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1,2-OXAZINES AND THEIR *N*-OXIDES IN SYNTHESIS

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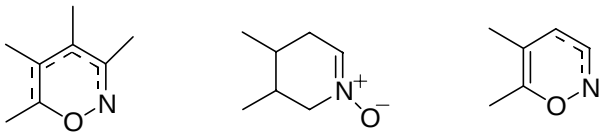
Abstract - The potential of 1,2-oxazines towards diverse transformations, mainly of synthetic utility, is presented using selected examples.

CONTENTS :

A. INTRODUCTION

1,2-Oxazines **A** and their *N*-oxides **B** (Cyclic nitronates) (Figure 1) have a sound presence in the literature though they fall behind their 1,3- and 1,4-counterparts.



A **B** **C**

Figure 1

Furthermore, the partially saturated members **A**, **B** outweigh by far their aromatic congeners **C**. Pertinent to the diverse chemistry of **A** or **B** is the facile cleavage of the ring *N-O* bond.[1,2] It is this feature that renders **A-C** potentially useful precursors to various molecules of interesting chemistry, high structural complexity or diverse biological properties, among them natural or non-natural products.[3-5]

Aspects of the chemistry of **A** or **B** are included in the elegant reviews of Kirby[1] and Gilchrist[2] with emphasis on their constituent precursors nitroso dienophiles. 1,2-Oxazines of type **A** have also been reported in the interesting reviews by Streith-Defoin[6] and Waldmann[7] on the synthetic applications of Hetero-Diels-Alder (HD-A) reaction and its asymmetric variant, respectively.

Reviews focussed on the potential of **A** or **B** to natural product synthesis have appeared recently. Thus, the chemistry of **B** as 1,3-dipoles through a [4+2]/[3+2] tandem cycloaddition strategy or the use of **A** to the synthesis of various alkaloids has been covered by Denmark[4b] or Defoin[6,8] respectively. **C** is essentially still unexplored.

However, there has not yet been an account fully dedicated to the diverse chemistry of this **A**, **B** or **C** heterocycle. It is, therefore, the purpose of this review article to highlight the dominant features of the chemistry of **A-C** by representative examples through a simple reaction classification.

B. DIHYDRO- and TETRAHYDRO-1,2-OXAZINES

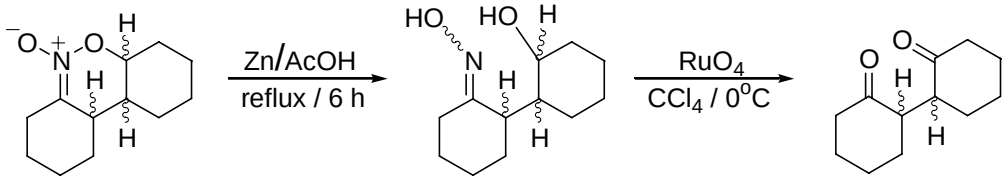
1. Ring Cleavage-Transformations

1.1 Reductive

This has been the most commonly reported reaction of 1,2-oxazine structure **A** or its N-oxide **B**. The key step is ring opening by the facile N-O bond cleavage.[2] Ring opening may be a straightforward reduction,

followed by other reactions such as hydrolysis, oxidation, etc or a rearrangement to other ring structures, mainly pyrroles or its derivatives. The reactions are generally subject to regio- and stereoselectivity control.

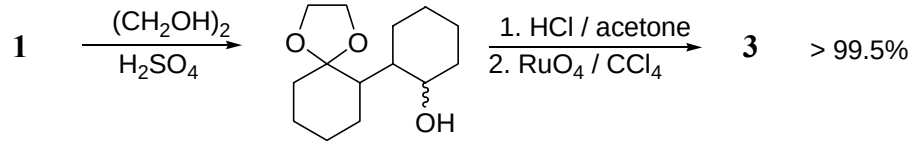
1,2-Oxazine *N*-oxides (**1**) give the diones (**3**) through a reduction-oxidation protocol (Scheme 1).[9-11]



1 **2** **3**

Scheme 1

Substantial epimerization in **3** led to an alternative route, through the acetal (**4**) (Scheme 2).

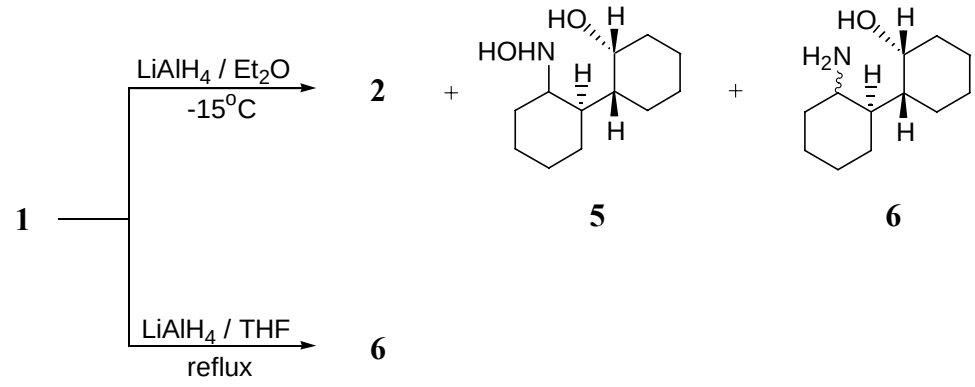


4

Scheme 2

Mild acid hydrolysis of **4** followed immediately by RuO_4 oxidation affords the racemic dione (**3**) exclusively.

Reduction of cyclic nitronates (**1**) has also been effected by a variety of reagents. Thus, HI reduction to oximes[12] and H_2/Pt reduction to amines[13] are known. Reduction with $LiAlH_4$ leads to various products depending on the reaction conditions (Scheme 3).

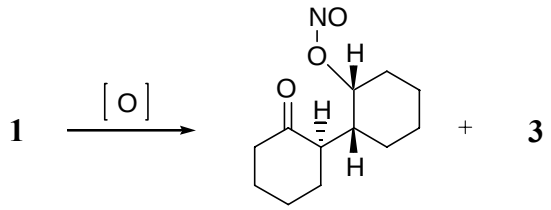


5 **6**

Scheme 3

The use of $TiCl_3$ as McMurry's reduction variant of Nef reaction simply deoxygenates **1.**[14]

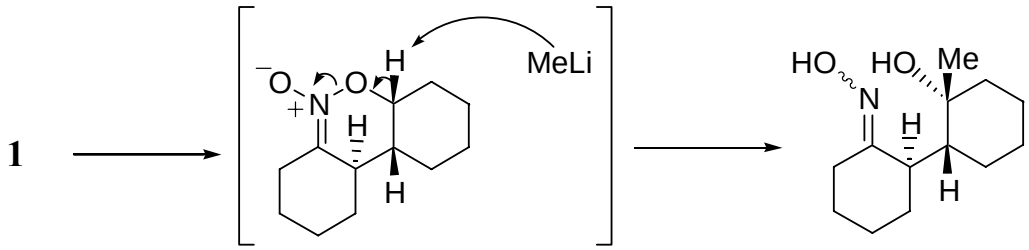
The oxidative version of Nef reaction has found many applications and can be effected by reagents such as O_3,[15] $KMnO_4$,[16] ^tBuOOH,[17] H_2O_2,[18] MoO_5[19] and iodoxybenzoic acid.[20] Inherent in the oxidation of cyclic nitronates is the fate of *N*-atom. Thus, direct oxidation of **1** leads to **3** and **7**, the latter as the major product (Scheme 4).[10]



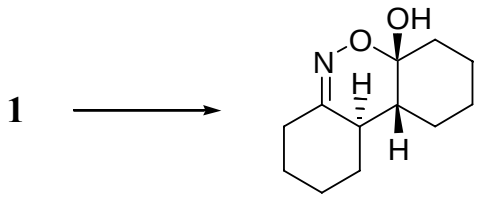
7

Scheme 4

Internal redox reaction of cyclic nitronates has been reported.[10] **1** with K^tOBu gives the hemiacetal (**8**) . The oxime ketone intermediate (**10**) has been trapped with MeLi, the latter acting as base and nucleophile, through **9** (Scheme 5).



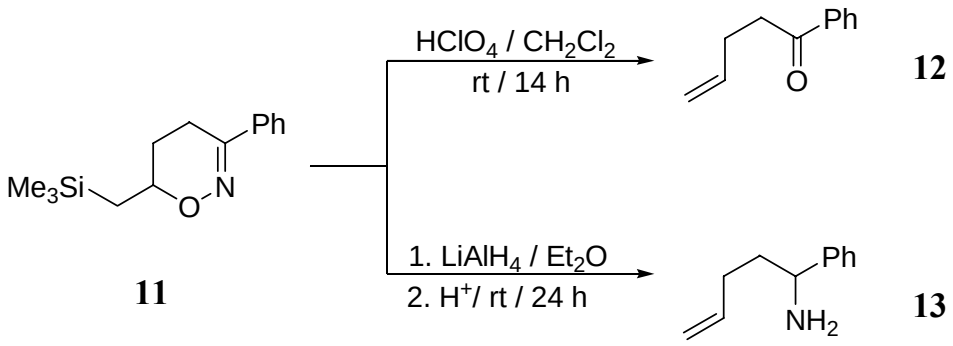
9 **10**



8

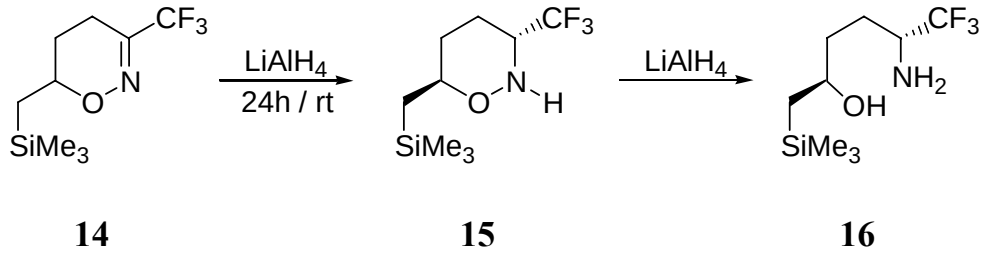
Scheme 5

Silylmethyl substituted 1,2-oxazines (**11**) can suffer ring cleavage through two alternative modes (Scheme 6).[21] Hydrolysis with catalytic amount of $HClO_4$ leads to the unsaturated ketone (**12**) while $LiAlH_4$ reduction gives the unsaturated amine (**13**). In both cases an acid-induced trimethylsilanol elimination generates the alkenic unit (Peterson reaction).



Scheme 6

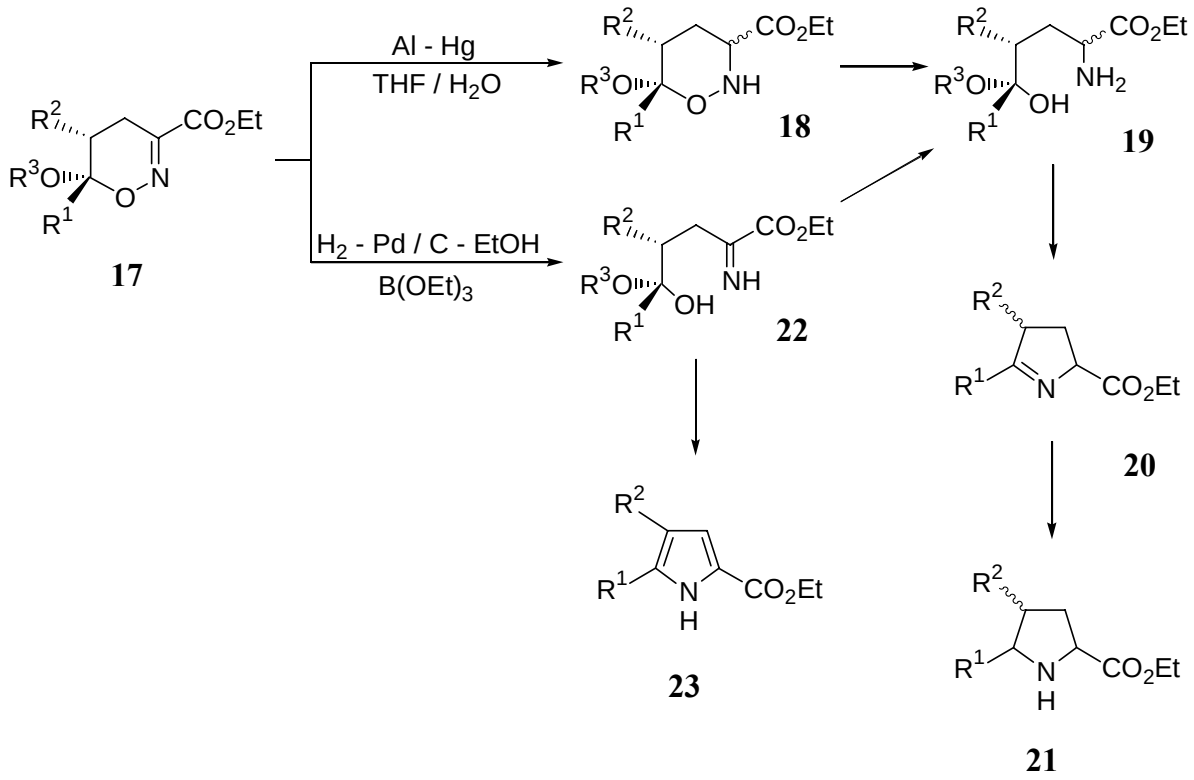
3-Trifluoromethyl substituted (**14**) counterparts of **11**, upon $LiAlH_4$ reduction lead to the amino alcohol (**16**) with high stereoselectivity (Scheme 7).[22]



Scheme 7

The silane (**14**) does not undergo acid-induced Peterson fragmentation.[21] The completely saturated 1,2-oxazine (**15)** has been isolated along with the silane (**16)** when "aged" $LiAH_4$ was used.

