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# The reverse Cope cyclisation: a classical reaction goes backwards

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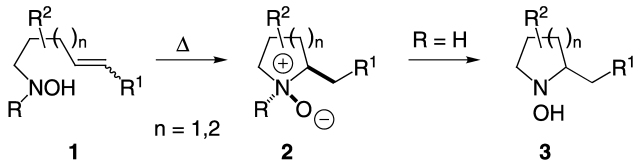
## 1. Introduction

Before beginning a discussion of this chemistry, it seems prudent to provide a definitive name for the process whereby an unsaturated hydroxylamine **1** undergoes a thermal cyclisation to give pyrrolidine- or piperidine-*N*-oxides **2** or the corresponding *N*-hydroxy derivatives **3** (Scheme 1)




**1** **2** **3**

**Scheme 1.**

This has variously been referred to as the retro- or reverse Cope elimination, cyclisation or reaction and, more recently, the Cope–House cyclisation by Holmes (Section 6), the latter to highlight the key contribution to its discovery made by House (Sections 2 and 3). The term EPOC reaction, proposed in an ironic riposte to an unfavourable referee's comment by Ciganek (Section 2), is perhaps the least serious, but not without some merit. While not wishing to detract in any way from House's contribution and with some trepidation in disagreeing with our learned friend and colleague, Professor Holmes, we propose that the best descriptive term is 'the reverse Cope cyclisation,' in line with Ciganek's more serious suggestion. This is also consistent with a recent short review of the subject.[1]

The road to the current state of progress in the reverse Cope cyclisation is paved with serendipity and features a relatively lengthy period of dormancy. In these respects, it has some similarities with its relative, the Cope elimination. Although first reported in 1900,[2] it was not until the seminal work of the Cope group, initiated during the late 1940s, that this now classical reaction of tertiary amine-*N*-oxides was brought to prominence.[3] Furthermore, as pointed out by Ciganek,[4] it is likely that Cope was well aware of the possibility of the occurrence of reverse Cope reactions; despite this, while it is very likely that he and LeBel did indeed effect such a transformation, they did not isolate and identify the definitive product.[5] Thus, while noting a significant loss of material during distillation of the Cope elimination product **4**, they suggested that this was due to polymerisation rather than formation of the much less volatile reverse Cope elimination product, the piperidine-*N*-oxide **5** (Scheme 2). As ever, hindsight is a wonderful thing!

*Keywords*: Reverse Cope; Cyclisation; Hydroxylamines; Pyrrolidines; Piperidines; *N*-Oxides; Pyrrolidine-*N*-oxides; Pericyclic reaction; Alkynyl hydroxylamines; Nitrones.

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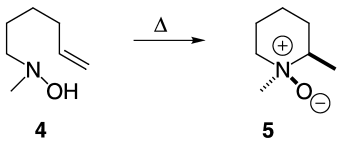
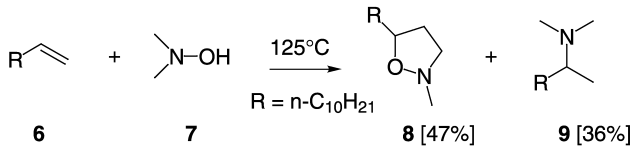



**Scheme 2.**

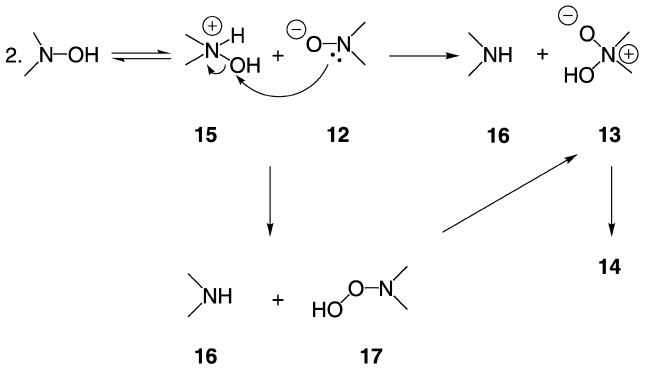
In addition, again as highlighted by Ciganek,[4] Cope and LeBel further reported[5] that partial pyrolysis of an isomeric mixture of the *trans*-*N*-oxide **5** and its *cis*-isomer allowed separation of the *trans*-isomer **5** into pentane. As it is highly unlikely that either very polar *N*-oxide isomer would be pentane-soluble, a more likely explanation is that the *trans*-isomer **5** selectively undergoes a Cope elimination by proton abstraction from the 2-methyl group, a pathway not available to the *cis*-isomer, to give the less polar hydroxylamine **4**. During subsequent manipulation in pentane, this must then have reverted selectively to the *trans*-*N*-oxide **5** by a reverse Cope cyclisation, prior to isolation and analysis. In retrospect, this has important implications for the mechanism of the reverse Cope process, as discussed below.

Interestingly, an isolated report, published in 1973,[6] may feature an example of an intermolecular reverse Cope elimination, given that one has sympathy with the complexities of hydroxylamine chemistry, wherein disproportionation can take a leading role. The exact example involved thermolysis at 125 °C of a mixture of 1-dodecene **6** and *N*,*N*-dimethylhydroxylamine **7** and gave two isolated products, the isoxazolidine **8** and the tertiary amine **9** (Scheme 3).




**Scheme 3.**

If one assumes a reverse Cope elimination takes place initially between the reactants, the first-formed product would be the amine-*N*-oxide **10**. This could then undergo reduction by the hydroxylamine **7** as suggested in Scheme 4. Thus, proton exchange, not unreasonable when one considers the relatively low p$K_a$ (13.7) of the hydroxyl group in hydroxylamine,[7,8] could generate the ammonium salt **11** accompanied by the oxide **12**. This could then deoxygenate the salt **11**, either directly, as shown, or by *N*-hydroperoxide formation and rearrangement, to give the observed amine **9**, together with the intermediate **13**; loss of water would then generate the reactive nitrone **14**. This then adds with characteristic regioselectivity by a [1,3]-dipolar cycloaddition mechanism to the alkene **6** to give the isoxazolidine **8**. The latter nitrone could also be generated by a similar process, but one which involves proton exchange between two hydroxylamine molecules, resulting in overall disproportionation; presumably, the dimethylamine was too volatile to isolate (Scheme 5). It is also conceivable that all of these transformations could involve initial homolysis of the O–H bond of the hydroxylamine to give a nitroxide. Intermediate **13** could also be obtained by attack of the oxide **12** onto the protonated species **15** at oxygen to give the peroxide **17** that could rearrange to the nitrone hydrate **13**.



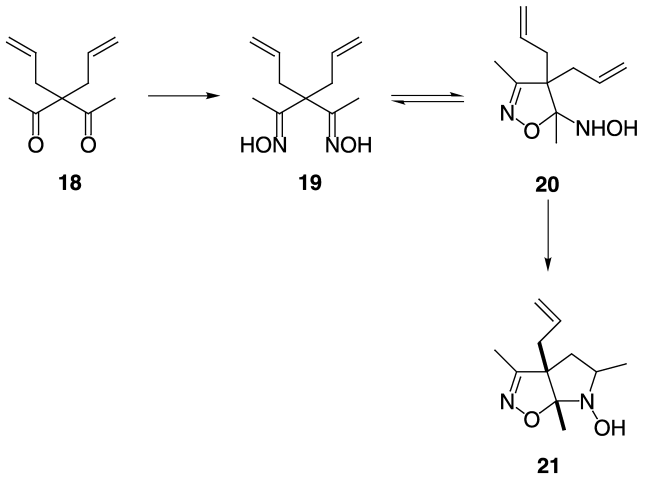

**Scheme 4.**




**Scheme 5.**

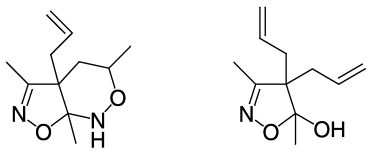
## 2. Discovery and mechanism

The first report of an authentic reverse Cope cyclisation was made by House in 1976.[8] This serendipitous discovery was made during attempts to prepare the dioxime **19** from the corresponding 1,3-dione **18** under standard conditions ($NH_2OH{\cdot}HCl$, NaOAc, aq. dioxane, reflux). Instead, the annulated pyrrolidine **21** was isolated as the main product and presumed to have arisen by a reverse Cope cyclisation of the 'anomeric' hydroxylamine **20**, which would be




**Scheme 6.**

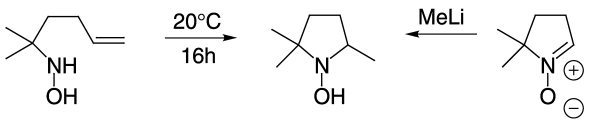
expected to be in equilibrium with the dioxime structure **19** (Scheme 6). The unexpected product **21** was isolated largely as a single diastereoisomer. The 5/5 ring fusion presumably dictates a *cis*-ring fusion, but the relative positioning of the new methyl group was not determined. A third minor product appeared to be a structural isomer rather than a stereoisomer and was not identified. In view of subsequent observations (see below), this might be the Meisenheimer rearrangement product **22** derived from the initial reverse Cope product **21**. That the equilibrium shown in Scheme 6 is reasonable is supported by the fact that the monoxime of dione **18** exists exclusively as the isoxazoline **23** (Scheme 7).[8]




