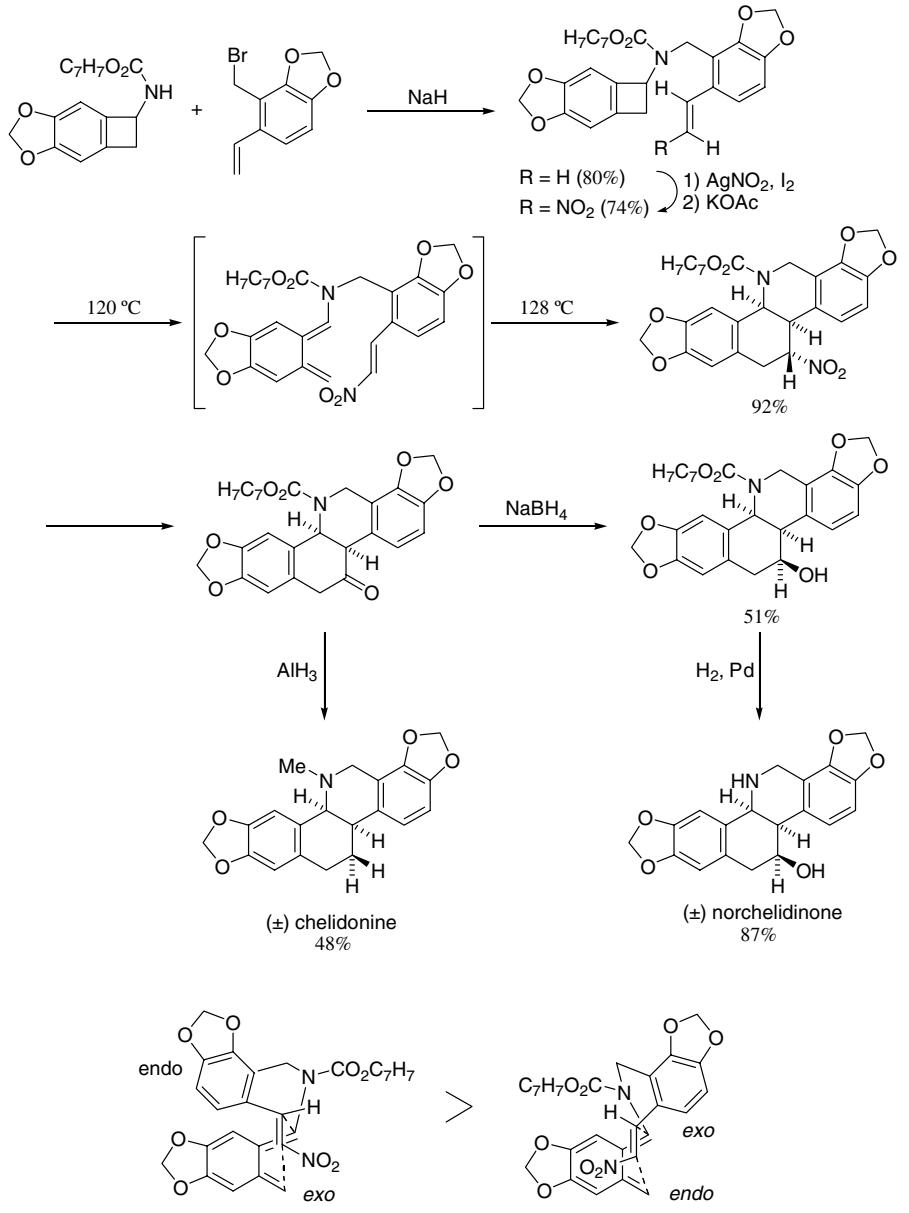



(8.22)

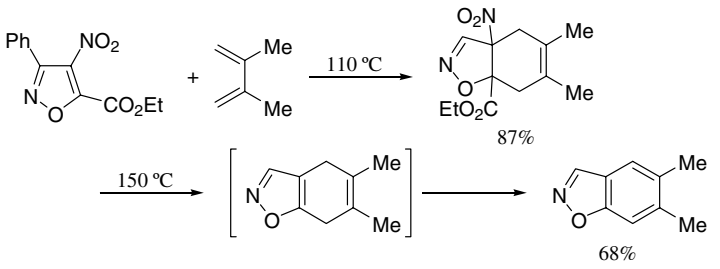
1-(*N*-acyl-*N*-alkylamino)-1,3-butadienes in a regioselective manner to afford intermediates of alkaloids.[35b]

Isoxazole ring systems play an important role in organic synthesis, and 4-nitroisoxazoles have been used as dienophiles in Diels-Alder reactions, as shown in Eq. 8.23.[36]

4-Nitro-2-phenyloxazole, obtained by thermal isomerization of the corresponding nitroisoxazole, is found to undergo Diels-Alder reactions with 2,3-dimethylbuta-1,3-diene (see Eq.

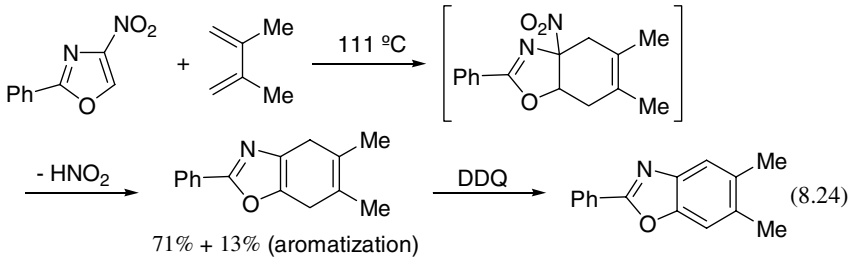



**Scheme 8.7.**



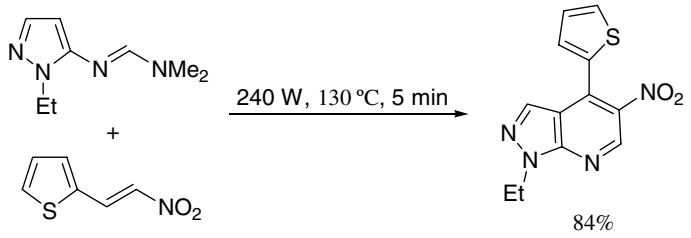

(8.23)

8.24).[37] Thus, nitroheterocycles are important synthons of five-membered heteroarynes in cycloaddition reactions, which are generally difficult to be generated.[38]



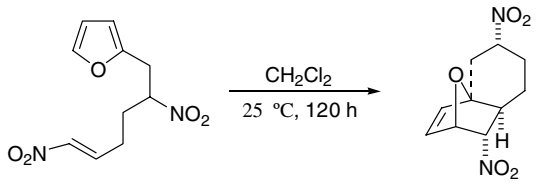

(8.24)

Microwave irradiation at solvent-free conditions induces pyrazoyl 2-azadienes to undergo Diels-Alder reactions with nitroalkenes, within 5–10 min good yields of pyrazolo[3,4-b]pyridines are obtained (see Eq. 8.25).[39] Without irradiation the reaction produces only traces of products on classical heating.




(8.25)

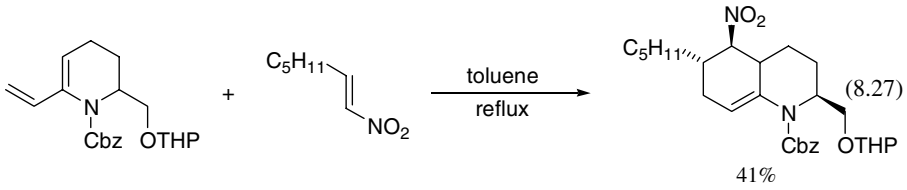
3,7-Dinitro-11-oxatricyclo[6.2.1.0$^{1,6}$]undec-9-ene has been prepared by an intramolecular Diels-Alder reaction of the furan with a nitroalkene group as shown in Eq. 8.26. This tricyclic compound is a versatile synthetic tool for the preparation of ergot alkaloids.[41]




(8.26)

Amino-substituted dienes are also important dienophiles in Diels-Alder reactions. Recently, chiral and achiral 2-amino-1,3-dienes have been prepared to study their reactivity (see also asymmetric Diels-Alder reaction Section 8.1.2). The reaction of 2,3-diamino-1,3-butadienes with nitrostyrene gives unusual [3+2]carbocyclization products, 2-aminocyclopentanones, which are not formed by the direct cycloaddition but derived from the Michael addition products (see section discussing the Michael addition Section 4.1.3).[42]

A typical regioselectivity and *endo/exo* selectivity has been reported in the Diels-Alder reaction of 2-(*N*-acylamino)-1,3-diene with nitroalkenes (Eq. 8.27).[43] Thus, *exo* products are predominantly formed, which is general for the Diels-Alder reaction of nitroalkenes with sterically hindered dienes.

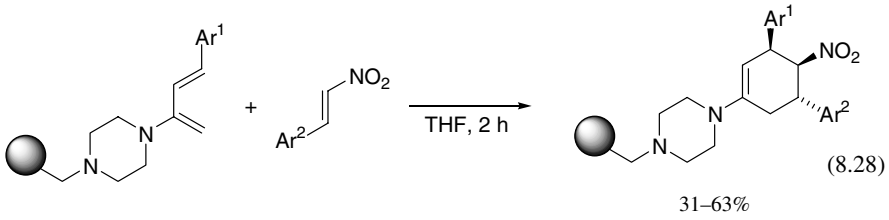



(8.27)

41%

The total synthesis of frodosin B, which is a potentially useful drug for HIV, has been reported (Scheme 8.8). The key steps in the synthesis are a Friedel-Crafts reaction to form the seven-membered ring and a Diels-Alder reaction of nitroethylene to build the six-membered ring, thereby fixing the double bond in the proper position.[44]

Resin-bound 2-aminobutadiene reacts with 1-nitro-2-arylethenes to give, after cleavage of the resin, nitrocyclohexanones in good yields with high purity (Eq. 8.28).[45]



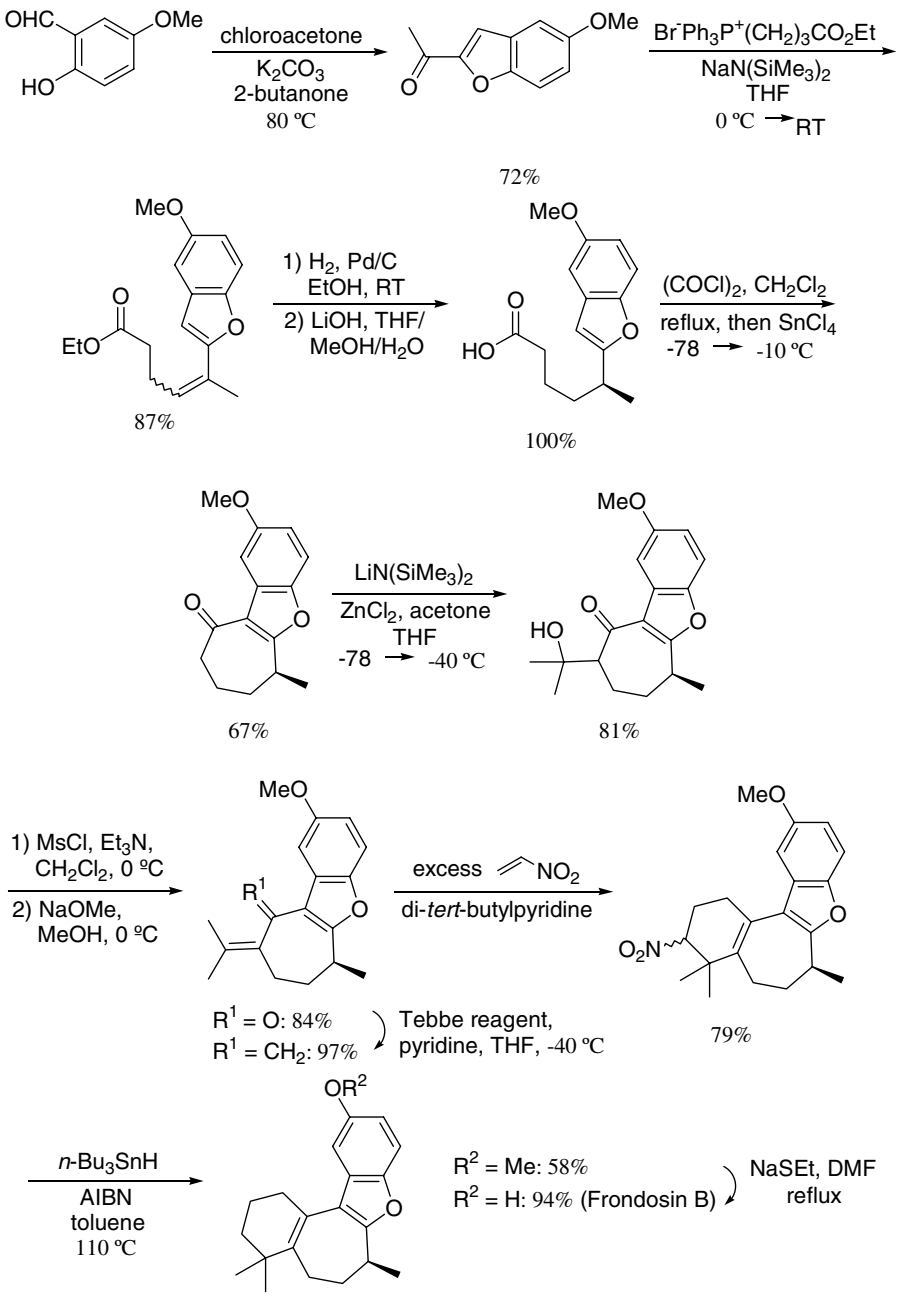

(8.28)

31–63%

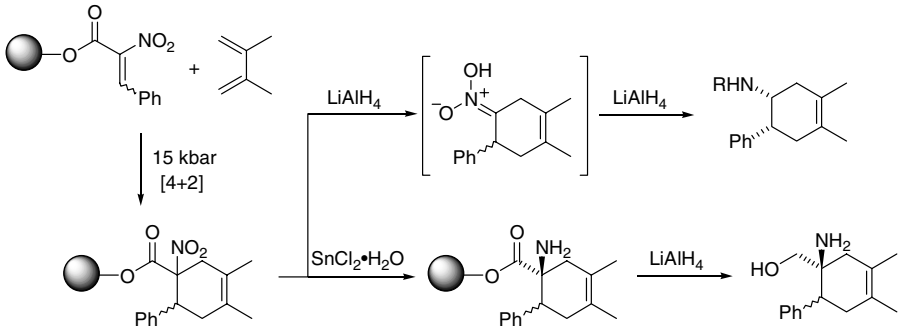
The preparation of resin-bound nitroalkenes via a microwave-assisted Knoevenagel reaction of resin-bound nitroacetic acid with aryl and alkyl substituted aldehydes is reported. The potential of these resin-bound nitroalkenes for application in combinatorial chemistry is demonstrated by a Diels-Alder reaction with 2,3-dimethylbutadiene (Scheme 8.9). It is also used for one-pot three-component tandem [4+2]/[3+2] reactions with ethyl vinyl ether and styrene.[46]

### 8.1.2 Asymmetric Diels-Alder Reaction

Asymmetric Diels-Alder reactions have been performed by using either chiral dienophiles or chiral dienes in the presence or the absence of catalysts.[47] The progress in this field is remarkable; catalytic asymmetric Diels-Alder reactions are generally carried out either by the use of chiral dienophiles or by the use of chiral dienes. Here, the reactions of chiral nitroalkenes with dienes or the reactions of nitroalkenes with chiral dienes are discussed. Many different chiral auxiliaries are now available, and some of them have been used in asymmetric Diels-Alder reactions of nitroalkenes.

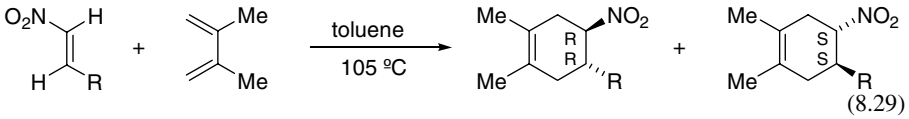

OHC
OMe
HO
chloroacetone
K2CO3
2-butanone
80 ºC
OMe
O
O
Br-Ph3P+(CH2)3CO2Et
NaN(SiMe3)2
THF
0 ºC → RT
72%
MeO
EtO
O
O
87%
1) H2, Pd/C
EtOH, RT
2) LiOH, THF/
MeOH/H2O
MeO
HO
O
O
100%
(COCl)2, CH2Cl2
reflux, then SnCl4
-78 → -10 ºC
MeO
O
O
67%
LiN(SiMe3)2
ZnCl2, acetone
THF
-78 → -40 ºC
MeO
HO
O
O
81%
1) MsCl, Et3N,
CH2Cl2, 0 ºC
2) NaOMe,
MeOH, 0 ºC
MeO
R1
O
excess
NO2
di-tert-butylpyridine
MeO
O2N
O
79%
R1 = O: 84%
R1 = CH2: 97%
Tebbe reagent,
pyridine, THF, -40 ºC
n-Bu3SnH
AIBN
toluene
110 ºC
OR2
O
R2 = Me: 58%
R2 = H: 94% (Frondosin B)
NaSEt, DMF
reflux

**Scheme 8.8.**




**Scheme 8.9.**

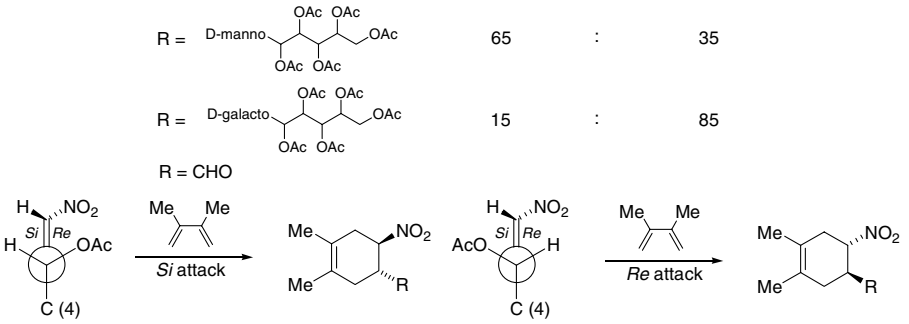
***8.1.2.1 Nitroalkenes with Chiral Auxiliaries*** The use of carbohydrates as chiral auxiliary in Diels-Alder reactions for the stereoselective preparation of carbocyclic and heterocyclic chiral rings is well documented.[48] For example, D-manno-nitroalkene reacts with 2,3-dimethyl-1,3-butadiene to give a 65:35 mixture of adducts, as shown in Eq. 8.29. The configurations at C-4 and C-5 have been determined to be (4*R*,5*R*) and (4*S*,5*S*), respectively. Hydrolysis of the product followed by degradative oxidation of the sugar side chains leads to enantiomerically pure *trans*-nitrocyclohexene aldehyde.[49]



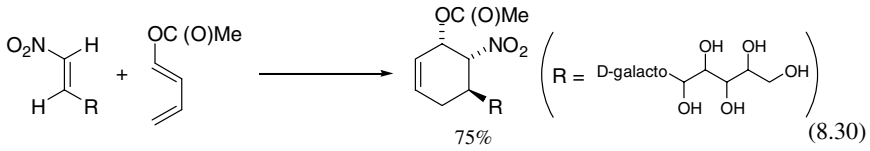

(8.29)

When D-galacto-1-nitroalkene is used, a 85:15 mixture of (4*S*,5*S*) and (4*R*,5*R*) is formed. Preferred attacks of dienes at the most stable conformers of these nitroalkenes are shown in Scheme 8.10.[50]

Uncatalyzed Diels-Alder reactions between 1-(trimethysiloxy)- or 1-acetoxy-1,3-butadiene and sugar-derived nitroalkenes having D-galacto or D-manno configurations proceed with complete regioselectivity. Diastereofacial selectivity is also complete with the D-galacto dienophile, whereas it is only moderate with the D-manno (Eq. 8.30).[51]

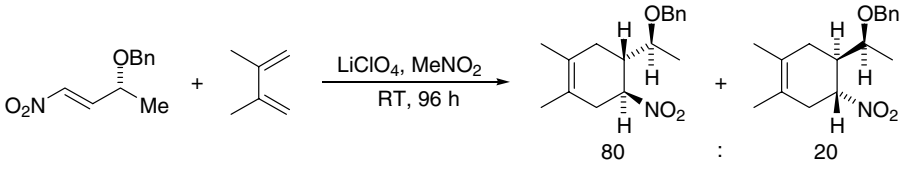



**Scheme 8.10.**



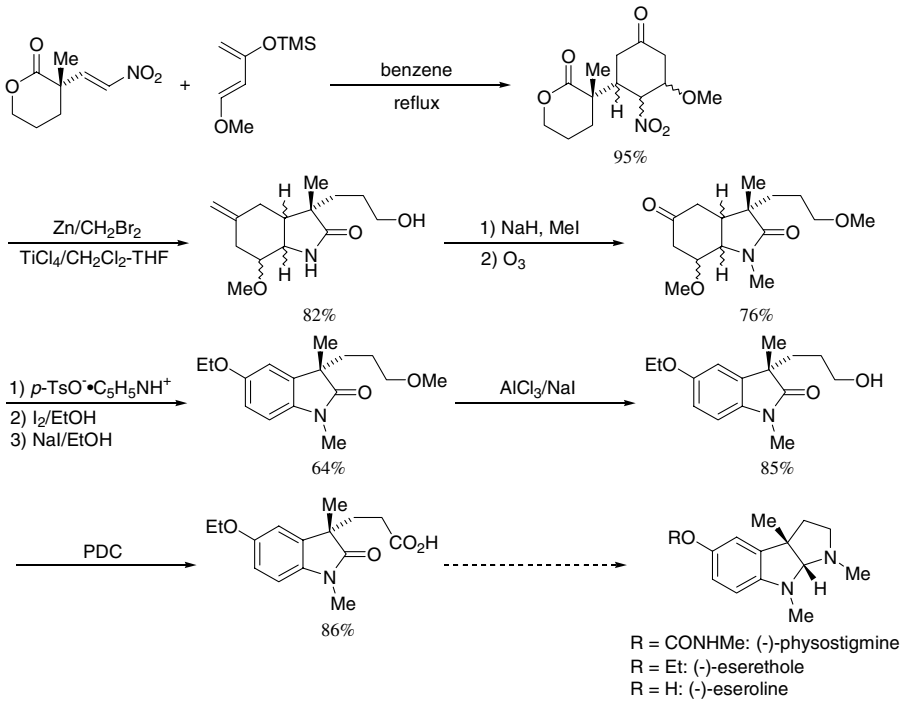

(8.30)

Diels-Alder reactions in which nitroalkenes act as dienophiles are accelerated in the presence of 4 M $LiClO_4$ in nitromethane. This acceleration is higher than that observed when $LiClO_4$ is used in diethyl ether. The diastereoselective Diels-Alder reaction using homochiral nitroalkenes shown in Eq. 8.31 has been demonstrated.[52]




(8.31)

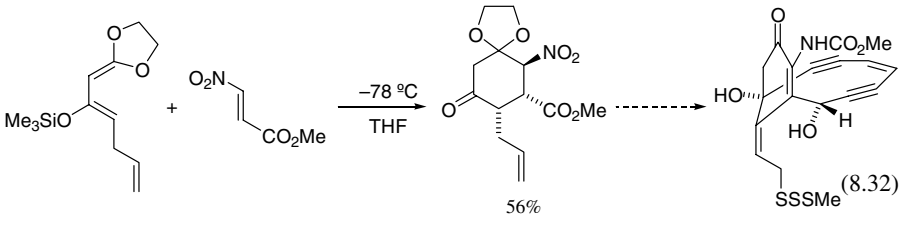
Node and Fuji have developed a new chiral synthesis of various alkaloids using chiral nitroalkene, (*S*)-(–)-2-methyl-2-(2′-nitrovinyl)-δ-valerolactone. Scheme 8.11 shows a total synthesis of (–)-physostigmine, a principal alkaloid of the Calabar bean.[53] The key nitroalkene is prepared by asymmetric nitroolefination of α-methyl-δ-lactone using a chiral enamine (see



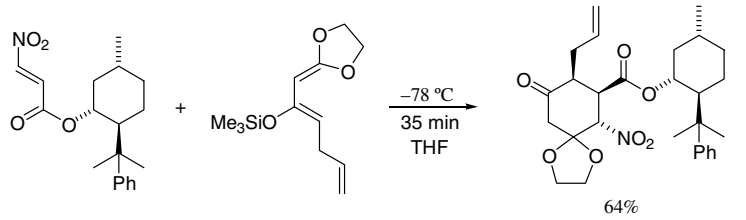

**Scheme 8.11.**

section discussing Michael addition Section 4.2). The Diels-Alder reaction of the chiral nitroalkene with Danishefsky's diene gives a diastereomeric mixture of the adduct. The *exo*-selectivity is general for this type of reaction, as discussed previously. The stereocontrol of newly created asymmetric carbons is not important because these isomers are converted into a single compound after aromatization of the resulting six-membered ring. Methylenation and reductive cyclization on treatment with $CH_2Br_2$ and Zn in the presence of $TiCl_4$ give the lactam in 82% yield. The lactam is converted into the target compound via the processes shown in Scheme 8.11.

Clive and coworkers have reported a total synthesis of calicheamicinone, the aglycon of the antitumor agent calicheamicin $\gamma_1$, starting from the Diels-Alder reaction of methyl 3-nitropropenoate with ketene acetal (Eq. 8.32).[54] An asymmetric Diels-Alder reaction between ketene acetal presented in Eq. 8.32 and 3-nitropropenoate derived from (–)-8-phenyl-menthol affords the optically pure adduct, which can be converted into either enantiomer of calicheamicinone (Eq. 8.33).[55]

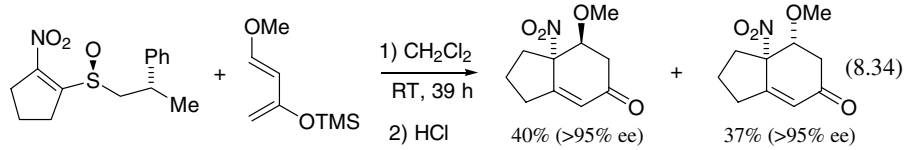



(8.32)

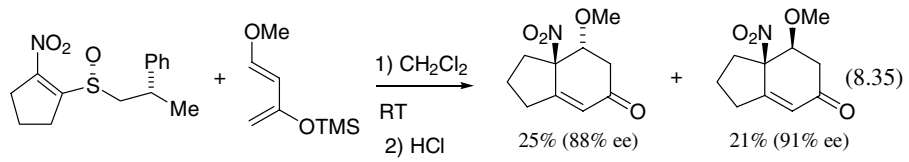



(8.33)

Asymmetric Diels-Alder reactions using chiral sulfinylalkenes have been extensively studied by Koizumi and coworkers.[55] Fuji and coworkers have extended this strategy to chiral 1-(alkylsulfinyl)-2-nitroalkenes. Such nitroalkenes react with reactive dienes such as Danishefsky's dienes to produce an adduct with a high enantiomeric excess (ee) (see Eqs. 8.34 and 8.35).[57]



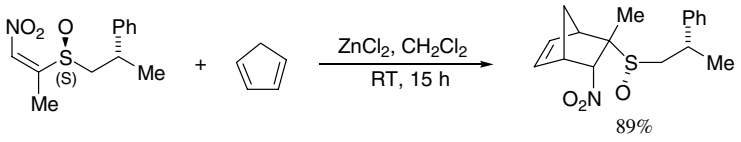

(8.34)




(8.35)

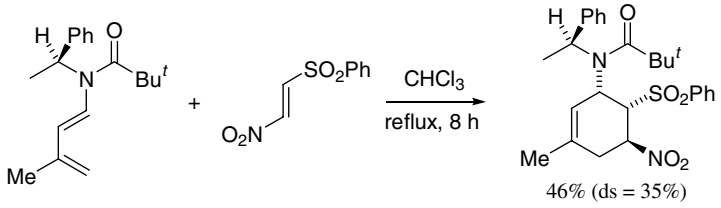
Simple dienes are not reactive enough toward chiral 1-(alkylsulfinyl)-2-nitroalkenes. To resolve this problem, the reaction of optically active 1-(alkylsulfinyl)-2-nitroalkenes with simple

dienes such as cyclopentadiene or 1,3-pentadiene has been carried in the presence of Lewis acids or under high pressure.[58] In these reactions, the *Z*-sulfinyl dienophiles show high diastereo- and *endo/exo* selectivity, as shown in Eq. 8.36.



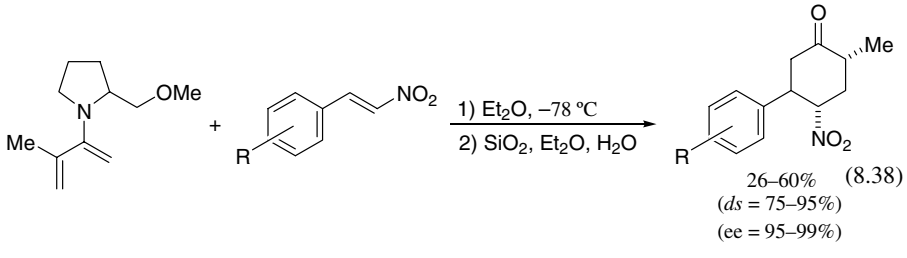
(8.36)

***8.1.2.2 Dienes with Chiral Auxiliaries*** The use of dienes with the chiral auxiliary attached to the C-1 position of the dienes is the most popular in asymmetric Diels-Alder reactions.[59] In 1980, Trost reported high asymmetric induction in the Diels-Alder reaction using 1-(S)-O-methylmandeloxy-1,4-butadiene.[59a] However, the result obtained by Trost et al. has remained unique for more than a decade, at least in terms of enantioselectivity. The asymmetric Diels-Alder reaction of chiral diene-amines with nitroalkenes gives aminocyclohexenes with good diastereoselectivity (Eq. 8.37).[60] The development in the area of chiral dienes is slow; it may be due to the difficulty of preparing these compounds.

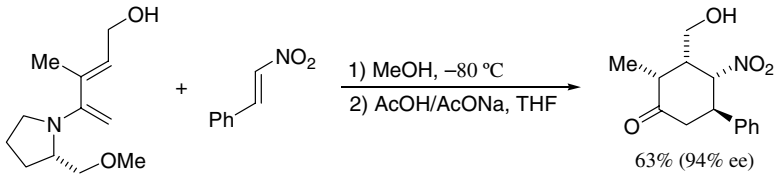


(8.37)

Recently, the research groups of Enders (Eq. 8.38)[61] and Barluenga (Eq. 8.39)[62] reported on the cycloaddition of chiral 2-aminobutadiene and described elegant solutions to the stereochemistry problems (regio-, diastereo-, and enantioselectivity). The reaction of 2-[(*S*)-2-methoxymethyl]pyrrolidin-1-yl]buta-1,3-diene with various 2-aryl-1-nitroethenes produces after hydrolysis 5-aryl-2-methyl-substituted 4-nitrocyclohexanones in excellent enantiomeric purity (ee = 75–95%) and with high diastereoselectivity (ds = 75–95%).[61]



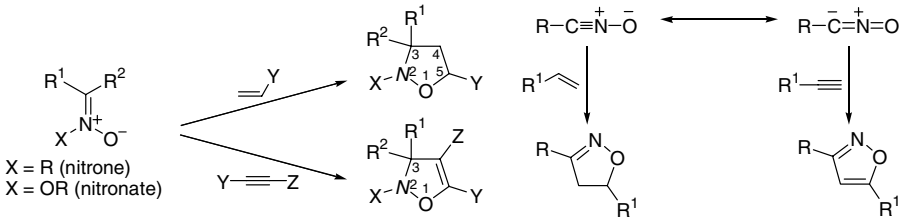
(8.38)



(8.39)

## 8.2 1,3-DIPOLAR CYCLOADDITION

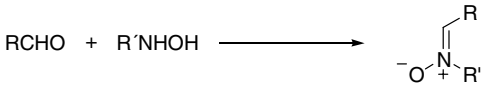
Since Huisgen's definition of the general concepts of 1,3-dipolar cycloaddition, this class of reaction has been used extensively in organic synthesis. Nitro compounds can participate in 1,3-dipolar cycloaddition as sources of 1,3-dipoles such as nitronates or nitroxides. Because the reaction of nitrones can be compared with that of nitronates, recent development of nitrones in organic synthesis is briefly summarized. 1,3-Dipolar cycloadditions to a double bond or a triple bond lead to five-membered heterocyclic compounds (Scheme 8.12). There are many excellent reviews on 1,3-dipolar cycloaddition;[63] in particular, the monograph by Torssell covers this topic comprehensively. This chapter describes only recent progress in this field. Many papers have appeared after the comprehensive monograph by Torssell. Here, the natural product synthesis and asymmetric 1,3-dipolar cycloaddition are emphasized.[63c] Synthesis of pyrrolidine and -izidine alkaloids based on cycloaddition reactions are also discussed in this chapter.



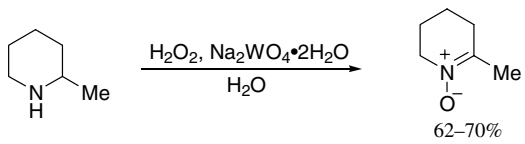

**Scheme 8.12.**

### 8.2.1 Nitrones

Nitrones have been generally prepared by the condensation of *N*-hydroxylamines with carbonyl compounds (Eq. 8.40).[63] There are a number of published procedures, including dehydrogenation of *N,N*-disubstituted hydroxylamines, *N*-alkylation of imines, and oxidation of secondary amines. Among them, the simplest method is the oxidation of secondary amines with $H_2O_2$ in the presence of catalytic amounts of $Na_2WO_4$; this method is very useful for the preparation of cyclic nitrones (Eq. 8.41).[64]

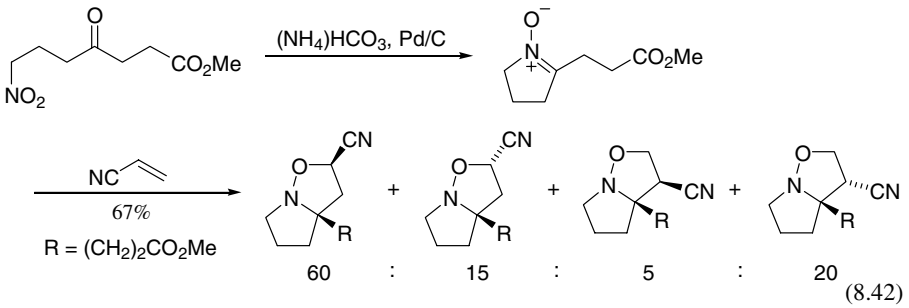


(8.40)



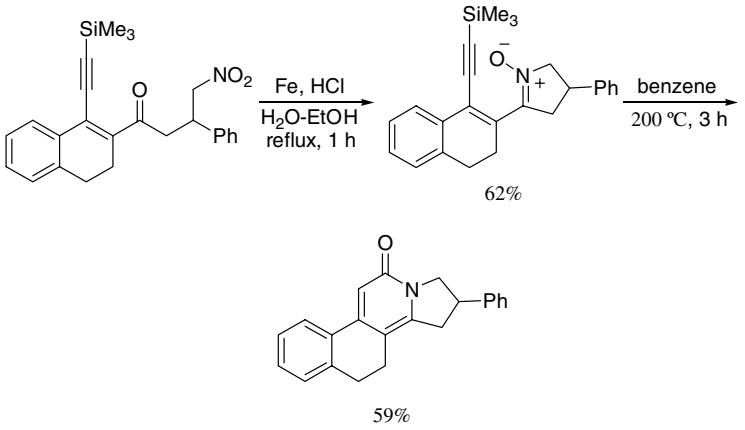

(8.41)

Reductions of γ-nitroketones yield cyclic nitrones, which undergo inter- and intramolecular cycloaddition to various alkenes. The result of addition to acrylonitrile is shown in Eq. 8.42, in which a mixture of regio- and stereoisomers is formed.[65]




(8.42)

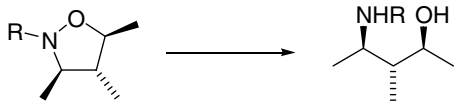
Conjugated nitrones are formed by intramolecular reductive cyclizations of nitro groups onto ketones; the resulting nitrones give starting materials for preparing azasteroids. An example is shown in Eq. 8.43.[66]




(8.43)

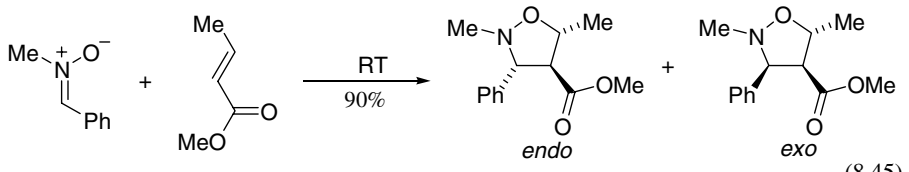
Nitrones, reactive 1,3-dipoles, react with alkenes and alkynes to form isoxazolidines and isoxazolines, respectively. With monosubstituted olefinic dipolarophiles, 5-substituted isoxazolidines are generally formed predominantly; however, with olefins bearing strongly electron-withdrawing groups, 4-substituted derivatives may also be formed.[63a]

The mechanism of 1,3-dipolar cycloaddition can be found in Ref. 63 and the references within. The reaction of nitrone with 1,2-disubstituted alkenes creates three contiguous asymmetric centers, in which the geometric relationship of the substituents of alkenes is retained. The synthetic utility of nitrone adducts is mainly due to their conversion into various important compounds. For instance, β-amino alcohols can be obtained from isoxazolidines by reduction with $H_2$-Pd or Raney Ni with retention of configuration at the chiral center (Eq. 8.44).



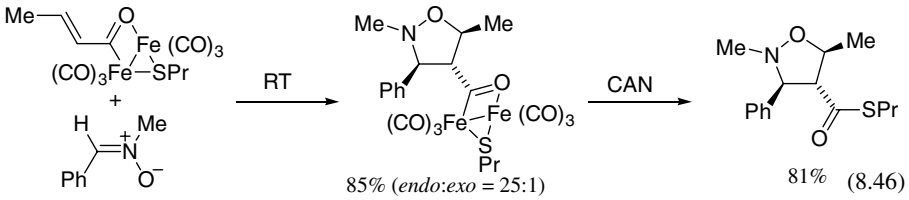

(8.44)

Concerted cycloaddition reactions provide the most powerful way to stereospecific creations of new chiral centers in organic molecules. In a manner similar to the Diels-Alder reaction, a pair of diastereoisomers, the *endo* and *exo* isomers, can be formed (Eq. 8.45). The *endo* selectivity in the Diels-Alder arises from secondary π-orbital interactions, but this interaction is small in 1,3-dipolar cycloaddition. If alkenes, or 1,3-dipoles, contain a chiral center(s), the approach toward one of the faces of the alkene or the 1,3-dipole can be discriminated. Such selectivity is defined as diastereomeric excess (de).



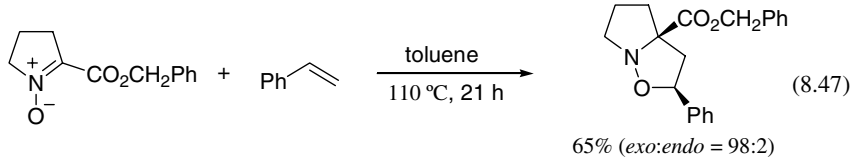

(8.45)

The reactions of acyclic nitrones with dipolarophiles give mixtures of *endo*- and *exo*-type products, which are often difficult to predict.[63a] The development of a dipolarophile that gives high stereo- and regioselectivity is important. A recent study reports that diiron acyl complexes undergo stereo- and regioselective [3+2] cycloaddition with various nitrones. For example, C-phenyl-N-methylnitrone gives a 1:1 end:exo ratio of products in its reaction with methyl crotonate. This nitrone reacts with diiron acyl complex to give a 25:1 end:exo ratio (Eq. 8.46).[67]



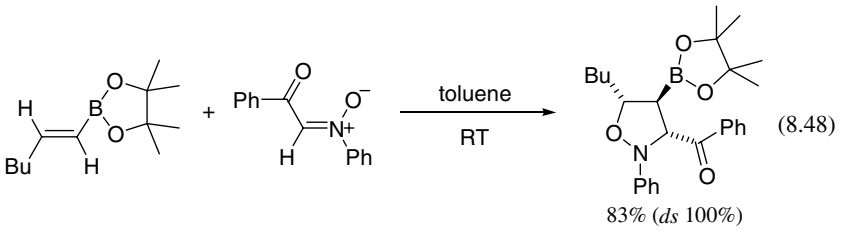

(8.46)

Cycloaddition of the cyclic nitrone derived from proline benzyl ester with alkenes proceeds readily to give isoxazolidines with good regio-and stereoselectivity (Eq. 8.47).[68] The reaction favors exo-mode addition. However, certain cycloadditions are reversible and therefore the product distribution may reflect thermodynamic rather than kinetic control.




(8.47)

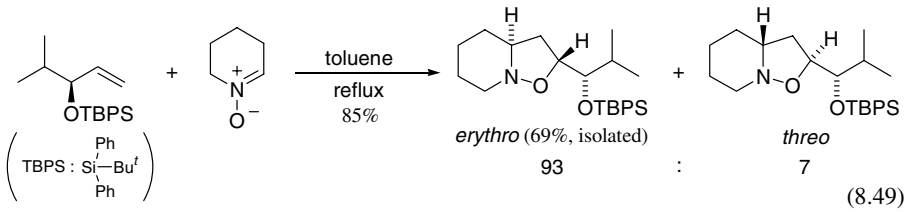
Alkenylboronic esters undergo regio- and stereoselective 1,3-dipolar cycloadditions with nitrones. These reactions lead to boronic ester-substituted isoxazolidines, which can be converted by oxidation with $H_2O_2$ to the corresponding 4-hydroxy derivatives (Eq. 8.48).[69] The high selectivity could be the result of a favorable interaction between the boronic ester and the amino group.




(8.48)

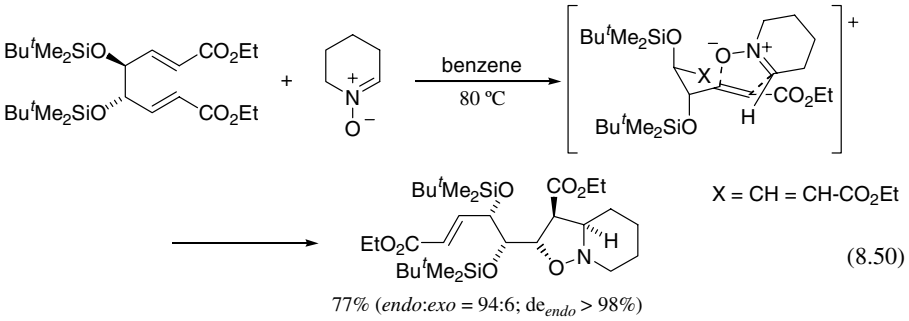
To control the stereochemistry of 1,3-dipolar cycloaddition reactions, chiral auxiliaries are introduced into either the dipole-part or dipolarophile. A recent monograph covers this topic extensively;[70] therefore, only typical examples are presented here. Alkenes employed in asymmetric 1,3-cycloaddition can be divided into three main groups: (1) chiral allylic alcohols, (2) chiral amines, and (3) chiral vinyl sulfoxides or vinylphosphine oxides.[63c]

Kibayashi and coworkers have used enantiometrically pure allylic silyl ethers obtained from amino acids in cycloaddition with nitrones (Eq. 8.49).[71] Cyclic nitrone reacts with a chiral allyl ether to give selectively the *exo* and *erythro* isomer (de 90%). Optically active alkaloids containing a piperidine ring such as (+)-monomorine,[71c] (+)-coniine,[71a] and (–)-oncinotine[71b] have been prepared from the addition product.



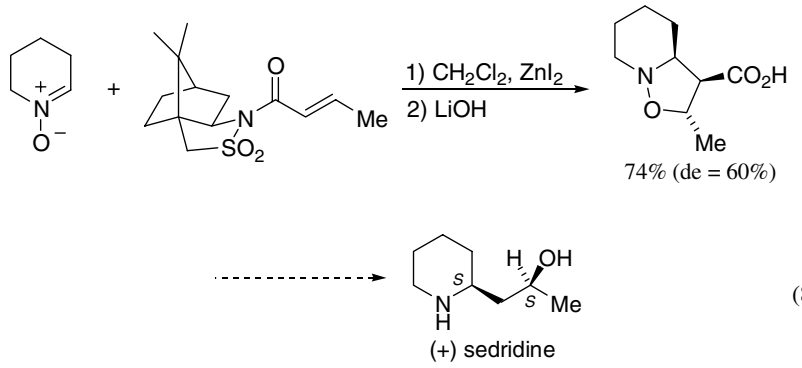

(8.49)

Saito and coworkers have used $C_2$-symmetrical alkenes derived from a variety of tartaric acid derivatives, for controller in discriminating π faces of dipolarophile in nitrone cycloaddition. Excellent *endo*/*exo* and diastereofacial selectivity (de) are obtained. *Endo* transition state assembly shown in Eq. 8.50 could be responsible for the formation of preferred distereoisomers.[72]



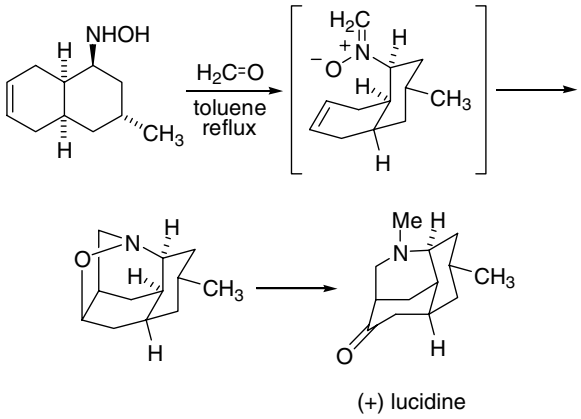

(8.50)

Asymmetric 1,3-dipolar cycloaddition of cyclic nitrones to crotonic acid derivatives bearing chiral auxiliaries in the presence of zinc iodide gives bicyclic isoxazolidines with high stereoselectivity (Eq. 8.51). The products are good precursors of β-amino acids such as (+)sedridine.[73] Many papers concerning 1,3-dipolar cycloaddition of nitrones to chiral alkenes have been reported, and they are well documented (see Ref. 63).