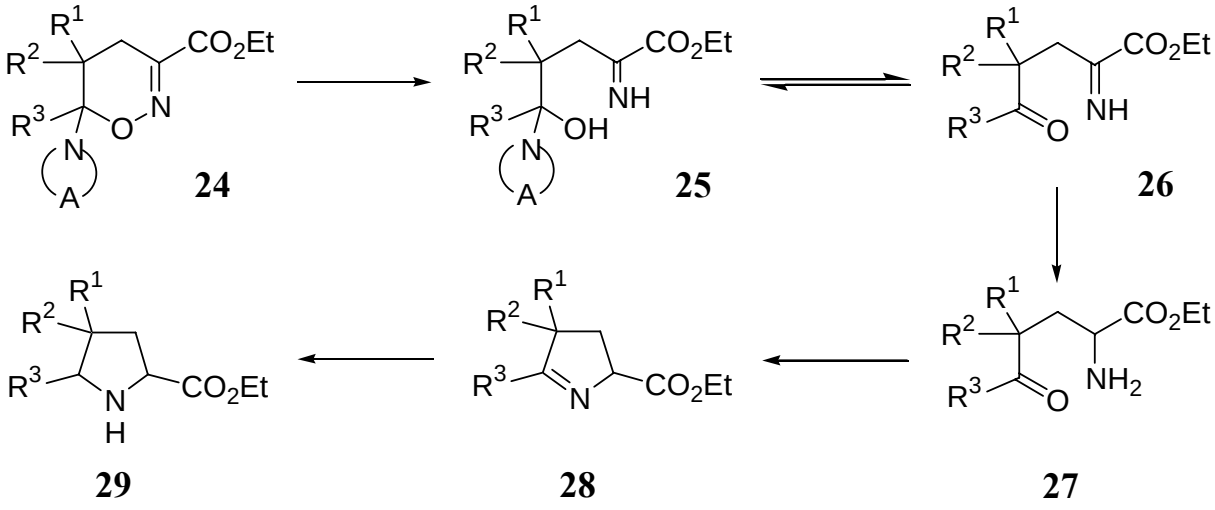
Ring *N-O* bond reductive cleavage of 1,2-oxazine esters (**17**) has been reported (Scheme 8).[23]



Scheme 8

5-Membered carbo(hetero)cycles fused to **17** have also been similarly reduced to the corresponding amino acid esters.[13]

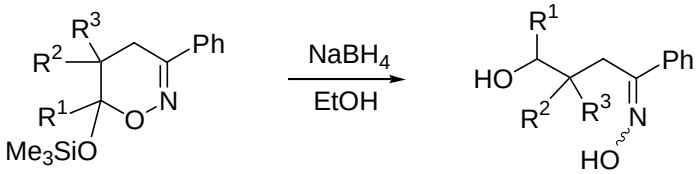
Reduction of 3-carboxylates of 4*H*-1,2-oxazines (**24**) to lipophilic proline analogues (**29**), similar to **21**, has been reported (Scheme 9).[24]



Scheme 9

The sequence of reduction steps is analogous to that in Scheme 8.

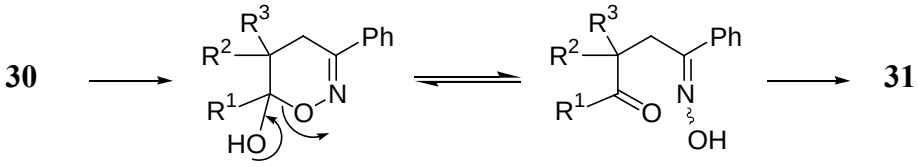
Silyloxy substituted 1,2-oxazines (**30**) are reduced with excess of $NaBH_4$/EtOH to 4-hydroxy ketoximes (**31**) (Scheme 10).[25]



30 **31**

Scheme 10

3-Trifluoromethyl substituted derivatives of **30** are similarly reduced to the corresponding **31**.[22] Under the reaction conditions, 1,2-oxazines (**30**) appear to be stable. It has been proposed that desilylation of **30** to the 6-hydroxy derivative (**32**) is the first step of the reduction (Scheme 11). This is in equilibrium with its acyclic carbonyl tautomer (**33**) which is intercepted by the reducing agent to give **31**.[26]

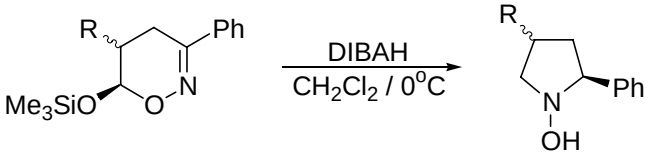


32 **33**

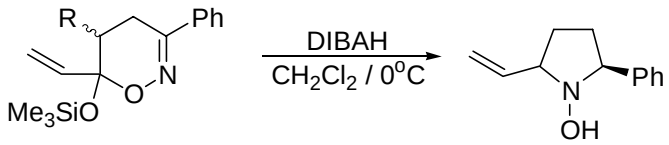
Scheme 11

1,2-Oxazines without 6-substitution[27] give mixtures of products due to concomitant reduction of the ester function.[28]

Reduction of **30** or **35**, under aprotic conditions, give *N*-hydroxypyrrolidines (**34**) or (**36**) as a mixture of diastereomers (Scheme 12).[25]



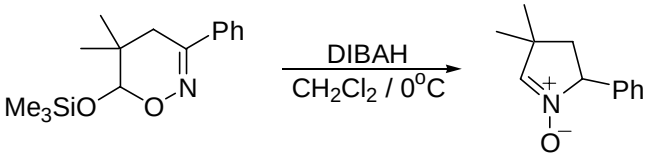
30 **34**



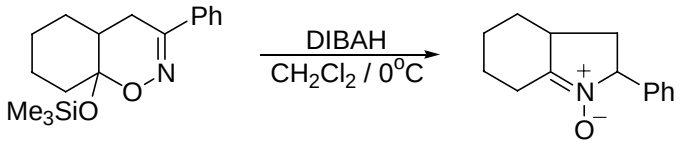
35 **36**

Scheme 12

However, the silyloxy substituted 1,2-oxazines (**37**) and (**39**), under similar conditions, furnish the nitrones (**38**) and (**40**) respectively (Scheme 13).[25]



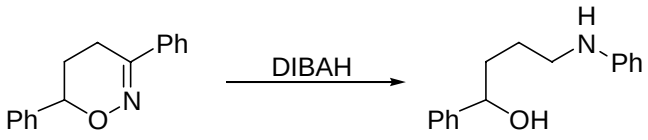
37 **38**



39 **40**

Scheme 13

Interestingly reduction of **41** leads to the 1,4-amino alcohol (**42**) (Scheme 14).

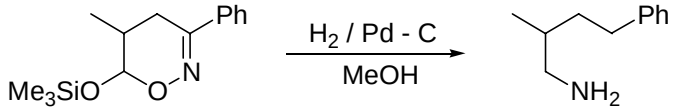


41 **42**

Scheme 14

It has been suggested that the substitution pattern of **41** favours a reductive Beckmann rearrangement. The latter involves initial complexation of Lewis acid DIBAH at *O* atom, followed by rearrangement and final reduction to **42**.[29] A similar rearrangement is assumed in the formation of *N*-hydroxypyrrolidines.[30] The intermediate DIBAH complex rearranges to the nitrone, a process known to occur with 6-silyloxy- or 6-alkoxy substituted 1,2-oxazines by proton acids.[31]

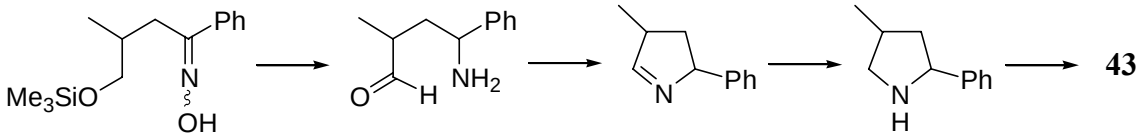
Catalytic hydrogenolysis of **30**, on the other hand, leads to the amine **(40)** (Scheme 15).[25]



30 **43**

Scheme 15

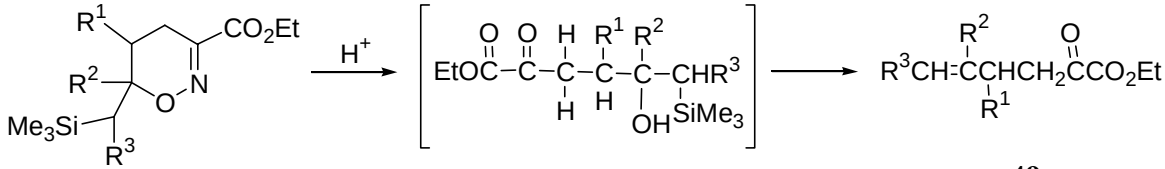
The surprising *N* transposition, at first glance, is explained by the reduction of the oxime ether (**44**) to the amino aldehyde (**45**) and *via* the pyrroline (**46**) and pyrrolidine (**47**) to **43** (Scheme 16).



44 **45** **46** **47**

Scheme 16

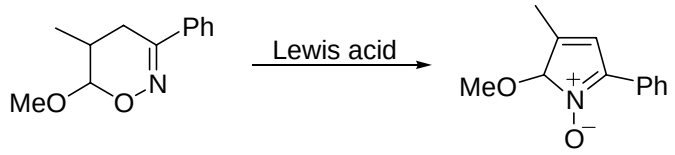
Acid hydrolysis of esters (**48**) provides access to *δ,ε*-unsaturated *α*-keto carboxylic acid esters (**49**) (Scheme 17).[32]



48 **49**

Scheme 17

Lewis acid hydrolysis of 6-alkoxy substituted 1,2-oxazines (**50**) leads to the nitrone (**51**) (Scheme 18).[33]

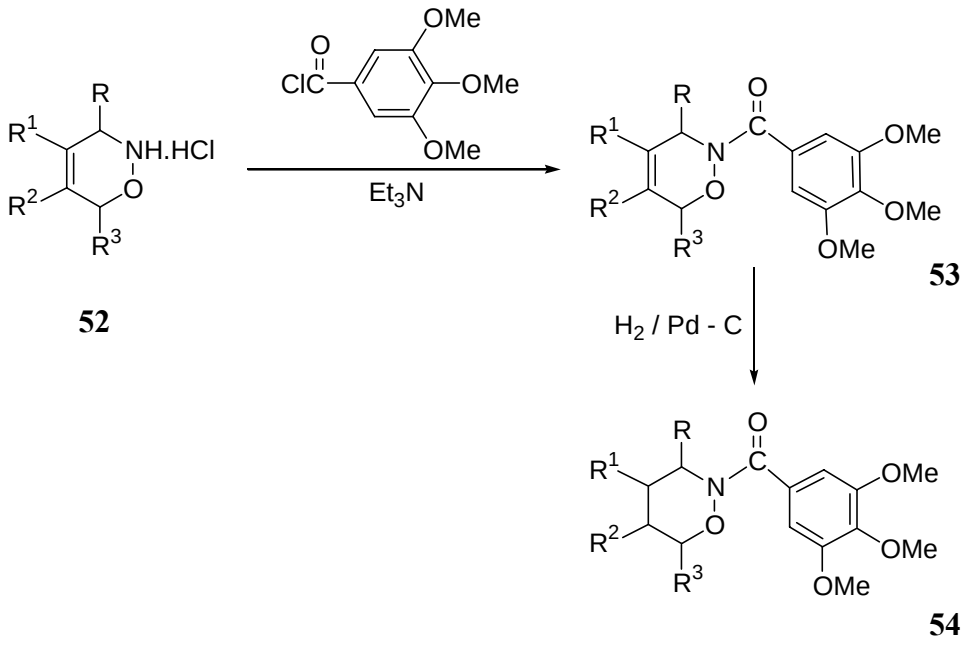


50 **51**

Scheme 18

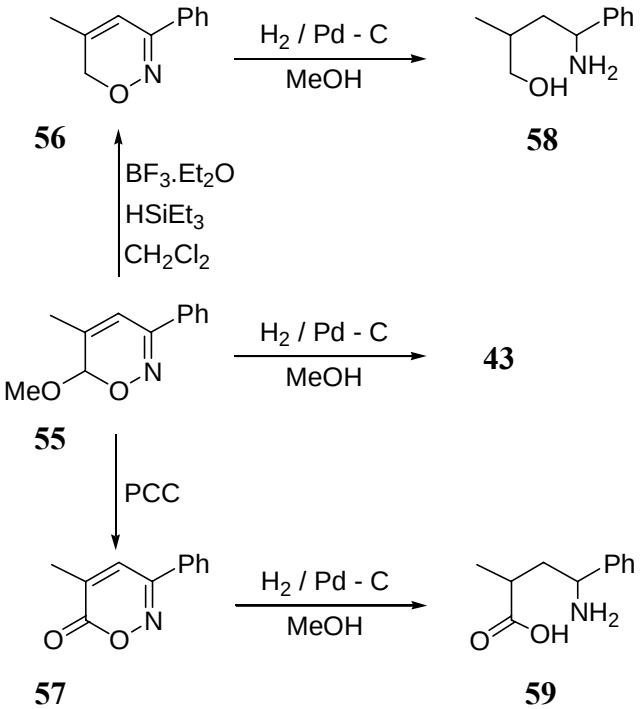
The reaction bears an analogy to that described in Scheme 11 and also to the known proton acid-induced rearrangement of **50**.[31]