**22** **23**

**Scheme 7.**

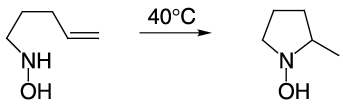
To further illustrate this unexpected observation, House then proceeded to synthesise the simpler and less structurally ambiguous hydroxylamine **24**. This was found to undergo smooth cyclisation to the *N*-hydroxypyrrolidine **25** upon standing at ambient temperature overnight or heating on a steam bath for 5 min. Its structure was proven by comparisons with authentic material and the derived *O*-benzoates obtained by the addition of methyl lithium to nitrone **26** (Scheme 8). House and Lee also defined some of the scope for the formation of piperidines by this pathway (see Section 3.3).[9]




**24** **25** **26**

**Scheme 8.**

Further examples of the type of cyclisation shown in Scheme 8 were provided 2 years later by Black and Doyle (see Scheme 18).[10] The simplest version of the reverse Cope cyclisation (Scheme 9) was unexpectedly observed upon mild heating or prolonged storage of the hydroxylamine **27**, an intermediate required during Oppolzer's studies of intramolecular [1,3]-dipolar cycloadditions, leading to the *N*-hydroxypyrrolidine **28**.[11]




**27** **28**

**Scheme 9.**

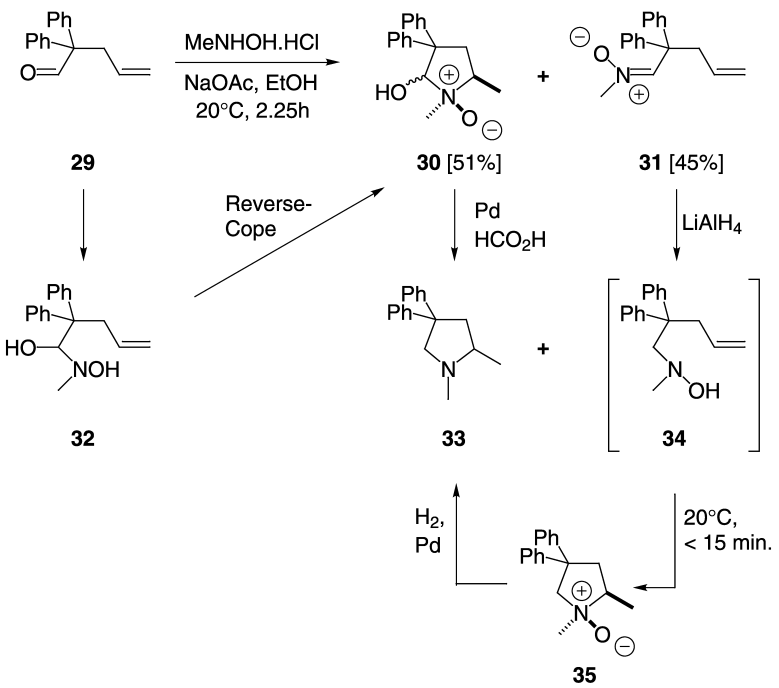
It seems likely that a further example of serendipitous science led Ciganek to deduce the existence of the reverse Cope cyclisation by a rather neat set of logical experiments. This all arose during a seemingly routine synthesis of the nitrone **31** from the aldehyde **29** and methylhydroxylamine (Scheme 10).[4,12] While the desired nitrone **31** was indeed isolated in 45% yield, a second major product (51%) was the α-hydroxypyrrolidine-*N*-oxide **30**, which was found, remarkably, to survive sublimation at 150 °C unchanged. Ciganek deduced that this could have been formed by reverse Cope cyclisation of the *N*-hydroxyhemiaminal **32**, in competition with simple dehydration to the nitrone **31**.

This idea was then correlated in a clever manner: careful partial reduction of the nitrone **31** lead to the (presumed) alkenylhydroxylamine **34**, which underwent rapid reverse Cope cyclisation during work-up to give the pyrrolidine-*N*-oxide **35** in ca. 90% yield. The two pathways were correlated by reduction of both *N*-oxides [**30** and **35**] to the same pyrrolidine **33**. One can only speculate if similar nitrone preparations carried out by others gave similar lower-than-expected yields but that the reason behind this remained obscure.

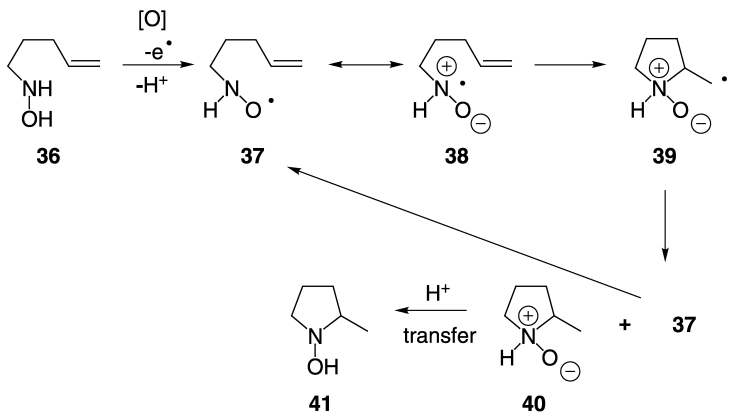
Other than just a few 'one-off' contributions, the topic lay apparently dormant for the whole of the 1980s. It was only during the early 1990s that this remarkable reaction was brought to prominence with the publication of seminal contributions from Ciganek of a seemingly long-term scope and limitations study[4,12,13] and from Oppolzer, who both defined the likely mechanism and also provided a most elegant illustration of the synthetic potential of the reaction.[14] This period then saw contributions from a number of other groups which have broadened the scope of the method, particularly as an efficient and usually highly stereoselective approach to pyrrolidines and related saturated five-membered heterocycles. A particularly notable feature of the reaction is that it is, effectively, a method for the addition of an amine nitrogen to an unactivated carbon–carbon double or triple bond. Initial mechanistic speculations by House suggested that the reverse Cope cyclisation operates by a radical-based mechanism. This conclusion was based on some electrochemical measurements and the experimental observation that the cyclisation appeared to be promoted by traces of oxidising agents. Thus, oxidation of an initial unsaturated hydroxylamine **36** could lead to an intermediate nitroxide **37** which, when represented as the radical cation **38**, shows how the central carbon–nitrogen bond formation could occur to give the pyrrolidine radical **39** (Scheme 11). This, in turn, could abstract a hydrogen radical from the starting material **36**, thereby initiating another cascade and leaving the resulting neutral species **40** to undergo a facile proton transfer to give the observed product **41**.

An inspiration for this suggestion came from earlier work by Motherwell and Roberts, who showed that nitroxide **43** could be efficiently generated by an oxidative cyclisation of the corresponding unsaturated hydroxylamine **42** using silver(I) oxide or carbonate (Scheme 12).[15] It is also conceivable that the pathway could be initiated by a hydroxylamine molecule being oxidised to a nitroso species; interaction of the latter with a second hydroxylamine could then give two molecules of the corresponding nitroxide [cf. **37**].

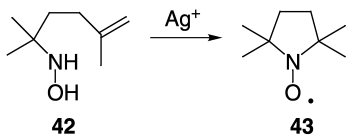
However, these ideas were soon undermined by the observations of Black and Doyle[10] who found that the



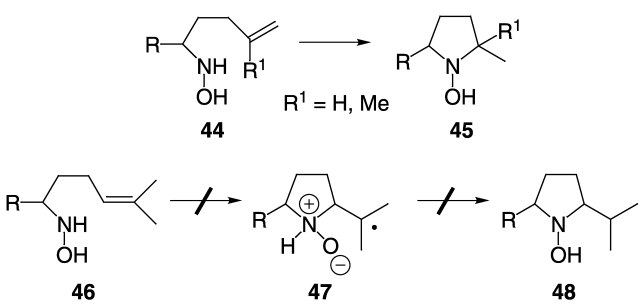

**Scheme 10.**




**Scheme 11.**



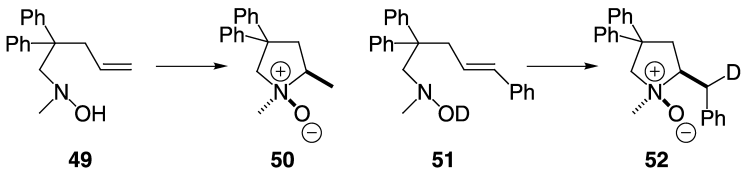

**Scheme 12.**




**Scheme 13.**

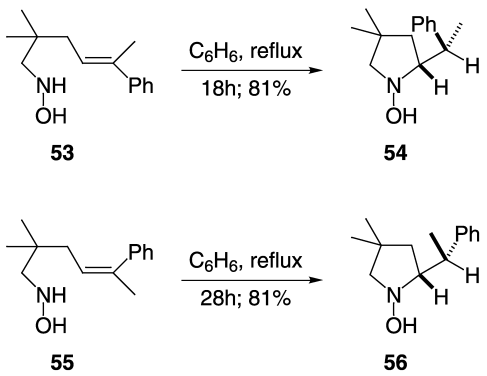
addition of radical inhibitors (hydroquinone, phenol or aniline) had no effect on the rate of reverse Cope cyclisations. Perhaps more seriously, they found that, while the hydroxylamines **44** underwent cyclisation with relative ease (20 °C for days or 80 °C, $C_6H_6$, 10–15 min) to give the *N*-hydroxypyrrolidines **45**, the homologous hydroxylamine **46**, having two distal substituents on the alkene function, failed to deliver the pyrrolidine **48** under similar or more forcing conditions, despite the fact that the radical intermediate **47** expected from the House mechanism should be more stable (Scheme 13). Steric arguments also do not provide support for the House mechanism in these cases.

