Conjugated Nitroalkenes: Versatile Intermediates in Organic Synthesis

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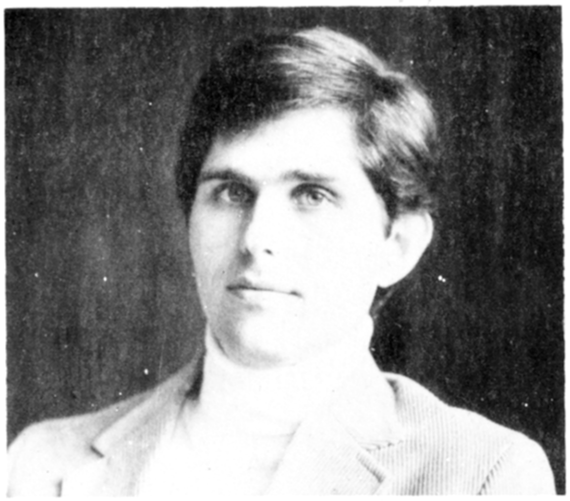
Contents

I. Introduction

The nitro group is a powerful electron-withdrawing substituent, and this property dominates the chemistry of all molecules containing this functional group. For example, nitroalkenes, being markedly electron deficient, are powerful dienophiles in the Diels–Alder reaction. Alternatively, these electrophilic alkenes readily undergo addition reactions with many different nucleophiles. The nitro group is particularly versatile in synthesis since it may be transformed into a legion of diverse functionality. It can be readily replaced by hydrogen in a denitration process or converted to a carbonyl substituent in the classical Nef reaction. Additionally primary nitro groups can be dehydrated to produce nitrile oxides or oxidized to produce carboxylic acids. Finally, the nitro substituent can be reduced to produce oximes, ketones, hydroxylamines, or amines. Clearly nitro compounds and nitroalkenes in particular are versatile compounds in synthetic organic chemistry.

This article covers a review of the literature on the synthesis and reactions of nitroalkenes in the time interval 1980–1985. Earlier work on nitroalkenes has been extensively reviewed.[1] In 1985 Yoshikoshi reviewed the condensation reactions of enol silanes, carboxylic acid dianions, ester enolates, and mono anions derived from β-dicarbonyl compounds with nitroalkenes as a route to 1,4-dicarbonyl species.[2] In the appropriate sections of this review, principally V.A.1., reference is given to this previous review to avoid duplication. In these sections only articles not explicitly described by the highly focused Yoshikoshi article wil be covered in detail.

Tony Barrett was born in Exeter, England, in 1952. He obtained his B.Sc. (1973) and Ph.D. (1975) at Imperial College, London, where he studied under the guidance of Professor Sir Derek H. R. Barton. In 1975, he joined the faculty at Imperial College where he remained until 1983 when he moved to Northwestern University, Evanston, Illinois, as professor of chemistry. His major research interests are the development of synthetic methodology, the applications of organometallics to the total synthesis of bioactive natural products, and the design of host–guest ensembles.



Greg Graboski was born in Catawissa, PA, in 1960. He obtained his B.A. at Shippensburg State College (1982) where he majored in chemistry. He is currently a graduate student at Northwestern University working in the area of β-lactam synthesis.

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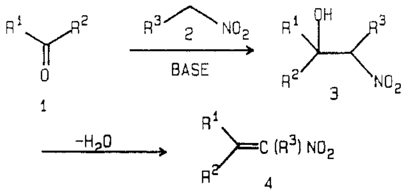
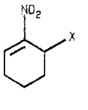
II. *Preparation of Nitroalkenes*

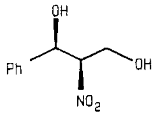
A. From Aldehydes and Ketones

The most versatile preparation of nitroalkenes **4** involves the Henry condensation reaction of an aldehyde or ketone **1** with a nitroalkane **2** followed by dehydration of the resultant β-nitro alcohol **3**.[1] The Henry condensation reaction is routinely effected under mildly basic conditions. Recently several reagents including dicyclohexylcarbodiimide (DCC),[3] pivaloyl chloride,[4,5] methanesulfonyl chloride,[1,6] or phthalic anhydride[1,7] have been used for the dehydration step. Knochel and Seebach[3] have reported that DCC in the presence of a copper(I) chloride catalyst in diethyl ether or dioxane is a convenient reagent for the conversion of **3** into **4**. For example the method was used to prepare **5a** (70%), **6** (75%), and **7** (94%).[3] Alcohol **5a** was readily transformed into **5b** (95%) and **5c** (82%), respectively, via reaction with pivalic anhydride with boron trifluoride etherate catalysis[4] or thionyl chloride in benzene at reflux. The 2,3-*syn*-nitro diol **8** was converted into the corresponding (*E*)-nitroalkene **9a** (90%) by dehydration via sequential reaction with pivaloyl chloride in dichloromethane at reflux and sodium acetate in diethyl ether. An identical procedure was used to transform 2-nitro-1,3-propanediol into the nitroalkene **9b**. The nitroalkenes **5b**, **9a**, **9b**, and related molecules are versatile, multiple coupling reagents for further transformations (see section V).





5a X=OH
b X=OCO^{t}Bu
c X=Cl
d X=N(Me)Ph



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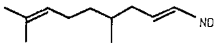

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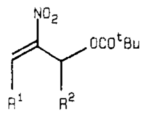
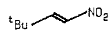


9a R^1=Ph, R^2=H
b R^1=R^2=H
c R^1=^{n}Bu, R^2=H



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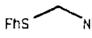
Recently the preparation of (*Z*)-1-nitro-1-(phenylthio)-1-alkenes[2,8] from aldehydes and (phenylthio)nitromethane (**10**) has been optimized.[9] Thus, for example, acetaldehyde was condensed with **10** using potassium *tert*-butoxide as a catalyst in THF–*t*-BuOH at 0 °C to produce **11**. Subsequent dehydration using methanesulfonyl chloride and triethylamine in dichloromethane at −78 °C to 0 °C gave **12** (≥ 89%). Yoshikoshi has reviewed the use of **12** in 3-methylfuran synthesis.[2] Additionally, we have demonstrated that **12** is a versatile reagent in both carboxylic acid and β-lactam chemistry (see section V). Sakakibara et al.[8] have prepared the corresponding (*Z*)-1-nitro-1-(phenylseleno)-1-alkenes using potassium fluoride as the base for the Henry condensation and acetic anhydride–boron trifluoride etherate to mediate the dehydration. Fuji and co-workers have described[10] the synthesis of related cyclic and acyclic 1-(ethylthio)-2-nitroalkenes. For example nitroacetone was converted into **13** by reaction with ethanethiol catalyzed by boron trifluoride etherate. Subsequent reaction with potassium fluoride in 2-propanol at reflux gave (*Z*)-**14** (56%) and (*E*)-**14** (39%).



