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The Nitrosocarbonyl Hetero-Diels–Alder Reaction as a Useful Tool for Organic Syntheses

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Abstract

Organic transformations that result in the formation of multiple covalent bonds within the same reaction are some of the most powerful tools in synthetic organic chemistry. Nitrosocarbonyl hetero-Diels–Alder (HDA) reactions allow for the simultaneous stereospecific introduction of carbon–nitrogen and carbon–oxygen bonds in one synthetic step, and provide direct access to 3,6-dihydro-1,2-oxazines. This Review describes the development of the nitrosocarbonyl HDA reaction and the utility of the resulting oxazine ring in the synthesis of a variety of important, biologically active molecules.

Keywords

cycloaddition; Diels–Alder reactions; nitrosocarbonyl compounds; oxazines; synthetic methods

1. Introduction

The nitroso hetero-Diels–Alder (HDA) reaction provides access to 3,6-dihydro-1,2-oxazines **3** from nitroso compounds **1** and dienes **2** (Scheme 1). The high regio- and stereoselective installment of nitrogen and oxygen functionality to 1,3-diene systems has resulted in the nitroso HDA reaction often being an important step in the synthesis of natural products and biological molecules.[1,2] Many aspects of the nitroso HDA reaction have been reviewed, ranging from the application of nitroso HDA reactions for the synthesis of azasugars,[3] HDA reactions with acylnitroso derivatives of amino acids,[4] asymmetric nitroso HDA reactions,[5,6] and the use of nitroso HDA reactions in natural product syntheses.[1,7]

While these reviews have demonstrated the importance of the nitroso HDA reactions in numerous synthetic endeavors, the chemistry surrounding the nitroso HDA reaction and the resulting 3,6-dihydro-1,2-oxazine functionality has not been described in detail within the

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Dedicated to Professor Jeremiah P. Freeman

literature. This Review will detail the rich chemistry of nitrosocarbonyl HDA reactions and their subsequent transformations to generate useful, biologically important molecules.

2. Nitroso Compounds

The nitroso functional group has been intensively studied since the first synthesis of nitrosobenzene by Baeyer more than one hundred years ago.[8] An early report found that nitroso compounds could add to activated methylene groups to form azomethine compounds (the Ehrlich–Sachs reaction),[9] and since this discovery, the nitroso group has been found to participate in nitroso aldol reactions,[10–13] ene reactions,[14] hetero-Diels–Alder reactions, and other fundamental organic processes.[7]

2.1. C-Nitroso Compounds and Simple Nitroso Compounds

The simplest nitroso compound, nitroxyl or hyponitrous acid (HNO), has seen limited use in cycloaddition reactions because of its high propensity to dimerize with loss of H_2O to form nitrous oxide.[15,16] In contrast, *C*-nitroso compounds have been used extensively as dienophiles in cycloaddition reactions (Figure 1).[4,10,17] Cyanonitroso (**4**),[17] arylnitroso (**9**), pyridylnitroso (**10**),[18] α-halonitroso (**5**),[19–21] α-acetoxy-nitroso (**6**),[22,23] vinylnitroso (**7**), iminonitroso (**8**),[24] acylnitroso (**11**),[17] and nitrosoformate ester **12**[25] compounds are all commonly used in HDA transformations.

The arylnitroso compounds **9** were among the first discovered, and are stable reagents that react slowly with dienes in [4+2] cycloaddition reactions.[4] Electron-withdrawing groups on the aromatic ring were found to greatly accelerate the reaction.[17] Similar effects were observed for nitrosoalkane compounds that were substituted at the α position, such as chloronitroso species **5**[19–21] and acetoxynitroso species **6**.[22,23] The most reactive nitroso compounds include those directly connected to an electron-withdrawing group, and nitroso compounds **4**, **8**, **11**, and **12** are among the most reactive nitroso dienophiles used in HDA reactions.

2.2. Heteroatom-Nitroso Compounds

Compounds in which the nitroso group is directly connected to a heteroatom that possesses a free electron pair are much less reactive than *C*-nitroso compounds toward dienes because of resonance stabilization of the nitroso moiety (Figure 2). Consequently, HDA reactions of hetero-atom-nitroso compounds are studied much less compared to their *C*-nitroso counterparts.

Deactivation of the dienophilic character of nitroso compounds through resonance stabilization can be overcome if no lone pairs of electrons are available for π donation. Some noteworthy examples that make use of this concept include *P*-nitrosophosphine oxides **13**[26–28] and *S*-nitrososul-fonyl compounds **14** (Figure 3).[29] The *N*-nitroso compounds **15** were found to be unreactive toward dienes,[30] even though the presence of the sulfonyl group should diminish the effect of lone-pair stabilization.

3. Nitrosocarbonyl Compounds

Nitrosocarbonyl compounds **11** and **12** are among the most reactive nitroso dienophiles. First proposed as transient intermediates in the oxidation of hydroxamic acids,[31] the only early evidence of the existence of acylnitroso **11** species were products resulting from nucleophilic attack at the acylnitroso carbonyl group[17] and [4+2] cycloaddition reactions.[32]

3.1. Preparation of Nitrosocarbonyl Compounds

Since acylnitroso compounds **11** are extremely reactive species, they are prepared and used in situ in chemical reactions (Scheme 2). By far the most common method for preparing acylnitroso compounds **11** is through oxidation of the corresponding hydroxamic acid **16**.[31] The generation of acylnitroso compounds **11** in this manner has been realized under a multitude of conditions, which include, but are not limited to, the use of periodate, Swern oxidation,[33] lead and silver oxide,[34] and Dess–Martin periodinane.[35] There are also a number of methods that generate acylnitroso compounds **11** from hydroxamic acids **16** through transition-metal-catalyzed oxidations in which peroxides are used as a stoichiometric oxidant.[36–41] A thorough study of metal catalysts that perform this transformation has been reported.[42]

Other methods commonly used to prepare acylnitroso species **11** include the oxidation of nitrile oxides **17**,[43] cycloreversion from 9,10-dimethylanthracene adducts **19**,[44] photochemical cleavage of 1,2,4-oxadiazole-4-oxides **18**,[45] and rearrangement of nitrocarbenes generated from diazo compounds **20**.[46]

3.2. Structure and Reactivity of Nitrosocarbonyl Compounds

Although acylnitroso compounds have been studied for well over 50 years, relatively little is known about their structure. Acylnitroso species were first detected spectroscopically in the gas phase in 1991 by neutralization-reionization mass spectrometry[47] and then in solution in 2003 by time-resolved infrared spectroscopy.[48] It is estimated that the lifetime of the acylnitroso species at infinite dilution in an organic solution is on the order of 1 ms.[48]

Acylnitroso compounds **11** can exist in either an s-*cis* or s-*trans* conformation along the carbonyl–nitrogen bond (Figure 4). It is evident from the data reported in the literature, the preference for a given acylnitroso species **11** to exist as either conformer must be calculated on a case-by-case basis. Additionally, the preference for either conformer is not necessarily minor, and the reported energy differences between the s-*cis* and s-*trans* conformers of various acylnitroso species have spanned from about 0–2 $kcalmol^{-1}$ to nearly 15 $kcalmol^{-1}$.[49–54]

In addition to participating in HDA reactions with dienes to provide *N*-acyl-3,6-dihydro-1,2-oxazines **24** (R =acyl) and in ene reactions to provide *N*-allylhydroxamates **25**, acylnitroso compounds **11** also undergo a number of other transformations (Scheme 3). The high stretching frequency of the carbonyl group of acylnitroso compounds **11** (1735 cm^{-1})[48] reflects their susceptibility to nucleophilic attack at the acylnitroso carbonyl group. The

corresponding carboxylic acids **21**, amides **22**, and *O*-acylhydroxamates **23** are obtained in the presence of nucleophiles such as water, amines, and hydroxamic acids, respectively.[17]

One of the earliest reactions observed with acylnitroso compounds **11** (R =alkyl, aryl) was their tendency to be deoxygenated by phosphines to yield isocyanates **27** through phosphonium intermediate **26** (Scheme 4).[55] In contrast, nitrosoformate esters **11** (R =alkoxy) yield products arising from the generation of the acylnitrene species **28** because of the unfavorable migratory aptitude of the alkoxy substitutent from phosphonium intermediate **26**.[25]

Acylnitroso compounds **11** have also been known to generate symmetrical anhydrides **31** and nitrous oxide in the absence of other reactants. Presumably, this process proceeds through nitroso dimer **29**, which undergoes a 1,2-acyl shift to give compound **30** followed by an intramolecular cyclization.[44]

4. Nitrosocarbonyl Hetero-Diels–Alder Reactions

The most common use of nitroso compounds has involved their ability to participate in [4+2] cycloaddition reactions. The first nitroso HDA reactions using aryl- and alkylnitroso compounds were reported by Wichterle[56] and Arbuzov[57] in 1947 and 1948, respectively. One of the earliest examples of a HDA reaction using an acylnitroso compound was reported by Kirby and Sweeny in 1973, where acylnitroso compounds were generated in the presence of thebaine (**32**) to afford cycloadducts **33** selectively (Scheme 5).[31]

The remarkable selectivity observed in acylnitroso HDA reactions provides access to 3,6-dihydro-1,2-oxazines and ultimately 1,4-amino alcohols. This section will document efforts toward the study of the mechanism, selectivity, and asymmetric variants of the acylnitroso HDA reaction.

4.1. Mechanism of the Nitrosocarbonyl HDA Reaction

The mechanism of the acylnitroso HDA reaction has been studied computationally by Leach and Houk,[58,59] and was found to proceed in a concerted fashion through a highly asynchronous transition state. In the calculated transition state, the C–N bond is shorter than the C–O bond, whereas in the product, the situation is reversed. Additionally, the authors found from RB3LYP/6-31G*//RB3LYP/6-31G* theory that the *endo* transition state was preferred over the *exo* transition state by 8.6 kcalmol^{-1} (**34**, Figure 5).[59] The n–π repulsion exhibited by the lone pair of electrons on the nitrogen atom, termed the “*exo* lone pair effect”,[60,61] is responsible for this strong preference for the placement of the nitrogen substituent in an *endo* position.

The combined preference for placement of the nitrogen substituent in an *endo* position with the shorter C–N bond in the transition state can explain the high regio- and stereoselectivities observed in acylnitroso HDA reactions.

4.2. Regioselectivity in Nitrosocarbonyl HDA Reactions

The regioselectivity of intermolecular acylnitroso HDA reactions has been studied experimentally[2,62] as well as through the use of computational methods.[59] Most unsymmetrical dienes add to nitroso compounds regioselectively, as shown in Scheme 6. 1-Substituted 1,3-dienes **35** provide oxazines **36** with high selectivity, whereas 2-substituted 1,3-dienes **37** provide the oxazines **38** with moderate selectivity. The regioselectivity in nitroso HDA reactions can be rationalized on the basis of frontier MO theory, and dienes with substituents that are strongly electron donating or electron withdrawing provide cycloadducts with higher regioselectivity than dienes with substituents that are only weakly electron donating or electron withdrawing.[59] It should also be noted that, in most cases, solvent polarity has been shown to have little effect on the regioselectivity in intermolecular nitroso HDA reactions;[62] however, as will be described in Section 8.2, the opposite is true of intramolecular nitroso HDA reactions.

Similar trends for regioselectivity are observed for substituted cyclic dienes in acylnitroso HDA reactions (Scheme 7). The oxidization of benzohydroxamic acid in the presence of substituted cyclohexadienes **39a** and **39b**, led to cycloadducts **40** and **41** with moderate regioselectivity.[62]

In most cases, arylnitroso and acylnitroso species yield products with the same regioselectivity; however, in a few cases the selectivites are reversed. For example, opposite regioselectivities were observed when *N*-acyl-1,2-dihydropyridines **42** were treated with arylnitroso and acylnitroso compounds. Arylnitroso compounds afforded adducts **43**,[63,64] while acylnitroso compounds (R^2 =alkyl) resulted in cycloadducts **44**.[64] The reason for this observed difference in regioselectivity has not been explained.

4.3. Stereoselectivity in Nitrosocarbonyl HDA Reactions

There are a number of reviews detailing the use of asymmetric nitroso HDA reactions in organic syntheses.[1,4–6,50] Methods for performing asymmetric nitroso HDA reactions include the use of chiral nitroso dienophiles, chiral dienes, and, with mixed success, the use of chiral catalysis. All three of these general approaches toward asymmetric nitroso HDA reactions will be described briefly in the following sections.

4.3.1. Chiral Dienophiles in Nitrosocarbonyl HDA Reactions—The use of chiral acylnitroso dienophiles, specifically as chiral auxiliaries, is the most common method for inducing chirality in acylnitroso HDA reactions. A variety of chiral acylnitroso species **45** that have been found to provide 1,3-cyclohexadiene adduct **46** with excellent diastereoselectivity have appeared in the literature (Figure 6).

All acylnitroso species **45** were prepared in situ by oxidation from the corresponding hydroxamic acid. Substituted pyrrolidines **45a**–**c** offered cycloadducts **46** in high diastereomeric excess.[49] Additionally, a variety of camphor derivatives **45d**–**f** have also been reported.[30,33,51] Other auxiliaries include imidazolidin-2-one **45g**[52] and compound **45h**,[65] derived from menthol.

Chiral α-substituted acylnitroso compounds that undergo asymmetric HDA reactions have included nitroso species **47** derived from α-amino acids,[4,66,67] and nitroso species **48** derived from mandelic acid (Figure 7).[53,54,68–71] These auxiliaries benefit from their relatively simple preparation from readily available sources of chirality.