Ciganek provided additional observations which were difficult to reconcile with a radical mechanism.[12] Firstly, reverse Cope cyclisation of a diphenyl-substituted precursor **49** gave a single diastereoisomer **50**, in which the new methyl group and the oxide oxygen were *cis* (Scheme 14). Subsequently, this has been shown to be a key




**Scheme 14.**

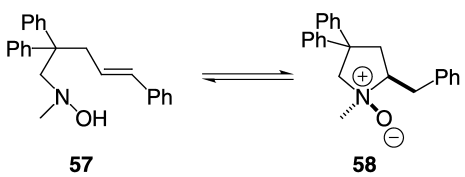
stereochemical theme running throughout the reverse Cope method. In a second experiment, cyclisation of the O-deuteriated hydroxylamine **51** gave only one isomer of the expected pyrrolidine-*N*-oxide **52**, again indicative of a concerted mechanism. Final definitive proof of a concerted mechanism was provided in a most elegant fashion by Oppolzer and his colleagues (Scheme 15).[14] They showed that the (*E*)-alkenylhydroxylamine **53** underwent reverse Cope cyclisation to provide only the pyrrolidine-*N*-oxide **54**, whereas the corresponding *Z*-isomer **55** was similarly converted into only the epimeric product **56**.




**Scheme 15.**

The conclusion must be that the cyclisation involves suprafacial formation of the new C–N and C–H bonds and thus proceeds by a planar five-membered transition state, in the same manner as the Cope elimination.[3,16,17] Both conclusions have subsequently been corroborated by ab initio and density function calculations,[17] which suggest an approximately synchronous process for both reactions.

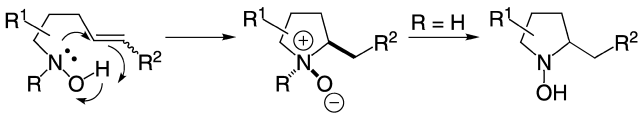
The observed solvent effects generally support these conclusions. Relatively polar solvents tend to favour the reverse Cope cyclisation, probably because these are more able to solvate the polar *N*-oxide (or hydroxylamine) products. A purely empirical judgement suggests that chloroform or perhaps methanol or DMSO are usually the solvents of choice. Revealing comparative data have been presented by Ciganek, some of which are not readily explained.[4,12] Although somewhat unusual, some reverse Cope cyclisations are themselves reversible at ambient temperature (Scheme 16): the highly substituted hydroxylamine **57** shows such behaviour in its interconversion




**Scheme 16.**

with the *N*-oxide **58**, which is very solvent dependent. In chloroform, methanol and DMSO containing TFA, the equilibrium lies entirely to the right in favour of the *N*-oxide **58**, whereas approximately equal amounts of **57** and **58** are observed in benzene, THF and neat DMSO, while acetone and acetonitrile strongly favour *N*-oxide **58** formation. The *N*-isopropyl homologue of hydroxylamine **57** shows complete conversion into the corresponding *N*-oxide in chloroform, but THF, DMF and DMSO all favour the hydroxylamine **57**. All this is not easily explained, but one message is clear: try a new reverse Cope cyclisation in chloroform first. However, despite the foregoing conclusions, spectacular success in this area has been achieved simply by thermolysis in benzene or xylene (see below).[14]

To conclude this section, the basic mechanism of the reverse Cope cyclisation is probably best represented as the $2\pi+2\sigma+2n$ process shown in Scheme 17. The requirement for a planar, five-centred transition state has considerable implications, both for the viability of the reaction and, naturally, for its stereochemical characteristics, as illustrated by much of the following chemistry.



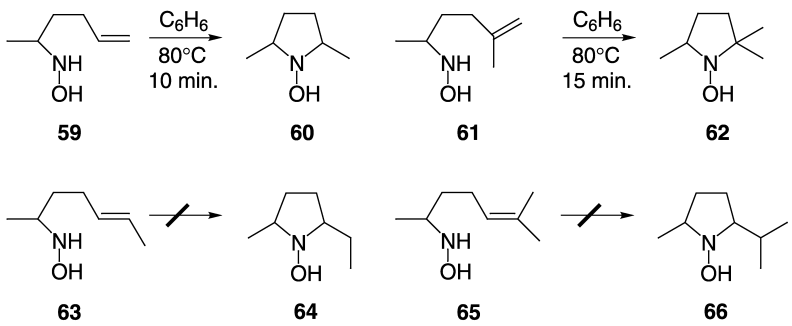

**Scheme 17.**

## 3. Scope and limitations

### 3.1. Basic pyrrolidine formation

In general, the reverse Cope cyclisation is most useful for the elaboration of pyrrolidine-*N*-oxides or *N*-hydroxypyrrolidines. Early results revealed the now-familiar facets of the substitution patterns, both at nitrogen and on the alkene function. Black and Doyle[10] observed that both the pent-4-enylhydroxylamine **59** and its 4-methyl homologue **61** underwent highly efficient cyclisation to the *N*-hydroxypyrrolidines **60** and **62**, respectively, during 10–15 min reflux in benzene or at ambient temperature for a few days (Scheme 18). In contrast, the hydroxylamines **63** and **65** having one or two substituent methyl groups at the distal end of the alkene function, failed to cyclise to the pyrrolidines **64** and **66**, respectively, upon heating until decomposition set in.

Although no stereochemistry was assigned to the 2,5-dimethylpyrrolidine **60**, it was clearly isolated as a single diastereoisomer, from the occurrence of two methyl

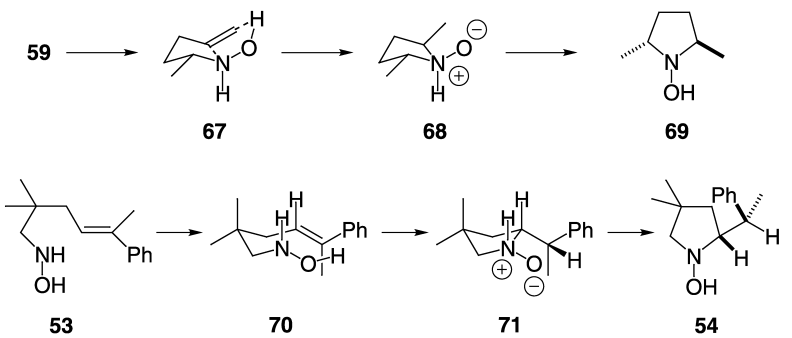



**Scheme 18.**

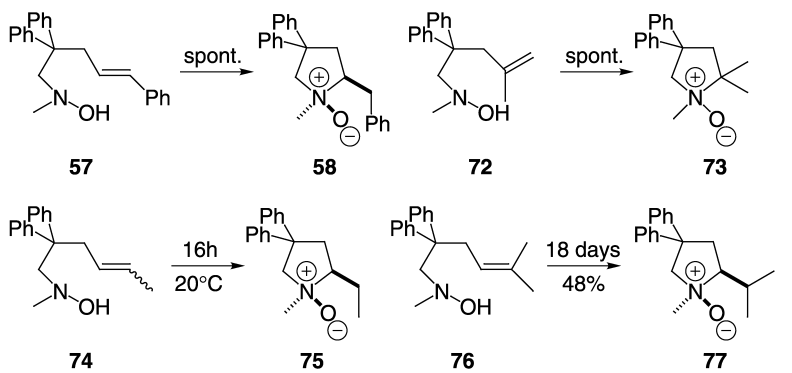
doublets at $\delta_H$ 1.15 and 1.22. These data, together with the requirement for a planar transition state and stereocontrol by the substituent methyl group, all suggest the formation of the *trans*-isomer **69** via a chair conformation **67** and an initial *N*-oxide **68** (Scheme 19).

Such an analysis is also consistent with the stereochemical outcomes of the cyclisations reported by Oppolzer (Scheme 15).[14] Thus, the (*E*)-isomer **53** should cyclise via the transition state conformation **70** to give, initially, the *N*-oxide **71** and, thence, the observed product **54**. Further revealing examples of this type have been provided by Ciganek (cf. Scheme 16).[4] Both the cinnamyl derivative **57** and the internally-substituted analogue **72** of a 2,2-diphenyl-substituted *N*-methylhydroxylamine underwent cyclisation during work-up, following their preparation by reduction of the corresponding nitrones, to give the pyrrolidine-*N*-oxides **58** and **73**, respectively, in essentially quantitative yields (Scheme 20). However, the related crotyl derivative **74** only partly cyclised to the *N*-oxide **75** under the same conditions and a further 16 h at ambient temperature was required for complete cyclisation. In contrast, the dimethyl analogue **76** gave only 48% of the *N*-oxide **77** after 18 days at ambient temperature in chloroform, together with 22% of the starting material **76**; the remainder was unidentified material.