(8.51)

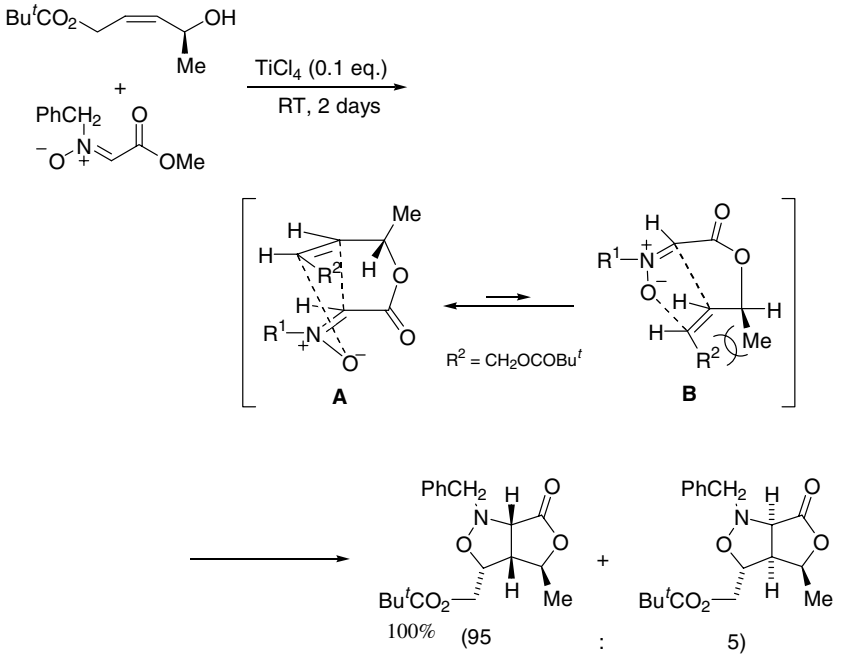
Diastereoselective intramolecular cycloaddition of nitrones is useful for constructing nitrogen- containing cyclic structures. The reaction serves as a key step in a number of natural product syntheses.[63] Tufariello and coworkers have used this strategy for preparing cocaine and other alkaloids.[74] As a classical example, enantioselective total synthesis of (+)-luciduline is presented in Scheme 8.13, in which a useful feature of the 1,3-dipolar addition of nitrones is nicely illustrated.[75]



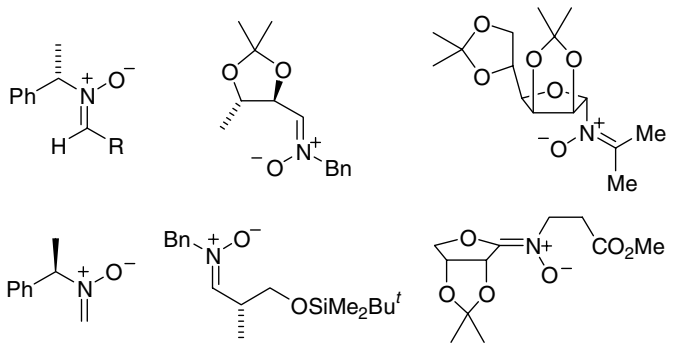

(+) lucidine

**Scheme 8.13.**

Tandem transesterification and diastereoselective intramolecular 1,3-dipolar cycloaddition of α-methoxycarbonylnitrones with chiral allyl alcohols give polycyclic compounds in one step with high stereoselectivity (Scheme 8.14).[76] Transition state A in Scheme 8.14 is more favorable than B because B has severe steric interaction (allylic 1,3-strain).[77]

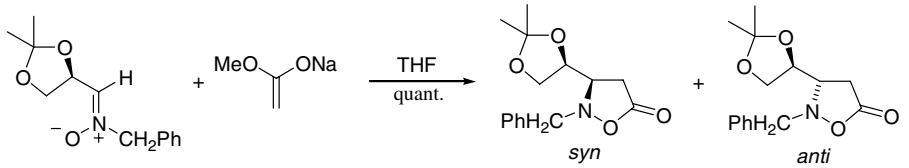



**Scheme 8.14.**



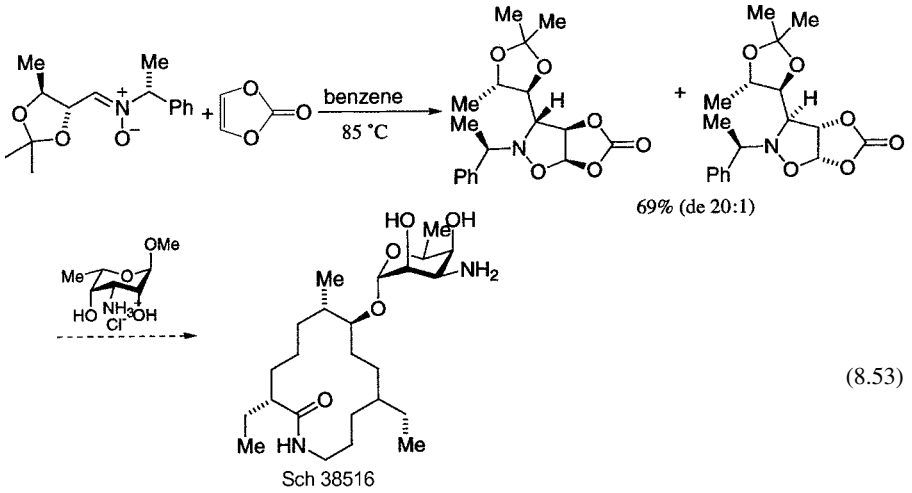
**Scheme 8.15.**

Various kinds of chiral acyclic nitrones have been devised, and they have been used extensively in 1,3-dipolar cycloaddition reactions, which are documented in recent reviews.[63] Typical chiral acyclic nitrones that have been used in asymmetric cycloadditions are illustrated in Scheme 8.15. Several recent applications of these chiral nitrones to organic synthesis are presented here. For example, the addition of the sodium enolate of methyl acetate to *N*-benzyl nitrone derived from D-glyceraldehyde affords the 3-substituted isoxazolin-5-one with a high *syn* selectivity. Further elaboration leads to the preparation of the isoxazolidine nucleoside analog in enantiomerically pure form (Eq. 8.52).[78]

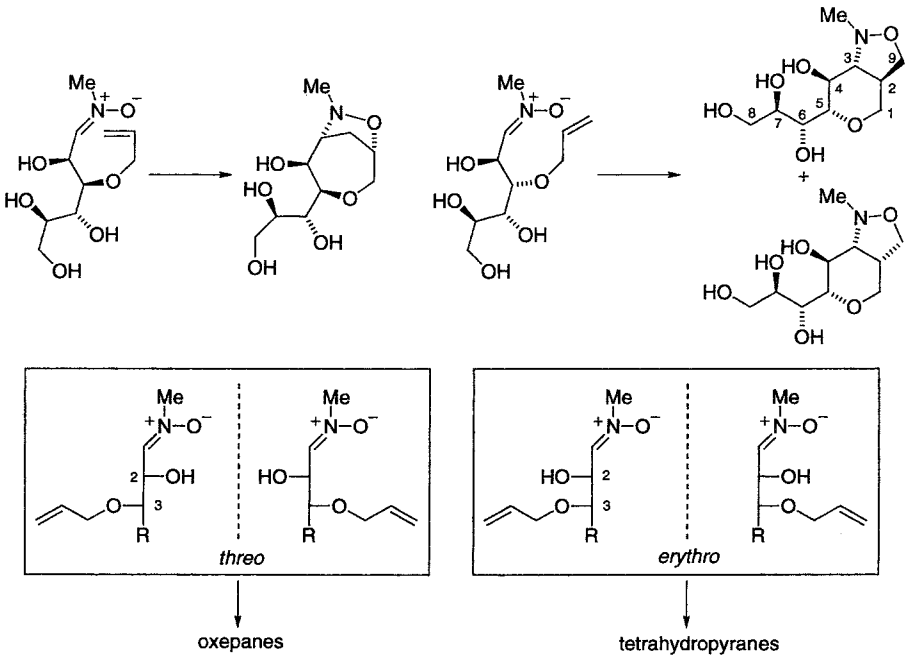


*syn* 95 : *anti* 5 (8.52)

Enantioselective total synthesis of antifungal agent Sch-38516 is reported. Stereocontrolled carbohydrate synthesis is based on the 1,3-dipolar cycloaddition of chiral nitrone to vinylene carbonate, as shown in Eq. 8.53.[79]



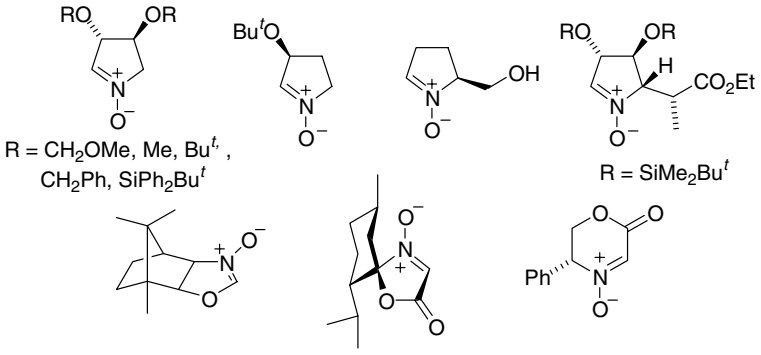
(8.53)




**Scheme 8.16.**

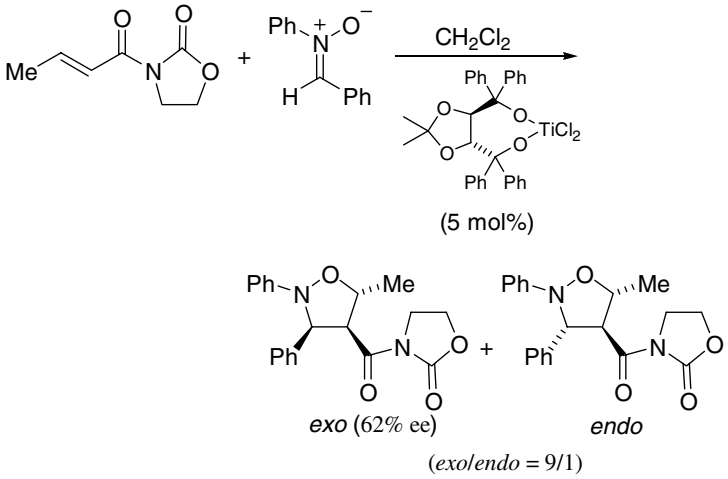
Intramolecular cycloadditions of chiral nitrones provide a useful tool for the preparation of bioactive heterocyclic compounds.[63] Shing et al. demonstrated that 1,3-dipolar cycloaddition of nitrones derived from 3-*O*-allyl-hexoses is dependent only on the relative configuration at C-2,3, as shown in Scheme 8.16. Thus 3-*O*-allyl-D-glucose and -D-altrose (both with *threo*-configuration at C-2,3) produce oxepanes selectively, whereas 3-*O*-allyl-D-allose and -D-mannose (both with *erythro*-configuration at C-2,3) give tetrahydropyranes selectively.[80]

An optically active cyclic nitrone in 1,3-dipolar cycloaddition was first reported by Vasella in 1985.[81] A variety of optically active cyclic nitrones have been devised since then. Some typical chiral nitrones described in Ref. 63c are shown in Scheme 8.17. Applications of these nitrones are also presented in this review.



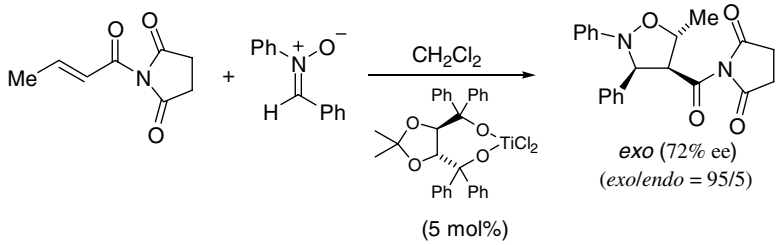

**Scheme 8.17.**

A new strategy for constructing chiral cyclic molecules is asymmetric cycloaddition catalyzed by chiral catalysts. Contrary to the broad application of catalysts in asymmetric Diels-Alder reaction,[47a] the use of metal catalysts in asymmetric 1,3-dipolar cycloaddition has been developed only recently. Kanemasa and coworkers have demonstrated that the stereochemistry of 1,3-dipolar cycloaddition can be controlled by the presence of $ZnI_2$ or other Lewis acids.[82] Extension of their work is nicely summarized in Ref. 63a. In 1994, two groups reported the first asymmetric 1,3-dipolar cycloaddition of achiral alkenes with achiral nitrones using a chiral TADDOL (tetraaryl-1,3-dioxolane-4,5-dimethanols) catalyst ($TiCl_2$-TADDOLate), as shown in Eq. 8.54.[83] Another approach using oxazaborolidinone as a chiral catalyst is also presented.[84] These catalysts have successfully been applied in a number of asymmetric reactions, especially in the Diels-Alder reaction.[85]




(8.54)

The *exo* selectivity of the $TiCl_2$-TADDOLate-catalyzed 1,3-dipolar cycloaddition is improved by the use of succinimide instead of oxazolidinone as auxiliary for the α,β-unsaturated carbonyl moiety (Eq. 8.55).[86] A strong bidentate coordination of the alkenyl moiety to the metal catalyst is important in these reactions.

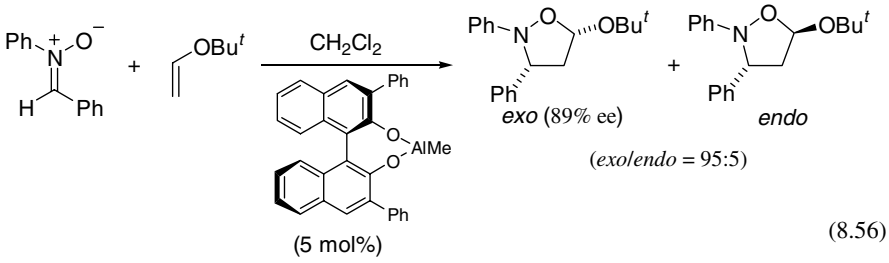



(8.55)

Seebach has developed immobilization of TADDOL with a high degree of loading on porous silica gel and applications in enantioselective addition of Eq. 8.54. This catalyst leads to 85%

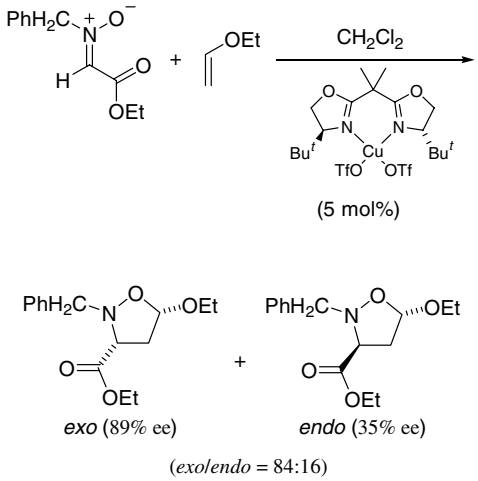
ds and 92.5% ee, which are comparable with those of Eq. 8.54.[88] Introduction of tosylato ligands in the catalyst $Ti(OTos)_3$-TADDOLate provides an excellent *endo* selectivity of the reaction of Eq. 8.54, in which 91–93% ee is obtained.[87]

The typical 1,3-dipolar cycloaddition reaction of nitrones with alkenes involves a dominant interaction of HOMO (nitrone) and LUMO (alkenes). The inverse-electron demand of the 1,3-dipolar cycloaddition reaction of nitrones with alkenes requires a dominant interaction of LUMO (nitrone) and HOMO (alkenes). Such a reaction requires an activation of the nitrone with a Lewis acid. In 1999, Jorgensen and coworkers reported that chiral 2,2′-dihydroxy-1,1′-binaphtol (BINOL)-AlMe complexes catalyzes a highly regio-, diastereo-, and enantioselective 1,3-dipolar cycloaddition reaction of aromatic nitrones with vinyl ether, giving the *exo*-diastereoisomer with 90% ds and 97% ee (Eq. 8.56).[89]



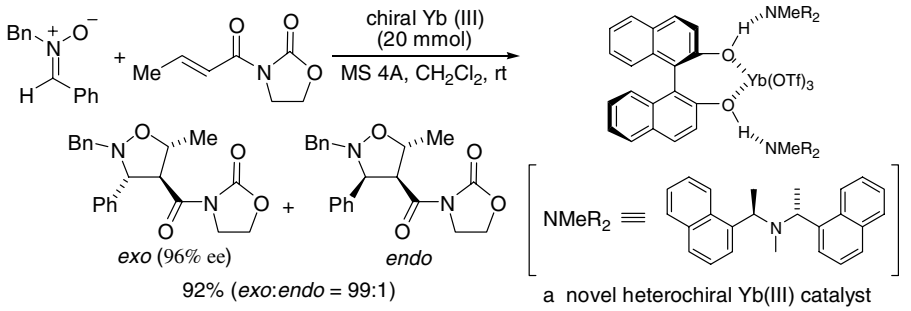

(8.56)

Copper(II)-bisoxazoline also catalyzes asymmetric 1,3-dipolar cycloaddition reactions of nitrones with electron-rich alkenes (Eq. 8.57).[90]



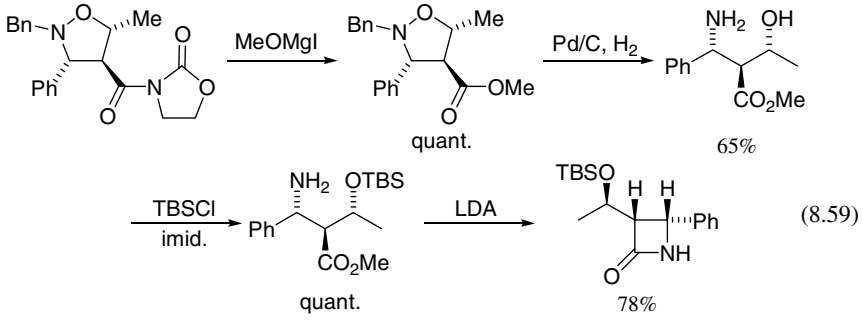

(8.57)

Catalytic enantioselective 1,3-dipolar cycloaddition between nitrones with alkenes using a novel heterochiral ytterbium(III) catalyst is reported (Eq. 8.58).[91] The desired isoxazolidine derivatives are obtained in excellent yields with excellent diastereo- and enantioselectivities.




(8.58)

The products are converted into β-lactams with high enantiomeric purity (ee 96%), as shown in Eq. 8.59.



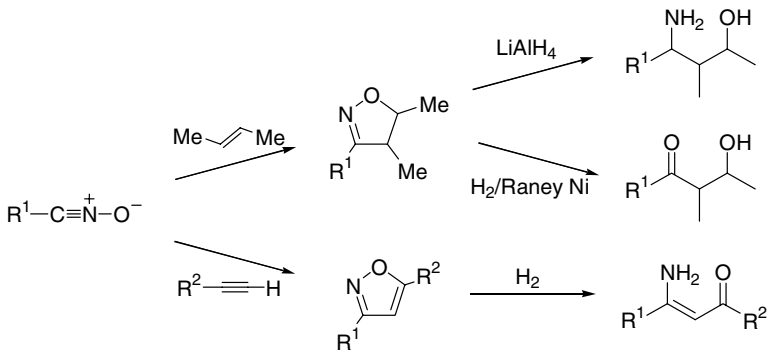

(8.59)

Reports on total synthesis of natural products using nitrones are numerous; some recent papers are as follows: marine alkaloid lepadiformine (Ref. 92) and β-lactam antibiotics (Ref. 93).

### 8.2.2 Nitrile Oxides

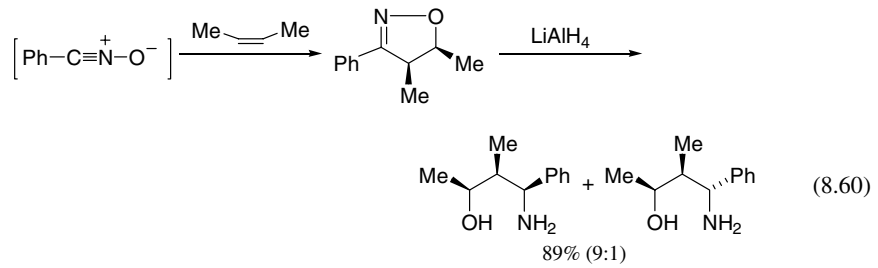
As discussed in Section 6.2, nitro compounds are good precursors of nitrile oxides, which are important dipoles in cycloadditions. The 1,3-dipolar cycloaddition of nitrile oxides with alkenes or alkynes provides a straightforward access to 2-isoxazolines or isoxazoles, respectively. A number of ring-cleaving procedures are applicable, such that various types of compounds may be obtained from the primary adducts (Scheme 8.18). There are many reports on synthetic applications of this reaction. The methods for generation of nitrile oxides and their reactions are discussed in Section 6.2. Recent synthetic applications and asymmetric synthesis using 1,3-dipolar cycloaddition of nitrile oxides are summarized in this section.

The review by Kozikowski[94] and the monograph by Torssell[63a] demonstrate the synthetic utility of the isoxazolines. Reduction of isoxazolines with $LiAlH_4$ or catalytic hydrogenation gives γ-amino alcohols, which have been used extensively in organic synthesis (Eq. 8.60).[95] With alkyl or other noncoordinating substituents at C-4 or C-5 of the isoxazoline ring, addition of hydride taking place *anti* to the substituents to give *erythro* amino alcohols. Hydroxy or

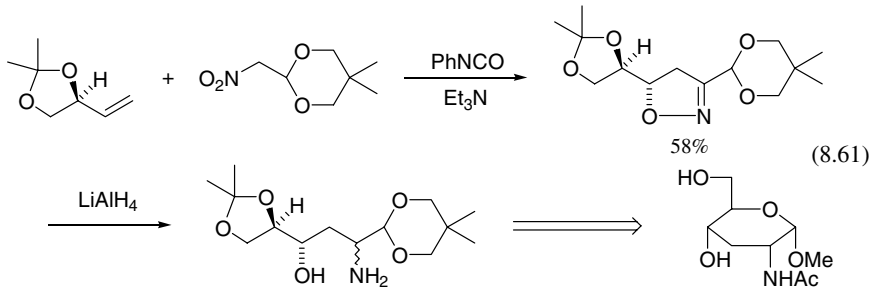


**Scheme 8.18.**

hydroxymethyl substituents, on the other hand, direct attack of $LiAlH_4$ to the *syn* face of the C=N double bond to give predominantly *threo* amino alcohols. Jager and coworkers have used this strategy for synthesis of glycosidase-inhibiting iminopolyols and amino sugars (Eq. 8.61).[63b,96] Recently, diastereoselective synthesis of highly substituted 2,5-diaminohexanes via nitrile oxide cycloaddition to an optically active vinylogous amino acid has been shown.[96d]

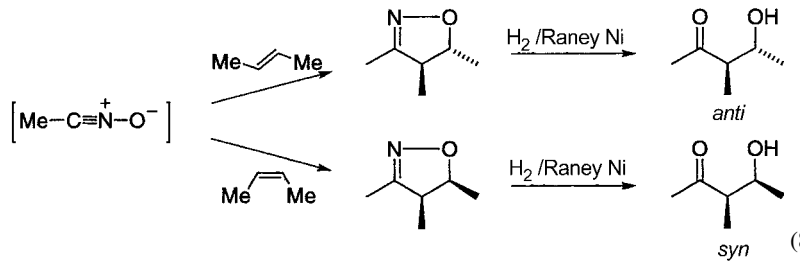


89% (9:1) (8.60)



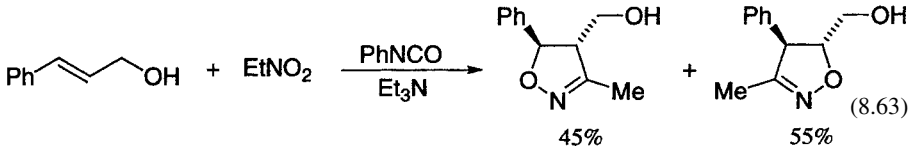
58% (8.61)

The conversion of isoxazolines to β-hydroxy ketones can be carried out by $H_2$ in the presence of Raney Ni under various conditions.[97] The reaction proceeds cleanly with complete stereospecificity (Eq. 8.62).



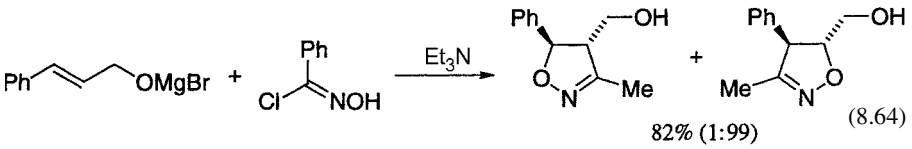
(8.62)

Thus, isoxazolines are converted into γ-amino alcohols and β-hydroxy ketones stereoselectively. However, the intermolecular cycloaddition involving 1,2-unsymmetrically substituted alkenes such as *trans*-cinnamyl alcohol proceeds nonregioselectively to give a mixture of the two regioisomers (Eq. 8.63).[98]



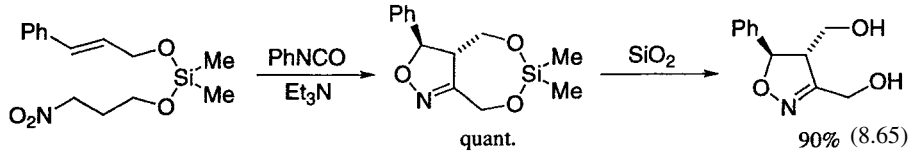
(8.63)

Several strategies have been proposed to improve the regioselectivity of nitrile oxide cycloaddition. Kanemasa and coworkers have reported high-rate acceleration and regioselectivity in nitrile oxide cycloadditions to the magnesium alkoxides of allylic and homoallylic alcohols (Eq. 8.64).[99]



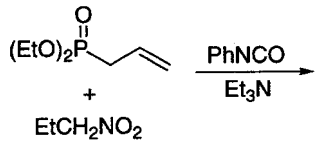
(8.64)

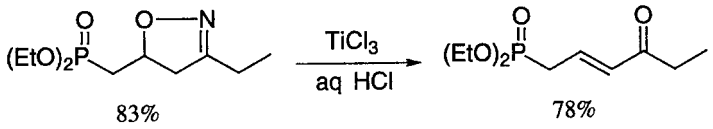
Another strategy to control the regio- and stereochemistry of cycloaddition is a silicon-tethered reaction, as discussed in the section of nitronates (Section 8.2.3) (Eq. 8.65).[100]



(8.65)

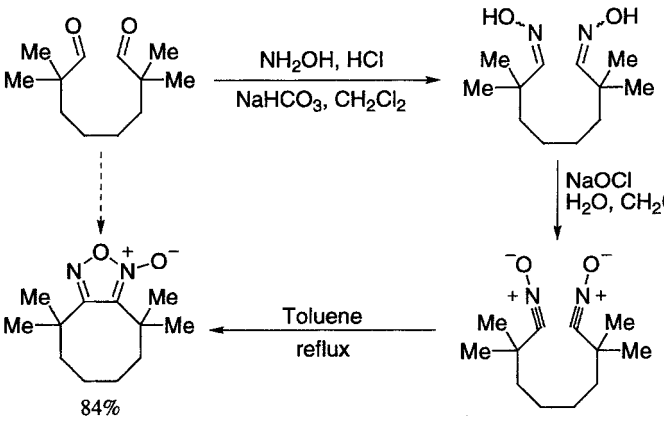
Isoxazolines are good precursors of α,β-unsaturated ketones.[63,94] This transformation is useful for synthesis of polyenes. For example, nitrile oxide cycloaddition chemistry is used to prepare 4-oxo-2-alkenylphosphonates, which are useful to synthesize a long polyethylenic unit via Woodworth-Emmons olefination (Eq. 8.66).[101]






(8.66)

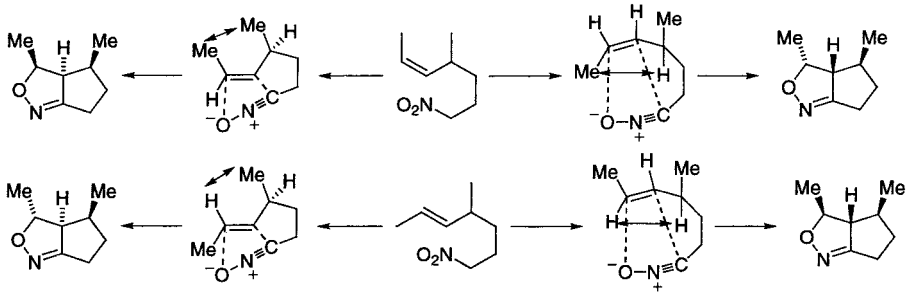
As a new utility of nitrile oxide in organic synthesis, synthesis of medium and large rings by intramolecular nitrile oxide dimerization is reported (Eq. 8.67).[102]



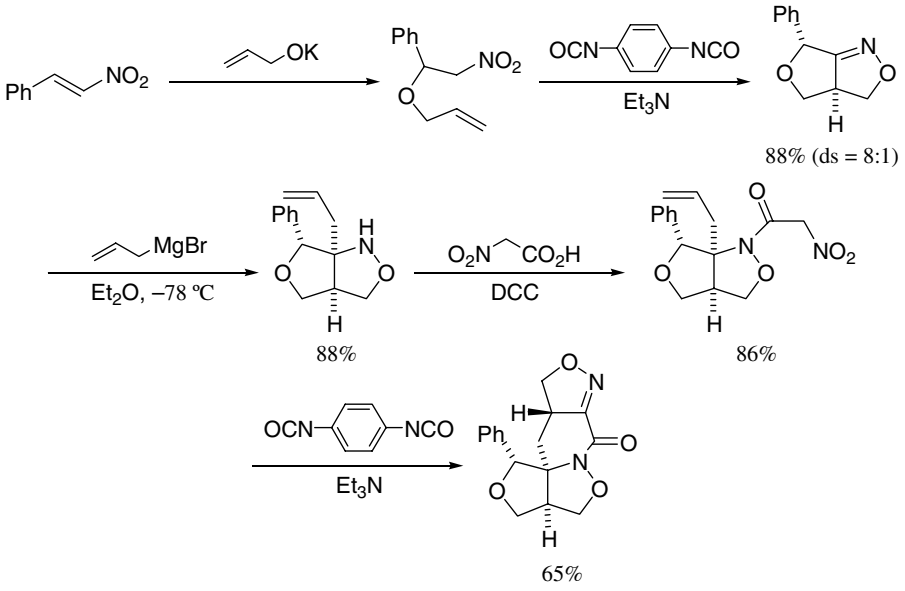

(8.67)

Intramolecular 1,3-cycloadditions of nitrile oxides (INOC) provide a useful tool for the construction of fused cyclic ring systems. The stereochemical outcome of this reaction is presumed to be a consequence of reaction through the transition state that minimizes allylic 1,3 strain (Scheme 8.19).[103]

Kurth and coworkers have reported sequential 1,3-dipolar cycloadditions in the synthesis of bis-isoxazolo-substituted piperidinones (Scheme 8.20).[104] The Michael addition of allyl alcohol to nitrostyrene followed by INOC gives a mixture of *cis*- and *trans*-furanoisooxazoles in 88% yield. The stereoselectivity is much improved by intramolecular silynitronate cycloaddition (ISOC) (see Section 8.2.3). The use of 1,4-phenylene diisocyanate as the dehydrating agent is recommended because the resulting urea polymer can be removed by simple filtration. The introduction of allyl group and formation of the nitroacetoamide provide a precursor of an isoxazoloisooxazoline-containing tetracycle. Finally, INOC of this precursor affords a desired tetracyclic compound stereoselectively.

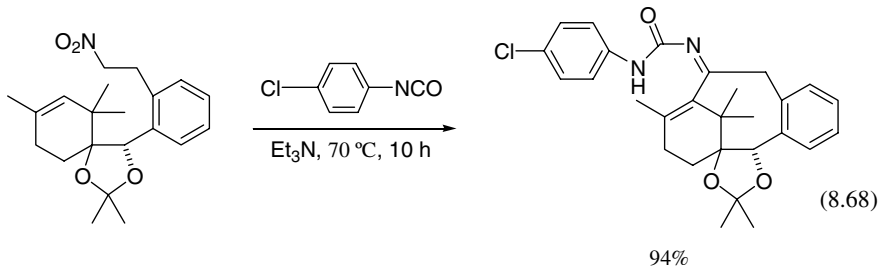


**Scheme 8.19.**

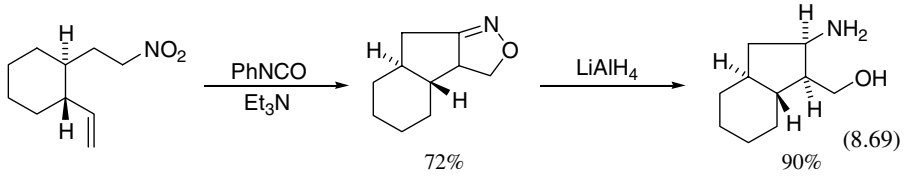



**Scheme 8.20.**

INOC has been used for the synthesis of tricylic compounds having the taxane A/B ring system with an aromatic C ring (Eq. 8.68).[105]

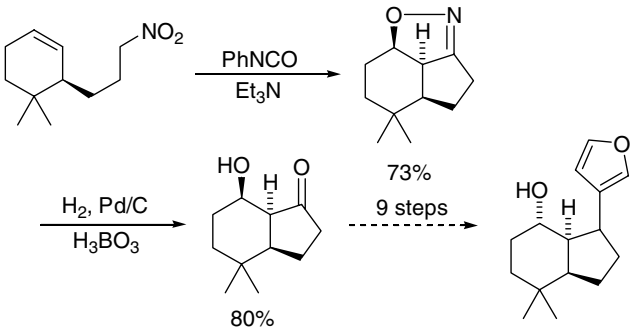



A potentially useful approach to the marine alkaloid papuamine based on INOC strategy is proposed as shown in Scheme 8.21. In fact, a *trans*-hydrindane intermediate has been synthesized in racemic form using a model sequence of reactions involving a nitrile oxide cycloaddition as a key step (Eq. 8.69).[106]



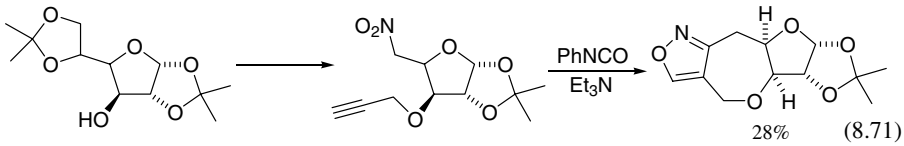

A diastereoselective synthesis of the model insect antifeedant related to 12-hydroxyazadiradione starting from α-cyclocitral has been reported. [The key steps involve INOC and a Stille

coupling reaction of a vinyl iodide with a stannylfuran (Eq. 8.70)].[107] Many related syntheses by means of INOC have been reported.[108]



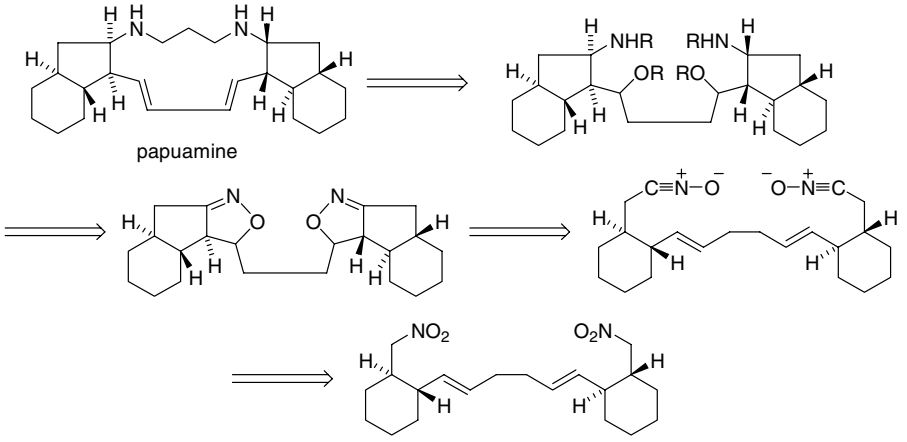

(8.70)

Asymmetric synthesis based on INOC using a chiral nitrile oxides is a standard method for obtaining enantiomerically pure compounds. A useful synthesis of enantiomerically pure pyrano- and oxepanoisoxazole derivatives by application of INOC is presented in Eq. 8.71.[109]

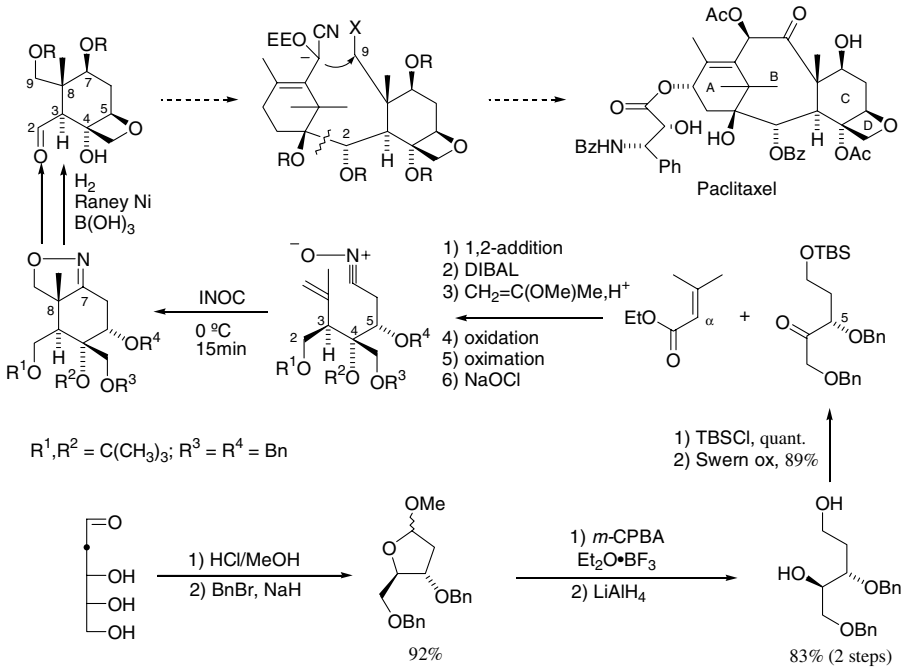



(8.71)

Takahashi and coworkers have used INOC for synthesis of the chiral CD rings paclitaxel, which is an antitumor agent. Synthetic strategy starting from 2-deoxy-D-ribose is demonstrated in Scheme 8.22.[110] The precursor of INOC was prepared by 1,2-addition of α,β-unsaturated ester to ketone. INOC and subsequent reductive cleavage by $H_2$/Raney Ni afford the desired CD ring structure.



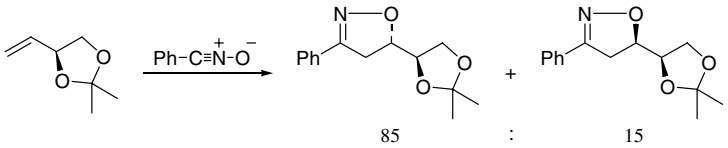

**Scheme 8.21.**



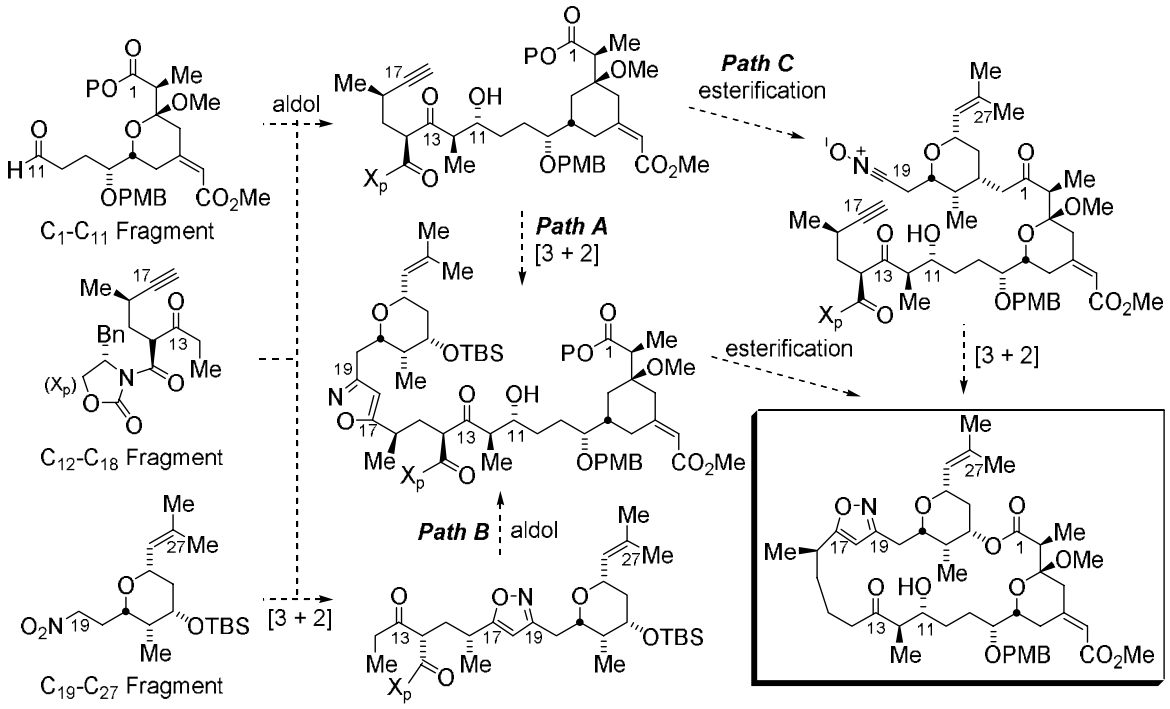

**Scheme 8.22.**

Evans and coworkers have reported the synthesis and absolute stereochemical assignment of (+)-miyakolide.[111] Miyakolide was isolated from a sponge of the genus Polyfibrospongia by Higa et al.[112] The elegant synthesis is illustrated in Scheme 8.23, in which the carbon skeleton is assembled in a convergent fashion from three fragments via esterification, [3+2] cycloaddition, and aldol reaction. Here, intermolecular and intramolecular [3+2] cycloadditions of nitrile oxides are used to assemble small components to complex large sized molecules.

1,3-Dipolar cycloaddition of nitrile oxides using chiral alkenes or chiral nitrile oxides has been extensively studied. It has been established that allylic substituents have a strong influence in determining the π-facial selectivity and that notable high levels of diastereoselectivity (de 56–93%) are observed for cycloaddition to chiral allyl ethers.[63c,113] For example, benzonitrile oxide adds to (*S*)-isopropylidenebut-3-ene-1,2-diol to afford an 85:15 mixture of the isoxazolines (Eq. 8.72).[114] The preferred formation of the adduct (*erythro*) has been rationalized by Houk et al. in terms of an inside alkoxide effect that involves allylic oxygen (Scheme 8.24).[115] The diastereomeric preferences observed in cycloaddition result from the alkoxy group preference for the inside conformation and the alkyl group preference for anti. Examples of the corresponding reactions with chiral allylamine derivatives have also been reported, but, in general, the degree of selectivity is lower and less predictable.[116]




(8.72)

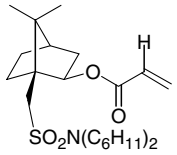
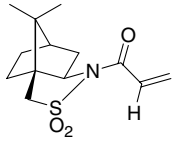
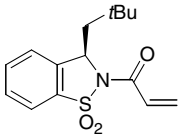
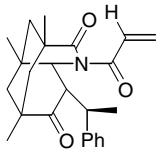
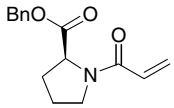
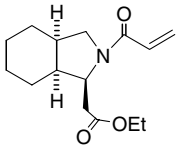
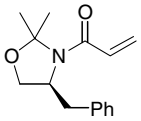

C1-C11 Fragment
C12-C18 Fragment
C19-C27 Fragment
aldol
[3 + 2]
Path A
[3 + 2]
Path B
aldol
Path C
esterification
esterification
[3 + 2]

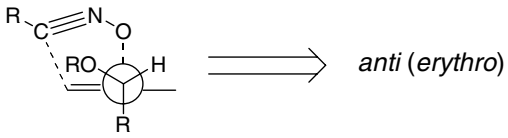
**Scheme 8.23.**

Cycloaddition of nitrile oxides to alkenes with various chiral auxiliaries are summarized in Table 8.1, which shows chiral alkenes and differential excess (de).

Compared with the related reactions of nitrones, there have only appeared a few publications of metal-assisted or metal-catalyzed 1,3-dipolar cycloadditions of nitrile oxides. This is due to

**Table 8.1. Asymmetric Induction in Nitrile Oxide (PhCNO) Cycloaddition to Optically Active Acrylates**

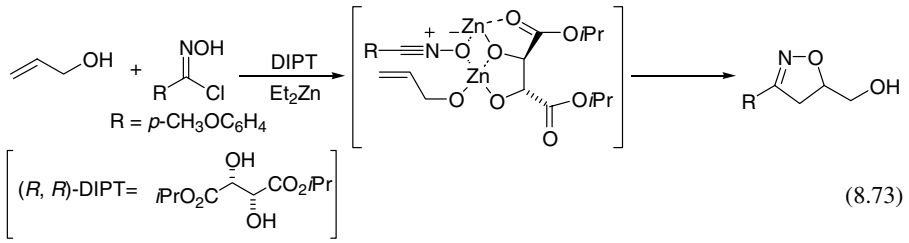
| Chiral alkene | de (%) | Ref. |
|---|---|---|
|  | 56 | 117 |
|  | 62–90 | 118 |
|  | 90 | 119 |
|  | 98 | 120 |
|  | 50 | 121 |
|  | 90 | 122 |
|  | 86 | 123 |




**Scheme 8.24.**

reactivity of nitrile oxides or the requirement of bases such as triethylamine for generation of nitrile oxides. Kanemasa and coworkers have solved some of these problems, as shown in Eq. 8.64.[99]

It has recently been found that $Et_2Zn$ promotes the 1,3-dipolar cycloaddition of nitrile oxides to allyl alcohol in the presence of catalytic amounts of diisopropyl tartrate (DIPT). By this method, 2-isoxazlines are obtained in good yields and up to 96% ee (Eq. 8.73).[124a] A positive nonlinear effect (amplification of ee of the product) has been observed in this reaction. There is an excellent review on positive and negative nonlinear effects in asymmetric induction.[124b]

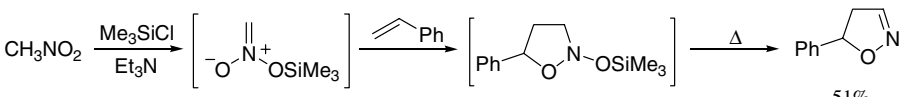



(8.73)

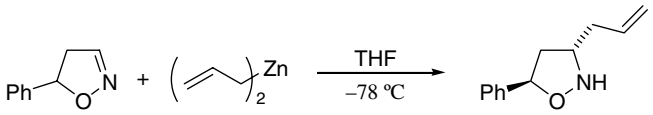
### 8.2.3 Nitronates

Alkyl and silyl nitronates are, in principle, *N*-alkoxy and *N*-silyloxynitrones, and they can react with alkenes in 1,3-dipolar cycloadditions to form *N*-alkoxy- or *N*-silyloxyisoxazolidine (see Scheme 8.25). The alkoxy and silyloxy groups can be eliminated from the adduct on heating or by acid treatment to form 2-isoxazolines. It should be noticed that isoxazolines are also obtained by the reaction of nitrile oxides with alkenes; thus, nitronates can be considered as synthetic equivalents of nitrile oxides. Since the pioneering work by Torssell et al. on the development of silyl nitronates, this type of reaction has become a useful synthetic tool. Recent development for generation of cyclic nitronates by hetero Diels-Alder reactions of nitroalkenes is discussed in Section 8.3.

A series of 3-substituted-2-isoxazoles are prepared by the following simple procedure; in situ conversion of nitroalkane to the silyl nitronate is followed by 1,3-dipolar cycloaddition to produce the adduct, which undergoes thermal elimination during distillation to furnish the isoxazole (Eq. 8.74).[125] Isoxazoles are useful synthetic intermediates (discussed in the chapter on nitrile oxides Section 8.2.2). Furthermore, the nucleophilic addition to the C=N bond leads to new heterocyclic systems. For example, the addition of diallyl zinc to 5-aryl-4,5-dihydroisoxazole occurs with high diastereoselectivity (Eq. 8.75).[126] Numerous synthetic applications of 1,3-dipolar cycloaddition of nitronates are summarized in work by Torssell and coworker.[63a]

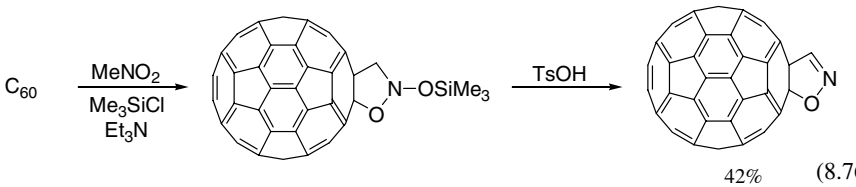



51%
(8.74)



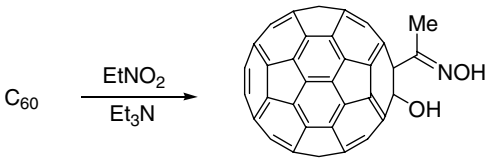

72% (ds = 6.9:1) (8.75)

Eguchi and Ohno have used silyl nitronate induced 1,3-dipolar cycloaddition for functionalization of fullerene $C_{60}$ (Eq. 8.76).[127a] Nitrile oxides also undergo 1,3-dipolar cycloaddition to $C_{60}$.[127b]



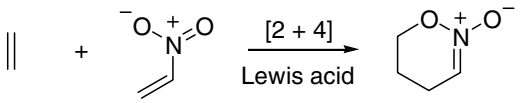

42% (8.76)

Nitroethane undergoes base-catalyzed addition to $C_{60}$ to give 2-hydroxy-1,2-dihydrofulleryl ketoxime by way of a unique intramolecular redox process, which is not observed in normal electron deficient alkenes (Eq. 8.77).[128] (See Section 4.3 Michael addition of nitroalkanes).




46% (8.77)

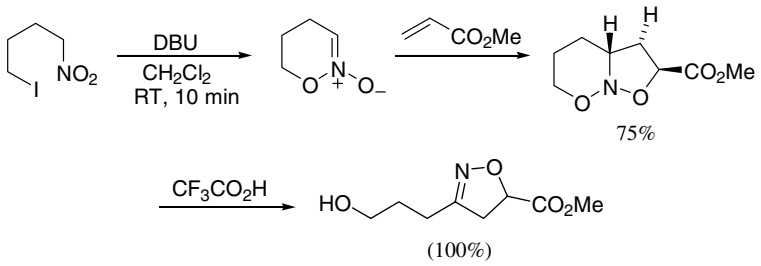
Denmark and coworkers have developed an elegant method for generating cyclic nitronates using nitroalkenes as heterodienes in the Diels-Alder reaction (Eq. 8.78). The synthetic utility of this reaction is discussed in Section 8.3.



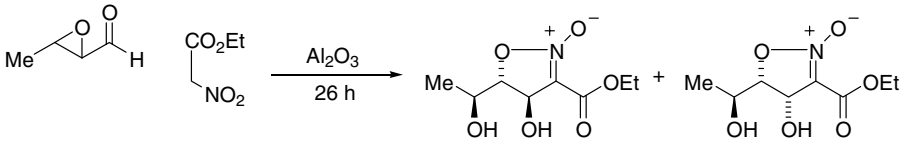

(8.78)

Recently, Kanemasa and coworkers found a new method for preparing cyclic nitronates. ω-Halo-α-nitropropane and -butane are cyclized with base to form cyclic nitronates which are labile 1,3-dipoles. They can be trapped by a variety of monosubstituted ethenes to give the corresponding adducts (Eq. 8.79).[129a] The N–O bonds in adducts are cleaved on treatment with acid to give functionalized isoxazeles. Cyclic nitronates are also prepared by intramolecular O-alkylation of ω-nitro alcohols via Mitsunobu condensation using triphenylphosphine and diethyl azodicarboxylate.[128b]

Another approach to cyclic nitronates has been developed by Rosini et al. in which nitro-aldol and subsequent cyclization is used as a key step. For example, 2,3-epoxy aldehydes react with ethyl nitroacetate on alumina surface in the absence of solvent to give 4-hydroxyisoxazoline 2-oxides in good yields (Eq. 8.80).[130]

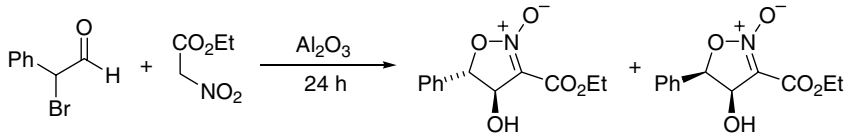



(8.79)



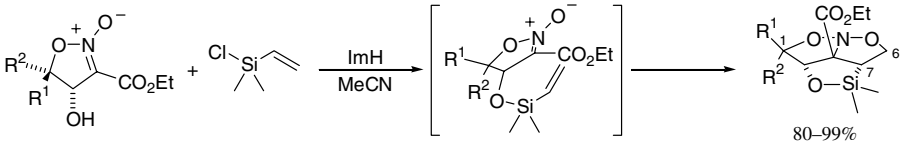

(8.80)

Treatment of 2-bromo aldehydes and ethyl nitroacetate with alumina gives 4-hydroxy-2-isoxazoline-2-oxides with high stereoselectivity (Eq. 8.81).[131]



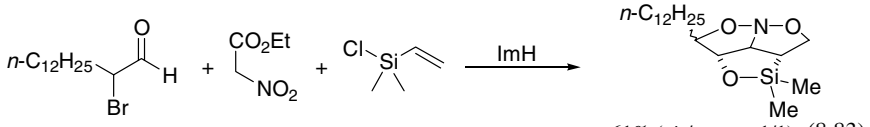

(8.81)

The products shown in Eqs. 8.80 and 8.81 are good precursors for biologically important compounds such as polyhydroxylated amino acids, aminopolyols, and amino sugars. Furthermore, 4-hydroxy-2-isoxazoline 2-oxides can be converted into tricyclic compounds via silicon-tethered 1,3-dipolar cycloaddition reactions, as shown in Eq. 8.82.[132] The temporary silicon connection methodology gives rise to the regio- and stereoselective formation of new bonds by temporarily linking together the two reactants by means of an eventually removable silicon atom.[133] This strategy is very useful for the control of stereochemistry in cycloaddition reactions (also see Section 8.3).