1,2-Oxazines (**52**) can be *N*-acylated prior to their catalytic reduction to **54** (Scheme 19).[34]



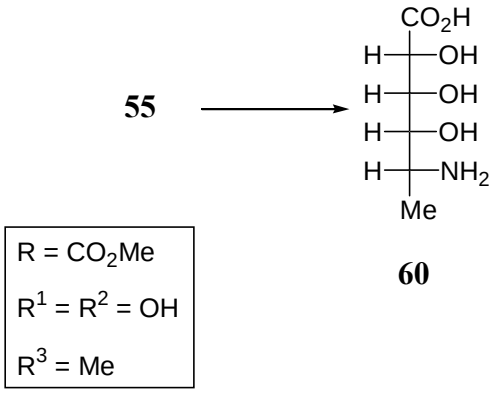
Scheme 19

Substituted 6*H*-1,2-oxazines (**55**)-(**57**) are catalytically hydrogenated (Scheme 20).[35]



Scheme 20

Conversely, hydrolysis, followed by catalytic reduction of **55** has been used to the synthesis of (±)-5-amino-5,6-dideoxyallonic acid (**60**) (Scheme 21).[36]

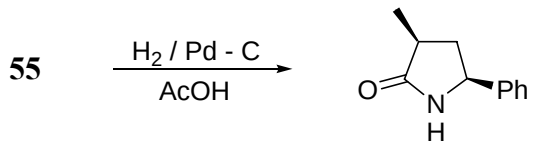


60

Scheme 21

The reactions are analogous to those in Schemes 7, 8 and 15. The amino alcohols (**58**), the amine (**43**) and the GABA derivative (**59**) are chemo- and stereoselectively obtained. Interestingly, if catalytic hydrogenation of **57** is performed in acetic acid the *γ*-keto acid is obtained.

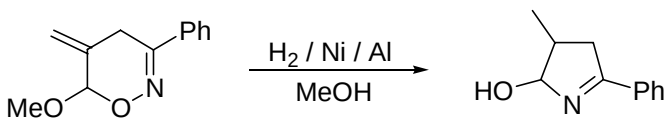
The reduction of **55** in acetic acid takes a different course giving *γ*-lactam (**61**) in moderate yield but diastereomerically pure (Scheme 22).



61

Scheme 22

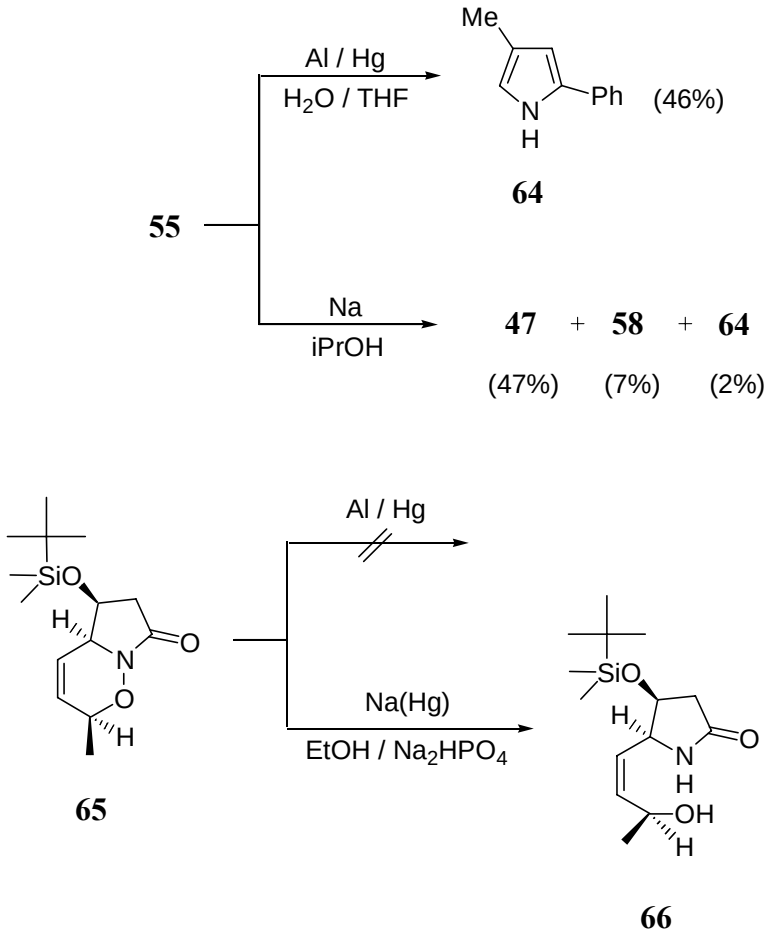
55 cannot be reduced on Raney nickel at room temperature but its isomer **(62)** gives pyrrole (**63**) (Scheme 23).[35]



62 **63**

Scheme 23

Reduction of **55** with electron transfer has been examined (Scheme 24).[35] With aluminum amalgam pyrrole (**64**) is obtained. The reaction serves as an efficient access to pyrroles.[17,26,37]

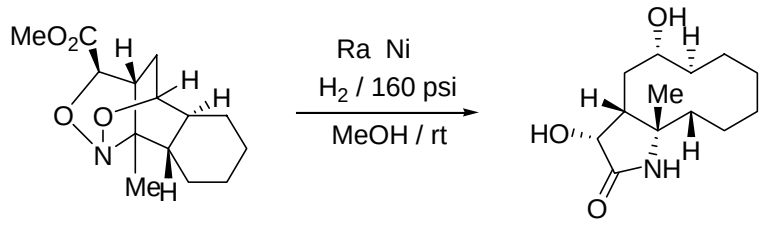


Scheme 24

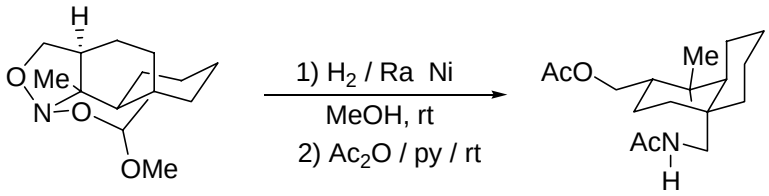
Compound (**64**) is probably formed *via* initial *N-O* cleavage to an imine which is further reduced to a *γ*-amino aldehyde, the latter cyclised to **64**. Reduction of **55** with Na/^{i}PrOH, on the other hand, probably follows a similar pathway through the *γ*-amino aldehyde. An alternative intermediate (**64**) is not likely as pyrroles are inert towards Na as a reducing agent.[38]

However, **65** can not be reduced with Al/Hg but it is effectively reduced with Na/Hg in EtOH to **66** (Scheme 24). The failure of the former reagent has been attributed to an increased reduction potential of this structure. The reductive cleavage is an efficient protocol for the synthesis of 1,4-amino and amido alcohols.[37]

Hydrogenolysis of N-O bond of polycyclic 1,2-oxazines (**67**) or (**68**) leads to polycyclic *a*-hydroxy lactams (**69**) or acyl-protected amino alcohols (**70**) respectively (Scheme 25).



67 **69**

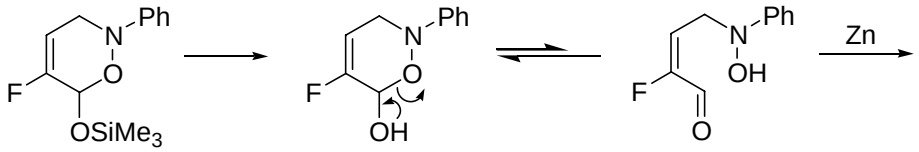


68 **70**

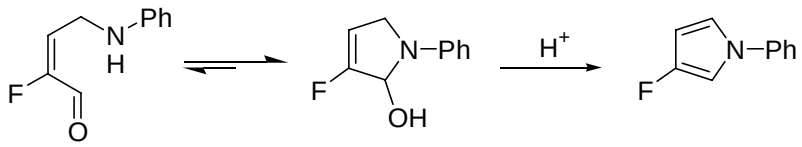
Scheme 25

The N-O rupture demonstrates the synthetic potential of the inter-/intra-tandem strategy, in all possible permutations, as developed by Denmark *et al*.[39]

Fluoro-6-silyloxy substituted 3,6-dihydro-2*H*-1,2-oxazines (**71**), upon acid hydrolysis, generate cyclic hemiacetals (**72**), which are in tautomeric equilibrium with the *N*-hydroxyamino aldehyde (**73**). Zn reduction removes the OH group and the resulting amine undergoes acid-catalysed recyclisation and dehydration to **76** (Scheme 26).[40]



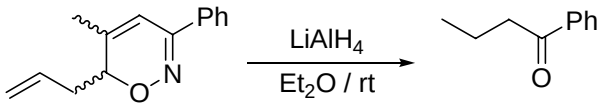
71 **72** **73**



74 **75** **76**

Scheme 26

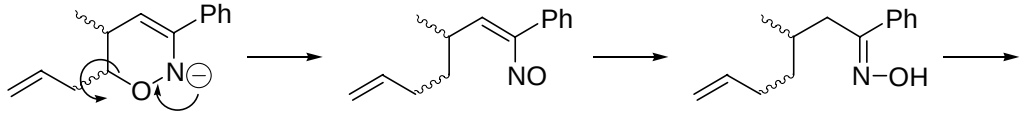
6-Allyl substituted 6*H*-1,2-oxazines (**77**) reduced by $LiAlH_4$ lead to ketone (**78**) (Scheme 27).[41]



77 **78**

Scheme 27

It has been suggested that initial hydride 1,4-addition to **79** is followed by cycloreversion of the heterocycle.[42] Reduction and hydrolysis of the resulting imine (**80**) finally gives **78** (Scheme 28).



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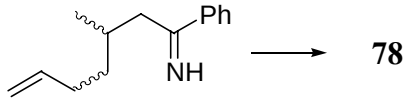
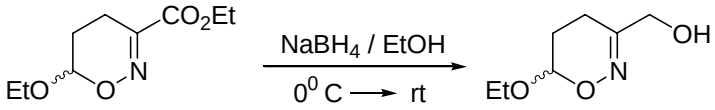


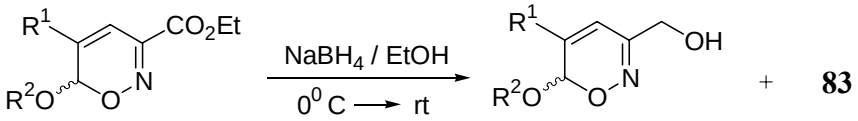
80

Scheme 28

$NaBH_4$ reduction of the carboxylates (**81**) and (**82**) furnishes the alcohols (**83**) and (**84**) respectively (Scheme 29).[41] Woodward[43] and Wade[28] have demonstrated that the reagent is ideal for the reduction of ester functions in *N*,*O*-heterocycles.[21,44]



81 **83**



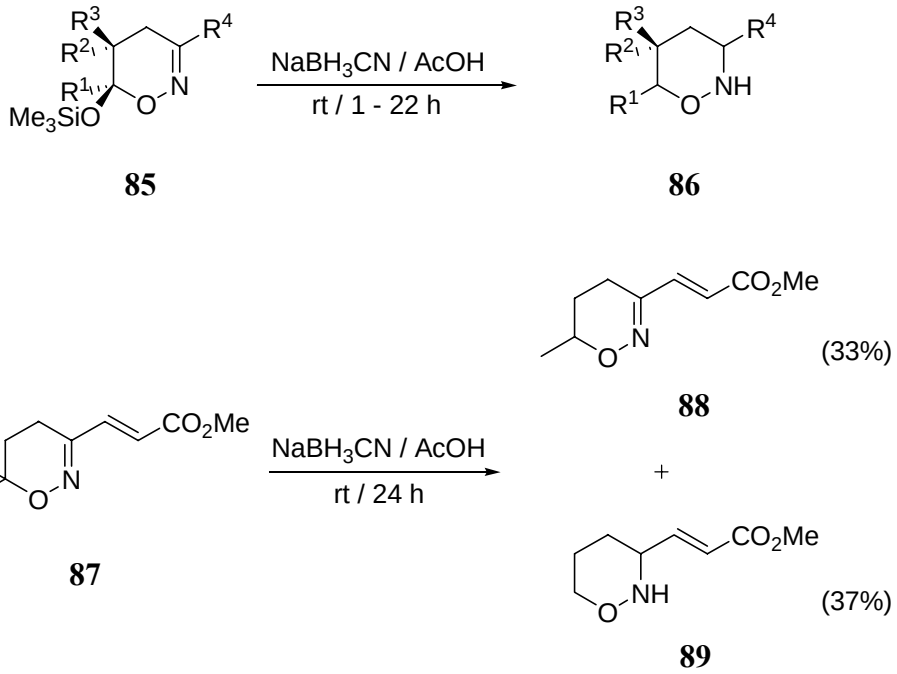
82 **84**

a: $R^1 = R^2 = Me$

b: $R^1 = H$, $R^2 = Et$

Scheme 29

Tetrahydro-2*H*-1,2-oxazines (**85**) have been used as useful intermediates in the synthesis of natural products[45] and non-natural cyclic amino acids.[43] An efficient and simple route to their synthesis is by $NaBH_3CN$ reduction in acetic acid of the easily accessible 6-silyloxy-4*H*-1,2-oxazines (**85**) or (**87**) (Scheme 30).[46]