A number of conclusions can be drawn from the foregoing discussion, which are backed up by subsequent results. First, *N*-methylhydroxylamines undergo cyclisation faster than the corresponding primary analogues. Secondly, distal substituents certainly retard the reverse Cope cyclisation, whereas internal substituents, at least methyl, seem to have little effect. Thirdly, the Thorpe–Ingold steric compression effect is enormously beneficial: the hydroxylamines **53**, **57**, **72** and **74** are clearly examples of this effect. It is most unusual to observe such facile cyclisations at ambient temperature with a distally substituted alkene in the absence of this or a related constraint. It does seem that the two reacting functionalities have to be held in close proximity for a facile cyclisation to occur. A further illustration of the

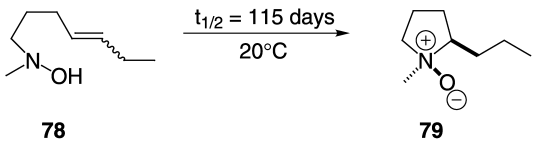



**Scheme 19.**




**Scheme 20.**

first effect is the finding[4] that the *N*-methylhydroxylamine **78** undergoes complete cyclisation to the *N*-oxide **79** (Scheme 21), although with $t_{1/2}$=115 days (!), whereas the related primary hydroxylamine **63** (Scheme 18) failed to cyclise.[10] The hydroxylamine **78** was a mixture of (*E*)- and (*Z*)-isomers and, while both underwent cyclisation, the latter isomer was less reactive in this respect, consistent with the transition state conformation **67** (Scheme 19); in the (*Z*)-isomer, the substituent ethyl group on the alkene would have to adopt a pseudoaxial position.



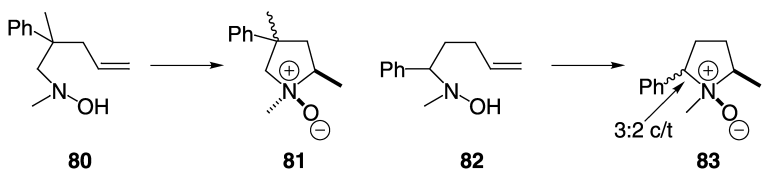

**Scheme 21.**

To return to some stereochemical features, while it is unsurprising that the substituted *N*-methylhydroxylamine **80** undergoes reverse Cope cyclisation to give a 3:2 mixture of the *N*-oxides **81**, perhaps less expected is the observation that a similar lack of stereoselectivity is shown in the cyclisation of the phenyl-substituted hydroxylamine **82**, which gives a 3:2 mixture **83** with a slight preference for the *cis*-isomer (Scheme 22). In a useful amplification of this phenomenon, Bagley and Tovey have shown that this is a general feature, and that increasing the size of the substituent adjacent to or attached to the nitrogen (cf. **82**) results in a distinct increase in the formation of the 2,5-*cis*-pyrrolidine-*N*-oxide. For example, the *N*-cyclohexyl-α-phenylhydroxylamine corresponding to precursor **82** cyclises to give essentially only the *cis*-isomer **84** (Scheme 23).[18] Presumably, this is a consequence of the substituent on nitrogen, which will inevitably destabilise the chair-like intermediate **85** [cf. **67** (Scheme 19)] related to that proposed to explain the formation of a single *trans*-2,5-substitution pattern from primary hydroxylamines. An alternative boat-like conformation **86**, in which the necessary planar, five-membered transition state essential for the reverse Cope cyclisation is retained, then explains the formation of largely or exclusively the 2,5-*cis*-diastereoisomers when either or both substituents $R^1$ and $R^2$ are increased in size.

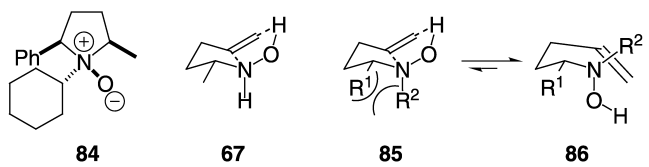
Preference for the formation of 2,5-*cis*-isomers can be further enhanced, as these are also the more thermodynamically-favoured isomers, by relying on the thermal reversibility of the reverse Cope cyclisation (see above). This is not as simple as it sounds; no doubt, thermolysis without solvent at 95 °C is currently the optimum method.[18] In contrast, heating in either chloroform or toluene gives mixed results, largely resulting from significant decomposition during the prolonged reaction times required to establish a synthetically-useful isomerisation.

### 3.2. Annulated pyrrolidines

The reverse Cope cyclisation can also be used to form annulated pyrrolidines. For example, addition of methylmagnesium chloride to the nitrone **87** gave the expected hydroxylamine **88**, which underwent partial cyclisation



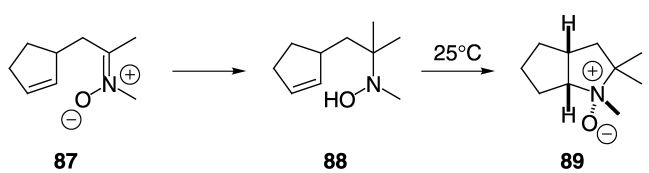

**Scheme 22.**



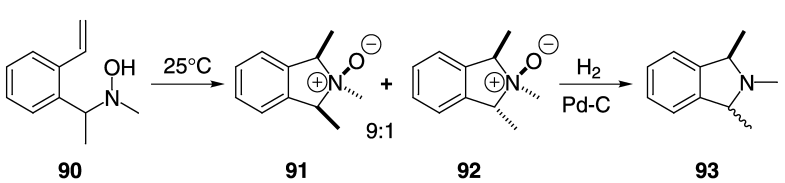

**Scheme 23.**

(2:1) during work-up, a process which was complete after 16 h at ambient temperature in dichloromethane (Scheme 24).[13] Although not assigned, the stereochemistry of the product **89** must surely feature a *cis*-ring fusion, although the relationship between this and the stereogenic nitrogen centre is unclear, but the isomer shown seems likely (cf. Scheme 19). No doubt, the Thorpe–Ingold effect engendered by the two methyl substituents is crucial in facilitating this cyclisation which, as yet, has not been developed further.

Isoindolines can similarly be prepared, again by Grignard addition to the corresponding nitrone, followed by cyclisation of the resulting hydroxylamine **90** during work-up, to give a 9:1 mixture of the *cis*- and *trans*-substituted products



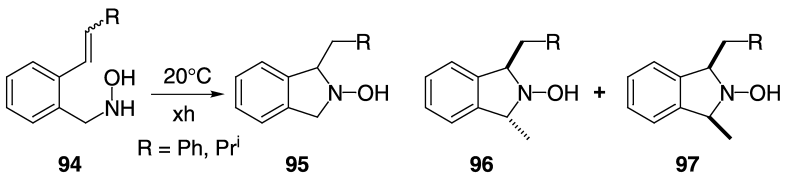

**Scheme 24.**



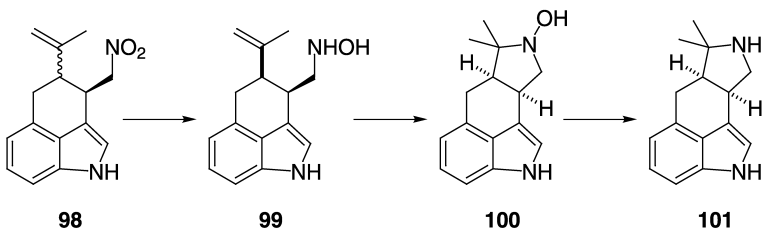

**Scheme 25.**

**91** and **92** (Scheme 25).[13] Unfortunately, both these and the reduction product **93** are reported to be rather unstable upon exposure to air. However, the corresponding *N*-hydroxyisoindolines derived from reverse Cope cyclisation of the corresponding primary benzylic hydroxylamines turn out to be stable, although clearly sensitive to oxidation in solution.[19] Such cyclisations are also successful when the alkene carries a distal substituent and therefore probably benefit from the rotational restriction imposed by the benzene ring on the two reacting groups (Scheme 26). Cyclisations of the simple styrenes **94** at ambient temperature or in refluxing chloroform lead smoothly to the monosubstituted *N*-hydroxyisoindolines **95**, the (*Z*)-isomers of the precursors **94** cyclising considerably faster, possibly because, to achieve the necessary planar transition state, the alkene function must twist out of conjugation. The already slightly-twisted (*Z*)-styryl function would therefore require less energy to achieve this required conformation. Cyclisations of hydroxylamines having an additional benzylic substituent, prepared either by nitrone reduction or Mitsunobu displacement,[20] gave gross mixtures of products **96** and **97** when these were formed at 60 °C, but largely single *trans*-isomers **96** at ambient temperature. This therefore may be another example of a thermal equilibration to the more thermodynamically-stable isomer (cf. Scheme 23).[18] A similar reverse Cope mechanism may explain the formation of the pyrrolidine **101** from the nitroalkene **98** during reduction with zinc amalgam in acidic methanol (Scheme 27).[21] This would require partial reduction to the hydroxylamine **99** and cyclisation, a not unreasonable idea in view of both the activating *cis*-disposition of the reacting groups, which are also constrained in their rotational freedom by the cyclohexyl residue, together with the fact that alkenes having an 'internal' methyl substituent are known to undergo such reactions without rate retardation (see above). Given the veracity of this suggestion, it seems likely that the overall 10% yield of the final product **101** could be greatly improved by employing a more selective approach to the hydroxylamine **99** and possibly isolation of the *N*-hydroxypyrrolidine **100**.