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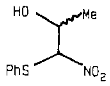

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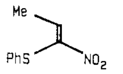

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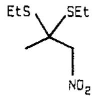

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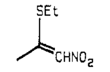

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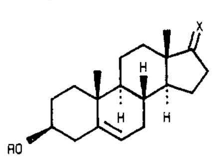
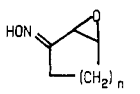
Barton and Zard have reported that ketones including 3β-hydroxyandrost-5-en-17-one **15a** reacted with nitromethane and ethylenediamine as a catalyst to directly provide the corresponding nitroalkenes **15b** (95%).[11] Such a direct diamine-catalyzed production of a simple *aliphatic* nitroalkene from a ketone was an unprecedented observation. The authors speculated that the reaction proceeded via the imine ion pair **15c** and intramolecular catalysis by the $-NH_3^+$ substituent. This proposal was consistent with the absence of catalysis by simple primary amines.



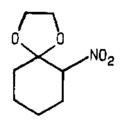
15a X=O, R=H
b X=CHNO$_2$, R=H
c X=NCH$_2$CH$_2$NH$_3^+$ CH$_2$NO$_2^-$, R=H
d X=CH(NO$_2$)CH$_2$OH, R=H Δ^{16}
e X=COCH$_2$OAc, R=Ac Δ^{16}

Corey and Estreicher[12] have described a convenient synthesis of the β-nitro enones **18a** (62%) and **18b** (65%) respectively from 2-cyclopentenone and 2-cyclohexenone. Peroxytrifluoroacetic acid oxidation of the oximes **16a** and **16b** in acetonitrile gave **17a** and **17b** and these nitro alcohols were directly oxidized in situ with pyridinium chlorochromate in dichloromethane. The nitro enones (**18**) were found to be powerful dienophiles in the Diels–Alder reaction (section IV.A). As an alternative method to prepare these important nitro enones, Vankar and Bawa[12] adapted earlier Corey nitromercuration chemistry. Thus, for example, **19** was reacted sequentially with mercuric chloride–sodium nitrite, sodium hydroxide, and 5% aqueous sulfuric acid to produce **18b** (76%). Zajac and co-workers have reported[13] a synthesis of cyclic nitroalkenes from β-nitro ketones. The method is of particular interest in that the reaction intermediates, β-nitro alcohols, were not prepared via the Henry reaction which is generally not convenient for cyclic systems. For example, 1-nitrocyclohexene (**21a**) was readily prepared from 2-nitrocyclohexanone via sodium borohydride reduction in ethanol to produce **20** (60%). Subsequent elimination mediated by sodium hydride followed by acidification gave **21a** (72%). The precursor 2-nitrocyclohexanone was readily available from the nitration of enol acetate **21b**.

In principle nitroalkenes should be available from the direct nitration of vinyl carbanions. However, this reaction is not practical due to potential anionic polym-



16a n=1
b n=2



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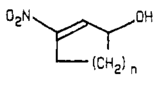
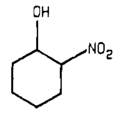


17a n=1
b n=2



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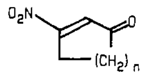
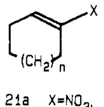
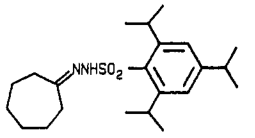


18a n=1
b n=2



21a X=NO$_2$, n=1
b X=OAc, n=1
c X=Li, n=2
d X=SnMe$_3$, n=2
e X=NO$_2$, n=2



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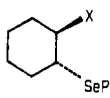
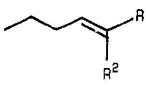
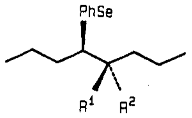


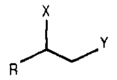
23a X=NO$_2$
b X=OH



25a R^1=^{n}Pr, R^2=NO$_2$
b R^1=NO$_2$, R^2=^{n}Pr



24a R^1=H, R^2=NO$_2$
b R^1=NO$_2$, R^2=H



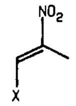
26a R=^{n}Bu, X=NO$_2$, Y=SePh
b R=^{n}Bu, X=SePh, Y=NO$_2$
c R=Ph, X=NO$_2$, Y=SePh

erization. Corey and Estreicher[14] have modified the Shapiro reaction in an elegant synthesis of nitroalkenes from ketones. For example cycloheptanone 2,4,6-triisopropylbenzenesulfonylhydrazone **22** was reacted with *sec*-butyllithium in TMEDA–cyclohexane at −80 °C to −10 °C to produce the vinyl anion **21c**. This was trapped with chlorotrimethylstannane to provide **21d** (84%). In Me$_2$SO **21d** reacted smoothly with tetranitromethane to give 1-nitrocycloheptene **21e** (87%). The method was additionally used to prepare alkyl-substituted 1-nitrocyclohexenes.

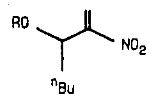
B. From Alkenes

Both Tomoda[15] and Seebach[16] have utilized selenium chemistry in the preparation of nitroalkenes. Tomoda has developed nitroselenation as a new and most useful method for the conversion of unactivated alkenes into β-nitro selenides. These on oxidation gave the derived selenoxide and thereby the nitroalkene. For example, cyclohexene reacted with phenylselenyl bromide, silver nitrite, and mercuric chloride in acetonitrile–THF at −78 °C to 22 °C to give the trans nitro selenide **23a** (81%). The mercuric chloride was added to suppress the formation of **23b** although its mechanistic role is not clear. On oxidation with hydrogen peroxide **23a** was converted into **21a** (93%). Both the nitroselenation (trans) and the selenoxide elimination (syn) reactions were stereospecific. Thus (*E*)- and (*Z*)-4-octenes were respectively converted into the single isomers, presumably **24a** (66%) and **24b** (77%) and subsequently **25a** (92%) and **25b** (90%). Although 1-hexene gave a mixture of Markovnikov **26a** and anti-Markovnikov isomers **26b** (75%, 78:22), styrene reacted to produce only **26c** (83%).

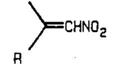
Seebach has employed phenylselenyl trifluoroacetate as a reagent for the functionalization of nitroalkenes via trans addition.[16] For example **27a** was reacted with phenylselenyl chloride and silver trifluoroacetate in dichloromethane to give **28a** (96%) (tentative stereochemical assignment). Methanolysis in the presence of sodium hydrogen carbonate gave **28b** (95%) and subsequent hydrogen peroxide oxidation regiospecifically gave **29a** (68% from **27a**). Alcohol **29a** was smoothly esterified with pivalic anhydride in the presence of boron trifluoride etherate to produce **29b** (70%). On prolonged esterification the product **29b** was isomerized in situ to produce **9c** (73%) as a single geometric isomer. Presumably the **29b** to **9c** isomerization proceeds via a [3,3] sigmatropic rearrangement. Additionally, **9c** should be thermodynamically favored relative to **29b** since the electron-deficient nitroalkene unit is trisubstituted.