4.3.2. Chiral Dienes in Nitrosocarbonyl HDA Reactions—The use of both chiral cyclic and acyclic dienes in diastereoselective acylnitroso HDA reactions has been reported in the literature. In general, the use of chiral acyclic dienes yields cycloadducts in lower diastereomeric excess than does the use of chiral acylnitroso dienophiles. This is probably a result of the asynchronous transition state of the nitroso HDA reaction, where the nitrogen substituent is hypothesized to be closer to the diene than the oxygen lone pairs of electrons. This, in turn, places the chiral moiety of 1-substituted acyclic dienes spatially distant from the bulk of the incoming nitroso dienophile. Nevertheless, chiral acyclic dienes, such as chiral *N*-dienyllactams **49**,[72,73] pseudoephedrine-derived oxazolidines **50**,[74] and chiral 1-sulfinyl dienes **51** (Figure 8)[75,76] have been successfully used in asymmetric nitroso HDA reactions.

Compared to chiral acyclic dienes, chiral cyclic dienes often yield cycloadducts with excellent diastereoselectivity. Hudlicky and Olivo have reported the use of chiral dienes **52a** and **52b**, obtained by microbial oxidation of halobenzenes, in asymmetric nitroso HDA reactions (Scheme 8).[77] Cycloadducts **53** were obtained in high yields with complete diastereo- and regioselectivity. The conversion of cycloadducts **53** into conduramine A-1 (**54**) was also described.

4.3.3. Catalytic Asymmetric Nitroso HDA Reactions—For many years, attempts at developing a catalytic asymmetric nitroso HDA reaction resulted in only extremely low *ee* values (ca. 15%).[78] It was not until 2004, when the Yamamoto research group published an asymmetric nitroso HDA reaction with pyridylnitroso species **55**, that an effective catalytic asymmetric nitroso HDA reaction was realized (Scheme 9).[79] This ground-breaking discovery is very useful for the synthesis of enantiomerically pure oxazines **56**; however, a similar method for the nitrosocarbonyl HDA reaction is still lacking.

The difficulties faced in the development of a catalytic asymmetric method for the nitrosocarbonyl HDA reaction have included an extremely facile background reaction and the susceptibility of nitrosocarbonyl species to dimerize. These problems plagued the study of aryl- and heteroarylnitroso species for some time before the discovery of the Yamamoto research group;[78] however, nitrosocarbonyl compounds are more reactive than aryl- or heteroarylnitroso species, and react as rapidly or more rapidly without catalysts than when bound to a Lewis acid.[36,38] A better understanding of the metal coordination chemistry of nitrosocarbonyl species will be essential for the development of a catalytic asymmetric nitrosocarbonyl HDA reaction.

5. Nitrosocarbonyl HDA Reactions on a Solid Phase

Although nitrosocarbonyl HDA reactions have been widely used in organic synthesis in solution, there have only been a few accounts of performing nitrosocarbonyl HDA reactions

on a solid support. One example reported by Krchnak et al.[80–82] utilized Wang resin supported hydroxamic acids **58** derived from alcohols **57** (Scheme 10). The hydroxamic acids **58** were oxidized using tetrabutylammonium periodate in the presence of dienes to yield cycloadducts **59**.

Other solid-supported nitroso HDA reactions reported by Quadrelli and co-workers include the generation of acylnitroso compounds from solid-supported nitrile oxides[83] and the photochemical generation of acylnitroso compounds from solid-supported 1,2,4-oxadiazole-4-oxides **60** and **64** (Scheme 11).[84] Upon irradiation, compounds **60** generated the solid-supported nitrile **61** and the acylnitroso compound **62**, which was trapped in situ with cyclopentadiene to afford cycloadduct **63**. Irradiation of 1,2,4-oxadiazole-4-oxide **64** provided benzonitrile and solid-supported acylnitroso compound **65**, which was subsequently trapped by dienes to yield cycloadduct **66**.

6. Chemistry of 3,6-Dihydro-1,2-oxazines

Most of the utility of the acylnitroso HDA reaction in organic syntheses stems from the rich chemistry of the resulting cycloaddition products. The rapid construction of a wide variety of functional groups in one molecule allows access to a number of molecular scaffolds from simple bicyclic cycloadducts **67** (Scheme 12). The structural modification of cycloadducts **67** can be divided into one of four main areas: cleavage of the N–acyl bond to yield oxazines **68**, cleavage of the N–O bond to yield amino alcohols **71**, cleavage of the C–O bond to yield compounds **72**–**75**, and alkene modification to afford compounds **69** and/or **70**. Additionally, compounds such as oxazines **67** have demonstrated the ability to undergo a number of rearrangements and other chemical reactions.

The carbonyl group of cycloadducts **67** is susceptible to hydrolysis under relatively mild conditions (R =alkyl or aryl).[85] This provides the basis for removing many of the chiral auxiliaries described in Section 4.3.1. The following section details various transformations of cycloadducts **67** commonly utilized in synthetic organic applications. Although most of the methodology has been developed using bicyclic oxazines **67**, much of the chemistry presented here is also applicable to monocyclic 3,6-dihydro-1,2-oxazines.

6.1. Alternate Routes to 3,6-Dihydro-1,2-oxazines

Although the nitroso HDA reaction is an excellent method for preparing 3,6-dihydro-1,2-oxazines, alternative methods for preparing these heterocyclic systems exist and have been reviewed.[86,87] Methods of preparing monocyclic 1,2-oxazines have included using alkene[88] and enyne[89,90] ring-closing metathesis reactions, the addition of nitrones to methoxyallenes[91] and activated cyclopropanes,[92,93] and the use of nitroso aldol reactions.[94]

An example of an alternative synthesis of bicyclic 1,2-oxazine systems involved an intramolecular nitrone [3+2] cycloaddition (Scheme 13).[95] Aldehyde **76**, derived from L-arabinose, was converted into nitrone **77**, which cyclized selectively to yield oxazines **78** and **79**.

6.2. N–O Bond Cleavage

Reductive cleavage of the N–O bond is one of the most widely utilized methods for derivatizing 1,2-oxazines. Common reagents that facilitate cleavage of the N–O bond include molybdenumhexacarbonyl ([$Mo(CO)_6$]),[96,97] zinc in acetic acid, catalytic hydrogenation, samarium diiodide,[98,99] and titanocene(III) chloride.[100] Other methods for reduction of the N–O bond include the use of photochemical,[101] enzymatic,[102] and other chemical[103] processes.

Reductive cleavage of the N–O bonds of monocyclic 1,2-oxazines **80** yielded 1,4-amino alcohols **81**, which have been cyclized using manganese dioxide to provide access to pyrroles **82** (Scheme 14).[104]

Treatment of racemic cycloadduct (±)-**83** with molybde-numhexacarbonyl yielded the aminocyclopentenol (±)-**84** (Scheme 15). The Miller research group has developed a kinetic enzymatic resolution method that yielded enantiomerically pure acetate (−)-**85** and aminocyclopentenol (−)-**84** by using an immobilized lipase from *Candida antarcti*ca.[105] Acetate (−)-**85** has been an important intermediate in the synthesis of 5′-norcarbocyclic nucleosides, which will be covered in Section 7.1.

Other methods for the reductive cleavage of the N–O bond have included eliminative ring-opening reactions similar to that reported by Kefalas and Grierson (Scheme 16).[106] 1,2-Oxazine **86** was treated with tetrabutylammonium fluoride (TBAF) to provide pyrrole **87**. The anion intermediate **88** generated by treatment with fluoride yielded the aldehyde intermediate **89**, which subsequently underwent dehydrative cyclization to afford pyrrole **87**. Intramolecular cyclization to pyrrolo-castanospermine **90** was effected using KH in DMF. This reaction sequence was similar to that reported for the base-catalyzed decomposition of dialkyl peroxides (the Kornblum–DeLaMare rearrangement),[107] and has also been reported for other monocyclic oxazine systems.[108]

6.3. C–O Bond Cleavage

The Miller research group reported that Lewis acids could mediate C–O bond cleavage of cycloadducts **91** and **92** in the presence of alcoholic solvents to afford hydroxamates **94**–**96** (Scheme 17).[109,110] Presumably, this transformation proceeded by coordination of the Lewis acid to the hydroxamate portion of the oxazine system through a structure similar to complex **93**. The reaction was found to be moderately selective for 1,4-*trans*-hydroxamate **94** over 1,2-*cis*-hydroxamate **96**. The formation of 1,2-*cis*-hydroxamate **97** was not observed.

The C–O bond has also been cleaved in the presence of Brønsted acids to yield products arising from intramolecular cyclizations (Scheme 18). For example, Procter and co-workers reported that treatment of cycloadduct **98**, derived from mandelic acid, with aqueous HCl in dioxane afforded hydroxylamine **100**.[111,112] Interestingly, hydroxamate **102** was obtained when cycloadduct **91** was treated under the same conditions.[109] It would appear that both reactions proceeded through the bicyclic intermediates **99** and **101**, respectively; however,

no explanation was given for the different products arising from hydrolysis. Recently, the treatment of cycloadduct **83** with Brønsted acids yielded the bicyclic hydroxamate **103**.[113]

Treatment of cycloadduct **91** with Grignard reagents in the presence of Cu^{II} resulted in the selective formation of hydroxamates **104** arising from attack at the "C" position and to minor amounts of hydroxamates **105** arising from attack at the "B" position (Scheme 19).[114] Similar reactivity was observed when bicyclic cycloadducts **67** were treated with dialkylzinc reagents in the presence of copper catalysts.[115,116] Even though attack at the carbonyl group was expected on the basis of studies by Keck et al.,[85] no products arising from attack at position "A" were observed. Again, this probably illustrates the weakening of the C–O bond that arises in metal-coordinated species such as complex **93**. This method was applied in the synthesis of hydroxamate **106**, a potent 5-lipoxygenase inhibitor.[114]

Other unexpected reactions have been reported when acylnitroso HDA cycloadducts were treated with Grignard reagents. Treatment of 9,10-dimethylanthracene adduct **107** with excess MeMgCl in THF led to the unusual dimeric nitrone compound **108** in 76% yield (Scheme 20).[117] The authors proposed a possible mechanistic explanation for this result; however, the details concerning the formation of compound **108** are still not clear.

Treatment of cycloadducts **108** with Pd^0 yielded π-allyl species **110**, which were trapped with nucleophiles and provided 1,4-*cis*-cyclopentenes **111** selectively (Scheme 21).[109,118] π-Allyl species **110** can be reductively transmetalated using In^I to form allylic indium(III) species, which are subsequently trapped with reactive aldehydes, ketones, and other electrophiles, such as Eschenmoser's salt.[119,120] Recently, the in situ prepared allylindium(III) species generated from cycloadduct **109** was trapped with 4-acetoxy-2-azetidinone to provide compound **112** with high regio- and stereospecificity.[120]

6.4. Cleavage and Modification of the Alkene Function

Compared to other functionality in bicyclic oxazines **113**, relatively little effort has been concentrated on modifying the alkene portion of the 3,6-dihydro-1,2-oxazine system. Accordingly, the strained nature of the 2-oxa-3-aza-bicyclo-[2.2.1]hept-5-ene system has been under-utilized for its potential to promote the selective functionalization of the alkene system. Only a handful of transformations have been made to the alkene moiety in bicyclic oxazines **113** (Scheme 22). The oxidative cleavage of cycloadducts **113** yielded diacid compounds **114**. Other studies have shown the alkene function of bicylic oxazines **113** to be suitable for ring-opening cross-metathesis reactions, thereby resulting in compounds **117a** and **117b**,[121,122] while alkylidenecyclopropanation of oxazine **113** yielded compound **116**.[123]

Additions to the alkene function of bicylic oxazine **113** (*n* =1) have often proceeded with high facial selectivity, but not with high regioselectivity. Consequently, dihydroxylation of cycloadducts **113** yielded diols **115**,[124–126] and alkylidene-cyclopropanation yielded compound **116**[123] with excellent selectivity. Dipolar cycloaddition reactions of oxazines **113** proceed with high facial selectivity, but with poor regioselectivity. Consequently, treatment of cycloadducts **113** with nitrile oxides[127,128] and organic azides[129] afforded dihydro-isoxazoles **118a**,**b** and triazolines **119a**,**b**, respectively, as regioisomeric mixtures.

6.5. Other Chemical Transformations and Rearrangements

In addition to the reactions outlined above, nitrosocarbonyl HDA cycloadducts have participated in a number of other unusual and mechanistically interesting transformations.[17,130] Kirby and Mackinnon reported that treatment of ergosteryl acetate (**120**) with acylnitroso compounds in refluxing benzene afforded cycloadduct **121** along with the unusual dihydrodioxazine **123** (Scheme 23).[131] When the reaction was repeated at 0°C, the regioisomeric cycloadducts **121** and **122** were obtained; however, heating the mixture to reflux resulted in cycloadduct **122** being transformed into the dioxazine compound **123** through a [3,3] sigmatropic rearrangement. Oxazine **121** did not undergo the rearrangement, which was explained by steric crowding of the dioxazine product.

7. Synthetic Applications of Intermolecular Nitroso-carbonyl HDA Reactions

The utility of the intermolecular nitrosocarbonyl HDA reaction in organic syntheses is reflected by the wide variety of molecules that are accessible. The following section will outline various classes of molecules that have been synthesized by using nitrosocarbonyl HDA methodology.

7.1. Carbocyclic Nucleosides

Carbocyclic nucleosides, in which the furanose oxygen atom of the nucleoside is replaced by a methylene unit, have received attention for their use as antiviral agents.[132–136] Aristeromycin (**125**) is the direct carbocyclic nucleoside analogue of adenosine (**124**) and has demonstrated potent antiviral properties linked to the inhibition of AdoHcy hydrolase (Figure 9).[137] The synthesis and study of carbocyclic nucleosides has been an important area of therapeutic research, and many methods have been developed that allow access to this class of molecules.