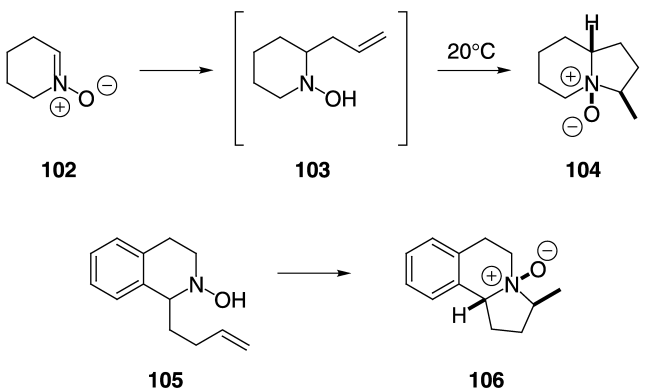
Annulated pyrrolidines having nitrogen at the ring junction are also accessible using the reverse Cope cyclisation. In a definitive example, Ciganek found that Grignard addition to the nitrone **102** gave the expected hydroxylamine **103**, which underwent cyclisation during work-up to give largely (85:15) the *cis*-perhydroindolizidine-*N*-oxide **104** (Scheme 28).[13] In just the same fashion, the hydroxylamine **105** gave only the pyrrolo[2,1-*a*]isoquinoline-*N*-oxide **106** as a single isomer. Further illustrations of this methodology have yet to be reported and the fact that the foregoing




**Scheme 26.**



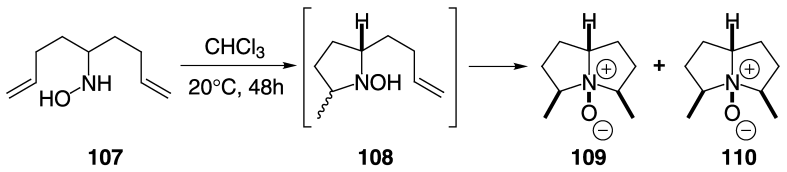

**Scheme 27.**



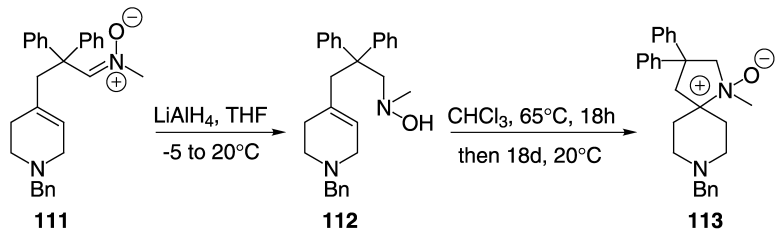

**Scheme 28.**

examples proceed so readily, presumably again assisted by the constraining ring, suggests that cyclisations of more highly-substituted examples, including those with a distal alkene substituent, should be viable.

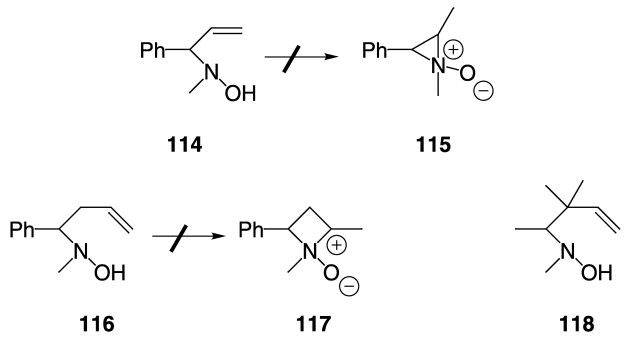
Two consecutive reverse Cope cyclisations are also possible (Scheme 29).[13] The precursor hydroxylamine **107** was obtained by cyanoborohydride reduction of the corresponding oxime and, after 2 days at ambient temperature, only 10% of the intermediate partially-cyclised hydroxylamine **108** remained. Rapid reduction of the *N*-oxides **109** and **110** using hexachlorodisilane was necessary to secure the corresponding pyrrolizidines, as, during the much slower reduction using $H_2$/Pd–C, a substantial quantity (some 40%) of the cycloreversion product **108** (isolated in a




**Scheme 29.**




**Scheme 30.**




**Scheme 31.**

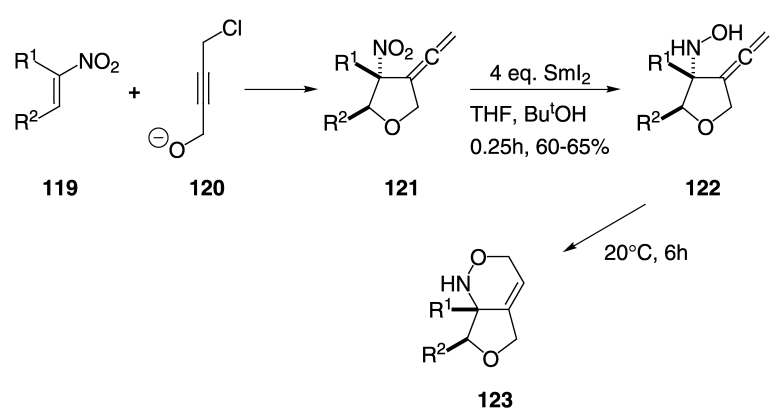
reduced form) was formed. Perhaps these somewhat slower cyclisations will also be viable using more highly-substituted substrates, but this has yet to be proven.

The *spiro*-pyrrolidine **113** can be prepared by reverse Cope cyclisation (Scheme 30).[13] The precursor hydroxylamine **112** was obtained by careful reduction of the corresponding nitrone **111**. Clearly, this is a much more difficult cyclisation, requiring overnight reflux, followed by 18 days at ambient temperature, to reach completion. No doubt, the very large Thorpe–Ingold effect of the *gem*-diphenyl group is crucial, the related unsubstituted analogue failing to cyclise. Despite this difficulty, there is clearly much synthetic potential in this method, given due regard to the substitution pattern.

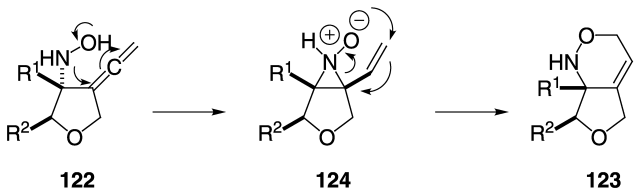
### 3.3. Other ring sizes

A few attempts have been made to extend the scope of the reverse Cope cyclisation to other ring sizes. On the grounds of ring strain alone, it is perhaps not surprising that the allylic hydroxylamine **114** failed to cyclise to the aziridine-*N*-oxide **115** (Scheme 31).[4] In any event, examples of the latter species, generated in other ways, are known to undergo exceptionally facile Cope eliminations to give hydroxylamines [cf. **114**].[22,23] An alternative decomposition pathway, which also occurs at low temperature (0 °C), is the cheletropic elimination of a nitrosoalkane.[22] Similarly, the homologous *N*-methylhydroxylamine **116** failed to cyclise to the corresponding azetidine-*N*-oxide **117**.[4,9] Despite the strain evident in any planar transition state leading to these ring sizes, it remains to be proven that more highly-substituted substrates also cannot be cyclised, as such reactions would benefit considerably from the Thorpe–Ingold buttressing effect. However, ominously, the hydroxylamine **118** also failed to cyclise before disproportionation to the related oxime set in.[9]

In an interesting caveat to these limitations, it is possible that a reverse Cope cyclisation constitutes a key step in novel routes to 3,6-dihydro-1,2-oxazines **123**. Elaboration of the nitrotetrahydrofurans **121** by sequential oxa-Michael addition-$S_N2'$ substitution reactions between a nitro-alkene **119** and the chloroynolate **120**, followed by careful reduction using samarium iodide, leads to the allenic