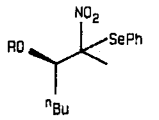
27a X=^{n}Bu
b X=H



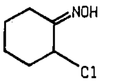
29a R=H
b R=^{t}BuCO



31a R=Ph
b R=Me



28a R=CF$_3$CO
b R=H



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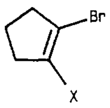


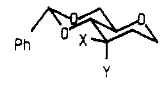
32a X=Br
b X=Li
c X=SnMe$_3$
d X=NO$_2$

α-Chloro or α-bromo oximes are readily available from alkenes via the addition of nitrosyl chloride (bromide) in the presence of hydrochloric (bromic) acid. Alternatively these oximes have been prepared from α-halo ketones and hydroxylamine.[17] Sakakibara and co-workers have reported that peroxytrifluoroacetic acid oxidation of such oximes in acetonitrile solution produced the corresponding nitroalkenes. Clearly the method is directly analogous to the Corey protocol for the preparation of **17b**.[12] Thus, for example, oxidation of **30** gave **21a** (42%). The method was applied to the synthesis of several cyclic and acyclic nitroalkenes; these were obtained in modest yields (31–66%). In a related protocol Yandovskii et al.[18] reported that two 1,1-disubstituted alkenes were oxidized by excess butyl or amyl nitrite in acetic acid to produce inter alia the nitroalkenes **31a** (27%) and **31b** (8%). In a further variation of the well-established alkene nitrosation protocol,[19] Kunai has developed an electrochemical method. Thus electrolysis of aqueous sodium nitrite at a platinum anode in a divided cell in the presence of cyclohexene gave **21a** (25–57% depending on the supporting electrolyte). The method was extended to the synthesis of 1-nitrocyclooctene (36%) and 1-nitro-1-hexene (63%).[19]

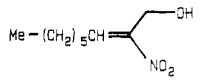
In an adaptation of the preparation of **21e** from **22** Corey[14] converted 1,2-dibromocyclopentene **32a** into **32d** via bromine lithium exchange, conversion of the resultant intermediate **32b** into **32c** and final nitration with tetranitromethane.

C. By Other Methods

Simple nitroalkanes have been oxidized to produce nitroalkenes using selenium chemistry. For example phenylselenyl bromide was added to the nitronate derived from **33a** using *n*-butyllithium in THF solution to produce **33b** (61%). Subsequent oxidation with hydrogen peroxide gave the base-sensitive nitroalkene **34** (71%). The method was general for acyclic and cyclic systems.[20] The intermediate α-nitro selenides were found to be useful intermediates for hydroxymethylation.[21] For example **35a** was converted into **35b** (81%) by Henry condensation with formaldehyde in the presence of calcium hydroxide. Subsequent selenoxide elimination of **35b** gave **36** (81%). Clearly this protocol is a most convenient procedure for preparing these most useful hydroxynitroalkenes (see sections II.B and V).



33a X=NO$_2$, Y=H
b X=NO$_2$, Y=SePh and/or X=SePh, Y=NO$_2$



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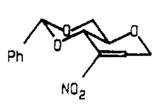

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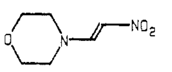

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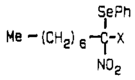


$\mathrm{Me-(CH_2)_6-\overset{SePh}{\underset{NO_2}{C}}-X}$

35a X=H
b X=CH$_2$OH

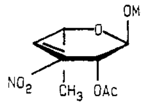
β-Nitro enamines are useful synthetic intermediates.[1] Royer and co-workers have described a method to prepare these species including **37** (70%) from the condensation of triethyl orthoformate, nitromethane and secondary amines.[22]

III. Reduction of Nitroalkenes

The direct reduction of nitroalkenes provides a convenient route to a variety of different functionalities including nitroalkanes, oximes, carbonyl compounds, hydroxylamines, and alkylamines.

A. Nitroalkane Production

The reduction of nitroalkenes to produce a nitroalkane can be achieved by several distinct methods. Reagents such as sodium borohydride, sodium cyanoborohydride, various complex metal hydrides, and catalytic hydrogenation have been employed for this purpose.[1] Of these, perhaps the most widely used method is the reduction using sodium borohydride. Recent examples of such reductions are the conversion of the steroidal nitroalkene **15b** to its saturated derivative[11] and the reduction of **38** to the corresponding nitro sugar, an intermediate in the preparation of 4-deoxydaunosamine and 4-deoxyristosamin.[23] A slight variation on the borohydride reduction used by Ho[24] offers a convenient synthesis of γ-nitroalkanoic esters, which are useful intermediates in cyclopentanone synthesis. This modification takes advantage of the fact that a nitronate anion is initially formed on reduction, and this species may be trapped by Michael addition to methyl acrylate to give the nitroalkenes **39** in good yield (62–95%).



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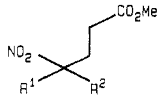
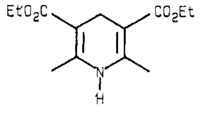


39a R^1=R^2=Me
b R^1=R^2=(CH$_2$)$_4$
c R^1=Ph, R^2=Et
d R^1=p-MeC$_6$H$_4$, R^2=Me



40

Unfortunately, in some cases, dimeric products are produced during the borohydride reduction. These arise from Michael addition of the nitronate intermediate with starting nitroalkene. Usually with aliphatic nitroalkenes the formation of these byproducts may be suppressed by reaction at reduced pH. In contrast, sodium borohydride reductions of β-nitrostyrenes often result in significant dimerization even when the reaction is run at pH 3. Some of the more recent reagents developed for nitroalkane production from nitroalkenes have addressed the dimerization problem to demonstrate their synthetic prowess.

It has recently been reported that the use of silica gel in a mixed chloroform–propanol solvent system assists the sodium borohydride reduction of nitroalkenes.[25] The products are obtained in high yield and purity and are largely free of dimeric contaminants. This method is operationally simple and gives pure products under mild conditions. Methanol has also been reported to activate the sodium borohydride reductions of nitroalkenes to give saturated nitro compounds without dimerization.[26] However, the yields are generally inferior to the silica method. Other trialkyl borohydride reagents such as tri-*sec*-butylborohydride and triethylborohydride have also been applied with success.[26] Pakrahsi[27] has reported that β-nitrostyrenes may be efficiently reduced to produce nitroalkanes (80–95%) using sodium borohydride in ethanol–dioxane at 30 °C. The solvent mixture prevented the production of dimeric products since the nitronate intermediates were of low solubility in this medium.

As is the case with borohydride reagents, there is the danger of reaction of other reduceable functionalities such as carbonyl groups, which may limit the synthetic usefulness of the method. However, in a recent report by Ohno and co-workers[28] the NADH mimic **40** was found to reduce nitroalkenes to nitroalkanes in excellent yields when activated by the presence of silica gel. Furthermore, this system was selective for the alkene and tolerated other easily reduceable functional groups such as aldehydes and ketones. Finally Chikashita et al.[29] have reported that 2-phenylbenzimidazoline in *n*-butyl alcohol at reflux is particularly efficient for the reduction of several β-nitrostyrene derivatives and heteroaromatic analogues to the corresponding nitroalkanes (70–93%).

