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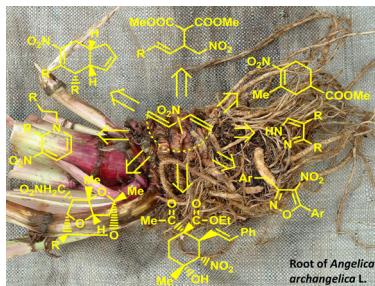
Conjugated Nitrodienes. Synthesis and Reactivity

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1. INTRODUCTION

The synthesis and reactivity of conjugated electron-deficient dienes and, particularly, their use in Diels–Alder reactions, remains a challenge in synthetic organic chemistry.^{1–11} The introduction of electron-withdrawing substituents on a conjugated dienic system allows the regiocontrolled synthesis of new cyclohexenes with a high level of functionalization. Since those substituents can be converted into other functionalities, or even be replaced by hydrogen—as in the case of arylsulfonyl¹ or nitro^{2,12} groups—their synthetic usefulness vastly increases. Although there are many examples of the use of sulfonyl dienes,^{1,3,4} only a limited amount of work has been done on nitrodienes. This is probably a consequence of difficulties related to their syntheses: because of their instability,^{2,4} some of these compounds must be prepared *in situ*, due to either their sensitivity to acids and bases or their tendency to dimerize, polymerize, or undergo oxidation under normal conditions.

Despite these challenges, the chemistry of nitrodienes has received increasing attention in recent years; together with their halogenated derivatives, they are employed to develop preparative methods for the synthesis of complex polyfunctional products of different classes, some of them of biological interest.^{2,12–14} These compounds are extraordinarily versatile reagents that can be used as suitable substrates in a wide variety of processes, which will be discussed throughout this paper.^{15,16}

Russian researchers mainly contributed to early works on conjugated nitrodienes. Thus, Guseinov¹⁷ and then Petrzilka¹⁸ wrote reviews on the chemistry of some 1-substituted alka-1,3-dienes and on the preparation and Diels–Alder reactions of heterosubstituted 1,3-dienes, respectively. In both cases, small sections with a few references on nitrodienes were included.

Perekalin^{19,20} published two reviews about the synthesis and reactivity of nitroalkenes. The latter²⁰ contains large sections on mono- and dinitrodienes, and many of the Russian publications on the preparation and reactivity of these compounds until 1991 are amalgamated. Afterward, an extensive review by Kaberdin²¹ on the synthesis and reactivity of nitrobutadienes and their halogenated derivatives contains 112 references, mainly Russian, covering the literature until 1996. In this review, methods for preparing these compounds are divided into two groups: the first is focused on the direct nitration of butadiene and some of its halogenated derivatives with different reagents, while the second describes elimination reactions from complex aliphatic nitro compounds.

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Bloom et al.^{25,26} have reported that some of the methods described in the earlier Russian literature, mainly those concerning the synthesis of 1-nitro-1,3-dienes,^{27–29} were inefficient, either because of their low yields or because the stereochemistry around the double bonds was unspecified. Furthermore, the products were obtained as mixtures, and competitive 1,4-additions were observed during their preparation. Since the paper of Guseinov¹⁷ cited above was written before this, references herein could have similar problems.^{30–32}

Here, we review the literature on the synthesis and reactivity of nitrodienes that has appeared in the past two decades. Some references before 1990 that have not been included in previous reviews are also amalgamated.

Perhalogenated nitrobutadienes have been excluded from this review as these substances show a reactivity that is influenced by both nitro and halogen groups. From our point of view, the extent of work on this topic that has been done after the paper of Kaberdin²¹ is beyond the scope of this review and deserves its own consideration.^{22–24}

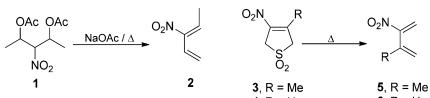
This paper has been arranged according to the structure of the dienes, including sections on the most striking reactivity.

2. 2-NITRO-1,3-DIENES

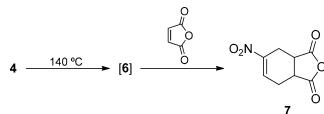
2.1. Cyclic and Acyclic Alkyl- or Aryl-Substituted 2-Nitro-1,3-dienes

Pioneering works on conjugated nitrodiene were reported by Buckley and Charlish,³³ who described the synthesis of 3-nitropenta-1,3-diene (**2**) by heating 2,4-diaceoxy-3-nitropentane (**1**) with a small amount of sodium acetate. These authors also prepared 2-methyl-3-nitrobuta-1,3-diene (**5**), which can be generated in situ by heating 3-methyl-4-nitro-3-sulfolene (**3**). Both compounds **2** and **5** proved to be too unstable²¹ to give Diels–Alder adducts, as either dienes or dienophiles. Following a similar procedure described for the synthesis of compound **5**, 3-nitro-3-sulfolene (**4**)³⁴ led to 2-nitrobuta-1,3-diene (**6**) (Scheme 1). As indicated in Scheme 2, the Diels–Alder reaction between **6** and maleic anhydride afforded cycloadduct **7** in 51% yield.

Scheme 1

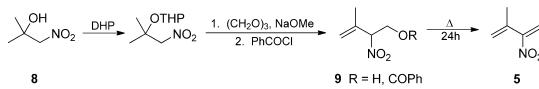


Scheme 2



Later, Barco et al.³⁵ reported the strong tendency of 2-nitro-1,3-diene **6** to undergo anionic polymerization by reaction with dienophiles bearing substituents such as secondary amino groups. The same authors^{6,36,37} described a three-step sequence for the preparation of **5** (Scheme 3); here, the precursor **9** was obtained in 65% yield from tertiary nitro alcohol **8**, prepared via a Knoevenagel condensation between nitromethane and the appropriate ketone. Because of its tendency to dimerize,^{36,37} compound **5** must be generated in situ for further reactions. 2-

Scheme 3



Nitrodienes **10–13** (Figure 1) were obtained⁶ using this same methodology.

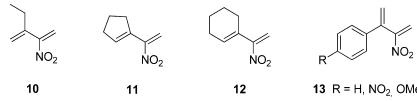
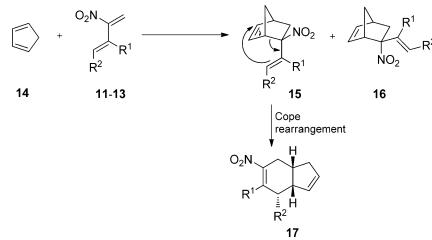


Figure 1.

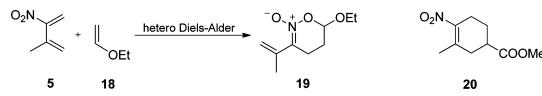
Reactions of 2-nitrodiene **5** and **11** with methyl acrylate gave⁶ the expected Diels–Alder adducts. On the other hand, reactions between nitrodiene **5** and **11–13** and cyclopentadiene (**14**) led to a mixture of products **15–17**, the latter resulting from a Cope rearrangement of the *exo*-nitro adducts **15** (Scheme 4). For a related cycloaddition, it is remarkable that, in an *endo*-nitro compound, the N=O double bond was involved in the rearrangement.⁶

Scheme 4



As shown in Scheme 5, the reaction between nitrodiene **5** and moderately electron-rich olefins such as ethyl vinyl ether

Scheme 5

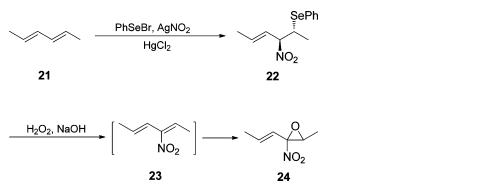


(**18**) yielded 87% hetero-Diels–Alder adduct **19**. However, with dienophiles bearing electron-withdrawing substituents, the cycloaddition occurs in the normal mode; thus, the adduct **20** was obtained in 98% yield from **5** and methyl acrylate.⁶

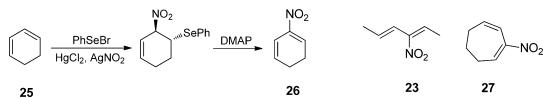
Bäckvall et al.¹⁶ made attempts to extend the methodology of nitroselenation of monoolefins³⁸ to the synthesis of 2-nitrodiene. Their synthesis started with nitroselenation of hexa-2,4-diene (**21**) to give the nitro compound **22**. Next, oxidative base-catalyzed elimination of the phenylselenyl group afforded 3-nitrohexa-2,4-diene (**23**), which could not be isolated (Scheme 6). Instead, the isolated product was 4,5-epoxy-4-nitrohex-2-ene (**24**) (40% yield), formed by trapping from in situ generated 3-nitrodiene **23**.¹⁶

One year later, the preparation of some 2-nitrobuta-1,3-dienes by nitroselenation from the corresponding conjugated dienes, followed by base-catalyzed elimination of the phenylselenyl group, was described.² Scheme 7 shows this process for the preparation of 2-nitrocyclohexa-1,3-diene (**26**) (38% yield) from cyclohexa-1,3-diene (**25**). Dienes **23** and **27** were synthesized in the same way from hexa-2,4-diene and

Scheme 6



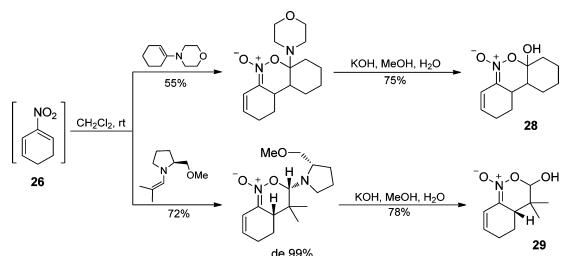
Scheme 7



cyclohepta-1,3-diene, respectively. These nitrodienes, as well as 2-nitro-1,3-pentadiene and 4-methyl-2-nitro-1,3-pentadiene, were trapped with enol ethers, leading to nitronates in 38–62% yields (based on their corresponding dienes).

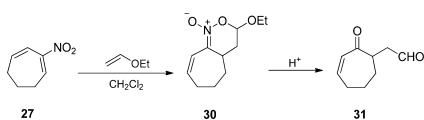
2-Nitro-1,3-dienes, generated in situ from their corresponding nitroseleno compounds, react readily with enamines as 4π electron components to afford products of [4 + 2] heterocycloaddition in good yields.¹⁵ Thus, the oxazine N-oxide derivatives **28** and **29** were obtained from **26** after alkaline hydrolysis of the initially formed stable adducts (Scheme 8).

Scheme 8



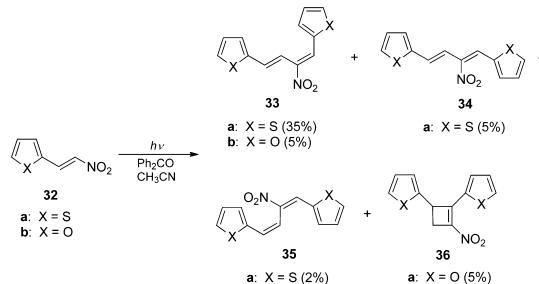
Heterocycloaddition between several 2-nitrodiene, either stable or unstable, and enol ethers gave adducts which, by acid hydrolysis, led to unsaturated 1,4-dicarbonyl compounds.² Scheme 9 illustrates this process for the synthesis of **31** (30% overall yield) from 2-nitrocyclohepta-1,3-diene (**27**) through nitronic ester **30**.

Scheme 9



The photochemical dimerization of 2-heteroaryl nitroethylene derivatives **32** in the presence of benzophenone as a triplet sensitizer led, through a concerted process, to a mixture of 2-heteroaryl-2-nitrodiene **33–35** in 2–35% yields (Scheme 10).³⁹ The products are dimeric structures of the starting material, involving loss of nitrous acid. In contrast to that observed for 1,3-diheteroaryl-2-propen-1-one derivatives, which gave cyclobutane dimers through a frontier orbital control reaction, the behavior of compounds **32** is in agreement with the nature of their HOMO–LUMO orbitals, which do not allow the superimposition of the reagents.

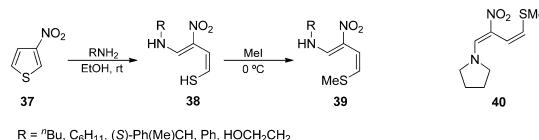
Scheme 10



2.2. Mono- and Dihetero-Substituted 2-Nitro-1,3-dienes

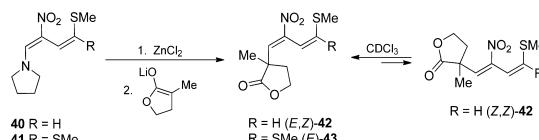
The ring-opening reaction⁴⁰ of 3-nitrothiophene (**37**) with primary or secondary amines, followed by S-methylation of the resulting thiol **38**, led to (*Z,Z*)-1-amino-4-(methylthio)-2-nitro-1,3-butadienes **39** (57% yield from *n*-butylamine) (Scheme 11). By a similar reaction with pyrrolidine, compound **40** was obtained in 24% yield.

Scheme 11



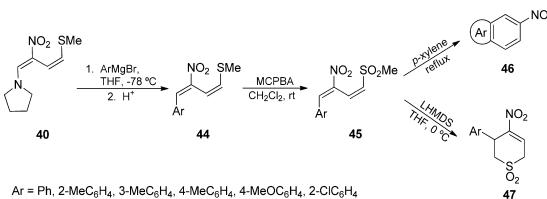
Treatment of 2-nitrodiene **40** and **41**⁴¹ with lithium enolates gave 2-nitrodiene lactones **42** and **43** (52% and 70% respective yields), by overall substitution of the dialkylamino group with the residue of the organometallic reagent.⁴² Interestingly, a solution of compound **42** in deuteriochloroform showed slow equilibration, leading to a mixture of (*E,Z*)- and (*Z,Z*)-isomers in a 4:1 ratio (Scheme 12).