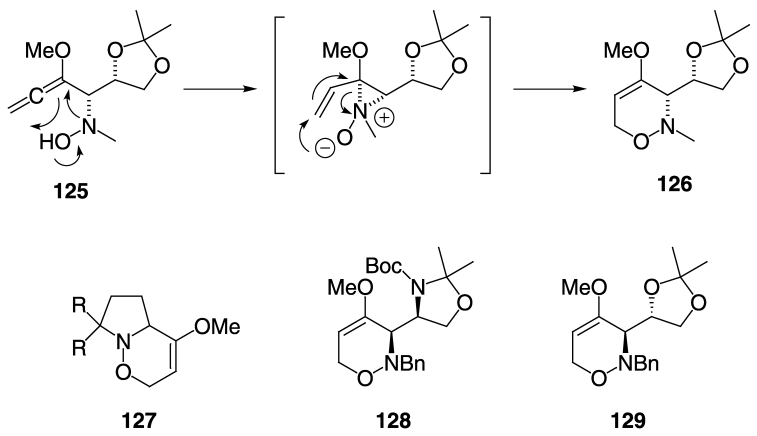



**Scheme 32.**

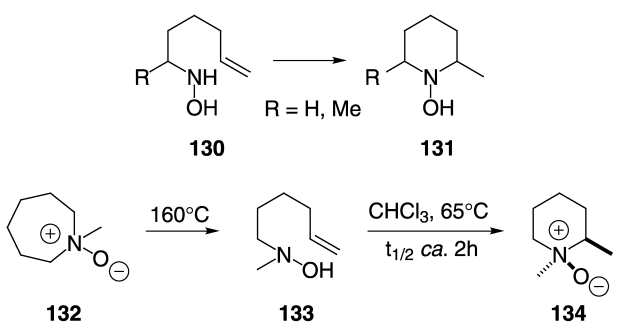



Scheme 33.

facile reverse Cope processes and by the knowledge that internal substituents can easily be accommodated (Scheme 33). This idea does require that the proposed intermediate *N*-oxides **124** undergo the second [2,3]-sigmatropic rearrangement step much faster than (what might be expected to be) a rapid proton transfer to the corresponding neutral *N*-hydroxy species. In much the same way, at least in the sense of precursors and products,




Scheme 34.

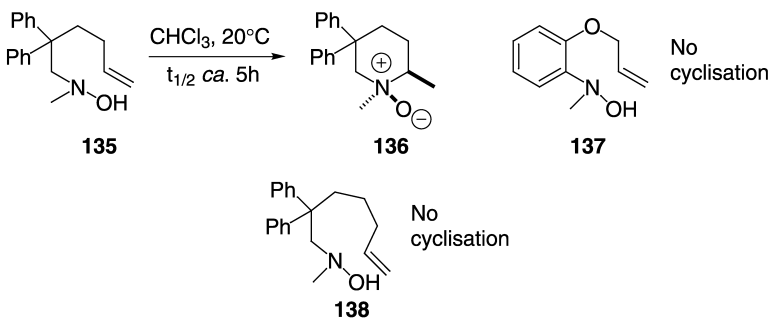



Scheme 35.

hydroxylamines **122** (Scheme 32).[24] On standing for 6 h at ambient temperature, these hydroxylamines are then converted into the oxazines **123** [$R^1$, $R^2$=*n*-alkyl, Ph or $(CH_2)_4$] in 62–92% yields. The corresponding cyclopentatetrahydrofuran [**122**; $R^1$, $R^2$=$(CH_2)_3$] by contrast took 15 days to undergo complete cyclisation. Initially, this was an unexplained phenomenon but, in a flight of fancy, one of the present authors (D.W.K.) suggested the involvement of a reverse Cope cyclisation when reviewing the preliminary communication of this work.[24a] This was inspired by the resemblance of the reaction conditions to many hydroxylamines [e.g. **125**] derived in a usually highly-stereoselective fashion from the corresponding nitrone and an excess of lithiated methoxyallene also undergo smooth, uncatalysed conversion into 1,2-oxazines [e.g. **126**] (Scheme 34).[25]

Similar chemistry can be used to obtain the annulated derivatives **127** from the corresponding pyrrolidine-based nitrones, together with the nitrogen analogues **128** and the *anti*-isomer **129** of the first example **126**, by precomplexation of the nitrone with diethylaluminium chloride. Whatever the mechanism, overall this is certainly useful chemistry!

In contrast to the failure to form isolable three- or four-membered cyclic *N*-oxides by reverse Cope cyclisations (Scheme 31), the method is most certainly applicable to piperidine formation, as first demonstrated by House and Lee.[9] However, more forcing conditions are usually required. For example, the unsaturated primary hydroxylamines **130** required heating in refluxing xylene for ca. 1 h (or neat at 160 °C) to secure the *N*-hydroxypiperidines [**131**; R=H, Me] (Scheme 35).[9] The 2,6-disubstituted piperidine [**131**; R=Me] was obtained as a mixture containing a

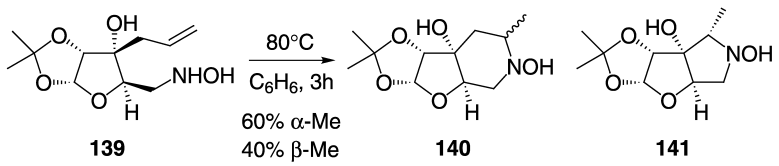



Scheme 36.

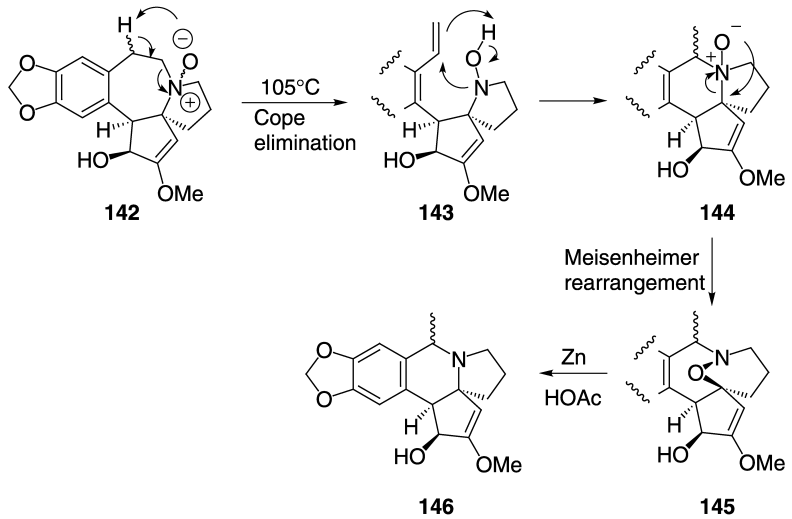
preponderance of the *trans*-isomer. However, as in the case of pyrrolidine synthesis, the corresponding *N*-methylhydroxylamines undergo cyclisation more easily. Thus, the hydroxylamine **133**, somewhat perversely prepared by a Cope elimination of the *N*-oxide **132**, while cyclizing very slowly at ambient temperature, underwent conversion into the piperidine-*N*-oxide **134** in refluxing chloroform with $t_{1/2}\simeq 2$ h.[4,12] Once again, Thorpe–Ingold restrictions accelerate the cyclisation, the *gem*-diphenyl analogue **135** converting into the *N*-oxide **136** at ambient temperature in chloroform with $t_{1/2}\simeq 5$ h (Scheme 36).[4] The aniline derivative **137**, however, failed to cyclise, despite the conformational restriction imposed by the benzene ring.[4] This can be explained by the much reduced basicity of the nitrogen. However, both of these activating effects in combination were insufficient to induce cyclisation of the one-carbon homologue **138** to the corresponding seven-membered *N*-oxide.[4] It may be that, in most cases, the reverse Cope cyclisations are restricted to the formation of five- and, to a lesser extent, six-membered rings. In the latter respect, there is still no published example of piperidine-*N*-oxide formation by reverse Cope cyclisation of an unsaturated hydroxylamine having a substituent at the alkene terminus, i.e. thus far, only α-methylpiperidines have been formed. Hence, it appears that this additional deactivating feature usually precludes the more difficult piperidine formation, when present. No doubt, given enough conformational constraint, such an example will some day come to light. An isolated example of the synthesis of an annulated piperidine illustrates a further synthetic potential of the reverse Cope method. The carbohydrate-derived hydroxylamine **139** was found to be isolable, but cyclised smoothly to a 3:2 mixture of the annulated piperidines **140** in 87% isolated yield, following a 3 h reflux in benzene (Scheme 37).[26] Unsurprisingly, in view of the foregoing examples (Schemes 24–26), the corresponding vinyl derivative was similarly converted into the 5/5 ring-fused system, but as a single isomer **141**.

A most interesting example of a reverse Cope cyclisation leading to a 'piperidine' accounts for the thermally-induced rearrangement chemistry of the homoharringtonine-*N*-oxides **142** (Scheme 38).[27] One pathway is a straightforward Meisenheimer rearrangement, while a second pathway, leading to the isolated products **145**, probably proceeds by an initial Cope elimination to give the *N*-hydroxypyrrolidine **143**, which then undergoes reverse Cope cyclisation to give the 'piperidine'-*N*-oxide **144**. This *N*-oxide then also undergoes a final Meisenheimer-type rearrangement to give the isolated products **145**. Subsequent reduction using zinc and acetic acid gives the ring-contracted homoharringtonine analogues **146**. Overall, these rearrangements are highly solvent dependent and probably quite restricted in their occurrence.