B. Production of Oximes and Carbonyl Compounds

Kabalka and Varma[30] have reported that alcoholic solutions of tin(II) chloride reduce nitroalkenes to the corresponding α-alkoxy oximes in high yield (see section V.D). The authors also noted that if ethanethiol was incorporated into the reaction mixture, the α-alkylthio oximes were alternatively produced in good yield. The authors have used this reduction to report a new two-step approach to α-substituted ketones.[30] Alternatively, the reduction of nitroalkenes with tin(II) chloride under basic conditions (forming sodium stannite) gave unsubstituted ketoximes in high yield.[31] It should be noted that aldoximes are not available under these conditions.

The chromium(II) chloride mediated reduction of nitroalkenes has been shown to give α-hydroxy oximes and has been used for a novel synthesis of a series of flavonols,[32] presumably via α-hydroxy oxime intermediates. In contrast, a recent report indicated that chromium(II) chloride reductions of nitroalkenes produced the corresponding unsubstituted carbonyl compounds directly, with no detectable oxime formation.[33]

Another method for the direct conversion of nitroalkenes into carbonyl compounds was reported in 1983 by Monti and co-workers.[34] They found that treatment of a series of nitroalkenes with Raney nickel and sodium hypophosphite at pH 5 in ethanol resulted in clean conversions to the aldehydes or ketones. This method also resulted in the reduction of oximes to ketones or aldehydes as well as nitroalkanes to amines. Esters, ketones, or unsubstituted alkenes were unaffected by the reaction conditions. Zinc in a methanolic solution of ammonia has also been used to convert steroidal nitroalkenes to ketoximes in 85–90% yield.[35]

Nitroalkenes may also be converted to oximes, ketones, or aldehydes by electrochemical methods. Shono and co-workers[36] described an electrochemical system using a platinum cathode in 20% H_2SO_4 in methanol that reduced nitroalkenes to oximes. Unfortunately this method suffered from modest yields along with product contamination with the corresponding acetals and ketones. A second electrochemical method reported by Torii et al.[37] gave either ketoximes or ketones from nitroalkenes by using aqueous perchloric acid in dichloromethane–dioxane with a lead electrode. The type of product obtained depended on the work up conditions used. The representative yields for ketones were in the range of 63–93% and 67–91% for oximes. No production of aldehydes or their oximes was reported. Reaction of lithium tris-*sec*-butylborohydride with a nitroalkene, followed by Nef hydrolysis of the trialkylboron nitronate with 4 N H_2SO_4, has been reported to be an alternative method to convert nitroalkenes to ketones.[38]

C. Production of Hydroxylamines and Alkylamines

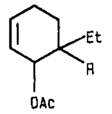
The conversion of nitroalkenes to alkylamines has been accomplished by the use of lithium aluminum hydride, catalytic hydrogenation, or electrochemical methods.[1] It has recently been reported that excess borane reduces nitroalkenes to amines at room temperature when used in THF solution in the presence of a catalytic amount of sodium borohydride.[39]

A variation of the sodium borohydride catalyzed borane reduction has also been reported to yield N-substituted hydroxylamines.[40] In this method, only 1 equiv of borane to nitroalkene is used. After the reaction is complete, the corresponding hydroxylamines were isolated after hydrolysis of the boron esters in 70–85% yield. With excess reducing reagent the corresponding alkylamines were obtained in good yields (74–85%).

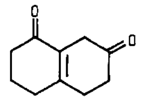
IV. Cycloaddition Reactions

A. Diels–Alder Reactions

Nitroalkenes are potent dienophiles, and they generally require low reaction temperatures for the Diels–Alder reaction to occur. Furthermore, the nitro group is very effective at controlling the regiochemistry of the reaction with unsymmetrical dienes. Several recent examples that illustrate this synthetic utility of nitroalkenes have been reported. Ono has used such chemistry to prepare **41b** and **42b**.[41] The initially formed Diels–Alder adducts **41a** and **42a** were chemoselectively denitrated with tributyltin hydride to produce **41b** and **42b**. Corey and Estereicher[12] have described the synthesis and reactions of nitro enones including 3-nitro-2-cyclohexenone **18b**. The powerful electron-withdrawing nitro substituent overwhelms the directing effect of the keto group in the reaction with dienes. Thus, for example, **18b** was reacted with **43** to produce **44**. This was not isolated but converted directly to **45** by reaction with DBN. The elimination of the nitro group to produce **45** established nitro enones such as **18b** as formal alkynone synthetic equivalents with reversed polarization.



41a R=NO$_2$
b R=H



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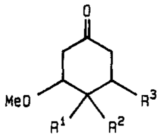
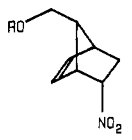
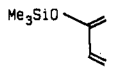


42a R^1=Me, R^2=NO$_2$, R^3=Et
b R^1=Me, R^2=H, R^3=Et



46a R=CH$_3$
b R=CH$_2$Ph



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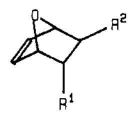
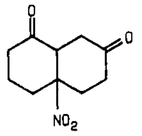
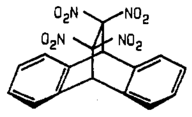


47a R^1=NO$_2$, R^2=CO$_2$Me
b R^1=CO$_2$Me, R^2=NO$_2$



44



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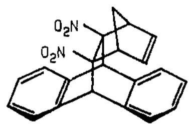


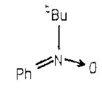
49

A recent report by Ranganathan and co-workers has shown that nitroethylene, the simplest of nitroalkenes, is a convenient reagent for [4 + 2] cycloadditions.[7] This electrophile undergoes reactions with activated dienes at low temperatures and can provide quick access to useful intermediates. For example, the cycloadducts **46** have been further elaborated to produce prostanoids. Another recent example of the synthetic applicability of nitroalkene [4 + 2] cycloadducts is the conversion of **47**, obtained from furan and β-nitroacrylate, to the synthesis of racemic showdomycin and related molecules.[42] Kurth[43] has reported that nitroalkenes including 1-nitro-1(*E*),6(*E*),8(*E*)-decatriene undergo efficient intramolecular Diels–Alder reactions. The method was applied to the stereoselective synthesis of several *trans*-perhydroindene derivatives.

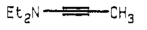
The in situ generation of the extremely electron-deficient species tetranitroethylene has been reported by Baum to react with anthracene to produce adduct **48** (63%), which when heated in the presence of cyclopentadiene formed **49**[44] (17%).

B. Other Cycloaddition Reactions

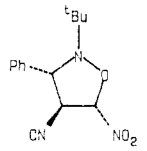
Padwa et al. have used nitroalkenes as substrates for the construction of β-lactams.[45,46] Crucial to their approach was the 1,3-dipolar cycloaddition of a nitrone to a substituted nitroalkene, followed by a thermally or photochemically induced ring contraction. For example, nitrone **50** was found to react with (*E*)-3-nitroacrylonitrile to produce isoxazolidine **51** (60%) accompanied by its regioisomer (40%). When heated, adduct **51** was converted into **52a**. Alternatively, when photolyzed, adduct **51** was converted into **52b**. Pennings and Reinhoudt have reported that nitroalkenes undergo a facile reaction with ynamines to produce nitrocyclobutenes, and cyclic four-membered nitrones.[47] These cyclic nitrones thermally isomerize to produce the corresponding *N*-vinyl nitrones. For example β-methyl-β-nitrostyrene was reacted with ynamine **53** to give a mixture of the nitrocyclobutene **54** and the cyclic nitrone **55**. The nitrone was rearranged in quantitative yields at room temperature to produce the corresponding vinyl nitrone **56**.