The Miller research group has published a number of reports regarding the use of nitrosocarbonyl HDA reactions to construct carbocyclic nucleoside analogues.[66,138–143] Enantiomerically pure acetate (−)-**85**,[105] obtained from the kinetic enzymatic resolution process described in Section 6.2, was used to synthesize carbocyclic uracil polyoxin C (**129**) and its epimer through the intermediate **128** (Scheme 24).[140,144] The opposite enantiomer of acetate (−)-**85** was used to synthesize the carbocyclic fragment of nucleoside Q.[145]

Cowart et al. have also published a method for synthesizing azacarbocyclic nucleoside analogues, such as compounds **133** and **135**, from cycloadduct **83** (Scheme 25).[126] Reduction of the N–O bond of acetonide **130** followed by inversion of the alcohol group through an oxidation/reduction sequence yielded alcohol **131**. The nucleoside base was installed under Mitsunobu conditions and yielded compound **132**, which was ultimately transformed into analogue **133**. This method suffered from low yields for the Mitsunobu reaction, so an alternative strategy was employed that made use of palladium-π-allyl chemistry to install the base directly from cycloadduct **83** and yielded hydroxamate **134**. Reduction of the hydroxamate followed by dihydroxylation and deprotection provided an efficient route to analogue **135**.

7.2. Azasugars

The nitroso HDA reaction allows the construction of 3,6-dihydro-1,2-oxazine rings that possess the required substitution pattern for the synthesis of many azasugars. The use of the nitroso HDA reaction for the synthesis of azasugars has been reviewed,[3,50] and allows access to both pyrrolidine and piperidine analogues of sugars.

Acyclic dienes **136a**[72,146–148] and **136b**[75] have been used for the synthesis of pyrrolidine-based sugar derivatives (Scheme 26). The cycloadducts **137** have been obtained in high yield and diastereoselectivity. Dihydroxylation afforded diol **138** with excellent facial selectivity, and reduction of the N–O bond followed by intramolecular condensation provided access to pyrrolidines **139**.

Piperidine-based sugar derivatives have been synthesized by utilizing an acylnitroso HDA reaction with 1,2-dihydro-pyridines **140** (Scheme 27).[3] While nitrosoformate esters yielded mixtures of cycloadducts **141** and **142**, the use of acylnitroso species derived from carboxylic acids yielded cycloadduct **141** exclusively. Facially selective dihydroxylation followed by catalytic hydrogenation yielded the azasugar derivatives **143** and **144**.

7.3. Tropane Alkaloids and Related Structures

Ever since the first landmark synthesis of tropinone (**145**) by Robinson in 1917,[149] the tropane alkaloids have continued to elicit the interest of synthetic organic chemists (Figure 10). This substance class includes nortropane (**146**), homotropane (**147**), scopine (**148**), and polyhydroxylated nortropanes such as calystegines (**149**).

A number of nitrosocarbonyl HDA approaches to the tropane alkaloids have been reported, and all follow the same general scheme first outlined by Kibayashi and co-workers (Scheme 28):[150] Reductive cleavage of the N–O bond of cycloadducts **150** provided the amino alcohols **151**. An intramolecular cyclization yielded the aza-bridged tropane system **152**.

This general approach to tropanes has been extended to the enantioselective total synthesis of (−)-epibatidine (**159**) (Scheme 29).[65,151] Chiral nitrosoformate ester **153** was generated in the presence of diene **154** and yielded the three cycloadducts **155**–**157** with moderate selectivity. Cycloadduct **155** was used to complete the synthesis of (−)-epibatidine (**159**) via intermediate **158**.

Other research groups have utilized similar approaches toward the synthesis of members of the tropane family such as nortropane (**146**),[152] homotropane (**147**),[153–155] scopine (**148**) and pseudoscopine,[156] and polyhydroxylated nortropanes **149**.[157,158]

7.4. Amaryllidacea Alkaloids and Related Structures

Alkaloids from plants in the *Amaryllidacea* family have been used in the treatment of cancer.[159] Members of this family of alkaloids include lycorine (**160**), pancratistatin (**161**), deoxypancratistatin (**162**), narciclasine (**163**), and lycoricidine (**164**; Figure 11).

Nitrosocarbonyl HDA reactions with substituted 1,3-cyclohexadienes have been used for the synthesis of the amaryllidacea alkaloids. The Hudlicky research group has published

synthetic routes to narciclasine (**163**).[77,160,161] Nitrosoformic acid (**166**) was oxidized in the presence of the chiral diene **165** and yielded cycloadduct **167** (Scheme 30).[160] A one-pot Suzuki–Miyaura reaction followed by reduction of the N–O bond yielded the key intermediate **169**, which was further elaborated to furnish narciclasine (**163**). Other routes to the amaryllidacea alkaloids and their core structure have been reported that utilize similar nitrosocarbonyl HDA reactions.[33,161–165]

The total synthesis of the related fused polycyclic piperidine-containing alkaloid (+)-streptazolin (**172**) has also been reported by the Miller research group (Scheme 31).[166,167] The chiral cyclopentenol (−)-**84** was converted into intermediate **170**, which underwent an intra-molecular aldol condensation to furnish compound **171**. Selective installment of the *Z* alkene was realized by using a silicon-tethered ring-closing metathesis strategy[167] and ultimately provided (+)-streptazolin (**172**).

7.5. Amino Acid Analogues and Related Structures

The nitrosocarbonyl HDA reaction has provided access to a number of novel amino acid analogues and other biologically important molecules. The Miller research group has reported the synthesis of a variety of therapeutically relevant molecules. A number of amino acid analogues have been synthesized that are structurally similar to antibacterial diacid compounds **173**[168] by the oxidative cleavage of nitrosocarbonyl HDA cycloadducts (Figure 12).[68,169–173] Other syntheses reported by Miller and co-workers have included the preparation of biologically active agents such as *meso*-DAP analogues,[174] BCX-1812 (**174**), LY354740 analogues **175**, 5-lipoxygenase inhibitors **106**,[114] phosphodiesterase inhibitors,[175–177] and the conformationally restricted substrate analogue of siderophore biosynthesis **176**.[178]

7.6. Natural Product Derivatization

Ever since Kirby and Sweeny reported acylnitroso HDA reactions with thebaine,[31] the acylnitroso HDA reaction has been used as a method for synthesizing natural product derivatives. The benefits of using nitroso HDA reactions for this purpose include the often exquisite stereo- and regioselectivity of the cycloaddition as well as the rich chemistry of their products.

The nitroso HDA reaction has been used in a number of studies to provide access to steroids as well as novel analogues and derivatives.[25,131,179–181] The Miller research group has recently disclosed a strategy that exclusively utilizes nitroso cycloadditions to prepare analogues of natural products from a variety of molecular classes.[182] Piperine (**177**), a major component naturally found in peppers, was treated with polymer-supported nitrosocarbonyl species to produce, after deprotection, the two cycloadducts **178** and **179** (Scheme 32).[183] The authors were surprised to find that treatment of compound **178** with TFA and triethylsilane as a cation scavenger produced hydroxylamine **180**. Under the same conditions, the cycloadduct **179** was recovered from the reaction unchanged.

Thebaine has provided an interesting look into how structurally novel derivatives of natural products can be prepared in a few steps by using the chemistry of nitroso HDA

cycloadducts. Gourlay and Kirby have reported a number of unusual reactions that use acylnitroso cycloadducts of the-baine.[17,184] In a recent example, Sheldrake and Soissons have reported the selective opening of the thebaine skeleton from cycloadducts **181** by using samarium diiodide (Scheme 33).[185] Similar to other reactions of acylnitroso HDA cycloadducts,[186] samarium diiodide facilitated cleavage of the N–O and C–C bonds in one pot and provided the novel derivative **182**.

8. Synthetic Applications of Intramolecular Nitroso-carbonyl HDA Reactions

Intramolecular nitrosocarbonyl HDA reactions have been used in the synthesis of natural products, alkaloids, and other biologically important molecules. Although intermolecular nitrosocarbonyl HDA reactions are often regioselective, tethering the nitrosocarbonyl group to the reacting diene imparts regiospecificity and additional diastereoselectivity. This section will survey the use of intramolecular nitro-socarbonyl HDA reactions in the synthesis of a variety of alkaloid classes and will again emphasize the utility of the nitrosocarbonyl HDA reaction as a method to construct complex structural systems.

8.1. Monocyclic Alkaloids

The simplest alkaloids that have been synthesized by utilizing intramolecular nitrosocarbonyl HDA reactions are monocyclic alkaloids. The synthesis of compounds **185** from acylnitroso species **183** represents a general method that often closely resembles the initial steps in the synthesis of monocyclic as well as polycyclic alkaloid systems (Scheme 34). Preliminary studies in this area by Keck[187] as well as by Kibayashi and co-workers[188–190] provided the necessary methodology required for more elaborate structures.

Recently, Kibayashi and co-workers published the enantioselective total synthesis of (+)-azimine (**189**) and (+)-carpaine (**190**), which highlighted the use of the intramolecular acylnitroso HDA reaction (Scheme 35).[191] Acylnitroso compound **186** underwent a spontaneous, stereoselective HDA reaction and formed oxazine **187**, which was transformed, over a number of synthetic steps, into the key monomeric intermediate **188**. Dimerization of compound **188** through the formation of the two ester bonds yielded the aforementioned natural products **189** and **190**.

8.2. Decahydroquinoline Alkaloids

Decahydroquinoline alkaloids have been synthesized by using similar methodology as for monocyclic alkaloids. The synthesis of (−)-lepadins A (**195a**), B (**195b**), and C (**195c**) was reported in 2001 (Scheme 36).[192,193] The synthesis of the lepadin family also illustrated an important difference between the intra- and intermolecular acylnitroso HDA reactions in regard to the effect of the solvent polarity on the reaction selectivity. The selectivity in intermolecular nitroso HDA reactions has generally been insensitive to solvent polarity; however, the use of aqueous media for intramolecular acylnitroso HDA reactions resulted in a significant enhancement of the diastereoselectivity.[194] Thus, cycloadduct **193** was formed more selectively over cycloadduct **192** when hydroxamic acid **191** was oxidized in aqueous solvent mixtures compared to in nonpolar solvents. Cycloadduct **193** was

transformed into the monocyclic intermediate **194**, which was further elaborated to (−)-lepadins **195a**–**c**. Kibayashi and co-workers have also used a similar approach for the synthesis of the pumiliotoxin alkaloids.[194–197]

8.3. Indolidizine and Pyrrolidizine Alkaloids

Pyrrolizidine and indolizidine alkaloids have been isolated from a wide variety of natural sources and have demonstrated interesting biological properties.[198] Representative compounds of this class of alkaloids that have been synthesized by using an intramolecular acylnitroso HDA strategy include swainsonine (**196**) and its derivatives,[199,200] fasicularin (**197**) and lepadiformine (**198**),[201] and other indolizidine alkaloids (Figure 13).[187,189,199,202–209]

The synthesis of a particularly interesting member of the pyrrolidizine class of alkaloids, (+)-loline (**202**) was achieved by using an intramolecular acylnitroso HDA strategy (Scheme 37).[210,211] Hydroxamic acid **199** was oxidized to yield the oxazine **200**. Subsequent modifications yielded the intermediate **201** which was converted into (+)-loline **202**.

8.4. Bridged Oxazinolactams Using Type II Intramolecular Cycloadditions

The vast majority of intramolecular acylnitroso HDA reactions have involved the use of dienes tethered at the 1-position. In “type II” intramolecular acylnitroso HDA reactions, the 2-position of the diene is tethered (Figure 14), which provides access to bridged oxazinolactam compounds.

Recently, the synthesis of the tricyclic core of the alkaloid stenine (**206**) was reported by using a type II intramolecular acylnitroso HDA reaction (Scheme 38).[212] Ethyl ester **203** was converted into a hydroxamic acid, which upon oxidation yielded the tricyclic structure **204**. Subsequent modification led to advanced intermediate **205**.

Other examples of the use of type II intramolecular acylnitroso HDA reactions in synthetic applications have been reported by the Shea research group,[213–216] and demonstrate the potential of these often overlooked variations of the more-typical type I intramolecular acylnitroso HDA reactions.

9. Summary and Outlook

Although the nitrosocarbonyl HDA reaction has been used toward the synthesis of a number of important biologically active substrates, there is still much room for method development surrounding the usage of the resulting 3,6-dihydro-1,2-oxazine ring in organic syntheses. The acylnitroso HDA reaction is a valuable tool for synthetic organic chemists, since it allows for the rapid construction of elaborate alkaloids in a stereocontolled manner. This Review is meant to serve as a reference to illustrate how the N–acyl, N–O, C–O, and C=C bonds of nitrosocarbonyl HDA cycloadducts can be functionalized. We encourage further research in nitrosocarbonyl HDA reactions so that the fundamental principles of the nitroso HDA reaction presented here can be applied to many new and exciting synthetic efforts.

10. Note Added in Proof

After submission of this manuscript, the recent study by Monbaliu et al., in which microreactor technology was used for HDA reactions of various nitroso dienophiles, was brought to our attention.[217] This is an excellent example of how new developments in the literature are improving the utility of an already powerful synthetic transformation.

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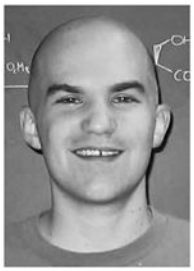
Biographies



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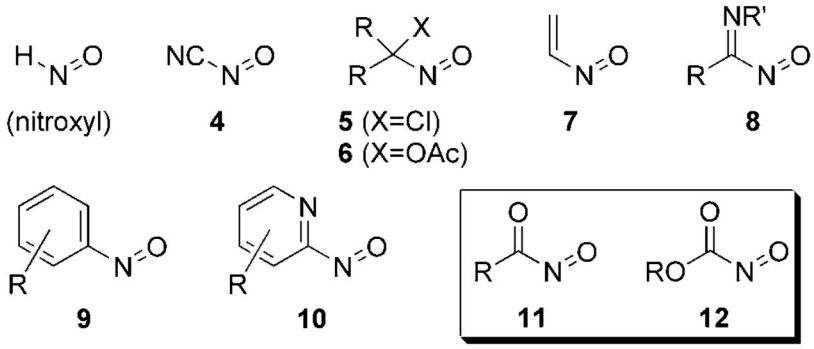


Figure 1.
Examples of *C*-nitroso compounds.