Scheme 12



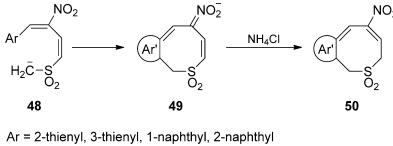
The reaction of **40** with aryl Grignard reagents gave 2-nitrodiene **44**,⁴³ which by sulfur oxidation with MCPBA yielded (*1E,3Z*)-1-aryl-4-(methylsulfonyl)-2-nitro-1,3-butadienes **45**. These versatile compounds undergo 6π -electrocyclization in refluxing xylene to give 72–92% yields of nitrobenzene ring-fused derivatives **46**,⁴³ whereas their reaction with LHMDS resulted in an intramolecular Michael addition to afford⁴⁴ thiopyran S,S-dioxides **47** (Scheme 13). In addition to these types of compounds, it should be noted that when the Ar

Scheme 13



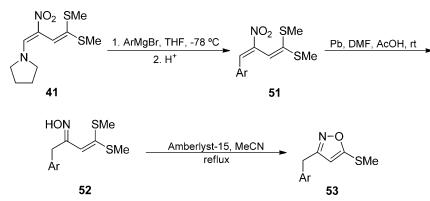
group is a homo- or heterosystem with low aromaticity (2- or 3-thienyl, 1- or 2-naphthyl), anions **48** derived from **45** undergo addition onto the aromatic ring, thus leading to eight-membered sulfur heterocycles condensed with the original Ar ring **50** through nitronates **49** (Scheme 14).⁴⁵

Scheme 14



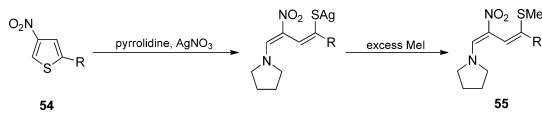
Previously,⁴⁶ 1,1-bis(methylthio)-3-nitro-4-pyrrolidino-1,3-butadiene (**41**), resulting from ring opening of 2-(methylthio)-4-nitrothiophene, has been transformed in high yield into 3-(aryl methyl)-5-(methylthio)isoxazole (**53**) through a reaction sequence involving (a) chemoselective replacement of the pyrrolidino group by an aryl residue, (b) reduction of the nitrovinylic moiety of **51** with lead powder in an acetic acid/DMF mixture, and (c) ring closure of the resulting vinyloximes **52** with methanethiol elimination (Scheme 15).

Scheme 15



The ring-opening reaction of 2-substituted 4-nitrothiophenes **54** with pyrrolidine/AgNO₃, followed by treatment with excess MeI, gave the polyfunctionalized 2-nitrodiene **55** (Scheme 16).^{46,47} Similarly, 3-nitro-4-(phenylsulfonyl)thiophene (**56**)

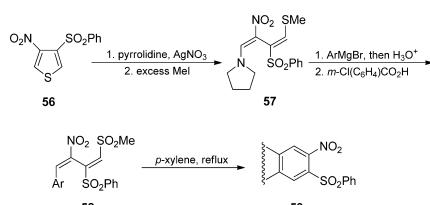
Scheme 16



yielded compound **57**, which, after replacement of the pyrrolidino moiety and oxidation of the methylthio group in **58**, led to naphthalene, phenanthrene, and benzothiophene derivatives **59** (Scheme 17).⁴⁸

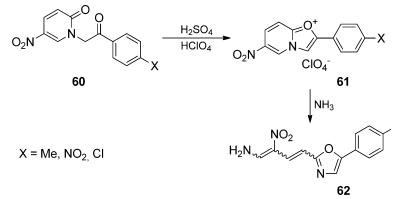
By treatment with sulfuric acid and a few drops of HClO₄, 5-nitro-2-pyridones **60** undergo cyclization to 6-nitrooxazolo[3,2-a]pyridinium perchlorates **61**, which were isolated as pure

Scheme 17



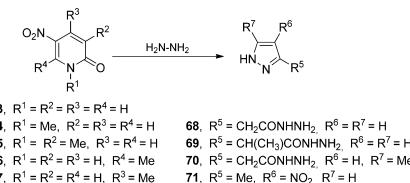
precipitates from anhydrous diethyl ether. Pyridine ring opening of these salts with anhydrous ammonia or primary or secondary amines led to 1-amino-2-nitro-4-(oxazolo[3,2-a]pyridin-6-yl)-1,3-butadienes **62** (Scheme 18).⁴⁹

Scheme 18



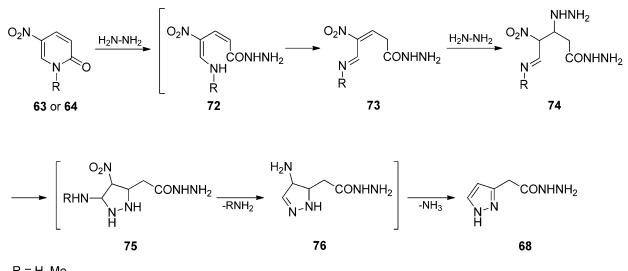
The reaction of 5-nitropyridin-2-(1*H*)-one (**63**) or its 1-methyl (**64**), 1,3-dimethyl (**65**), or 6-methyl (**66**) derivative with hydrazine hydrate provides a new synthetic route to pyrazole derivatives similar to **68–70** bearing a hydrazide moiety. However, it should be noted that 4-methyl-5-nitropyridin-2(*H*)-one (**67**) gave 3-methyl-4-nitro-1*H*-pyrazole (**71**) under the same conditions (Scheme 19).⁵⁰

Scheme 19



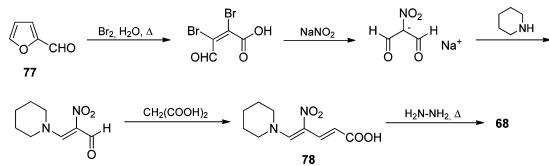
A hypothetical mechanism to justify the formation of **68** using **63** or **64** as the starting compound involves the formation of acyclic hydrazone **72**, which undergoes nitroaminodiene–nitroenamine isomerization to give **73**; then attack from a second hydrazine molecule and intramolecular cyclization of intermediate **74** leads to tetrahydropyrazole derivative **75**, which, by subsequent elimination of ammonia (or methylamine), reduction of the nitro group, and elimination of the second ammonia molecule from structure **76**, yields (1*H*-pyrazol-3-yl)acetohydrazide (**68**) (Scheme 20).⁵⁰

Scheme 20



To demonstrate the participation of an acyclic 2-nitro-aminodiene in the mechanism of recyclization of nitropyridine derivatives to pyrazoles, the model compound 4-nitro-5-piperidinopenta-2,4-dienoic acid (**78**) was prepared from furfural (**77**) following the route shown in Scheme 21. When the model compound was heated with hydrazine hydrate, it yielded 86% **68**.⁵⁰

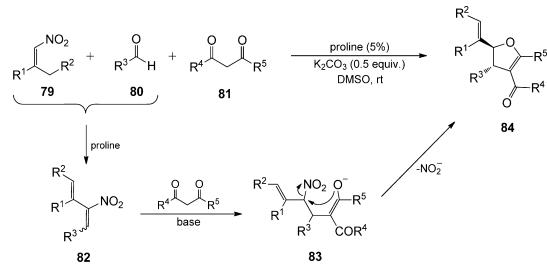
Scheme 21



2.3. Participation in Three-Component Condensation Reactions

Recently, Zhong et al.⁵¹ reported the synthesis of substituted dihydrofurans **84** (Scheme 22) by proline-catalyzed three-

Scheme 22

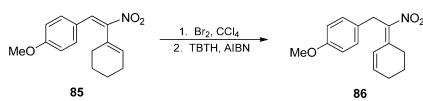


component condensation reactions among nitroalkenes **79**, aldehydes **80**, and 1,3-dicarbonyl compounds **81**. According to the authors, the process occurs via nitrodiene intermediates **82** and involves substitution of the allylic nitro group of intermediate **83** under very mild conditions.

2.4. Transformation into 1-Nitro-1,3-dienes

As shown in Scheme 23, the reaction of 2-nitro-1,3-diene **85** with bromine, followed by treatment with TBTH/AIBN,

Scheme 23

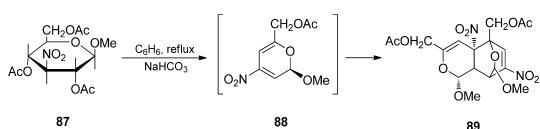


promoted skeletal rearrangement leading to 53% 1-nitro-1,3-diene **86**. This compound proved to be unstable and decomposed at room temperature after 48 h.⁵²

2.5. Chiral 2-Nitro-1,3-dienes

As far as we know, the only report on chiral 2-nitro-1,3-diene **88** as the reaction intermediate of an intermolecular Diels–Alder addition, leading to crystalline dimer **89** in 43% yield.⁵³ As indicated in Scheme 24, intermediate **88** was generated by treatment of methyl 2,4,6-tri-O-acetyl-3-deoxy-3-nitro- β -D-glucopyranoside (**87**) with sodium hydrogen carbonate in refluxing benzene (similar results were obtained with the *manno* or *galacto* stereoisomer). The first synthetic step of this route is closely related to that depicted in Scheme 1.³³

Scheme 24



3. 1-NITRO-1,3-DIENES

3.1. Cyclic and Acyclic Alkyl-, Aryl- or Keto-Substituted 1-Nitro-1,3-dienes

Although methods for the preparation of 1-nitroalkenes have been known for a long time, this is not the case for 1-nitro-1,3-dienes. As pointed out by Bloom et al.^{25,26} (see the Introduction), procedures for the preparation of these compounds were inefficient and their chemistry was scarcely investigated.^{27,54–56} Furthermore, several of the 1-nitro-1,3-dienes described proved to be unstable under normal conditions. Thus, 1-nitrobuta-1,3-diene^{6,16,25,26} (**90**) (Figure 2) quickly decomposes at room temperature,^{25,26} being stable

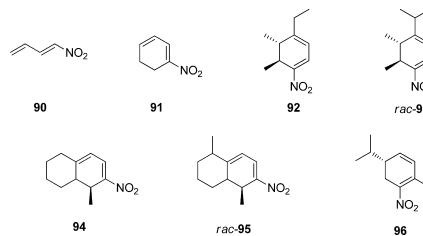
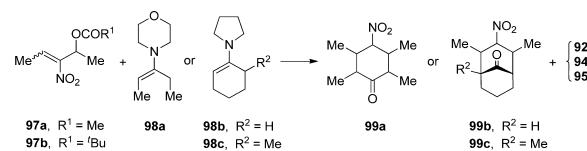


Figure 2.

for only one week at $-20\text{ }^\circ\text{C}$. Concerning cyclic 1-nitro-1,3-dienes, 1-nitrocyclohexa-1,3-diene (**91**) suffered rapid oxidation to nitrobenzene by exposure to air,²⁶ while **92** and **93** proved to be very sensitive to light and temperature, so that their elemental analyses and optical rotations were not truly reliable.⁵⁴

Seebach et al.⁵⁴ reported that 1-nitro-1,3-cyclohexadienes **92**, **94**, and **95** were isolated as byproducts (10–20% yields) from the [3 + 3] carbocyclization reactions between, either racemic or optically active, nitroallylic esters **97** and enamines **98**, in which the major products were the cyclic γ -nitroketones **99** (Scheme 25). Within the same paper, preparation of racemic 4-isopropyl-2,3-dimethyl-1-nitro-1,3-cyclohexadiene (**93**) (37% yield) was described from *rac*-**97a** and 3-pyrrolidino-2-methylpentene.

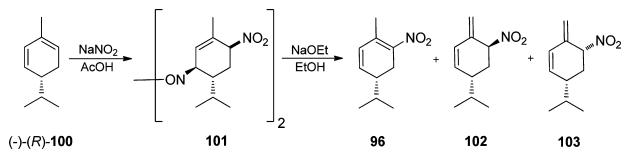
Scheme 25



In contrast to the instability of **91–93**, 2-nitro-1,5-*p*-methadiene (**96**) has been isolated as a component from the root oil of *Angelica archangelica* L.⁵⁷ This compound was prepared by a two-step process: treatment of $(-)(R)$ - α -phellandrene (**100**) with sodium nitrite and acetic acid afforded the dimer **101**, which, by subsequent reaction with sodium ethoxide in ethanol, led to a mixture of **96**, **102**, and **103**, with the former (62% yield) as the major product (Scheme 26).

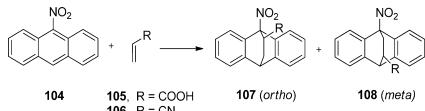
Anthracene and other aromatic or heteroaromatic compounds can behave as the diene component in [4 + 2] cycloadditions.⁵⁸ The similarity between 1-substituted 1,3-butadienes and 9-substituted anthracenes prompted the reinvestigation⁵⁹ of the Diels–Alder reactivity of 9-nitro-anthracene (**104**) with acrylic acid (**105**) or acrylonitrile (**106**). The corresponding products were obtained as a mixture

Scheme 26



of the *ortho/meta* adducts in ratios (i.e., **107:108**) of 19:81 (94% yield for R = COOH) and 63:37 (20% yield for R = CN) (Scheme 27).

Scheme 27



Bartoli et al.^{60,61} have studied conjugate additions between organometallic reagents and **104**⁶⁰ or 1-nitronaphthalene.⁶¹ After treatment with a MeCOOH–MeCOOK buffer solution, the products (70–78% yields) were *cis*-9-alkyl-10-nitro-9,10-dihydroanthracenes **109** and mixtures of *cis*- and *trans*-4-alkyl-2-methoxy-1-nitro-1,4-dihydroronaphthalenes **110** (Figure 3).