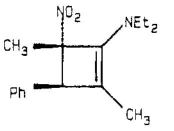
50



53



51



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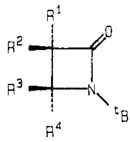
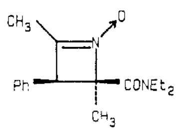


52a R^1=CN, R^2=R^3=H, R^4=Ph
b R^1=R^3=H, R^2=CN, R^4=Ph



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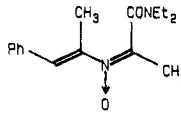


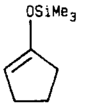
56

V. Addition Reactions of Nitroalkenes

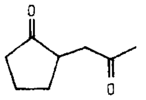
A. With Carbon-Centered Nucleophiles

1. Enolates, Enol Silanes, and Enamines

Yoshikoshi[2] has recently reviewed his group's work on the condensation reactions of enol silanes with nitroalkenes as a general method to 1,4-dicarbonyl species. These elegant transformations are exemplified by the condensation of **27b** and **57** in the presence of a Lewis acid to produce **58**. Since the review is current, the reader is referred to this article for details for this most useful chemistry.

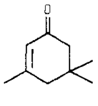


57

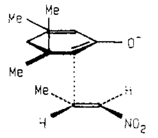


58

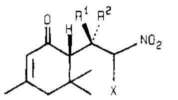
Nitroalkenes have been shown to be efficient reagents for bicycloannulation.[48] Thus metallation of **59** with lithium diisopropylamide in THF at −78 °C followed by the addition of (*E*)-1-nitropropene gave on quenching with acetic acid **60a** (46%) and **60c** (28%). If the reaction mixture was not quenched but instead refluxed in the presence of HMPT for 16 h, two tricyclooctanones **61a** (58%), **61b** (5%), and the nitro ketone **62a** (4%) were formed. Clearly during the bicycloannulation reaction the intermediates **60b** and **60d** were interconverting presumably via fragmentation to give the starting materials. Additionally Michael cyclization of the nitronates **60b** and **60d** established the bicyclic framework, and final nucleophilic displacement of nitrite by the enolate anion in **62b** completed the annulation. In the initial condensation presumably the major adduct **60a** formed was produced via the less sterically congested transition state **63a** rather than **63b**. The bicyclization reaction was extended to produce ketones including **64**. The Cory method underscores the synthetic potential of nitroalkenes with the development of a most elegant example. In this chemistry 1(*E*)-nitropropene is synthetically equivalent to **65**.



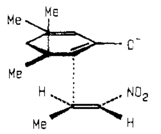
59



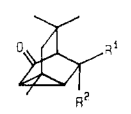
63a



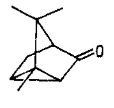
60a X=H, R^1=H, R^2=Me
b X=Li (nitronate form), R^1=H, R^2=Me
c X=H, R^1=Me, R^2=H
d X=Li (nitronate form), R^1=Me, R^2=H



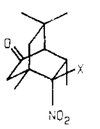
63b



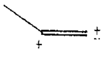
61a R^1=H, R^2=Me
b R^1=Me, R^2=H



64

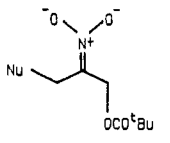


62a X=H
b X=Li (nitronate form)

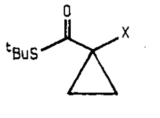


65

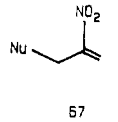
Seebach and co-workers have introduced 2-nitro-3-(pivaloyloxy)propene (**9b**) as highly versatile reagents for multicomponent coupling reactions. Nitroalkene **9b** was found to react rapidly (−78 °C) and smoothly with diverse nucleophiles by attack at C-1 rather than the hindered ester carbonyl. The resultant nitronate **66** slowly eliminated the pivaloate substituent to provide the nitroalkene product **67**. This was further tranformed by the addition of a second nucleophile. Thus the pivaloate substituent is triply advantageous: it is too bulky to undergo deacylation, it enhances the electrophilicity of **9b**, and it is a sufficiently poor leaving group so that the elimination **66** to **67** requires higher temperatures than the initial addition. The general protocol is conveniently illustrated by two specific examples. The enolates derived from camphor and **68a** reacted with **9b** to respectively produce **69** (67%) and **68b** (82%).[49]



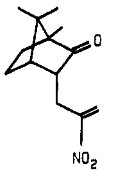
66



68a X=H
b X=CH$_2$C(NO$_2$)=CH$_2$

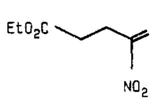


67

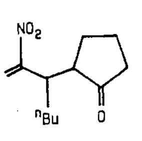


69

Nitroalkene **9b** has been sequentially coupled with two different nucleophiles, and although Seebach has published many examples, one will serve as an illustration. Thus reactions of **9b** with the enolate derived from ethyl acetate gave **70** (87%). Subsequent reaction of **70** with acetophenone enol silane[2] gave **71** (70%). This most useful chemistry has been extended to several other nitroalkenes includng **5b**, **9c**, and **29b**. For example, cyclopentanone enolate reacted respectively with **29b** and **9c** to produce **72** (73%) and **73** (75%). Clearly these results show that the reactions involve an addition elimination mechanism not S_N2 attack. Presumably **72** was obtained only as the *Z* isomer on account of thermodynamic control.[16] Additionally Seebach has reported that these nitroallylating reagents can be used for [3+3] carbocyclization. The method is exemplified by the condensation of **9c** with **74b** to produce **75** (37%, >90% ee).



70



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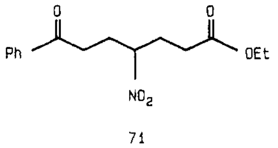
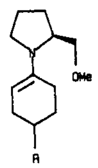
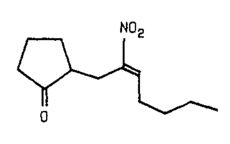


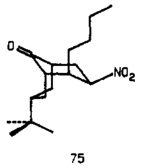
71



74a R=H
b R=^{t}Bu

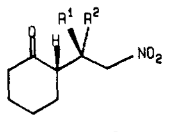


72

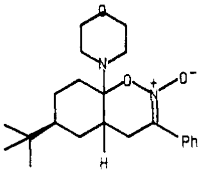


75

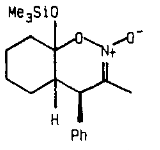
Following the pioneering work of Valentin,[1] the Michael addition of enolate anions and enamines has emerged as a useful method to produce γ-nitro ketones with reasonable to excellent diastereoselectivity. The condensation of 4-substituted (*E*)-β-nitrostyrene with cyclic lithium enolates and enamines preferentially produced the *u*-diastereoisomers (3:1–99:1) including **76a**.[1,51] Recently Seebach[52] and Mukaiyama[53] have reported alternative reagents to preferentially form the corresponding diastereoisomer **76c,d**. For example (trimethylsilyloxy)cyclohexene condensed with β-nitrostyrene on dichloro(diisopropoxy)titanium catalysis to produce the cycloadducts **77a** (11%), **77b** (10%), and **77c** (75%). This result is most informative. Indeed perhaps all nitroalkene enolate or enamine reactions proceed via cycloaddition. On reaction with potassium fluoride in methanol, both **77a** and **77b** were converted into the *u*-diastereoisomer **76a** whereas **77c** gave **76c**. Thus the *l*:*u* diastereoselectivity was 3:1. Mukaiyama[53] reported that the tin(II) enolate from cyclohexanone reacted with β-nitrostyrene to produce **76c** and **76a** (64%) with superior diastereoselectivity (>93:7). These studies were extended to several other ketones and nitrostyrenes.