Figure 2.
Resonance stabilization of X–N=O compounds.

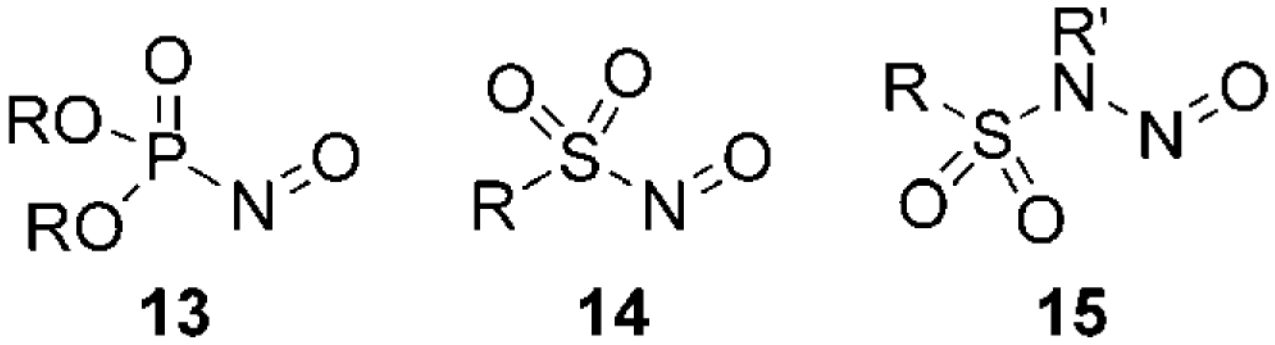


Figure 3.
Examples of nitroso compounds with heteroatoms.

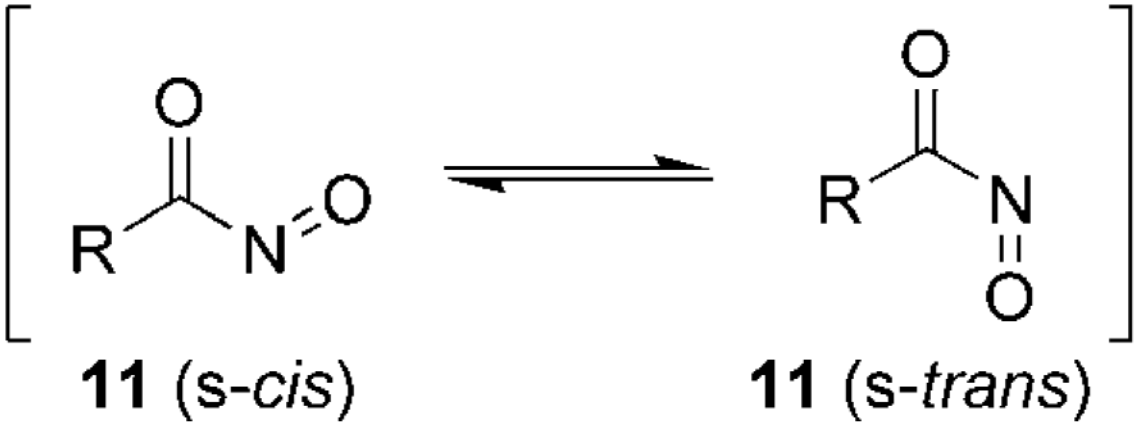


Figure 4.
s-*cis* and s-*trans* Isomers of nitrosocarbonyl compounds.

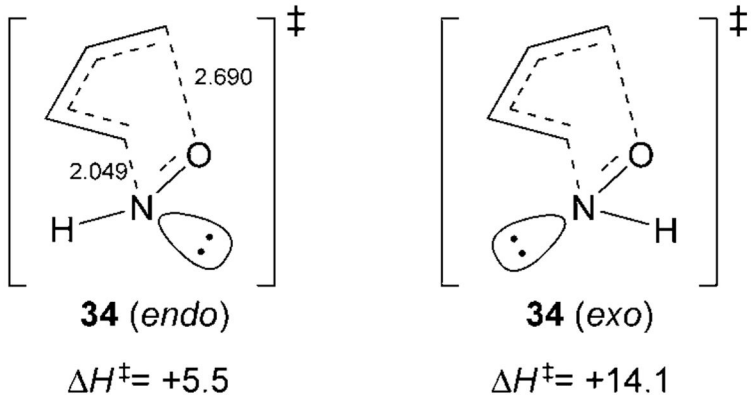


Figure 5.
Computed energies for transition states of the nitroso HDA reaction.

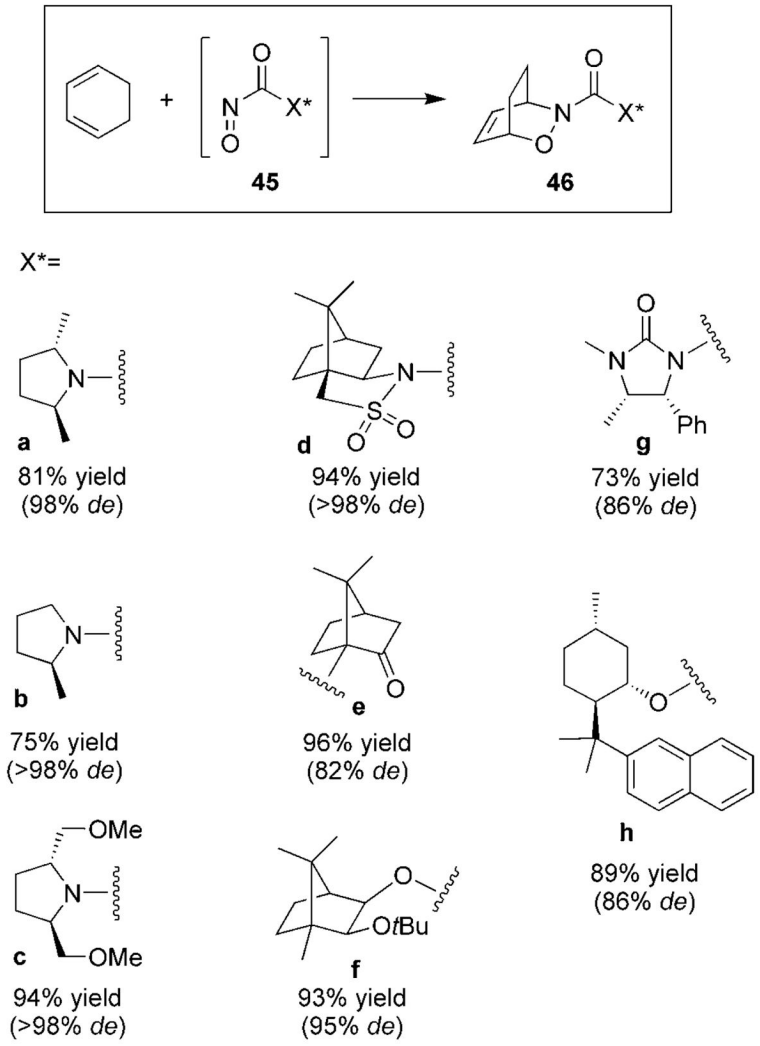
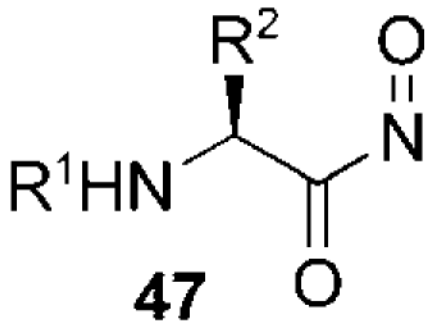
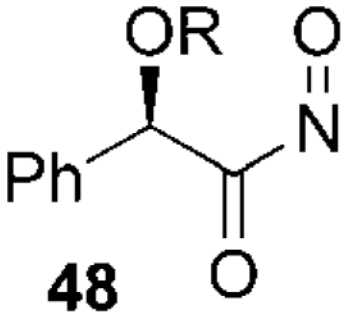


Figure 6.
Examples of chiral nitrosocarbonyl compounds.



47



48

Figure 7.
Other chiral nitrosocarbonyl species.

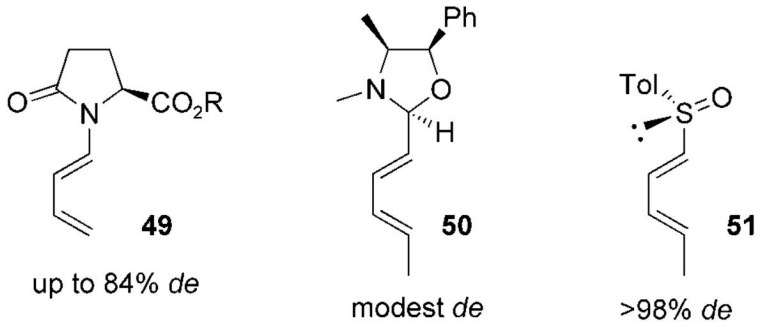


Figure 8.
Examples of chiral acylic dienes.

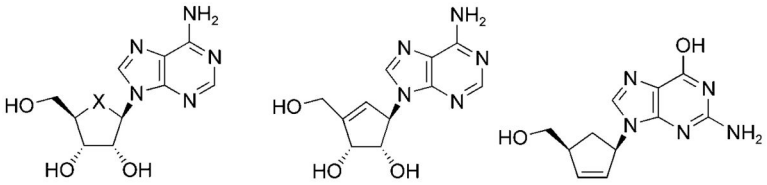


Figure 9.
Representative carbocylic nucleosides.

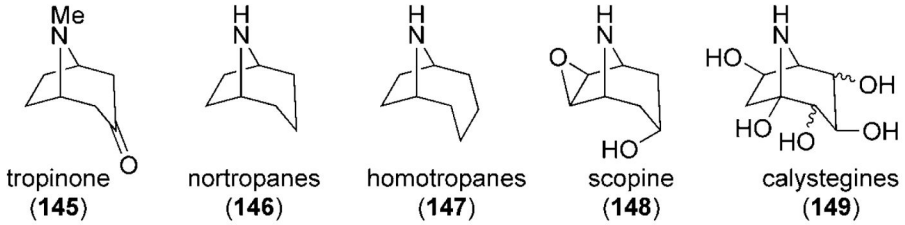


Figure 10.
Structures of the tropane alkaloid family.

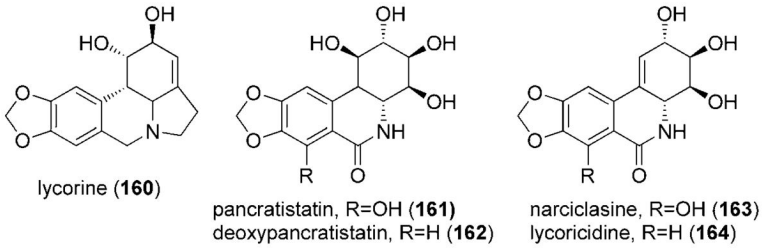
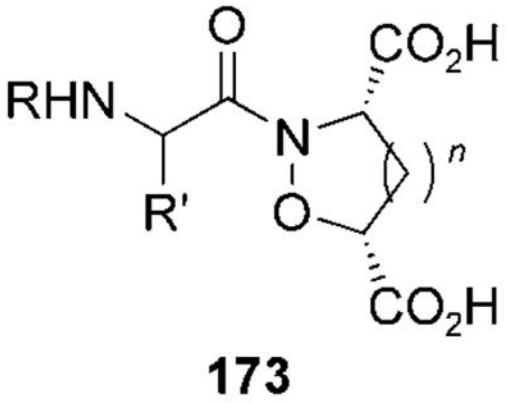


Figure 11.
Structures of *amaryllidacea* alkaloids.



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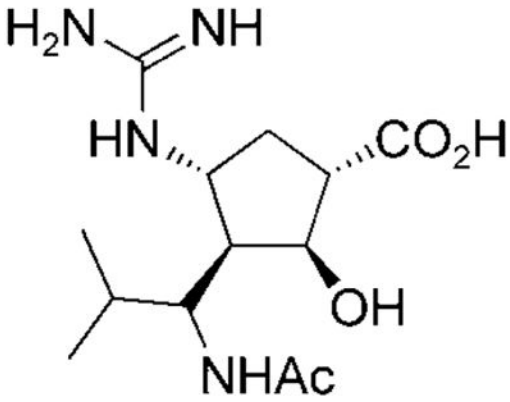
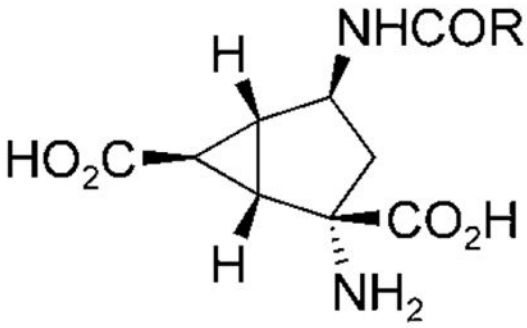


BCX-1812 (**174**)



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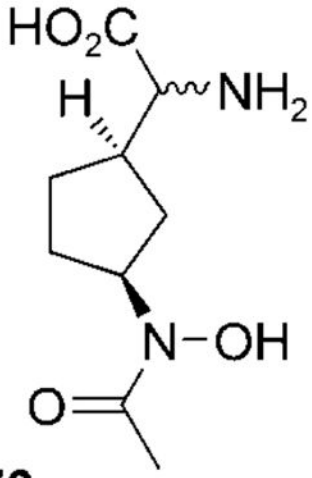


176

Figure 12.
Representative amino acid derivatives and related structures.

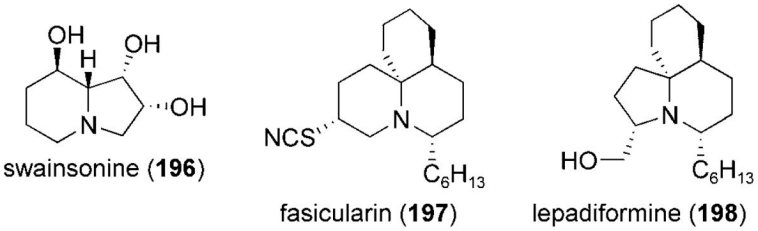


Figure 13.
Representative indolidizine and pyrrolidizine alkaloids.