85 **86**

88

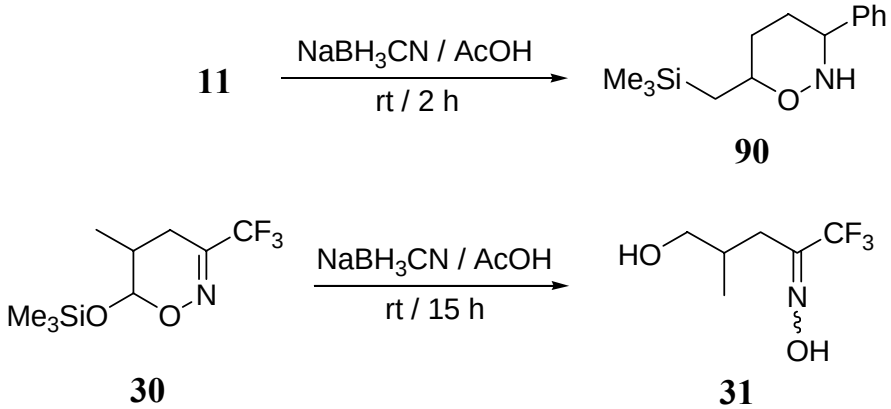
87

89

Scheme 30

Besides the hydride transfer at *C*-3, there is also reduction at the acetal moiety. The formation of **86** or **89** is highly diastereoselective. Remarkably, **87** show lower diastereoselectivity than their 3-Ph counterparts. The stereochemical outcome of the reaction is apparently independent of the *trans*/*cis* ratio of the precursor. It is also of interest to compare the reduction outcomes in Schemes 10, 12, 13, and 15.

Similarly, 6-silyl or silyloxy substituted 1,2-oxazines (**11**) and trifluoromethyl analogue of **30** are reduced by the reagent to **90** and **31** respectively (Scheme 31).[46]



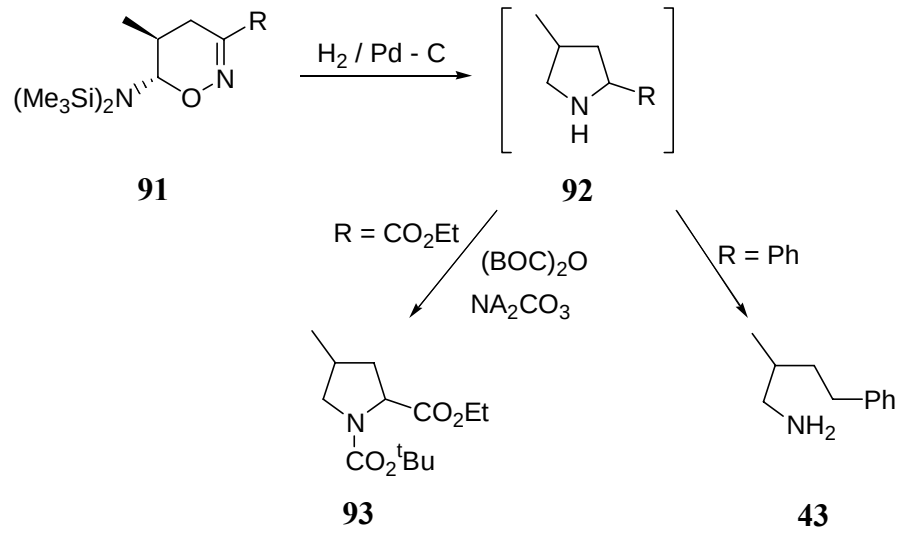
90

30 **31**

Scheme 31

The analogy with the Schemes 7 and 10 is again of interest.

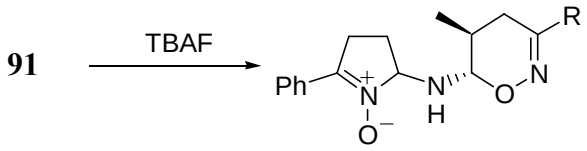
Catalytic reduction of 6-silylamino substituted 4*H*-1,2-oxazines (**91**) follows a route similar to their 6-silyloxy counterparts (**30**) and that of 6*H*-1,2-oxazines (**56**) and (**57**) (Scheme 32).[47]



91 **92** **93** **43**

Scheme 32

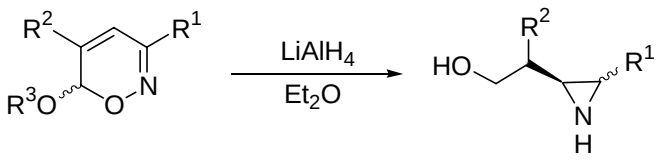
The proposed intermediate (**92**) decomposes rapidly if R=CO_2Et, thus, it is trapped by acylation to **93**. However, **91**, when treated with TBAF or triethylamine trishydrofluoride, do not suffer desilylation of the ring. Instead **94** is obtained as a mixture of three diastereomers (Scheme 33).[47]



91 **94**

Scheme 33

6*H*-1,2-Oxazines (**95**) or (**97**) rearrange to aziridines (**96**) or (**98**) by $LiAlH_4$ (Scheme 34).[41]



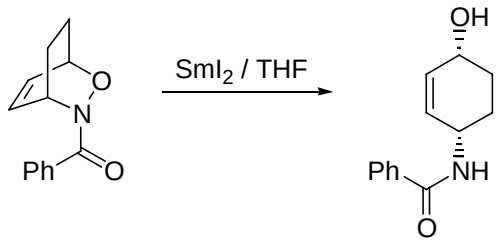
95 R^1= Ph **96**

97 R^2= CF_3 , CO_2Et **98**

Scheme 34

The ring contraction to an azirine intermediate prior to its ultimate reduction to **96** (or **98**) bears an analogy to a Neber rearrangement.

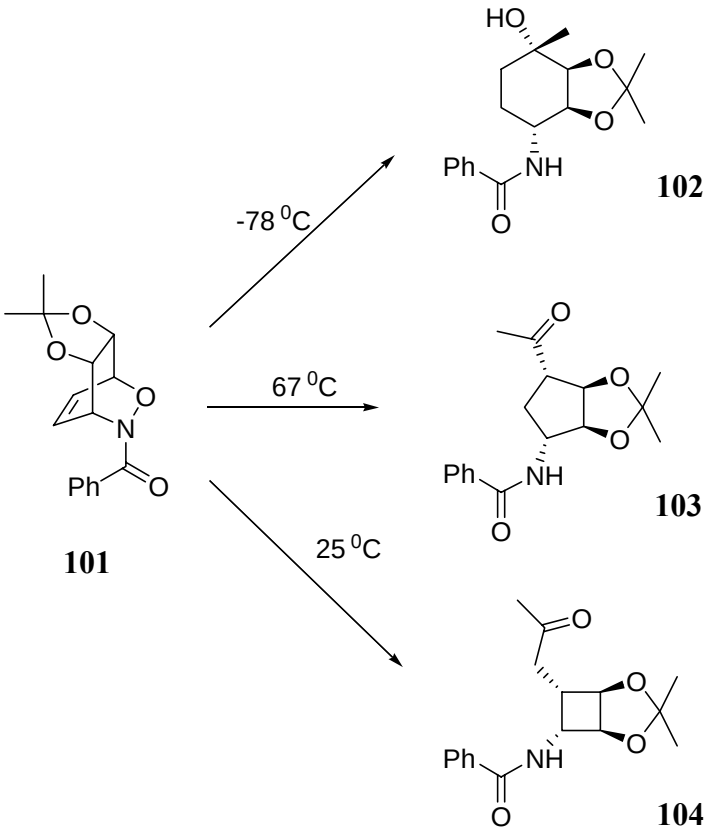
N-Acylated 1,2-oxazines (**99**) are reductively rearranged to the amido alcohol (**100**) by SmI_2 (Scheme 35).[48]



99 **100**

Scheme 35

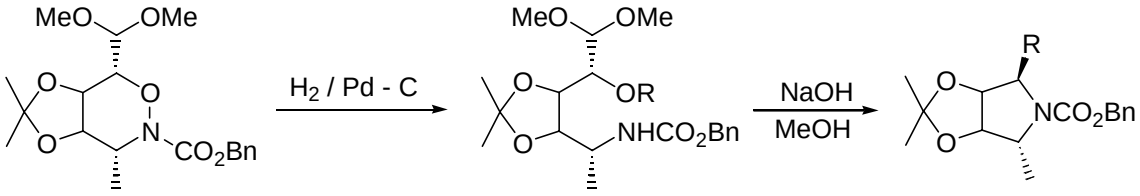
Similarly the tricyclic 1,2-oxazine (**101**) has been rearranged by this reagent into the diols (**102**), (**103**), (**104**) (Scheme 36).[48]



Scheme 36

NMR spectral analysis of the reaction mixture revealed that the ring contraction of **101** to the isomeric structures (**103**) and (**104**) occurs with complete stereochemical control. Temperature variation proved crucial to the reaction course. Thus, **104** has been the sole product at low temperature while **103** has been isolated from reflux in THF (Scheme 36). A radical mechanism *via* initial reductive cleavage of the *N-O* bond is followed by a radical *O* to *C* transfer and a *5-endo-* or *4-exo-trig* cyclisation to **103** or **104** respectively.

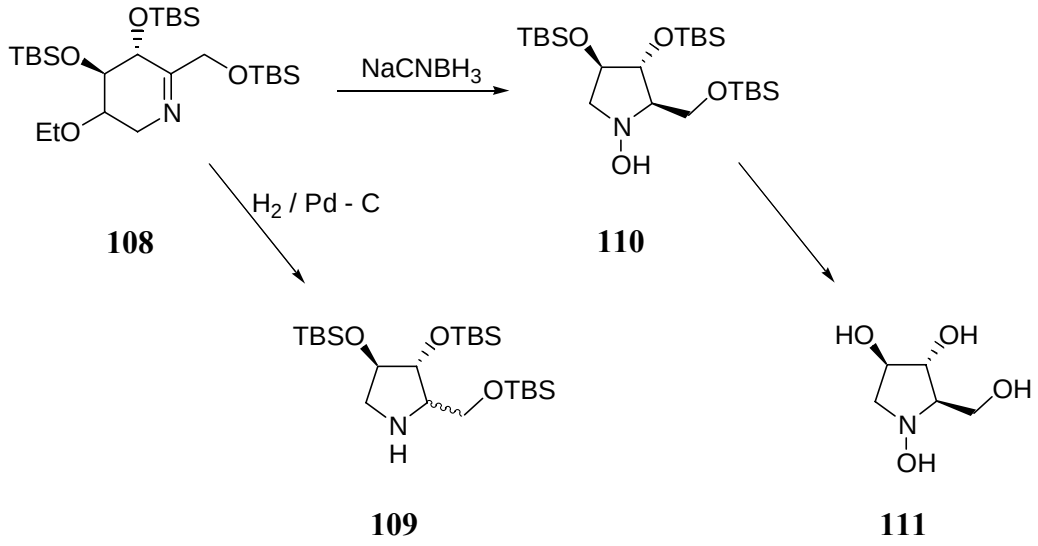
N-Acylated 1,2-oxazines (**105**) rearrange to pyrrolidines (**107**) (Scheme 37).[49]



105 **106** **107**

Scheme 37

1,2-Oxazines (**108**) are reductively rearranged to highly substituted pyrrolidines (**109**)-(**111**) (Scheme 38).[50]

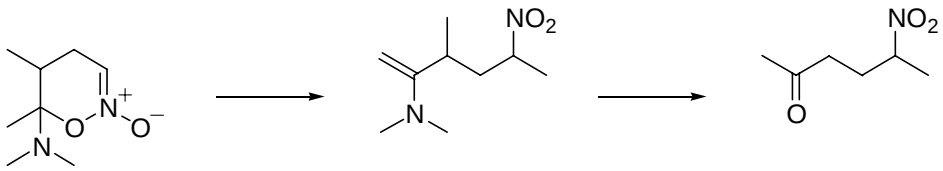


108 **110** **109** **111**

Scheme 38

Substituted pyrrolidines shown in Schemes 37 and 38 are significant proline analogues.