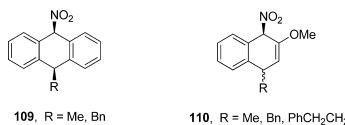
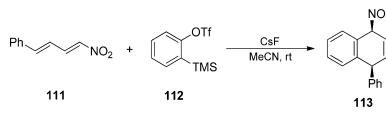


Figure 3.

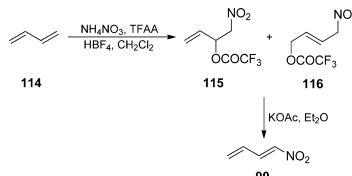
Functionalized 1,4-dihydroronaphthalenes have been obtained through an inverse electron-demand aryne Diels–Alder reaction with acyclic dienes bearing electron-withdrawing substituents.⁶² Thus, 75% 1-nitro-4-phenyl-1,4-dihydroronaphthalene (**113**) (apparently unstable to flash chromatography on silica gel) was obtained from 1-nitro-4-phenylbuta-1,3-diene (**111**) and benzyne, generated from 2-(trimethylsilyl)phenyl triflate (**112**) and CsF in acetonitrile (Scheme 28).

Scheme 28



As mentioned above, Bloom et al.²⁵ reported the first general synthesis of 1-nitrobuta-1,3-dienes from buta-1,3-dienes. As indicated in Scheme 29 for **90** (89% overall yield), the reaction proceeded via 1,2- and 1,4-nitrotrifluoroacetoxylation of **114**, leading to **115** and **116**, followed by alkaline elimination under mild conditions.

Scheme 29



In addition to **90** and **91** (see Figure 2), the above methodology allowed the preparation of 1-nitro-1,3-dienes **117**–**122** (Figure 4) from the corresponding dienes, with yields

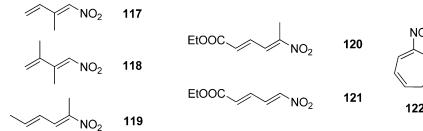
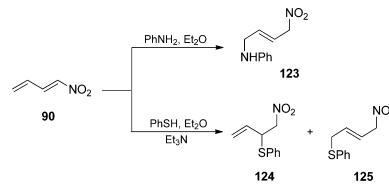


Figure 4.

ranging between 55% and 94% (35% for **120**).²⁵ The elimination step was performed using potassium acetate in ether for all of the syntheses, except for the preparation of 2-methyl-1-nitrobuta-1,3-diene (**117**), which used sodium hydride in tetrahydrofuran.

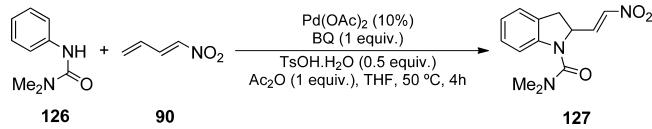
The addition of nucleophiles, such as aniline or thiophenol, to 1-nitrodiene has been studied by Bloom and Mellor.²⁵ Regioselectivity in the addition to **90** depended strongly on the nature of the nucleophile; thus, aniline gave a 57% yield of the 1,6-adduct **123**, while thiophenol gave a 54% yield of the 1,4-adduct **124** and a 13% yield of 1,6-adduct **125** (Scheme 30). Previously, the addition of ethanethiol to **90**, yielding only the 1,4-adduct, has been reported.⁶³

Scheme 30



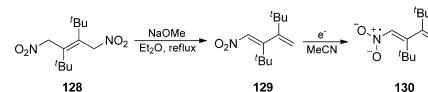
An efficient Pd(II)-catalyzed 1,2-carboamination of dienes has been reported.⁶⁴ The reaction proceeds under very mild conditions and enables the synthesis of indolines from N-arylpureas, involving an *ortho* C–H insertion/carbopalladation/cyclization sequence. Thus, 70% **127** was obtained from *N,N*-dimethyl-*N'*-phenylurea (**126**) and **90** (Scheme 31).

Scheme 31



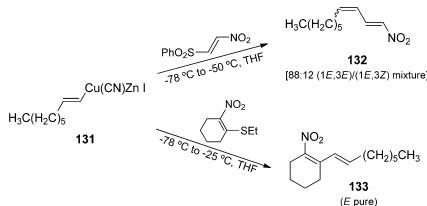
On the other hand, treatment of 1,4-dinitro-2,3-di-*tert*-butyl-2-butene (**128**) with sodium methoxide in boiling ether led to 1-nitro-2,3-di-*tert*-butyl-1,3-butadiene (**129**). Electrolytic reduction of this compound in acetonitrile (with tetra-*n*-propylammonium perchlorate as the supporting electrolyte) afforded nonplanar anion radical **130**, whose ESR spectrum was studied (Scheme 32).⁶⁵

Scheme 32



As shown in Scheme 33, an efficient and highly stereoselective method for the preparation of (*1E,3E*)- and (*1E,3Z*)-

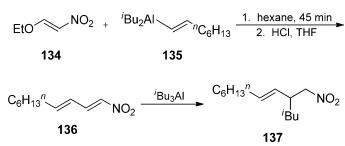
Scheme 33



1-nitro-1,3-dienes **132** (81% yield) and **133** (90% yield) involves^{66,67} the addition of the copper–zinc organometallic compound **131** to β -(phenylsulfonyl)- or β -(alkylthio)-nitroalkenes, followed by *in situ* elimination of the sulfur group.

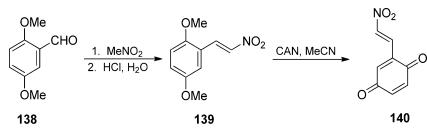
Treatment of (*E*)-1-ethoxy-2-nitroethylene (**134**) with the aluminum derivative **135** followed by acid hydrolysis has been described⁶⁸ as a useful method to prepare conjugated nitrodiene as (*1E,3E*)-1-nitrodeca-1,3-diene (**136**). This compound reacts in a fairly regiocontrolled fashion (1,4-addition) with triisobutylaluminum to yield 76% (*E*)-2-isobutyl-1-nitrodec-3-ene (**137**) (Scheme 34).

Scheme 34



Noland and Kedrowski⁷ carried out cycloaddition reactions in which the 1-nitro-1,3-diene system is part of 2-(2-nitrovinyl)-1,4-benzoquinone (**140**). This compound was prepared in 28% overall yield by treatment of 2,5-dimethoxybenzaldehyde (**138**) with nitromethane, followed by cerium ammonium nitrate oxidation of the resulting 2,5-dimethoxy- β -nitrostyrene (**139**) (Scheme 35).

Scheme 35

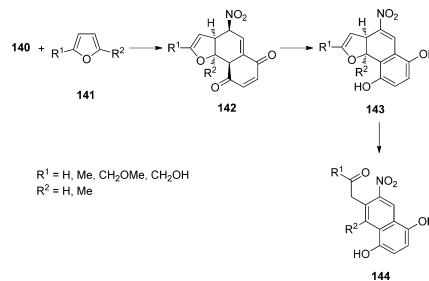


Nitrodiene **140** reacted as the diene component in inverse-electron-demand Diels–Alder reactions with electron-rich heterocycles, such as furans, indoles, or dihydropyrans, thus leading to angular-fused quinoid heterocycles.⁷ Consequently, the cycloaddition reactions with furans **141** led to products of type **142**, which often aromatize to **143** or even to **144** (Scheme 36).

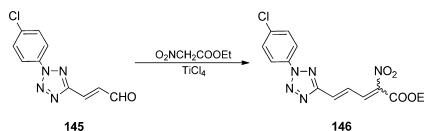
Tetrazolylacroleins, easily available through a four-step pathway from 2-aminopyridines, have been used for the preparation of tetrazolyldiene systems such as **146**. Thus, treatment of **145** with reagents containing active methylene groups, such as ethyl nitroacetate in the presence of titanium(IV) chloride, afforded a 1:0.7 (*Z,E*)-mixture of dienes **146** in 78% yield (Scheme 37).⁶⁹

The Wittig-type reaction between aldehydes and an α -nitrophosphonate anion in tetrahydrofuran under reflux led to

Scheme 36

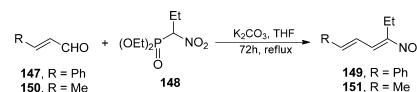


Scheme 37



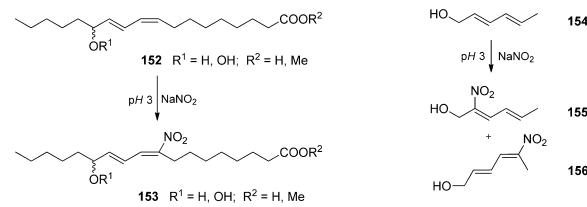
trisubstituted nitroalkenes.⁷⁰ When α,β -unsaturated aldehyde **147** and the α -nitrophosphonate anion of **148** (generated *in situ*) were used, the (*E,E*)-4-nitro-1-phenylhexa-1,3-diene (**149**) (Scheme 38) was obtained in 61% yield. However, only 16% **151** could be obtained from the previously isolated potassium salt of **148** and crotonaldehyde **150**.

Scheme 38



Reactions^{71–75} of hydroxy and hydroperoxy derivatives of polyunsaturated fatty acids or esters **152** with nitrite ions, under acidic conditions, gave 1-nitro-1,3-dienes **153** in low yields. A similar treatment with (*E,E*)-2,4-hexadien-1-ol (**154**) as the starting material led to a mixture of 1-nitro-1,3-dienes **155** and **156** in 9% and 7% yields, respectively (Scheme 39). Despite

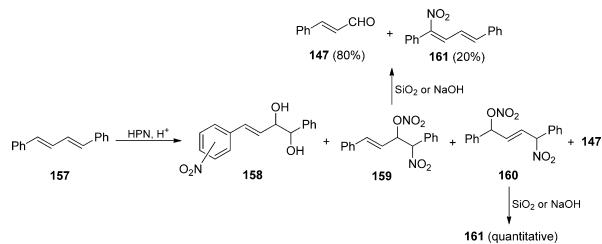
Scheme 39



limitations of these syntheses, the acid-promoted reactions of NO_2^- with polyunsaturated fatty acids may represent a convenient route for the small-scale preparation of pharmacologically active nitrated lipids.⁷⁴

Unstable peroxy nitrous acid, HPN, generated from the relatively stable peroxy nitrite anion ($\text{O}=\text{NOO}^-$) has been used⁷⁶ in reactions promoting an electron-transfer process in the radical nitration of unsaturated and aromatic systems. Thus, treatment of 1,4-diphenylbutadiene (**157**) with peroxy nitrous acid afforded quantitatively a mixture of diol **158** (15%), the 1,2-adduct **159** (10%), the 1,4-adduct **160** (65%), and cinnamaldehyde (**147**) (10%) (Scheme 40). Both nitrates **159** and **160** were essentially stable under the reaction conditions; however, they underwent either total or partial

Scheme 40

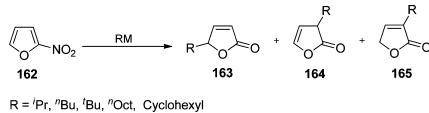


transformation into nitrodiene **161** with silica gel or upon treatment with 10% aqueous NaOH.

3.2. Mono- and Dihetero-Substituted 1-Nitro-1,3-dienes

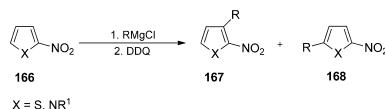
Mixtures of 5-alkyl- and 3-alkyl-2-furanones **163**–**165** have been obtained by the reaction of 2-nitrofuran (**162**) and several Grignard, alkylolithium, dialkylcadmium, and heterocuprate reagents (Scheme 41).⁷⁷ Since alkylated nitro compounds

Scheme 41



were not recovered even under mild hydrolysis conditions (-10°C , 0.3 N HCl), the formation of the resulting lactones could be rationalized through a one-step conjugate 1,6- or 1,4-addition of the organometallic reagents, followed by hydrolysis. Except for the case of *tert*-butyllithium, which gave only the 1,6-adduct, the processes showed low regioselectivities. On the other hand, it is noteworthy that, in contrast to the nitrodienic reactivity observed for 2-nitrofuran, treatment of 2-nitrothiophene or 1-alkyl-2-nitropyrrroles **166** with RMgX , followed by oxidative workup, led to mixtures of the corresponding alkylated substitution products **167** and **168** (Scheme 42).⁷⁷

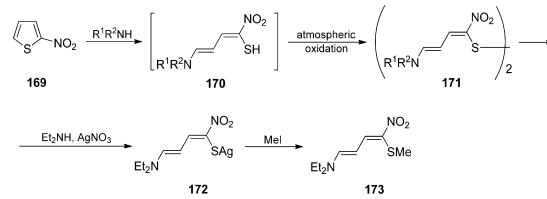
Scheme 42



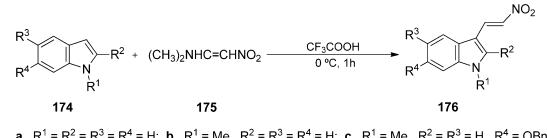
As shown in Scheme 11, the ring-opening reaction⁴⁰ of 3-nitrothiophene in the presence of amines gave thiol 2-nitrodiene. Previously, Guanti et al.⁷⁸ described that the ring-opening reaction of 2-nitrothiophene (**169**) occurred in the presence of secondary amines to yield disulfide 1-nitro-1,3-dienes **171**, formed through the nonisolated thiols **170**. Treatment of disulfides **171** with diethylamine and silver nitrate led to silver (*Z,E*)-4-(diethylamino)-1-nitrobuta-1,3-diene-1-thiolate (**172**), which was then converted into the methylthio derivative **173** (Scheme 43).