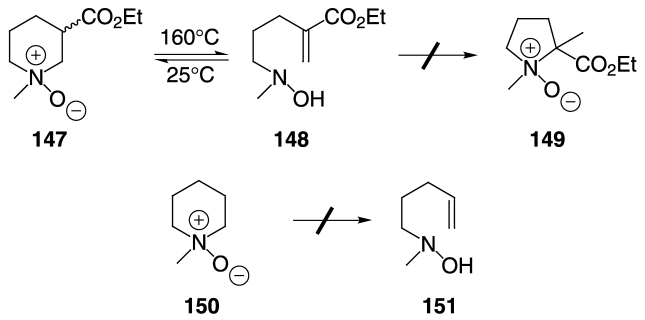
A final caveat regarding piperidine formation features a competition reaction between intramolecular Michael addition and reverse Cope cyclisation. On standing at ambient temperature, the hydroxylamine **148** cyclises to give the piperidine-*N*-oxide **147**, presumably by a Michael addition, rather than the pyrrolidine-*N*-oxide **149**, which would be formed by a reverse Cope process (Scheme 39).[4] This reactivity reflects the reverse processes: the hydroxylamine **148** can be formed from the *N*-oxide **147** by thermolysis, probably by a retro-Michael elimination rather than a Cope elimination which requires an unattainable



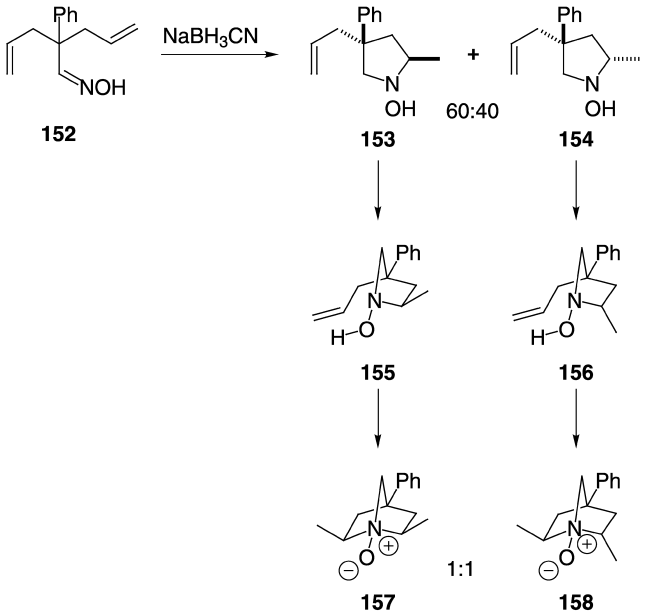

**Scheme 37.**



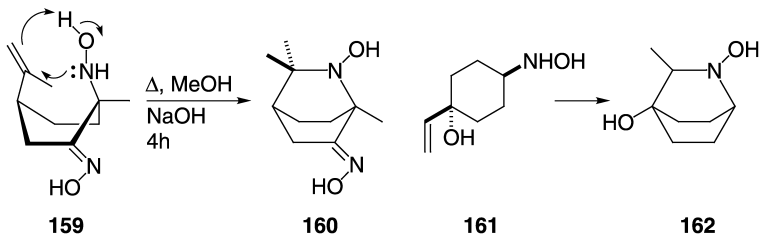

**Scheme 38.**




Scheme 39.




Scheme 40.



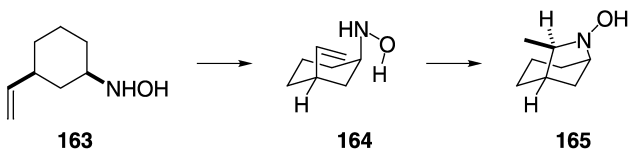

Scheme 41.

planar, five-membered transition state in this case. This is substantiated by the fact that the piperidine-*N*-oxide **150** does not break down to the hydroxylamine **151** when heated, as it also cannot undergo a Cope elimination for the same reason. Of course, this pattern of reactivity may not apply to other systems, which can undergo both retro-Michael and Cope eliminations.

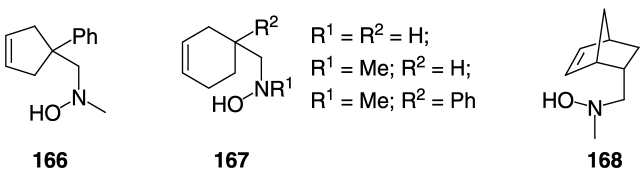
### 3.4. Transannular cyclisations

Given that the required planar transition state can be achieved with some ease, transannular variations of the reverse Cope cyclisation should then be viable and even favoured by the very conformational constraints that distinguish such precursors. This is, however, at present, a rather poorly developed area. A first example was reported by Ciganek (Scheme 40).[13] Cyanoborohydride reduction of the oxime **152** gives a quantitative yield of the *N*-hydroxypyrrolidines **153** and **154** in a 60:40 ratio, the cyclisation being clearly assisted by the presence of the phenyl substituent [cf. Scheme 20]. Subsequent transannular cyclisation is then effected during a 27 h reflux in chloroform (or at ambient temperature for 34 days) to give an equilibrium mixture of the two *N*-oxides [**157** and **158**] in equal amounts, together with 17% of the uncyclised *N*-hydroxypyrrolidine **154**. Separate experiments established the reversible nature of the final cyclisation, the stereochemical outcome suggesting the intermediacy of the transition state conformations **155** and **156**, which does explain why the minor *N*-hydroxypyrrolidine **154** undergoes a slower cyclisation due to an *endo*-methyl group. This also explains why the *endo*,*endo*-isomer of the final bicyclic products is not observed.

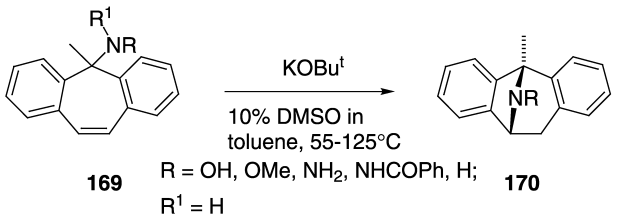
Our interest in such transannular cyclisations was provoked by a report that the hydroxylamine **159** underwent acid-catalysed cyclisation to the isoquinuclidine skeleton **160** (Scheme 41), whereas a series of derived amines failed to cyclise under similar conditions.[28] That this was indeed a reverse Cope process was proven by the fact that the hydroxylamine **159** underwent the same cyclisation in the presence of base, while the corresponding *O*-methyl or *O*-benzyl derivatives did not cyclise in the presence of acid or base.[29] Once again, an internal methyl group is found not to inhibit cyclisation, while the necessary boat-like conformation suggested some useful generality for this type of reaction. We were, however, concerned that this was a rather special case and therefore elected to test the cyclisation using simpler substrates. We were pleased to observe that the hydroxylamine **161** cyclised in refluxing chloroform to give only the bicyclic product **162** (Scheme 41). In both cases, it was encouraging to find that a less reactive primary hydroxylamine function participated easily in these cyclisations, suggesting that it might be possible to carry out such reactions using a terminally-substituted alkene, especially using a more reactive *N*-methylhydroxylamine. However, this has yet to be tested. We were also able to show that cyclisation of a cyclohexane having a 1,3-substitution pattern was also viable (Scheme 42). The hydroxylamine **163** was found to



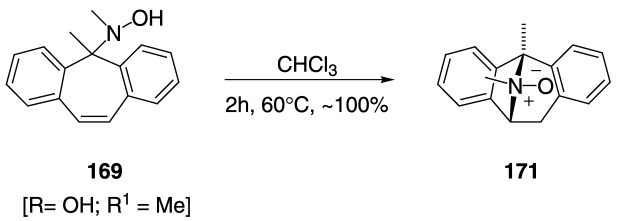

Scheme 42.




**Scheme 43.**




**Scheme 44.**




**Scheme 45.**

cyclise to the bicycle **165** under similar conditions; the high stereoselectivity in favour of essentially only the isomer shown probably reflects a preference for conformation **164**, in which interactions between the vinyl group and axial C–H bonds are avoided.

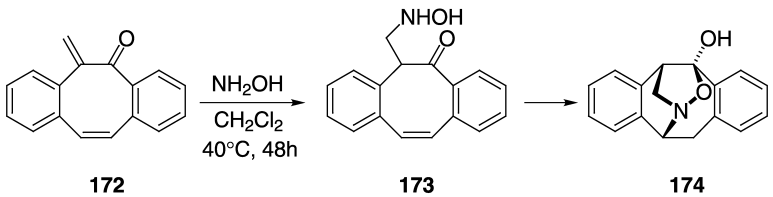
Naturally, not all model systems work; examples which do not undergo reverse Cope cyclisation include the structures **166**–**168** shown in Scheme 43.[4,9] Presumably, in each case, the required planar transition state cannot be accessed with sufficient ease.