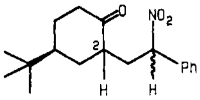
76a R^1=H, R^2=Ph
b R^1=H, R^2=Me
c R^1=Ph, R^2=H
d R^1=Me, R^2=H



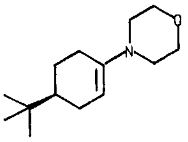
79a β-H, β-morpholino
b α-H, α-morpholino



77a β-H, α-OSiMe$_3$
b β-H, β-OSiMe$_3$
c α-H, β-OSiMe$_3$



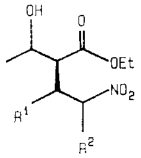
80a β-2-H
b α-2-H

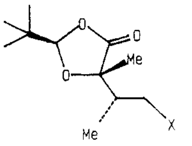


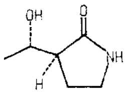
78

Seebach has also noted that (*E*)- and (*Z*)-1-nitropropene reacted with cyclohexanone enolate to produce both **76b** and **76d**. The (*E*)-alkene gave mostly the *l*-diastereoisomer **76b** (89:11) whereas the *Z* isomer preferentially produced the *u*-isomer **76d** (88:12). The dependence of diastereoselectivity on nitroalkene geometry is again consistent with a cycloaddition type mechanism.[54] In contrast the condensation reactions of analogous enamines with (E)- or (Z)-nitroalkenes gave predominantly the *u*-stereochemistry in the Michael adducts. This was consistent with reversible Michael reaction and (Z)- to (E)-nitroalkene isomerization.[55] Recent results from the Valentin group[56] underscore the importance of a cycloaddition mechanism for these transformations. Thus α-nitrostyrene reacted with the conformationally locked enamine **78** to produce **79a** and **79b** (3:1); subsequent hydrolysis at pH 5 gave **80a** and **80b**.

Seebach has extensively studied absolute stereochemical control in the condensation of chiral enamines or enolates with nitroalkenes. Using Frâter methodology the enolate dianion derived from ethyl (*S*)-(+)-3-hydroxybutyrate was condensed with nitroalkenes. The product **81** derived from nitroethylene was obtained with a diastereoselectivity of 95:5. With other nitroalkenes the diastereoselectivity of addition α to the carbonyl was equally impressive. However stereochemical control at the other centers (R^1CH, R^2CH) was totally absent.[57] Raney nickel catalyzed hydrogenation of **81** gave lactam **82** (87%). Recently this study has been extended to several chiral cyclic enolates. The synthetic versatility of this excellent science is attested by one example. Enolate **83** reacted with (*E*)-1-nitropropene to produce **84a** (58%, 93% diastereoselectivity). The product **84a** was easily transformed into diverse natural products. Thus Raney nickel catalyzed hydrogenation, palladium on carbon catalyzed hydrogenation in the presence of hydrochloric acid, and oxidation using sodium nitrite and butyl nitrite in Me_2SO gave respectively **85** (78%), **84b** (95%), and **84c** (93%).


81 R^1=R^2=H


84a X=CH_2NO_2
b X=$CH_2NH_3^+$ Cl^-
c X=CO_2H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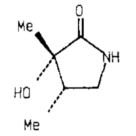
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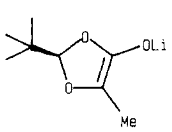
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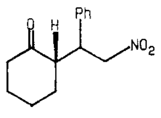
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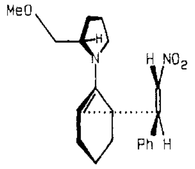
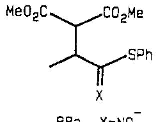
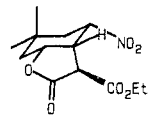

87

In an extension of his studies on enamine–nitroalkene reactions, Seebach examined the reactions of chiral enamines including **74**. On reaction with (*E*)-β-nitrostyrene, **74a** produced ketone **86** (94%, ds > 96%, 97% ee). The authors suggested that this most impressive diastereoselectivity resulted from reaction via transition state **87**.[59] This chemistry has also been applied for the alkylation of β-tetralones with good enantioselectivities.[60]

Recently we have developed a method for the preparation of α-substituted phenylthio esters from the nitroalkene **12**. Thus, for example, addition of dimethyl potassiomalonate to **12** gave nitronate **88a**. This was not isolated but directly ozonolyzed in situ to produce the phenylthio ester **88b** (60%).[61]


88a X=NO_2^-
b X=O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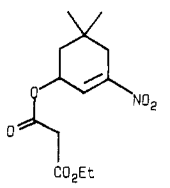
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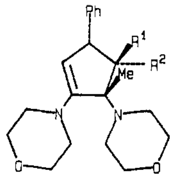
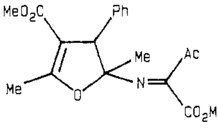

91a R^1=NO_2, R^2=H
b R^1=H, R^2=NO_2

Sakakibara[62] and Destro[63] have reported further uses of nitroalkenes in cyclization reactions. Sakakibara reported that the cyclization of **89** smoothly and stereospecifically provided **90** (55%). Comparable intermolecular reactions were not stereochemically controlled. A new synthesis of substituted cyclopentenones from the reaction of nitroalkenes with dienamines has been developed by Destro. Thus, for example, 2,3-dimorpholino-1,3-butadiene was found to react with β-nitrostyrene to produce **91a** (51%) and **91b** (15%). These enamines were hydrolyzed to the corresponding ketones (97% and 35% respectively).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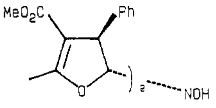
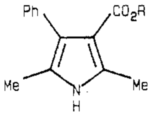
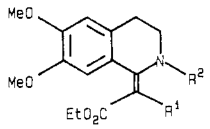
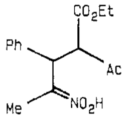
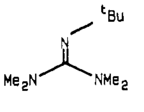

95


93a R=Me
b R=Et


96a R^1=R^2=H
b R^1, R^2=C(Ph)=C(Me)