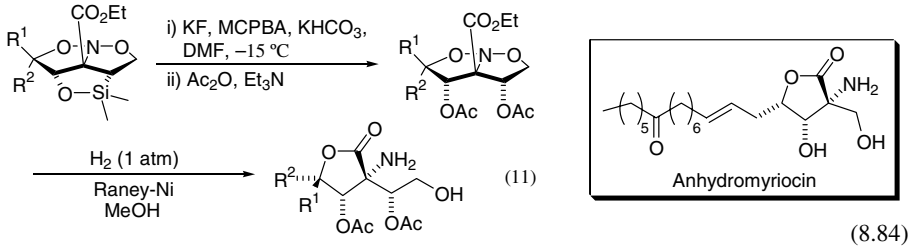

(8.82)

One-pot multi-bond-forming reactions are one of the ways to address the ever growing demand for efficiency in organic synthesis. Rosini and coworkers have developed (tandem) processes for the synthesis of a highly functionalized tricyclic system. The reaction is simply performed by bringing together, at room temperature, α-bromo aldehydes, ethyl nitroacetate, and chlorodimethylvinylsilane in the presence of imidazole as the base (Eq. 8.83).[134]



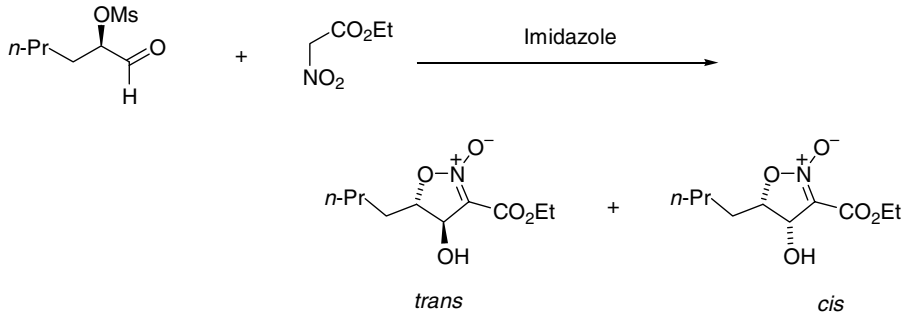

61% (*cis*/*trans* = 1/1) (8.83)

The cleavage of the tricyclic structure such as the product presented in Eq. 8.83 leads to a linear aminopolyhydroxylated structure (Scheme 8.25).[135] Two-step unfolding (silyl ether hydroxydesilylation/nitroso acetal hydrogenolysis) can be useful in the preparation of hydroxylated amino acids (Eq. 8.84).




(8.84)

The present tandem nitro aldol-cyclization process is used for the preparation of the enantiomerically pure 4-hydroxy-2-isoxazoline-2-ones. They are prepared starting from chiral α-mesyloxy aldehydes and ethyl nitroacetate under mild reaction conditions (Eq. 8.85).[136]

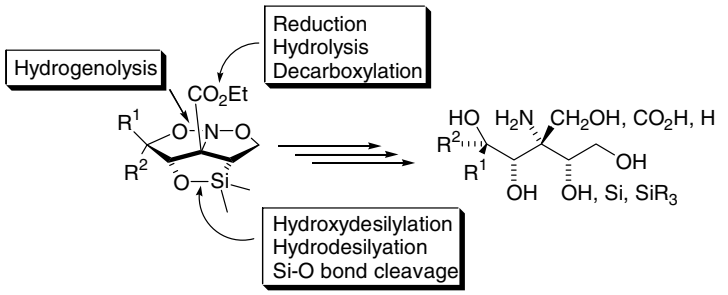



93% (*trans*/*cis* = 43/57)

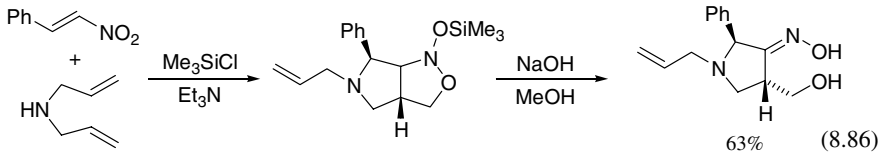
(8.85)

Hassner and coworkers have developed a one-pot tandem consecutive 1,4-addition intramolecular cycloaddition strategy for the construction of five- and six-membered heterocycles and carbocycles. Because nitroalkenes are good Michael acceptors for carbon, sulfur, oxygen, and nitrogen nucleophiles (see Section 4.1 on the Michael reaction), subsequent intramolecular silyl nitronate cycloaddition (ISOC) or intramolecular nitrile oxide cycloaddition (INOC) provides one-pot synthesis of fused isoxazolines (Scheme 8.26). The ISOC route is generally better than INOC route regarding stereoselectivity and generality.

Michael additions of secondary allylamines to nitroalkenes followed by treatment with $Me_3SiCl$ and $Et_3N$ afford highly functionalized pyrrolidines via the stereoselective ISOC reaction (Eq. 8.86).[137]



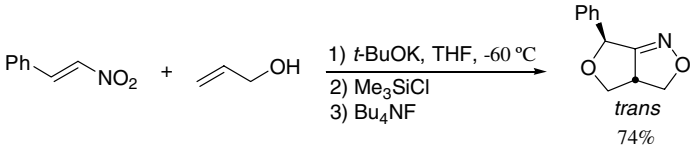

**Scheme 8.25.**



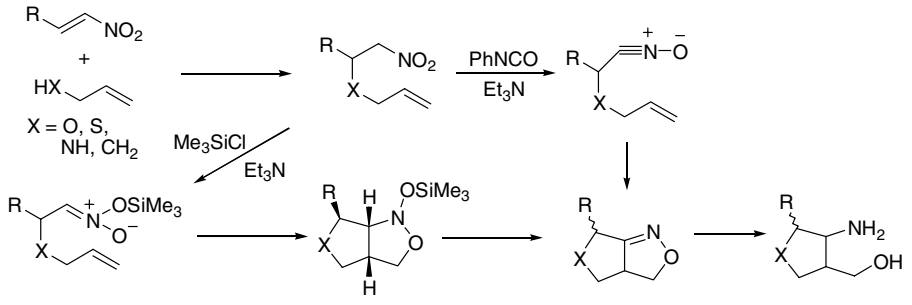

(8.86)

Scheme 8.27 presents a highly stereoselective one-pot tandem 1,4-addition-ISOC for the construction of functionalized carbocycles. Addition of Grignard reagents to nitroalkenes and subsequent ISOC are carried out in one pot. The advantages of ISOC over INOC, namely, greater stereoselectivity and adaptability to one-pot conditions, have been demonstrated in Scheme 8.27.[138]

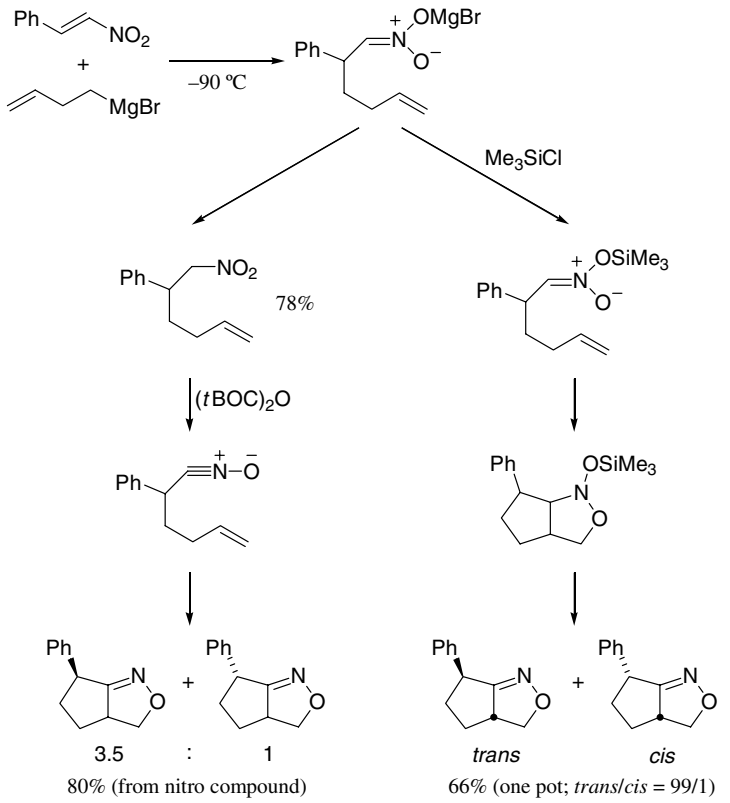
One-pot tandem reactions, starting with nitroalkenes and allyl alcohols leading to functionalized tetrahydrofurans, have been reported (Eq. 8.87).[139]




(8.87)

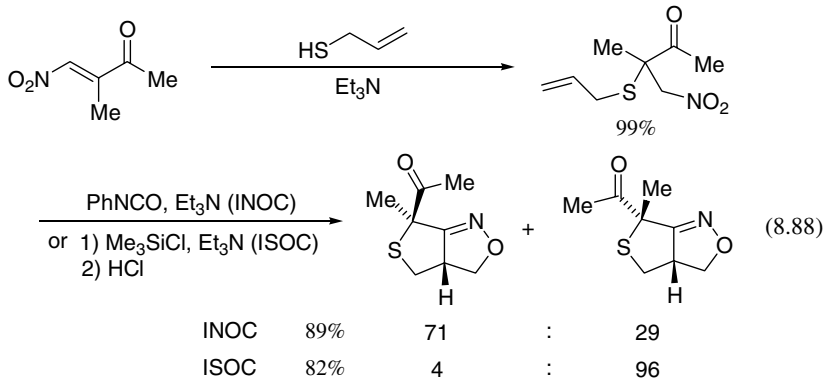



**Scheme 8.26.**



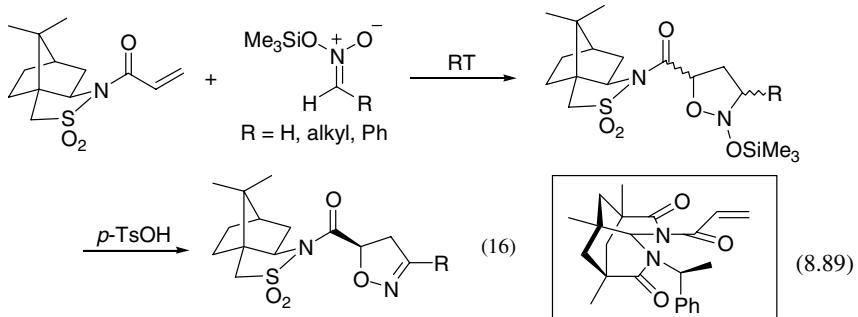

**Scheme 8.27.**

β-Nitrosulfides, formed by Michael addition of allyl mercaptan to β-nitroenones, undergo either INOC or ISOC to give tetrahydrothiopheno[3,4-c] isoxazolines. In this case, stereoselectivity of ISOC is also better than that of INOC (Eq. 8.88).[140]

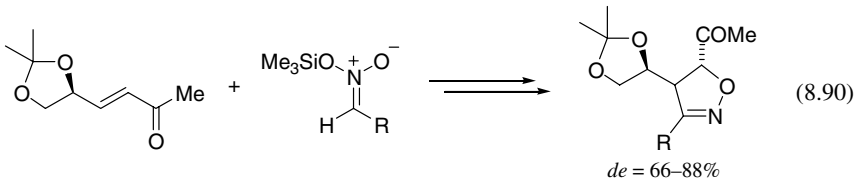



(8.88)

Asymmetric 1,3-dipolar cycloaddition of nitronates using chiral alkenes has been reported, as shown in Eq. 8.89[141,142] and Eq. 8.90.[143]

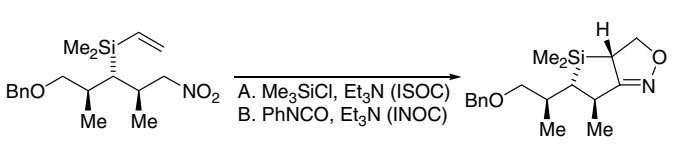



(8.89)



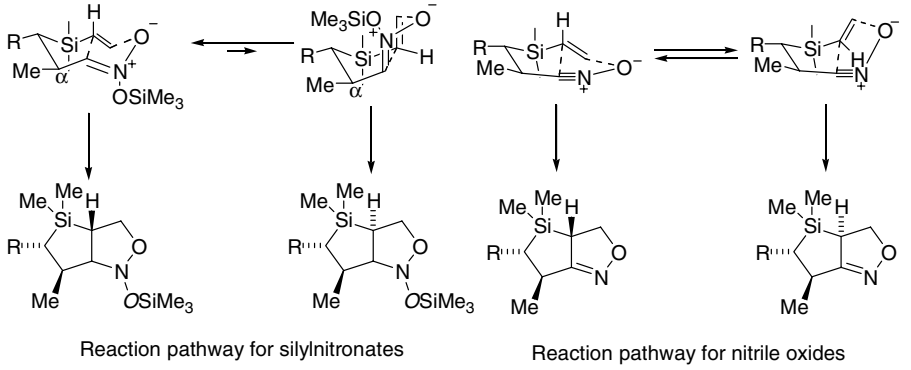

(8.90)

Recently, silicon-tethered diastereoselective ISOC reactions have been reported, in which effective control of remote acyclic asymmetry can be achieved (Eq. 8.91).[144] Whereas ISOC occur stereoselectively, INOC proceeds with significantly lower levels of diastereoselection. The reaction pathways presented in Scheme 8.28 suggest a plausible hypothesis for the observed difference of stereocontrol. The enhanced selectivity in reactions of silyl nitronates may be due to 1,3-allylic strain. The near-linear geometry of nitrile oxides precludes such differentiating elements (Scheme 8.28).



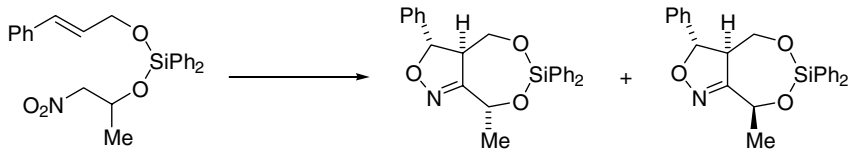

| | Stereo selectivity | Yield (%) |
|---|---|---|
| A | > 20:1 | 61 |
| B | 1:2 | 82 |

(8.91)




**Scheme 8.28.**

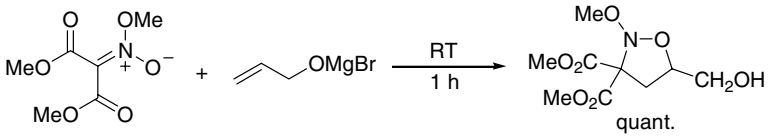
The use of silylketals derived from allylic alcohols and 1-substituted nitroethanols for the stereocontrolled synthesis of 3,4,5-trisubstituted 2-isoxazolines via intramolecular 1,3-dipolar cycloaddition has been demonstrated. Here again, the use of silyl nitronates (ISOC) increases the level of selectivity compared to INOC (Eq. 8.92).[145]




| | | | |
|---|---|---|---|
| PhNCO, $Et_3N$ | 40 | : | 60 |
| $Me_3SiCl$, $Et_3N$ | 70 | : | 30 |

(8.92)

Nitronates show a similar reactivity to that of nitrones, and nitrones are one of 1,3-dipoles that have been successfully developed to catalyzed asymmetric versions, as discussed in the section on nitrones (Section 8.2.1). However, asymmetric nitronate cycloadditions catalyzed chiral metal catalysts have not been reported. Kanemasa and coworkers have demonstrated that nitronate cycloaddition is catalyzed by Lewis acids (Eq. 8.93).[146] This may open a new way to asymmetric nitronate cycloaddition catalyzed by chiral catalysts.

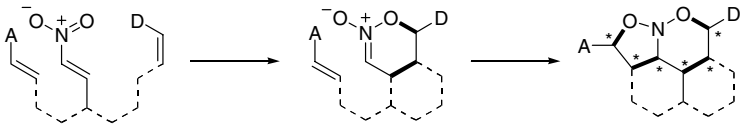



(8.93)

1,3-Dipolar addition to nitroalkenes provides a useful strategy for synthesis of various heterocycles. The [3+2] reaction of azomethine ylides and alkenes is one of the most useful methods for the preparation of pyrolines. Stereocontrolled synthesis of highly substituted proline esters via [3+2] cycloaddition between *N*-methylated azomethine ylides and nitroalkenes has been reported.[147] The stereochemistry of 1,3-dipolar cycloaddition of azomethine ylides derived from aromatic aldehydes and L-proline alkyl esters with various nitroalkenes has been reported. Cyclic and acyclic nitroalkenes add to the *anti* form of the ylide in a highly regioselective manner to give pyrrolizidine derivatives.[148]

## 8.3 NITROALKENES AS HETERODIENES IN TANDEM [4+2]/[3+2] CYCLOADDITION

Recently, Denmark and coworkers have developed a new strategy for the construction of complex molecules using tandem [4+2]/[3+2]cycloaddition of nitroalkenes.[149] In the review by Denmark, the definition of tandem reaction is described; and tandem cascade cycloadditions, tandem consecutive cycloadditions, and tandem sequential cycloadditions are also defined. The use of nitroalkenes as heterodienes leads to the development of a general, high-yielding, and stereoselective method for the synthesis of cyclic nitronates (see Section 5.2). These dipoles undergo 1,3-dipolar cycloadditions. However, synthetic applications of this process are rare in contrast to the functionally equivalent cycloadditions of nitrile oxides. This is due to the lack of general methods for the preparation of nitronates and their instability. Thus, as illustrated in Scheme 8.29, the potential for a tandem process is formulated in the combination of [4+2] cycloaddition of a donor dienophile with [3+2]cycload-

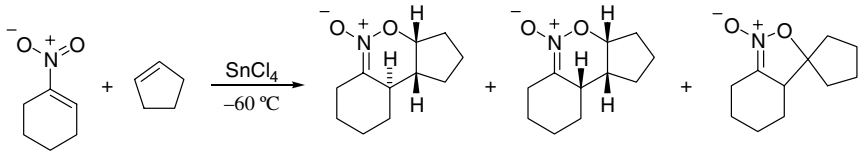


**Scheme 8.29.**

dition of an acceptor dipolarophile. The resulting tandem process can construct new bonds, up to four new rings, and up to six new stereogenic centers. Various heterocycles have been prepared by the cycloaddition using nitroalkenes as heterodienes. The historical background of the tandem [4+2]/[3+2] cycloaddition is well documented in the review.[149]

### 8.3.1 Nitroalkenes as Heterodienes

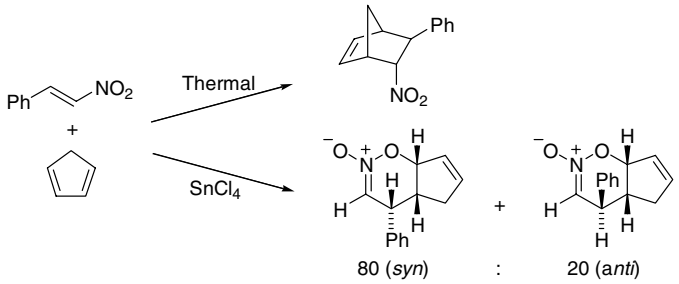
The introduction of heterodienes has extended the synthetic versatility of cycloaddition reactions in organic synthesis.[150] Denmark and coworkers have developed the use of nitroalkenes as dienes in [4+2] cycloaddition. Nitroalkenes react with simple alkenes in the presence of $SnCl_4$ as a promoter. For example, the reaction of nitrocyclohexene with cyclopentene gives three products. The major product is *anti*-isomer, which arises from an *exo* approach of cyclopentene toward nitrocyclohexene (see Eq. 8.94).[151]



24 (*anti*) : 2 (*syn*) : 1

(total yield 80%) (8.94)

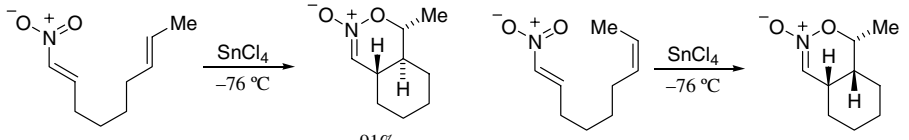
The reaction of nitrostyrene with cyclopentadiene gives the normal Diels-Alder adduct. However, the Lewis acid-catalyzed cycloaddition affords two isomeric nitronates, *syn* and *anti* in an 80-to-20 ratio. The major isomer is derived from an *endo* transition state. The preference of *syn*-fused cycloadducts can be understood by considering secondary orbital interactions (Eq. 8.95).[152]



80 (*syn*) : 20 (*anti*)

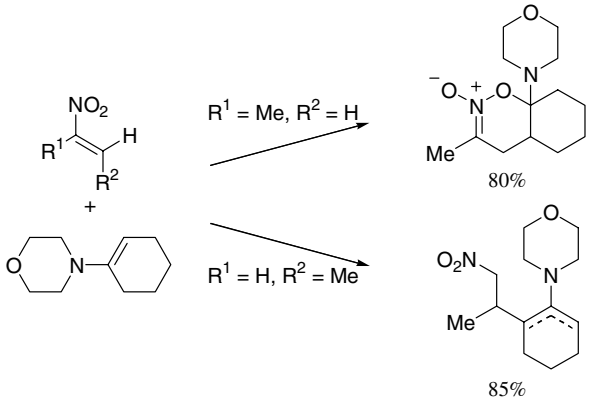
(total yield 66%) (8.95)

Intramolecular [4+2] cycloaddition of *E,E*- or *E,Z*-nitrodienes gives *trans*-nitronates or *cis*-nitronates, respectively, with high stereoselectivity (Eq. 8.96).[153] These products have been converted into γ-lactones by the Nef reaction.



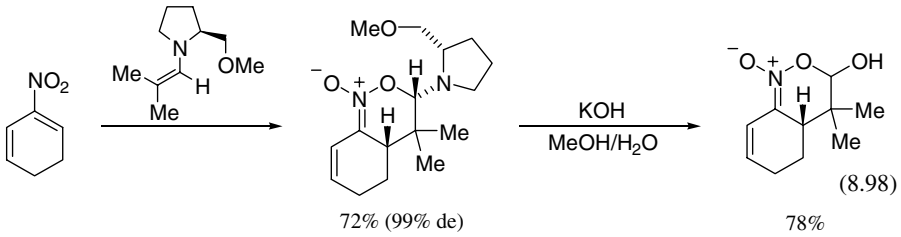

(8.96)

The powerful nucleophilicity of enamines allows the addition of nitroalkenes to take place without the presence of Lewis acids. The isolation of secondary products, which can be explained by an initial Michael addition, suggests the participation of zwitterionic intermediates in the mechanism of the reaction (Eq. 8.97).[154]



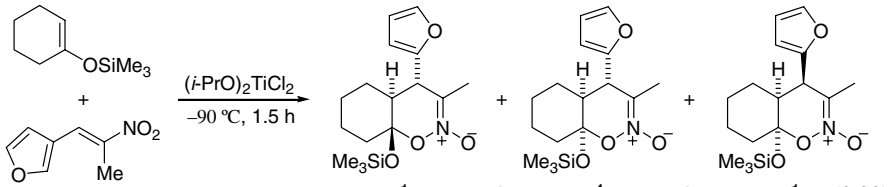

(8.97)

An interesting Diels-Alder reaction using chiral enamines is reported by Backvall, in which a cyclic nitronate is formed in good yield and excellent diastereoselectivity (Eq. 8.98).[155]



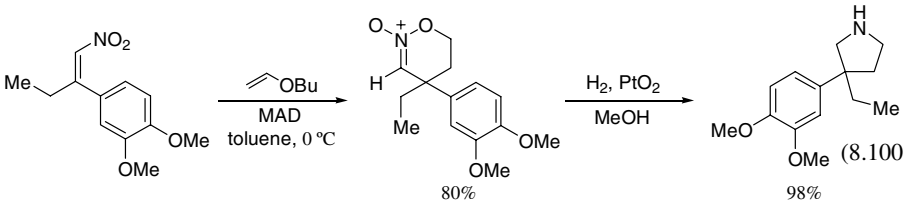

(8.98)

The use of oxygen-containing dienophiles such as enol ethers, silyl enol ethers, or ketene acetals has received considerable attention. Yoshikoshi and coworkers have developed the simple addition of silyl enol ethers to nitroalkenes. Many Lewis acids are effective in promoting the reaction, and the products are converted into 1,4-dicarbonyl compounds after hydrolysis of the adducts (see Section 4.1.3 Michael addition).[156] The trimethylsilyl enol ether of cyclohexanone reacts with nitrostyrenes in the presence of titanium dichloride diisopropoxide [Ti(O*i*-Pr)$_2$Cl$_2$], as shown in Eq. 8.99.[157] *Endo* approach (with respect to the carbocyclic ring) is favored in the presence of Ti(O*i*-Pr)$_2$Cl$_2$. Titanium tetrachloride affords the nitronates nonselectively.




(8.99)

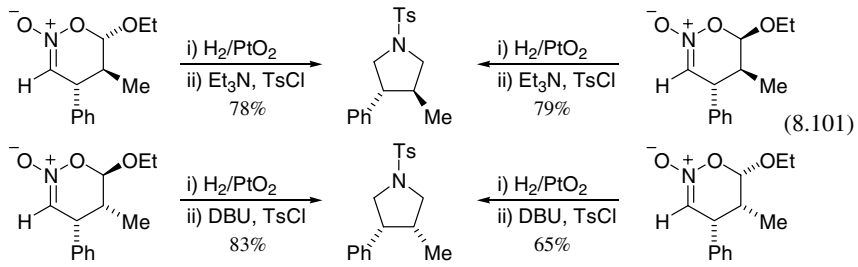
Denmark and coworkers have found that methylaluminum bis (2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) or methylaluminum bis(2,6-diphenylphenoxide) (MAPh) is effective as the Lewis acid promoter for cycloaddition of 2,2-disubstituted 1-nitroalkenes (Eq. 8.100).[158] Other Lewis acids such as $SnCl_4$, $TiCl_4$, and $TiCl_2(Oi\text{-}Pr)_2$ fail to promote the cycloaddition of 2,2-disubstituted 1-nitroalkenes. The products are converted into 3,3-disubstituted pyrrolidines via hydrogenolysis.[158] Reductive cleavage of N–O bonds produces oxime hemiacetals, which are further reduced to amido aldehydes and finally to pyrrolidines. This reaction provides a useful synthetic method for pyrrolidines, which is discussed later.



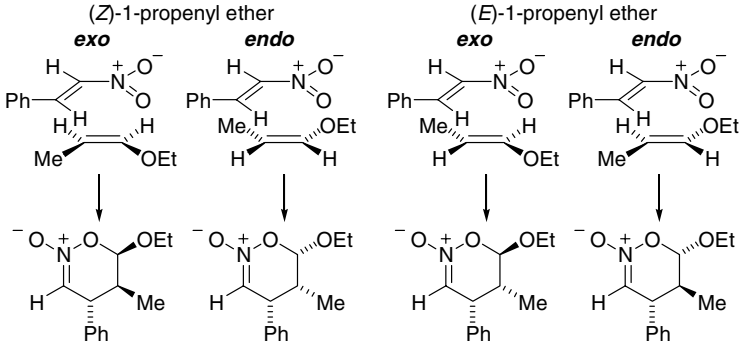

(8.100)

The mode of cycloaddition of (*E*)- and (*Z*)-1-propenyl ether with (*E*)-nitrostyrene (exo versus endo) and attendant stereostructure of the final product is dependent on the configuration of the vinyl ether and the Lewis acids employed (Scheme 8.30). Reactions conducted with $TiCl_2(O\text{-}i\text{-}Pr)_2$ produce nitronates that are enriched in isomers derived from an *endo* (EtO) approach of the dienophiles. It is believed that the transition structure of the titanium-promoted nitroalkene [4+2] cycloaddition is highly polarized, placing a partially positive charge on the nitrogen atom of the alkene. Therefore, the participating vinyl ether assumes an *endo* orientation of the electron-rich alkoxy group due to stabilizing interactions. In contrast, reactions performed using MAPh produce nitronates that are enriched in isomers derived from an *exo* approach. A preference for the *exo* orientation of a vinyl alkoxy group in nitroalkene [4+2] cycloaddition promoted by MAPh is the general trend. It is believed that the bulk of the aluminum-based Lewis acid forces the alkoxy group to take up an *exo* orientation to minimize nonbonded interactions.

Hydrogenolysis of the individual nitronate diastereomers presented in Scheme 8.30 provides the corresponding *trans*- and *cis*-3,4-disubstituted pyrrolidines in good yields (Eq. 8.101).[158]



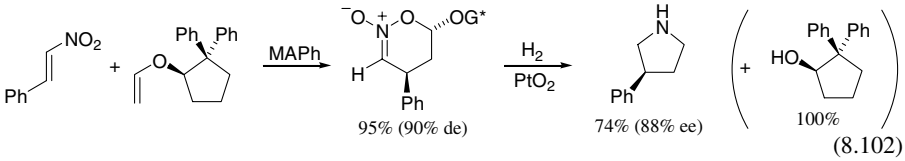

(8.101)



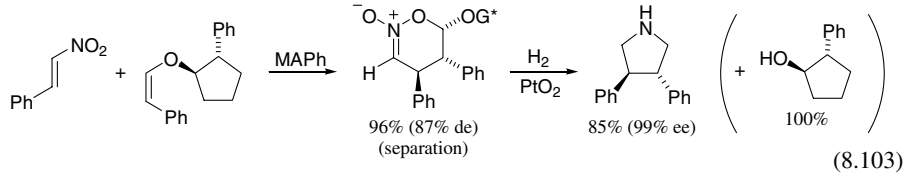

| Lewis acid (equiv) | Enol ether | Yield (%) | Ratio *exo*/*endo* | Ratio *cis*/*trans* |
|---|---|---|---|---|
| MAPh (2.0) | *E* | 88 | 58:42 | 58:42 |
| MAPh (3.0) | *Z* | 92 | 88:12 | 12:88 |
| $TiCl_2(OPr\text{-}i)_2$ (3.0) | *E* | 89 | 6:94 | 6:94 |
| $TiCl_2(OPr\text{-}i)_2$ (3.0) | *Z* | 84 | 10:90 | 90:10 |

**Scheme 8.30.**

2-Substituted 1-nitroalkenes undergo highly diastereoselective Lewis-acid-promoted [4+2] cycloadditions with chiral vinyl ethers derived from (*R*)-2,2-diphenylcyclopentanol and (1*R*, 2*S*)-2-phenylcyclohexanol to afford cyclic nitronates in high yields. The resulting nitroates are reduced with hydrogen at 160 psi in the presence of platinum oxide to afford enantiomerically enriched pyrrolidines in good yields, as shown in Eqs. 8.102 and 8.103.[159] The chiral auxiliaries are recovered in nearly quantitative yields after hydrogenation.

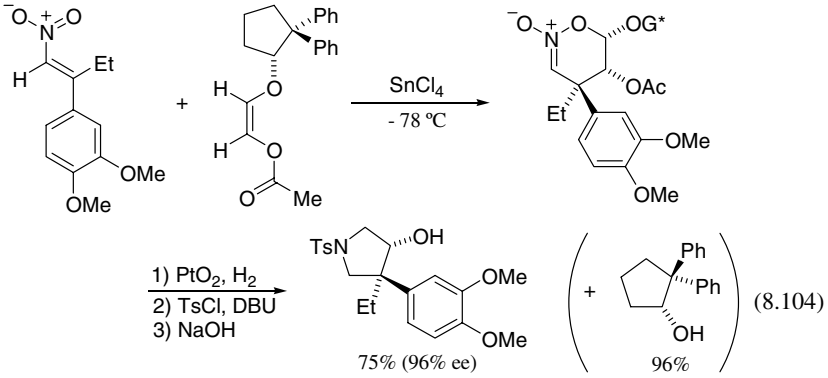



(8.102)



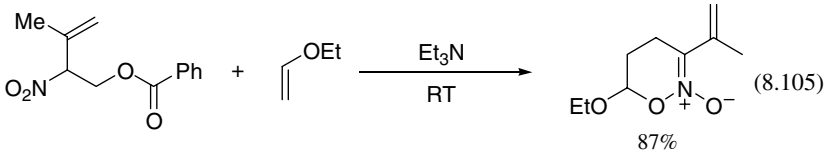

(8.103)

2-(Acyloxy)vinyl ethers undergo regioselective [4+2] cycloadditions with nitroalkenes to produce substituted 5-acetoxy nitronates in good yields. The resulting nitronates can be converted into 3-hydroxy-4-substituted-pyrrolidines by hydrogenolysis. A chiral 2-acetoxy-vinyl ether derived from (*R*)-2,2-diphenylcyclopentanol is employed in the cycloaddition-hydrogenation sequence to prepare optical active *N*-tosyl-3-hydroxypyrrolidines in 96% ee (Eq. 8.104).[160]



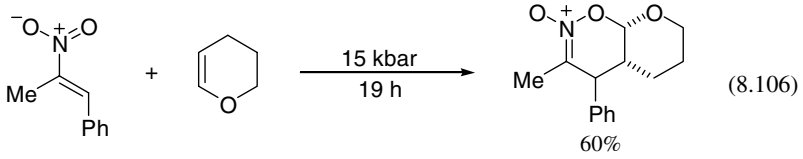

(8.104)

A few examples of cycloadditions between nitroalkenes and vinyl ethers without the use of Lewis acids have been reported (Eq. 8.105), in which additional activating electron-withdrawing groups are generally required.[161]




(8.105)

High-pressure promoted cycloadditions of nitroalkenes and enol ethers eliminate the use of Lewis acids (Eq. 8.106).[162] Thus, even sterically hindered nitroalkenes react with 2,3-dihydrofuran to give the *exo* cyclic nitronates stereoselectively without using Lewis acids.

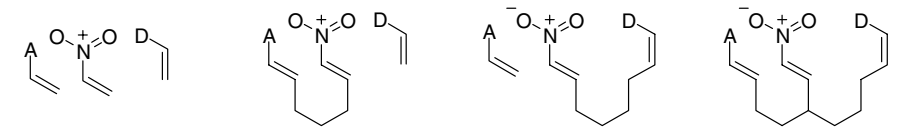



(8.106)

### 8.3.2 Tandem [4+2]/[3+2] Cycloaddition of Nitroalkenes

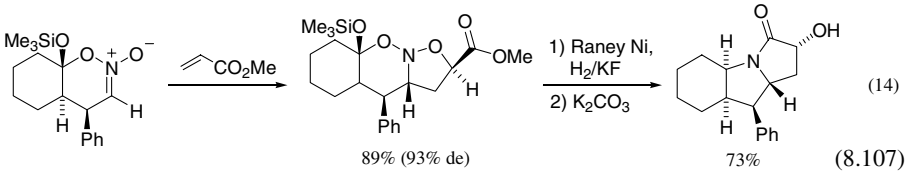
Hetero Diels-Alder reactions using nitroalkenes followed by 1,3-dipolar cycloadditions provide a useful strategy for the construction of polycyclic heterocycles, which are found in natural products. Denmark has coined the term tandem [4+2]/[3+2] cycloaddition of nitroalkenes for this type of reaction. The tandem [4+2]/[3+2] cycloaddition can be classified into four families as shown in Scheme 8.31, where A and D mean an electron acceptor and electron donor, respectively.[149] In general, electron-rich alkenes are favored as dienophiles in [4+2] cycloadditions, whereas electron-deficient alkenes are preferred as dipolarophiles in [3+2] cycloadditions.

***8.3.2.1 Inter [4+2]/inter [3+2]*** The tandem intermolecular [4+2]/intermolecular [3+2] cycloadditions create bicyclic nitroso acetals with up to six stereogenic centers, which can be controlled by the choice of the stereochemistry of each component and the Lewis acids. The nitronate derived from 2-nitrostyrene and 1-trimethylsilyloxycyclohexene reacts with methyl acrylate to give the nitroso acetal in good yield and high diastereoselectivity (Eq. 8.107).[154]



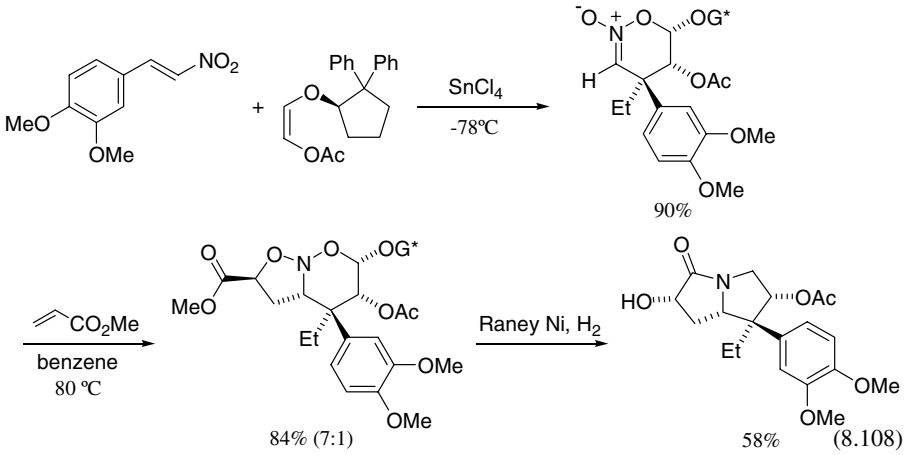

**Scheme 8.31.**

However, α-substituted dipolarophiles give poor selectivity and β-substituted dipolarophiles such as methyl crotonate fail to react.



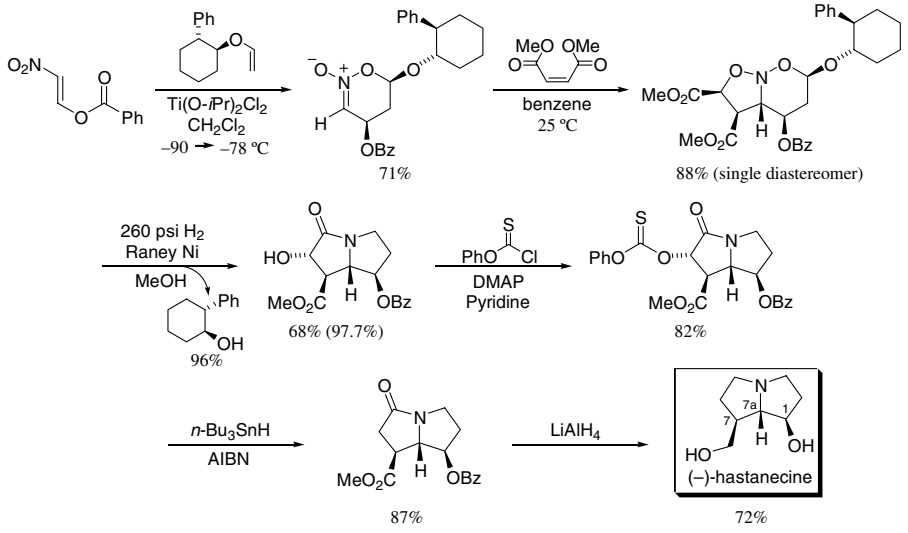

(14) (8.107)

Denmark and coworkers have succeeded in distinguishing the enantiofaces of achiral nitroalkenes using chiral dienophiles. For example, the nitronate shown in Eq. 8.108 reacts with methyl acrylate to give a nitroso acetal in a 7:1 mixture of two diastereomers. The structure of the major diastereomer arises as the result of a steric approach-controlled *exo* cycloaddition (to the face of the nitronate opposite the 3,4-dimethoxylaryl ring). Hydrogenolytic cleavage of the major nitroso acetal gives the α-hydroxy lactam in which four stereogenic centers are created with relative and absolute stereocontrol in only three steps from the simple starting materials (Eq. 8.108).[160]




(8.108)

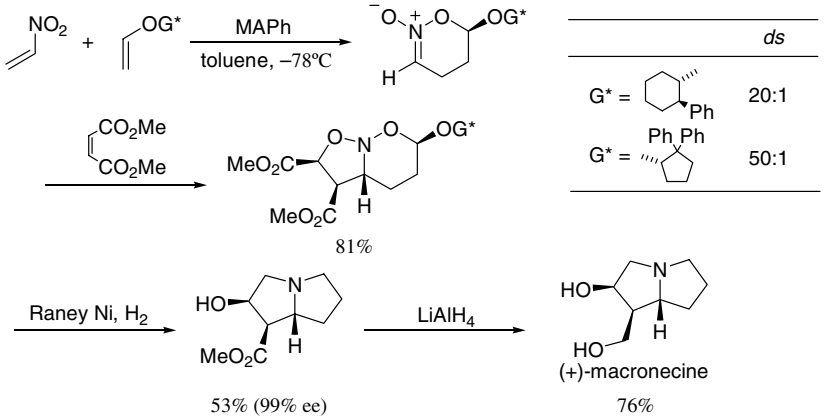
The strategy based on tandem cycloaddition leads to a short and efficient asymmetric synthesis of the pyrrolizidine necine base (–)–hastanecine, as shown in Scheme 8.32.[163] Pyrrolizidine alkaloids have a long history for attracting the interest of synthetic chemists because of their physiological properties.[164] The method of Denmark shown in this scheme is very simple and applied to synthesis of various alkaloids. The Lewis acid-promoted [4+2] cycloaddition between 2-acyloxy nitroalkene and chiral vinyl ether gives a nitronate that




**Scheme 8.32.**

undergoes simple [3+2] cycloaddition with dimethyl maleate. The resulting nitroso acetal has all the required stereocenters for (–)-hastanecine.

The simplest nitroalkene, nitroethene, undergoes Lewis acid-promoted [4+2] cycloaddition with chiral vinyl ethers to give cyclic nitronates with high diastereoselectivity. The resulting cyclic nitronates react with deficient alkenes to effect a face-selective [3+2] cycloaddition. A remote acetal center controls the stereochemistry of [3+2] cycloaddition. This strategy is applied to synthesis of the pyrrolizidine alkaloids (+)-macronecine and (+)-petasinecine (Scheme 8.33).[165]



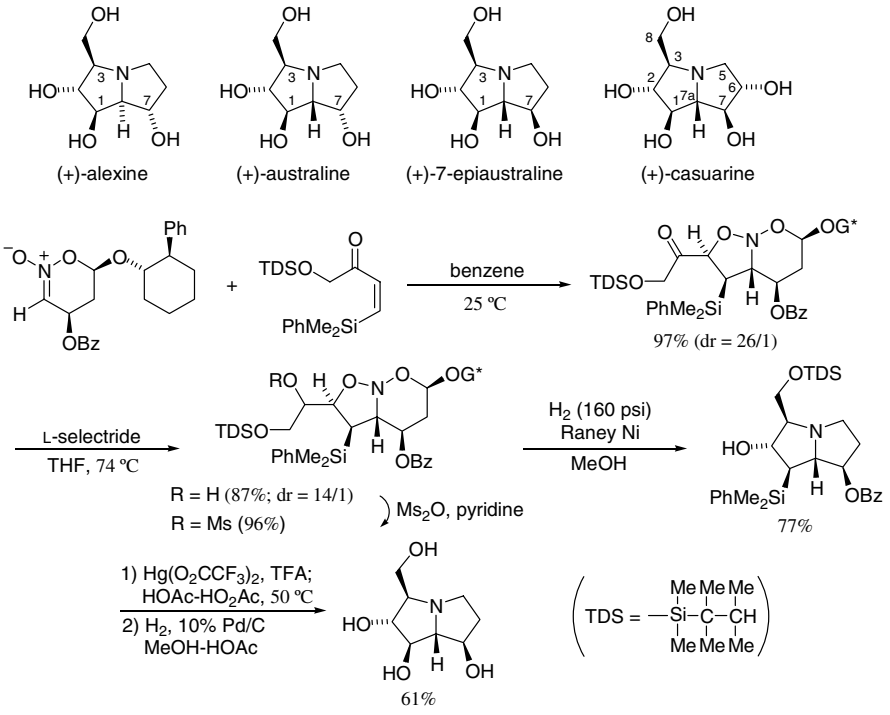

**Scheme 8.33.**

Polyhydroxy pyrrolizidine and indolizidine alkaloids display a variety of interesting biological activities. The alexines,[166] australines,[167] and casuarines[168] are a unique subset of pyrrolizidine alkaloids. The presence of a hydroxymethyl group adjacent to the ring nitrogen distinguishes this group from the larger class of necine bases. These alkaloids display glycosidase inhibitory properties[169] as well as viral and retroviral suppression characteristics.[170] To synthesize such polyhydroxy pyrrolizidines, the dipolarophile must contain the hydroxy functionality. Scheme 8.34 presents a total synthesis of (+)-7-epiaustraline, in which functionalized vinyl silane is used as a dipolarophile.[171]

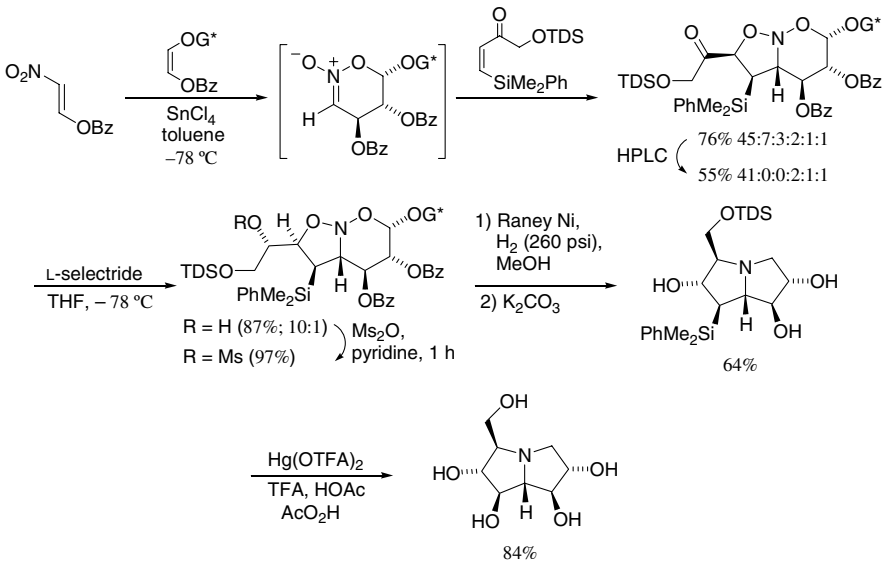
Similarly, (+)-casuraline, a pentahydroxy pyrrolizidine alkaloid, is prepared by a tandem [4+2]/[3+2] cycloaddition involving nitroalkene, chiral vinyl ether, and vinyl silane. This process creates five of the six stereocenters present in this potent glycosidase inhibitor (Scheme 8.35).[172]

Intermolecular [3+2] cycloadditions between cyclic nitronates and a series of dipolarophiles have been examined as discussed so far. In summary, remarkably high facial selectivity is observed which is attributed to a combination of steric shielding from the nitronate substituent and an inherent facial bias from the chiral conformation of the nitronate. Monosubstituted dipolarophiles provide cycloadducts with extensive head-to-head regioselectivity. Regioselectivity with disubstituted dipolarophiles varies with the substituents. With regard to the β-substituents, head-to-tail regioselectivity is favored by O>C>Si>H. Stereoselectivity is dependent on the steric nature of the dipolarophiles. The *exo* approach of dipolarophiles bearing bulky substituents is generally favorable (Scheme 8.36).[173]

High-pressure promoted tandem [4+2]/[3+2] cycloadditions of nitrostyrenes with enol ethers has been reported, which do not require the Lewis acids. The products are converted into

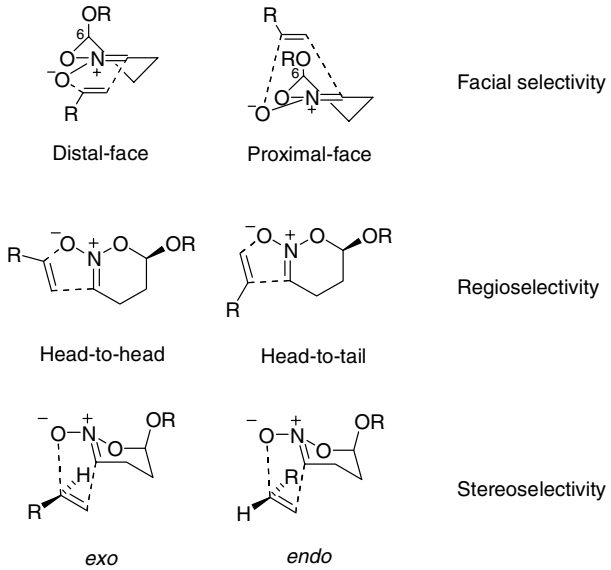



**Scheme 8.34.**

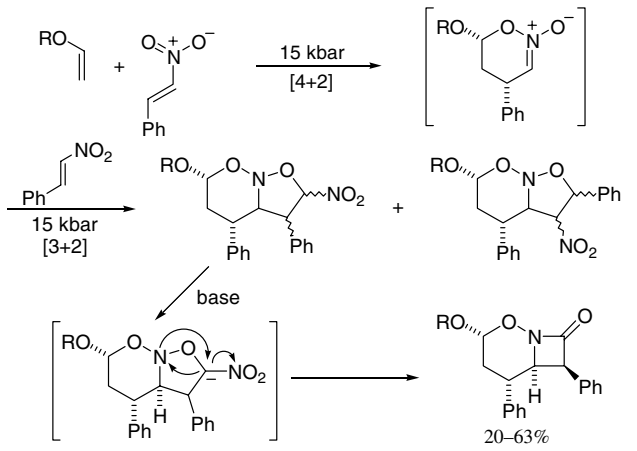



**Scheme 8.35.**

a novel class of di- and tricyclic *N*-oxy-β-lactams (Eq. 8.109).[174] High pressure is also applied to perform tandem [4+2]/[3+2] cycloaddition of enol ethers with nitrostyrene and resin-bound acrylate.[175]