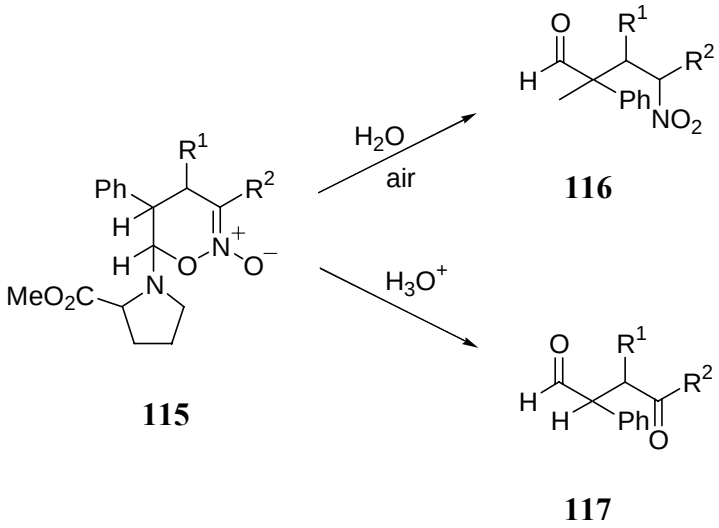
6-Amino substituted 4*H* 1,2-oxazine *N*-oxides (**112**) are cleaved to the nitroalkyl enamines (**113**) further hydrolysis of which furnishes the nitroketones (**114**) (Scheme 39).[51]



112 **113** **114**

Scheme 39

Similarly 6-amino substituted *N*-oxides (**115**) are readily hydrolysed, when left in the air for 24 h, to the nitroalkyl aldehydes (**116**) (Scheme 40).[52] On the other hand, **115** by acid hydrolysis give the keto aldehyde (**117**) through a Nef reaction (Scheme 40).[51]



115 **116** **117**

Scheme 40

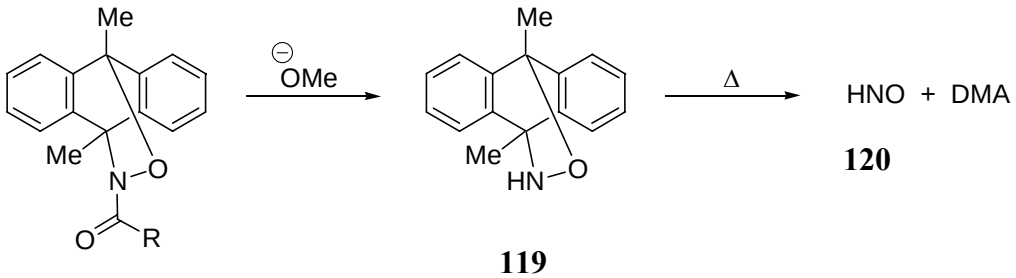
1.2 Non-Reductive

The most common reaction course followed in the transformations included in this section is a ring contraction rearrangement, as in many of the examples presented in section 1.1. This is an efficient route to mono(bi)cyclic polyhydroxylated alkaloids.[53]

1.2.1 Thermally or Photochemically-induced

The cycloadduct 1,2-oxazine (**118**), derived from a [4+2] cycloaddition of 9,10-dimethylanthracene (DMA) with a transient nitrosocarbonyl dienophile, upon alkaline hydrolysis gives **119**. The latter

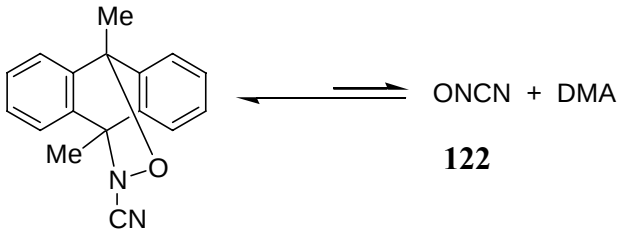
undergoes thermal fragmentation or otherwise a *retro*-Diels-Alder reaction to **120** and the free DMA (Scheme 41).[54]



118 **119** **120**

Scheme 41

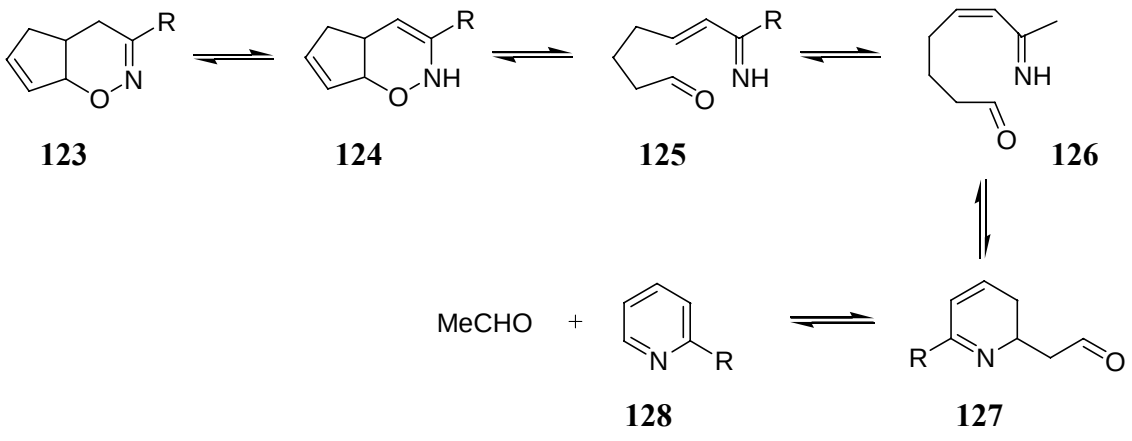
Similarly, the cycloadduct (**121**) dissociates readily to **122** and free DMA. Interestingly, the liberated **122** should be trapped (it has been trapped by thebaine) as it otherwise recombines to **121** (Scheme 42).[55]



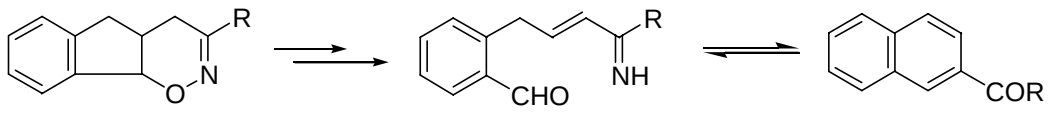
121 **122**

Scheme 42

When strongly heated (*ca*. 250 ^{o}C) fused 1,2-oxazines (**123**) suffer ring *N-O* cleavage through the sequence shown (Scheme 43).[56]



123 **124** **125** **126** **128** **127**

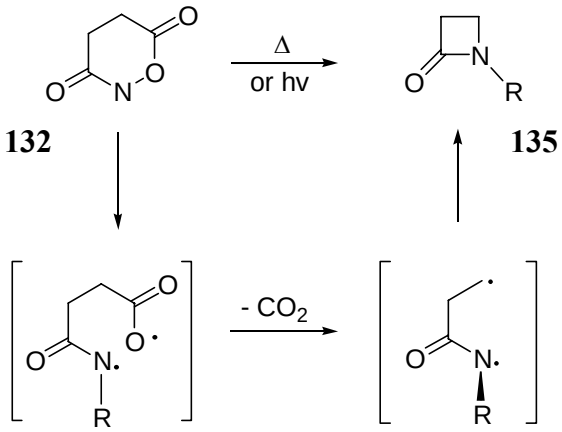


129 **130** **131**

Scheme 43

Pyridines (**128**) are obtained in good to moderate yields on thermolysis of **123**. Thermolysis in solution gives intractable mixtures. Thermolysis of **129** gives the ketone (**131**) in moderate yield. The sequence of events, similar in both cases, has been suggested to incorporate tautomerization (**123** to **124**), electrocyclic ring opening[57] (**124** to **125**), double bond isomerization (**125** to **126**), recyclisation (**126** to **127**) and aromatization (**127** to **128**). In the case of **129**, the aldehyde undergoes an aldol type ring closure to **131**.

Thermolysis of 1,2-oxazine 3,6-diones (**132**) leads to *β*-lactams (**135**) (Scheme 44).[58] Same result has been obtained by photolysis of **132**.

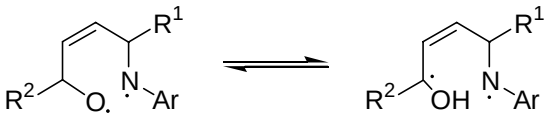


132 **135**

133 **134**

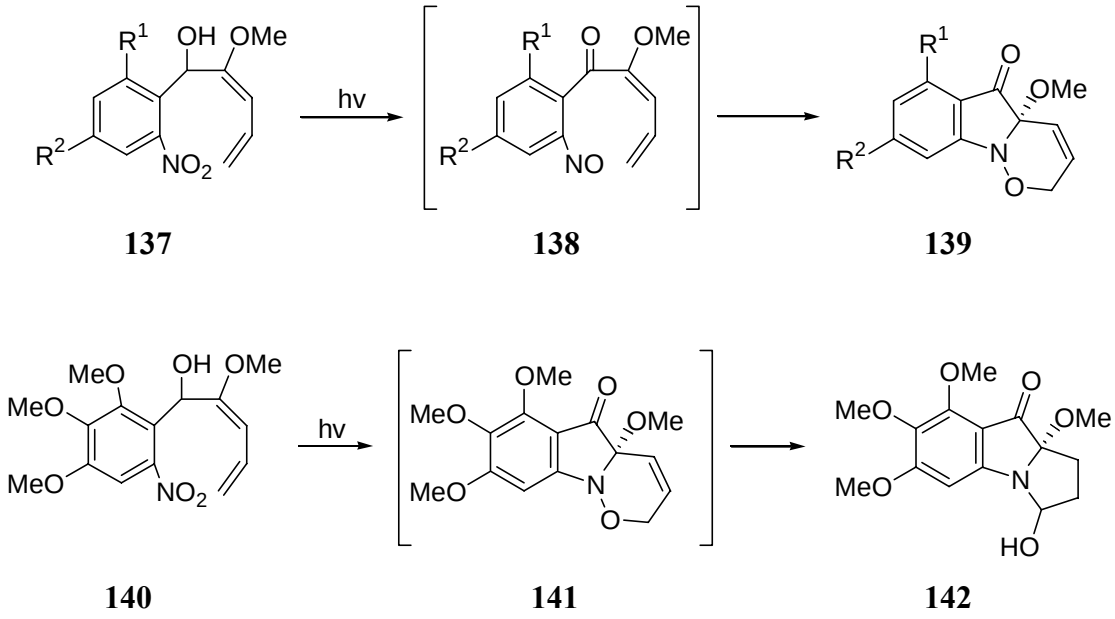
Scheme 44

A diradical mechanism through **133** and **134** has been proposed. Similarly, 3,6-dihydro-1,2-oxazines have also been photochemically converted into pyrroles.[59] A diradical intermediate (**136**) has also been invoked in the study of this rearrangement.



136

An interesting photochemical route to mitomycins and FR-900482 drugs by Danishefsky *et al.*[60] invokes a 1,2-oxazine structure (**139**) or (**141**) as a "permissible intermediate" (Scheme 45).



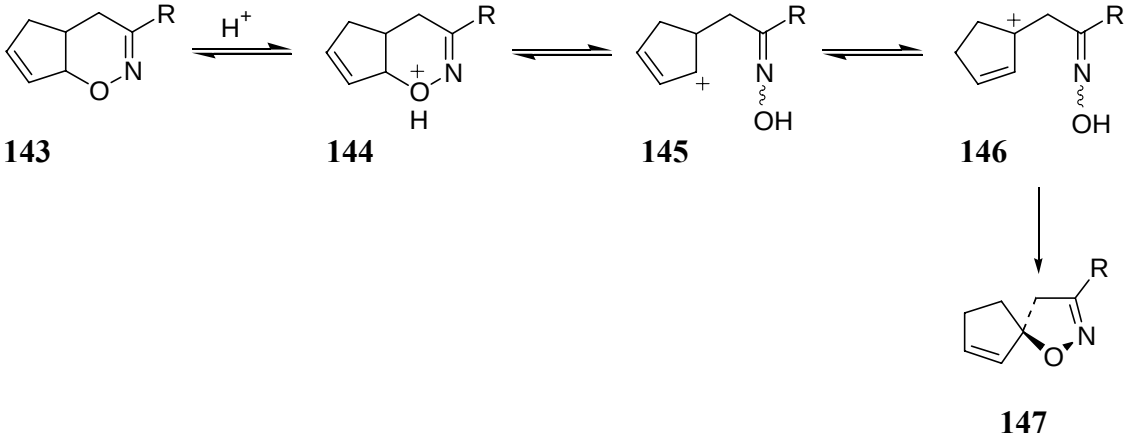
137 **138** **139**

140 **141** **142**

Scheme 45

1.2.2 Acid-catalysed

When heated in formic or acetic acid, **143** rearranges to the *spiro*-isomer (**147**) (Scheme 46).[56]



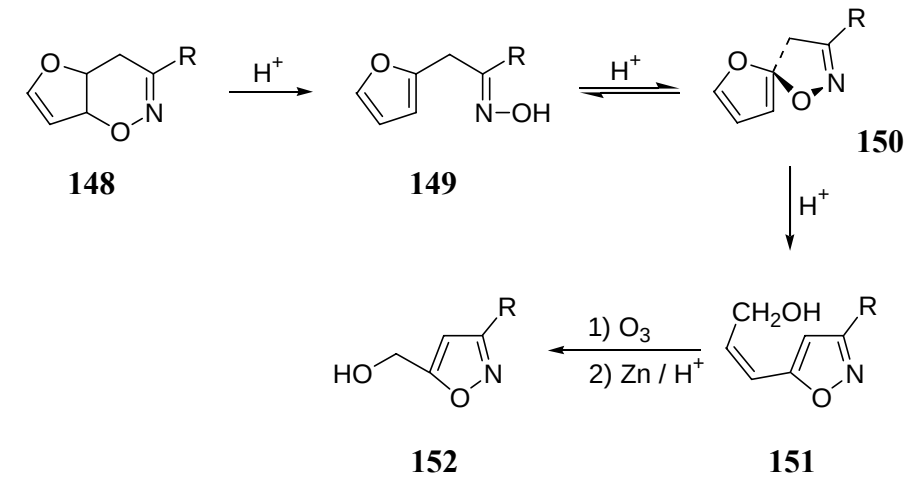
143 **144** **145** **146**

147

Scheme 46

O- Protonation of **143**, ring opening, rearrangement of the carbocation (**145**) to a more stable allylic and tertiary one (**146**) and finally cyclisation to **147** are the suggested rationale.