94

Nitroalkenes have been used widely in the synthesis of pyrroles. There are five distinct general protocols for effecting such transformations. Each will be exemplified by a specific example. Boberg[64] reported that β-methyl-β-nitrostyrene condensed with methyl acetoacetate in diethyl ether followed by acidification of the intermediate **92** (75%) to produce **93a** (96%). Alternatively reaction of the same styrene with ethyl acetoacetate gave the nitrolic acid **94**. Reduction of this material optimally with sodium sulfide–ammonium chloride gave pyrrole **93b** (37%). Gômez-Sânchez[65] has developed a conceptually similar pyrrole synthesis via the intermediacy of **95** and reaction with ammonia. Adduct **95** (71%) was prepared from β-nitrostyrene and methyl acetoacetate by condensation in the presence of methanolic sodium methoxide. These workers have additionally studied the preparation of sugar pyrroles using enamine nitroalkene condensation chemistry.[66] Meyer has also utilized related chemistry in a general pyrrole synthesis.[67] For example β-methyl-β-nitrostyrene was condensed with **96a** to produce **96b** (95%). Finally and most recently Barton and Zard[68] have reported a conceptually unique pyrrole synthesis from nitroalkenes and isocyanoacetate esters. For example, 2-nitropropene condensed with methyl isocyanoacetate in THF in the presence of base **97** to produce **98** (60%). The product **98**, a trail marker pheromone, was produced via intermediate **99**.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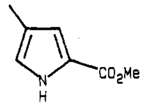
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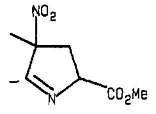
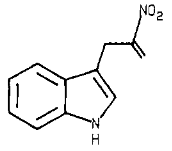

99

2. *Other Carbon-Centered Nucleophiles*

The nitroallylation chemistry developed by Seebach has been proven to be a very versatile method in organic synthesis. For example nitroalkene **9b** was found to react with nucleophiles derived from acids with pK_a values ranging from 4 to above 40! In addition to enolate anion and enamine chemistry **9b** and analogues were found to nitroallylate indoles, dithiane anions, and aryl-, vinyl-, or alkynyllithiums, and primary or secondary or tertiary alkyllithium reagents. The scope of the reaction is further underscored by several examples. Thus **9b** was reacted respectively with indole, 2-lithio-2-phenyl-1,3-dithiane, 1-lithionaphthalene, and (*Z*)-1-lithiohexene to respectively produce **100** (69%), **101** (85%), **102** (85%), and **103** (69%).[5,69] Additionally the method has been used to prepare double addition products. For example, **102** was further reacted with ethyl lithioacetate to produce **104** (66%). In these double addition reactions (see also section V.A.1.) superior yields were obtained when the more reactive nucleophile was added first. Additionally the nitroalkene products may be transformed further in a myriad of ways. The Diels–Alder reaction of **101** to produce **105** (85%) (see section IV.A.) and the reduction of **104** by hydrogenation over Raney nickel to give **106** (82%) are but examples. This most useful chemistry has been extended[16] to other nitroallylating reagents including **5b**, **9c**, and **29b**.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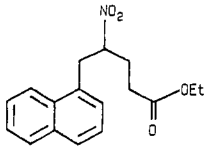
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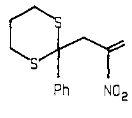
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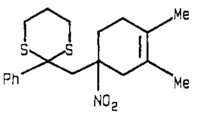
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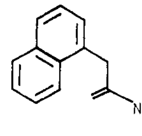
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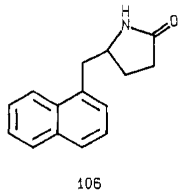
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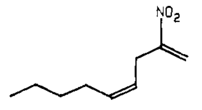
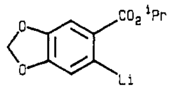

103

Paulsen[70] has employed the addition of aryllithium reagent **107** to nitroalkene **108** at −110 °C to provide **109** (77%) as a key step in the synthesis of (+)-lycoricidin from D-glucose. Additionally in our studies on the chemistry of nitroalkene **12** we have converted this material into **110a** (39%) by reaction with phenyllithium followed by ozonolysis of the intermediate nitronate salt in situ.[71]

Nucleophilic alkenes may be condensed with nitroalkenes under Lewis acid catalysis. Fuji reported the aluminum chloride catalyzed condensation of 2,3-dimethylbutadiene with **111a** in dichloromethane to produce **111b** (84%).[72] The reaction was extended to several conjugated dienes to produce the corresponding adducts. The authors argued that the reaction proceeded via the Diels–Alder adduct **112**, and such a mechanism is consistent with the observed stereospecificity. Allylsilanes, in the presence of aluminum chloride, were found to readily add to nitroalkenes. Additionally the intermediate silyl nitronates could be either hydrolyzed under acidic conditions (Nef reaction) or reduced with titanium trichloride to produce the corresponding γ,δ-enones. For example allyltrimethylsilane was condensed with β-methyl-β-nitrostyrene to produce **113** (51%).[73] Clearly this method is complementary to the Yoshikoshi chemistry with enol silanes.[2]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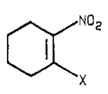
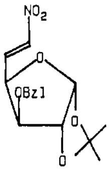

111a X=SEt
b X= (Z)-CH$_2$C(Me)=C(Me)CH$_2$SEt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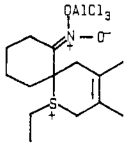
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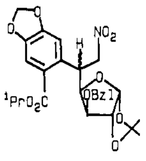
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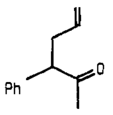
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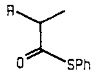
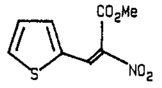

110a R=Ph
b R=MeO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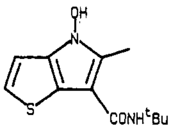
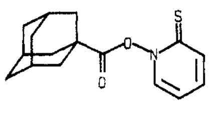

115

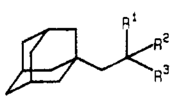
Isonitriles have also been added to nitroalkenes as a method of preparing heterocyclic molecules. Foucaud[74] has covered this chemistry in a brief review on isonitriles. For example *tert*-butyl isonitrile was condensed with **114** to produce **115**.

B. With Carbon-Centered Radicals

Recently Barton has discovered an intriguing and previously unappreciated aspect of nitroalkene chemistry; the addition of carbon-centered radicals. The chemistry is exemplified by a reaction that demonstrates a radical chemistry alternative to the Arndt–Eistert reaction. Thus ester **116** was irradiated in dichloromethane–toluene solution in the presence of nitroethylene and camphorsulfonic acid at −10 to −20 °C to produce the nitrosulfide **117a** (97%).[75] The product was produced via a chain radical process and the sulfonic acid was added to suppress anionic polymerization of the nitroethylene. The product nitrosulfide **117a** was readily transformed into **117b** (68%) or **117c** (95%), respectively, via reaction with sodium methoxide, ammonium acetate, and titanium(III) chloride in aqueous methanol or with potassium carbonate and hydrogen peroxide in methanol and THF. This very elegant and novel radical decarboxylation chemistry was extended to other carboxylic acids, to 1- and 2-nitropropenes, to a radical variant of Seebach nitroallylation, and to the facile construction of the 25-hydroxy vitamin D_3 side chain from a bile acid.