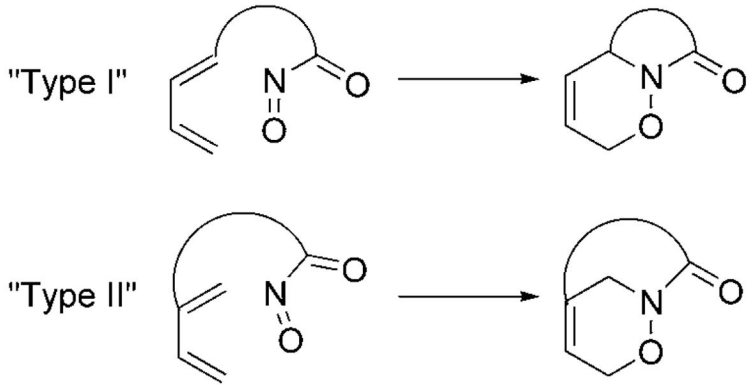
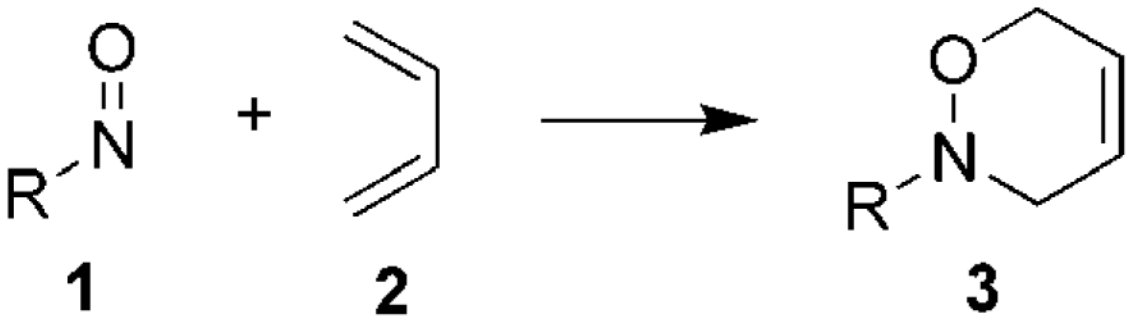
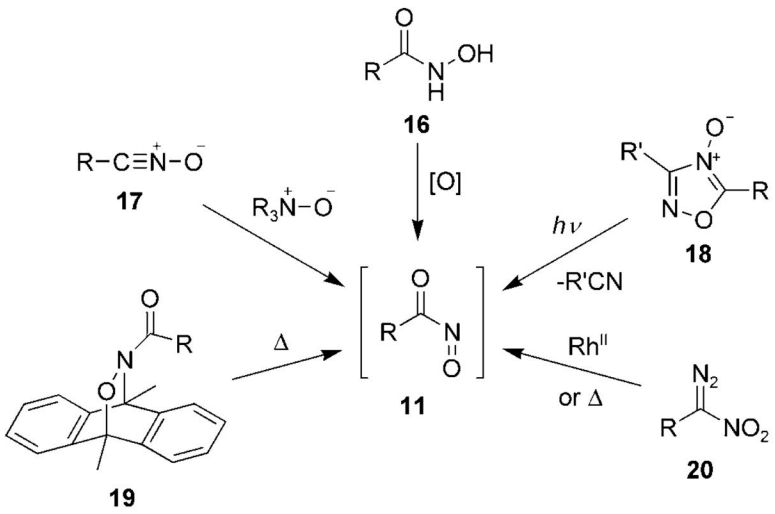


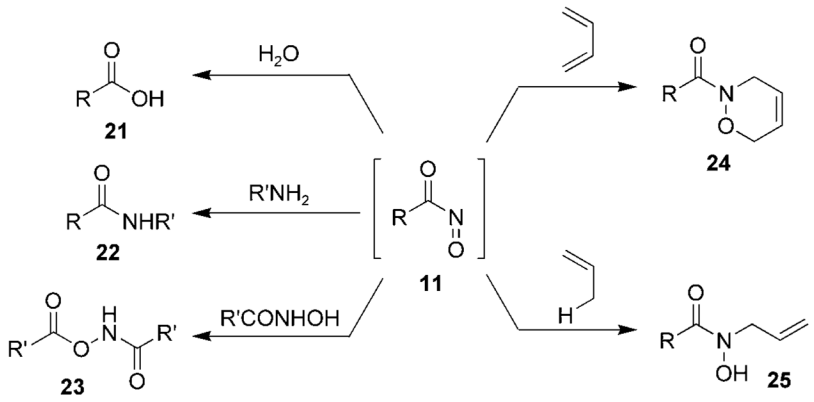
Figure 14.
Type I and type II intramolecular nitrosocarbonyl HDA reactions.



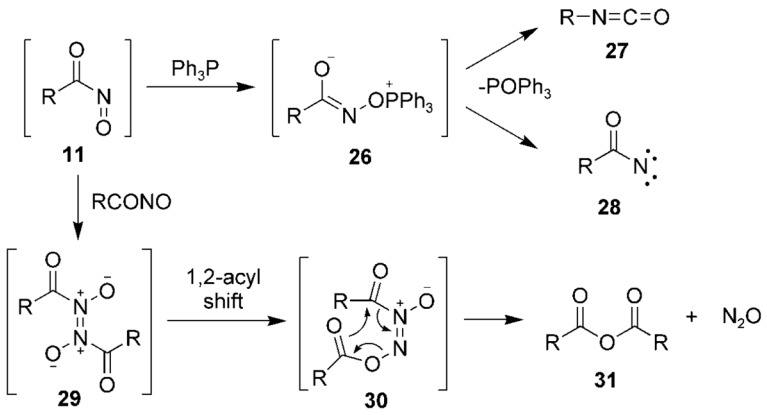
Scheme 1.
The nitroso hetero-Diels–Alder reaction.



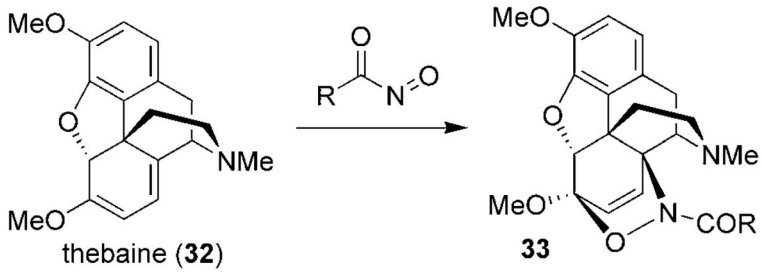
Scheme 2.
Common synthetic routes to nitrosocarbonyl species.



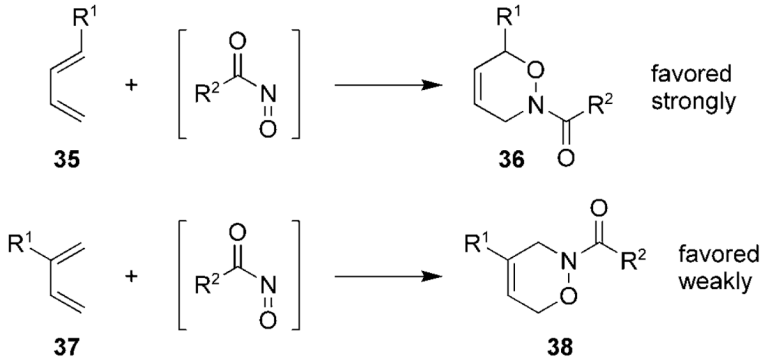
Scheme 3.
Reactions of nitrosocarbonyl compounds.



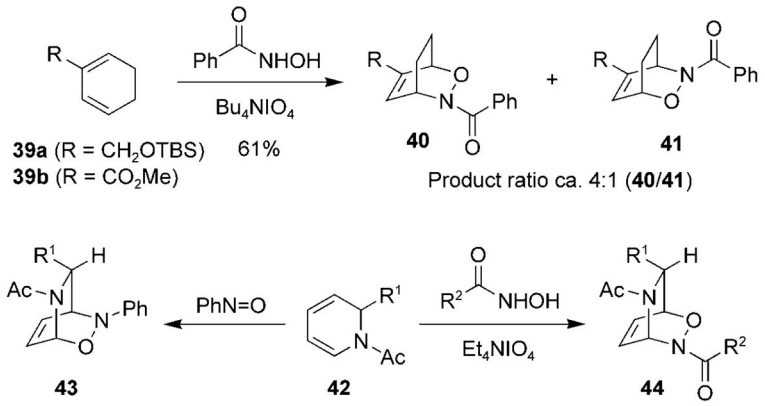
Scheme 4.
Other reactions of nitrosocarbonyl compounds.



Scheme 5.
The cycloaddition reported by Kirby and Sweeny.[31]

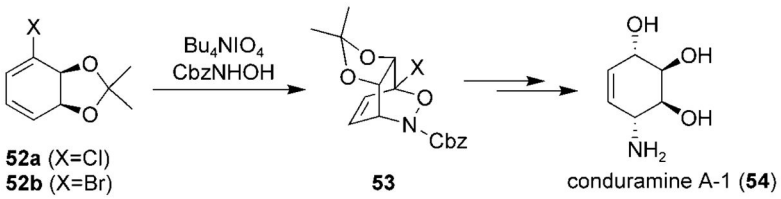


Scheme 6.
General selectivity observed for unsymmetrical dienes.



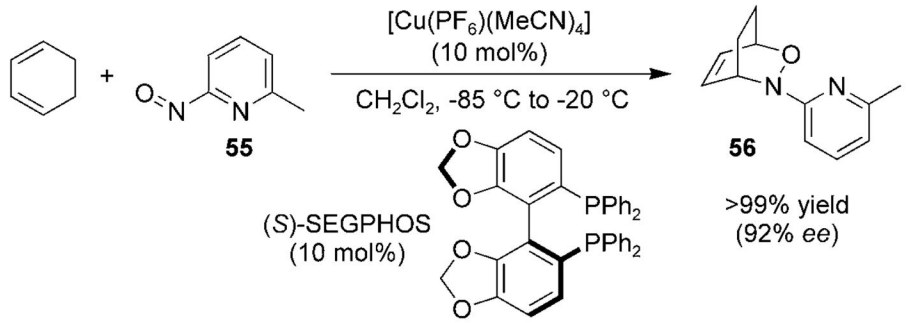
Scheme 7.

Examples of regioselectivity in nitrosocarbonyl HDA reactions. TBS =*tert*-butyldimethylsilyl.

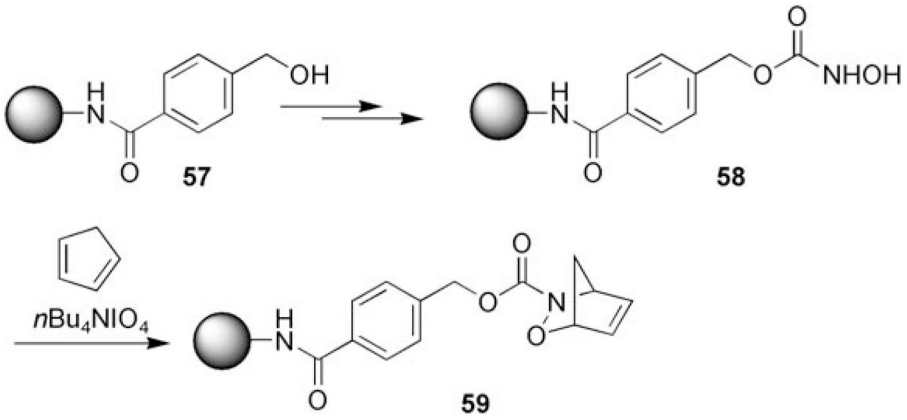


Scheme 8.

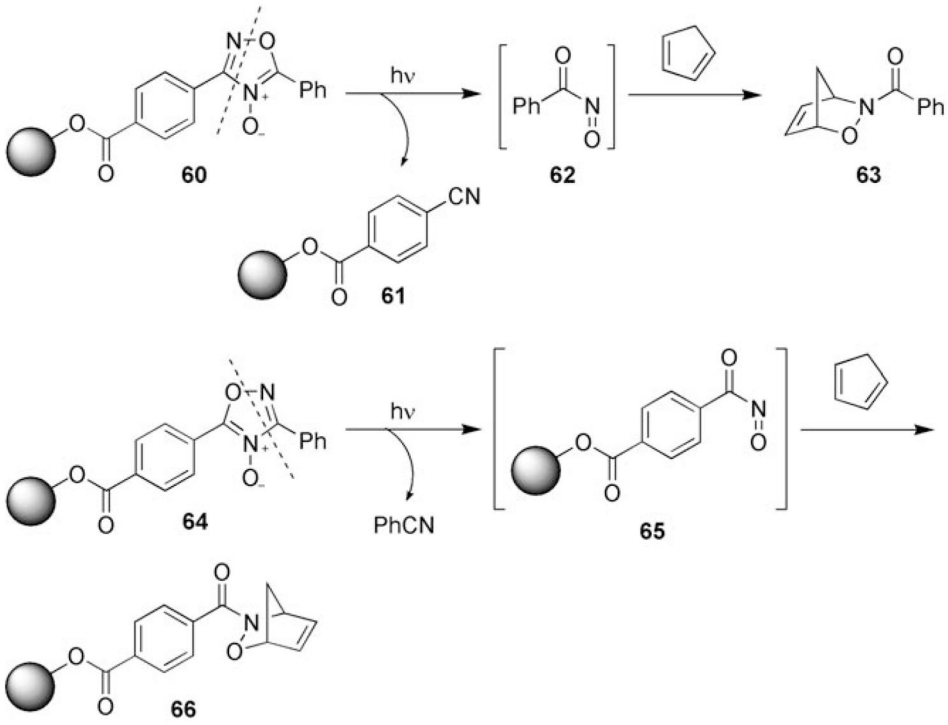
Stereoselective nitrosocarbonyl HDA reaction in the presence of a chiral diene. Cbz =benzyloxycarbonyl.