3-(2-Nitrovinyl)indoles, such as **176**, are interesting because their reduction gives biologically important tryptamines. Those compounds were obtained in 40% to nearly quantitative yields by reaction of the corresponding indoles **174** and 1-(dimethylamino)-2-nitroethylene (**175**) in trifluoroacetic acid (Scheme 44).⁷⁹ 3-(2-Nitrovinyl)indoles can be considered as 1-nitrodienes; thus, **176a** behaves as a diene component and undergoes normal-electron-demand Diels–Alder reaction with *p*-benzoquinone.^{7,80}

Scheme 43

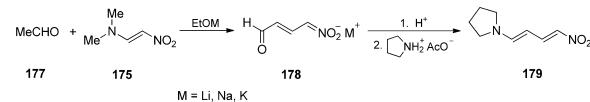


Scheme 44

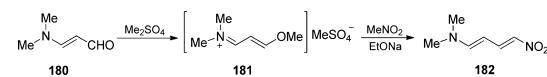


Nitrodienamines are useful intermediates in organic synthesis, because of both their diene character and their similarity to nitroenamines.⁸¹ These compounds present a reactivity that is based on their enaminic character, as well as on their “push–pull” nature. However, despite their importance, nitrodienamines have been scarcely used, one reason being the difficulties encountered in their preparation; thus, Severin and Ipach reported two general methods for the synthesis of nitrodienamines: (a)⁸² treatment of acetaldehydes, such as **177**, with **175**, followed by reaction of the resulting 4-*ac*-nitrocrotonaldehyde (**178**) with pyrrolidinium acetate to yield 1-nitro-4-pyrrolidino-1,3-butadiene (**179**) (Scheme 45), and (b)⁸³ treatment of the methyl sulfate salt **181**, derived from **180**, with nitromethane to give 1-(*N,N*-dimethylamino)-4-nitro-1,3-butadiene (**182**) (Scheme 46).

Scheme 45



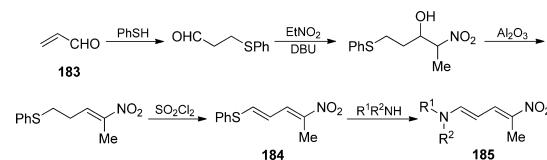
Scheme 46



Ono et al.⁸⁴ have described an efficient method for the synthesis of 1-(phenylthio)-4-nitropenta-1,3-diene (**184**) or 1-(dialkylamino)-4-nitropenta-1,3-dienes **185** starting from acrolein (**183**) (Scheme 47). In this process, the products were diethylamino or pyrrolidine derivatives which have doubly conjugated dienic systems with electron donor and acceptor substituents. The authors reported nonlinear optical activity for the push–pull diene **185**.

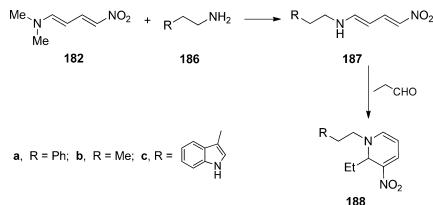
The reaction between **182** and 2-phenethylamine (**186a**) in benzene at room temperature led to **187a** (95% yield),⁸⁵ which

Scheme 47



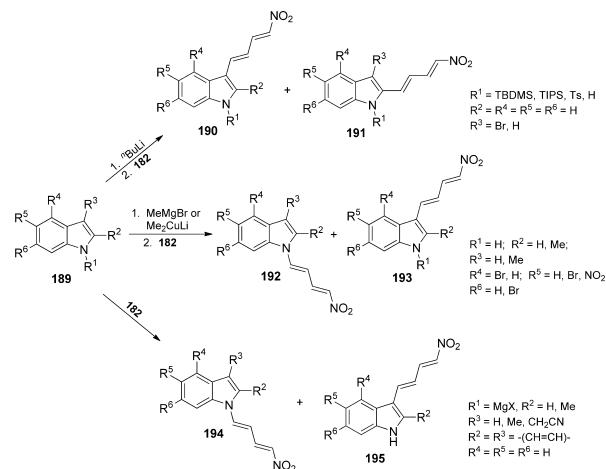
was then treated with propionaldehyde to give⁸ 2-ethyl-3-nitro-1-(2-phenethyl)-1,2-dihydropyridine (**188a**) in 82% yield (Scheme 48). Similar procedures were carried out by using either propylamine (**186b**) or tryptamine (**186c**) as the starting material, followed by treatment with acetaldehyde.^{8,86}

Scheme 48



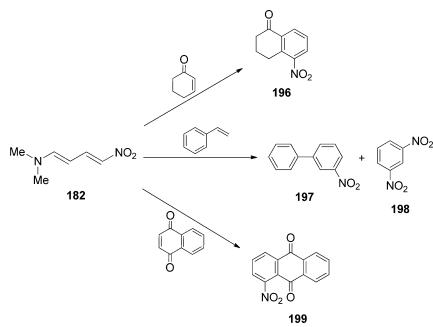
Other reactions of nitrodienamines **182** with indoles **189** and other unsaturated compounds have been investigated: (a) with 1-protected indolylithium, yielding **190** and **191** (Scheme 49);⁸⁷ (b) with indole-derived organocopper or Grignard reagents (Scheme 50).

Scheme 49



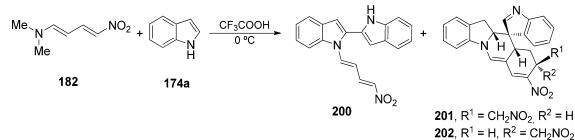
compounds, affording **192–195** (Scheme 49);^{88,89} (c) with α,β -unsaturated carbonyl compounds, styrenes, and quinones, leading to **196**, **197 + 198**, or **199**, respectively (Scheme 50).

Scheme 50



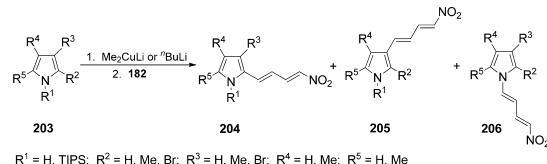
The reaction between **182** and indole (**174a**) in trifluoroacetic acid led to a mixture of three complex condensation products, **200–202** (10.3%, 21.8%, and 19.9% respective yields),⁹¹ each one of them bearing two indole fragments (Scheme 51).

Scheme 51



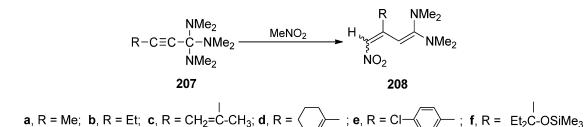
On the other hand, **204–206** were obtained by condensation of nitrodienamine **182** with pyrrole derivatives resulting from the reaction of **203** with organocupper, alkylolithium, or Grignard reagents (Scheme 52).

Scheme 52



Condensation reactions between orthoamides of alkyne carboxylic acids **207** and nitromethane yielded the push–pull 2-substituted 4,4-diamino-1-nitrodiene **208** (Scheme 53).

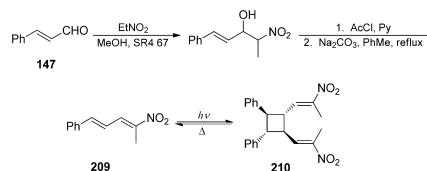
Scheme 53



Crystal structure analysis of **208f** showed that the distance between C-2 and C-3 is by far the shortest in its butadiene system, whereas for **208e** the C1–C2, C2–C3, and C3–C4 bonds are all of nearly equal length.⁹³

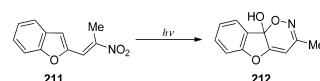
In a method similar to that indicated in Scheme 47, 4-nitro-1-phenylpenta-1,3-diene (**209**) has been prepared⁹⁴ by reaction of **147** and nitroethane in methanol with Permutit Deacidite FF-1P (SR4 67), followed by a two-step O-acetylation/elimination protocol on the intermediate alcohol. Next, compound **209** was photodimerized to cyclobutane **210** by irradiation with a Hanovia medium-pressure mercury arc (Scheme 54). This process has been used to synthesize fused

Scheme 54



6-hydroxy-1,2-oxazines from heterocyclic nitroalkenes; thus, as indicated in Scheme 55, irradiation of 2-(2-nitroprop-1-enyl)benzofuran (**211**) in an acetone solution yielded the 6-hydroxy-1,2-oxazine (**212**), with analogous rearrangements

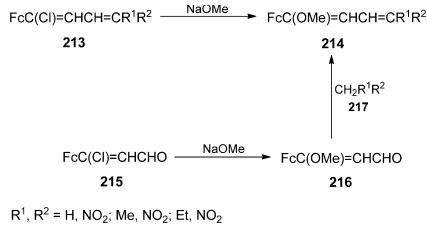
Scheme 55



observed to their corresponding oxazines with 2-(2-nitroprop-1-enyl)furan and its 5-methyl derivative and with 2-(2-nitroprop-1-enyl)indole.^{95,96}

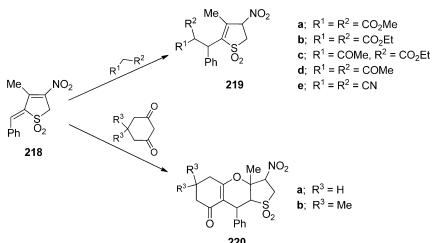
Ferrocenyl-containing nitrodienes **214** have been synthesized from dienes **213** and sodium methoxide or by reaction of 3-chloro-3-ferrocenylpropenal (**215**) with sodium methoxide, followed by treatment of aldehyde **216** with nitroalkanes **217** (Scheme 56).⁹⁷

Scheme 56



Berestovitskaya et al.⁹⁸ reported that the 1-nitrodiene system within 2-benzylidene-3-methyl-4-nitro-2,5-dihydrothiophene 1,1-dioxide (**218**) reacts readily and regioselectively with CH acids to give the corresponding 1,6-addition products **219**. However, similar reactions with readily enolizable cyclic β -diketones (dimedone and cyclohexane-1,3-dione) were accompanied by subsequent intramolecular heterocyclization, leading to thieno[3,2-*b*]chromene derivatives **220** (Scheme 57).

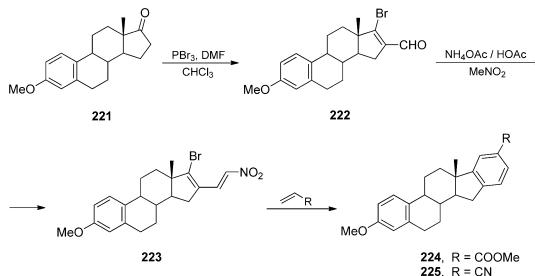
Scheme 57



Estranes **224** and **225** were prepared from methoxyestrone **221** through aldehyde **222**, which reacted with nitromethane to give 4-bromo-1-nitro-1,3-diene **223** in 79% yield. Reaction of this compound with either methyl acrylate or acrylonitrile enabled the formation of the second aromatic ring, affording **224** and **225** in 39% and 35% yields, respectively (Scheme 58).⁹⁹

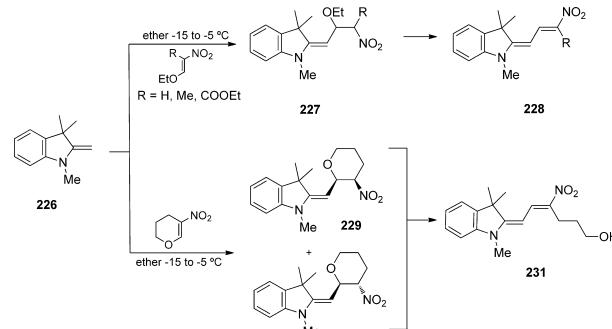
The reaction of electron-rich 2,3-dihydro-2-methylene-1,3,3-trimethyl-1*H*-indole (**226**) (Fischer's base) with acyclic or cyclic nitrovinyl ethers yielded the corresponding 1-nitro-1,3-

Scheme 58



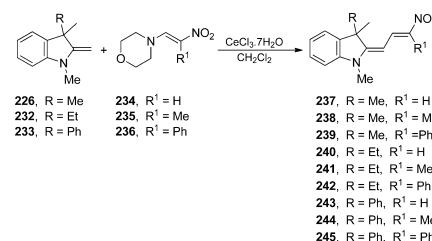
dienes **228** and **231**¹⁰⁰ (Scheme 59) through their corresponding Michael adducts **227** and **229 + 230**.

Scheme 59



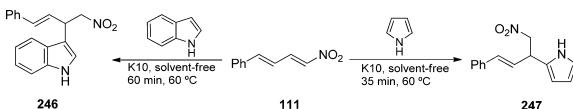
Compound **226**, as well as its analogues **232** and **233**, reacted with β -nitroenamines **234–236** (electron-poor reagents) in dichloromethane in the presence of 1 equiv of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ to give the corresponding 1-nitrodiene polymethine dyes **237–245** (Scheme 60).¹⁰¹

Scheme 60



The Michael addition of indole and pyrrole to **111** gave compounds **246** and **247**, respectively, with ca. 90% yields.¹⁰² Montmorillonite K10 was found as an efficient catalyst for these reactions, which occurred under solventless conditions (Scheme 61).

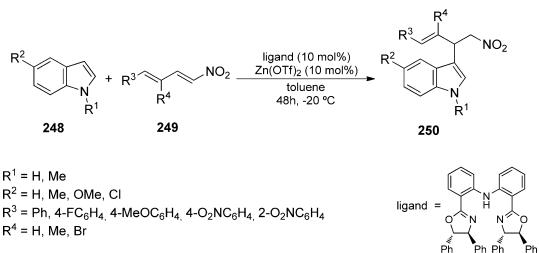
Scheme 61



More recently, Peng and Du¹⁰³ reported the asymmetric Friedel–Crafts alkylation of indoles with nitrodienies catalyzed by diphenylamine-linked bisoxazoline–Zn(OTf)₂ complexes. According to the authors, metal complex catalytic systems for these types of reactions have advantages over others (such as chiral Brønsted acids and secondary amines), requiring low catalyst loading and shorter reaction times. Thus, 3-alkylindoles 250 were obtained in 23–91% yields (47–89% ee) from reactions between 248 and 249 (Scheme 62).