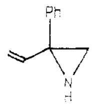
116



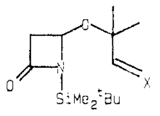
117a R^1=H, R^2=S- R^3=NO_2
b R^1=H, R^2, R^3=O
c R^1=OH, R^2, R^3=O

C. With Nitrogen-Centered Nucleophiles

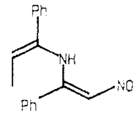
Seebach nitroallylation has been applied to nitrogen centered nucleophiles. The reaction of **5b** with *N*-methylaniline to produce **5d** (66%) is an example.[4,5,16] Hassner reported that the vinylaziridine **118** reacted with β-nitrostyrene on heating to produce **119** (80%).



118



121a X=O
b X= (Z) -C (SPh) NO_2



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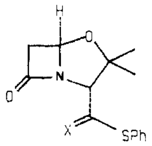
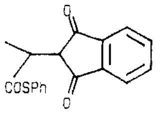


122a X=NO_2^-
b X=O



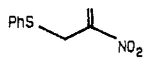
120

The product **119** probably arose via initial nitrogen-centered nucleophilic attack and a subsequent retro-ene azetidine fragmentation.[76]

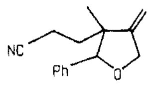
Recently we have observed that **12** will react with nitrogen-centered nucleophiles to produce, on ozonolysis, the corresponding amino acid phenylthio ester derivatives.[71,61] For example, **12** was reacted with potassium phthalimide under these conditions to produce **120** (68%). Additionally the method can be used to prepare bicyclic β-lactams.[9] Thus, for example, the nitroalkene **121b** (67%) was prepared from the aldehyde **121a** by the Henry condensation (see section II.A, compound 12). On reaction with tetrabutylammonium fluoride in THF at −55 °C followed by direct ozonolysis at −78 °C **121b** was converted into the oxadethiapenam **122b** (64%) accompanied by the C-3 epimer (14%). Clearly the fluoride was mediating desilylation and the resultant nitrogen-centered anion smoothly cyclized to produce the nitronate **122a**. Workup by ozonolysis converted this into **122b** by the McMurray's oxidative Nef reaction. This β-lactam methodology, which is an adaptation of Shibuya chemistry,[77] is applicable to both the dethiapenam and dethiacepham nuclei.[9]

D. With Oxygen- and Sulfur-Centered Nucleophiles

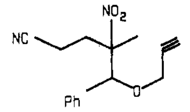
Seebach has reported that nitroallylation may be efficiently applied to diverse nucleophiles. The production of **123** (62%) from **9b** and thiophenol is an example with a sulfur centered species.[5] The adducts derived from the addition of oxygen-centered nucleophiles to nitroalkenes have been converted into tetrahydrofurans, thio esters, α-oximino ethers, and chromenes etc. Ono has utilized nitroalkene chemistry to prepare precursor molecules for radical cyclizations. For example β-methyl-β-nitrostyrene was reacted with 3-propynol followed by acrylonitrile to produce **124** (74%). Subsequent tributylstannane reduction gave **125** (79%).[78] Nitroalkene **12** has been used to prepare α-oxygenated phenylthio esters. For example, reaction of **12** with methanolic sodium methoxide followed by ozonolysis of the resultant nitronate gave **110b** (79%). Kabalka in his extensive studies on nitroalkene reductions has developed a method to prepare α-alkoxy ketones. For example 1-nitrocyclohexene reacted with tin(II) chloride in ethanol solution to produce 2-ethoxycyclohexanone (79%) on acid hydrolysis of the intermediate oxime.[29,30] The reaction was extended to α-alkylthio ketones. Salicylaldehydes have been condensed with substituted β-nitrostyrenes to produce chromene derivatives including **126** (85%). The reaction required a basic alumina catalyst and ultrasonication for good conversions.[79] These adducts including **126** have been transformed into flavonols[80] via photochemically mediated methanol addition. Russel[81] has shown that 1,1-diphenyl-2,2-dinitroethylene reacted



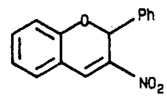
123



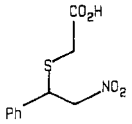
125



124



126



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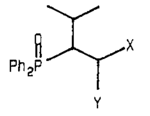
with diverse nucleophiles including oxygen- and sulfur-centered species to produce either addition products or benzophenone. Wadia[82] has reported a mechanistically intriguing reaction of several β-nitrostyrenes: these were found to react with hydrogen peroxide and triethylamine to produce diaryl acetylenes.

Although control of absolute stereochemistry during the addition of carbon-centered nucleophiles to nitroalkenes has been extensively investigated, there have been few attempts reported to control the addition of other nucleophiles. Kobayashi has reported that the enantioselectivity of addition of thiols of β-nitrostyrene was subject to control by chiral amine additives. In the optimum example thioglycolic acid was added to β-nitrostyrene in the presence of quinine to give the adduct **127** (86%) in 58% enantiomeric excess.[83] Clearly efficient absolute stereochemical control in the addition of diverse nucleophiles to nitroalkenes especially only using catalytic chiral auxiliaries remains a glittering prize.

E. With Other Nucleophiles

Russian workers have extensively studied the addition reactions of diverse phosphorus(III) and (V) reagents with nitroalkenes to produce exotic phosphacycles, hydroximoyl phosphates, etc.[84] Yamashita and co-workers have reported that diphenylphosphine oxide smoothly condensed with nitroalkenes to produce the corresponding β-nitroalkyldiphenylphosphine oxides including **128a** (95%).[85] These are certainly potentially useful intermediates for further elaboration. For example ozonolysis of the nitronate derived from **128a** gave the corresponding aldehyde **128b** (90%).

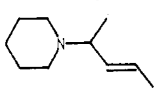


128a X=H, Y=NO_2
b X, Y=O

F. With Electrophiles

Nitroalkenes are very poor nucleophiles and in general do not readily react with electrophiles. Seebach has utilized the reaction between phenylselenyl trifluoroacetate in his preparative work on nitroalkenes (section II.B.). However, nitroalkenes can be deprotonated and the resultant anions used in synthesis. Of course anionic polymerization is a danger with this protocol especially with simple nitroalkenes. Barton used such a method in a high yielding corticosteroid synthesis.[11] Thus (*E*)-nitroalkene **15b** was condensed with formaldehyde in the presence of triethylamine to give **15d** (99%). This was subsequently converted into **15e** (84% overall) via sequential reaction with acetic anhydride, chromium(II) chloride, and titanium(III) chloride.

Nitroalkenes have been isomerized with base to produce allyl nitro compounds. When the isomerization reaction was carried out in the presence of a nucleophile and palladium(0) catalyst, substitution via a π-allyl palladium mechanism was observed.[86] For example using this protocol (*Z*)-2-nitro-2-pentene in DMF was reacted with piperidine catalyzed by tetrakis(triphenylphosphine)palladium(0) and 1,2-bis(diphenylphosphino)ethane to produce **129** (75%). The reaction was extended to the synthesis of alicyclic sulfones and to displacement reactions by malonate anions.[87]



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