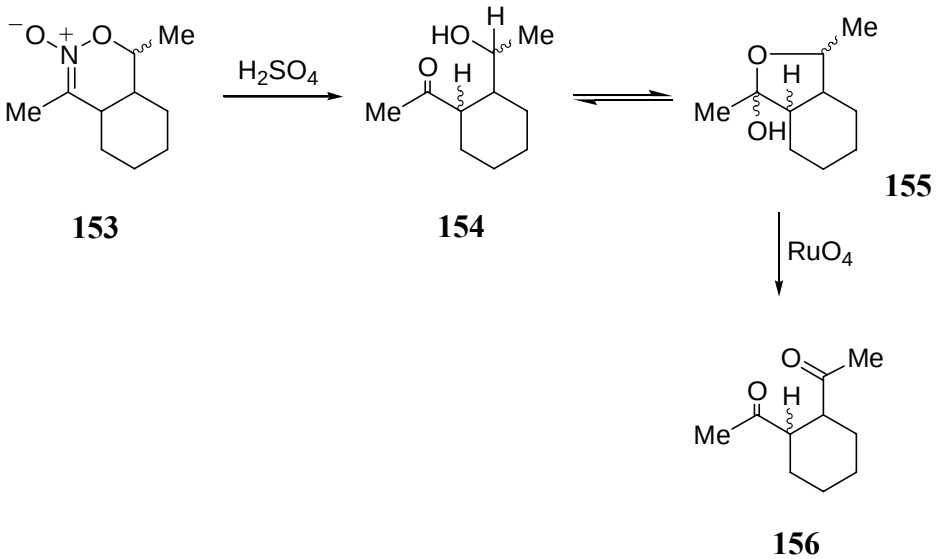
A similar transformation has been reported with **148** under milder conditions (Scheme 47).[56]



Scheme 47

The isoxazole (**151**) has been isolated in good yield. The oxime (**149**) has been isolated and resubjected to the reaction conditions to furnish **151** in high yield. **150** is not isolated in this reaction as it rearranges by the acid.

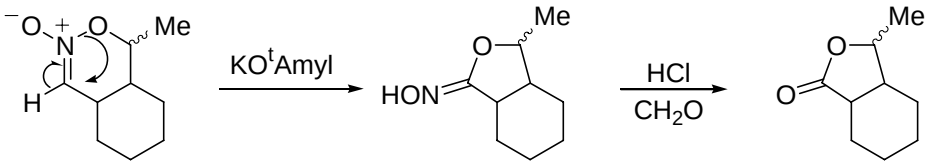
Nef hydrolysis of **153** leads to ketone (**154**), the latter being oxidized to the diketone (**156**) (Scheme 48).[11,61]



Scheme 48

1.2.3 Base-induced

1,2-Oxazine *N*-oxides (**157**) suffer base-catalysed transformation to lactones (**159**) (Scheme 49).[61,62]

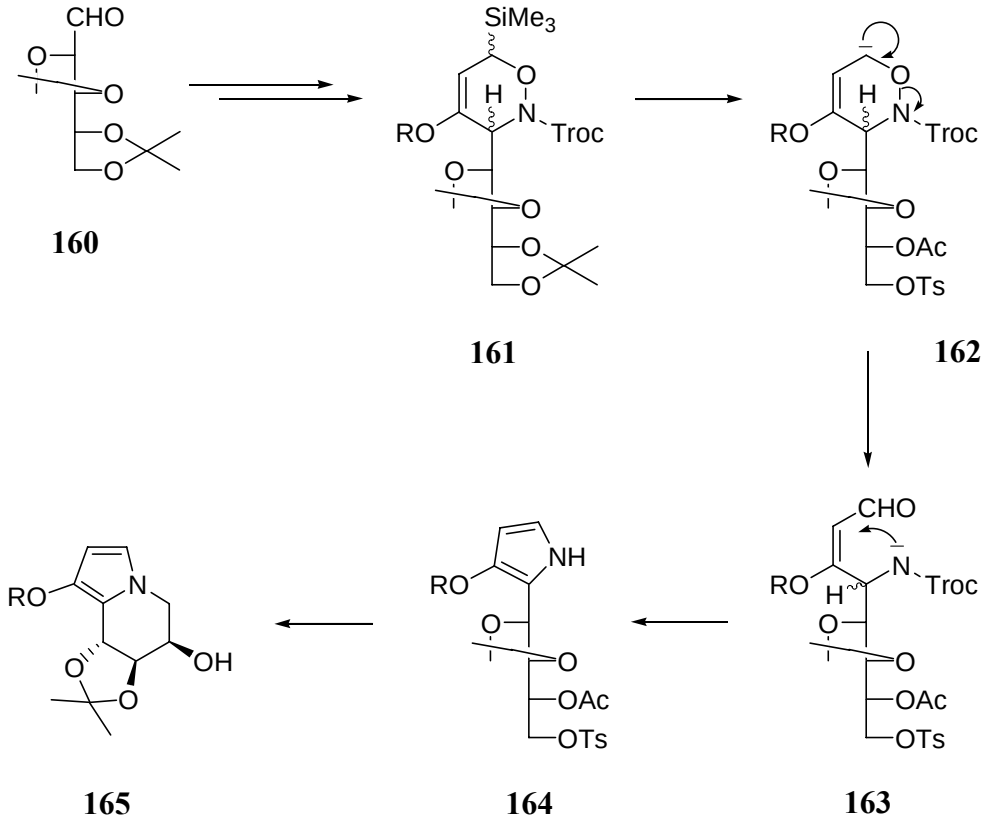


157 **158** **159**

Scheme 49

Fragmentation to a nitrile oxide is followed by its immediate collapse to **158** and ultimately to **159**. This mechanism finds precedent in silyl nitronate chemistry.[63]

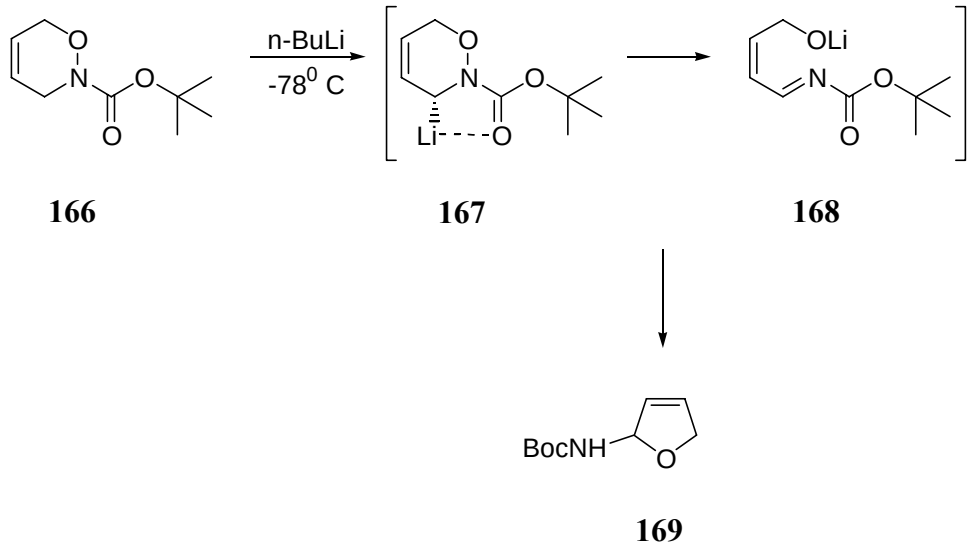
Fluoride ion-catalysed rearrangement of 3-trialkysilyl substituted 1,2-oxazines (**161**) to pyrrole castanospermine analogues (**164**) and (**165**) has been reported (Scheme 50).[64]



160 **161** **162** **163** **164** **165**

Scheme 50

1,2-Oxazines (**166**) upon lithiation, undergo an interesting ring contraction to furans (**169**) (Scheme 51).[65,66]



166 **167** **168**

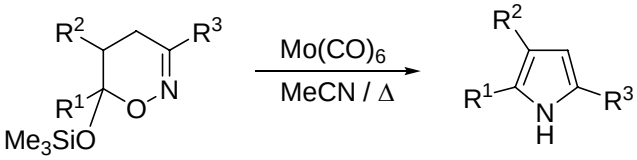
169

Scheme 51

Initial formation of **167** is followed by ring opening to the *α,β*-unsaturated imine (**168**). The *Z*-stereochemistry of the double bond in **168** favors intramolecular cyclisation to **169**.

1.2.4 Transition Metal-induced

6-Silyloxy substituted 1,2-oxazines (**170**) rearrange to substituted pyrroles (**171**) by $Mo(CO)_6$ (Scheme 52).[67-69]

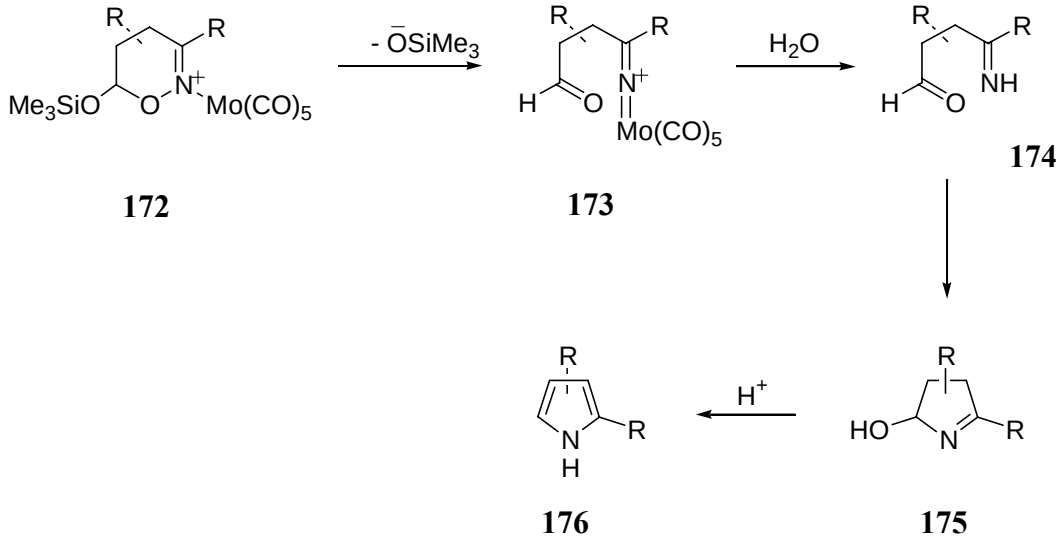


170 **171**

Scheme 52

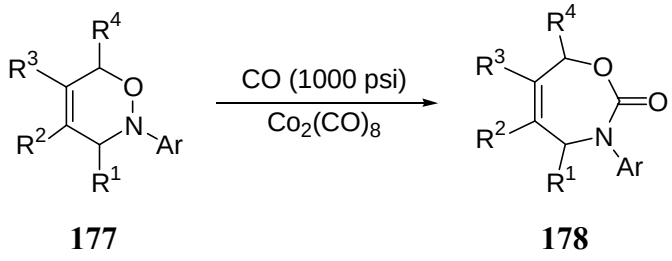
Closely related conversions are those of 6-dialkylamino substituted 1,2-oxazines into corresponding pyrroles with $Fe_3(CO)_{12}$[70]

The intermediacy of complexes (**172**) and (**173**) has been proposed in this process (Scheme 53).[70]



Scheme 53

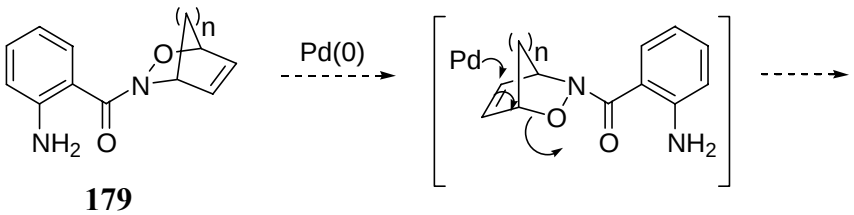
Besides ring contraction rearrangements, ring expansion of 1,2-oxazines also induced by transition metal reagents, has been reported.[71] Thus, 1,2-oxazines (**177**) are converted to cyclic carbamates (**178**) by carbonylative ring expansion catalysed by $Co_2(CO)_8$ (Scheme 54).