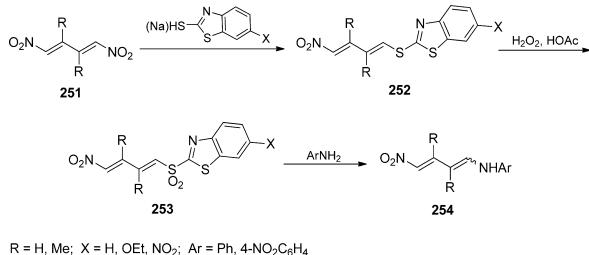
Lipina et al.¹⁰⁴ have described the preparation of 1-nitro-1,3-dienes **252** by reaction of 1,4-dinitro-1,3-dienes **251** with either thiols or thiolates. The sulfur-containing substituents were subsequently oxidized to give the corresponding 1-nitro-4-benzothiazolylsulfonyl dienes **253**. Several of these sulfonyl dienes reacted with aromatic amines through the vinylogous substitution of a sulfonyl by an amino group to yield 1-

Scheme 62



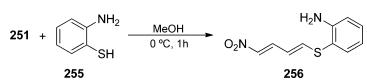
(arylamino)-4-nitrodiene 254 (Scheme 63).^{105,106} N,S -Binucleophiles exhibited a similar reactivity, but through the sulfur atom in preference to through the nitrogen atom; thus, unsubstituted 1,4-dinitrobuta-1,3-diene 251 ($R = H$) reacted even with neutral 2-aminobenzenethiol (255) to give 32% butadiene 256 (Scheme 64).¹⁰⁶

Scheme 63



atom in preference to through the nitrogen atom; thus, unsubstituted 1,4-dinitrobuta-1,3-diene 251 ($R = H$) reacted even with neutral 2-aminobenzenethiol (255) to give 32% butadiene 256 (Scheme 64).¹⁰⁶

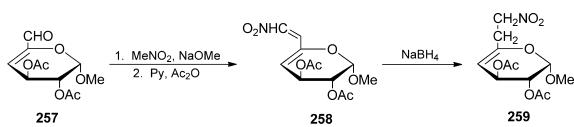
Scheme 64



3.3. Chiral 1-Nitro-1,3-dienes

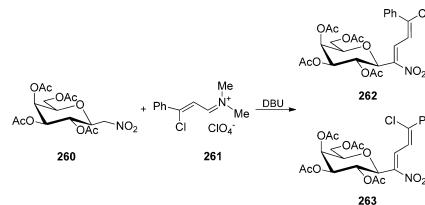
To the best of our knowledge, the first example of the preparation of sugar-derived 1-nitro-1,3-dienes was reported by Horton and Liav.¹⁰⁷ These authors described the synthesis of methyl 2,3-di-*O*-acetyl-4,6,7-trideoxy-7-nitro-*cis*- β -L-threo-hepto-4,6-dienopyranoside (258) by the reaction between methyl 2,3-di-*O*-acetyl-4-deoxy- β -L-threo-hex-4-enodialdo-1,5-pyranoside (257) and nitromethane, with subsequent acetylation. Next, selective sodium borohydride reduction of the double bond in the resulting nitrodiene 258 yielded compound 259 (Scheme 65).

Scheme 65



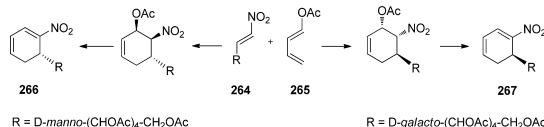
An interesting approach to the preparation of branched-chain sugars involves the reaction of acidic CH sugars with methiniumium salts in the presence of a base. Thus, treatment of anhydronitroheptitol 260 with β -(chlorovinyl)-methiniumium perchlorate 261 in the presence of DBU led to a nonseparated (*E,Z*)-mixture (39% yield) of the sugar-derived 1-nitrodiene 262 and 263 (Scheme 66).¹⁰⁸

Scheme 66



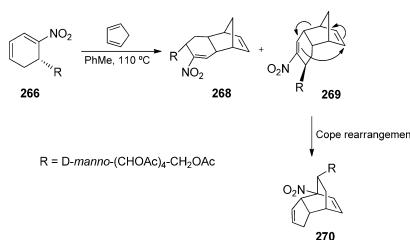
In the course of our research on asymmetric Diels–Alder reactions between sugar-derived nitroalkenes 264 and 1-acetoxybuta-1,3-diene (265), enantiomerically pure chiral 1-nitrocyclohexa-1,3-dienes 266 and 267 were prepared in 13% and 68% overall yields, respectively. In contrast to other conjugated nitrodienes, these compounds were crystalline and stable for several months at room temperature (Scheme 67).^{5,109}

Scheme 67



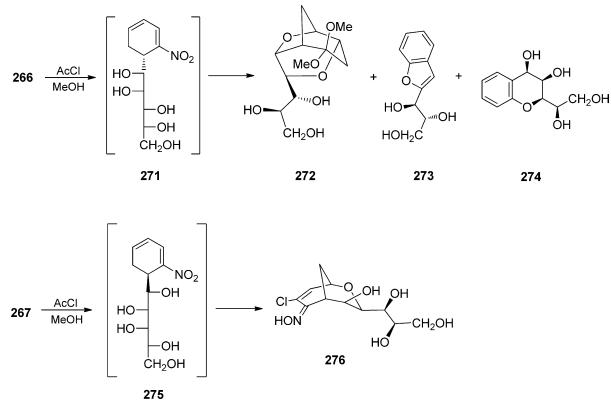
In each case, the reaction between these glyconitrocyclohexadienes and cyclopentadiene led, almost exclusively, to compounds arising from a tandem consecutive Diels–Alder–Cope rearrangement of the corresponding major cycloadducts. Thus, starting from 266, the major product (70% yield) was 1-nitrotricyclo[5.2.2.0^{2,6}]undecadiene 270, which is actually the consequence of a sigmatropic Cope rearrangement of the initially formed *endo*-norbornenic cycloadduct 269. Also, a very small quantity of 269 and its *exo*-isomer 268 were isolated by preparative thin-layer chromatography from the reaction mixture (Scheme 68).¹¹⁰

Scheme 68



As shown in Scheme 69, deacetylation of pentaacetylated sugar-derived 1-nitro-1,3-cyclohexadienes 266 and 267 with acetyl chloride in methanol followed a pathway arising from configurational and conformational differences between their respective sugar side chains, as well as differences between the configurations of the carbon on the nitrocyclohexadiene ring bearing that sugar side chain. Once deacetylated, intramolecular nucleophilic attacks from hydroxyl groups on electrophilic carbons of the nitrodiene system occurred; thus, dioxatricyclo-decane dimethyl ketal 272 (10%), benzofuran 273 (39%), and chromane-1,3-diol 274 (5%) were the major products formed from *D-manno*-nitrocyclohexadiene 266 via 271. In contrast, *D-galacto*-nitrocyclohexadiene 267 led exclusively to bicyclic oxime 276 (83%) via 275.¹¹¹

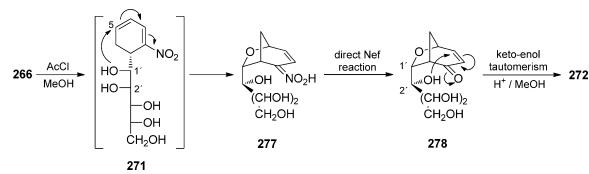
Scheme 69



As a common feature, many of the 1- and 2-nitrodienes present low stabilities, and therefore, they should be generated *in situ* from their appropriate precursors. This characteristic, together with the presence of nucleophilic hydroxy groups in the same molecule, could explain why some of these compounds, such as (pentahydroxypentyl)nitrocyclohexadienes 271 and 275 (Scheme 69), may appear as nonisolated intermediates.

The formation of tricyclic ketal 272 could be rationalized through a process involving deacetylation of the sugar side chain of 266, followed by conjugate intramolecular nucleophilic addition from OH-1' to the spatially close C-5 carbon of the intermediate 271. Then a direct Nef reaction on 277 and a second addition from OH-2' to the resulting α,β -unsaturated carbonyl system of 278 would lead to an enol which, by tautomerization and ketalization with methanol, would lead to compound 272 (Scheme 70).¹¹¹

Scheme 70

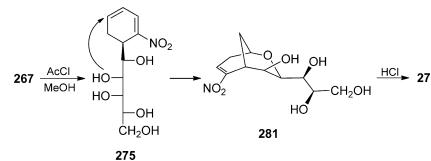


As indicated in Scheme 71, Baños et al.¹¹¹ propose that benzofuran 273 and chromane-1,3-diol 274 could also arise from deacetylated nitrodiene 271, which, under acidic conditions, isomerizes to the *aci*-nitro tautomer 279 in equilibrium with its protonated form, 280. Then intramolecular nucleophilic attack from the second hydroxyl group of the sugar side chain (path a) and sequential loss of water and nitroxyl, followed by aromatic stabilization, would give 273. Path b leading to 274 follows a similar mechanism, although further dehydration would be less favorable, because there would be less aromatic stabilization in the pyran moiety.

equilibrium with its protonated form, 280. Then intramolecular nucleophilic attack from the second hydroxyl group of the sugar side chain (path a) and sequential loss of water and nitroxyl, followed by aromatic stabilization, would give 273. Path b leading to 274 follows a similar mechanism, although further dehydration would be less favorable, because there would be less aromatic stabilization in the pyran moiety.

As shown in Scheme 72, the formation of oxime 276 was justified as a result of the intramolecular cyclization of

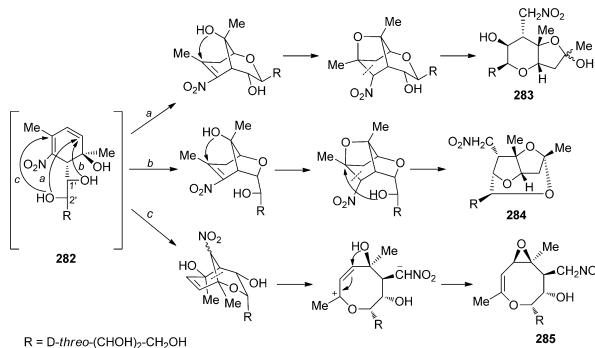
Scheme 72



deacetylated *D*-galacto-nitrocyclohexadiene 275, followed by HCl addition to the double bond of 281 and transformation of the nitro group into an oxime.¹¹¹

A case similar to that presented in Scheme 69, where intramolecular nucleophilic attacks from hydroxyl groups on a nitrodiene system were proposed, was observed during a study into Diels–Alder reactions between sugar-derived nitroalkenes with 2,5-dimethylfuran under high pressure; here, the presence of intermediate 1-nitro-1,3-nitrodienes 282 in the reaction mixture supported mechanisms leading to bicyclic and tricyclic oxygenated heterocycles 283–285 (Scheme 73).¹¹²

Scheme 73



Likewise, nitrodienes 286–288 (Figure 5) have been proposed as intermediates¹¹³ in similar mechanisms. The

Scheme 71

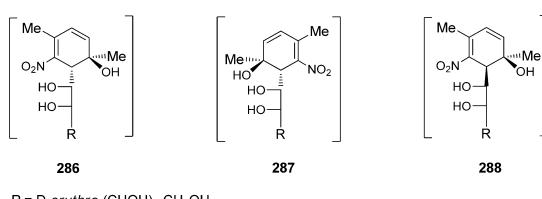
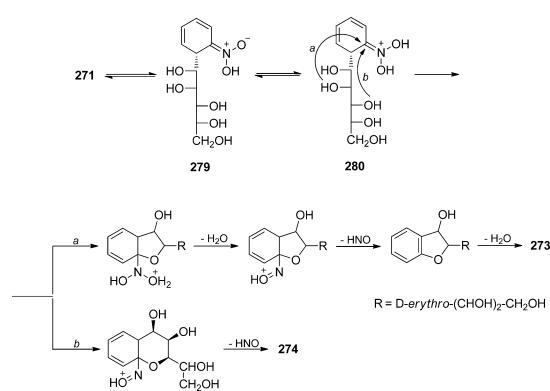
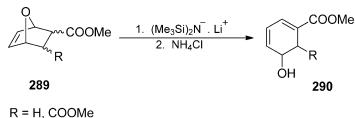


Figure 5.

formation of cyclohexadienes from 7-oxabicyclo[2.2.1]heptenes bearing electron-withdrawing substituents was described by Brion,¹¹⁴ who reported a highly stereoselective synthesis (51–85% yields) of cyclohexadienol 290 and cyclohexenol systems by a base-induced β -elimination of the heteroatom bridge of

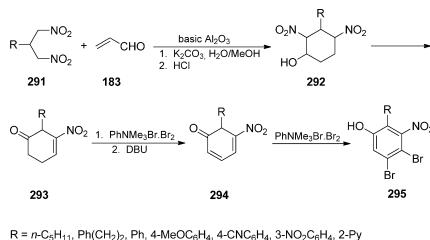
substituted 7-oxabicyclo[2.2.1]heptenes **289** and heptanes (Scheme 74).

Scheme 74



1-Nitro-1,3-dienes have also been proposed as intermediates in the preparation of substituted phenols from 2-alkylated 1,3-dinitropropanes.¹¹⁵ Thus, proceeding by a one-pot tandem Michaelis-Menten reaction with acrolein **183**, compounds **291** formed a diastereoisomeric mixture of the cyclohexanols **292** (68–88% yields) which, after treatment with potassium carbonate followed by acidic workup, led to nitrocyclohexenones **293**. Finally, the reaction of these crude compounds with phenyltrimethylammonium tribromide and DBU yielded nitrodibromophenols **295** (37–68% overall yields from **292**) via **294** (Scheme 75).