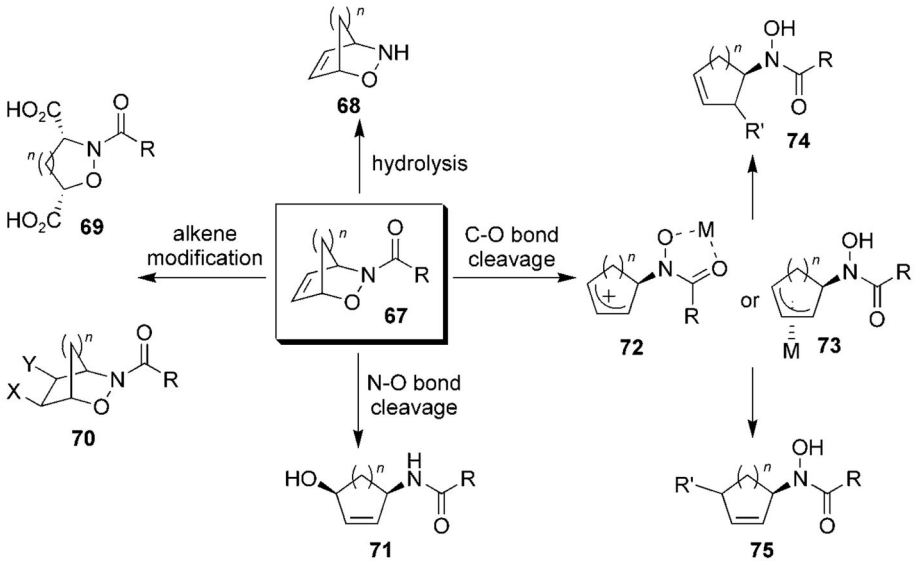
Scheme 9.
Catalytic asymmetric pyridylnitroso cycloaddition.



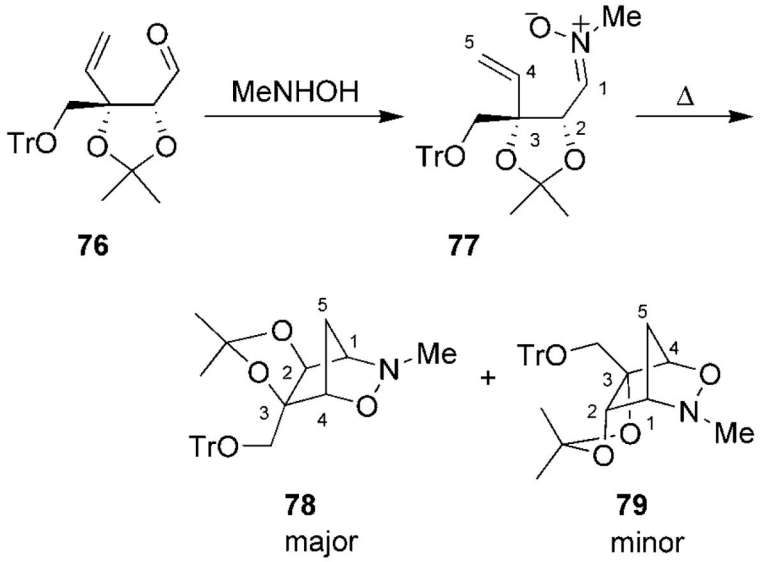
Scheme 10.
Nitrosocarbonyl HDA reaction on a solid phase.



Scheme 11.
Another nitrosocarbonyl HDA reaction on a solid phase.

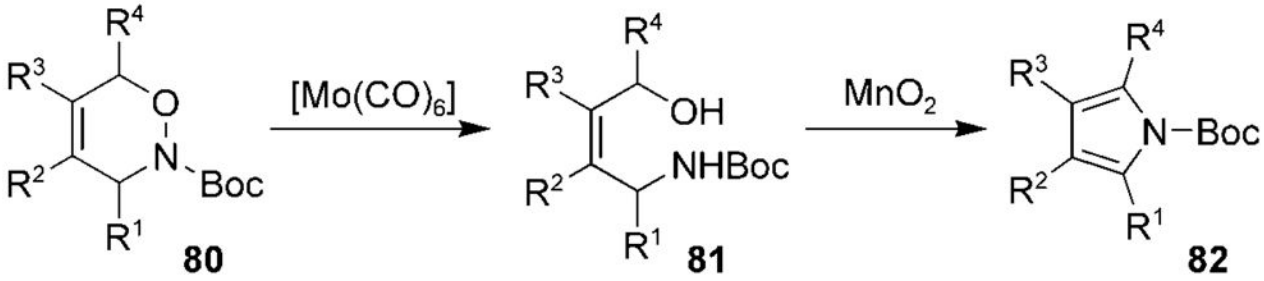


Scheme 12.
Modification of bicyclic 3,6-dihydro-1,2-oxazines.



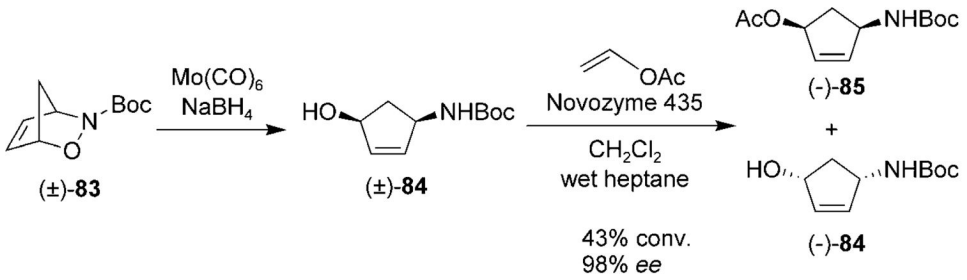
Scheme 13.

[3+2] Cycloaddition for the synthesis of 3,6-dihydro-1,2-oxazines. Tr =triphenylmethyl.

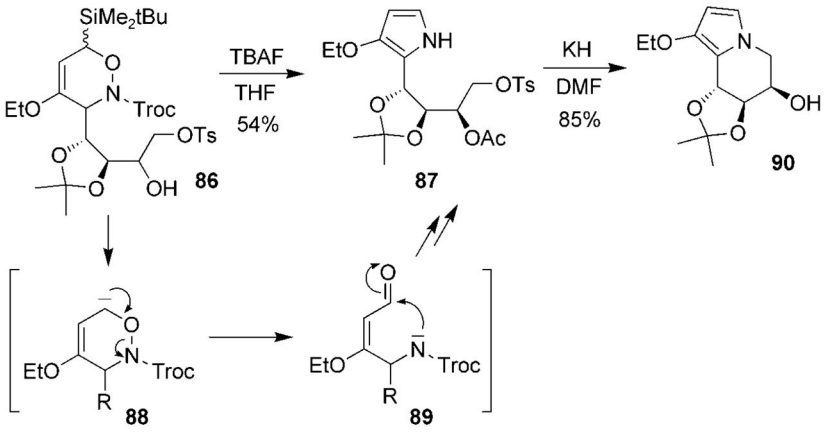


Scheme 14.

Pyrrole synthesis by reductive cleavage of a N–O bond. Boc =*tert*-butoxycarbonyl.

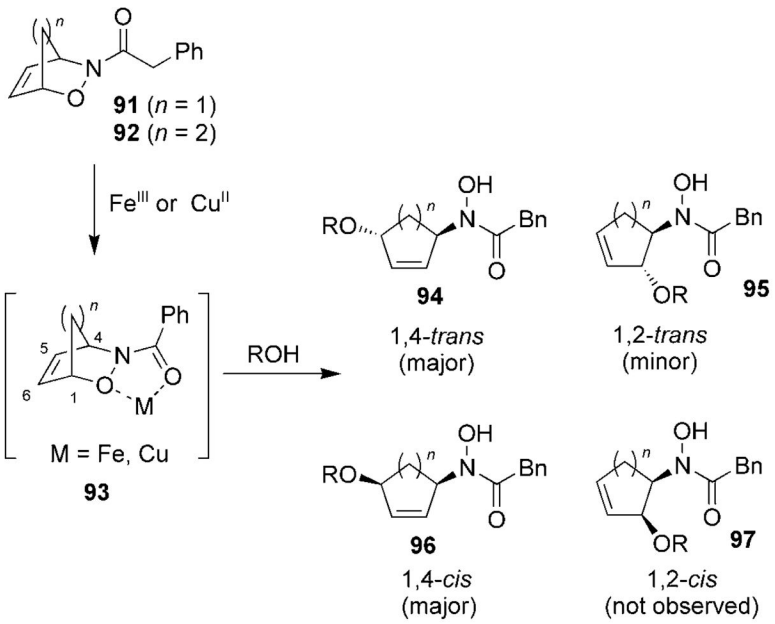


Scheme 15.
Enzymatic resolution of a racemic alcohol.



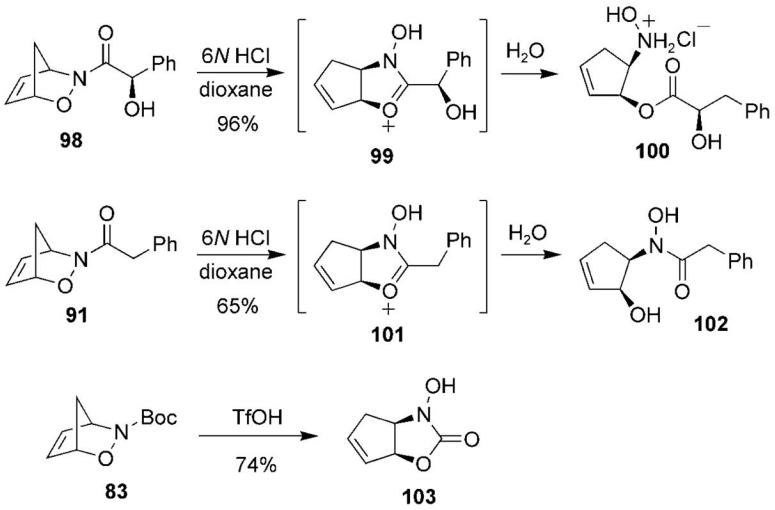
Scheme 16.

An alternative method for cleavage of the N–O bond. Troc =trichloroethoxycarbonyl, Ts =toluene-4-sulfonyl.



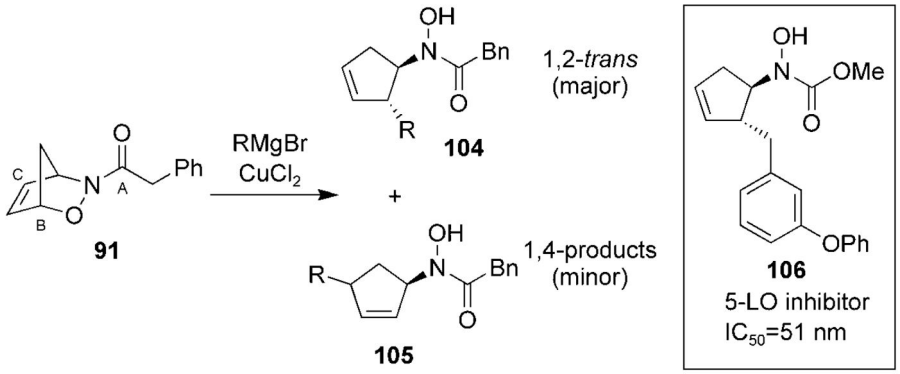
Scheme 17.

Lewis acid mediated cleavage of a C–O bond. Bn =benzyl.

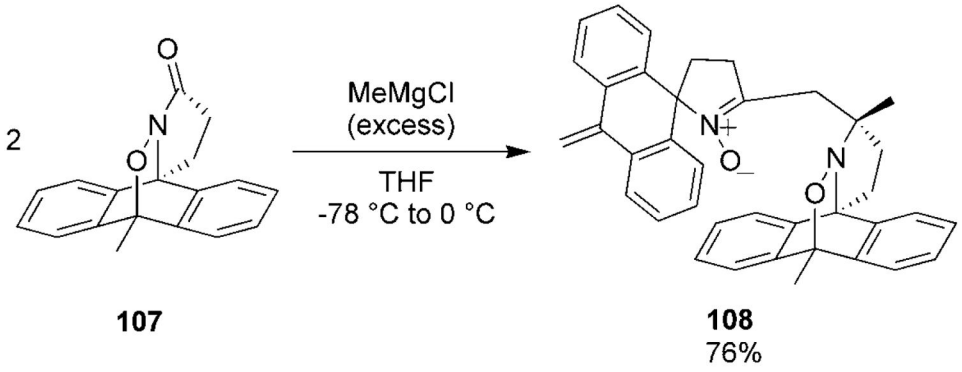


Scheme 18.

Brønsted acid mediated cleavage of a C–O bond. TfOH = trifluoromethanesulfonic acid.

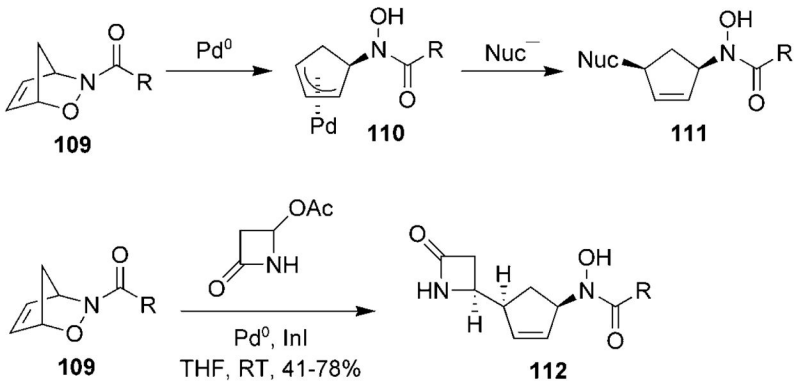


Scheme 19.
Cleavage of a C–O bond with Grignard reagents.