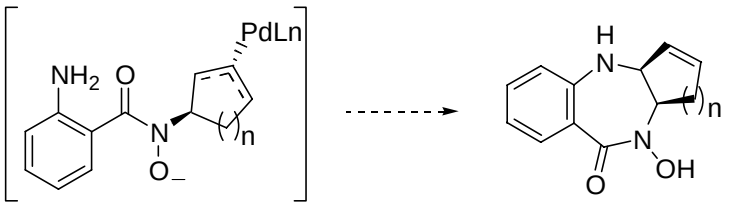
177 **178**

Scheme 54

An interesting ring expansion has been recently reported.[72] Ring opening of acylnitroso-derived HD-A adduct (**179**) by Pd(0), followed by ring expansion through metal complex ring activation gives 1,4-benzodiazepines (**180**) (Scheme 55).



179



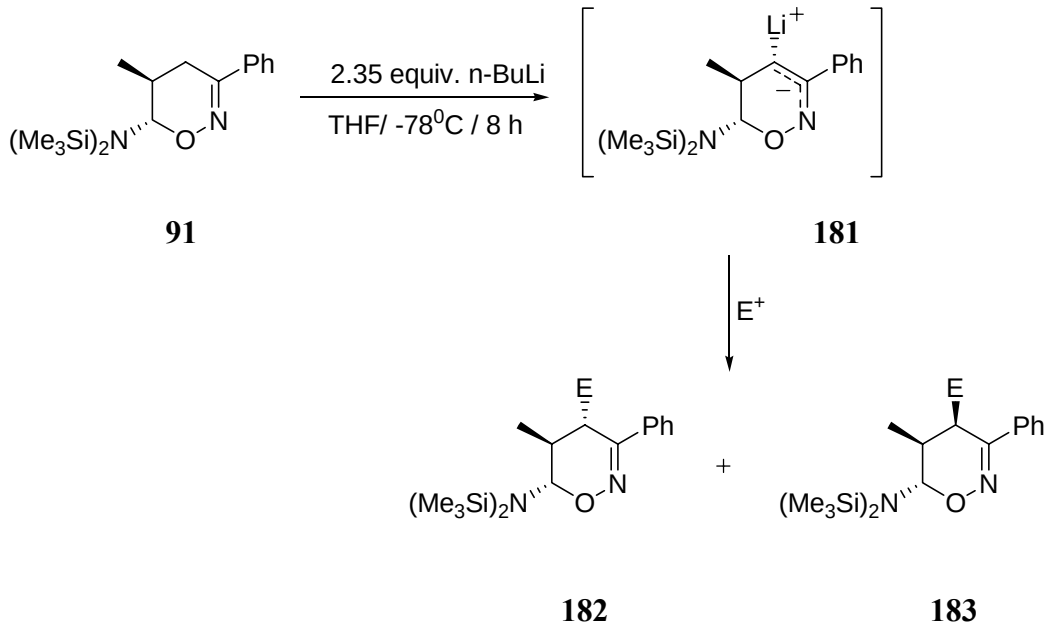
180

Scheme 55

2. Reactions with Electrophiles/Nucleophiles

Electrophiles attack unactivated 1,2-oxazines when the latter are deprotonated by strong bases, usually through lithiation, with high diastereoselectivity. However, 6-substitution appears to be a crucial determinant in the success of this process.[47,51]

Indeed, 6-silyloxy- or alkoxy substituents hinder the electrophilic attack at *C*-4. The 6-silylamino-analogues (**91**) undergo lithiation at *C*-4 to **181** with *n*-BuLi, upon prolonged treatment. However, alkylation of the latter with reactive species such as methyl iodide or allyl bromide to **182** and **183,** in the presence of TMEDA, does not proceed to completion (Scheme 56).[47]



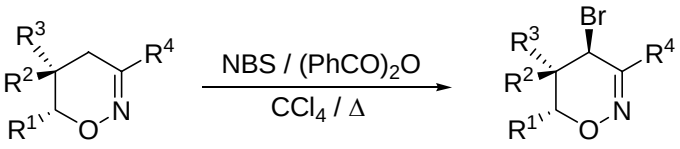
91 **181**

182 **183**

Scheme 56

1,2-Oxazines (**184**) are brominated at *C*-4 to **185** in good yield either on treatment with NBS in the

presence of dibenzoyl peroxide ($(PhCO)_2O$) or by reaction with *n*-Buli in *n*-hexane/THF followed by Br_2 (Scheme 57).[52]

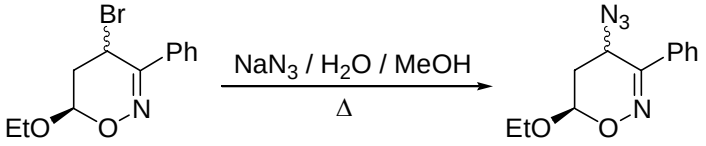


184 **185**

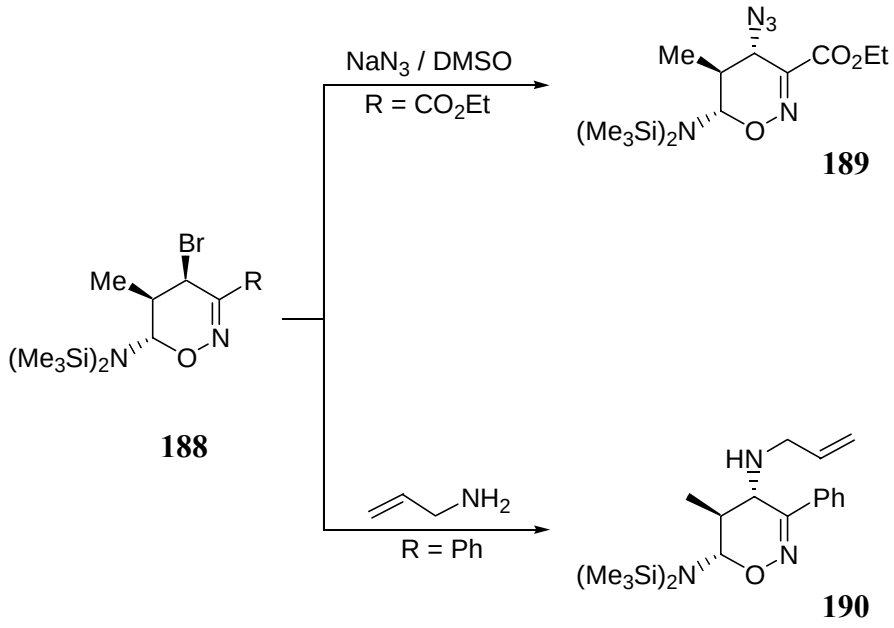
Scheme 57

A number of substituents R^1-R^4 are tolerated on the ring and the reaction occurs readily with 3-phenyl or 3-ethoxycarbonyl substituted derivatives with surprisingly high diastereoselectivity. The 3-trifluoromethyl substituted ones, on the other hand, fail to undergo bromination.

Nucleophiles attack activated positions of 1,2-oxazines. Accordingly, nucleophilic substitution of **186** and **188** has been reported and synthetically useful precursors **187**, **189** or **190** have been obtained (Scheme 58).

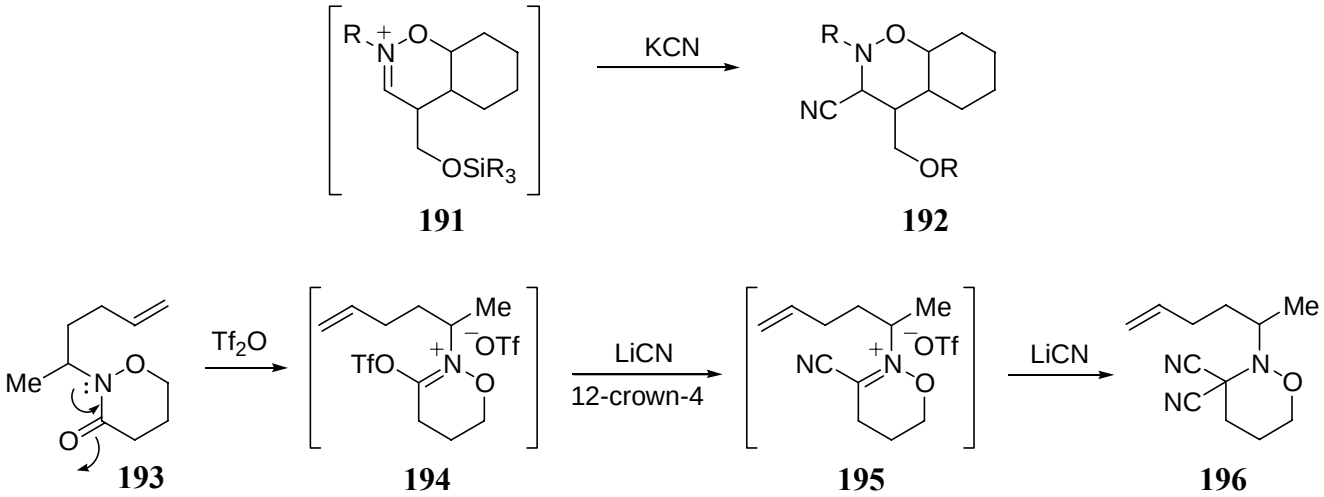


186 **187**



Scheme 58

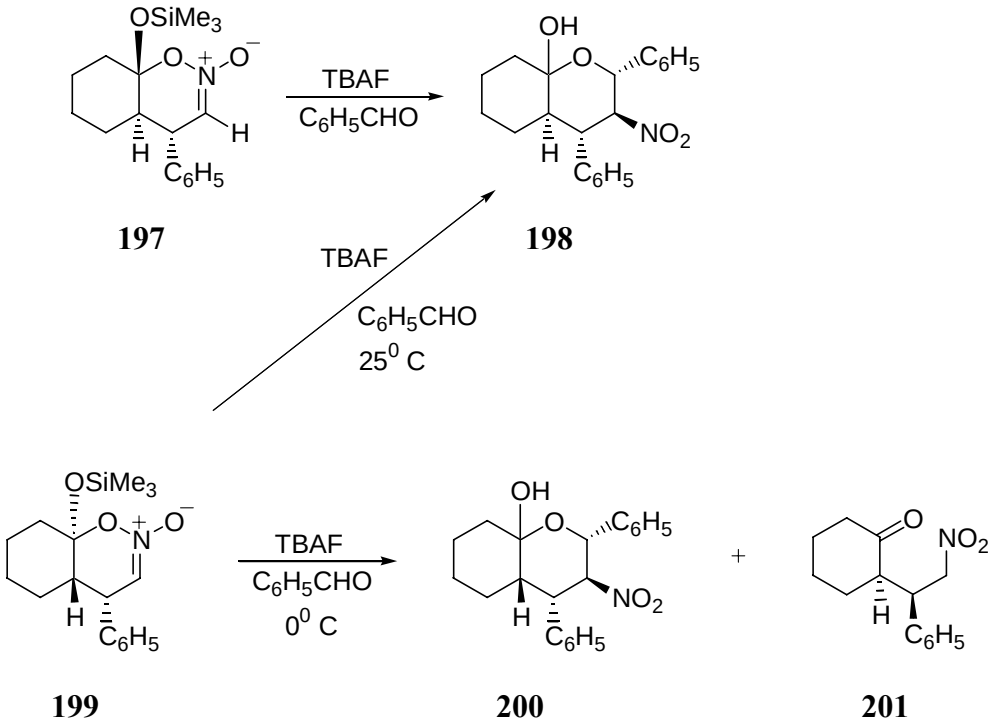
Nucleophilic addition has also been reported for transient 1,2-oxazinium species (**191**), (**194**), (**195**) (Scheme 59).[73]



191 **192** **193** **194** **195** **196**

Scheme 59

1,2-Oxazine *N*-oxides are reactive nucleophiles. Thus, **197** reacts with benzaldehyde in the presence of TBAF to give the hemiacetal (**198**) with high diastereoselectivity (Scheme 60).[74]



197 **198** **199** **200** **201**

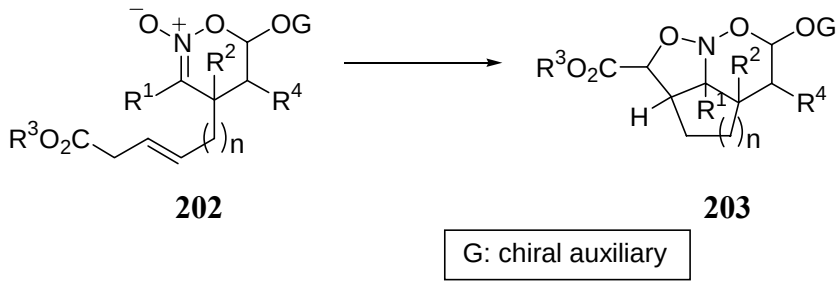
Scheme 60

Compound (**199**) does not react as cleanly. Fluoride ion is a sufficiently strong base to cause

epimerization of α-carbonyl position at room temperature. On the other hand, hydrolysis occurs at lower temperatures to **200** and **201**.