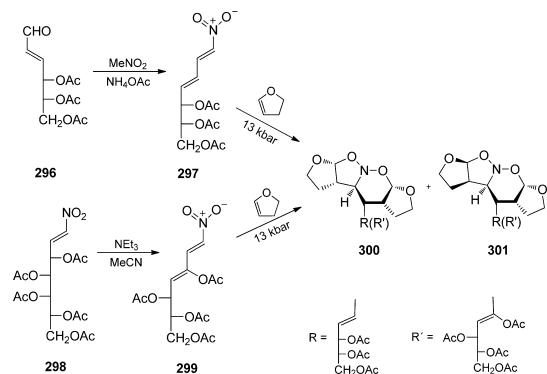
Scheme 75



α,β -Unsaturated aldehydes or α -nitroalkenes have been used as starting materials to prepare chiral acyclic 1-nitro-1,3-dienes. Thus,¹¹⁶ treatment of **296** with nitromethane and ammonium acetate gave a 60% yield of the stable nitrodiene **297**, whereas the reaction of **298** and triethylamine led to stable 3-acetoxynitrodiene **299** in 20% yield after chromatographic separation. High-pressure [4 + 2]/[3 + 2] reactions between each one of these chiral nitrodienes and 2,3-dihydrofuran led to cycloadducts **300** and **301** as a mixture that was separated by preparative thin-layer chromatography (Scheme 76).

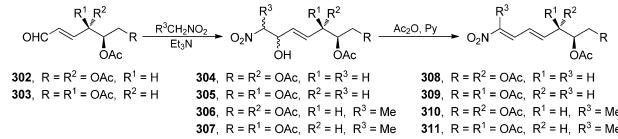
The nitroaldol reaction between 2,3-dideoxy- α,β -unsaturated aldehydo sugars **302** and **303** and nitroalkanes, such as nitromethane or nitroethane, yielded nitroaldols **304**–**307**, which furnished chiral nitrodienes **308**–**311** by conventional

Scheme 76



acetylation (Scheme 77).¹¹⁷ These compounds are useful intermediates for the preparation of higher acyclic nitrogen-

Scheme 77

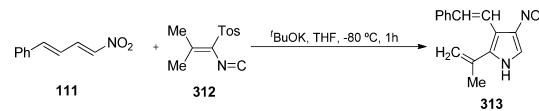


containing deoxy sugar derivatives with potential antimicrobial activity. Moreover, even the nitrodienes **309** and **311**, at concentration levels of 100 μ g/mL, showed appreciable inhibition of the growth of mycobacterial cells.

3.4. Reactions with Isocyanides, Aldehydes, Ketones, or β -Dicarbonyl Compounds

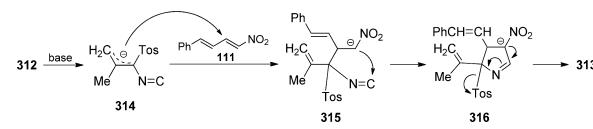
2-Alk-1'-enylpyrroles have been obtained, in excellent yields, by a base-induced cycloaddition of 1-tosylalk-1-enyl isocyanides to Michael acceptors.^{118,119} Thus, treatment of nitrodiene **111** with compound **312**, prepared by a formal Knoevenagel condensation between TosMIC and acetone, gave a 78% yield of 4-nitro-3-(2-phenylethenyl)-2-(2-propenyl)pyrrole (**313**) (Scheme 78).

Scheme 78



Following the corresponding pathway proposed¹¹⁹ as for α,β -unsaturated carbonyl compounds, the process could be rationalized as indicated in Scheme 79: addition of allylic anion **314** to Michael acceptor **111**, followed by ring closure to the isocyano carbon of **315** and elimination of *p*-toluenesulfinate in **316**, led to pyrrole **313**.

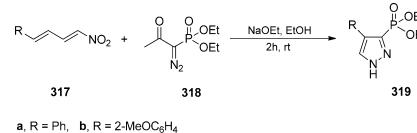
Scheme 79



A one-pot regioselective synthesis of highly functionalized phosphophenylpyrazoles has been carried out via a 1,3-dipolar cycloaddition between conjugated nitroalkenes or nitrodienes **317** and diethyl (1-diazo-2-oxopropyl)phosphonate (**318**) (Bestmann–Ohira reagent) in the presence of a nucleophilic base and a protic solvent.¹²⁰ Thus, 1-nitro-1,3-dienes **317a** and **317b** led to **319a** (58%) and **319b** (60%), respectively (Scheme 80).

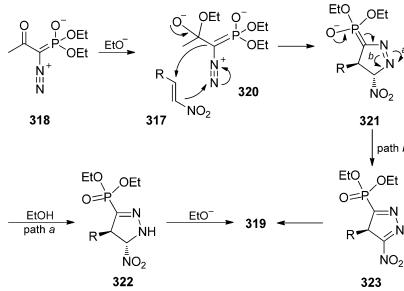
In relation to the mechanism that could explain the formation of **319**,¹²¹ the results suggested that the alkoxide

Scheme 80



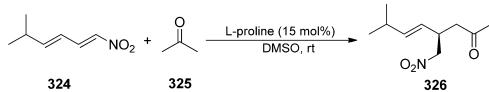
ion played the role of a nucleophilic base in these processes and that the base-mediated acyl cleavage of **318** was taking place prior to the 1,3-dipolar cycloaddition between **317** and **320**. The results also inferred subsequent protonation of the resulting cycloadduct **321** and base-assisted E1cB elimination of HNO_2 (path a, through **322**) or elimination of the NO_2 group, followed by intramolecular proton transfer (path b, through **323**), both of which would lead to phosphorylpyrazole **319** (Scheme 81).

Scheme 81



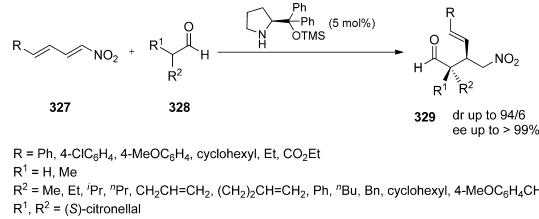
List et al.¹²² have reported the first cases of Michael reaction of unmodified ketones and nitroalkenes via enamine catalysis using L-proline. With nitrodiene **324** and acetone (**325**), the 1,4-adduct **326** was obtained in 85% yield, although the enantiomeric excess was not determined (Scheme 82).

Scheme 82



Asymmetric organocatalyzed Michael addition between α,β - and γ,δ -unsaturated nitro compounds **327** and aldehydes **328** with 5 mol % (*S*)-diphenylprolinol silyl ether afforded good to excellent yields of synthetically useful compounds **329** (Scheme 83), which can be converted to more complex molecules, such

Scheme 83

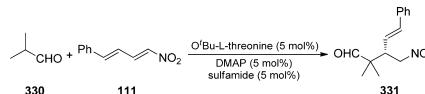


as tetrahydropyran or cyclohexene derivatives.^{9,123} The influence of the catalyst on stereoselectivity has been investigated by isotopic labeling experiments, which have shown that mechanisms through the enamine and enol may operate simultaneously.¹²⁴ In addition, similar processes for the one-pot enantioselective organocatalytic Michael reaction of aromatic ketones^{125,126} with nitrodienes or carbonyl compounds with nitrodienes/nitroenynes^{124,127,128} were carried out with various chiral amine thioureas as catalysts.

Nugent et al.¹²⁹ have reported the asymmetric Michael addition between α -branched aldehydes and nitroalkenes with a three-component organocatalyst system. The adducts were

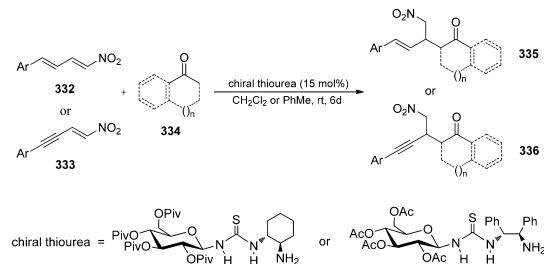
obtained in good to high yields and excellent enantiomeric excess; thus, the reaction of isobutyraldehyde (**330**) and **111** afforded **331** in 98% yield and 97% enantiomeric excess (Scheme 84).

Scheme 84



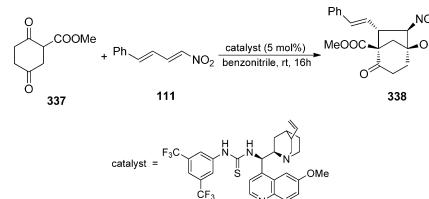
Recently, enantioselective Michael reactions of aromatic ketones **334** with aryl-1-nitrodienes **332** or aryl1-nitroenynes **333** in the presence of sugar-derived thioureas as chiral catalysts have been reported.^{125,130} In the nine cases studied, the corresponding adducts **335** and **336** were obtained with enantiomeric excesses ranging between 84% and 99% (Scheme 85).

Scheme 85



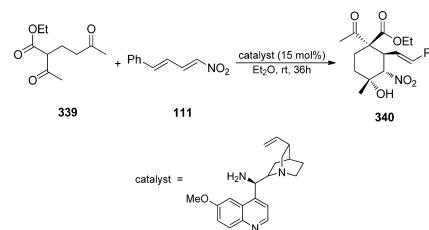
Asymmetric tandem Michael–Henry reactions catalyzed by cinchona alkaloid derivatives have been developed.^{131,132} Following this methodology, trisubstituted carbon nucleophiles (**337**, **339**, or **341**) and **111** afforded vicinal quaternary and tertiary stereocenters with high regio- and stereoselectivity. Thus, bicyclo[3.2.1]octane **338** (73%) (Scheme 86),¹³¹ cyclohexanol **340** (91%) (Scheme 87),¹³² or cyclopentanone **342** (72–99%) (Scheme 88)¹³³ was obtained.

Scheme 86

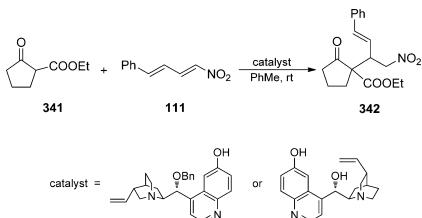


Asymmetric conjugate addition between cyclohexanone **343** and **111** afforded adduct **344** with high diastereo- and

Scheme 87

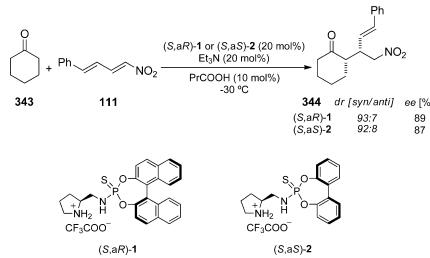


Scheme 88



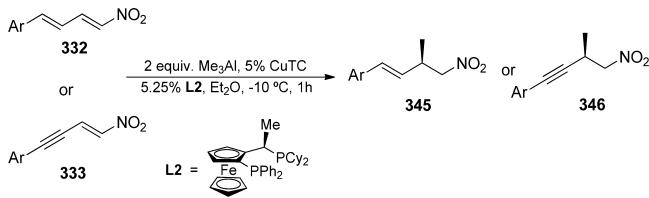
enantioselectivity. The reaction was carried out in the presence of two bifunctional organocatalyst systems: (a) with secondary pyrrolidinylthiophosphoramido^{134,135} bearing a tropos-biphenyl group [(S,aR)-1 or (S,aS)-2] (Scheme 89) or (b) with pyrrolidinylthioimidazole and chiral thioureido acid.¹³⁶

Scheme 89



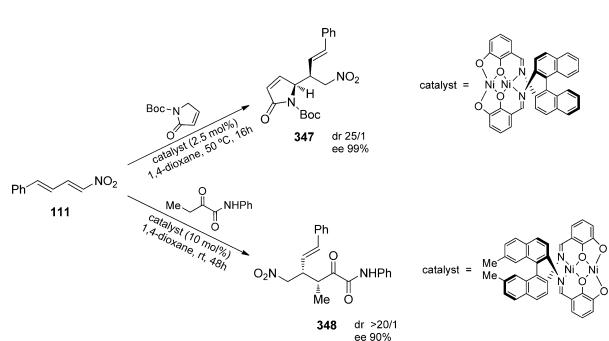
Alexakis et al.¹³⁷ described enantioselective and regiodivergent copper-catalyzed conjugate 1,4- and 1,6-additions of trialkylaluminum reagents to nitrodiene 332 or nitroenyne 333 to yield compounds 345 or 346, respectively (Scheme 90).

Scheme 90



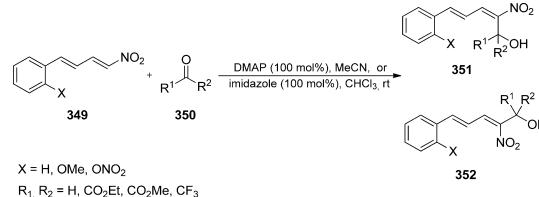
On the other hand, 347 (83%) and 348 (70%) were obtained by direct catalytic asymmetric vinylogous Mannich-type and Michael reactions of α,β -unsaturated γ -butyrolactam¹³⁸ or α -ketoanilides¹³⁹ with nitrodiene 111 under homodinuclear nickel Schiff base catalysis (Scheme 91).