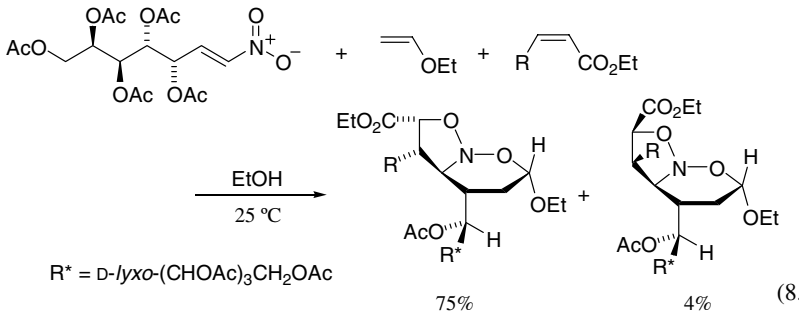



**Scheme 8.36.**



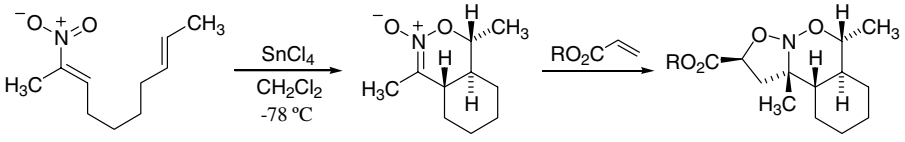

(8.109)

Asymmetric tandem cycloaddition of a chiral carbohydrate nitroalkene with ethyl vinyl ether in the presence of electron-withdrawing alkenes produces a facile assembly of bicyclic systems, which can further be selectively cleaved to give homologated carbohydrates (Eq. 8.110).[176]




(8.110)

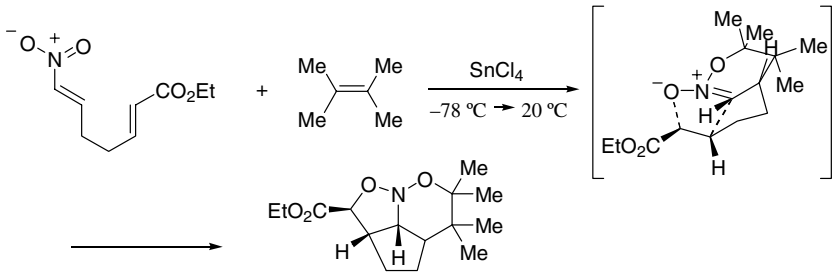
***8.3.2.2 Intra [4+2]/inter [3+2]*** This type of tandem reaction using nitroalkenes has not been extensively explored, and one example has been reported (Eq. 8.111).[153]



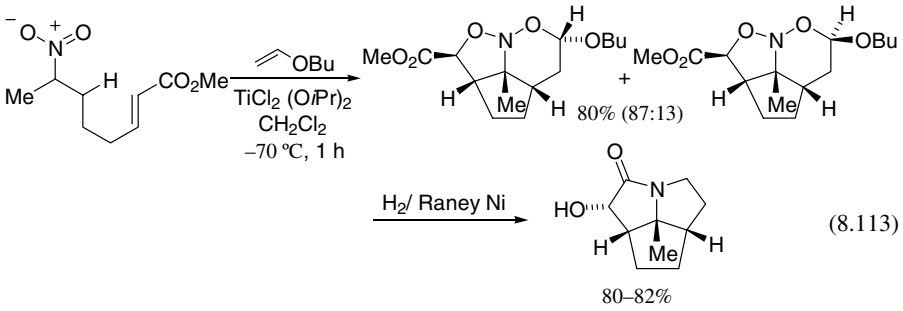

(8.111)

***8.3.2.3 Inter [4 +2]/intra [3+2]*** This type of tandem reaction using nitroalkenes has been explored most extensively. Four subfamilies of tandem cycloaddition exist, which arise from the four different points of attachment of the dipolarophilic tether. They are defined as fused, spiro, and bridged modes, as depicted in Scheme 8.37.[149]

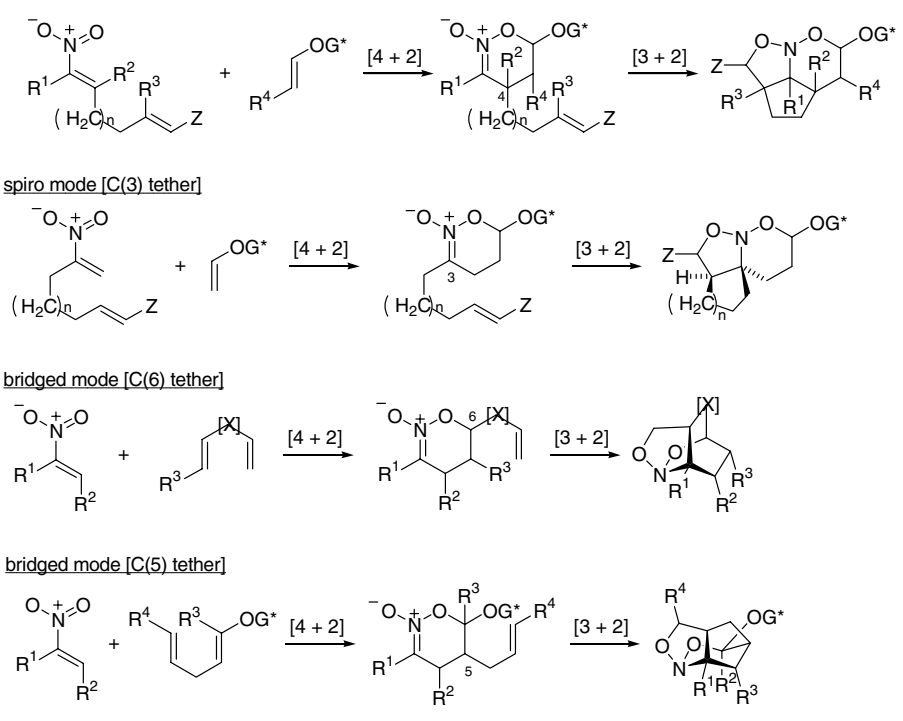
Di- and trisubstituted nitroalkenes tethered to dipolarophiles (unsaturated esters, nitriles) undergo tandem [4+2]/[3+2] cycloadditions with 2,3-dimethyl-2-butene or butyl vinyl ether in the presence of Lewis acids (Eq. 8.112). For the dimethylene tether, the *E*-configuration of the dipolarophile is preferred, and the products arise selectively from a *syn-endo* pathway.[177]




(8.112)

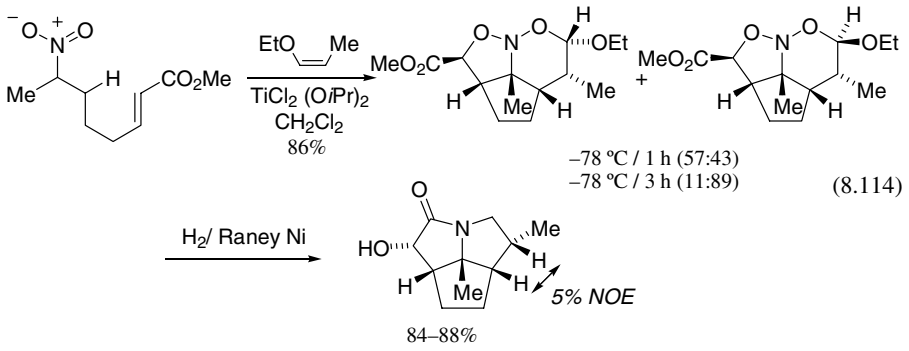



(8.113)

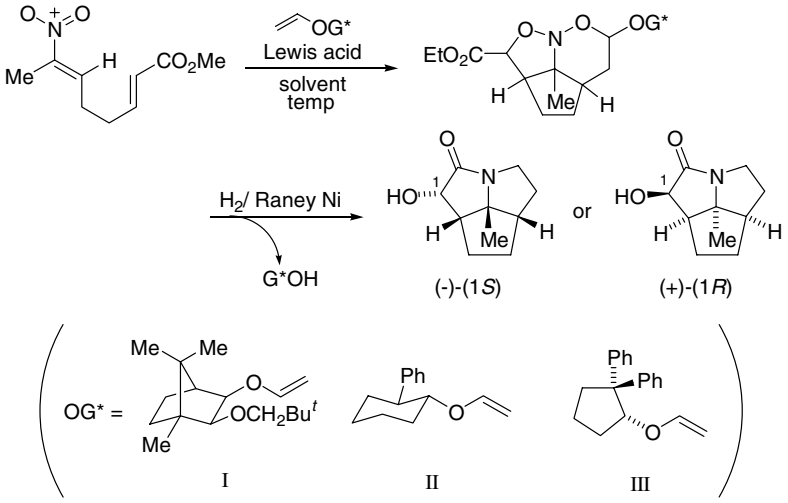



**Scheme 8.37.**

The synthetic potential of the tandem [4+2]/[3+2] cycloaddition process is greatly enhanced by the employment of vinyl ether dienophiles. For example, the use of vinyl butyl ether as a dienophile leads to a tricyclic nitroso acetal, which gives a tricyclic lactam, as shown in Eq. 8.113.

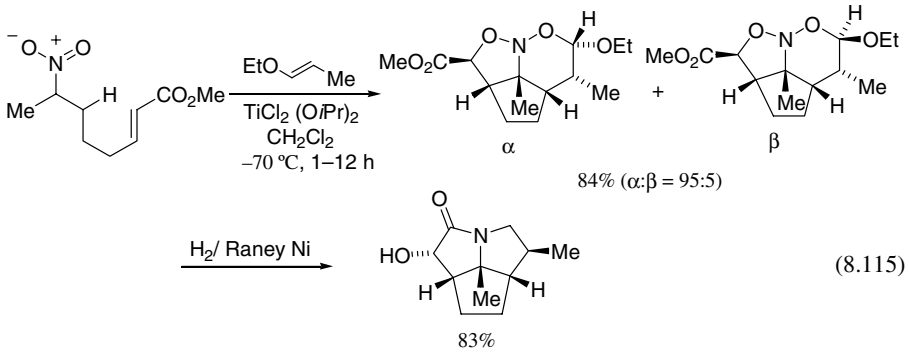



(8.114)




| Chiral vinyl ether | Lewis acid | Nitroso acetal yield (%) | Lactam yield (%) | Lactam ee (%) (config) |
|---|---|---|---|---|
| II | $Ti(OiPr)_2Cl_2$ | 73 | 76 | 98 (1*S*) |
| II | MAD | 88 | 73 | 72 (1*S*) |
| II | MAPh | 85 | 76 | 79 (1*R*) |
| I | $Ti(OiPr)_2Cl_2$ | 82 | 86 | 98 (1*S*) |
| I | MAD | 86 | 67 | 2 (1*S*) |
| I | MAPh | 83 | 88 | 99 (1*R*) |
| III | $Ti(OiPr)_2Cl_2$ | 88 | 70 | 98 (1*S*) |
| III | MAPh | 86 | 74 | 93 (1*R*) |

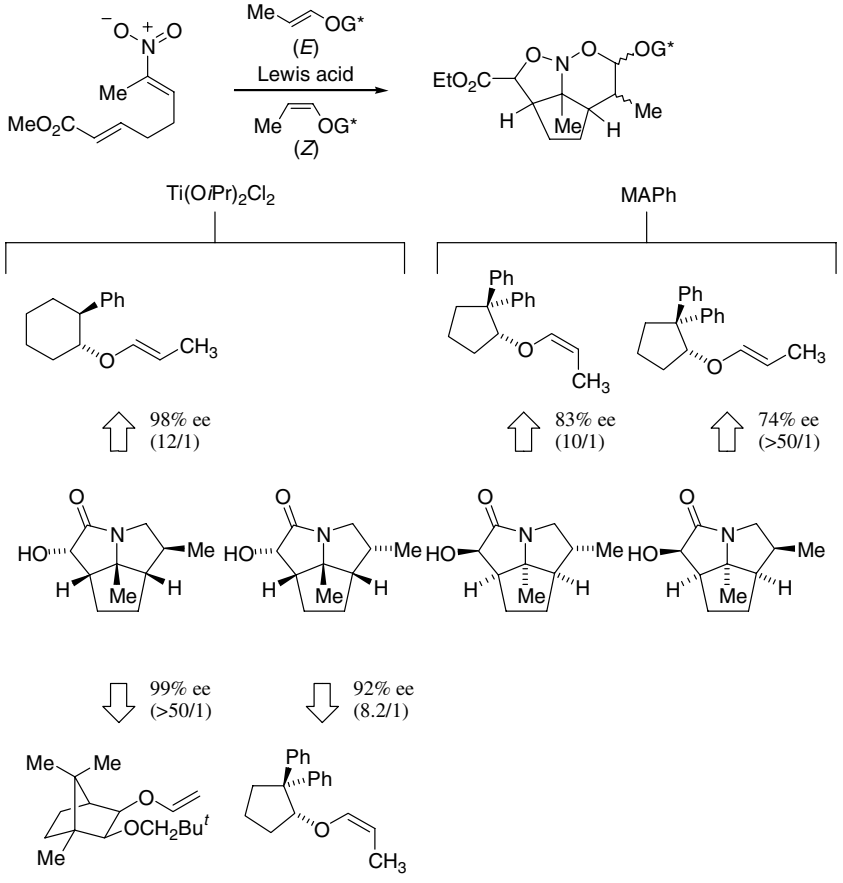
**Scheme 8.38.**




(8.115)

Two simple acyclic molecules are transformed into a single tricyclic compound bearing four contiguous stereogenic centers in high yield.[177]

Extension of this tandem process to create five contiguous stereogenic centers has been accomplished by using 2-substituted vinyl ethers (Eq. 8.114).[178] The results for the cycloaddition




**Scheme 8.39.**

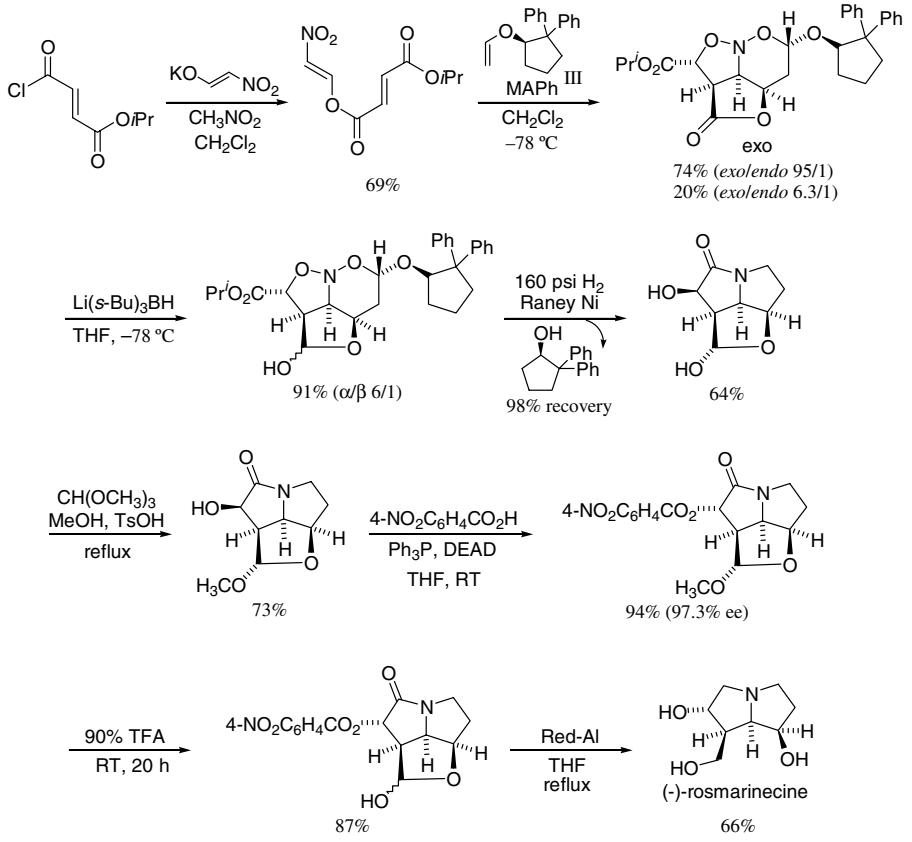
of the same nitroalkene substrate with ethyl (*Z*)-1-propenyl ether or ethyl (*E*)-1-propenyl ether are shown in Eq. 8.114 and Eq. 8.115, respectively.

The extremely high selectivity for tandem cycloaddition, the ease of manipulation of the nitroso acetals, and the release of the vinyl ether appendage in the hydrogenolytic cleavage constitute ideal features for asymmetric modifications of the cycloadditions with chiral vinyl ethers. As discussed in Section 8.3.2.1 (Inter [4+2]/inter [3+2] cycloadditions of nitroalkenes), the stereochemical course depends on the Lewis acids. The results are summarized in Scheme 8.38.[179] The high levels and complementary selectivity with three chiral vinyl ethers and two kinds of Lewis acids (Ti- and Al-based Lewis acids) are presented in this scheme.

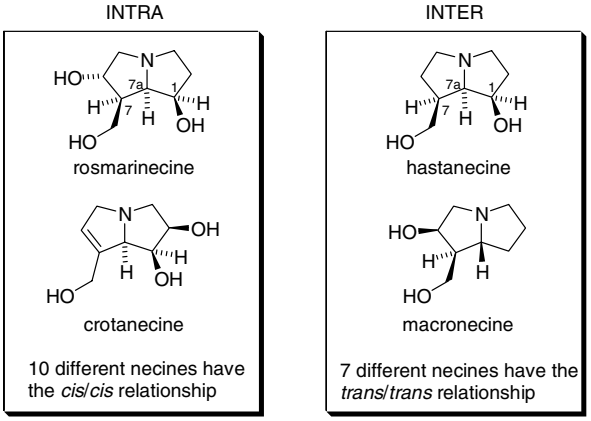
Extension of the enantioselective cycloaddition methods using chiral propenyl ethers is summarized in Scheme 8.39.[179]

The synthesis of pyrrolizidine alkaloid (–)-rosmarinecine illustrates the power of the fused mode tandem cycloaddition, as shown in Scheme 8.40.[180] The all-*cis* relationship at the three contiguous centers C(1), C(7), and C(7a) can be constructed in a single-pot reaction with correct stereochemistry but C(6) cannot.

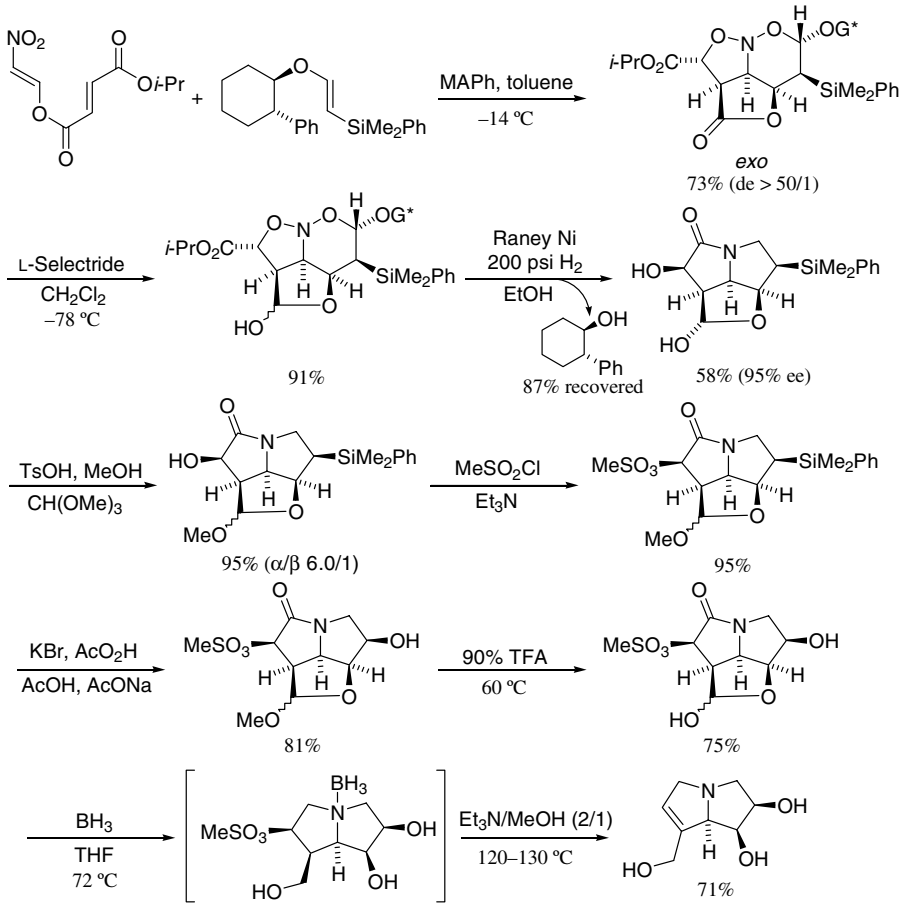
The tandem [4+2]/[3+2] cycloaddition of nitroalkenes is an extremely flexible method for the synthesis of necins. All of the stereochemical attributes are subject to a high level of



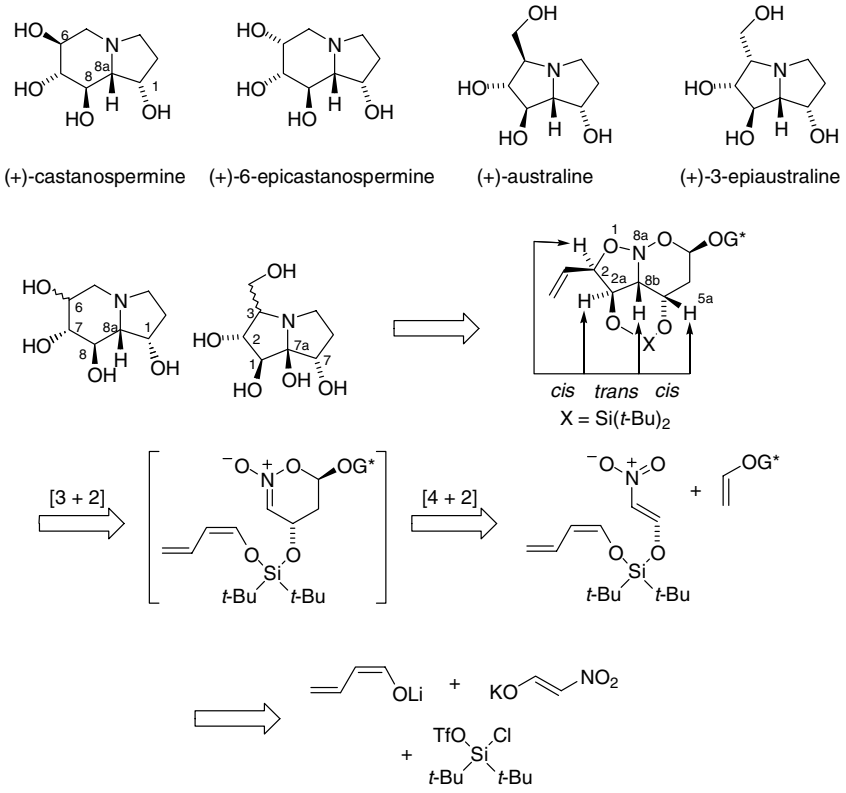

**Scheme 8.40.**




**Scheme 8.41.**




**Scheme 8.42.**

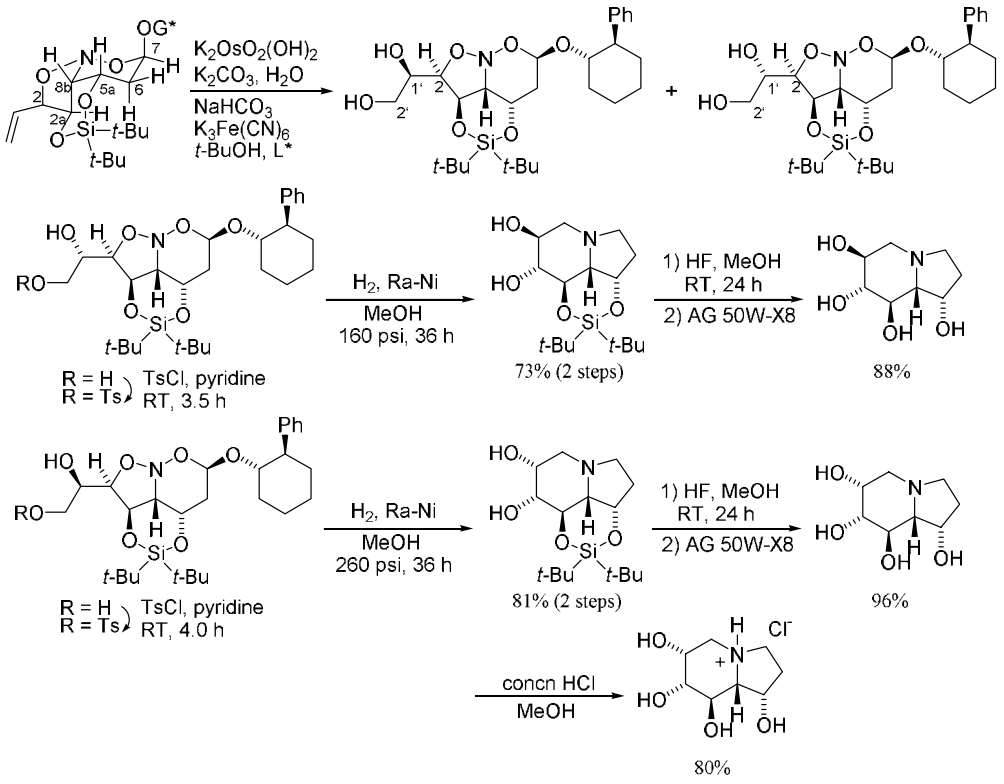



**Scheme 8.43.**

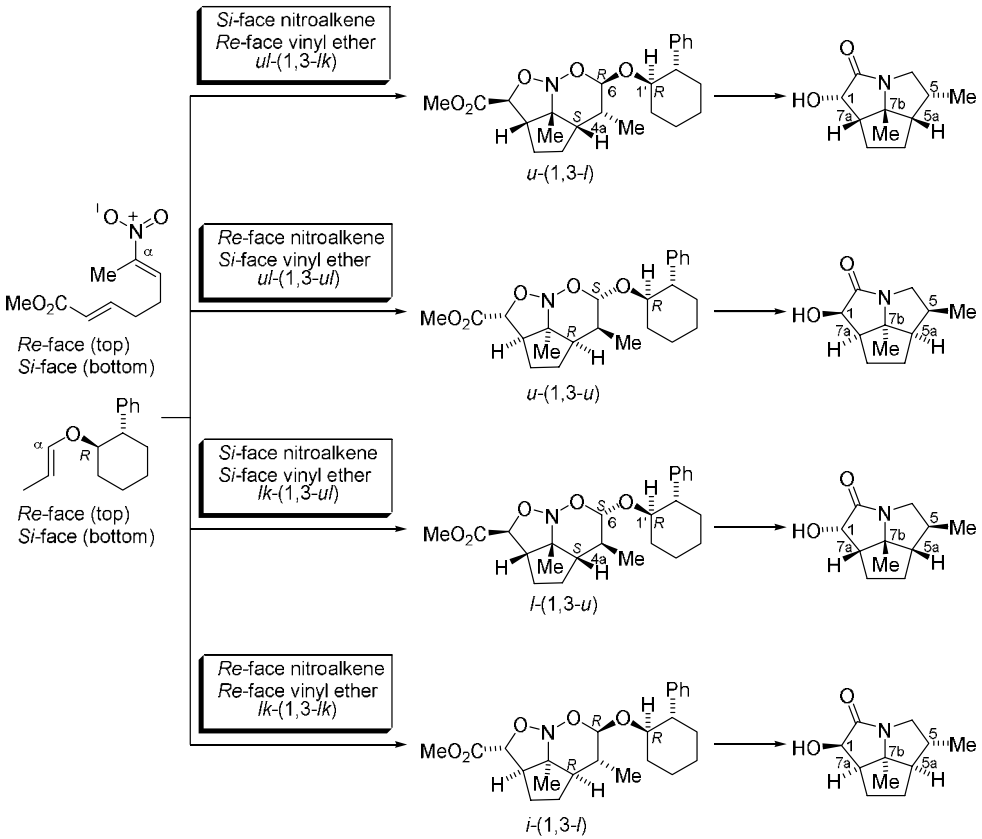
predictability and control. Furthermore, the installation of functional groups at key stereocenters can be achieved by appropriate modification of dienes and dienophiles. Finally, choice of chiral auxiliary and Lewis acid sets the absolute configuration of the molecule as a whole. There are 21 structurally 7-hydroxymethyl-substituted necines. Ten of these have the all-*cis* relationship exemplified in (–)-rosmarinecine and could arise from tandem inter [4+2]/intra [3+2] process, as shown in Scheme 8.40. Another seven necines have the all-*trans* relationship, as exemplified in (–)-hastanecine and could arise from a tandem inter [4+2]/inter [3+2] process (Scheme 8.32). Examples of different necines are classified as shown in Scheme 8.41.

The synthesis of (+)-crotanecine is accomplished in 10 steps in a 10.2% overall yield, as shown in Scheme 8.42. The key step in the asymmetric synthesis is a Lewis acid-promoted, tandem inter [4+2]/intra [3+2] cycloaddition between a (fumaroyloxy)nitroalkene and chiral β-silylvinyl ether, in which the substituted silanes are used as hydroxy synthons.[181]

The total syntheses of the potent glycosidase inhibitors (+)-castanospermine, (+)-6-epicastanosperimine, (+)-australine, and (+)-3-epiaustraline have been reported. These four natural products are derived from a single common intermediate, the nitroso acetal (as shown in Scheme 8.43), which is created in the key step by the asymmetric tandem [4+2]/[3+2] cycloaddition between silaketal nitroolefin and chiral vinyl ether.[182] The strategy of the synthesis is outlined in Scheme 8.43. Scheme 8.44 presents a total synthesis of (+)-castanosperimine and (+)-6-epicastanosperimine from the common intermediate prepared by tandem [4+2]/[3+2] cycloaddition.

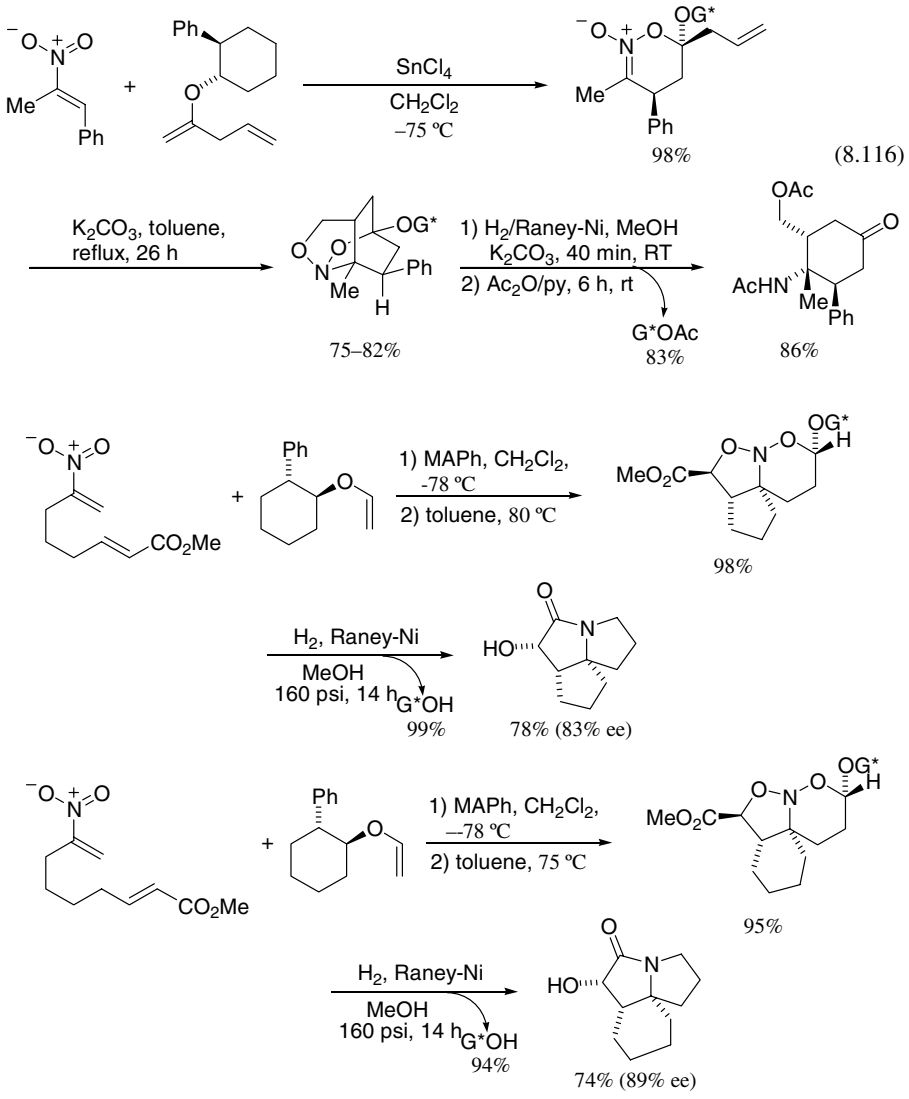

OG*
K2OsO2(OH)2
K2CO3, H2O
NaHCO3
K3Fe(CN)6
t-BuOH, L*
Ph
HO
RO
t-Bu
R = H
R = Ts
TsCl, pyridine
RT, 3.5 h
H2, Ra-Ni
MeOH
160 psi, 36 h
73% (2 steps)
1) HF, MeOH
RT, 24 h
2) AG 50W-X8
88%
TsCl, pyridine
RT, 4.0 h
260 psi, 36 h
81% (2 steps)
96%
concn HCl
MeOH
Cl-
80%

**Scheme 8.44.**

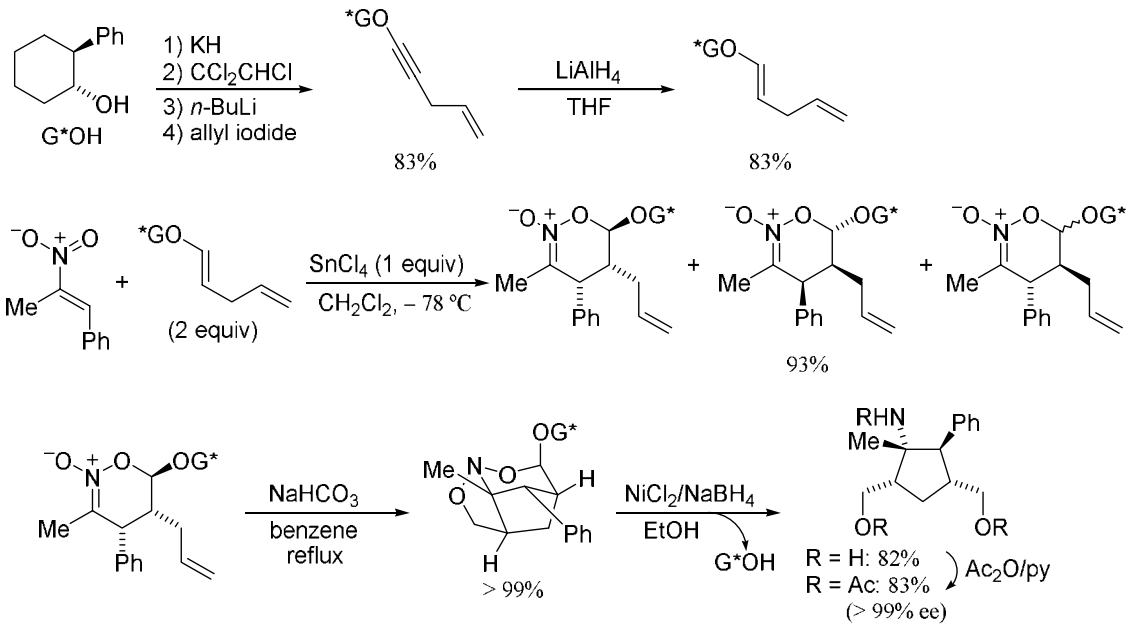

Si-face nitroalkene
Re-face vinyl ether
ul-(1,3-lk)
Re-face nitroalkene
Si-face vinyl ether
ul-(1,3-ul)
Si-face nitroalkene
Si-face vinyl ether
lk-(1,3-ul)
Re-face nitroalkene
Re-face vinyl ether
lk-(1,3-lk)
Re-face (top)
Si-face (bottom)
Re-face (top)
Si-face (bottom)
u-(1,3-l)
u-(1,3-u)
l-(1,3-u)
i-(1,3-l)

**Scheme 8.45.**

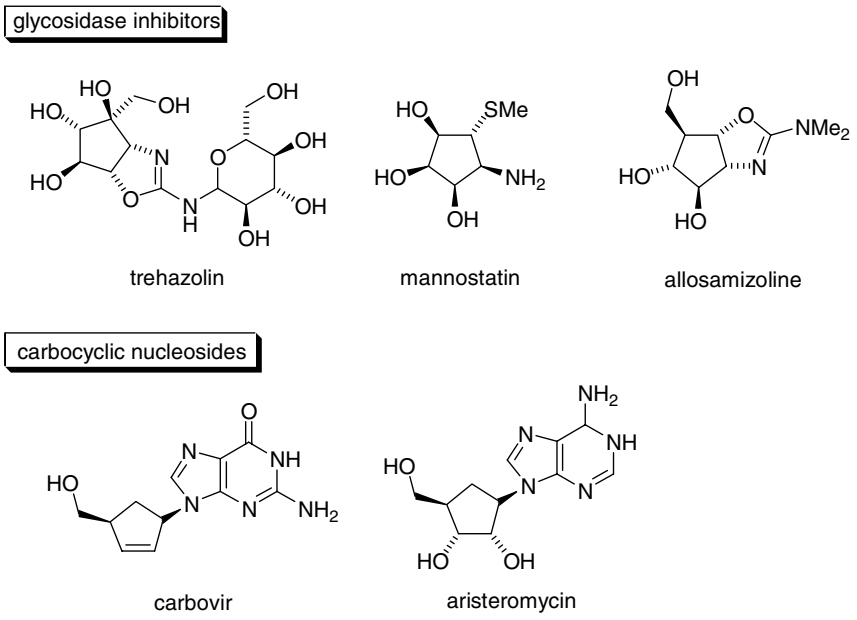
The influence of Lewis acids on the stereochemical course of the [4+2] cycloaddition of nitroalkenes and chiral propenyl ether is examined. The possible stereochemical courses are shown in Scheme 8.45. All of the Lewis acids induce the *exo* approach to favor *ul*-relative diastereoselection. Within the titanium-based Lewis acids, increasing the halide-to-alkoxide ratio increases the degree of *ul* (relative) selectivity. $TiCl_4$, $TiBr_3$(O*i*-Pr), $SnCl_4$, and ATPh are the most effective for *ul* selectivity. The internal diastereoselectivity is also dependent on the Lewis acid; most titanium isopropoxide-halides and $SnCl_4$ are highly selective for 1,3-*lk* approach, with the selectivity increasing with increasing halide content. Two aluminum-based Lewis acids are selective in the opposite sense of internal diastereoselection. The switch in internal diastereoselectivity is thought to arise from subtle changes in the steric nature of the Lewis acid-nitroalkene complex.[183]




**Scheme 8.46.**


Ph
OH
G*OH
1) KH
2) CCl2CHCl
3) n-BuLi
4) allyl iodide
*GO
83%
LiAlH4
THF
*GO
83%
Me
Ph
(2 equiv)
SnCl4 (1 equiv)
CH2Cl2, – 78 °C
OG*
93%
NaHCO3
benzene
reflux
> 99%
NiCl2/NaBH4
EtOH
G*OH
RHN
OR
R = H: 82%
R = Ac: 83%
(> 99% ee)
Ac2O/py

**Scheme 8.47.**




**Scheme 8.48.**

When α-tethered nitroalkenes bearing three or four methylene chains and ester-activated dipolarophiles react with vinyl ethers, spiro mode tandem cycloaddition takes place to give tricyclic spiro nitroso acetals in good yield and high diastereoselectivity (Scheme 8.46).[184]

The third member of the tandem inter [4+2]/intra [3+2] cycloaddition family is classified as the bridge mode, in which the dipolarophile is attached to the dienophile. Simple, 1,4-pentadienes as well as 2-alkoxy-1,4-pentadienes can function effectively as dienophiles and dipolarophile combinations with excellent chemical selectivity and regio- and diastereoselectivity. Hydrogenation of the bridged nitroso acetals produces hydroxymethylated derivatives in high diastereo- and enantioselectivity (Eq. 8.116).[185]

When 1-alkoxy-1,4-pentadienes are used instead of 2-alkoxy-1,4-pentadienes, tandem inter [4+2]/intra [3+2] cycloaddition of nitroalkenes followed by hydrogenolysis affords a versatile asymmetric synthesis of highly functionalized aminocyclopentanes (Scheme 8.47).[186]

Aminocyclopentanols comprise an important structural motif, which is common to a variety of biologically interesting compounds including glycosidase inhibitors and carbocyclic nucleosides (Scheme 8.48). Asymmetric synthesis of highly hydroxylated aminocyclopentanes using the bridged mode (β-tether) process provides a useful strategy for the synthesis of such compounds.[187]

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186b. Denmark, S. E., and J. A. Dixon. *J. Org. Chem.*, **63**, 6167 (1998).
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*The Nitro Group in Organic Synthesis.* Noboru Ono
Copyright © 2001 Wiley-VCH
ISBNs: 0-471-31611-3 (Hardback); 0-471-22448-0 (Electronic)

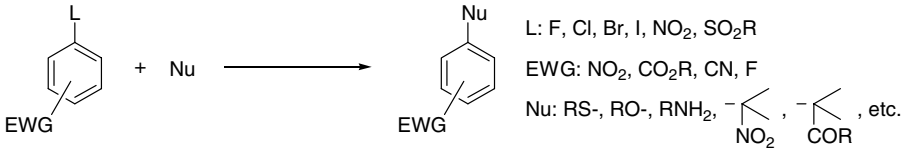
# 9

# NUCLEOPHILIC AROMATIC DISPLACEMENT

Aromatic nitro compounds undergo nucleophilic aromatic substitutions with various nucleophiles. In 1991 Terrier's book covered (1) $S_NAr$ reactions, mechanistic aspects; (2) structure and reactivity of anionic σ-complexes; (3) synthetic aspects of intermolecular $S_NAr$ substitutions; (4) intramolecular $S_NAr$ reactions; (5) vicarious nucleophilic substitutions of hydrogen (VNS); (6) nucleophilic aromatic photo-substitutions; and (7) radical nucleophilic aromatic substitutions. This chapter describes the recent development in synthetic application of $S_NAr$ and especially VNS. The environmentally friendly chemical processes are highly required in modern chemical industry. VNS reaction is an ideal process to introduce functional groups into aromatic rings because hydrogen can be substituted by nucleophiles without the need of metal catalysts.

## 9.1 $S_NAr$

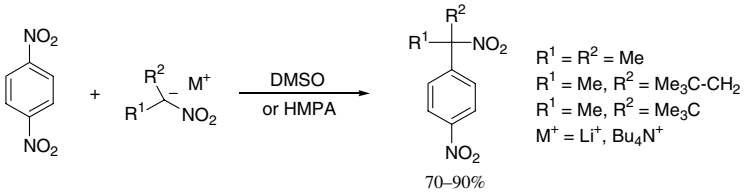
A general nucleophilic aromatic substitution ($S_NAr$) is shown in Scheme 9.1; here, Nu represents an anionic or a neutral nucleophile and L is a leaving group. Aromatic nitro compounds are most suitable for $S_NAr$ because the nitro group with its strong electron-withdrawing character activates this reaction. The nitro group shows also a high nucleofugacity, and its departure from the aromatic system frequently occurs if there is appropriate activation by other electron-withdrawing groups (Scheme 9.1). In this section, synthetically useful $S_NAr$ reactions are summarized. Other details of $S_NAr$ can be found in Ref. 1.



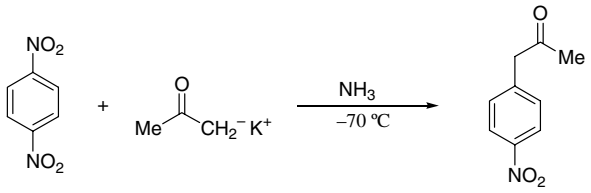

**Scheme 9.1.**

Intermolecular displacements of a nitro group from *p*-dinitrobenzene proceed very rapidly to give various substitution products. *o*-Dinitrobenzene is as reactive as *p*-dinitrobenzene, but *m*-dinitrobenzene is less reactive.

The anions derived from nitroalkanes, ketones, esters, and nitriles react with *p*-dinitrobenzene to give the corresponding products, as shown in Eq. 9.1[2] and Eq. 9.2.[3]



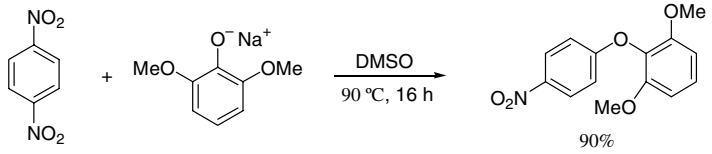

(9.1)




(9.2)

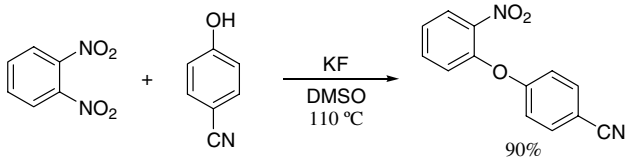
Diaryl ethers, diaryl thioethers, and diarylamines are important subunits in a number of synthetically challenging and medicinally important natural products. They are also important in the field of electronic materials. An array of macrocycles containing biaryl ether bridges exists in nature. These compounds range from the macrocyclic (+) K-13, OF4949 to the bicyclic piperazinomycin bouvardin and to the exceedingly structurally complex polycyclic glycopeptide antibiotics exemplified by vancomycin (Scheme 9.2).[4] Although the classical Ullmann ether synthesis has been used for the construction of such frameworks,[5] $S_NAr$-based reactions afford wider applications in the synthesis of such natural products.[4]

$S_NAr$ reactions also provide an important strategy for the preparation of various kinds of diaryl ethers. *p*-Dinitrobenzene reacts with even sterically hindered phenols to give the corresponding diaryl ethers (Eq. 9.3).[6]



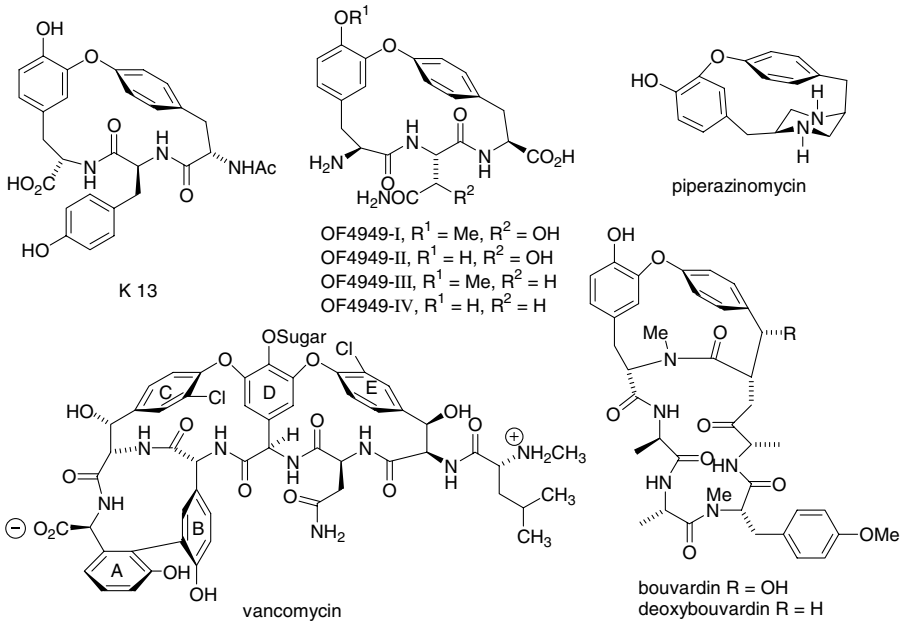

(9.3)

The reaction of *p*-cyanophenol with *o*-dinitrobenzene in the presence of KF in DMSO gives the corresponding diaryl ether in 95% yield (Eq. 9.4).[7]

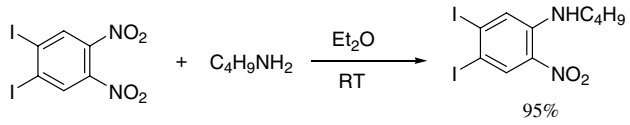



(9.4)

$S_NAr$ substitutions of activated aromatic halides, especially aromatic fluorides, provide useful means for the construction of aromatic diethers or amines. Primary and secondary amines react with 1,2-dihalo-4,5-dinitrobenzene to give nitro group substitution at room temperature. The halogen substituents on the ring remain unsubstituted and can be used in further transformation (Eq. 9.5).[8]

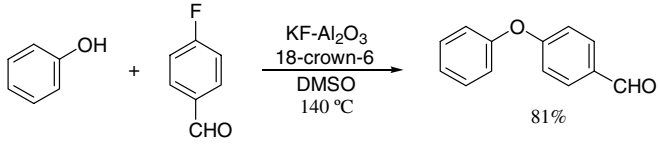



**Scheme 9.2.**

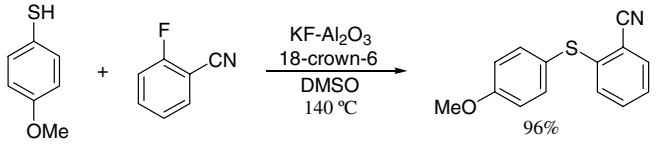



(9.5)

Sawyer and coworkers have developed an efficient alternative Ullmann synthesis of diaryl ethers, diaryl thioethers, and diarylamines using the $S_NAr$ reaction. Phenol, thiophenol, or aniline reacts with an appropriate aryl halide, in the presence of KF-alumina and 18-crown-6 in acetonitrile or DMSO to give the corresponding diaryl ether or diaryl thioether as shown in Eqs. 9.6 and 9.7.[9a]



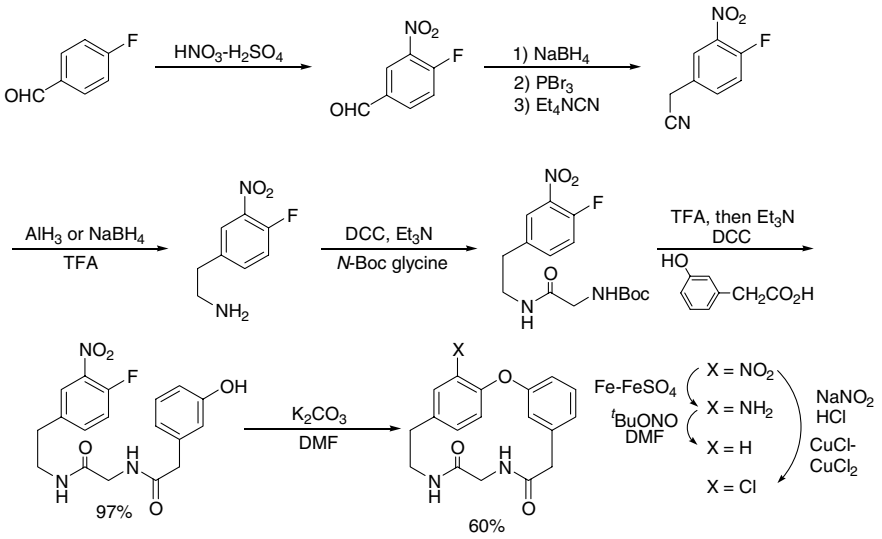

(9.6)



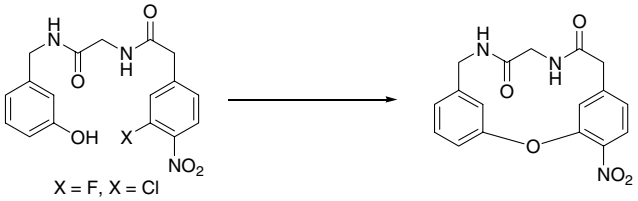

(9.7)

Zhu and coworkers have developed $S_NAr$-based macrocyclization via biaryl ether formation.[4] The first example of $S_NAr$-based macrocyclization for synthesis of model carboxylate-binding pocket C-O-D rings of vancomycin was reported in 1994 (Scheme 9.3).[10]

To study generality of $S_NAr$-based macrocyclization, effects of leaving groups and bases have been examined in synthesis of 14-membered macrocycles (Eq. 9.8).[11] Evidently, fluorides




**Scheme 9.3.**



X = F, X = Cl (9.8)

X = F

| Entry | Base (equiv) | Additive | Temperature, time | Yield (%) |
|---|---|---|---|---|
| 1 | $K_2CO_3$ (3) | no | RT, 20 h | 66 |
| 2 | CsF (5) | no | RT, 20 h | 62 |
| 3 | $K_2CO_3$ (3) | 18-crown-6 | RT, 6 h | 82 |
| 4 | $Li_2CO_3$ (30) | no | RT, 4 days | No reaction |
| 5 | $NaHCO_3$ (3) | no | RT, 2 days | Trace |

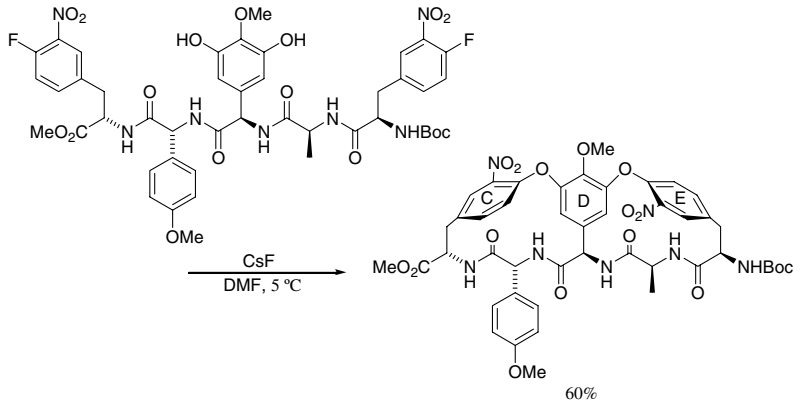
X = Cl

| Entry | Base (equiv) | Additive | Temperature, time | Yield (%) |
|---|---|---|---|---|
| 6 | $K_2CO_3$ (3) | no | RT, 2 days | No reaction |
| 7 | $K_2CO_3$ (3) | no | 40 °C, 24 h | Degradation |
| 8 | $K_2CO_3$ (3) | 18-crown-6 | RT, 2 days | Degradation |
| 9 | $K_2CO_3$ (3) | no | 80 °C, 6 h | 80 |

All reactions were run in dry DMF at a concentration of 0.01 M.