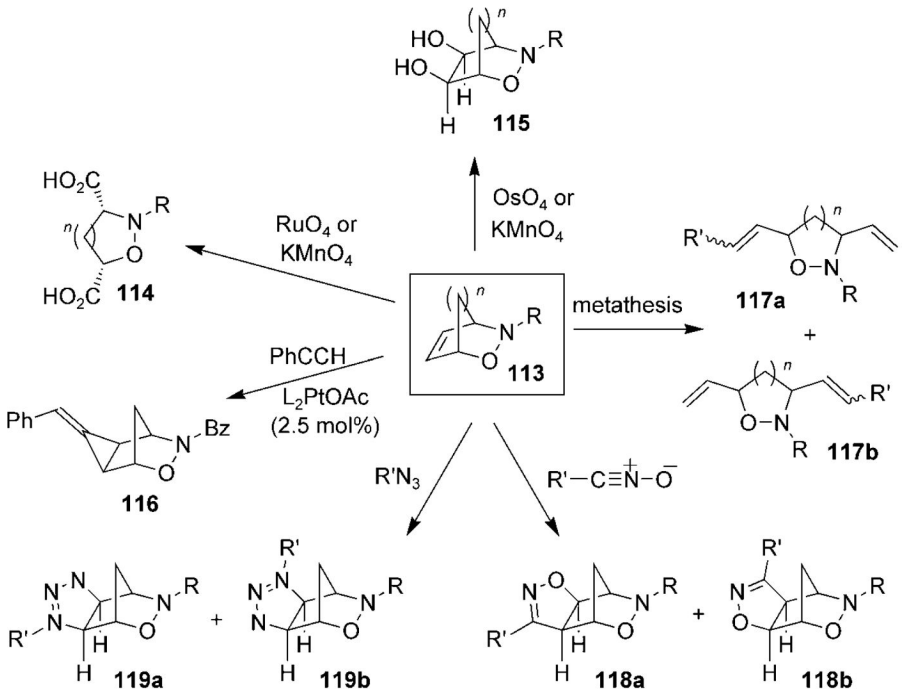


107 **108** 76%

Scheme 20.
An unusual reaction with a Grignard reagent.

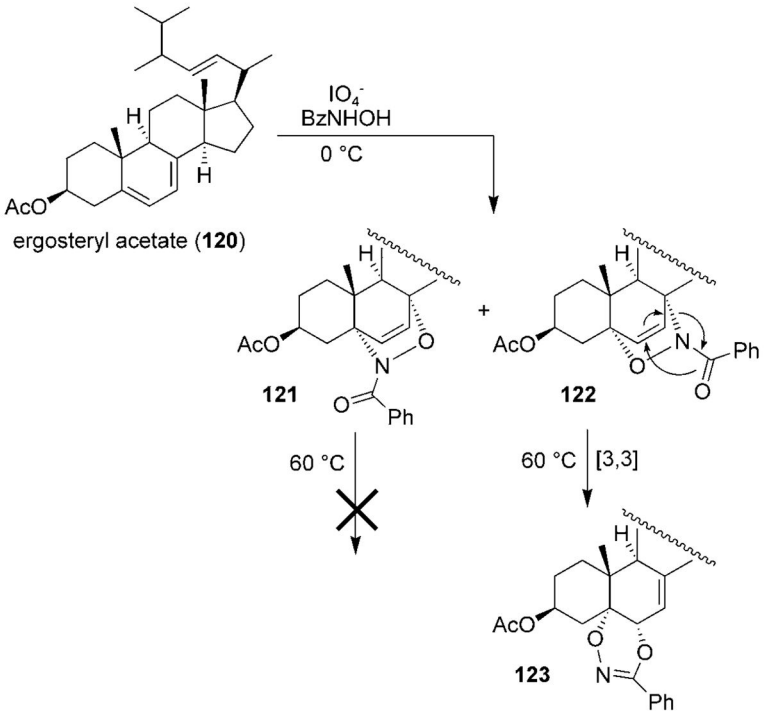


Scheme 21.
Pd/In-mediated cleavage of a C–O bond.

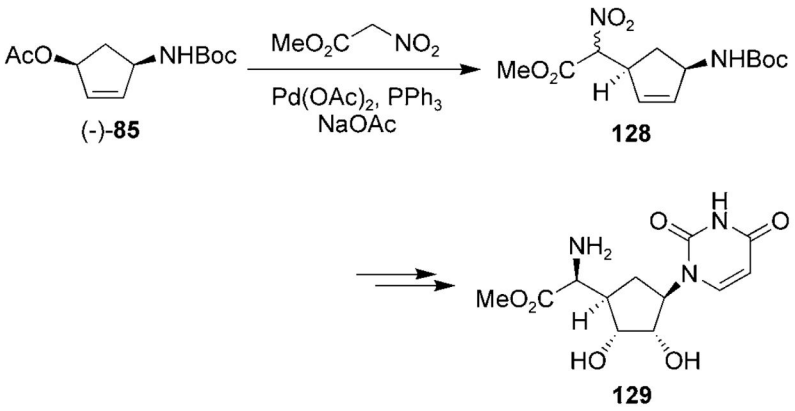


Scheme 22.

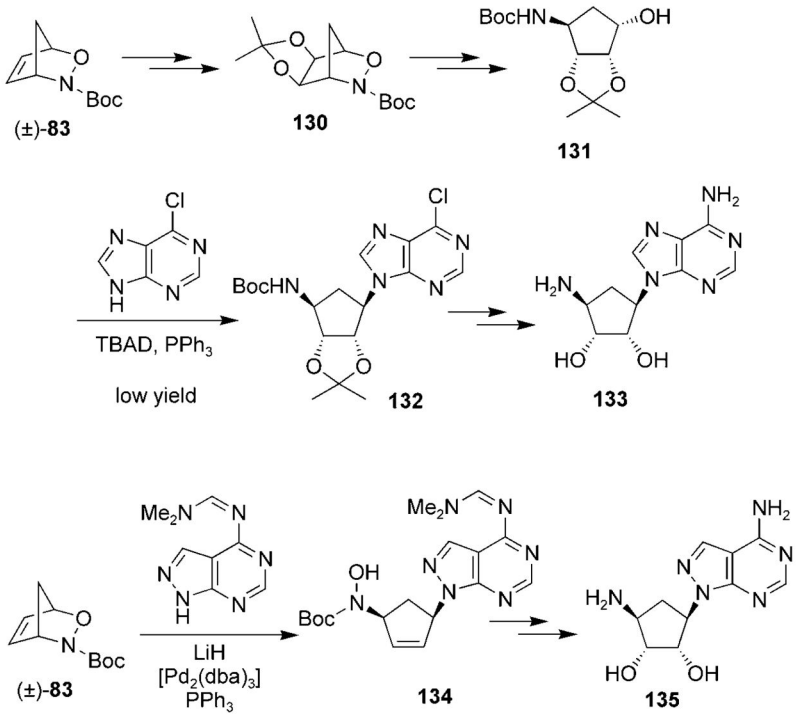
Examples of alkene modification of bicyclic cycloadducts. Bz =benzoyl.



Scheme 23.
[3,3] Rearrangment of an ergosteryl cycloadduct.

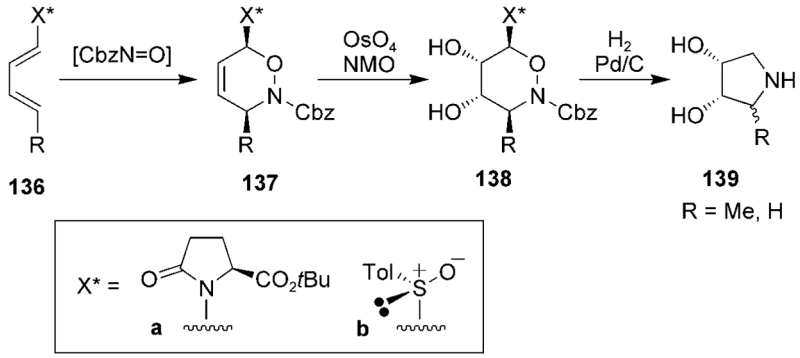


Scheme 24.
Synthesis of the carbocyclic uracil polyoxcin C.



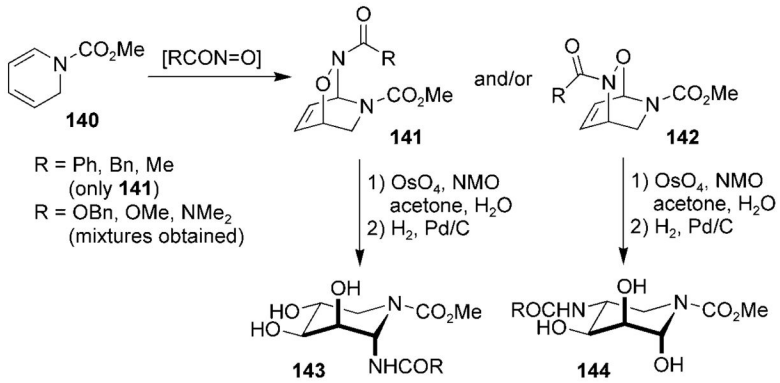
Scheme 25.

Synthesis of azacarbocyclic nucleoside analogues., dba = *trans*,*trans*-dibenzylideneacetone, TBAD =di-*tert*-butyl azodicarboxylate.



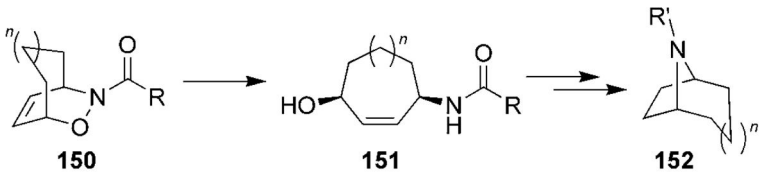
Scheme 26.

Synthetic route to pyrrolidines. NMO =4-methylmorpholine *N*-oxide, Tol =tolyl.

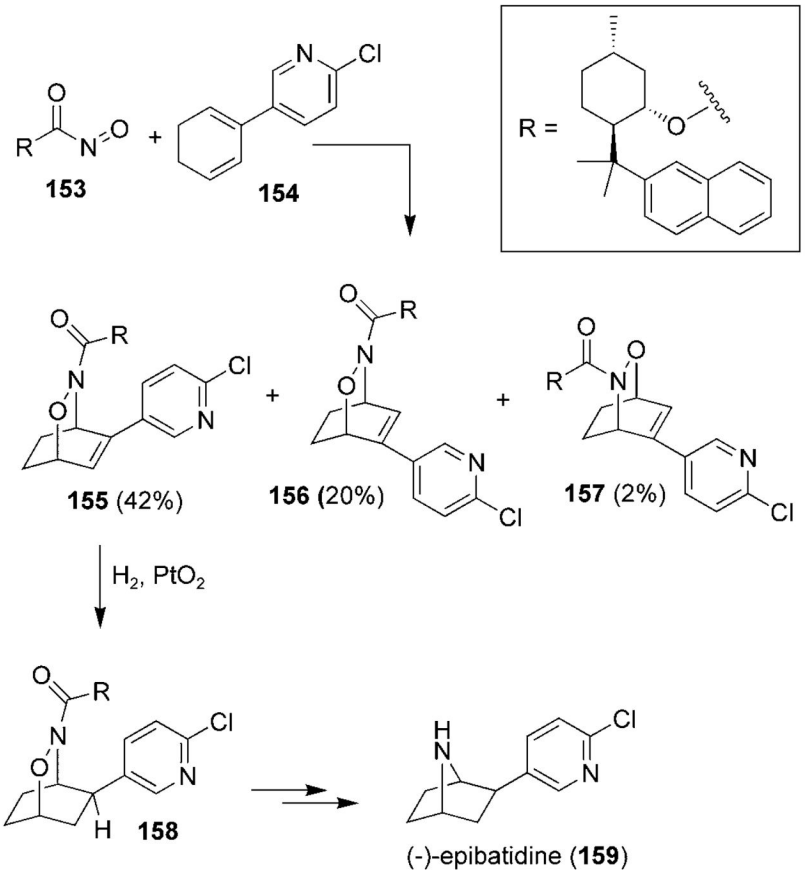


Scheme 27.

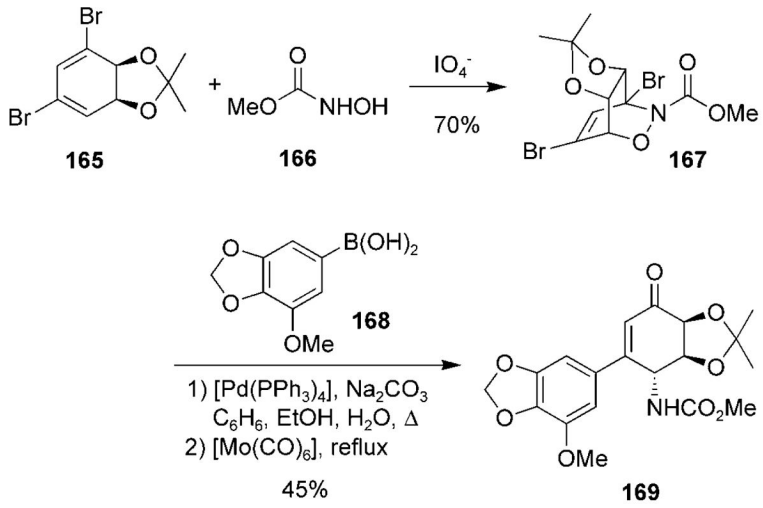
Route to aza sugars from 1,2-dihydropyridines.