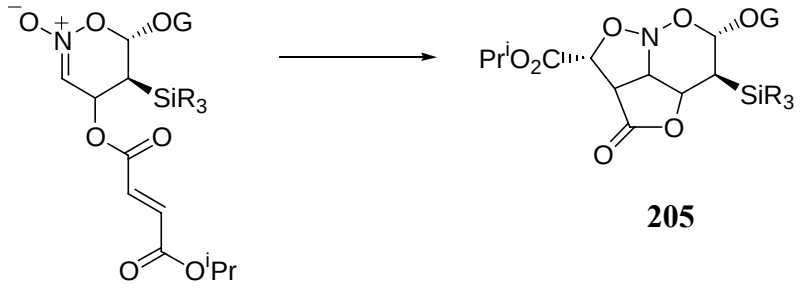
3. Cycloadditions

Nitronates as dipoles in [3+2] cycloadditions have been discovered by Tartakovskii and later have been developed by him[75-77] and Carrie.[78] Their cyclic counterparts (**202**, **204**, **206**) function well as 1,3-dipoles, inter- or intramolecularly.[62c,75-82] Tricyclic derivatives (**208**) react similarly, though more slowly, probably as being more hindered (Scheme 61).

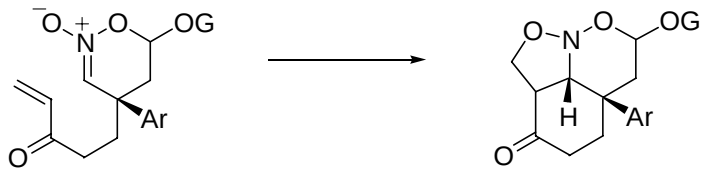


202 **203**

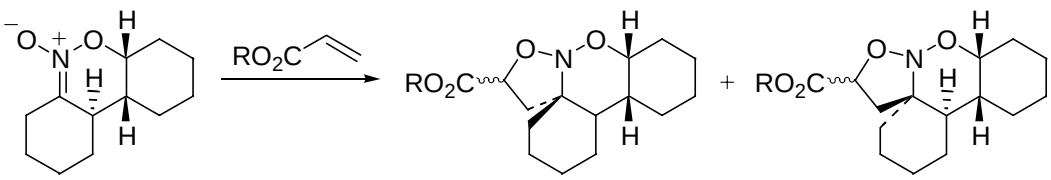
G: chiral auxiliary



204 **205**



206 **207**

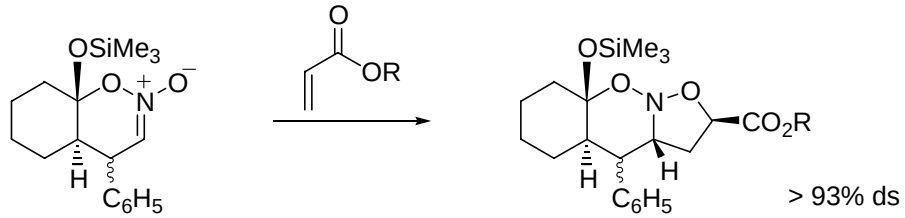


208 **209** **210**

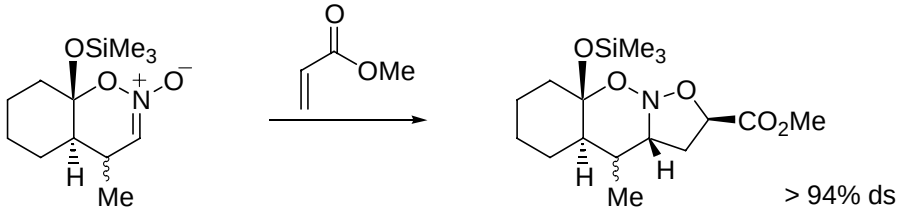
Scheme 61

High diastereoselectivity has been observed in the intramolecular cycloaddition of **202**, **204** and **206** to the corresponding adducts (**203**, **205**, and **207**) respectively. Little *exo*/*endo* selectivity has been observed in **208** but expectedly complete regioselectivity. The former has been attributed to secondary orbital interactions.

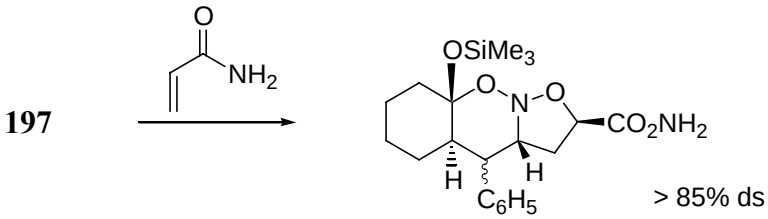
Silyloxy substituted *N*-oxides (**197**) and (**212**) are also effective 1,3-dipoles (Scheme 62).[74,83]



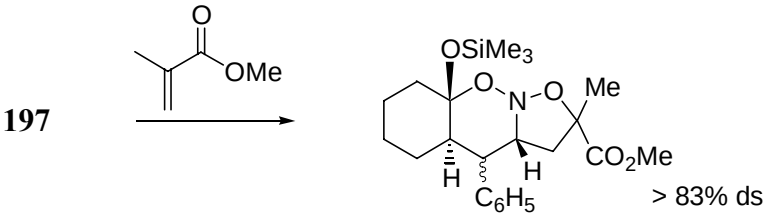
197 **211**



212 **213**



214



215

Scheme 62

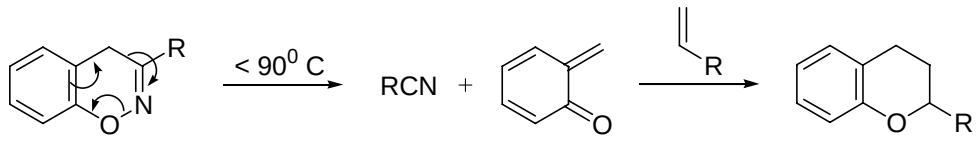
All reactions proceed with good diastereoselectivity. In combination with the [4+2] cycloaddition that generates the *N*-oxides, this tandem cycloaddition strategy allows for the effective assembly of subsets of polycyclic systems. The recent review by Denmark *et al*.[4b] has substantially covered the subject. The examples shown here are merely for the clarity of presentation.

C. CARBO(HETERO)CYCLO-FUSED 1,2-OXAZINES

Despite the accumulation of knowledge on 1,3- and 1,4-benzoxazines[84-86] their 1,2-isomeric analogues have not received much attention. As already demonstrated in the previous chapter, the chemistry of structure **C** (see introduction) is dominated by the cleavage of the *N-O* bond.

1. Ring Cleavage – Transformations

Thermolysis of 1,2-benzoxazines (**216**) causes rupture of the *N-O* and *C-C* bonds to *o*-quinone methides (**217**) (Scheme 63).[87]

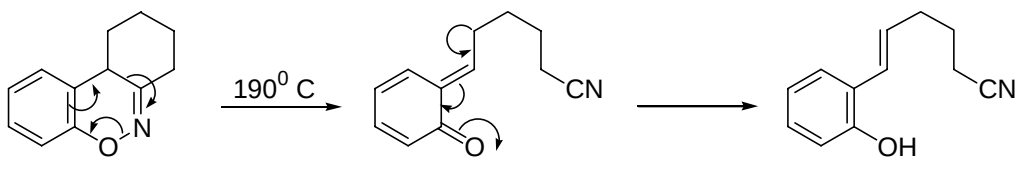


216 **217** **218**

Scheme 63

The fragmentation of **216** is, thus, an alternative to the conventional routes towards **217**.

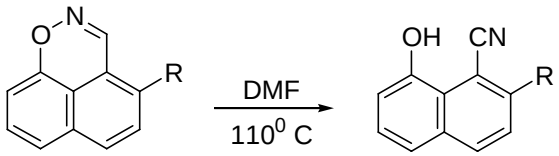
Interestingly tricyclic 1,2-benzoxazines (**219**), when treated under similar, though more forcing conditions, show no Diels-Alder reaction. Instead, **221** is isolated whose formation is rationalized by initial ring opening followed by tautomerization/aromatization of **220** (Scheme 64).[87]



219 **220** **221**

Scheme 64

Peri-annelated 1,2-oxazines (**222**) readily cleave by thermal treatment to the nitriles (**223**) and (**224**) (Scheme 65).[88]



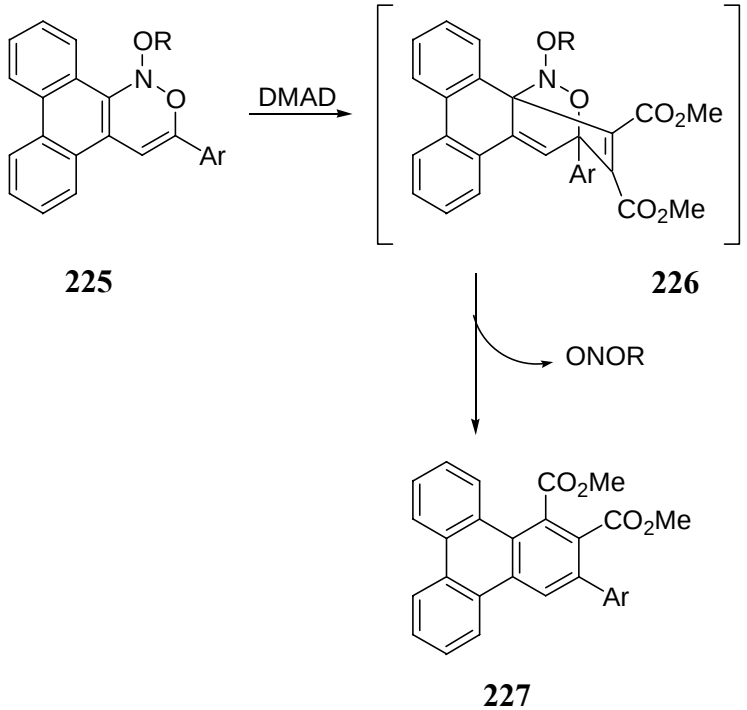
222 a. R= H **223**

b. R= OH **224**

Scheme 65

2. Cycloadditions

Phenanthrene-fused 1,2-oxazines (**225**) have been used as Diels-Alder dienes to give polycyclic aromatics (**227**) (Scheme 66).[89]



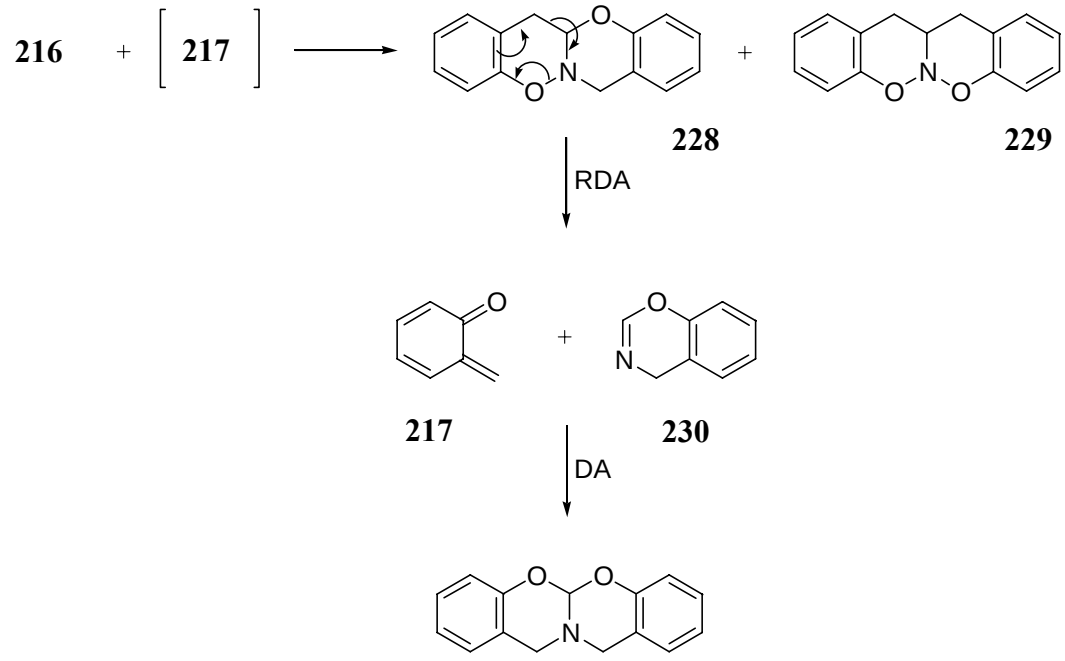
225 **226**

227

Scheme 66

An interesting sequence of tandem *retro*-Diels-Alder-Diels-Alder (RDA-DA) reactions of 1,2-benzoxazines (**216**) has been reported.[5] Upon thermolysis, in the absence of an alkene dienophile, **216**

leads to the linear *N*-bridged polycyclic benzoxazinobenzoxazine isomers (**228**), (**229**) and (**231**) (Scheme 67).[90]



Scheme 67

CONCLUSION

It is clear that both partially saturated and ring-fused 1,2-oxazines have proved and will continue to be an enduring challenge as potential precursors to molecules of diverse structure, substitution and properties, especially biologically active carbo(hetero)cyclic congeners.

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