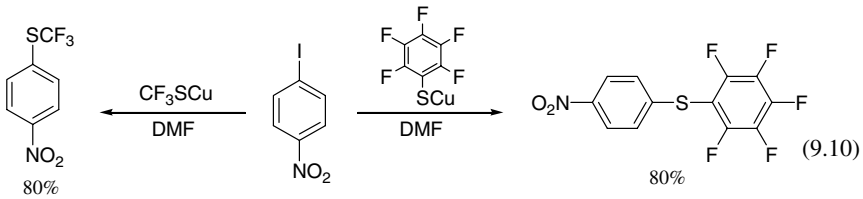
show better reactivity than the corresponding chlorides. Although chlorides are more readily prepared than the corresponding fluorides, the use of the fluorides is recommended for these cyclizations.

Double intramolecular $S_NAr$ reaction leads to a model bicyclic C-O-D-O-E ring, as shown in Eq. 9.9.[12] Synthesis of a model 22-membered AB-C-O-D ring of vancomycin using similar strategy has been reported.[13] Total synthesis of vancomycin has been accomplished by Nicolaou and coworkers.[14]




60% (9.9)

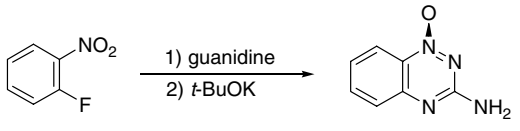
Aromatic fluoro compounds are prepared by the reaction of aromatic nitro compounds with metal fluorides in good yields.[15] Trifluoromethylthio and pentafluorophenylthio copper reagents are readily prepared by the reaction of the corresponding disulfides with copper in DMF. They react with nitro aromatic iodides to give the corresponding sulfides in good yields (Eq. 9.10).[16] The reaction of silver trifluoromethanethiolate with KI in acetonitrile leads to the formation of a nucleophilic reagent of trifluoromethanethiolate. This reagent is capable of converting fluoro-, chloro-, bromo-, and iodoaromatics into the corresponding trifluoromethyl aryl sulfides under mild conditions.[16b]



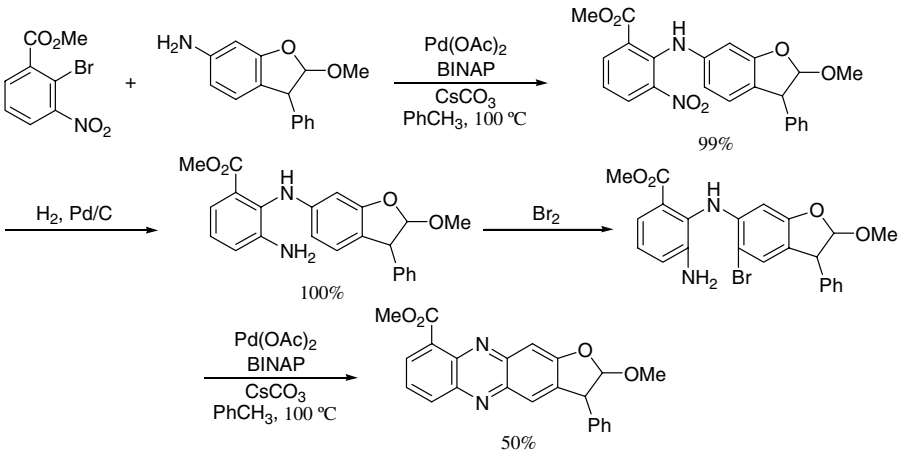

80% 80% (9.10)

Hartwig and Buchwald have developed a new methodology for arylation of amines or phenols with aryl halides and palladium catalysts.[17] This reaction provides a very useful strategy for the preparation of various heterocyclic compounds such as phenazines, as shown in Scheme 9.4.[18]

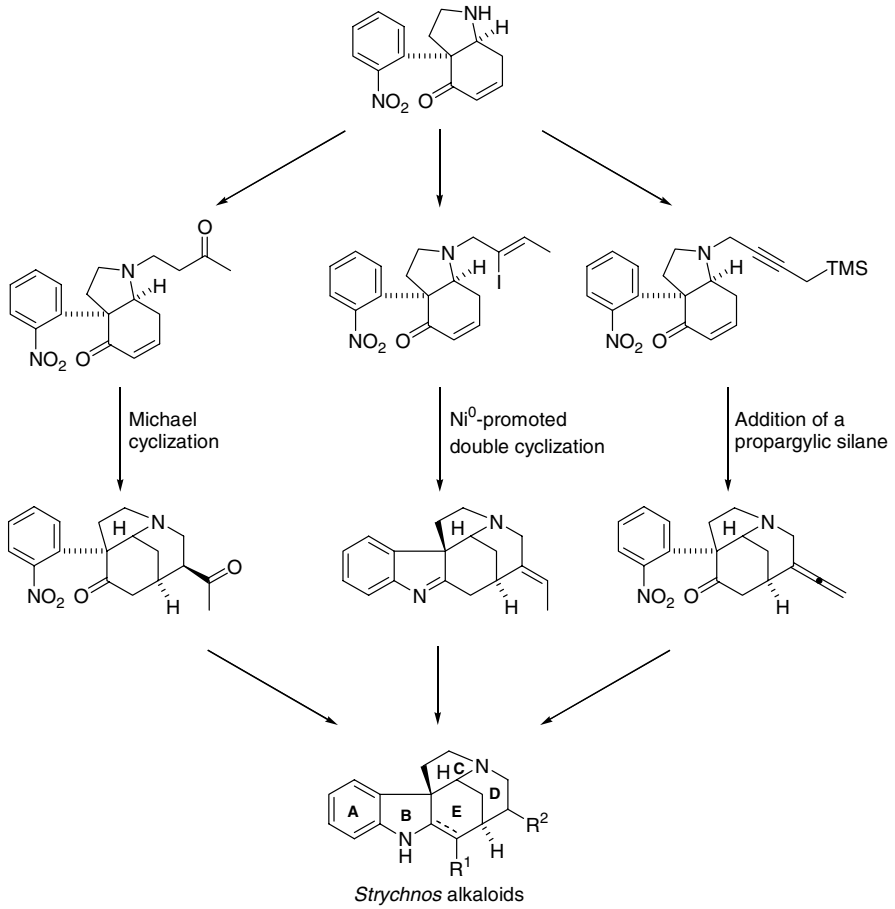
The $S_NAr$ reaction followed by intramolecular cyclization provides a useful method for the preparation of heterocyclic compounds, as summarized in Ref. 1. Reaction of 1-fluoronitrobenzene or 1,2-dinitrobenzene with guanidine in hot THF followed by treatment with *t*-BuOK gives 3-amino-1,2,4-benzotriazene 1-oxide in good yield (Eq. 9.11).[19]




82% (9.11)



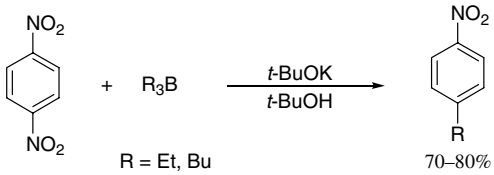

**Scheme 9.4.**




**Scheme 9.5.**

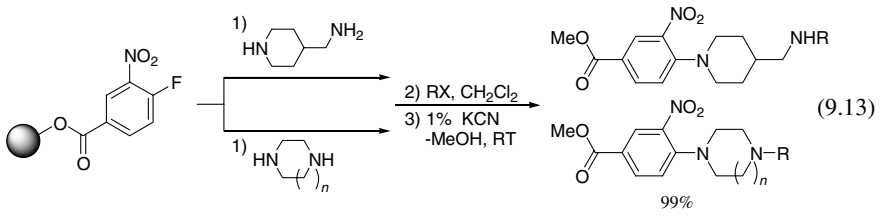
Bonjoch and coworkers have developed a general synthetic entry to strychnos alkaloids of the curan type via a common 3a-(2-nitrophenyl)hexahydroindole-4-one intermediate. Total synthesis of (–)-strychnine is presented in Scheme 9.5.[20] The first step is based on the $S_NAr$ reaction of *o*-iodonitrobenzene with 1,3-cyclohexanone.

Recently, an interesting reaction of *p*-dinitrobenzene with trialkylborane has been reported, in which the nitro group is replaced by an alkyl group in good yield (Eq. 9.12).[21] The reaction is not a simple ionic reaction, but proceeds via free radical intermediates.

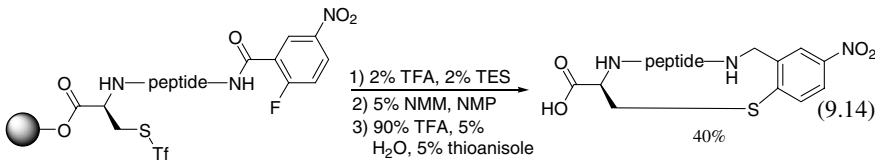



(9.12)

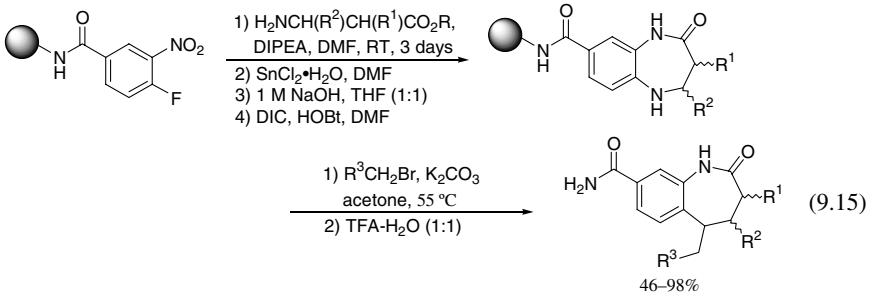
Biologically important arylamines, various kinds of heterocycles, and macrocyclic compounds have been prepared by using resin-bound nitro halo compounds via $S_NAr$ reactions. Such a process is very important for combinatorial synthesis of biologically important compounds. Typical examples are presented in Eqs. 9.13–9.21.[22–31]



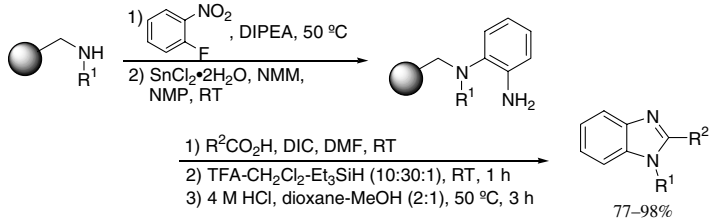

(9.13)



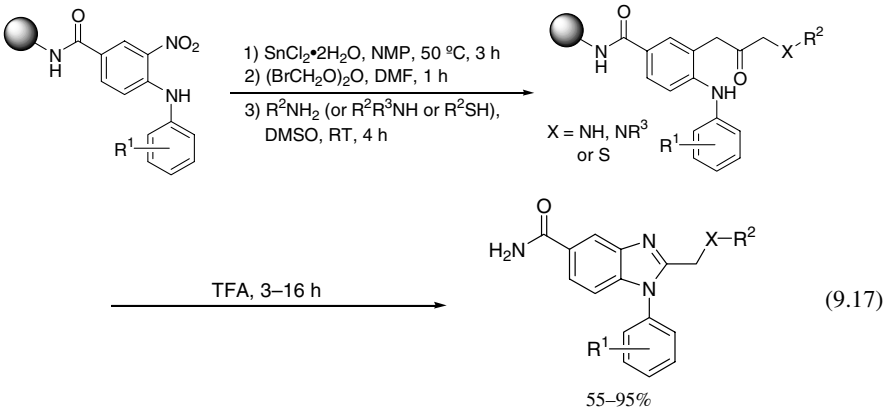

(9.14)




(9.15)




(9.16)

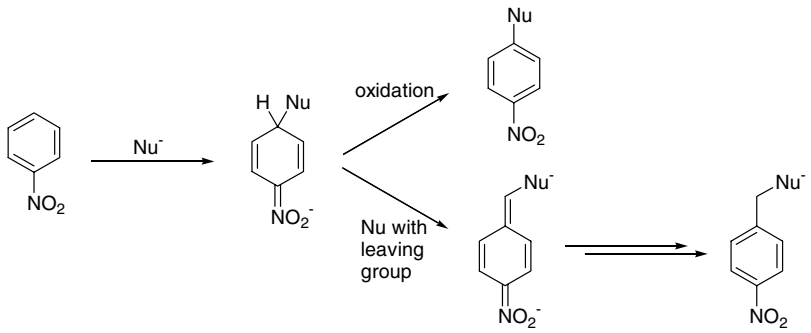



(9.17)

Fullerene is nitrated with $N_2O_4$ to give hexanitro[60]fullerene $C_{60}(NO_2)_4$, which undergoes $S_NAr$ reaction with various nucleophiles.[32]

## 9.2 NUCLEOPHILIC AROMATIC SUBSTITUTION OF HYDROGEN (NASH)

Recently, nucleophilic aromatic substitution of hydrogen (NASH) has become a useful tool in organic synthesis.[33] The reaction proceeds via initial addition of the nucleophile to the ring with formation of a σ-complex-type intermediate (Scheme 9.6). It subsequently lead to nucleophilic aromatic substitution of hydrogen in aromatic ring via various "oxidative pathways." Spontaneous oxidation or oxidation of σ-complex-intermediates with external oxidizing agents gives the final product. Another approach is vicarious nucleophilic substitution (VNS), which provides the possibility of replacement of hydrogen atoms in electrophilic arenes with α-functionalized alkyl substituents. The VNS, pioneered by Makosza and coworkers, offers a selective mild method for the controlled substitution of hydrogen atoms of aromatic systems.[33,34] Recently, much attention has been paid to the development of new environmentally favorable routes for preparing commercially relevant chemical intermediates and products. NASH process is an ideal process because NASH reactions generate functionalized aromatics without the need for halogenated materials.

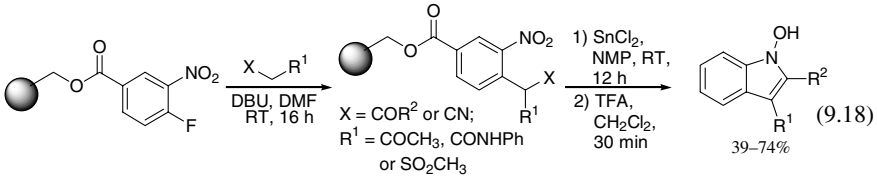



**Scheme 9.6.**

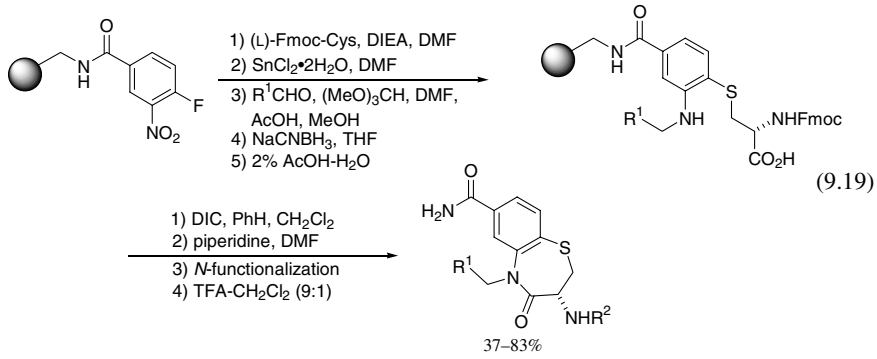
### 9.2.1 Carbon Nucleophiles

The reaction of nitrobenzene with the anion derived from acetone gives a mixture of *p*-nitrophenyl acetone and *o*-nitrophenyl acetone, where nitrobenzene acts as an oxidizing agent. The reaction of *p*-chloronitrobenzene with acetonate ion gives 2-substituted-4-chloronitrobenzene in about 50% yield.[35] Tertiary carbanions derived from 2-phenylpropanenitrile, in liquid ammonia, add to heterocyclic nitroarenes, such as nitropyridines or nitrothiophenes, to form corresponding σ-adducts, which are oxidized with $KMnO_4$ to give substitution products.[35d] This type of reaction is named oxidative nucleophilic substitution of hydrogen (ONSH).

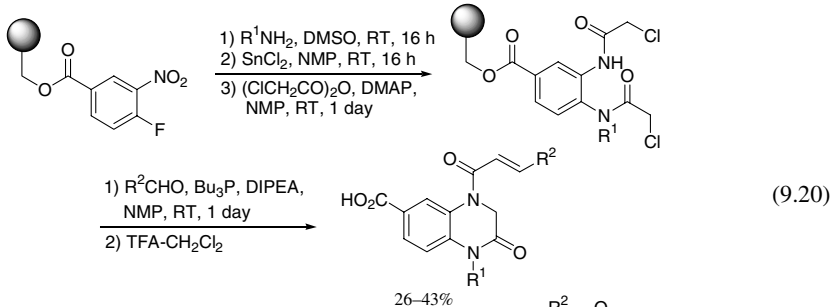
The combination of silyl enol ethers and fluoride ion provides more reactive anions to give alkylated nitro compounds in good yields after oxidation with DDQ, as shown in Eq. 9.22.[36] This process provides a new method for synthesis of indoles and oxyindoles (see Chapter 10, *Synthesis of Heterocyclic Compounds*).



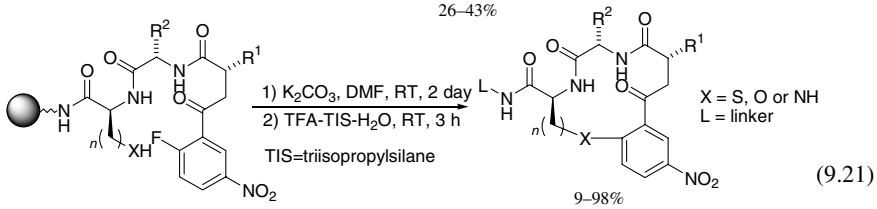

(9.18)



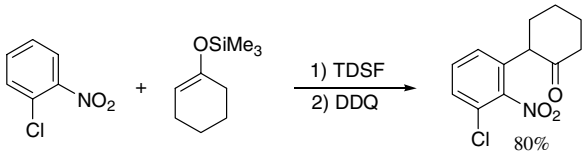

(9.19)




(9.20)



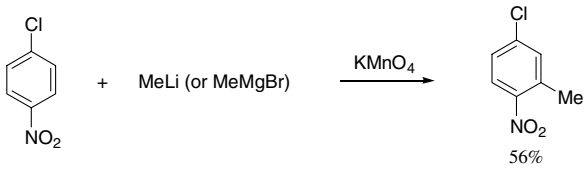

(9.21)




(9.22)

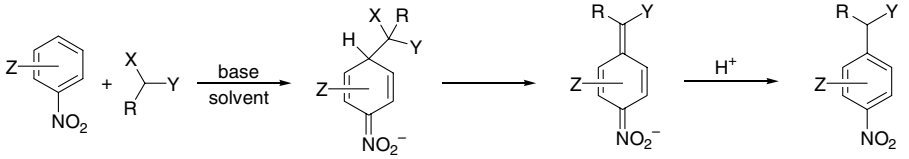
TDSF = tris(dimethylamino)sulfonium difluorotrimethylsiliconate

Alkyl lithium and alkyl Grignard reagents react with aromatic nitro compounds in a similar way to give alkylated products (Eq. 9.23).[37]




(9.23)

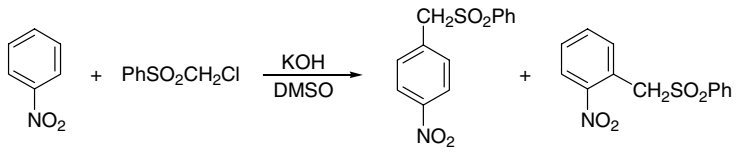
Typical VNS consists of a reaction between a nitroarene such as nitrobenzene and a carbanion containing a leaving group X at the carbanionic center. In the first step, addition of the carbanion to the nitroarene results in the formation of σ-adduct, which undergoes β-elimination of HX to form the nitrobenzylic carbanion, which is subsequently protonated during the work-up procedure (Scheme 9.7).




X = Cl, Br, PhO, PhS, etc.; Y = $SO_2Ph$, $SO_2N$, CN, $CO_2Et$, Cl, Ar, etc.
Typical base/solvent system used for the reaction: KOH, NaOH, *t*-BuOK/DMF, THF, $NH_3$ (*l*).

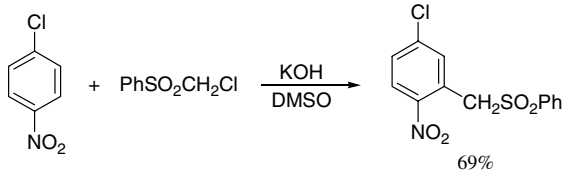
**Scheme 9.7.**

Carbanions of α-chloroalkyl phenyl sulfones react with nitrobenzenes to effect direct nucleophilic replacement of hydrogens located *ortho* and *para* to the nitro group (Eq. 9.24).[38] A very important feature is that VNS of hydrogen usually proceeds faster than conventional $S_NAr$ of halogen located in equally activated positions (Eq. 9.25).[38] The rule that VNS of




75% (47:53)

(9.24)

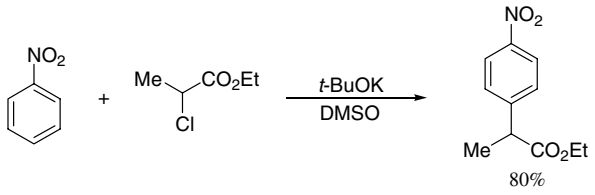



69%

(9.25)

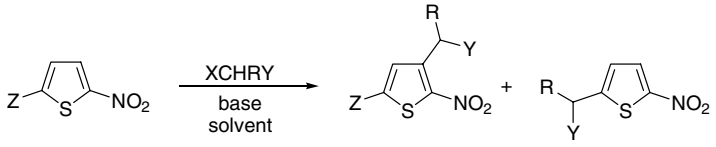
hydrogen proceeds faster than $S_NAr$ of halogen located in equally activated positions holds in all cases. The most convincing example of such behavior is the reaction with 1-fluoro-2,4-dinitrobenzene, which is widely used in peptide chemistry because of the very high rate of replacement of fluorine by amino groups. Nevertheless, reactions of 1-fluoro-2,4-dinitrobenzene with α-halocarbanions proceed according to the VNS of hydrogen pathway.[39]

Alkyl 2-chloropropionates react with nitroaromatic compounds on treatment with base to give alkyl 2-(4-nitroaryl)propionates in good yield (Eq. 9.26).[40]




(9.26)

Similar results are obtained in VNS alkylations with carbanions derived from $ClCH_2CO_2R$,[41] $Cl_2CHCO_2R$,[42] $PhOCH_2CN$,[43] $CHCl_3$[44] and $CH_2(SPh)_2$.[45] The reaction is not limited to nitrobenzene derivatives. Nitronaphthalenes,[46] nitro[10]annulenes,[47] and a wide range of nitro derivatives of aromatic heterocycles such as furan,[48] thiophene,[48,49] pyrrole,[48] pyrazole,[50] imidazole,[51] thiazole,[52] pyridine,[53] indole,[54] benzoxazole,[55] quinoline,[56] and benzofuroxane[57] also undergo VNS reactions, usually in excellent yield. In general, nitrothiophene derivatives are more reactive toward VNS reactions than the corresponding nitrobenzene derivatives. 2-Nitrothiophene and its derivatives react with a variety of carbanions; usually the hydrogen at the three position of thiophene is replaced (Scheme 9.8).[48,49]



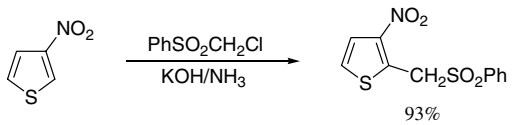

Z = H, Br, I, CN.
XCHRY = $ClCH_2SO_2Ph$, $ClCHMeSO_2Ph$, $ArOCH_2CN$, $PhSCH_2But$, $Cl_2CHCO_2Et$, $CHCl_3$, $CHBr_3$.
Base/solvent: *t*-BuOK, $KOH/NH_3$ *(l)*, DMSO, DMF, THF.
Yield: 50–90%

**Scheme 9.8.**

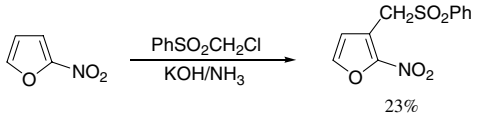
The VNS reaction of 3-nitrothiophene occurs only at the C-2 position; for example, VNS with chloromethylphenylsulfone gives 2-phenylsulfonylmethyl-3-nitrothiophene in 93% yield (Eq. 9.27).[48]

Typical VNS reaction of nitro heterocycles are presented in Eq. 9.28–9.31. Nitrofurans and nitropyrroles are less reactive toward VNS reactions than nitrothiophenes.

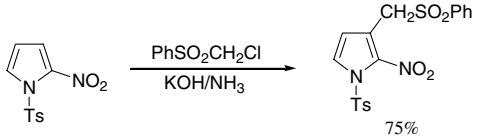
Control of the regioselectivity of VNS is important. It is governed by three major factors: the structure of the nitroarene; the nature of the nucleophile, and the reaction conditions, especially solvent and base. The different effect of methoxy and hydroxy groups is interesting; the reaction of 1-methoxy-2,4-dinitrobenzene with chloromethyl phenyl sulfone proceeds in



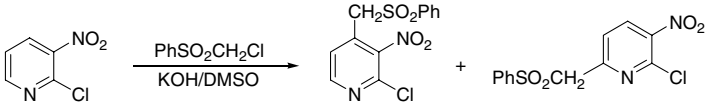

(9.27)



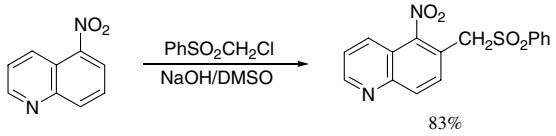

(9.28)




(9.29)

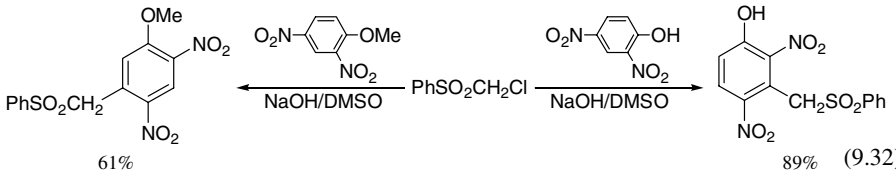



(9.30)



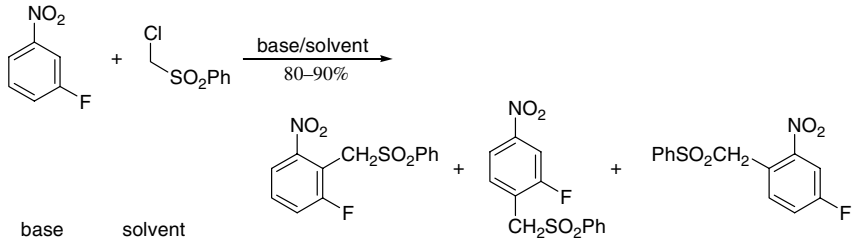

(9.31)

the 5-position, whereas 2,4-dinitrophenol, which enters the reaction as the phenoxide, substitution takes place in the 3-position (Eq. 9.32).[58]




(9.32)

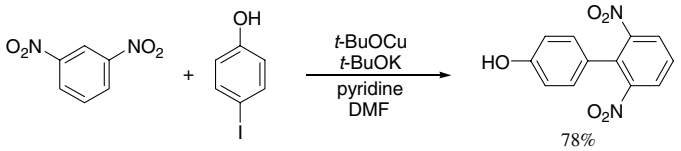
The regiochemistry of substitution is also strongly affected by the size of the nucleophiles. Bulky nucleophiles tend to react in the *para*-position, although these carbanions react with *para*-substituted nitroarenes satisfactorily in the *ortho*-position at low temperature.[59] The effects of solvent and bases are also important in controlling the regiochemistry of VNS. Carbanions of chloromethyl phenyl sulfones generated with *t*-BuOK in THF exhibit a strong tendency to react with nitroarenes in the *ortho*-position. This is due to an attractive interaction of the potassium cation of the relatively tight ion-pairs with the oxygen of the nitro group (Eq. 9.33).[60]




| base | solvent | | | |
|---|---|---|---|---|
| NaOH | DMSO | 32% | 57% | 11% |
| *t*-BuOK | THF | 93% | 0% | 7% |

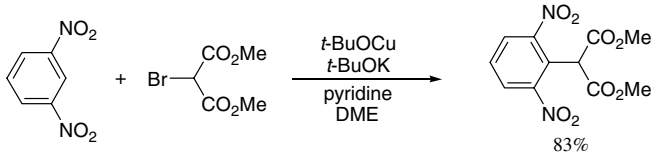
(9.33)

A copper salt assists the control of the regioselectivity in VNS for *m*-dinitrobenzene. For instance, the reaction of *m*-dinitrobenzene with 4-iodophenol in the presence of copper *tert*-butoxide gives asymmetrical biphenyl in 78% yield (Eq. 9.34).[61]



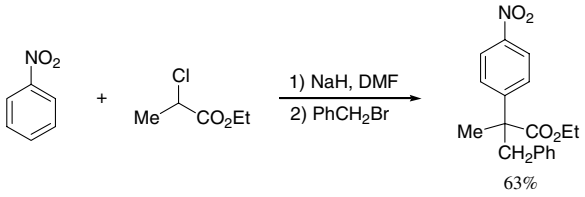

(9.34)

The regioselective cross-coupling between anions of bromomalonate esters or bromoacetate esters and *m*-dinitrobenzene proceeds in the presence of copper *tert*-butoxide to give the 2-substituted product. Without the copper salt, the 4-substituted isomer is the only product (Eq. 9.35).[62]



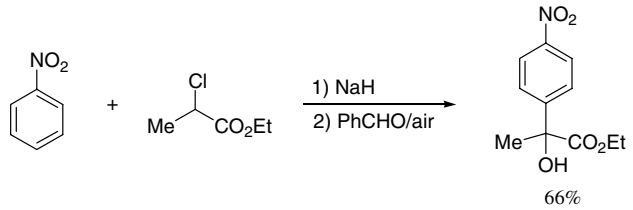

(9.35)

Recently, the VNS intermediates have been used for further introducing electrophiles. For example, reaction of the enolate of ethyl 2-chloropropionate with nitrobenzene followed by subsequent reaction with an alkylating agent gives a series of esters bearing a quaternary center (Eq. 9.36).[63]



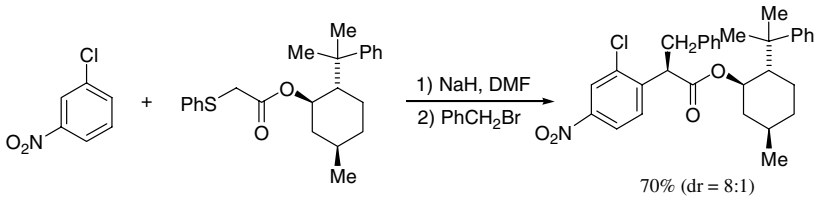

(9.36)

The anion produced by VNS of nitroarenes and α-chloro esters is hydroxylated by the action of air and benzaldehyde, thereby producing α-hydroxy esters (Eq. 9.37).[64]



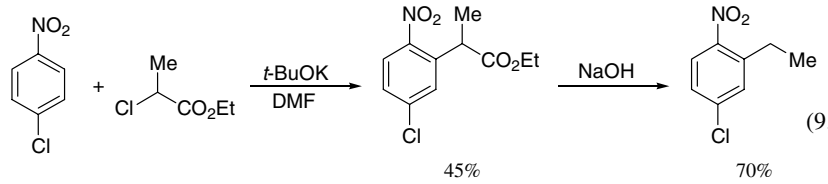

(9.37)

Asymmetric aromatic VNS of hydrogen has been reported; the enolates of chiral cyclohexylphenylsulfanylacetates react readily with 3-chloronitrobenzene, followed by subsequent stereoselective alkylation (Eq. 9.38).[65]



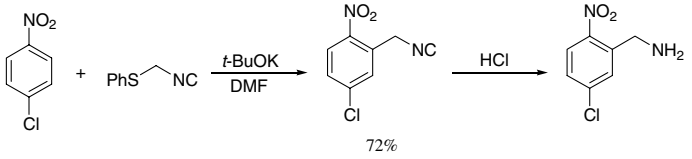

(9.38)

The transformation of products obtained by VNS provides a useful tool in organic synthesis. Alkyl substituents can be introduced using VNS reaction with carbanions containing one group acting as an efficient carbanion-stabilizing and leaving group. Early examples of methylation of nitroarenes have been accomplished with anions derived from DMSO or related compounds.[66] A more attractive and useful method for introducing alkyl groups into nitro compounds is a method based on VNS using α-chloroesters followed by decarboxylation (Eq. 9.39).[67]



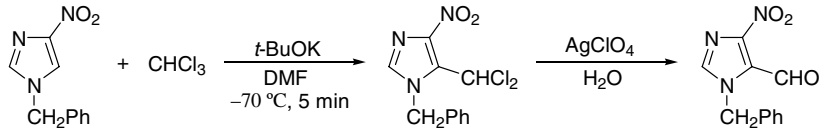

(9.39)

A convenient method for introducing an aminomethyl group into nitroarenes can be accomplished by the use of the anion of phenylthiomethylisocyanide (Eq. 9.40).[68]



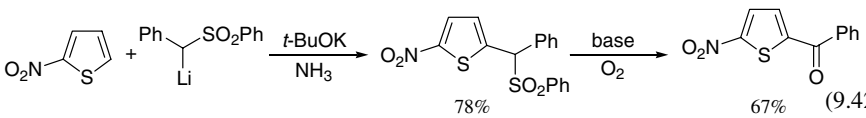

(9.40)

The introduction of a formyl or acyl group can be achieved by transformation of VNS products. Hydrolysis of dichloromethylnitroarenes, VNS products between heteroaromatic nitro compounds and chloroform, is a method of choice for the preparation of heterocyclic aldehydes, as shown in Eq. 9.41, in which 4-nitroimidazole is converted into 5-formyl-4-nitroimidazole.[69]



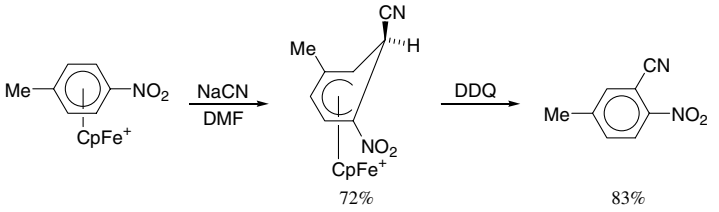

(9.41)

VNS products derived from α-chloroalkyl sulfones are converted into the corresponding aldehydes or ketones via oxidation (Eq. 9.42).[70]




(9.42)

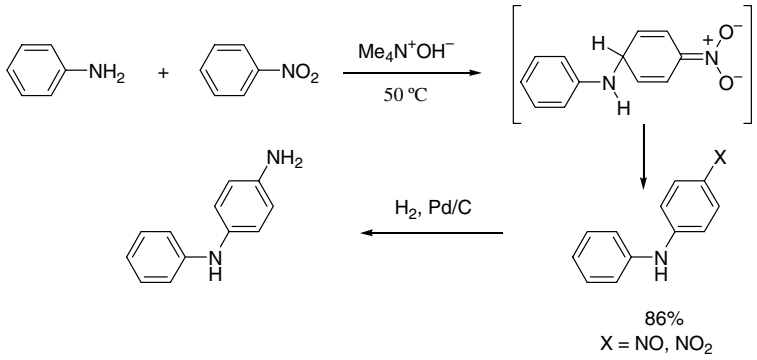
Arenes, on complexation with Cr, Fe, Mn, and so forth, acquire strongly electrophilic character; such complexes in reactions with nucleophiles behave as electrophilic nitroarenes.[71] Synthesis of aromatic nitriles via the temporary complexation of nitroarenes to the cationic cyclopentadienyliron moiety, cyanide addition, and oxidative demetalation with DDQ has been reported (Eq. 9.43).[72]




(9.43)

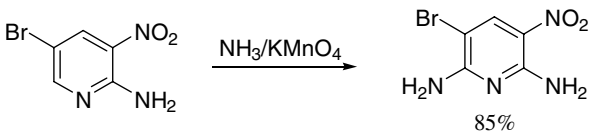
### 9.2.2 Nitrogen and Other Heteroatom Nucleophiles

Amination of aromatic nitro compounds is a very important process in both industry and laboratory. A simple synthesis of 4-aminodiphenyl amine (4-ADPA) has been achieved by utilizing a nucleophilic aromatic substitution. 4-ADPA is a key intermediate in the rubber chemical family of antioxidants. By means of a nucleophilic attack of the anilide anion on a nitrobenzene, a σ-complex is formed first, which is then converted into 4-nitrosodiphenylamine and 4-nitrodiphenylamine by intra- and intermolecular oxidation. Catalytic hydrogenation finally affords 4-ADPA. Azobenzene, which is formed as a by-product, can be hydrogenated to aniline and thus recycled into the process. Switching this new atom-economy route allows for a dramatic reduction of chemical waste (Scheme 9.9).[73] The United States Environmental Protection Agency gave the Green Chemistry Award for this process in 1998.[74]



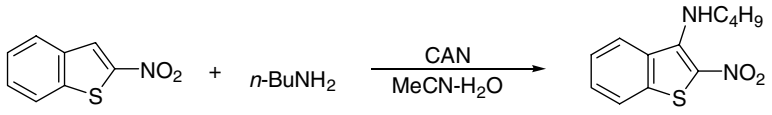

**Scheme 9.9.**

Amination of heterocyclic nitro compounds such as nitroquinolines, nitroisoquinolines, or nitropyridines can be carried out by means of a liquid ammonia-$KMnO_4$ system, which has been studied by Wozniak and coworkers (Eq. 9.44). Frontier molecular orbital calculation can predict the reactivity and regioselectivity of this amination.[75] In a similar way, nitroquinolines are methylaminated with a liquid methylamine solution of $KMnO_4$.[76]



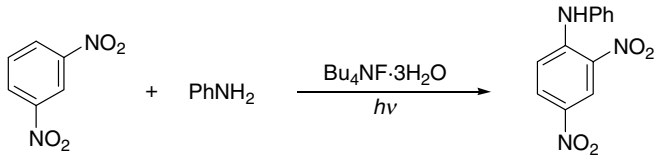

(9.44)

Another approach for oxidative nucleophilic substitution of hydrogen can be carried out with primary amines and CAN in aqueous MeCN (Eq. 9.45).[77]



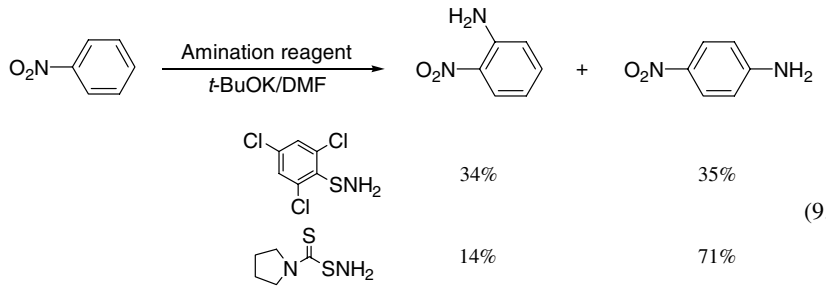

42% (9.45)

Interesting direct amination of nitroarenes has been reported; aromatic photo substitution of *m*-dinitrobenzene with primary amines is promoted by the presence of fluoride ion to give useful yields of the product (Eq. 9.46).[78]



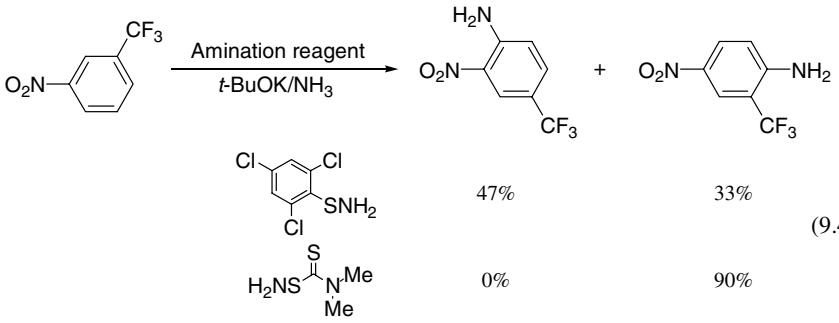

54% (9.46)

Amination of nitroarenes via VNS reactions with hydroxylamine has been known for almost 100 years.[79] However, this reaction was limited to highly electrophilic arenes such as *m*-dinitrobenzene and bicyclic nitroarenes. Recently, several modified reagents and procedures have appeared for amination of nitroarenes. A better aminating agent, 4-amino-1,2,4-triazole or sulfenamide, has been used by Katritzky[80] and Makosza.[81] Several sulfenamides have been tested to select the most effective aminating agents. 2,4,6-Trichlorobenzenesulfenamide and *N*-tetramethylenethiocarbamoylsulfenamide give satisfactory yields of amination under usual VNS conditions (Eqs. 9.47 and 9.48). The former reagent shows a preference for *ortho*-substitution, whereas the latter compound reacts at the *para*-position of the nitroarene ring.




34% 35%

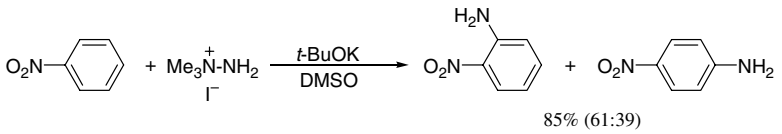
14% 71% (9.47)




47% 33%

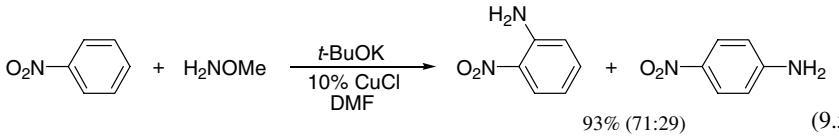
0% 90% (9.48)

1,1,1-Trimethylhydrazinium iodide is a novel, highly reactive reagent for aromatic amination via VNS, as shown in Eq. 9.49, in which the regioselectivity is different from that obtained with other reagents.[82]



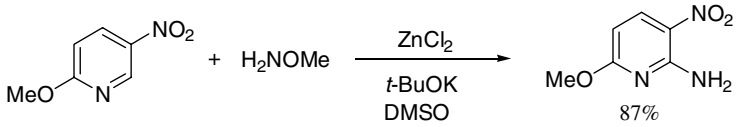

(9.49)

Seko and coworkers have discovered a convenient copper-catalyzed direct amination of nitroarenes with *O*-alkylhydroxylamines (Eq. 9.50).[83]



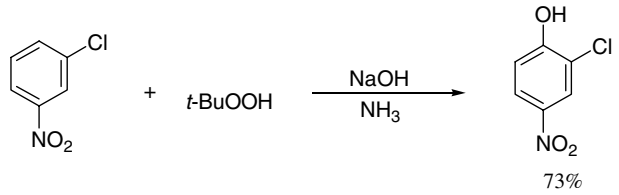

(9.50)

Direct amination of 3-nitropyridines with methoxyamine in the presence of zinc chloride under basic conditions proceeds to give 2-amino amino-3-nitropyridines (Eq. 9.51).[84]




(9.51)

Carbo- and heterocyclic nitroarenes react with anions of *tert*-butyl and cumyl hydroperoxides in the presence of strong bases to form substituted *o*- and *p*-nitrophenols. Regiochemistry of the hydroxylation can be controlled to a substantial extent by selection of proper conditions (Eq. 9.52).[85]

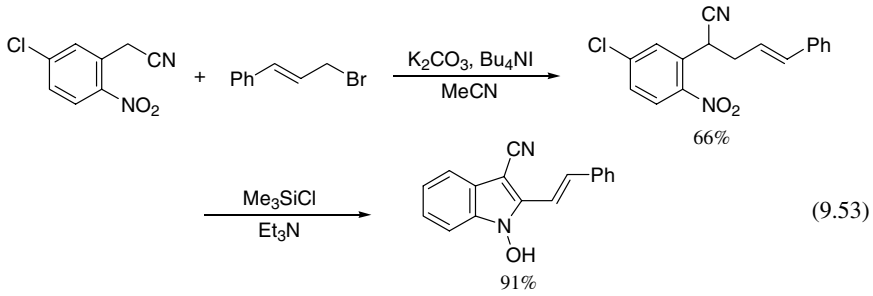



(9.52)

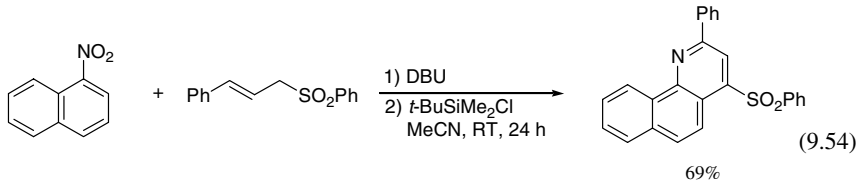
### 9.2.3 Applications to Synthesis of Heterocyclic Compounds

Because the nucleophiles can be introduced at the *ortho*-position of the nitro group, various heterocycles can be prepared via VNS and related reactions. Indoles and related compounds are prepared via the VNS reaction and subsequent cyclization. The VNS reaction of nitroarenes followed by cyclization with $Et_3N$-$Me_3SiCl$ gives 1-hydroxyindoles (Eq. 9.53).[86] Cyclization is also catalyzed on treatment with bases, in which nitroso intermediates are postulated.