Scheme 91



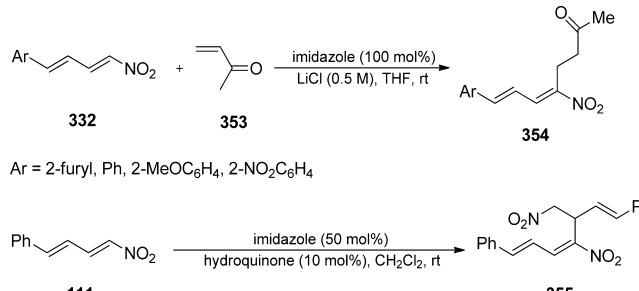
Morita–Baylis–Hillman reactions between conjugated 1-nitrodienes 349 and various carbonyl compounds 350 occurred smoothly in the presence of either (dimethylamino)pyridine or imidazole, affording the corresponding multifunctionalized adducts 351 and 352 in good to excellent yields (Scheme 92).¹⁴⁰

Scheme 92



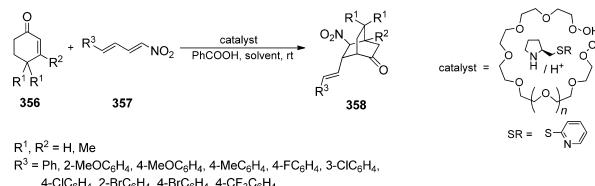
A vinylogous process similar to that illustrated in Scheme 92 is a Rauhut–Currier reaction, where nitroalkenes or nitrodienes react with methyl vinyl ketone (353) or acrylates in the presence of a catalyst system of imidazole–LiCl or imidazole–hydroquinone.¹⁴¹ Arising from either hetero- or homocoupling, the process afforded the Rauhut–Currier adducts 354 (33–44%) and 355 (46%) (Scheme 93).

Scheme 93



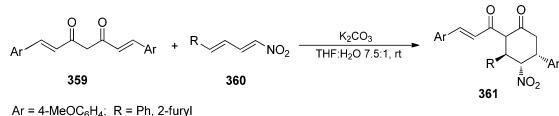
An unusual organocatalyzed Diels–Alder reaction between cyclohexenones 356 and nitrodienes 357 has been described.¹⁴² It was found that supramolecular self-assembled catalysts formed from chiral amines and poly(alkene glycol)s promoted the process effectively via enamine activation, providing cycloadducts 358 (63–99%) with excellent chemo-, regio-, and enantioselectivities (Scheme 94).

Scheme 94



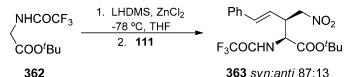
Reactions between curcumins 359 and nitrodienes 360 proceeded with complete diastereoselectivity, affording 80–83% yields of highly functionalized cyclohexanones 361 with three adjacent chiral centers (Scheme 95). The authors found that the best results for these processes were achieved when potassium carbonate and water were used as the base and cosolvent, respectively.¹⁴³

Scheme 95



A study directed toward the synthesis of amino acids revealed that chelated enolates are versatile nucleophiles for Michaeli additions on nitroalkenes and nitrodienes. Scheme 96 shows

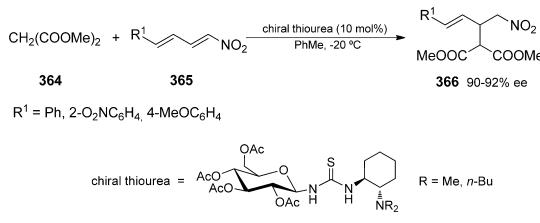
Scheme 96



the reaction of glycine derivative **362** and **111** to yield adducts **363**; in this case, zinc enolates gave the best yields, whereas the best selectivities were achieved with the TFA protecting group and lithium enolates.¹⁴⁴

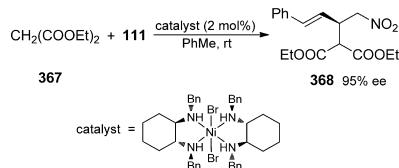
Different chiral bifunctional tertiary amine thioureas based on saccharides have been developed and used as catalysts in highly enantioselective Michael additions of malonates to nitroolefins. The method has been extended to the reaction between dimethyl malonate (364) and 1-nitro-4-arylbutadienes 365, leading to adducts 366 with 90–92% enantiomeric excess and yields ranging between 86% and 92% (Scheme 97).¹⁴⁵

Scheme 97



Evans et al.¹⁴⁶ carried out a similar reaction by using diethyl malonate (367) and nitrodiene 111 with a readily prepared catalyst consisting of Ni(II) coordinated to two chiral diamine ligands; the corresponding product 368 was obtained in 95% yield and 95% enantiomeric excess (Scheme 98).

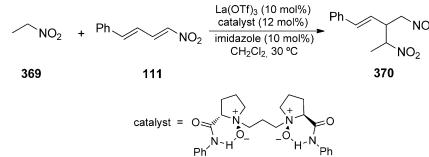
Scheme 98



The diastereoselective Michael addition between nitroethane **369** and **111** in the presence of a chiral catalyst, based on complexes of La(OTf)₃ and an *N,N'*-dioxide with imidazole as a base, gives the 1,4-adduct **370** (79% yield, 81:19 *syn:anti* ratio, 85% ee).¹⁴⁷ The same reaction with a chiral amine thiourea catalyst afforded **370** in 88% yield, 82:18 *syn:anti* ratio, and 89% ee (Scheme 99).¹⁴⁸

A tutorial review from Csáký et al.¹⁴⁹ on conjugate addition reactions of carbon nucleophiles to electron-deficient dienes amalgamates explanations on the stereochemical and stereo-

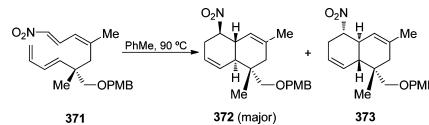
Scheme 99



selective course for those reactions as illustrated in Schemes 82, 83, 85, 87, and 97.

Williams et al.^{150,151} have described the stereocontrolled preparation of decalins 372 and 373 by intramolecular Diels–Alder reactions of 1-nitrodeca-1,3,7,9-tetraene 371. The authors reported that geometrical constraints imposed by the C3=C4 double bond in 371 explain the higher *trans*-selectivity, resulting in *trans*-decalins 372 and 373 obtained in a ratio of 88:12 (Scheme 100).

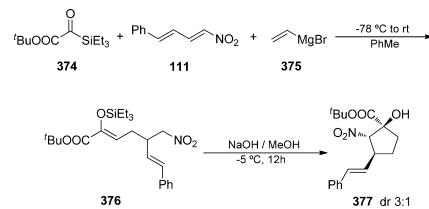
Scheme 100



3.5. Participation in Three-Component Condensation Reactions

The three-component coupling reaction of silyl glyoxylate 374, nitrodiene 111, and vinyl Grignard reagent 375 selectively afforded (*Z*)-silyl enol ether 376 (66%) through a vinylogous Michael cascade. Then a Henry diastereoselective cyclization led to functionalized nitrocyclopentanol 377 in 64% yield (Scheme 101).¹⁵²

Scheme 101

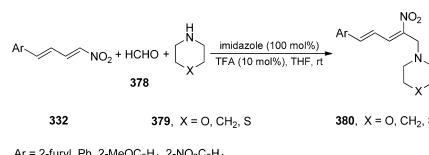


The α -aminoalkylation of nitrodiene **332** with formaldehyde (**378**) and morpholine **379** ($X = O$), piperidine **379** ($X = CH_2$), or thiomorpholine **379** ($X = S$) yielded Morita–Baylis–Hillman adducts **380** in 54–76% yields (Scheme 102).¹⁵³ The nitrodienes **332** were not significantly affected by the nature of the aryl group. The authors described the catalytic role of imidazole and TFA involving a dual activation mechanism.

3.6. 6π -Electrocyclization

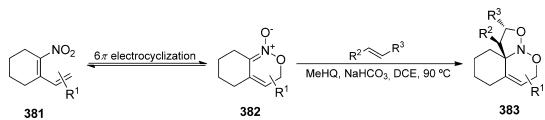
1-Nitro-1,3-dienes **381** underwent¹⁵⁴ a 6π -electrocyclization ring closure under heat to afford nitronate intermediates **382**

Scheme 102



that could be trapped through a one-pot, two-step series of [3 + 2] domino dipolar cycloadditions; the products were highly functionalized nitroso acetals **383** (Scheme 103). In a related

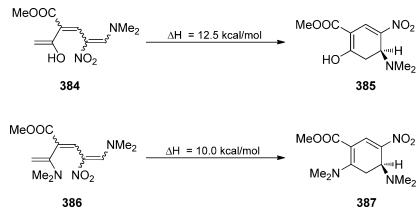
Scheme 103



antecedent with these reactions, Kwon and Henry have prepared tetracyclic coumarin derivatives through phosphine-catalyzed annulation reactions of allenoate precursors.¹⁵⁵

The electrocyclization reaction of 1-amino-1,3,5-hexatrienes has been studied computationally with GAUSSIAN 98 and the hybrid density functional B3LYP method.¹⁵⁶ Calculations showed that the activation energy for electrocyclization is strongly linked to substitution on the triene; thus, with the presence of electron-withdrawing groups, as in the cases of 2-nitro-substituted **384** and **386** (Scheme 104), activation

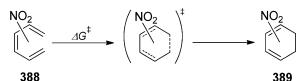
Scheme 104



barriers are lowered by 17–19 kcal/mol versus that of the parent 1,3,5-hexatriene, one of reasons being that these compounds have the conformation required for ring closure leading to **385** and **387**, respectively.

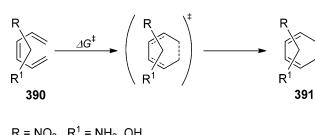
Theoretical calculations, using a two-layer ONIOM method, have been developed to predict the free activation energy for 6π -electrocyclization of a variety of substituted hexatrienes, including those with nitro groups, as indicated in Scheme 105,

Scheme 105



for the conversion of **388** to nitrocyclohexa-1,3-dienes **389**.¹⁵⁷ The results, which were obtained with an accuracy of about 1.0 kcal/mol, showed that a nitro group at C-1 of the triene slightly reduced the free activation energy of the process, while the effect was much more pronounced when this group was at C-2. Thus, in the latter case, the cyclization rate is predicted to be 2×10^4 times faster than that of the nonsubstituted hexatriene. In the same paper,¹⁵⁷ a similar study for the conversion of disubstituted hexatrienes **390** to compounds **391** (Scheme 106)

Scheme 106



revealed extraordinarily low free activation energies for some captodative substituted cases (2-NO₂-3-NH₂, 20.4 kcal/mol; 2-NO₂-3-OH, 19.8 kcal/mol; 2-NH₂-4-NO₂, 20.8 kcal/mol; 2-NO₂-5-NH₂, 16.7 kcal/mol and 2-NO₂-5-OH, 20.9 kcal/mol). These values are about 10 kcal/mol lower than that of the nonsubstituted hexatriene, and therefore, their electrocyclization could proceed smoothly, even at room temperature.

4. DINITRO-1,3-DIENES

4.1. Mono- and Dihetero-Substituted Dinitro-1,3-dienes

As indicated in the Introduction, reviews from Guseinov¹⁷ and Petrzilka¹⁸ assimilated a few references of Russian journals on the preparation and reactivity of 1,4-dinitro-1,3-dienes, covering the period of 1907–1960. Some years later, Kaberdin²¹ published an extensive review on 1,2-, 1,3-, and 1,4-dinitrodiienes containing mainly Russian references up until 1996.

Interest in the synthesis of some 1,4-dinitrodiienes has risen considerably due to the biological activity of these compounds; thus, 1,4-dinitro-1,3-butadiene¹⁵⁸ and some of its derivatives are of economic importance in agriculture, due to their fungicidal activity. The maximum activity against the plant pathogens *Colletotrichum lagenarium* (cucumber anthracnose) and *Alternaria solani* (tomato early blight) has been observed for compound **392** (Figure 6, R = Me). When R is H or ethyl, activity is negligible.¹⁵⁹

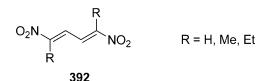
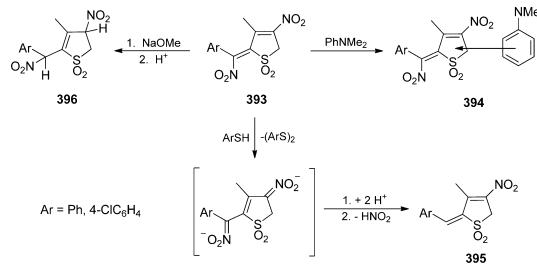


Figure 6.

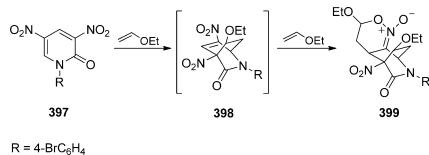
1,4-Dinitro-1,3-dienes can undergo electron transfer, nucleophilic addition, or vinyl substitution,¹⁶⁰ with an example of this type of substitution shown in Scheme 63. On the other hand, dihydrothiophene 1,2-dioxides **393** reacted with *N,N*-dimethylaniline to yield stable molecular crystalline complexes **394**, where the acceptor is the electron-deficient sulfonitrodiene heterocycle.¹⁶¹ Interaction with aromatic thiols occurred in a different way: they were oxidized to disulfides, while 1,4-dinitrodiene **393** led to 1-nitrodiene **395**. Treatment of **393** with sodium methoxide and subsequent acidification with acetic or hydrochloric acid afforded¹⁶² 1,1-dioxide **396** (Scheme 107).

Scheme 107



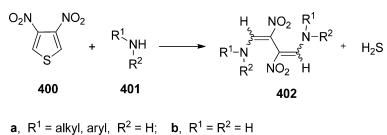
3,5-Dinitro-2-pyridone **397** can react with ethyl vinyl ether as a very electron-deficient heterodiene by [4 + 2]/[4 + 2] cycloaddition.¹⁶³ The first cycloaddition led to a very unstable intermediate, **398**, which, in the presence of a second equivalent, yielded the stable nitronate **399** (Scheme 108).