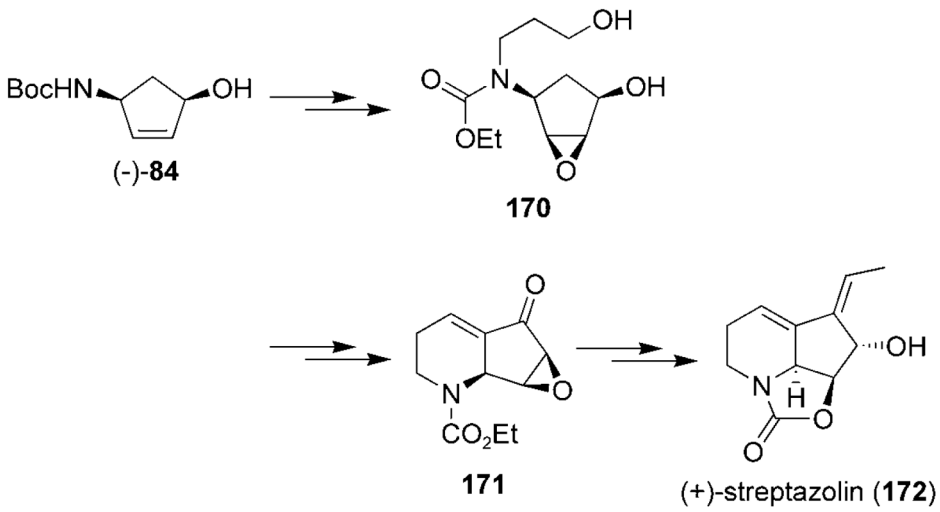
Scheme 28.
General synthetic route to tropane alkaloids.



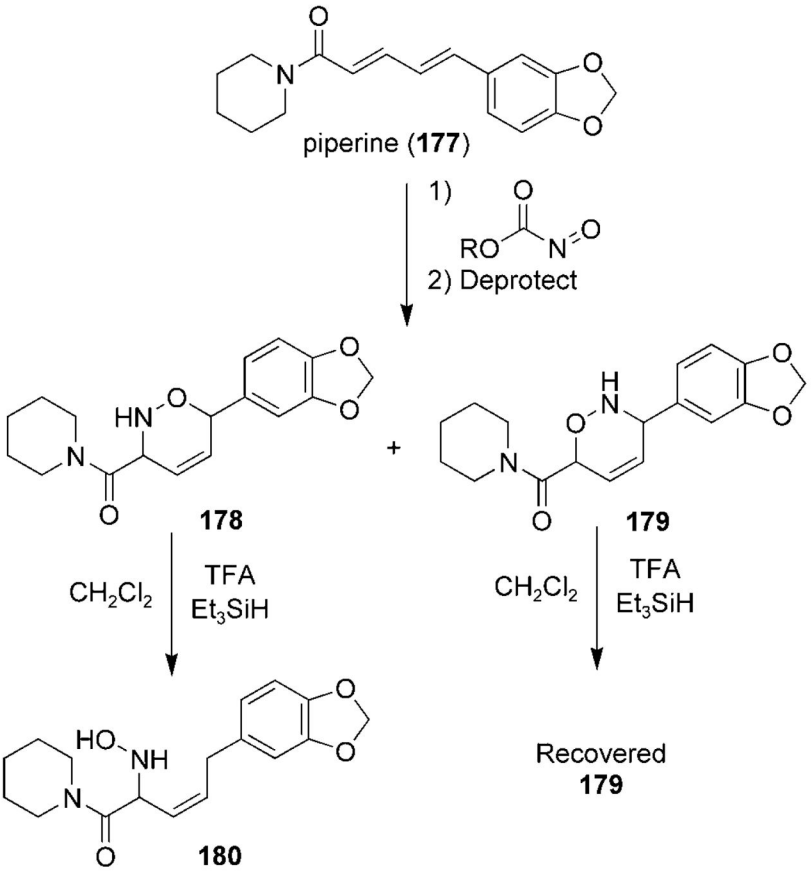
Scheme 29.
Total synthesis of (−)-epibatidine.



Scheme 30.
Synthetic route to narciclasine.

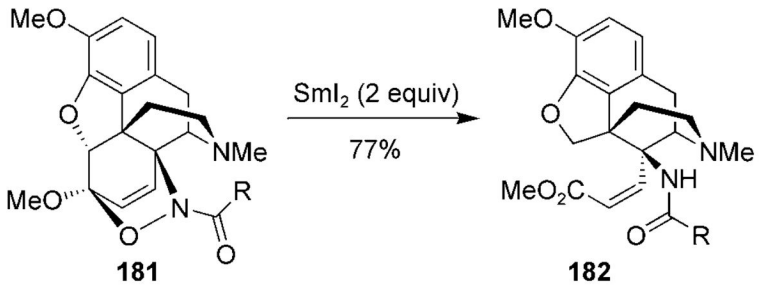


Scheme 31.
Synthetic route to (+)-streptazolin.

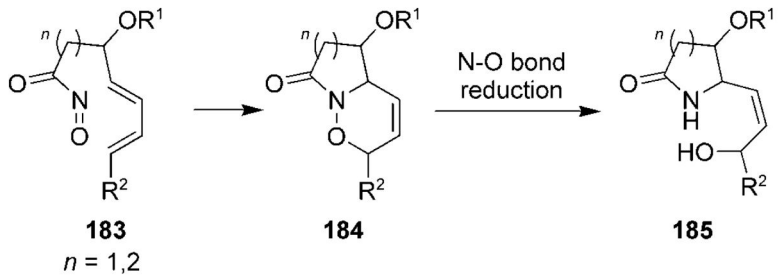


Scheme 32.

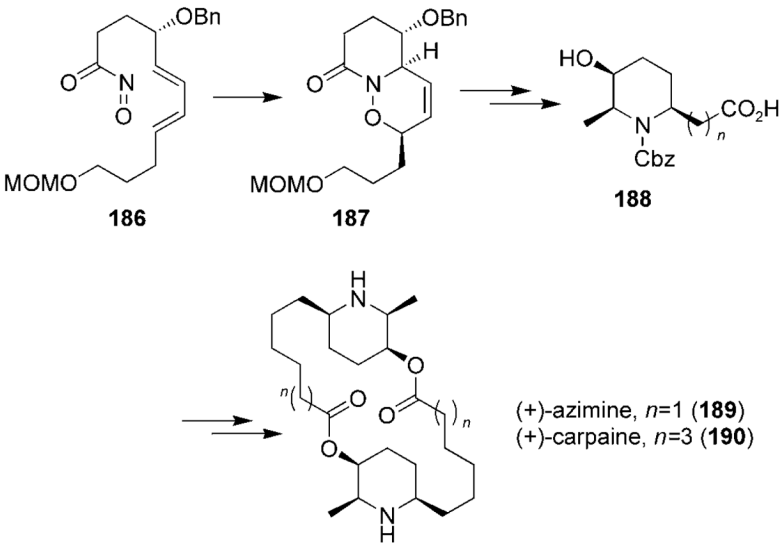
A nitroso-Diels–Alder reaction with piperine (**177**). TFA = trifluoroacetic acid.



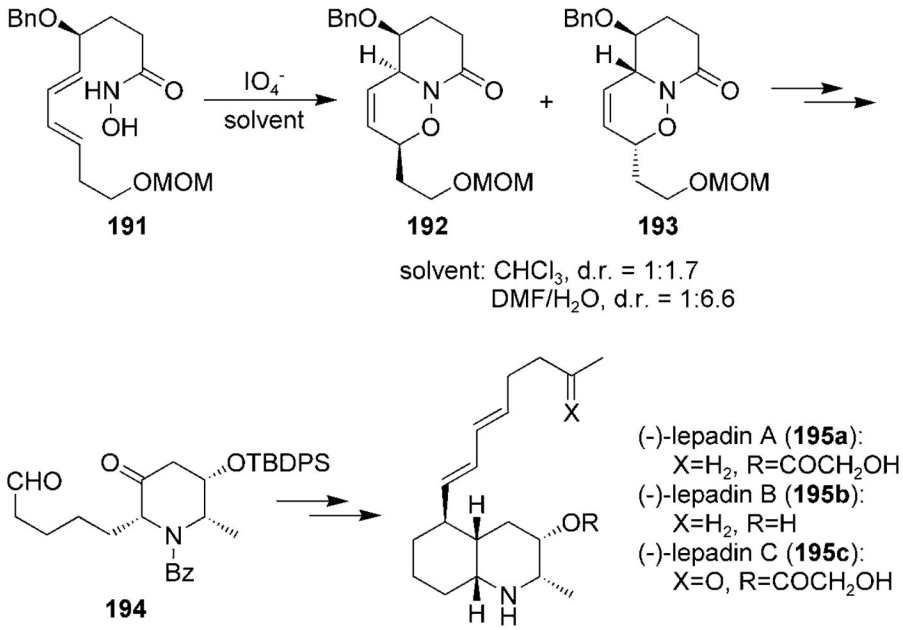
Scheme 33.
Thebaine analogues from an unexpected ring cleavage.



Scheme 34.
General route to monocyclic alkaloids.

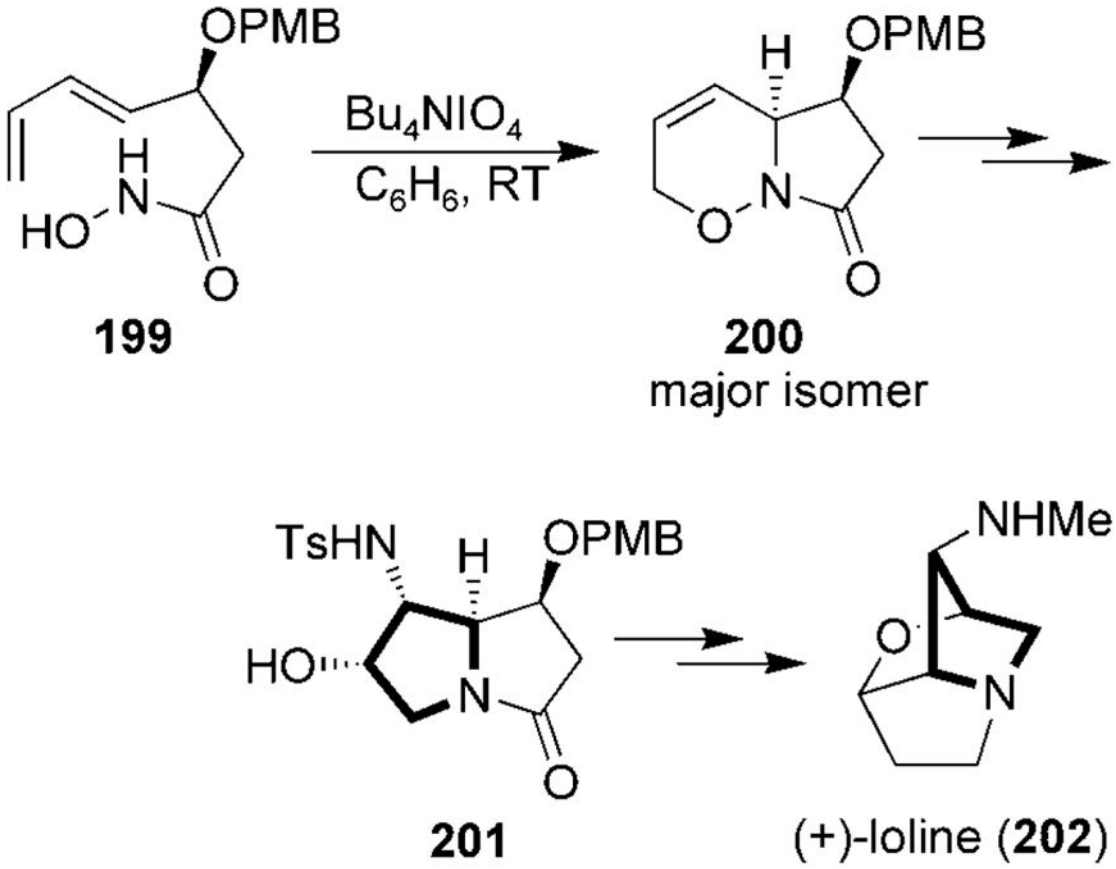


Scheme 35.
Synthesis of (+)-azimine and (+)-carpaine.

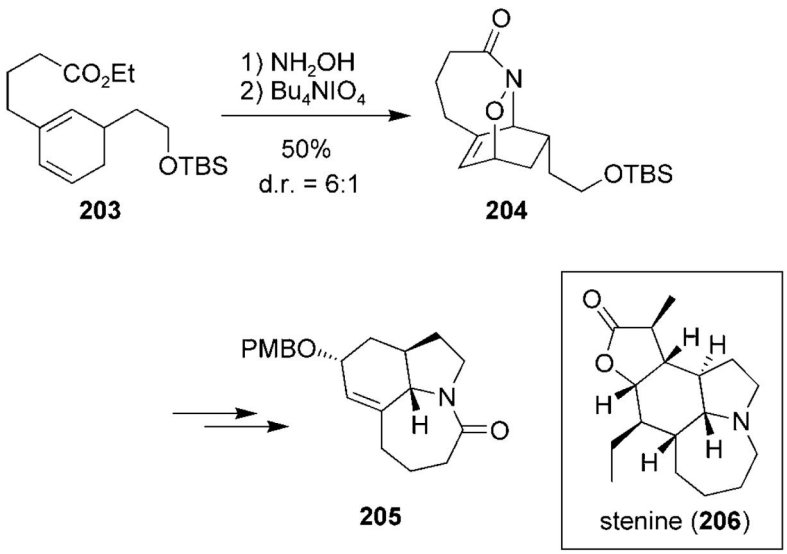


Scheme 36.

Total synthesis of (−)-lepadins A, B, and C. MOM = methoxymethyl, TBDPS =*tert*-butyldiphenylsilyl.



Scheme 37.
Total synthesis of (+)-loline. PMB =*para*-methoxybenzyl.



Scheme 38.

A recent example of a type II intramolecular nitrosocarbonyl HDA reaction.