The novel cyclization takes places by the silane-mediated condensation of nitroarenes with allylic carbanions, in which a six-membered nitrogen-containing ring is constructed (Eq. 9.54).[87]

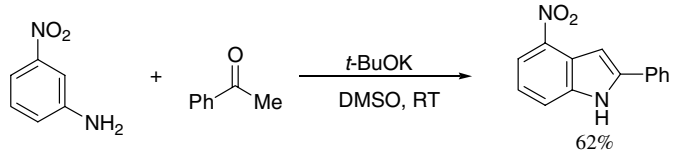



(9.53)



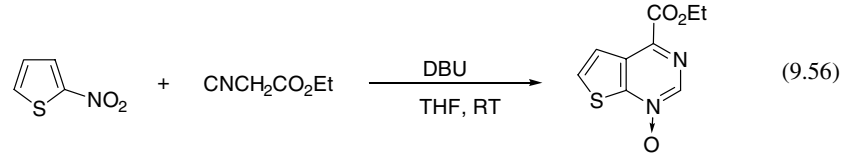

(9.54)

Base-promoted condensation of ketones with 3-nitroaniline results in the formation of indoles. The reaction proceeds in one pot via a NASH-type reaction and subsequent cyclization (Eq. 9.55).[88]

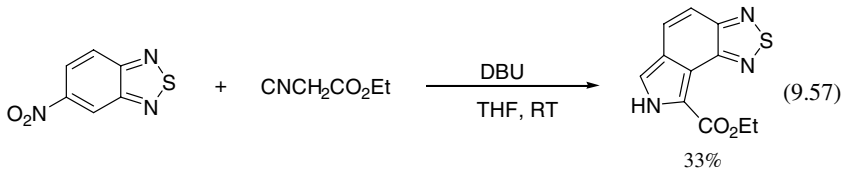



(9.55)

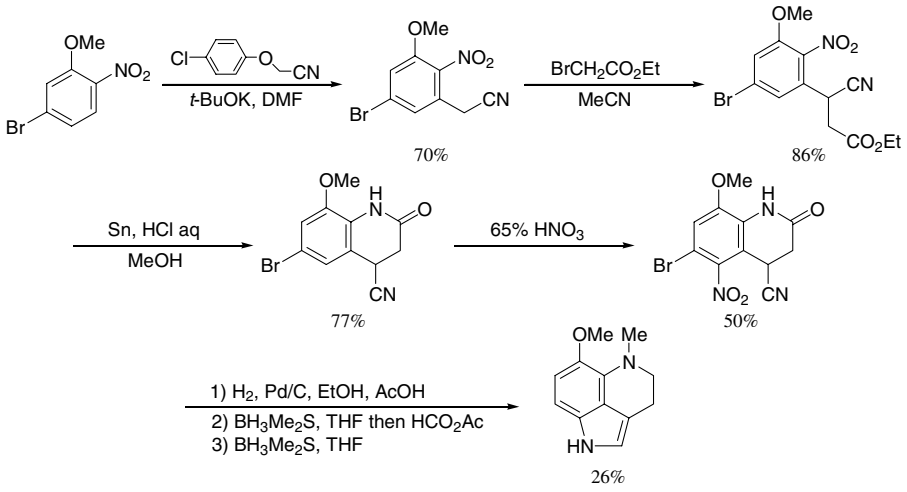
The foregoing examples show that the nucleophilic attack to nitroarenes at the *ortho*-position followed by cyclization is a general method for the synthesis of various heterocycles. When nucleophiles have an electrophilic center, heterocyclic compounds are obtained in one step. Ono and coworkers have used the anion derived from ethyl isocyanoacetate as the reactive anion for the preparation of heterocyclic compounds. The carbanion reacts with various nitroarenes to give isoindoles or pyrimidines depending on the structure of nitroarenes (Eqs. 9.56 and 9.57).[89] The synthesis of pyrroles is discussed in detail in Chapter 10.



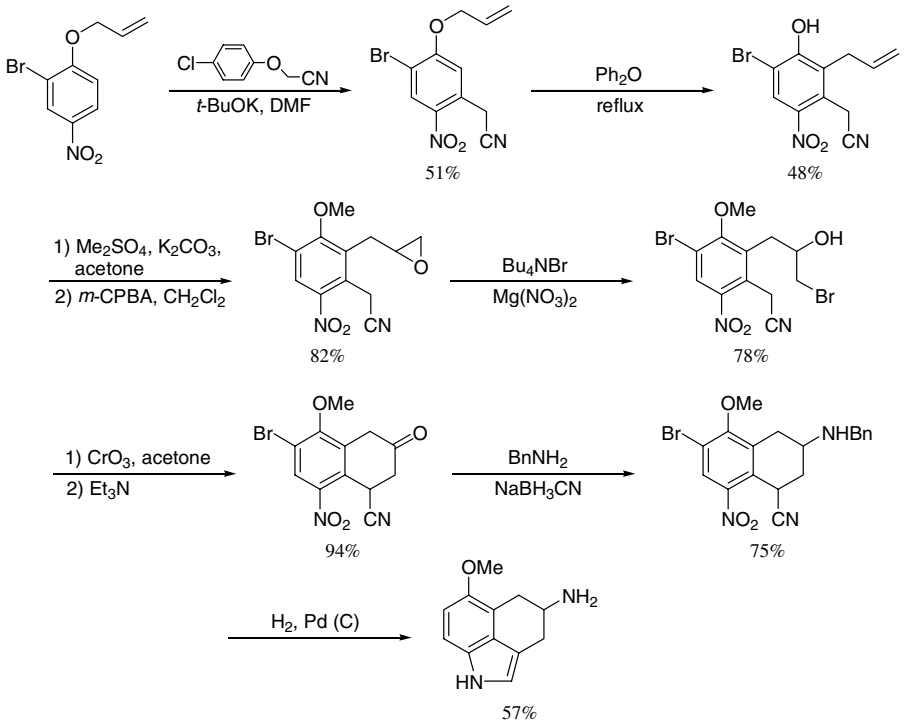

(9.56)



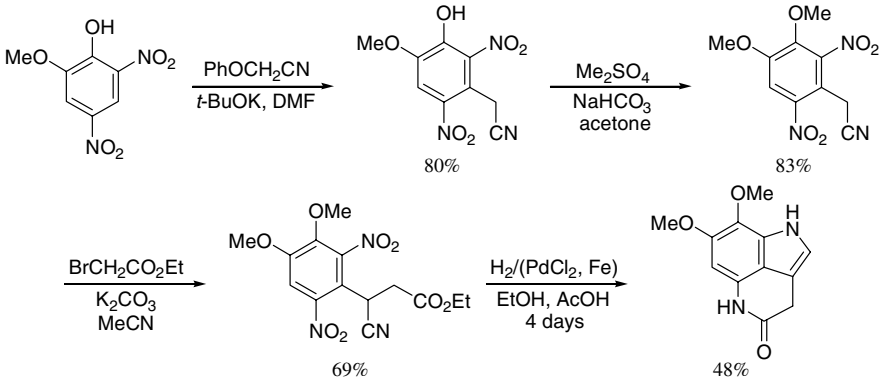

(9.57)




**Scheme 9.10.**

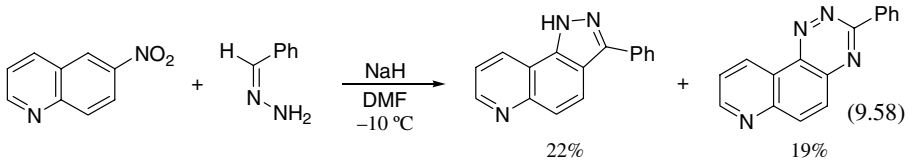



**Scheme 9.11.**

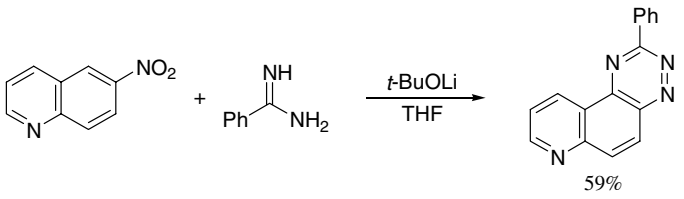



**Scheme 9.12.**

There are many variants of such syntheses of heterocycles. Recent examples are presented in Eqs. 9.58 and 9.59.[90] Because these transformations do not require aromatic halides or transition metals, they may provide a clean technology for production of biologically important materials.




(9.58)




(9.59)

To date, there are only few examples of applying the VNS reaction in the synthesis of natural products. Several natural products such as *O*-methylnordehydrobuffotenine (Scheme 9.10),[91] an alkaloid of animal origin, 1,3,4,5-tetrahydro[*cd*]indole (Scheme 9.11),[92] and 7,8-dimethoxy-2-oxo-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline as key intermediates for marine alkaloids (Scheme 9.12)[93] have been prepared via VNS reactions.

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*The Nitro Group in Organic Synthesis.* Noboru Ono
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# 10

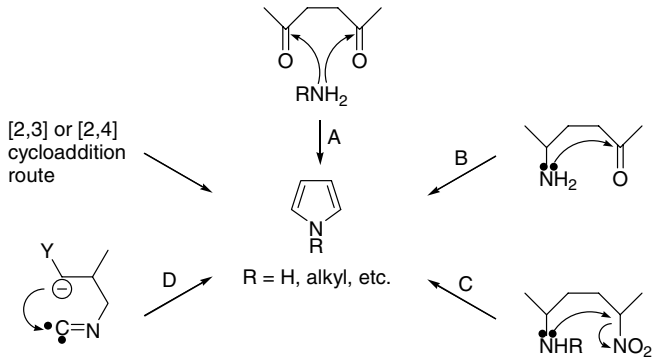
# SYNTHESIS OF HETEROCYCLIC COMPOUNDS

As discussed in Chapter 6, nitro compounds are converted into amines, oximes, or carbonyl compounds. They serve as useful starting materials for the preparation of various heterocyclic compounds. Especially, five-membered nitrogen heterocycles, such as pyrroles, indoles, and pyrrolidines, are frequently prepared from nitro compounds. Syntheses of heterocyclic compounds using nitro compounds are described partially in Chapters 4, 6 and 9. This chapter focuses on synthesis of hetero-aromatics (mainly pyrroles and indoles) and saturated nitrogen heterocycles such as pyrrolidines and their derivatives.

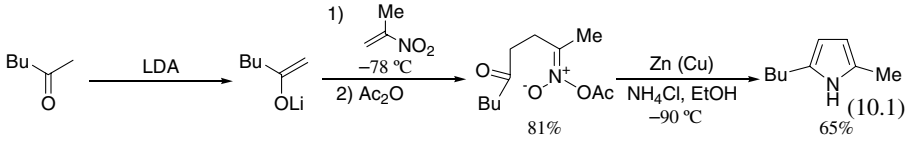
## 10.1 PYRROLES

Many natural products, such as the bile pigments, porphyrins, and related macrocycles, contain the pyrrole ring as a characteristic subunit and play an important role in nature.[1] Pyrrole derivatives comprises a series of compounds with potential biological significance. Many methods are available for the synthesis of pyrroles as illustrated in Scheme 10.1. In the context of porphyrins and bile acid pigments, most procedures are based on the Paal-Knorr reaction (routes A and B) involving the reaction of α-amino ketones (normally generated in situ by reduction, usually with zinc dust, of an α-keto oxime) with β-ketoesters or β-diketones.[2] Because nitro compounds are good precursors for preparing amines and ketones, they have been used for the preparation of pyrroles in various ways. In recent years, isonitrile cyclization using nitroalkenes and ethyl isocyanoacetate has become a useful method for pyrrole synthesis (route D).

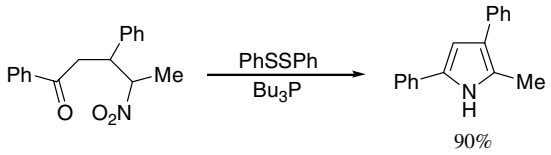
A convenient and general method has been developed for the synthesis of alkylpyrroles starting from ketones and nitroalkenes via reduction of the intermediate acetic nitronic anhydride as shown in Eq. 10.1. Ketone enolates react with a variety of nitroalkenes to yield the Michael adducts, lithium nitronates, which are trapped with acetic anhydride to give the corresponding acetic nitronic anhydrides. The acetic nitronic anhydrides are easily converted into alkylpyrroles by reduction with Zn(Cu).[3]




**Scheme 10.1.**

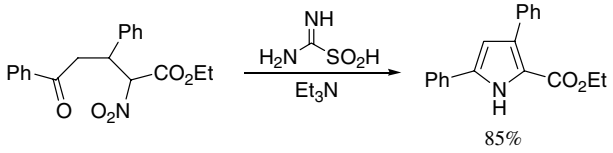



The Michael addition of nitroalkanes to α,β-unsaturated ketones gives γ-nitroketones, which are converted into pyrroles by reduction of the nitro group with $Bu_3P$ and PhSSPh (Eq. 10.2).[4]



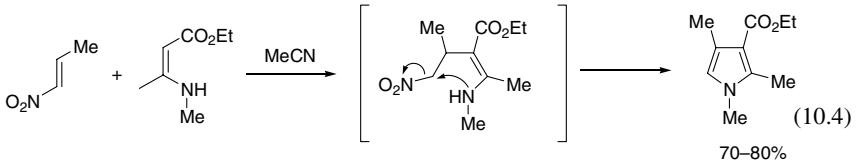

(10.2)

As a new and practical synthesis of pyrroles, Zard and coworkers have presented the reduction of γ-nitroketones with formamidinesulfinic acid (Eq. 10.3).[5]



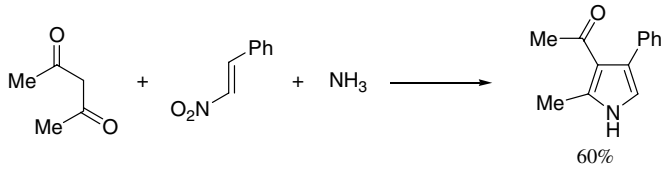

(10.3)

The condensation of nitroalkenes with enamino- ketones or enamino-esters (Grob-Camenisch reaction) has been widely used for pyrrole synthesis (Eq. 10.4).[6a] This process is now carried out with resin-bound enamino-ketones for combinatorial syntheses of pyrroles.[6b]



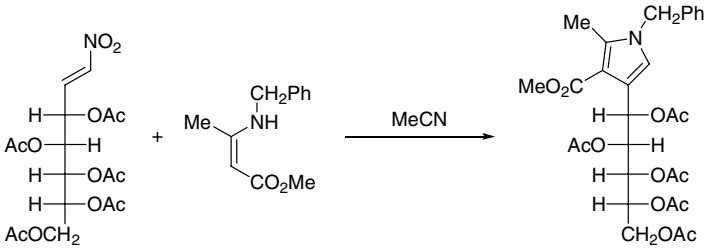

(10.4)

Various variants of this process are presented for pyrrole synthesis. For example, reactions of 1,3-dicarbonyl compounds with β-nitrostyrene followed by treatment with amines give 3-acylpyrroles (Eq. 10.5).[7]

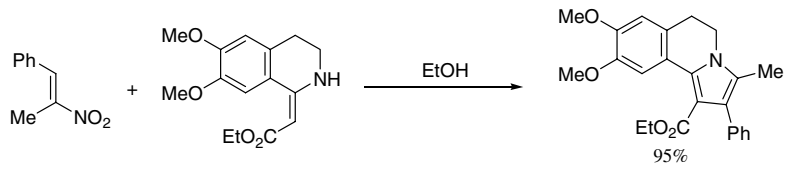



(10.5)

Reactions of 3-aminocrotonic esters with sugar nitro-olefins give 3-(pentaacetoxypentyl)pyrroles (Eq. 10.6).[8]



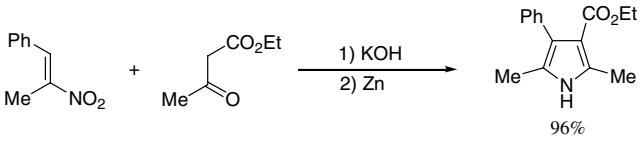

(10.6)




(10.7)

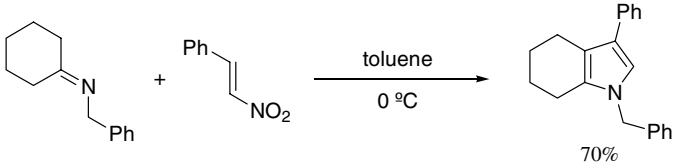
Another pyrrole synthesis based on intramolecular substitution of the nitro group by amino function is presented in Eq. 10.7, in which the Michael addition of enamines to nitroalkenes is used.[9]

The Michael addition to nitroalkenes followed by cyclization provides a general method for the synthesis of various pyrroles. The reaction of nitroalkenes with acetoacetate followed by reduction with Zn in acetic acid provides another route to 2-methyl-3-pyrrolecarboxylates (Eq. 10.8).[10]



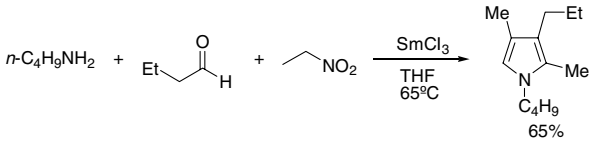

(10.8)

Reaction of cyclohexanone imines with nitroalkenes provides a new synthetic method of tetrahydroindole derivatives (Eq. 10.9).[11]




(10.9)

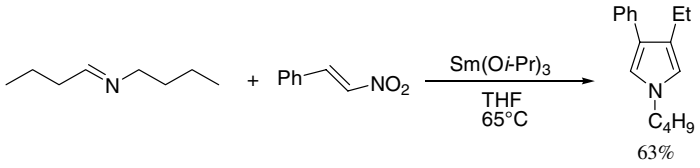
A one pot samarium-catalyzed three-component reaction of aldehydes, amines, and nitroalkanes leads to pyrroles. The reaction proceeds via imines, generated from the amine and carbonyl compound, followed by the Michael addition of the nitro compound (Eq. 10.10).[12a] In




(10.10)

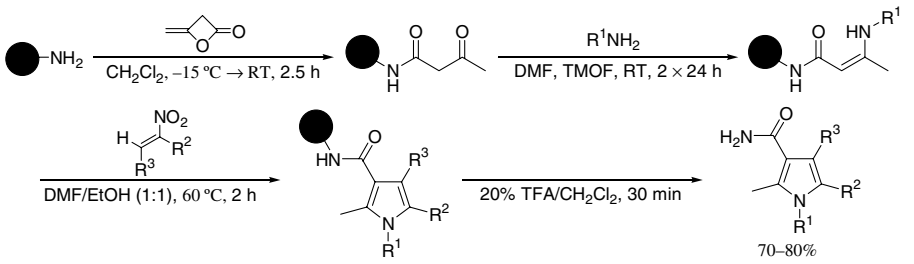
a related reaction, a three-component coupling of the α,β-unsaturated carbonyl compounds amines and nitroalkanes on the surface of silica gel in the absence of a solvent under microwave irradiation gives highly substituted pyrroles.[12b]

Various types of alkylpyrroles are prepared under mild conditions by reacting nitroalkenes with imines in the presence of $Sm(O\textit{i}\text{-}Pr)_3$ (Eq. 10.11).[13] Thus, the Grob-Camenish type reaction is accelerated by samarium catalysts.




(10.11)

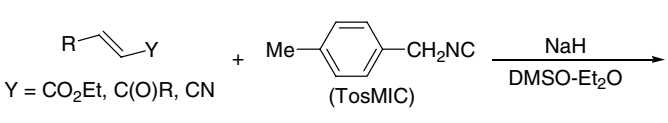
All of these reactions proceed in a similar pathway which involves the Michael type additions of enamines to nitroalkenes or addition of nitroalkanes to imines and cyclization. This process has been achieved by solid-phase variation (Scheme 10.2).[14]




**Scheme 10.2.**

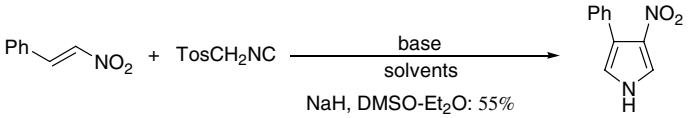
Isonitrile cyclization provides a useful alternative method of the Knorr type cyclization for pyrrole synthesis. In 1972, Leusen and coworkers reported pyrrole synthesis based on the reaction of tosylmethyl isocyanide (TosMIC) with electron-deficient alkenes (Eq. 10.12).[15]

The most important advantage of this procedure is that α-free pyrroles are obtained directly. Reaction of nitroalkenes with TosMIC gives 3-nitropyrroles in 55–85% yield (Eq. 10.13).[16] The

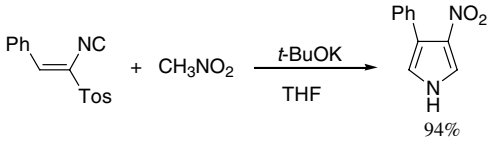



(10.12)

pyrrole synthesis shown in Eq. 10.13 is important because it is the only direct method to obtain 3-nitropyrroles unsubstituted in 2 and/or 5 positions. Such pyrroles are also prepared by the reaction of 1-isocyano-1-tosyl-1-alkenes with nitromethane (Eq. 10.14).[17] An improvement of yields in the reaction shown in Eq. 10.13 is accomplished by using 2.4 equivalents of *t*-BuOK at low temperature (–80 °C) in THF.[18]

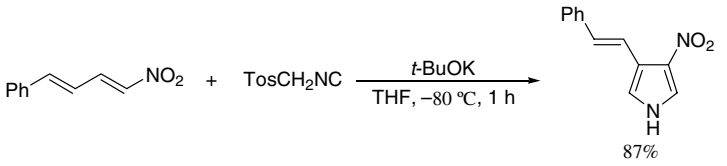



(10.13)

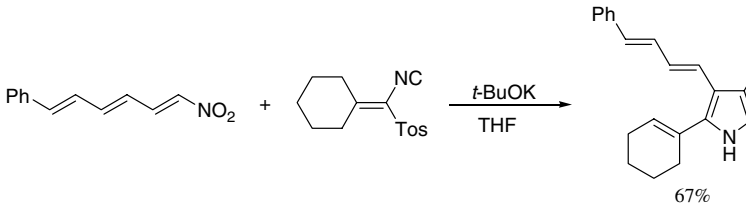



(10.14)

Nitrodienes[19] and nitrotrienes[20] can be used in Leusen-pyrrole synthesis to give 3-alkenyl-4-nitropyrroles or 2-alkenyl-3-alkadienyl-4-nitropyrroles, as shown in Eqs. 10.15 and 10.16, respectively.

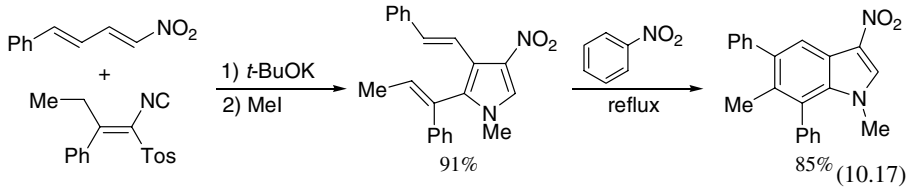



(10.15)




(10.16)

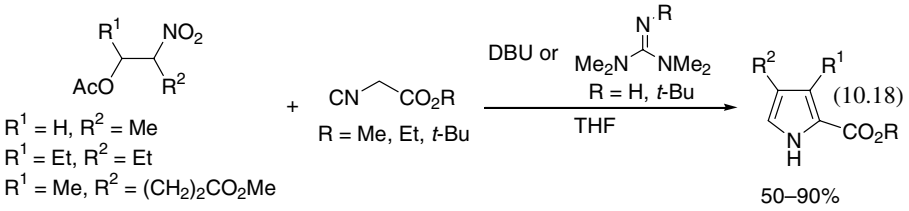
2,3-(Dialkenyl)-4-nitropyrroles are prepared by the reaction of nitrodienes with 1-isocyano-1-tosyl-1-alkenes. 3-Nitroindoles are prepared in good yields via a thermal 6π-electrocyclization of 2,3-(dialkenyl)-4-nitropyrroles in nitrobenzene. Nitrobenzene causes aromatization of the initially formed dihydroindoles (Eq. 10.17).[21]

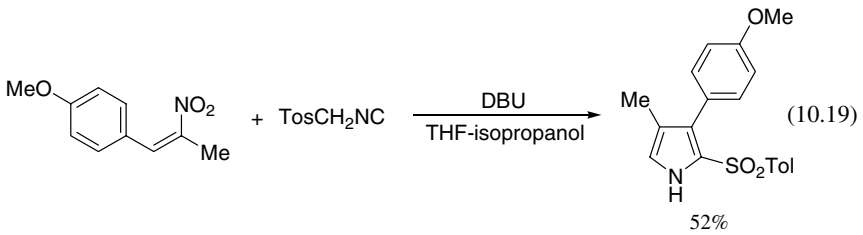



(10.17)

Barton and Zard found that the base-catalyzed reaction of nitroalkenes or β-nitroacetates with alkyl isocyanoacetate or TosMIC gives pyrrole-2-carboxylates or 2-sulfonylpyrroles, respectively (see Eqs. 10.18 and 10.19).[22] This reaction is very convenient for the synthesis of

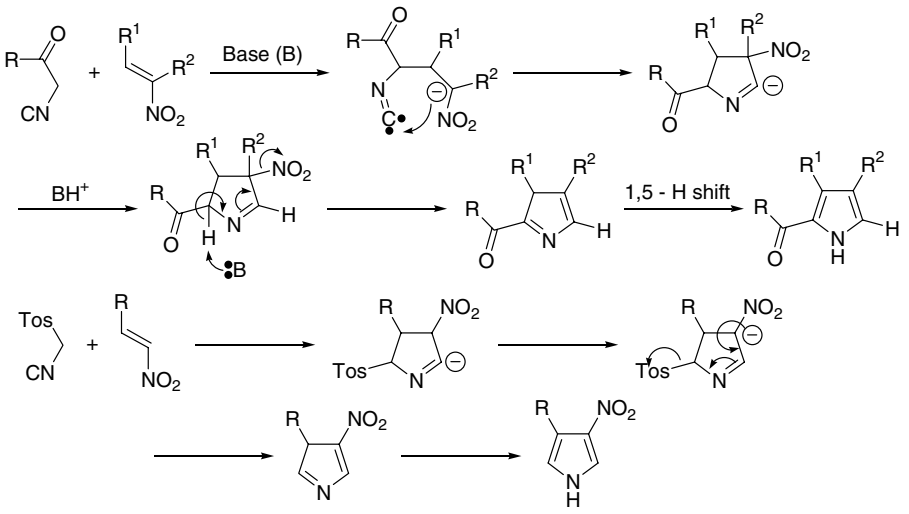
pyrroles with various substituents ($R^1$ and $R^2$) at the β-positions. The limitation of this reaction is that pyrroles unsubstituted in the 2-position, cannot be prepared. The yields are generally excellent (80–90%), but the yield is moderate, if $R^1$ is H. Nonionic strong bases such as DBU and guanidine are generally used in the Barton-Zard reaction.



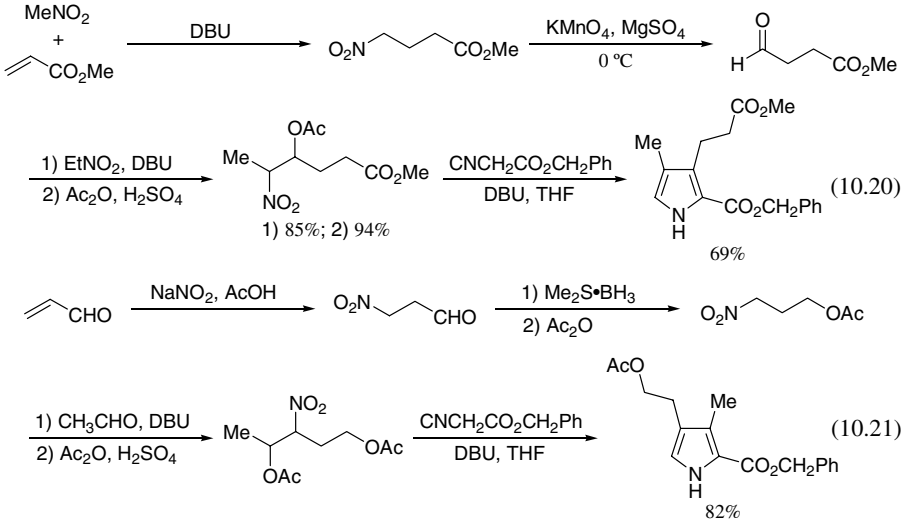

The reaction pathways for the pyrrole formation are summarized in Scheme 10.3. The group that is eliminated at the final stage is a nitrite ion (Barton-Zard reaction) or a toluenesulfinate ion (Leusen reaction), depending on the reaction pattern.

Benzyl isocyanoacetate is a useful reagent for the preparation of benzyl 5-unsubstituted pyrrole-2-carboxylates, which are widely used in the synthesis of porphyrins.[23] Ono and coworkers have prepared pyrroles substituted with various substituents at the β-positions.[23a] Because the requisite β-nitro acetates (or nitroalkenes) are readily available by the Henry

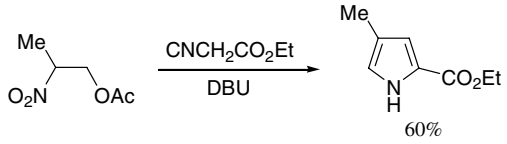



**Scheme 10.3.**

reaction, various substituents are easily introduced into the 3- and 4-positions of pyrroles (Eqs. 10.20 and 10.21).

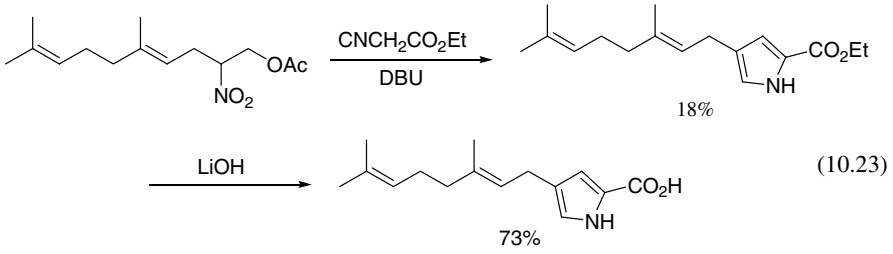



The Barton-Zard pyrrole synthesis has now been extensively applied to synthesis of natural and unnatural products containing pyrrole units. Methyl 4-methylpyrrole-2-carboxylate is the trail-maker pheromone of the Texas leaf-cutting ant *Atta texana*.[24] It is readily prepared by the Barton Zard method in 60% yield (Eq. 10.22).[22]




(10.22)

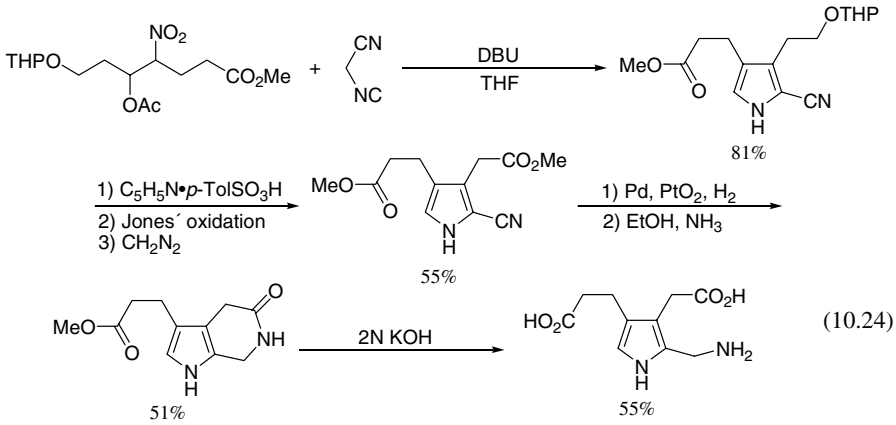
Pyrrolostatin is a novel lipid peroxidation inhibitor, which is isolated from *Streptomyces chrestomyceticus*. Its structure consists of a pyrrole-2-carboxylic acid with a geranyl group at the 4-position. It is readily prepared by applying the Barton-Zard pyrrole synthesis, as shown in Eq. 10.23.[24]




(10.23)

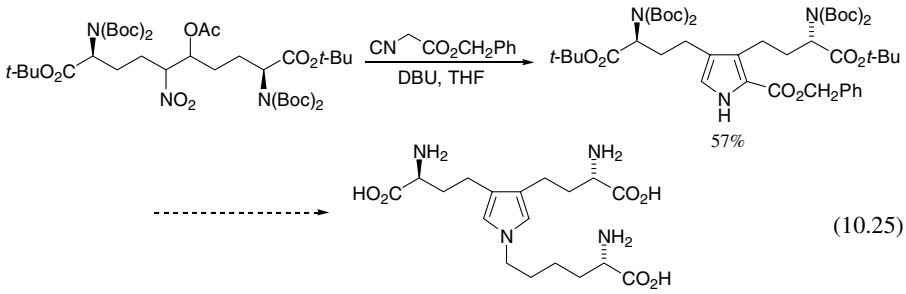
Many other biologically active pyrroles have been prepared by this reaction. 2-Cyano-3,4-disubstituted pyrroles are prepared by the reaction of isocyanoacetonitrile with β-nitro acetates.

This is used for synthesis of porphobilinogen (Eq. 10.24).[25] Porphobilinogen is the key building block in the biosynthesis of pigments of life such as porphyrins, heme, and vitamin $B_{12}$. Interesting application of porphobiliogen to synthesis of immunocomponents for the measurement of lead (Pb) by fluorescence polarization immunoassay has been reported.[26]




(10.24)

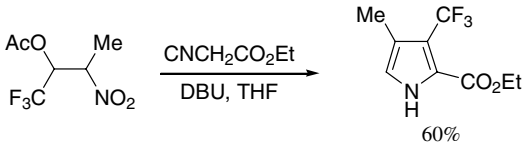
Total synthesis of (+)-deoxypyrrolorine, a potential biochemical marker for diagnosis of osteoporosis, is shown in Eq. 10.25.[27] Osteoporosis is a crippling degenerative bone disease that affects the aged population, particularly postmenopausal women.



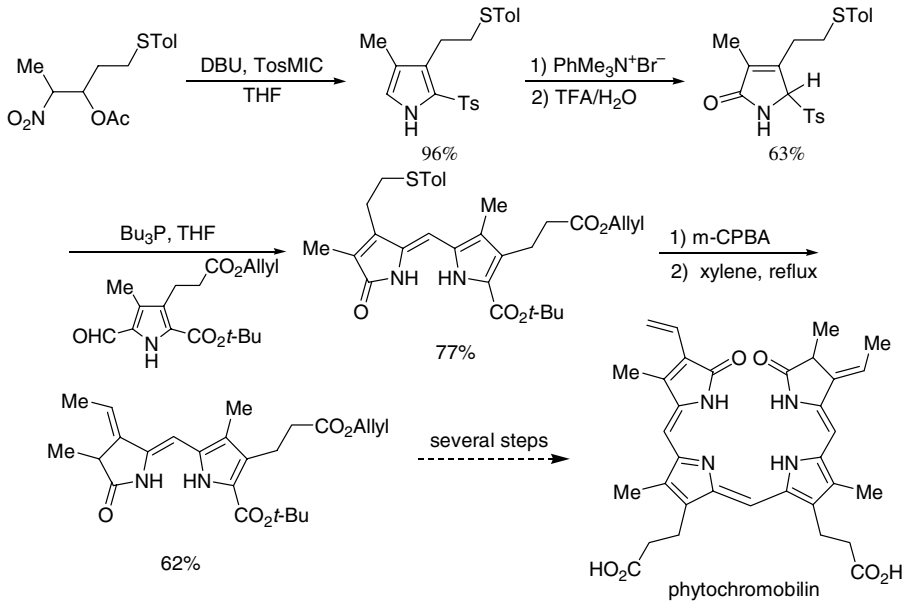

(10.25)

Total synthesis of phytochromobilin starting from 2-tosylpyrroles, which are prepared by β-nitro acetates with TosMIC (Scheme 10.4) has been reported.[28] Phytochrome is a chromoprotein concerned in a variety of processes in higher plants such as growth, development, and morphogenesis.[29]

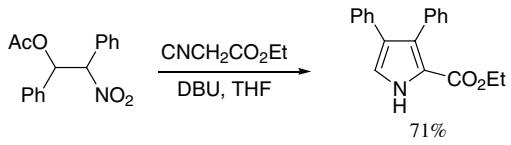
Barton-Zard pyrrole synthesis is also applied to synthesis of pyrroles with a variety of substituents. Pyrroles substituted with long alkyl substituents at the 3 and 4 positions,[30] pyrroles with β-$CF_3$ (Eq. 10.26),[31] 3,4-diarypyrroles (Eq. 10.27),[32] and pyrrole-2-phophonates (Eq. 10.28)[33] are prepared in a similar manner based on isonitrile cyclization.



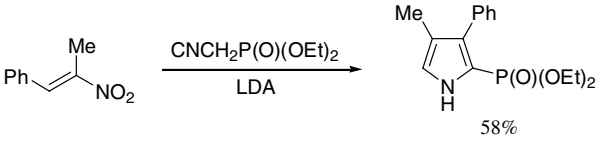

(10.26)




**Scheme 10.4.**

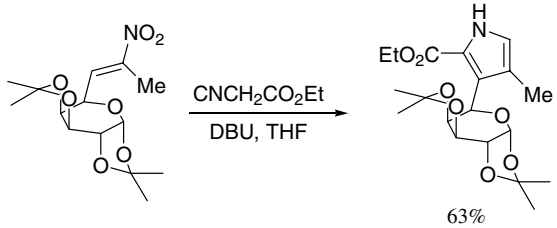



(10.27)



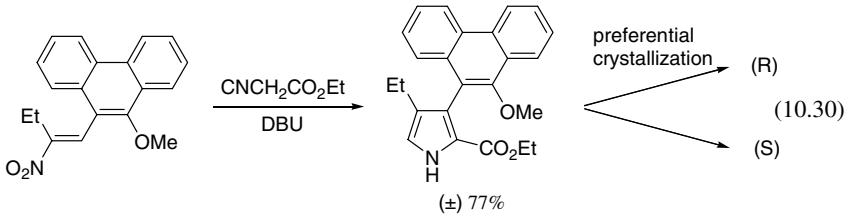

(10.28)

Nitroalkenes derived from galactose or other carbohydrates are converted directly into pyrroles substituted with such carbohydrates at the β-position. They are important precursors for water-soluble porphyrins (Eq. 10.29).[34] Such kinds of porphyrins are good candidates for photodynamic therapy of cancer and have been extensively studied.



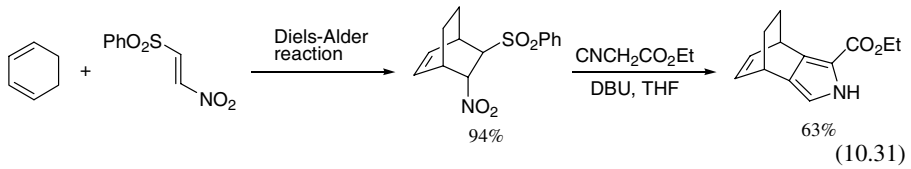

(10.29)

Aida and coworkers have used the Barton-Zard reaction in the synthesis of axially dissymmetric pyrroles as shown in Eq. 10.30.[35]

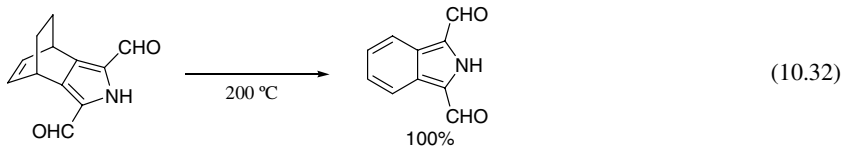



(10.30)

The combination of the Diels-Alder reaction of β-sulfonylnitroethylene and the Barton-Zard reaction provides a new synthesis of pyrroles fused with polycyclic skeletons (Eq. 10.31).[36] Pyrroles fused with bicyclo[2.2.2]octodiene are important precursors for synthesis of isoindoles via the retro Diels-Alder reaction (Eq. 10.32).[37]

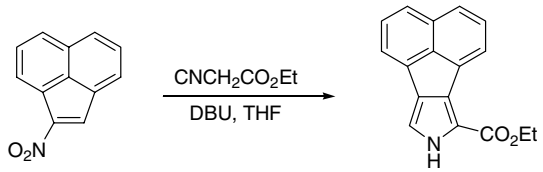



(10.31)

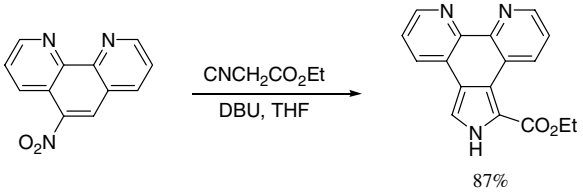



(10.32)

For example, 2,7-diformylisoindole is obtained in quantitative yield by heating the corresponding pyrrole fused with bicyclo ring. Certain aromatic nitro compounds are reactive enough to undergo the Barton-Zard reaction. For instance, polycyclic aromatic nitro compounds are generally reactive toward the anion of ethyl isocyanoacetate to give pyrroles fused with polycyclic aromatic rings, as shown in Eqs. 10.33 and 10.34.[38]

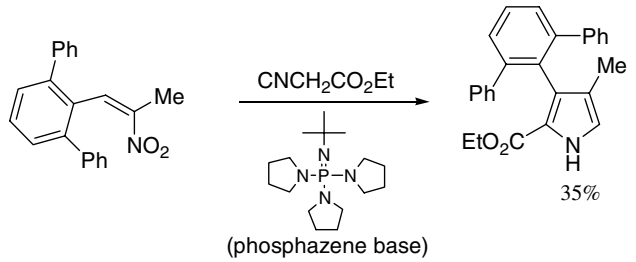



(10.33)



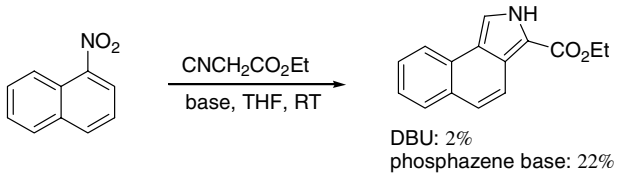

(10.34)

DBU is most widely employed as the base in the Barton-Zard reaction. Stronger nonionic bases such as $P(MeNCH_2CH_2)_3N$ and the phosphazene base (supplied by Fluka) are more effective to induce pyrrole formation in the reaction of nitroalkenes with isocyano esters than DBU.[39] Sterically hindered nitroalkenes are converted into the corresponding pyrroles using these bases, as shown in Eq. 10.35,[39b] but DBU is not effective in this transformation.



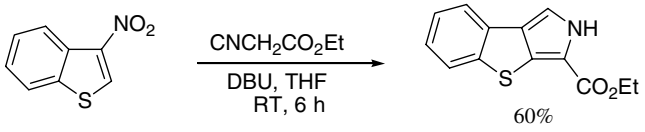

(10.35)

This strategy using super nonionic strong base is also applied to less reactive aromatic nitro compounds. The reaction of 1-nitronaphthalene with ethyl isocyanoacetate proceeds very slowly in the presence of DBU, but this reaction is accelerated by the use of phosphazene base to give the corresponding pyrrole in reasonable yield (Eq. 10.36).[40]



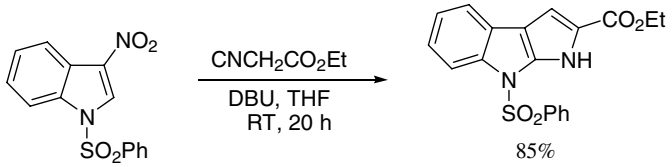

(10.36)

Heterocyclic aromatic nitro compounds are more reactive toward nucleophiles than carbocyclic aromatic nitro compounds. Various heterocyclic aromatic nitro compounds are thus converted into the corresponding pyrroles by the Barton-Zard reaction (Eq. 10.37).[38b,41]

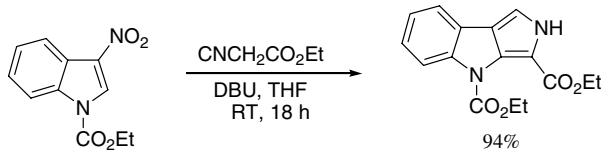



(10.37)

The 3-nitroindoles show interesting reactivity toward the anion of ethyl isocyanoacetate; *N*-sulfonyl derivatives give the pyrrolo[2,3-b]indole ring system (Eq. 10.38).[42] On the other hand, *N*-alkoxycarbonyl derivatives give the normal product, the pyrrolo[3,4-*b*]indole ring system (Eq. 10.39).[43]

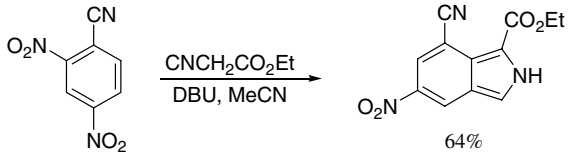



(10.38)




(10.39)

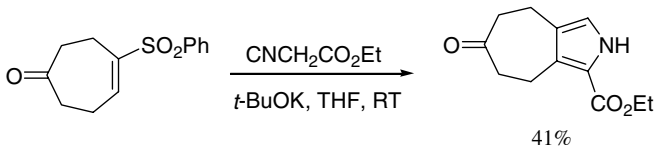
Monocyclic nitro aromatics such as *m*-dinitrobenzene and its derivatives also react with ethyl isocyanoacetate to give the corresponding isoindoles (Eq. 10.40).[44]




(10.40)

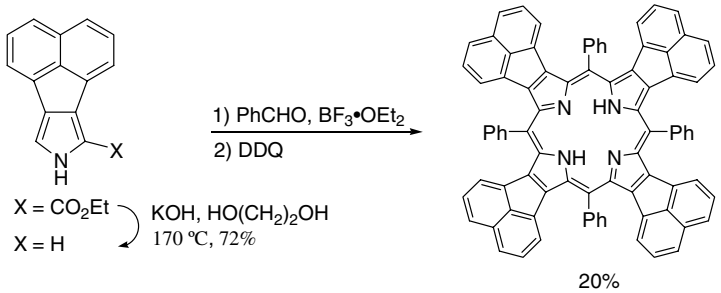
Polymer-supported reagents and other solid sequestering agents may be used to generate an array of 1,2,3,4-*tetra*substituted pyrrole derivatives using the Barton-Zard reaction as a key pyrrole formation reaction. Pure pyrroles are obtained without any chromatographic purification steps.[45]

Nitroalkenes can be replaced by α,β-unsaturated sulfones in the Barton-Zard pyrrole synthesis. Each method has its own merit. Nitroalkenes are more reactive than α,β-unsaturated sulfones; therefore, nitroalkenes should be used in less reactive cases. On the other hand, cyclic α,β-unsaturated sulfones are more easily prepared than cyclic nitroalkenes; pyrrole synthesis using sulfones is the method of choice in such cases, as shown in Eq. 10.41.[46]




(10.41)

Pyrroles prepared by the Barton-Zard reaction are very important as precursors of porphyrins and also of conducting polymers. The ester group at the 2-position is readily removed on heating with KOH in ethylene glycol at 170 °C to give α-free pyrroles, which are useful for preparing porphyrins (Eq. 10.42)[47] or polypyrroles (Eq. 10.43).[38a,48]

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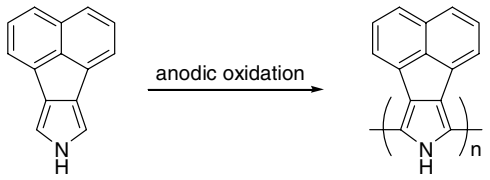
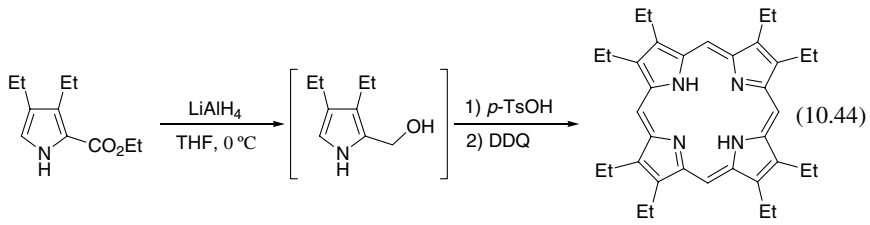
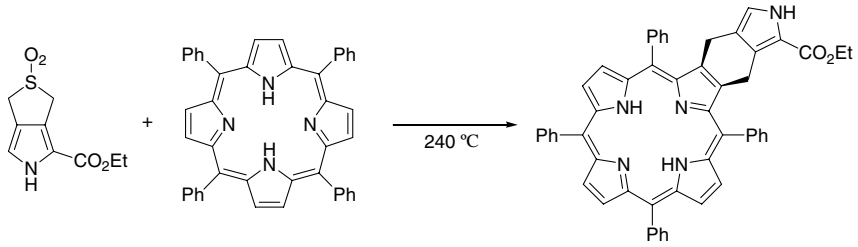


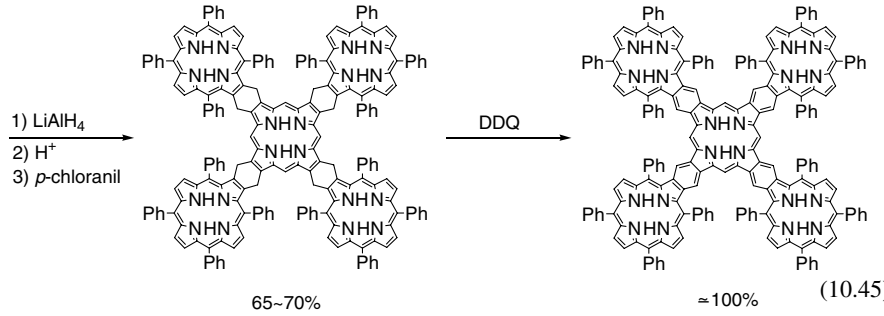

(10.43)

In 1988, Ono and Maruyama reported a very simple synthesis of octaethylporphyrin (OEP) from 3,4-diethylpyrrole-2-carboxylate, as shown in Eq. 10.44.[49] Reduction of this pyrrole with $LiAlH_4$ gives 2-hydroxyethylpyrrole, which is converted into OEP on treatment with acid and an oxidizing agent. This route is very convenient for synthesis of porphyrins. This method is now used extensively for synthesis of β-substituted porphyrins.[50] For example, a highly conjugated porphyrin, shown in Eq. 10.45, has been prepared by this route.[51] The requisite pyrroles are prepared from nitro compounds or sulfones; thus, various substituents are readily introduced into porphyrins.