Scheme 108



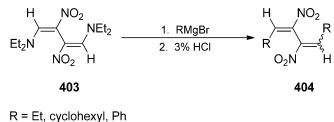
Schemes 11 and 43 show that 3-nitrothiophene and 2-nitrothiophene underwent ring-opening reactions with amines leading to 2-nitro-1,3-dienes and 1-nitro-1,3-dienes, respectively. Similarly,^{164–166} 3,4-dinitrothiophene (**400**) reacted with primary or secondary amines **401** to give 2,3-dinitro-1,3-dienes **402** (35–97%), with two (nitrovinyl)amine fragments coupled through C-2 (Scheme 109).

Scheme 109



Treatment of 1,4-bis(diethylamino)-2,3-dinitro-1,3-butadiene (**403**) with various Grignard reagents led to (*E,E*)-2,3-dinitro-1,3-butadienes **404** as major products, together with small quantities of their (*E,Z*)-stereoisomers (88–94% overall yields).¹⁶⁷ As shown in Scheme 110, the process involves

Scheme 110

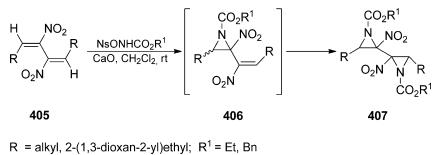


replacing both diethylamino groups by the aryl or alkyl groups from the Grignard reagent. Thus, nitrodiene **403** has been used to prepare 4,5-dinitro-1,3,5,7-octatetraenes.¹⁶⁸

4.2. Acyclic Alkyl- and Aryl-Disubstituted Dinitro-1,3-dienes

A direct aza-Michael-initiated ring-closure reaction on (*E,E*)-1,4-dialkyl-2,3-dinitro-1,3-butadienes **405** afforded (\pm)-2,2'-dinitro-2,2'-biaziridines **407** in good yields, through the nonisolated intermediates **406** (Scheme 111).¹⁶⁹ The authors

Scheme 111

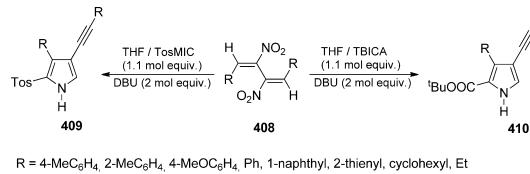


postulate that this process depends on the charge distribution at the C-1 and C-4 ends of the dinitrobutadiene system. Thus, they observed that, for both (*E,E*)-1,4-diphenyl-2,3-dinitro-1,3-butadiene **404** ($\text{R} = \text{Ph}$) and (*E,E*)-1,4-diamino-2,3-dinitro-1,3-butadiene **402a**, the reaction does not occur.

Reactions of 1,4-dialkyl- and 1,4-diaryl-2,3-dinitro-1,3-butadienes **408** with either TosMIC or TBICA and DBU gave good to moderate yields of 2-tosyl- or 2-(*tert*-

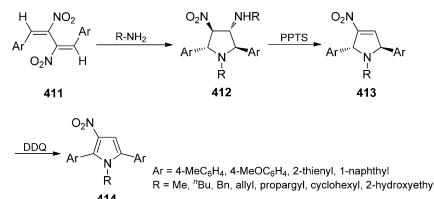
butoxycarbonyl)-4-ethynylpyrrole derivatives **409** and **410**, respectively (Scheme 112).¹⁷⁰

Scheme 112



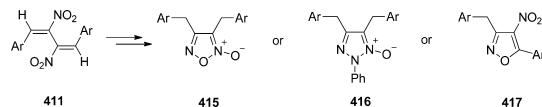
(*E,E*)-1,4-Diaryl-2,3-dinitrobutadienes **411** reacted with several primary alkylamines in excess to afford the corresponding *N*-alkyl-3-(alkylamino)-2,5-diaryl-4-nitropyrrrolidine derivatives **412** as single diastereomers, in almost quantitative yield. These compounds were convenient intermediates for the synthesis of pyrrolines **413** or pyrroles **414** (Scheme 113).¹⁷¹

Scheme 113



In addition, nitrodienes **411** have been used as starting materials for the preparation of disubstituted 1,2,5-oxadiazole 2-oxides **415**,¹⁷² 2-phenyl-2*H*-1,2,3-triazole 1-oxides **416**,¹⁷² and 3,5-disubstituted 4-nitroisoxazoles **417**^{173,174} (Scheme 114).

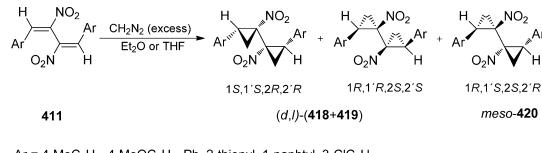
Scheme 114

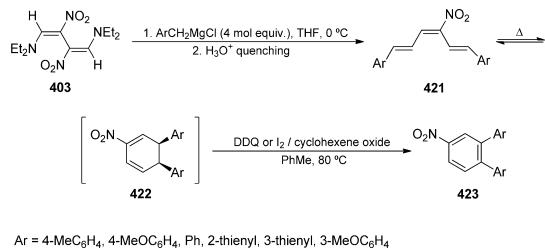


The reaction of (*E,E*)-1,4-diaryl-2,3-dinitrobutadienes **411** with an excess of diazomethane in anhydrous ether led to a mixture with two major products. Stereoselective HPLC analysis showed the presence of optically inactive **420** and a racemic mixture (**418** + **419**) of the possible six enantiomers and two *meso*-forms (Scheme 115). The stereochemistry in this process supports the participation of singlet carbene as the reactive species generated under the experimental conditions.¹⁷⁵

As shown in Scheme 116, nitrodiene **403** has been transformed into 1,2-diaryl-4-nitrobenzenes **423** through (*E,E,E*)-1,6-diaryl-3-nitro-1,3,5-hexatrienes **421** and the non-isolated nitrocyclohexadienes **422**. The first step of the reaction should involve a double 1,4-addition of the Grignard reagent to

Scheme 115

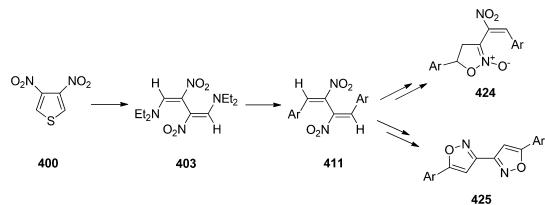


Scheme 116

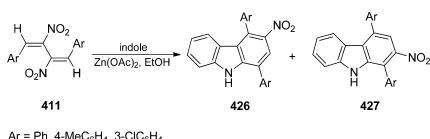
$\text{Ar} = 4\text{-MeC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4, \text{Ph}, 2\text{-thienyl}, 3\text{-thienyl}, 3\text{-MeOC}_6\text{H}_4$

the nitrovinyl systems of **403**, followed by acidic quenching. Then thermally induced 6π -electrocyclization of **421** and oxidative treatment with DDQ or iodine would lead to **423**.¹⁷⁶

Dell'Erba et al.^{177,178} have reported the synthetic potential of several nitro and dinitrodiienes prepared by a ring-opening reaction from 3-nitrothiophene and 3,4-dinitrothiophene, respectively. As an example, compounds **424** and **425** were obtained from **400** through acyclic 2,3-dinitrodienes **403** and **411** (Scheme 117).

Scheme 117

Starting from the same ring-opening reaction of nitrothiophenes described above, Bianchi et al.¹⁷⁹ have recently reported an original route to prepare newly functionalized indoles and carbazoles. These compounds were obtained as a result of a single or double Michael addition of indole to different nitrodiienes. Thus, isomeric nitrocarbazoles **426** and **427** were prepared from **411** (Scheme 118).

Scheme 118

$\text{Ar} = \text{Ph}, 4\text{-MeC}_6\text{H}_4, 3\text{-ClC}_6\text{H}_4$

5. CONCLUDING REMARKS

The present review summarizes recent methods described for the preparation of conjugated nitrodiienes as well as their synthetic uses. These compounds have attracted a growing interest in recent years because some of them are promising candidates regarding biological activity, as well as because of their recognized importance as reaction intermediates in the preparation of polyfunctionalized products. Research in this field has been mainly focused on hetero-, alkyl-, and aryl-substituted nitro- and dinitrodiienes, as well as on their catalyzed addition reactions. Additionally, research carried out on the synthesis of sugar-derived chiral nitrodiienes has been valuable, including applications to asymmetric synthesis. Due to its strong electron-withdrawing nature, the nitro group exerts a pronounced influence on the reactivity of conjugated dienes, which is more pronounced in addition or cycloaddition

reactions. Furthermore, the presence of the nitro group establishes differences in the reactivity between the two $\text{C}=\text{C}$ double bonds, allowing regiocontrolled synthesis of a large variety of highly functionalized systems. Applications to Diels–Alder processes take precedence because, in some cases, nitrodiienes can participate in reactions of either normal electron demand or inverse electron demand. Additionally, these compounds can act as heterodiienes, and some adducts can undergo Cope rearrangements. Therefore, due to their synthetic potential, further development in this area may provide more useful or effective methods for the construction of complex organic molecules.

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Notes

The authors declare no competing financial interest.

Biographies



Roberto Ballini received his master's degree in chemistry from the University of Camerino (Italy). After experience at the ENI-ANIC (Petroleum Industry) in Ravenna, he began his academic career in 1975 as a research fellow at the University of Camerino. Then he became Assistant Professor of Organic Chemistry (1978), was promoted to Associate Professor (Organic Chemistry), and then was promoted to Full Professor of Organic Chemistry in 2000. He is the Dean of the School of Sciences and Technology of the University of Camerino since 2010. His current research field concerns the chemistry of aliphatic nitro compounds and sustainable synthetic processes covering aspects of heterogeneous catalysis, one-pot reactions, solvent-free reactions, and use of alternative solvents. Roberto Ballini is the coauthor of more than 230 papers, including several reviews.



Noelia Araújo studied chemistry at the University of Extremadura, where she received her B.Sc. in 2003. In 2008, she received her Ph.D. at the University of Extremadura under the supervision of Profs. María V. Gil, E. Román, and José A. Serrano. During her Ph.D. studies, she did a three-month stay at the University of Camerino, under the supervision of Prof. Roberto Ballini. At this moment, she is a postdoctoral researcher at the University of Oxford in the group of Prof. George Fleet. Her research interests focus on nitro compound chemistry, as well as on synthesis and biological evaluation of carbohydrate derivatives.



María V. Gil studied chemistry at the University of Extremadura and completed her degree in 1996. She received her Ph.D. from the same university in 2000 under the supervision of Professors Emilio Román and José A. Serrano. She then pursued studies with Professor Roberto Ballini at the University of Camerino (Italy). In 2002, she was appointed as Research Assistant in Organic Chemistry and in 2006 was promoted to Assistant Professor. Since 2009 she has been a Professor of Organic Chemistry at the University of Extremadura. Her research concentrates on asymmetric synthesis in the field of nitro compounds.



Emilio Román was born in 1952 in Montánchez (Cáceres, Spain). He graduated with a degree in chemistry from the University of Extremadura (Badajoz, 1974), where he also received his Ph.D. degree (1978) under the supervision of Profs. Manuel Gómez Guillén and Juan Antonio Galbis, working on the synthesis of C-nucleoside analogues from 2-amino sugars. In 1983 he became Associate Professor at the same university, and in 1985, he spent a research period in the laboratories of Professor Ernest L. Eliel (University of North Carolina at Chapel Hill), where he worked on asymmetric Diels–Alder reactions with sugar-derived nitroalkenes. His current interest research is focused on the application of aliphatic nitro compounds derived from sugars for the preparation of acyclic and cyclic enantiomerically pure molecules.



José A. Serrano was born in 1951 in Madrigal de la Vera (Cáceres, Spain). He graduated with a degree in chemistry from the University of Extremadura (Badajoz, 1974), where he also received his Ph.D. degree (1980) under the supervision of Prof. Gómez Guillén, working on reactions between amino sugars and β -dicarbonyl compounds. In 1985 he became Associate Professor in the Department of Organic and Inorganic Chemistry of the University of Extremadura. Since then, his research has been mainly focused on studies on the reactivity of α,β -unsaturated aldehydes, nitroalkenes, and nitrodiienes derived from sugars. He is also working on reactions on water, as well as on the use of ultrahigh pressure as an activation method in asymmetric Diels–Alder reactions between furan derivatives and sugar-derived nitroalkenes.

ACKNOWLEDGMENTS

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DEDICATION

Dedicated to Professor José Fuentes on the occasion of his retirement.

ABBREVIATIONS

AIBN	azobisisobutyronitrile
BQ	1,4-benzoquinone
CAN	cerium ammonium nitrate
CuTC	copper(I) thiophene-2-carboxylate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,1-dichloroethene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DHP	3,4-dihydropyran
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide

DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
ESR	electron spin resonance
HPLC	high-pressure liquid chromatography
HPN	peroxy nitrous acid
LHMDS	lithium hexamethyldisilazide
MCPBA	3-chloroperoxybenzoic acid
MeHQ	methylhydroquinone
Ns	(4-nitrophenyl)sulfonyl
PCy ₂	dicyclohexylphosphine
PMB	4-methoxybenzyl
PPTS	pyridinium 4-toluenesulfonate
TBDMS	tert-butyldimethylsilyl
TBICA	tert-butyl isocyanoacetate
TBTH	tributyltin hydride
Tf	triflate (trifluorosulfonyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TosMIC	(4-tolylsulfonyl)methyl isocyanide
Ts	4-tolylsulfonyl
TsOH	4-toluenesulfonic acid

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