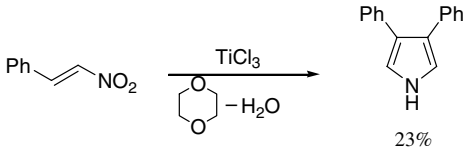

(10.44)



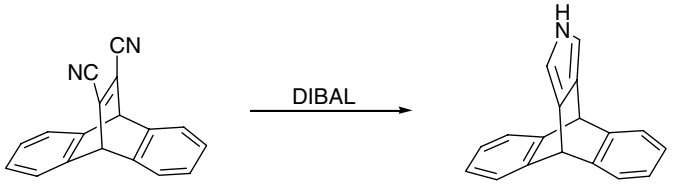




(10.45)

Reduction of nitrostyrene with aqueous $TiCl_3$ gives a 3,4-diarypyrrole directly in moderate yield (Eq. 10.46).[52] The reaction proceeds via dimerization of anion radicals of nitrostyrene and reduction of the nitro function in the dimer to imines. Reduction of dinitrile with diisobutylaluminum hydride (DIBAL) gives α-free pyrroles (Eq. 10.47);[53] both reactions may proceed in a similar mechanism. These pyrroles are useful intermediates for functionalized porphyrins.

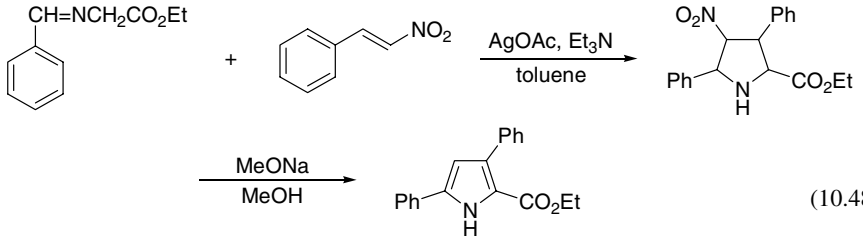



23% (10.46)




33% (10.47)

1,3-Dipolar cycloaddition reaction of azomethine ylides to alkynes or alkenes followed by oxidation is one of the standard methods for the preparation of pyrroles.[54] Recently, this strategy has been used for the preparation of pyrroles with $CF_3$ or $Me_3Si$ groups at the β-positions.[55] Addition of azomethine ylides to nitroalkenes followed by elimination of $HNO_2$ with base gives pyrroles in 96% yield (Eq. 10.48).[56]

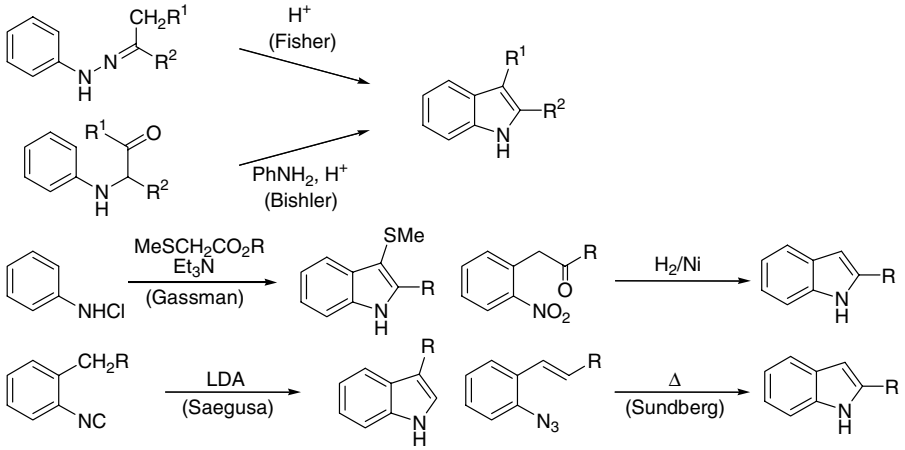



96% (10.48)

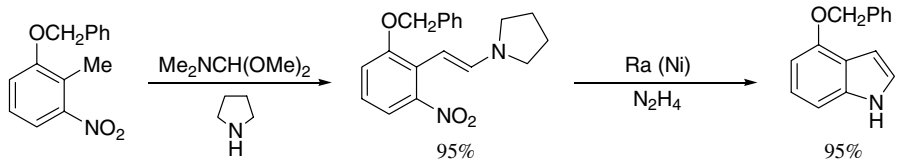
## 10.2 SYNTHESIS OF INDOLES

The indole unit occurs in nature in a wide variety of structures, and there are over thousands of known indole alkaloids. Many of these naturally occurring compounds have important physiological activity.[57] Although the continuing enormous interest in indoles has generated a large amount of information, this section is limited to recent development of indole synthesis using nitro compounds. 3-Substituted indoles are usually most easily prepared by substitution reactions on an existing indole nucleus, but, for indoles with other substitution patterns, it is necessary to synthesize the indole ring system. There are two general approaches to their synthesis: one based on benzenoid precursor with a nitrogen substituent and a free *ortho* position [Fisher synthesis (see Ref. 1), Bishler synthesis,[58] and Gassman synthesis[59]] and the other on a precursor with adjacent carbon and nitrogen substituents (Reissert synthesis,[60] nitrene cyclization,[61] and isonitrile cyclization[62]) (see Scheme 10.5). Because aromatic nitro compounds are good precursors for the introduction of nitrogen substituents such as $NH_2$, NC, and nitrene, many indoles have been prepared starting from nitroarenes.

The Batcho indole synthesis involves the conversion of an *o*-nitrotoluene to a β-dialkylamino-*o*-nitrostyrene with dimethylformamide acetal, followed by reductive cyclization to indoles. This provides a useful strategy for synthesis of substituted indoles (Eq. 10.49).[63]

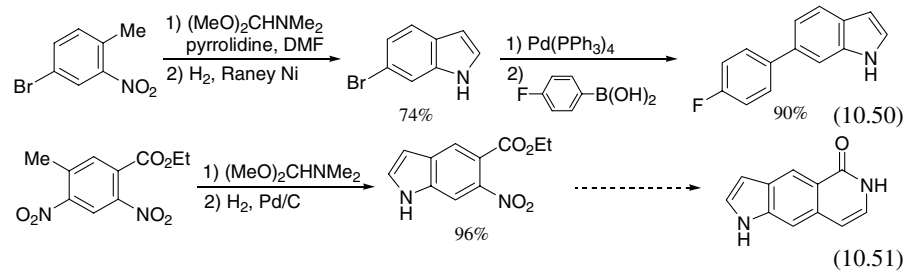


**Scheme 10.5**



(10.49)

This method has been applied to a large-scale preparation of 6-bromoindole, which reacts with various arylboronic acids via the Suzuki reaction to afford 6-arylindoles (Eq. 10.50).[64] 6-Bromo-5-methoxyindole for use in the synthesis of marine bromoindole[65] and 5-amino-7-ethoxycarbonylindole for use in synthesis of 1*H*-pyrrolo[3,2-*g*]quinazoline ring system (Eq. 10.51)[66] have been prepared from the appropriate *o*-nitrotoluene.

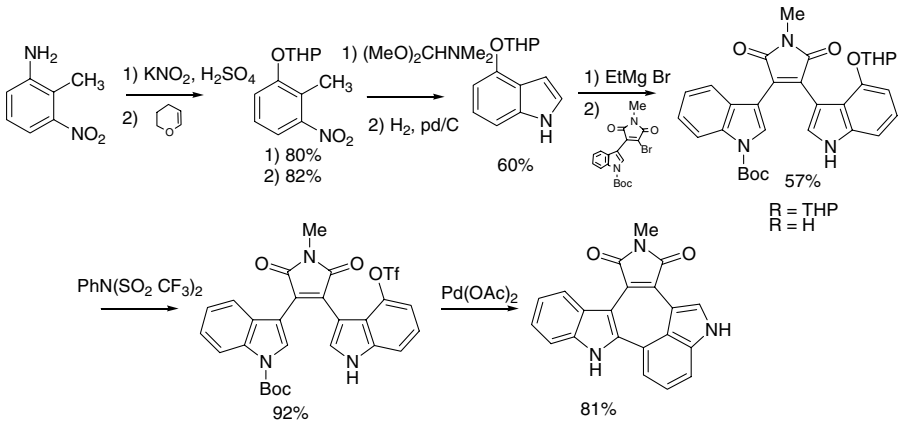


(10.50)

(10.51)

Batcho indole synthesis is a useful tool for synthesis of natural products. As outlined in Scheme 10.6, the Batcho indole synthesis is used for total synthesis of the slime mold alkaloid arcyriacyanin.[67] Such indolocarbazole alkaloids represent a growing number of natural products isolated from soil organism, slime molds, and marine sources. They are important as antitumor compounds and protein kinase C and topoisomerase inhibitors.

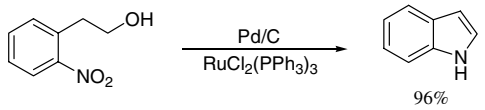
Recently, synthesis of the 4-arylindole portion of the antitumor agent diazonamide has been achieved starting from 3-bromo-2-methylnitrobenzene via Suzuki coupling and the Batcho reaction.[67b]




**Scheme 10.6.**

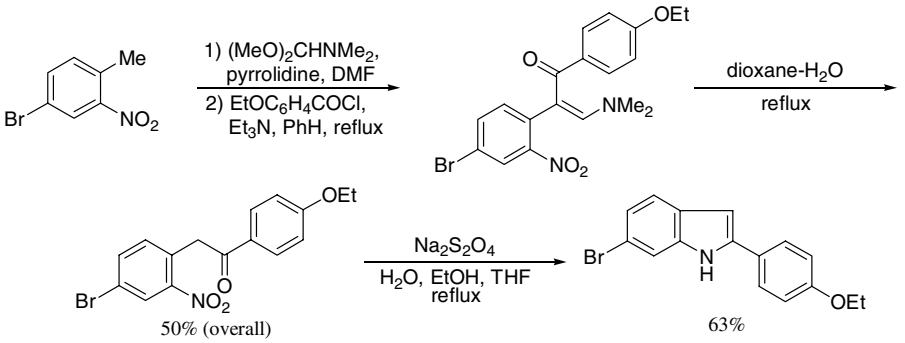
An important extension of this indole synthesis is the functionalization of the intermediate of indole. For example, acylation of the intermediate is possible (Scheme 10.7).[68]

The 2-aminophenethyl alcohols resulting from condensation of *ortho*-nitrotoluenes are good precursors for preparation of indoles. Watanabe and coworkers have developed ruthenium-catalyzed dehydrogenative *N*-heterocyclization for synthesis of indoles and other heterocycles from 2-aminophenethyl alcohols or 2-nitrophenylethyl alcohols (Eq. 10.52). [69a] The oxidative cyclization of 2-aminophenethyl alcohols are also catalyzed by Pd-based catalysts.[69]



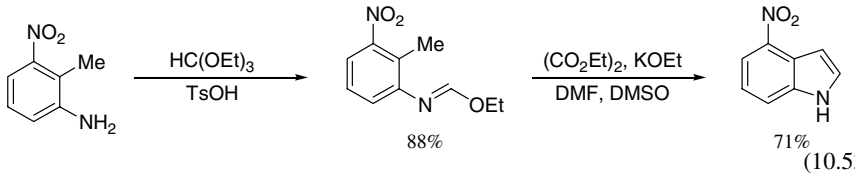

(10.52)

A neat synthesis of 4-nitroindole depends on an acylation-deacylation sequence from 2-methyl-3-nitroaniline, as shown in Eq. 10.53.[70] On the other hand, treatment of *N*-protected indoles with acetyl nitrate generated in situ at low temperature gives the corresponding



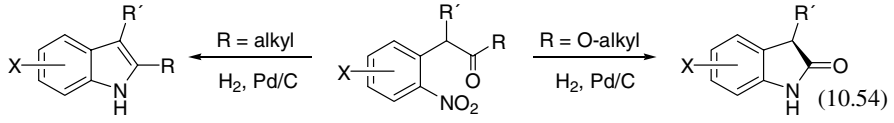

**Scheme 10.7.**

3-nitroindoles in good yields.[71] The regioselective synthesis of nitroindoles is important for functionalization of indoles.[72]

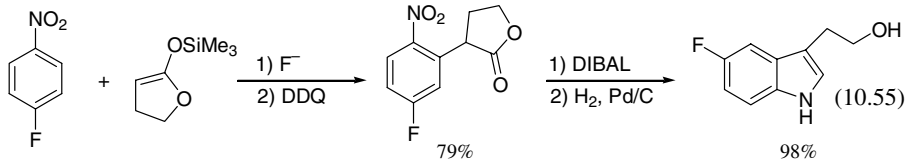



(10.53)

As discussed in Chapter 9, various nucleophiles can be introduced at the *ortho* position of nitroarenes via the VNS process. This provides a useful strategy for the synthesis of indoles. One of the most attractive and general methods of indoles and indolinones would be the reductive cyclization of α-nitroaryl carbonyl compounds (Eq. 10.54). The VNS and related reactions afford α-nitroaryl carbonyl compounds by a simple procedure. For example, alkylation of 4-fluoronitrobenzene with a lactone silyl enol ether followed by reductive cyclization leads to tryptophols (Eq. 10.55).[73]

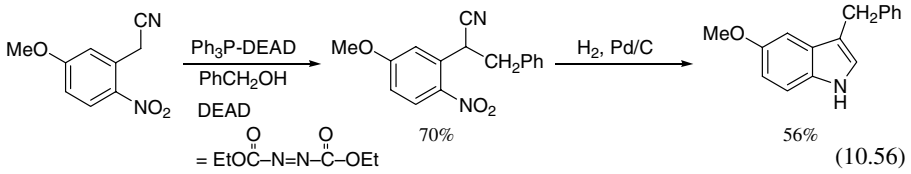



(10.54)



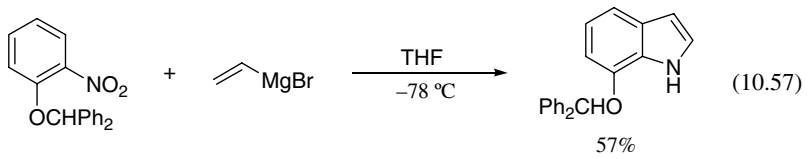

(10.55)

The cyanomethylation of nitroarenes followed by alkylation and reductive cyclization yields indoles (see Chapter 9, which discusses the VNS reactions) (Eq. 10.56).[74]

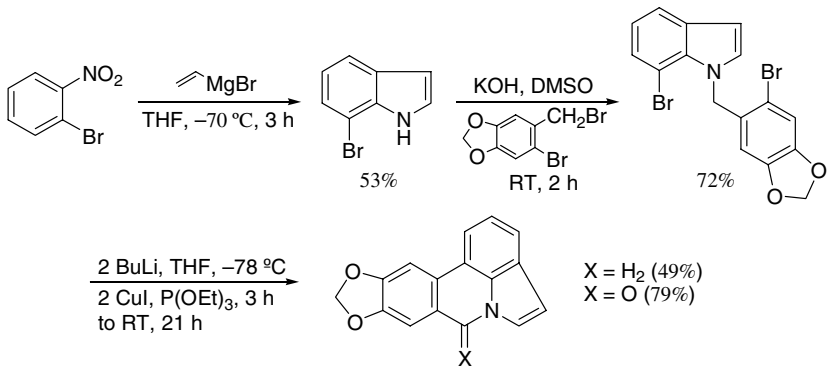



(10.56)

Improvement was reported in the synthesis of 7-alkoxyindoles by reaction of alkoxynitrobenzenes with vinylmagnesium bromide (Eq. 10.57).[75] This reaction proceeds via the addition of the Grignard reagent *ortho* to the nitro group and subsequent [3,3]sigmatropic rearrangement (Bartori indole synthesis).[76] This indole synthesis is applied to a short synthesis of the pyrrolophenanthridone alkaloid hippadine, as shown in Scheme 10.8.[77]

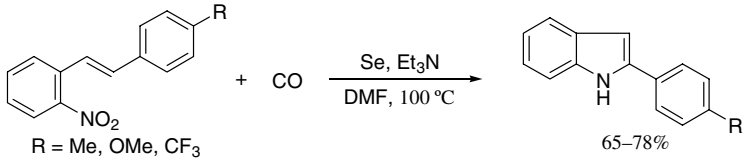



(10.57)



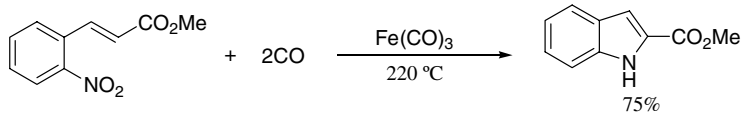

**Scheme 10.8.**

The intramolecular cyclization of nitrenes obtained either from deoxygenation of *o*-nitrostyrene by trialkyl phosphites[78] or from thermal or photochemical decomposition of *o*-azidostyrenes[79] provides a useful method for the construction of indole nucleus (Cadogan-Sundberg indole synthesis). Holzapfel has used this method to synthesize several carbazoles and norharman from the appropriate 2-nitrobiphenyls and also several 2-methoxycarbonylindoles from methyl *o*-nitrocinnamates.[80] The novel generation of nitrenes from *o*-nitrostilbenes using CO and Se leads to an efficient synthesis of 2-arylindoles (Eq. 10.58).[81] A new synthetic approach to the natural product arcyriaflavin-A, based on nitrene insertion, has been reported.[81b]



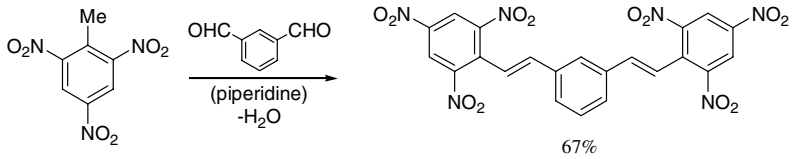

(10.58)

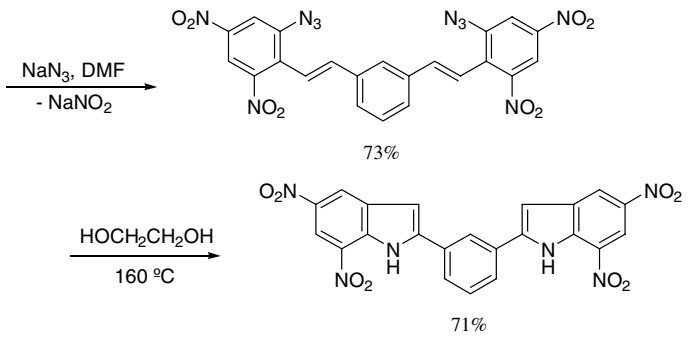
The metal carbonyls $Fe(CO)_5$, $Ru_3(CO)_{12}$, and $Rh_6(Co)_{16}$ are catalysts for the deoxygenation of *o*-nitrostyrenes under carbon monoxide pressure to give indole derivatives (Eq. 10.59).[82]




(10.59)

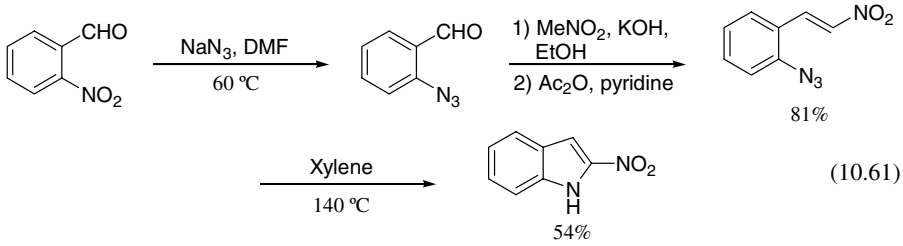
The Sundberg indole synthesis using aromatic azides as precursors of nitrenes has been used in synthesis of various indoles. Some kinds of aryl azides are readily prepared by $S_NAr$ reaction of aromatic nitro compounds with an azide ion. For example, 2,4,6-trinitrotoluene (TNT) can be converted into 2-aryl-4,6-dinitroindole, as shown in Eq. 10.60.[83]





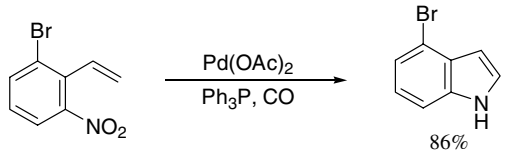

(10.60)

The previously unknown 2-nitroindoles have been conveniently prepared from *o*-nitrobenzaldehyde via the Sundberg indole synthesis (Eq. 10.61).[84]



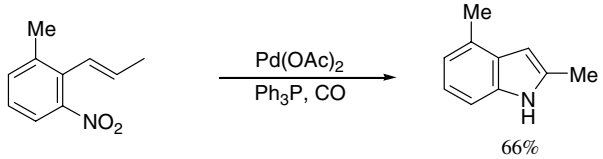

(10.61)

Soderberg and coworkers have developed a palladium-phosphine-catalyzed reductive *N*-heteroannulation of 2-nitrostyrenes forming indoles in good yields.[85] For example, reaction of 6-bromo-2-nitrostyrene with carbon monoxide in the presence of a catalytic amount of palladium diacetate (6 mol%) and triphenylphosphine (24 mol%) in acetonitrile at 70 °C, gives 4-bromoindole in 86% yield (Eq. 10.62). Several functional groups, such as esters, ethers, bromides, triflates, and additional nitro groups, have been shown to be compatible with the reaction conditions.



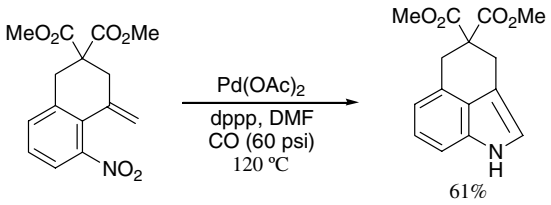

(10.62)

With the use of this methodology, 2,4-dimethylindole, 4-(hydroxymethyl)-2-methylindole, and 4-(methoxymethyl)-2-methylindole are readily obtained, as shown in Eq. 10.63.[86] These indoles have been recently isolated from European Basidmycetes.[87] Watanabe and coworkers have used a catalytic amount of $PdCl_2(PPh_3)_2$-$SnCl_2$ under carbon monoxide for reductive *N*-heterocyclization of *o*-nitrostyrenes.[88]



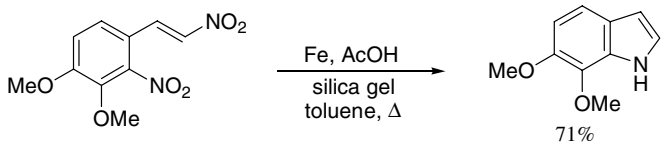

(10.63)

Fused indoles, as shown in Eq. 10.64, are also prepared by this method.[85a]



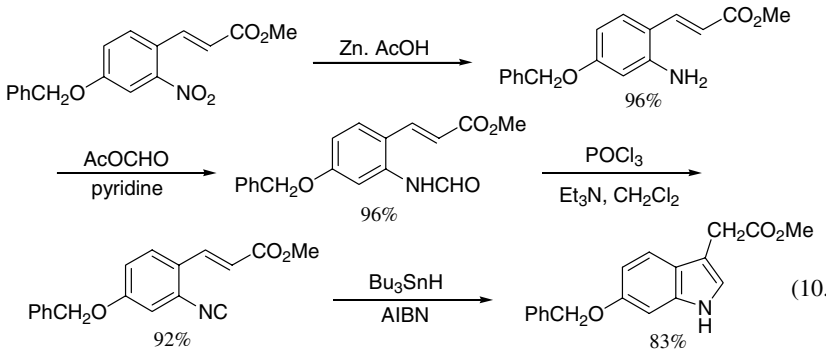

(10.64)

Similar to the Fisher indole synthesis, reductive cyclization of nitro aromatics offers a powerful means of forming indoles. Reductive cyclization of *ortho*, 2′-dinitrostyrenes has occurred in many ways, by $TiCl_3$, $NaBH_4$-Pd/C, $H_2$-Pd/C, and other reductive methods.[89] Corey and coworkers have used the Borchardt modification (Fe-AcOH, silica gel, toluene at reflux for the reductive cyclization of *o*-β-dinitrostyrenes) to prepare 6,7-dimethoxyindole (Eq. 10.65) in a total synthesis of aspidophytine (see Schemes 3.3 and 3.4 in Section 3.2.1).[89d]




(10.65)

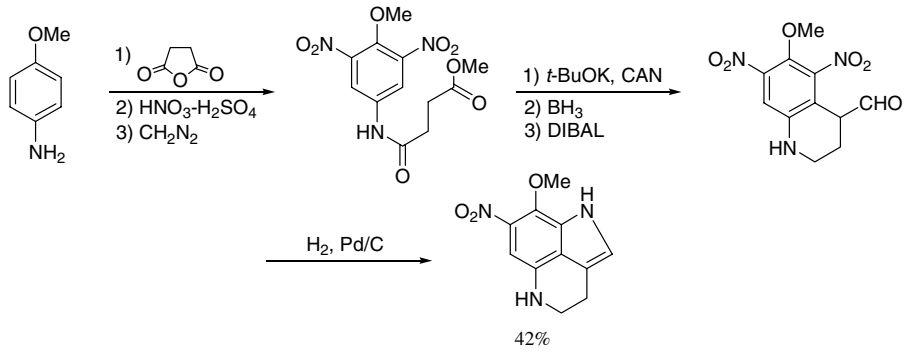
Tin-mediated-radical cyclization of isonitriles provides a useful strategy for the preparation of indoles (Fukuyama reaction).[90] This radical cyclization is used for synthesis of 6-hydroxyindole-3-acetic acid, which is the aromatic subunit of Nephilatoxin. The requisite isonitriles are prepared from nitroarenes via amines (Eq. 10.66).[91]




(10.66)

The classic Reissert indole synthesis, involving the reductive cyclization of *o*-nitrophenylpyruvic acid, has been used for synthesis of 2-ethoxycarbonyl-4-alkoxymethylindoles.[92] The modified Reissert reaction, involving the reductive cyclization of an *o*-nitrophenyl acetoaldehyde, has been adapted to solid-phase synthesis.[93]

Kraus has reported the synthesis of a tricyclic indole related to the pyrroloiminoquinone marine natural products (Scheme 10.9), in which an intramolecular $S_NAr$ and the reductive cyclization of a nitro aldehyde are involved as key steps.[94] Related target compounds have been prepared by Joule and coworkers via a similar strategy.[95]

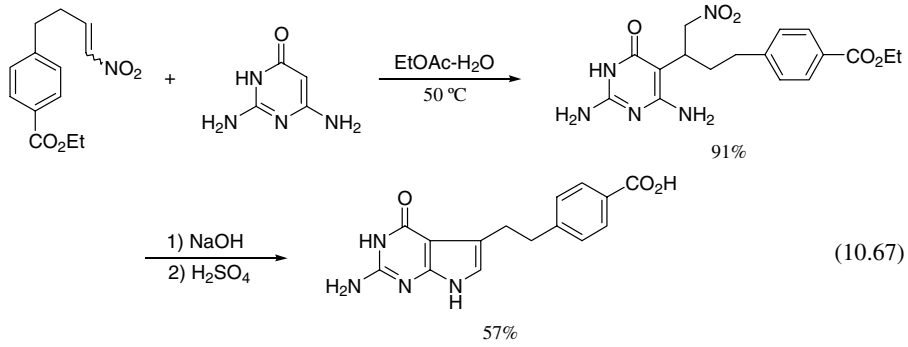



**Scheme 10.9.**

Rawal and Kozmin have utilized a Reissert type reaction in the total synthesis of tabersonine. The requisite nitro ketone is prepared by $S_NAr$ reaction of *o*-nitrophenylphenyliodonium fluoride with ketone silyl enol ether (Scheme 10.10).[96]

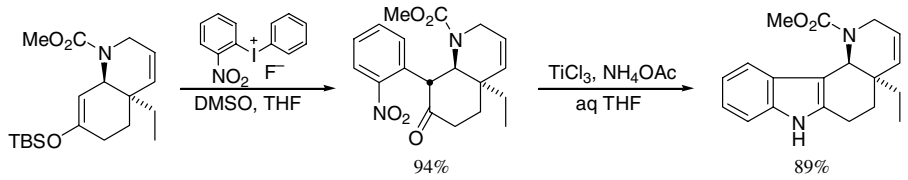
The reductive cyclization of *o*-nitrophenylacetic acids or esters gives oxyindoles, which has been applied to preparation of 6-hydroxy-7-methoxyoxyindole in a synthesis of (+)-paraherquamide B (Scheme 10.11).[42]

The pyrrolo[2,3-*d*]pyrimidine anticancer agent is prepared utilizing, as a key sequence, Michael condensation of 2,6-diamino-4(3*H*)-pyrimidinone with nitroalkenes, followed by the Nef reaction that leads to the annulated pyrrole ring (Eq. 10.67).[98]

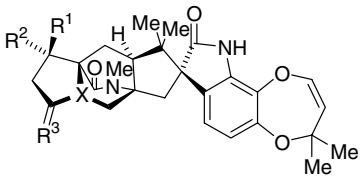



(10.67)

Annulation of pyridine to indole is accomplished by a tandem aza-Wittig/electrocyclization strategy as shown in Eq. 10.68.[99]

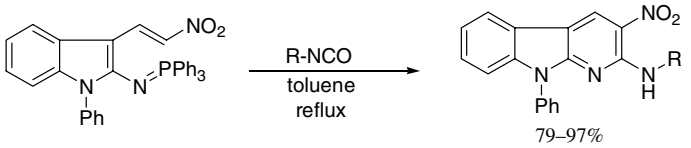



**Scheme 10.10.**



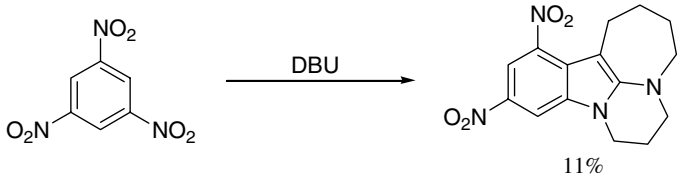
(–)-paraherquamide A, $R^1$ = OH, $R^2$ = Me, $R^3$ = $H_2$, X = N
(–)-paraherquamide B, $R^1$ = H, $R^2$ = H, $R^3$ = $H_2$, X = N
(–)-paraherquamide C, $R^1$ = $R^2$ = $CH_2$, $R^3$ = $H_2$, X = N
(–)-paraherquamide D, $R^1$ = O, $R^2$ = $CH_2$, $R^3$ = $H_2$, X = N
(–)-paraherquamide E, $R^1$ = H, $R^2$ = Me, $R^3$ = $H_2$, X = N

**Scheme 10.11.**




(10.68)

A novel indole ring formation involving DBU nucleophilic addition to 1,3,5-trinitrobenzene has appeared as shown in Eq. 10.69.[100]

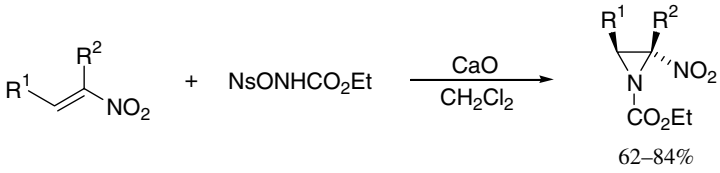



(10.69)

## 10.3 SYNTHESIS OF OTHER NITROGEN HETEROCYCLES

### 10.3.1 Three-Membered Ring

The direct aziridination of nitroalkanes has been reported for the first time. Treatment of nitroalkene with an excess of CaO and $NsONHCO_2Et$ (Ns = 4-nitrobenzenesulfonyl) gives the α-nitroaziridine in good yields (Eq. 10.70).[101] The reaction proceeds via aza-Michael reaction followed by a ring closure.



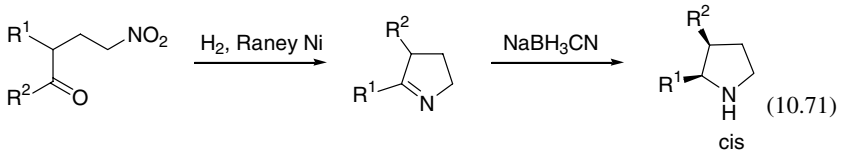

(10.70)

### 10.3.2 Five- and Six-Membered Saturated Rings

Pyrrolidines are structural subunits found in many natural and unnatural products, which have important biological activity.[102] Depending on the substitution pattern and functionalization, pyrrolidines have been shown to be effective antibacterials,[103] neuroexcitatory agents,[104] potent venom,[105] and glyosidase inhibitors.[106]

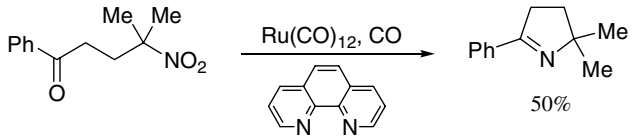
Nitro compounds have been extensively used for synthesis of pyrrolidines as discussed in Chapter 4 on the Michael addition and Chapter 8 on cycloaddition. Tandem [2 + 4]/[2 + 3]

cycloaddition using nitroalkenes provides an excellent route to stereoselective synthesis of pyrrolidines. This section describes the routes to the synthesis of pyrrolidines based on the Michael addition. The Michael addition of nitro compounds to α,β-unsaturated carbonyl compounds or esters followed by reduction gives pyrrolidines or related compounds. *cis*-2,3-Disubstituted pyrrolidines are available from nitro ketones, which are prepared by the Michael addition of nitromethane to enones. Reduction of the nitro ketones with Raney Ni gives the pyrrolines, which, on $NaBH_3CN$ reduction, give quantitative yields of *cis*-2,3-disubstituted pyrrolidines (Eq. 10.71).[107]



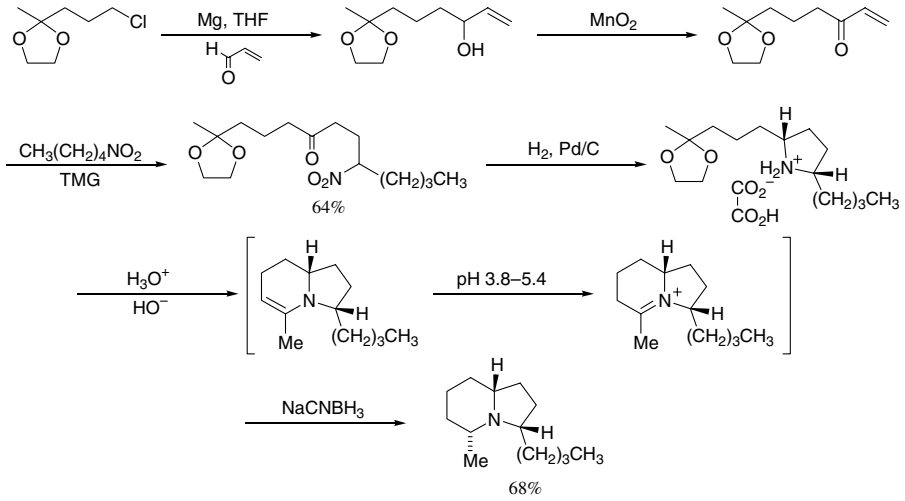

(10.71)

Ruthenium complex catalyzes reductive *N*-heterocyclization of γ-nitroketones to give pyrroline derivatives (Eq. 10.72).[108]

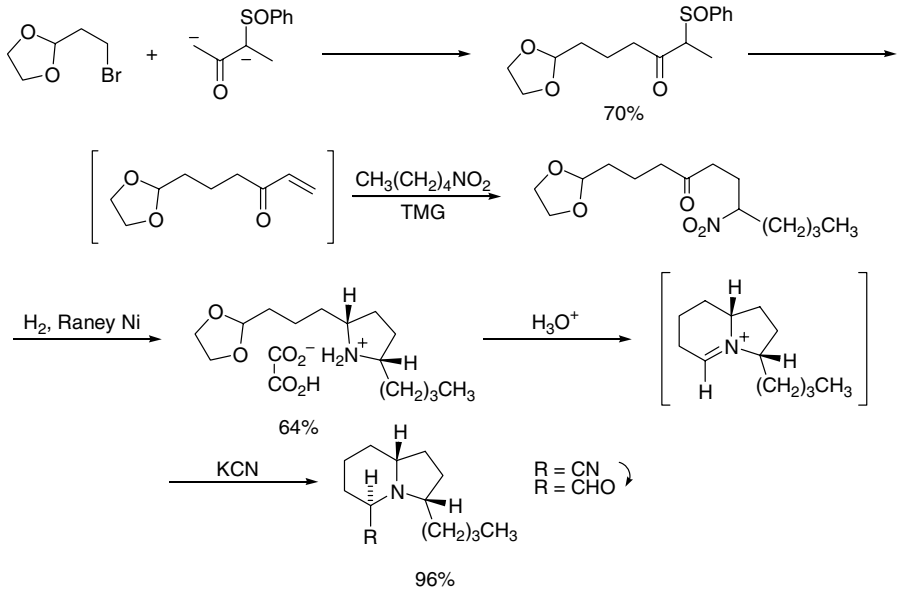



(10.72)

*cis*-2,5-Disubstituted pyrrolidines are prepared by the Michael addition of nitro compounds to enones followed by reduction with $H_2$-Pd/C. This strategy has been widely used for synthesis of various alkaloids. Stevens and Lee have reported stereoselective total synthesis of the tail pheromone of the Pharaoh ant (Scheme 10.12)[109] and gephyrotoxin 223, neurotoxic alkaloids



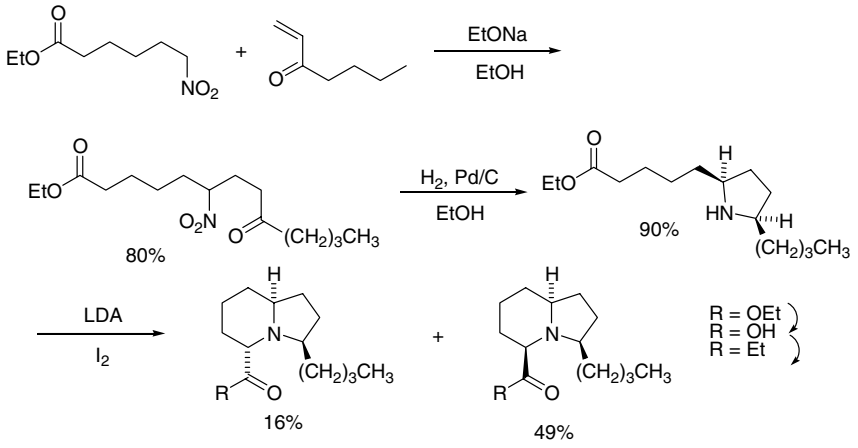

**Scheme 10.12.**



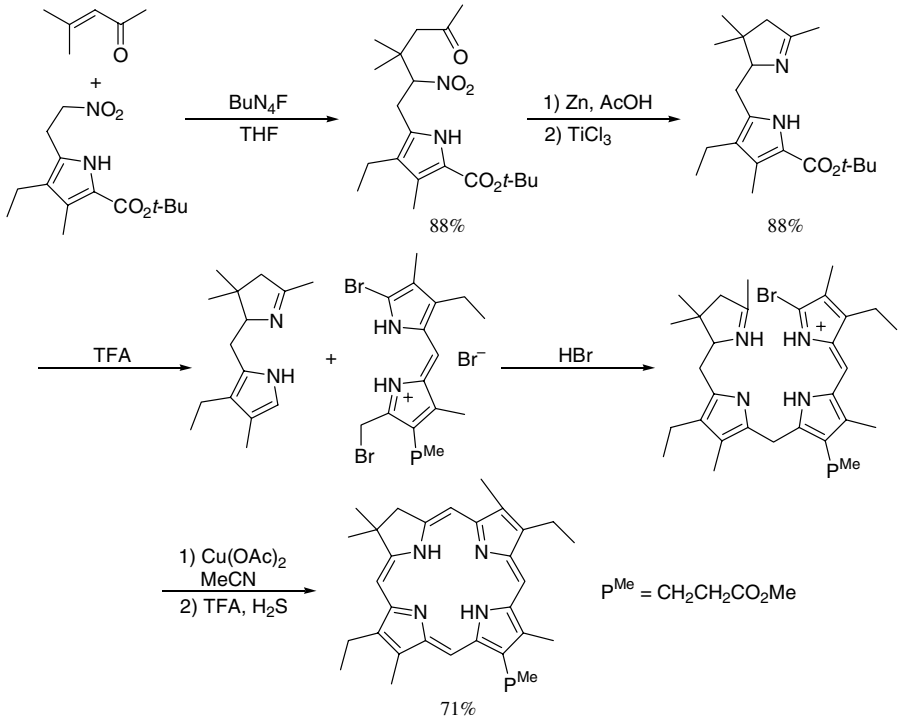

**Scheme 10.13.**

(Scheme 10.13).[110] New alkaloids from ants, (3*R*, 5*S*, 9*R*)-3-butyl-5-(1-oxopropyl)indolizidine and (3*R*, 5*R*, 9*R*)-3-butyl-5-(1-oxopropyl)indolizidine, are identified and synthesized as outlined in Scheme 10.14.[111]

Battersby and coworkers have developed selective methods for total synthesis of chlorins on a model system, as shown in Scheme 10.15, in which the Michael addition of 5-(2-nitroethyl) pyrrole to enone and reductive cyclization are used as key steps.[112]

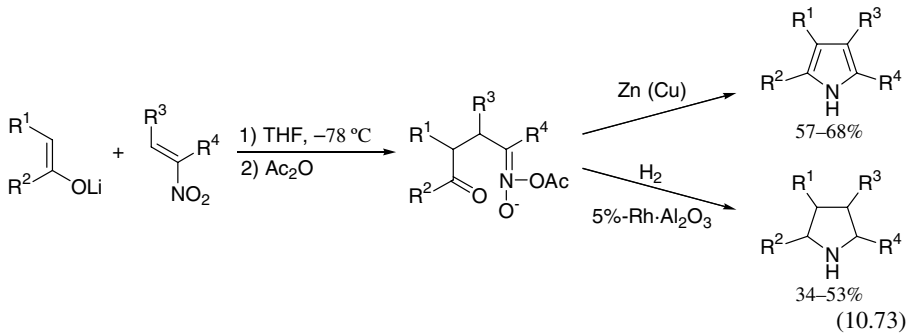



**Scheme 10.14.**



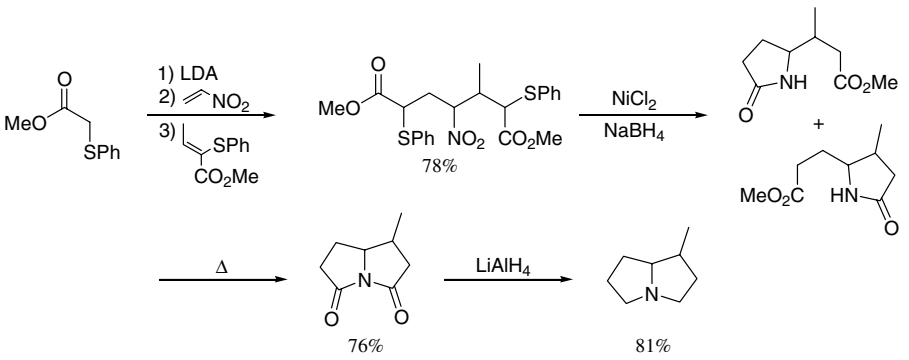

**Scheme 10.15.**

The Michael addition of lithium enolates to nitroalkenes followed by reaction with acetic anhydride gives acetic nitronic anhydrides, which are good precursors for 1,4-diketones, pyrroles, and pyrrolidines (Eq. 10.73).[113]




(10.73)

Nitroalkenes are shown to be effective Michael acceptor B units in three sequential reactions (A + B + C coupling) in one reaction vessel. The sequence is initiated by enolate nucleophiles (A) and is terminated by aldehydes or acrylate electrophiles (C). The utility of this protocol is for rapid assembly of complex structures from simple and readily available components. A short total synthesis of a pyrrolizidine alkaloid is presented in Scheme 10.16.[114]

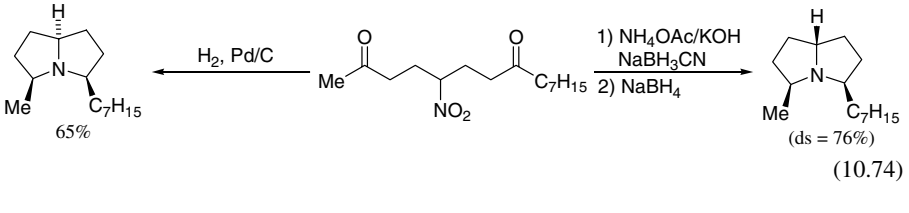



**Scheme 10.16.**

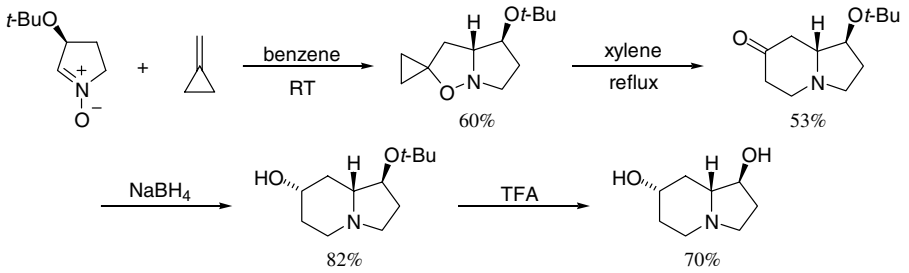
The pyrrolizidines and indolizidines are a group of alkaloids that are characterized by the presence of the basic azabicyclo[3.3.0]octane and azabicyclo[4.3.0]nonane frameworks, respectively. These alkaloids exhibit remarkably diverse types of biological activity and have been reported to act as antitumor, hypotensive, anti-inflammatory, carcinogenic, or hepatoxic agents. Various pyrrolizidines and indolizidines have been prepared by 1,3-dipolar cycloaddition.[115] Synthesis of these is described in the section 8.2 discussing cycloaddition.

An interesting strategy for the synthesis of pyrrolizidines and indolizidines has been developed by Brandi and co-workers. Cycloaddition between nitrones or nitrile oxides with methylenecyclopropanes generates strained tricyclic spiro compounds, which are prone toward further transformations, such as rearrangement, ring opening, and new ring closure (Scheme 10.17).[116]

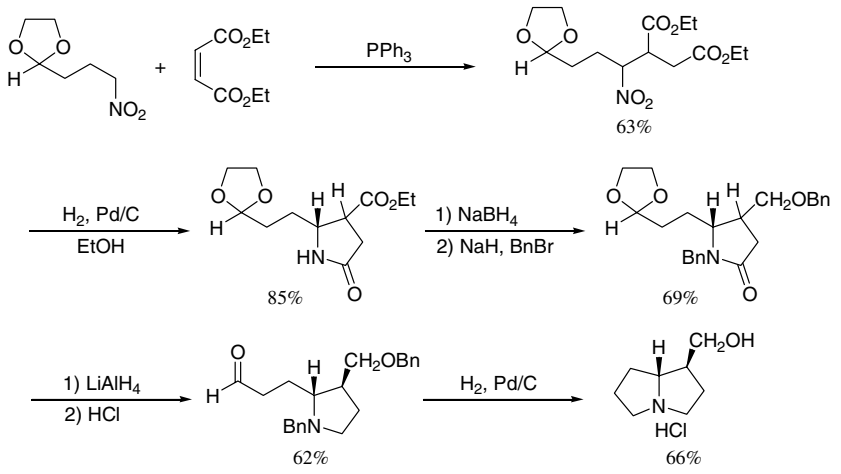
The Michael reaction of nitromethane with methyl vinyl ketone and 1-decene-3-one followed by reductive cyclization gives two isomeric pyrrolizidines, depending on reduction conditions (Eq. 10.74).[117]




(10.74)




**Scheme 10.17.**



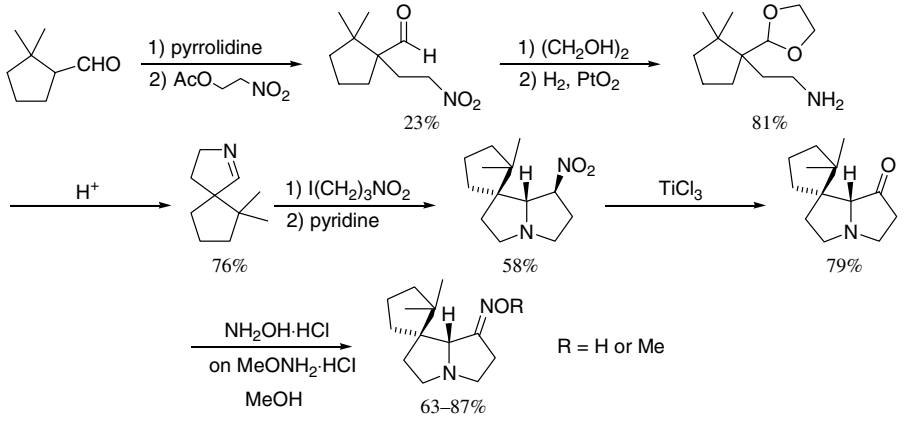

**Scheme 10.18.**

Another Michael addition route for synthesis of the pyrrolizidine alkaloide trachelanthamidin is shown in Scheme 10.18.[118]

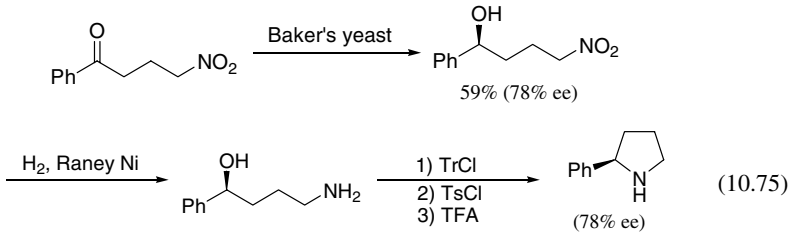
A novel spiropentanopyrrolizidine oxime has been isolated from skin extracts of the Panamanian poison frog. This alkaloid can be synthesized via the Michael addition of cyclopentanecarboxaldehyde to nitroethene (Scheme 10.19).[119]

Baker's yeast reduction of γ-nitroketones offers the corresponding chiral nitro alcohols, which are useful building blocks for the synthesis of chiral natural compounds.[120] For example, optically active 2-substituted pyrrolidine can be prepared using the chiral nitro alcohol (Eq. 10.75).[121]

The enantioselective reduction of γ-nitroketones and γ-nitrodiketones by the chiral reducing agent (+)- or (−)-diisopinocamphenylchloroborane (DIP-Cl$^{TM}$) gives nitro alcohols having from 33 to 86% ee and nitrodiols with complete diastereoselectivity and > 95% ee.[122]



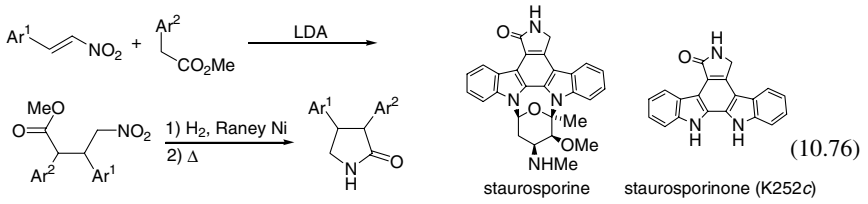

**Scheme 10.19.**




(10.75)

A short and efficient route to enantiopure 3,5-diarylpyrrolizidines using chiral nitrodiols has been reported (Scheme 10.20).[123]

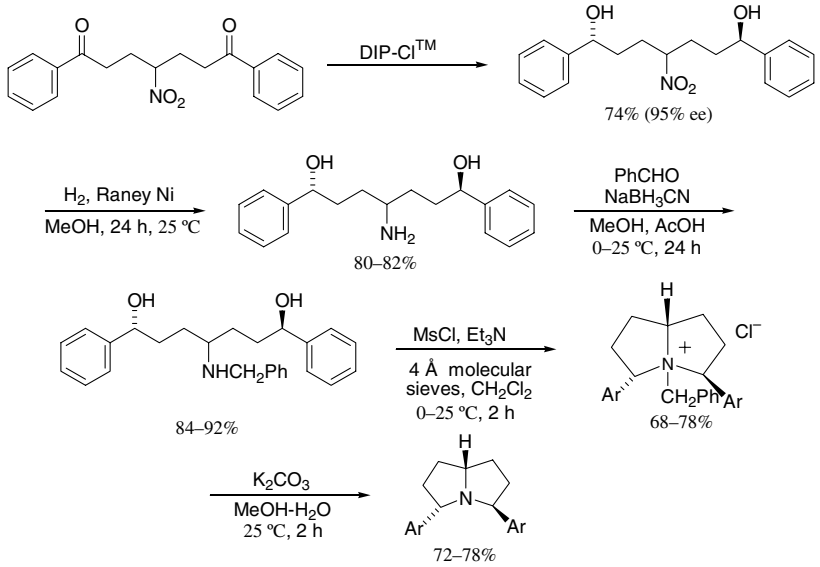
The Michael addition of the carbanions derived from esters to nitroalkenes followed by reductive cyclization has been used extensively for the preparation of pyrrolidin-2-ones (Eq. 10.76).[124] This strategy is used for synthesis of the carbazole alkaloid staurosporine aglycon (K-252c).[124c]



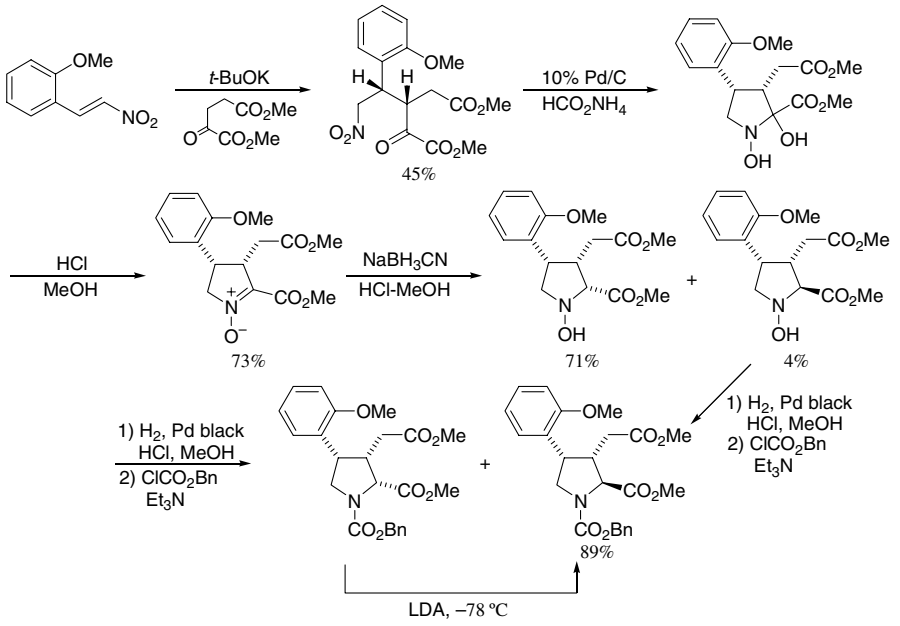

(10.76)

The synthesis of kainic acid, acromelic acid, and related compounds such as domoic acid has been the subject of considerable investigation.[125] A simple and direct route to neurophysiologically active kainic acid analogs has been reported, as shown in Scheme 10.21.[126]

Hydroxylated six-membered ring nitrogen containing heterocycles is a common feature of many natural products and biologically active compounds.[127] Willis and coworkers have



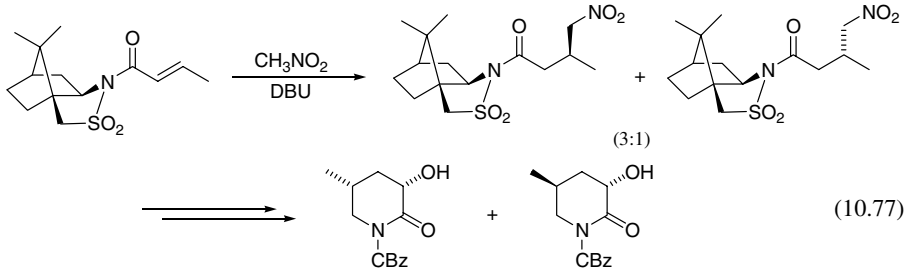

**Scheme 10.20.**




**Scheme 10.21.**

developed an efficient approach for the preparation of them. Enzyme-catalyzed reduction of 5-nitro-2-oxopentanoic acid to the corresponding (*S*)- and (*R*)-2-hydroxy acids. Subsequent esterification, catalytic hydrogenation of the nitro group using $Pt_2O$ catalyst, and spontaneous intramolecular cyclization give enantio-pure 3-hydroxy-piperidin-2-one, as shown in Scheme 10.22.[128]

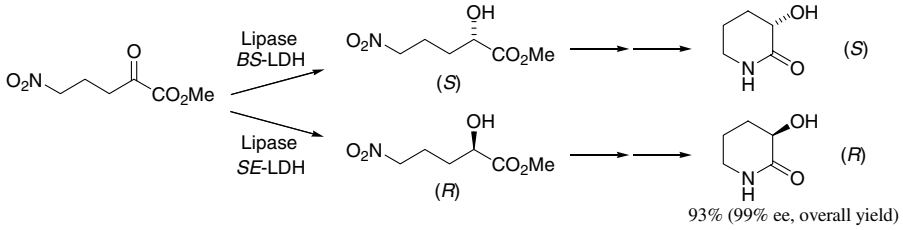
Asymmetric Michael addition of nitromethane to a crotonyl camphorsultam gives access to the enantio-pure 2-oxoesters, which may be converted into the 3-hydroxy-5-methylpiperidin-2-one (Eq. 10.77).[129]



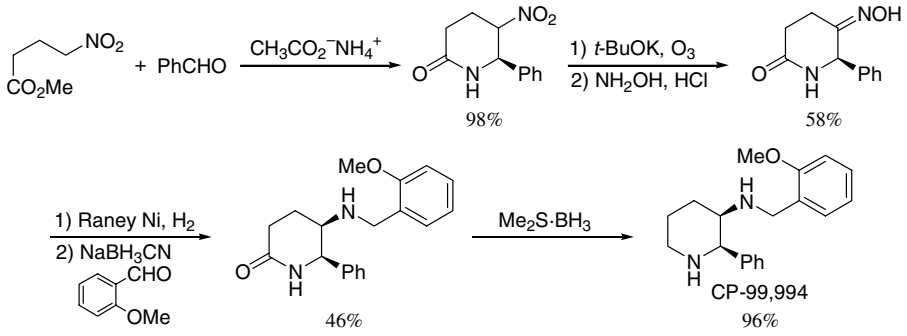

(10.77)

The reaction of γ-nitrobutenoate with aldehydes and ketones in the presence of ammonium acetate gives 3-nitropiperidines.[130] This reaction is used for synthesis of CP-99,994, a highly potent substance P antagonist (Scheme 10.23).[131]

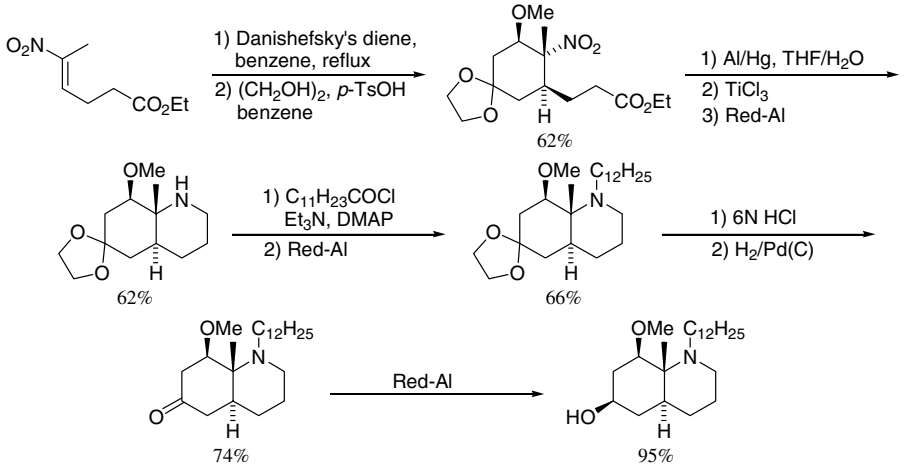
A novel synthetic approach toward the AB-ring system of 9-azasteroids using the Diels-Alder reaction of nitroalkene and subsequent reductive cyclization has been shown (Scheme 10.24).[132]



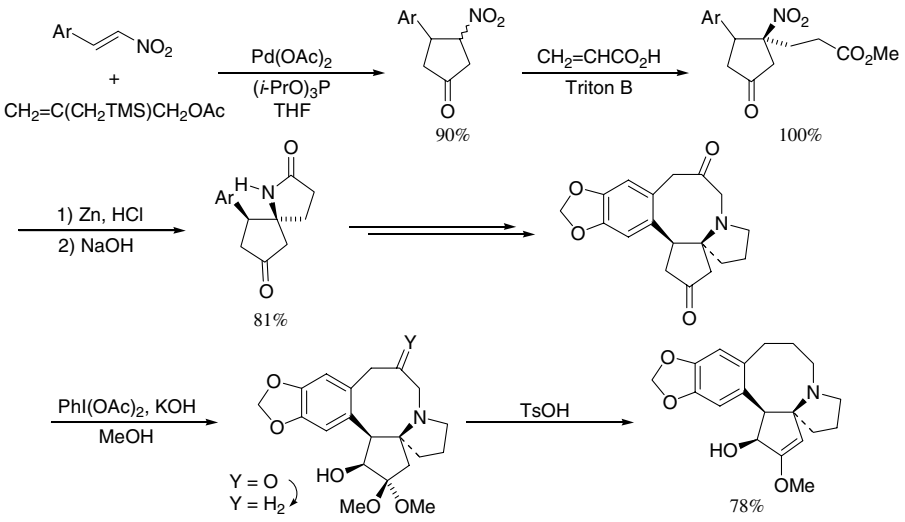

**Scheme 10.22.**




**Scheme 10.23.**




**Scheme 10.24.**

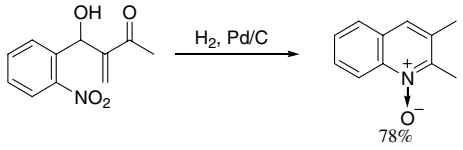



**Scheme 10.25.**

Palladium-mediated methylencyclopentane annelation of nitrostyrene is used for a total synthesis of cephalotaxine, which is the predominant alkaloid of the cephalataxus species (Scheme 10.25).[133]

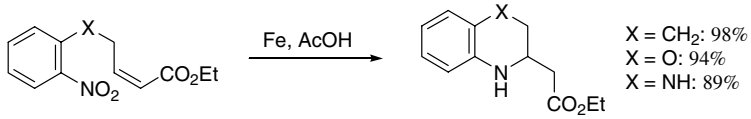
### 10.3.3 Miscellaneous

The reduction of aromatic nitro compounds to amino derivatives and cyclizations to various heterocyclic compounds are presented in Chapter 9. Recent advances are presented here. Reaction of 2-nitrobenzaldehyde with vinyl carbonyl compounds in the presence of 1,4-diazbicyclo[2.2.2]octane affords Baylis-Hillman products, the catalytic reduction of which results in direct cyclization to quinoline derivatives (Eq. 10.78).[134]



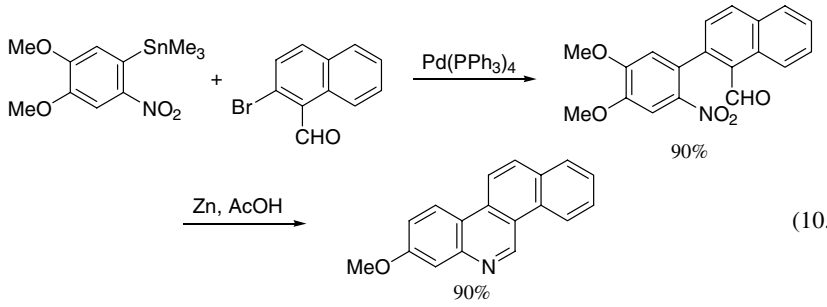

(10.78)

Tandem reduction-Michael addition using suitably substituted nitroarenes provides a general route to aryl-fused nitrogen heterocycles (Eq. 10.79).[135]



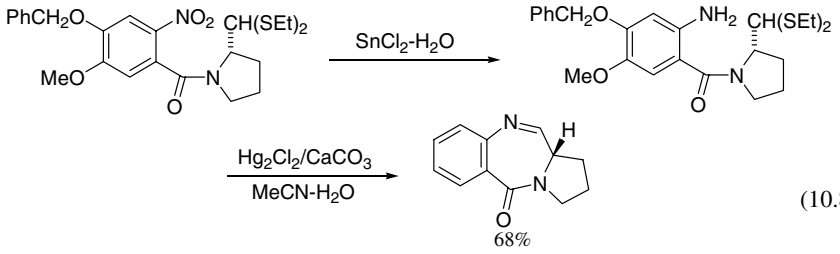

(10.79)

Reductive cyclization of 2-formyl-2′-nitrobiaryl compounds gives phenanthridine derivatives.[136] The Stille coupling of nitroarylstannanes with 2-bromobenzaldehyde are used for the preparation of the requisite 2-formyl-2′-nitrobiaryls. Subsequent treatment of biphenyl derivatives with zinc dust in acetic acid gives the phenanthridine derivatives as shown in Eq. 10.80.[137]



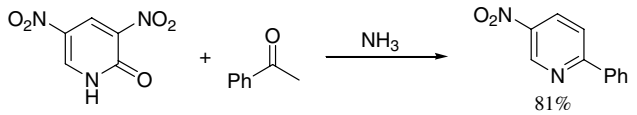

(10.80)

The carbinolamine-containing pyrrolo[2,1-*c*][1,4]benzodiazepine family of antitumor antibiotics is produced by various *Streptomyces* species; well-known members include abthramycine, tomaymycine, and DC-81.[138] Various approaches to the synthesis of these compounds have been investigated over past years; reductive cyclization of suitably substituted nitroaldehydes is the frequently used method (Eq. 10.81).[139]



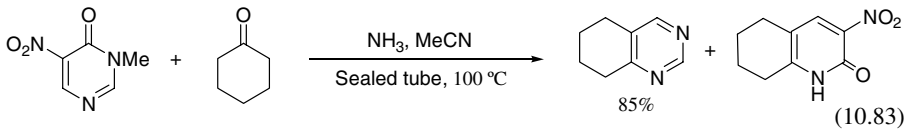

(10.81)

Nitroenamines and related compounds have been used for synthesis of a variety of heterocyclic compounds. Rajappa has summarized the chemistry of nitroenamines (see Section 4.2).[140] Ariga and coworkers have developed the synthesis of heterocycles based on the reaction of nitropyridones or nitropyrimidinone with nucleophiles. For example, 2-substituted 3-nitropyridines are obtained by the reaction of 1-methyl-3,5-dinitro-2-pyridones with ketones in the presence of ammonia (Eq. 10.82).[141]




(10.82)

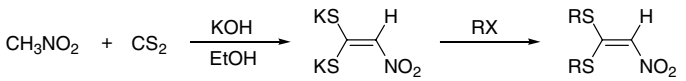
3-Methyl-5-nitropyrimidin-4(3*H*)-one reacts with ketones in the presence of ammonium salts to give 4,5-disubstituted pyrimidines or 5,6-disubstituted 3-nitro-2-pyridones depending on reaction conditions (Eq. 10.83).[142]



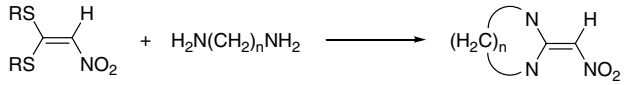

(10.83)

2,2-Dithio-1-nitroalkenes are prepared by the reaction of nitromethane with $CS_2$ and KOH followed by alkylation with alkyl halides (Eq. 10.84).[43] They are important reagents for synthesis

of functionalized nitro compounds such as 2-amino-2-thio-1-nitroalkenes or 2,2-diamino-1-nitroalkenes (Eq. 10.85).[144]



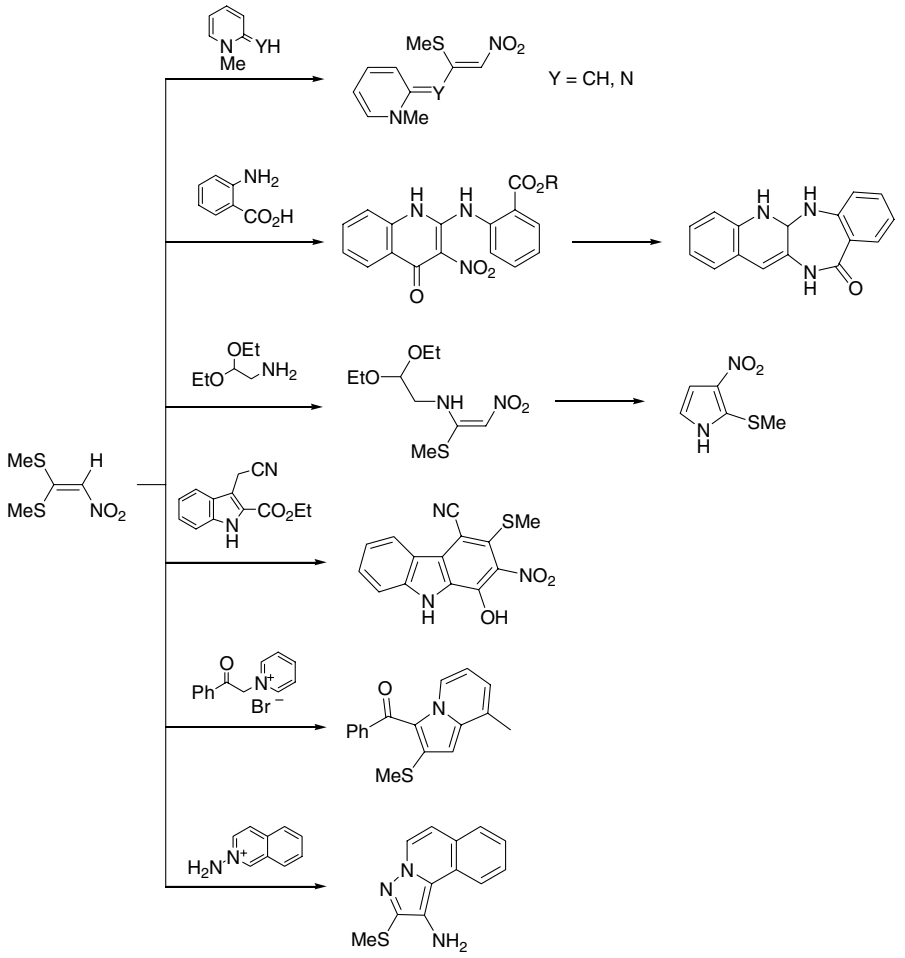

(10.84)



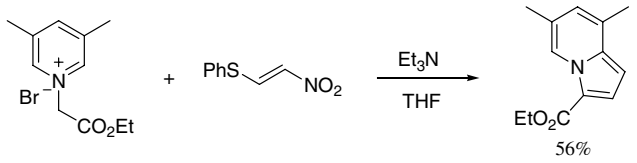

(10.85)

Nitroketene dithioacetal reacts with anthranilic esters to afford quinolone derivatives, which are converted into diazepinones by reductive cyclization. The review by Kolb covers synthetic application of nitroketene dithioacetal for heterocyclic compounds (see Scheme 10.26).[145]

Tominaga and coworkers have reported the formation of indolizine by the reaction of azomethine ylide with 1-nitro-2-phenylthioethylene (Eq. 10.86).[146]

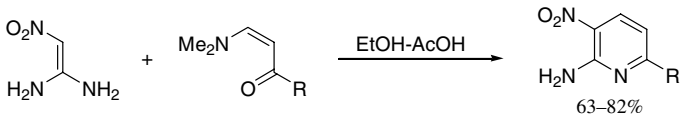



**Scheme 10.26.**



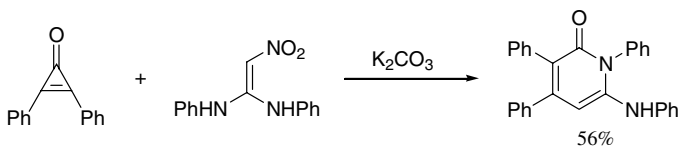

(10.86)

Reaction of nitroketene aminals with enaminoketones provides a route for the derivatives of 2-amino-3-nitropyridines (Eq. 10.87).[147]



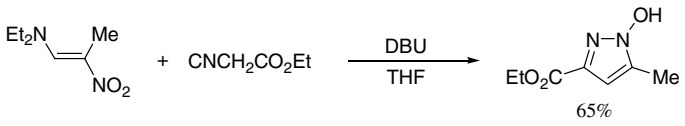

(10.87)

Reaction of diphenylcyclopropanone with nitroketene aminals gives 6-amino-2-pyridones (Eq. 10.88).[148]




(10.88)

Reaction of 1-diethylamino-2-nitroalkenes with ethyl isocyanoacetate in the presence of DBU at room temperature, followed by quenching with HCl, leads to 1-hydroxypyrazoles in good yield (Eq. 10.89).[149]




(10.89)

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# SUBJECT INDEX


Acetyl nitrate, 15
Acosamine, synthesis, 51
Acylation, nitroalkanes, 128–130
Acyl imidazoles, acylation, 129
Addition elimination process, 100–103
Aliquat, Michael addition, 106
Alkaloids, synthesis, 241, 282–295, 320, 340, 341, 345, 347, 352, 353, 354, 355
Alkenylation using nitroalkanes, 221
Alkenyl phosphonates, synthesis, 79
Alkoxycarbonyl imidazoles, 129
7-Alkoxyindoles, synthesis, 341
Alkylation
  O-alkylation, nitronate formation, 268
  of nitroalkanes, 126–128
  via radical process, 133–138
  with transition metal catalysts, 138–147
Alkylidene transfer reagents, nitroalkanes, 191, 220–221
Alkyl nitrate, nitration, 10
Allethrine, synthesis, 89
L-Allothreonine, synthesis, 83
Allylation
  allylic nitro compounds, 185–189
  nitro compounds, Pd catalyzed, 115, 140–147
  radical allylation, 151–152
Allylic nitro compounds
  allylic rearrangement, 192
  denitration, 107, 213
  elimination, 222
  Pd catalyzed reaction, 187
  preparation, 37, 38, 104, 167
  $S_N1$ reaction, 187
  substitution, ionic process, 185, 188–189
Allylic strain, 75, 83
Allylsilane, 9
Allylstannane, 9, 97, 151–152
$Al_2O_3$, nitro aldol reaction, 35, 166–167
Amberlite
  nitration, 18
  nitro aldol reaction, 35
Amberlyst A-21
  Michael addition, 106
  nitro aldol reaction, 36
Amination
  with hydroxyamine, methoxyamine, or sulfeneamides, 317–318
  of nitroalkenes, 76
  of nitro arenes, 316–318
Amines, via reduction of nitro compounds, 170–178
  *See* β-amino alcohols and amino acids
  Fe + AcOH, 355
  $HCOONH_4$ + Pd/C, 171, 173, 353
  $LiAlH_4$, 173, 245
  $NaBH_4$ + $CoCl_2$, 237
  $NaBH_4$ + $NiCl_2$, 64, 175
  $Na_2S$, 171
  $Ni_2B$, 174
  Pd/C + $H_2$, 51, 64, 65, 130, 172, 348, 355
  Raney Ni + $H_2$, 38, 48, 54, 111, 130, 172, 352, 354
  $SmI_2$, 175
  $SnCl_2$, 114, 245, 356
  Zn + AcOH, 356
  Zn(Cu), 349
α-Amino acids, synthesis, 79, 130
γ-Amino acids, synthesis, 90, 172
γ-Amino alcohol, via nitrile oxide addition, 260
β-Amino alcohols, 46, 172–173
4-Aminodiphenyl amine, synthesis, 316
δ-Aminolevulinic acid, synthesis, 130
Amino sugars, synthesis, 259
Amprenavir, HIV protease inhibitor, synthesis, 63–64
Anion radicals, 133, 182–183
Anthracyclinones, synthesis, 223

Aphanorphine, synthesis, 239
Arcyriacyanin, synthesis, 339
Arylation
  of amines, 306
  of nitroalkanes, Pd catalyzed, 149
  of nitroalkanes, $S_NAr$, 147–149
  of phenols, 306
2-Aryl-4, 6-dinitroindoles, synthesis, 342
6-Arylindoles, synthesis, 339
Aryllead triacetate, arylation of nitroalkanes, 149
Arylnitromethanes, 10
(–)-Arysteromycin, synthesis, 205
Arylsulfonylnitromethanes, 127, 146–147, 169
Aspidophytine, synthesis, 42
Asymmetric reaction
  *See* Diels-Alder reaction
  Michael Addition, 86, 99, 101–102, 115–119, 353
  nitrile oxide addition, 266
  nitro aldol reaction, 56–65
  nitronate addition, 272–274
  nitrone addition, 252–257
  tandem cycloaddition, 284
(+)-Australine and its epimer, synthesis, 290
9-Azasteroids, synthesis, 353
2,2-Azobisisobutyronitrile (AIBN), radical initiator, 193–211
Azomethine ylides, pyrrole synthesis, 338

Baker's yeast, asymmetric reduction, 46, 108–109, 162, 166, 352
Barton-Zard pyrrole synthesis, 330
Bartori indole synthesis, 341
Batcho indole synthesis, 338
Baylis-Hillman reaction product, 355
Benzoylperoxide, radical initiator, 193
Benzyl isocyanoacetate, pyrrole synthesis, 330
1-Benzyloxynitroalkene, 80
Biotin, synthesis, 71
Biotol, terpene synthesis, 210
Bismuth reagents, arylation of nitro compounds, 148
Brefeldin A, synthesis, 219
Brevicomine, synthesis, 166
4-Bromoindoles, synthesis, 343
2-Bromo-2-nitropropane, 151–152
Butadiene teromerization, Pd catalyzed, 138

Calicheamicinone, synthesis, 247
Calphostin D, synthesis, 165
Carbocyclic nucleosides, synthesis, 143–145, 205, 295
Carbon-disaccharide, synthesis, 200
Carboxylic acids, from primary nitroalkanes, 163
(+)-Casuraline, synthesis, see [4 +2]/[3 + 2] cycloaddition, 282
Cephalotaxine, synthesis, 355
Cedrene, synthesis, 210
Cetyltrimethylammonium chloride (CTACl), phase transfer catalyst
  Michael addition, 104
  Nitro aldol reaction, 36
Chelidonine, synthesis, 240
Chiral auxiliaries
  (2*R*, 3*R*, 4*R*, 4*S*)-1-amino-3,4-dimethoxy-2,5-bis(methoxymethyl)pyrrolidine, 78
  (*S*)-1-Amino-2-(methoxymethyl)-pyrrolidine, 95
  Diels-Alder reaction, 245
  (*R*)-2,2-diphenylcyclopentanol, 278
  (*S*)-2-(1-ethyl-1-methoxypropyl)-pyrrolidine, 91
  (*S*)-2-(methoxymethyl)pyrrolidine (SMP) and its enantiomer (RMP), 77, 100
  Michael addition, 77–79, 101–103
  nitron addition, 256
  (*S*)-1-phenylethylamine, 95
  (*R*) or (*S*)-4-phenyl-2-oxazolidinone, 78
  (*S*)-prolinol, 77
  TADDOLs, 99, 256–257
  tandem [4 + 2]/[3 + 2]cycloaddition, 279–295
Chiral enolates, addition to nitroalkenes, 90
Chiral catalysts
  allylation of nitro compounds, chiral ligands, 145
  heterobimetallic complex, (*R*)-LLB, (*R*)-LSB, nitro aldol reaction, 57–63
  Michael addition, 118–119
  1,3-dipolar cycloaddition of nitrile oxides, 267
  1,3-dipolar cycloaddition of nitrones, 256–258
Chiral nitroolefins, synthesis of alkaloids, 101–102
Chiral nitrones, 254–255
Chiral sulfoxides
  Diels–Alder reaction, 247
  Michael addition, 102

Chiral vinyl ethers, asymmetric tandem [4 + 2]/[3 + 2]cycloaddition, 287–290
Chlorins, synthesis, 348
Chloromethyl phenyl sulfone, 313
Cobaloximes, alkyl radical precursors, 136
Combinatory synthesis, heterocycles, 308, 310
Copper bisoxazolines, 1,3-dipolar addition, 257
(+)-Crotanecine, synthesis, 289
Cyanomethylation of nitroarenes, 341
2-Cyanopyrroles, 331
Cyclic nitrones, 252
Cyclic nitronates, 239, 267, 268, 274, 276, 278, 279, 281, 282
Cycloaddition
  *See* Diels-Alder reaction
  1,3-dipolar addition of nitrones, 249–258
  1,3-dipolar addition of nitronates, 267–274
  1,3-dipolar cycloaddition of nitrile oxide, 258–267
  tandem [4 + 2]/[3 + 2] addition, 274–295
Cyclopentenones, synthesis, 201

Daunosamine, synthesis, 50–51, 62
Dehydration
  of β-nitro alcohol, 38
  with dicyclohexylcarbodiimide (DCC), 39
  with methanesulfonyl chloride, 39
  with phthalic anhydride, 39
Dendritic polymers, synthesis, 111, 207
Denitration
  ionic reaction, 211–214
  α-nitro ketones, 47, 128, 211, 212
  radical reaction, 106, 193–211, 244
1-Deoxy-1-nitro sugars, 153, 190
Dialkyl 1-nitroalkanephosphonate, 23
1,2-Diamines, synthesis, 77–78, 109
Dianion of nitro compounds, 37
3,4-Diarylpyrroles, synthesis, 332, 337
3,5-Diarylpyrrolizidines, synthesis, 352
Diastereoselective reaction
  Diels-Alder reaction, 235
  Michael addition, 116
  nitro aldol reaction, 51–63
  silicon-tethered method in 1,3-dipolar cycloaddition, 260
1,8-Diazabicyclo[5.4.0]undec-7-ene(DBU)
  for nitro aldol reaction, 31–32
  for Michael addition, 104–105, 110, 116, 220–222
  for pyrrole synthesis, 330–336
Di-*t*-butyl dicarbonate, generation of nitrile oxides, 168
Diels-Alder reaction
  1-acetoxy-1,3-butadiene, 235, 245
  2-aminobutadiene, 243, 248
  asymmetric reaction, 245–248
  intramolecular reaction, nitrotrienes, 206
  1-methoxy-1,3-butadiene, 235
  1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene), 235, 237, 238, 239, 246, 247
  nitroalkenes as dienophiles, 231–244, 353
  nitro heterocycles, as dienophiles, 242
  3-(2-nitrovinyl)indoles, 237
  2-(2-nitrovinyl)furans, 237
  2-phenylsulfinyl-1-nitroalkenes, 238
  quinodimethene, 240
  *N*-tosyl-3-nitroindole, 240
  1-trimethylsilyloxy-1,3-butadiene, 235
  3-trimethylsilyoxy-1,3-butadiene, 236
Dihydrojasmone, synthesis, 47, 166
1,4-Dihydronicotinamide
  radical denitration, 193
  radical desulfonylation, 127
(+)-Dihydromevinol, synthesis, 200
(+)-Dihydromevinolin, synthesis, 113
Dihydrobenzopyran, synthesis, 153
*threo*-Dihydrosphingosine, synthesis, 61
5,6-Dihydroxyindole, synthesis, 41
1,4-Diketones, synthesis, 47, 95, 107–108, 110, 131, 161, 221
1,5-Diketones, synthesis, 201
6,7-Dimethoxyindole, 344
Dimethyldioxirane, 20, 161
2,4-Dimethylindole, 343
1,3-Dinitro compounds, 85
Dinitrogen pentoxide ($N_2O_5$), nitration, 5–6
1,3-Dipolar cycloaddition, 249–295
  *See* Chiral catalysts, chiral nitrones, chiral auxiliaries
  Fullerene ($C_{60}$), 268
  intramolecular nitrile oxide cycloaddition (INOC), 261–265, 270–274
  intramolecular silyl nitronate cycloaddition (ISOC), 270–274
  nitronates, 267–275
  nitrile oxides, 167–169

Elimination of $HNO_2$, 110, 137, 147, 218–225, 237–239, 242
Enantioselective reaction
  allylation of nitroalkanes, 145
  nitro aldol reaction, 61–63, 203
  Michael addition, 203
  Diels-Alder reaction, 243–248
Endo and exo selectivity, *See also* Diastereoselective reaction
  Diels-Alder reaction, 235–236, 277
  nitrones, 252–257
  nitronates, tandem reaction, 283
Epibatidine, synthesis, 114
Ergot alkaloid, synthesis, 242
Ethyl isocyanoacetate, pyrrole synthesis, 330–336
Ethyl nitroacetate, 141, 169
Ethyl β-nitroacrylate, 220
Ethyl 3-nitropropanoate, 18, 218

Facial selectivity, 283
Fisher indole, synthesis, 338–339
Flavonones, synthesis, 206
α-Fluoro nitro compounds, synthesis, 152, 210
Fluoro nitro sugars, synthesis, 49
Frodosin B, synthesis, 243

Geminal dinitro compounds, 150
Geminal halo nitro compounds, *See also* α-Halo nitro compounds, 150, 224

α-Halo esters, 312, 314
α-Halo nitro compounds, 23, 134
Henry traction
  *See* Nitro aldol reaction
Heterodienes, cycloaddition, 143, 268, 275–295
(–)-15-Hexadodecanolide, synthesis, 202
HIV protease inhibitor KNI-272, synthesis, 58
Homoallyl alcohols, 213
(–)-Horsfiline, synthesis, 101, 163
β-Hydroxy-α-amino acids, synthesis, 83
β-Hydroxy ketones, via nitrile oxides addition, 259
6-Hydroxyindole, 344
6-Hydroxy-7-methyoxyindole, synthesis, 345
2-Hydroxymethyl-3-hydroxypyrrolidine, synthesis, 205
3-Hydroxy-5-methylpiperidin-2-one, synthesis, 353

Iminopolyols, synthesis, 259
Indoles, synthesis, 171, 338–346
Indolizidines, 350
Isocyanoacetonitrile, pyrrole synthesis, 331
Isoindoles, 334–336
(+)-Isomintlactone, synthesis, 162
Isoxazoles, 258
Isoxazolines, 259

(*Z*)-Jasmone, synthesis, 47, 107, 164

Kainic acid, synthesis, 214, 352
Knovenagel reaction, 40

La-binaphthol (LLB),
  chiral catalyst for nitro aldol reaction, 56–63
  chiral catalyst for Michael addition, 119
Lactonic pheromones, synthesis, 166
Leusen pyrrole synthesis, 328–330
Lewis acid catalyzed reaction
  [4 + 2] cycloaddition, 274–294
  methylaluminum bis(2,6-diphenyl-phenoxide)(MAPh), 277–278, 293
  Michael addition, 86, 91–95
  $SnCl_4$, 275–276, 280, 293
  substitution of R-$NO_2$, 188, 190–191
  $Ti(OR)_2Cl_2$, 277
  $ZnCl_2$, 101–102, 129
Levoglucosenone, 116
(+)-Lucidine, synthesis, 253

Macrocyclization, 304
Macrocyclic lactones, synthesis, 128, 133
Macronecine, 289
Methyl α-methylenealkanoates, synthesis, 128
2-Methyl-2-nitropropane, 21
Methyl nitroacetate, 41, 127, 142, 144, 145, 219, 220
Methyl 3-nitroacrylate, 11, 220, 228–235, 238, 247
Methyl 2-nitropropanoate, 143
Methyl 3-nitropropanoate, 128, 219
Michael addition
  *See* Asymmetric reaction, diastereoselective reaction
  of active methylene compounds, 84–86

of enolates, 87–88
Grignard reagents, 95–97
intramolecular reaction, 112–115
to nitroalkenes, 70–103, 349, 350–353
of nitro compounds, 103–119, 220, 347, 348, 351, 353
Microwave irradiation, 41
(+)-Miyakolide, synthesis, 264
Muscone, synthesis, 204

NaTeH, denitration, 193–194
Nef reaction
with acid, 159–160
into carboxylic acids, 162–164
into ketones or aldehydes of nitroalkanes, 80, 87, 107, 159–164
with $KMnO_4$, $O_3$, dimethyldioxirane, anodic oxidation, 161
of nitroalkenes, 165–167
tetrapropylammonium perruthenate (TPAP), 162
$TiCl_3$, 103, 110, 163, 167
Nitration
of alkanes, 7–11
of alkenes, 11–15
of alkyl halides, 17–20
of aromatic compounds, 3–7
with NO, 13
with $N_2O_4$, 7
with $N_2O_5$, 5–6
with $N_2O_4$ and $O_3$, 6, 9
with nitronium tetrafluoroborate, 13
Nitric oxide (NO), 11–12
Nitrile oxides, *See* 1,3-dipolar cycloaddition, cycloaddition,
Nitriles, from nitroalkanes, 169–170
with $MeSi_3I$, $Bu_3P$ + diethyl diazocarboxylate (DEAD), $PI_3$, $PCl_3$, $(Me_2N)_3P$, 169
with $Me_3SiSiMe_3$, 170
β-Nitro acetate, 71, 330–333
Nitroadamantane, 21
Nitro-aldol reaction (Henry reaction), 30–65
Nitroalkanes
from alkyl halides, 18
azides, 25
amines 20
nitroalkenes, 44
oximes, 21
Nitroalkene dithioacetals, synthesis of heterocycles, 357
Nitroalkenes
from alkenes, 11–15
*See* Diels-Alder reaction, Michael addition
β-nitro alcohols, 38–44
Nitroalkyl pyridines, 18
Nitro alkyl radicals, for alkylation, 137–138, see $S_{RN}1$
β-Nitro-α-amino acids, synthesis, 107
Nitroaziridines, synthesis, 346
Nitro compounds, preparation, 1, 3–25
Nitrocycloalkenes, 12, 15
Nitrocyclohexane, 118, 149, 160, 177, 203, 221, 222
Nitrocyclohexene, 12, 13, 72, 76, 77, 96, 98, 149, 160, 183, 206
Nitrocyclopropane, 11, 150
Nitro-1,3-dienes, 43
β-Nitroenamines, 76, 100, 129
Nitroethane, 7, 41, 49, 56, 129, 130, 140, 153, 328, 108, 166, 168
α-Nitro ethers, 153
β-Nitro ethers, Michael addition, 74–76
Nitroethylene, nitroethene, 39, 73, 74, 87, 88, 90, 91, 95, 162, 206, 232, 234, 350
α-Nitro esters
Pd catalyzed allylation, 141–144
$S_{RN}1$ reaction, 134, 182, 135
synthesis, 128
Nitrogen dioxide ($N_2O_4$), 6
Nitrogen trioxide ($NO_3$), 6
2-Nitroindoles, synthesis, 343
3-Nitroindoles, synthesis, 240, 340
4-Nitroindoles, synthesis, 340
Nitroisoxazoles, 24
α-Nitro ketones, 16, 46–48, 129–130, 169
β-Nitro ketones, 137
Nitromethane, 37, 38, 42, 43, 45, 49, 57, 58, 59, 60, 62, 63, 64, 71, 80, 107, 108, 109, 114, 115, 116, 117, 119, 129, 130, 136, 138, 139, 144, 146, 148, 185, 187, 189, 192, 195, 202, 216, 223, 224, 353, 357
Nitromethylation
of aldehydes, 44–45
of alkanes, 138
of aromatics, 137, 148
C-glycosyl compounds, 49
via $S_{RN}1$ reaction, 135–136, 184–185
α-Nitro nitriles, for $S_{RN}1$, 134

Nitronium tetrafluoroborate, 9, 13, 15, 16
Nitroolefination, 100
(*S*)-5-Nitropentan-2-ol, 108
1-Nitro-2-phenylsulfonylethylene, 102, 217, 334
1-Nitro-2-phenylthioethylene, 76, 357
3-Nitropiperidines, 353
1-Nitropropane, 37, 55, 77, 106, 109, 127, 149, 153
2-Nitropropane, 86, 104, 106, 107, 110, 115, 117, 118, 133, 134, 136, 148, 188, 183, 220, 222, 191, 216
1-Nitro-1-propene, 39, 74, 75, 78, 87, 89, 91, 92, 93, 326
2-Nitro-1-propene, 39, 89, 93, 95, 100
3-Nitropyridine, 356
2-Nitropyrrole, 313
3-Nitropyrrole, 240, 329
β-Nitrostyrene, 44, 74, 75, 77, 86, 91, 93, 94, 96, 97, 98, 99, 113, 168, 170, 176, 177, 327, 328, 352
Nitro sugars, synthesis, 24, 48–51, 137
α-Nitro sulfides, 150, 212, 213
β-Nitro sulfides, 71–73, 79, 212, 213, 216
α-Nitro sulfones
  β-Nitro sulfones, 217
  β-Nitro sulfoxides, 102
  Pd-catalyzed allylation, 141
  preparation, 150
  $S_{RN}1$ reaction, 134
Nitrothiazoles, 135
Norslanadione, synthesis, 206
Nucleophilic aromatic displacement ($S_NAr$), 302
  of *o*-dinitrobenzene, 303
  of *p*-dinitrobenzene, 302, 303, 308
Nucleophilic aromatic substitution of hydrogen (NASH), 309
  *m*-chloronitrobenzene, 315, 318
  *o*-chloronitrobenzene, 311
  *p*-chloronitrobenzene, 311, 315
  *m*-dinitrobenzene, 313, 314, 317
  *m*-fluoronitrobenzene, 313
  3-nitroaniline, 319
  nitrobenzene, 309, 311, 312, 314, 318
  2-nitrofurans, 313
  4-nitroimidazole, 315
  2-nitropyrroles, 313
  6-nitroquinoline, 321
  2-nitrothiophene, 312, 315
  3-nitrothiophene, 312
Nucleosides, synthesis, 205, 210

Octaethylporphyrin, 337
Organometallic reagents
  addition to nitroalkenes, 95–99
1-Oxabuta-1,3-diene, 235
Oxidation to nitro compounds
  of amines 20–22
  of isocyanates 25
  of β-nitro alcohol to α-nitro ketone, 46
  of oximes, 21–23
  with OXONE, 23
  with *m*-perbenzoic acid (*m*-CPBA), 21
  with peroxytrifluoroacetic acid, 21
Oximes, reduction of nitro compounds, 176–177

Paar-Knorr reaction, pyrrole synthesis, 110, 325–326
Pancratistatin, 218
(+)-Paraherquamide B, synthesis, 345
Pd(0) catalysis, see allylation of nitro compounds
Penicillaric acids, synthesis, 81
Phenanthridines, 355
Phenylacetone, synthesis from nitroalkenes, 165
1-Phenylheptane-1,5-dione, synthesis, 201
Phenylisocyanate, generation of nitrile oxides, 167–168
Phenylnitromethane, 18
Phenylthiomethyl isocyanide, 315
1-(Phenylthio)-nitroalkenes, 81–83
Phenylthionitrometane, 80
Pheromone, synthesis, 35, 48, 331
Phosphazene base, pyrrole synthesis, 335
Phytochromobilin, synthesis, 332–333
Polyoxin C, synthesis, 81
Porphobilinogen, synthesis, 332
Porphyrins, synthesis, 337
Polypyrroles, 336
Proazaphosphatrane, base for nitro aldol reaction, 37
L-Proline, asymmetric Michael addition, 118
(–)-Psudophymaminol, synthesis, 101
Pyrazoles, synthesis, 358
Pyrazolo[3,4-*b*]pyridine, synthesis, 242
(–)-Pyrenophorin, synthesis, 108
Pyridinium chlorochromate (PCC), 46
Pyrimidines, synthesis, 345
Pyrroles, synthesis, 177, 325–338

Pyrrolidines, synthesis, 277, 347–351
Pyrrolidin-2-ones, synthesis, 90, 352
Pyrrolines, synthesis, 347
Pyrrolizidines, synthesis, 350
Pyrrolo[2, 1-*c*][1, 4]benzodiazepine, synthesis, 356
Pyrrolo[2,3-*d*]pyrimidines, synthesis, 345
Pyrrolostatin, synthesis, 331
Pummerer rearrangement, 222

Radical reaction
  addition, 209
  cyclization, 210
  elimination, 214–218
  substitution, 133–138, see $S_{RN}1$
Recifeiolide, synthesis, 139
Retro Diels-Alder reaction, 334
D-Ribo-nitro-aldol, synthesis, 50
Ring cleavage of cyclic α-nitro ketones (retro Henry reaction), 131–133
(–)-Rosmarinecine, synthesis, 288

Scandium triflate, 109
Secondary nitro group, denitration, 197
(+)-Sedridine, synthesis, 252
Selenation
  nitroalkanes, synthesis of nitroalkenes, 153
  nitroalkenes, Michael addition, 74
Silver nitrite, synthesis of nitro compounds, 17
Silyl nitronates,
  1,3-dipolar cycloaddition, 75, 268–273
  nitro aldol reaction, 54–55
$SmI_2$, reduction of nitro compounds, 175
$Sm(O\textit{i}\text{-}Pr)_3$, 328
Sodium nitrite,
  Nef reaction, 163
  nitration of alkyl halides, 18–19
Sodium perborate, 21
Sodium salt of methylmercaptan,
Sodium sulfide, 215
$S_N1$ reaction of nitro compounds,
  deoxy nitro sugars, 154, 190
  allylic nitro compounds, 187
$S_N2$ reaction of nitro compounds
  Lewis acid assistance, α-nitro sulfides, β-nitro sulfides, 189–191
  Intramolecular reaction, 191–192
Spiro ketals, pheromones, synthesis, 131, 166
$S_{RN}1$ reaction, 133–136, 154, 182–185
  alkyl mercury halides, 136
  deoxy nitro sugars, 185
  geminal dinitro compounds, 134
  geminal halonitroalkanes, 134
  Kornblum reaction, 184
  α-nitro nitriles, 184
  *p*-nitrobenzyl halides, 133
  tertiary nitro compounds, 184
$S_{RN}2$, 137
Staurosporine, synthesis, 352
Stereoselective reaction
  nitro aldol reaction, 51
(–)-Strychnine, synthesis, 308
β-Sulfonyl nitroalkenes, 217
Sundberg indole synthesis, 342

Tandem [4 + 2]/[3 + 2] cycloaddition, 279–295
  (+)-australine, synthesis, 290
  (+)-castanospermine, synthesis, 290
  (+)-casuarine, synthesis, 283
  (+)-crotanesine, synthesis, 289
  3,4-disubstituted pyrrolidines, cis and trans, 277
  (+)-7-epiaustraline, synthesis, 282
  (–)-hastanecine, synthesis, 280
  (+)-macronecine, synthesis, 281
Tandem Michael addition, 92, 114
Taxane, synthesis, 201
Tethered reaction, 260
Tetrabutylammonium fluoride (TBAF), 52, 80–81, 104–106
Tetradecano-14-lactone, synthesis, 202
(+)-13-Tetradodecanolide, synthesis, 202
Tetramethylguanidine (TMG)
  for nitro-aldol, 32, 36
  for Michael addition, 103–105, 117
Tetranitromethane, nitration, 5, 16
D-Threonine, synthesis, 83
Tosylmethyl isocyanide (TosMIC), pyrrole synthesis, 328–330
2-Tosylpyrrole, synthesis, 332
Trialkylborane, alkyl radical precursor, 97, 138, 308
Tributyltin hydride ($Bu_3SnH$),
  radical denitration, 109, 111–113, 193–211, 216–218
  indole synthesis (Fukuyama reaction), 344
Triethylsilane, ionic hydrogenation, 213
Trifluoroacetyl nitrate, nitration, 16

Trimethylsilyl iodide, 169
1,3,5-Trinitrobenzene, indole synthesis, 346
2,4,6-Trinitrotoluene, indole synthesis, 342
Triton B, Michael addition, 109
Trovafloxacin, synthesis, 151
Tuberine, synthesis, 79

Ultrasound irradiation, 41
α,β-Unsaturated carbonyl compounds, synthesis, 88, 147, 167, 222, 224–225, 260
α,β-Unsaturated nitriles, 224
α,β-Unsaturated sulfones, pyrrole synthesis, 336
Urea-hydrogen peroxide (UHP), oxidation of amines or oximes, 21

Vancomycin, synthesis, 306
Vicarious nucleophilic substitution (VNS), 309–318
Vicinal dinitro compounds, radical elimination, 214–215

Ytterbium triflate, Michael addition, 106

Zirconium tetra *tert*-butoxide, oxidation of amines, 21
Zinc reagents, Michael addition, 97–99