Somewhat related transannular cyclisations leading to the azabicyclo[3.2.1]octanes **170** in general require activation by a strong base and forcing conditions for a variety of amine derivatives **169** (Scheme 44).[30] Clearly, in the case of the hydroxylamine derivative at least, such basic conditions should not be necessary as was indeed observed.[30] This has been further demonstrated by Ciganek,[4] who showed that the *N*-methylhydroxylamine [**169**; R=OH; R$^1$=Me] cyclised smoothly to the *N*-oxide **171** simply by heating in chloroform (Scheme 45). Interestingly, the corresponding primary hydroxylamine, while undergoing cyclisation by prolonged (16 h) reflux in toluene,[30] did not cyclise under the milder conditions shown in Scheme 45, again attesting to the activating effect of an *N*-methyl substituent.

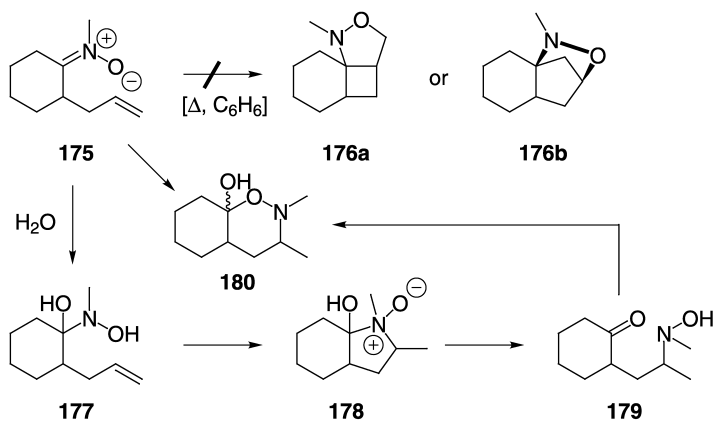
In an extension of this method to the homologous system **174**, a novel strategy was employed which could be applicable to many other transannular reverse Cope cyclisations (Scheme 46).[31] This consists of Michael addition to the enone function **172** to give the presumed hydroxylamine **173**, followed by a relatively facile and regiospecific cyclisation to the observed product **174**. Perhaps not surprisingly, none of the regioisomer where the nitrogen had become attached to the more distant end of the alkene was observed.

## 4. Alternative strategies for hydroxylamine formation

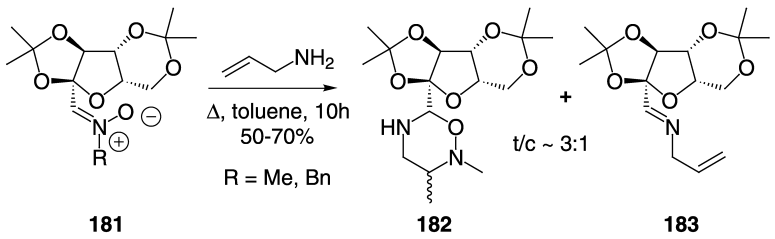
In general, hydroxylamines are not the easiest class of compounds to prepare.[32] Not surprisingly, therefore, a significant number of the more recent developments of the reverse Cope cyclisation also feature some new ways to access the necessary hydroxylamines. Firstly, it is worth mentioning one of the very few examples of a reverse Cope cyclisation reported during the 1980s. The nitrone **175** was found to be not amenable to intramolecular [1,3]-dipolar cycloaddition, presumably because this would involve




**Scheme 46.**




**Scheme 47.**




**Scheme 48.**

cyclobutane formation [**176a**] or a rather strained conformation leading to a perhydroindane **176b**. However, on being left at ambient temperature for 7 days, around 50% of the sample had converted into the oxazine **180** (Scheme 47).[33]

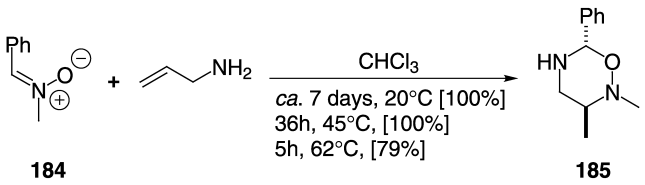
The sequence of events presumably involves hydration of the nitrone and reverse Cope cyclisation of the resulting hydroxy-hydroxylamine **177** to give the *N*-oxide **178**. This can then rearrange, effectively by a Meisenheimer rearrangement,[34] by ring opening to the keto-hydroxylamine **179** and reclosure to the observed product **180**. This isolated example may be a pointer to some future developments and also echoes the original observation of the reverse Cope cyclisation discovered by House (Scheme 6) and also the related cyclisations observed by Ciganek during nitrone formation (Scheme 10).

Our own involvement in the reverse Cope cyclisation began in a somewhat related manner. In an effort to improve the fairly abysmal levels of stereoselection observed in [1,3]-dipolar cycloadditions between the nitrones **181**, derived from the readily available hexulofuranosonic acid,[35] and *N*-acyl or *N*-carbamoyl derivatives of allylamine, we heated the nitrones with the unprotected allylamine. While we appreciated that the free amine group would probably add to the nitrone, it was reasoned that this would be an equilibrium process and would thus not interfere with the desired dipolar cycloaddition. In the event, three products were isolated after refluxing the reactants together in toluene for 10 h (Scheme 48).[36] These turned out to be the isomeric oxadiazinanes [**182**; R=Me, in a *trans*/*cis* ratio of ca. 3:1], together with a trace of the imine **183**. A similar result was obtained, but with slightly better yields, using the *N*-benzylnitrone [**182**; R=Bn].

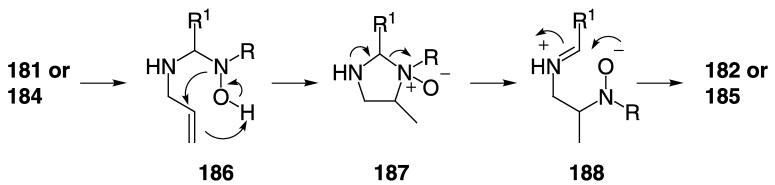
This unexpected result was further exemplified by treating the easily-handled benzaldehyde-derived nitrone **184** with allylamine in chloroform, when essentially quantitative yields of a single *trans*-oxadiazinane **185** could be obtained (Scheme 49).

We speculated that a reverse Cope cyclisation was a pivotal step in a four-step sequence leading to the observed product (Scheme 50). Addition of allylamine to a nitrone would give a hydroxylamine **186** (cf. Schemes 6, 10 and 47), which could undergo reverse Cope cyclisation to give an imidazolidine-*N*-oxide **187**. This could then undergo rapid ring opening triggered by the nucleophilic secondary amine to give the iminium species **188**, which could then undergo a facile 6-*endo* ring closure to give the observed products [**182** or **185**].

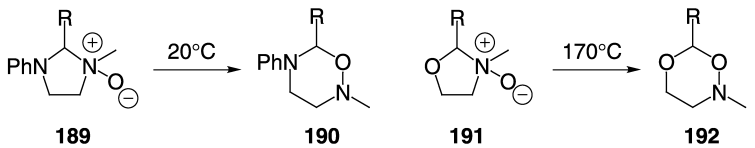
The latter steps amount to an *N*- to *O*-alkyl transfer, i.e. a Meisenheimer rearrangement.[34] All attempts to observe the intermediate *N*-oxide **187** were unsuccessful. This was not too surprising in view of the known analogous rearrangement of the *N*-oxides **189**, derived from the corresponding imidazolidines and *m*CPBA, to the oxadiazinanes **190**, which occurs at ambient temperature (Scheme 51).[37] A further precedent comes from an earlier report[38] of a similar rearrangement of a physostigmine-*N*-oxide. By contrast, the related oxazolidine-*N*-oxides **191** require thermolysis at



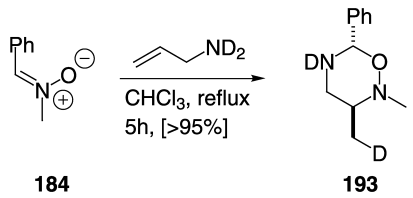

**Scheme 49.**



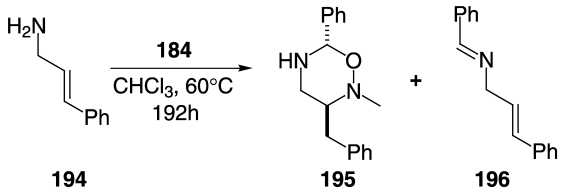

**Scheme 50.**

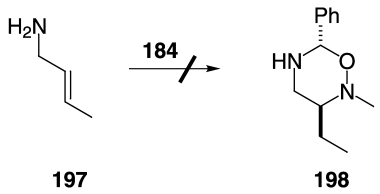



**Scheme 51.**

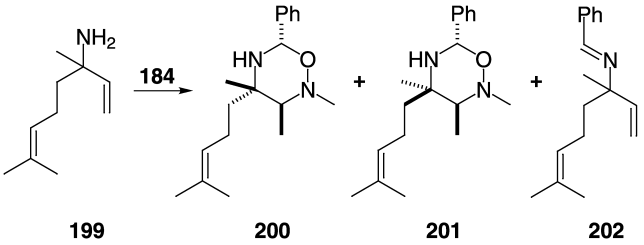



Scheme 52.




Scheme 53.

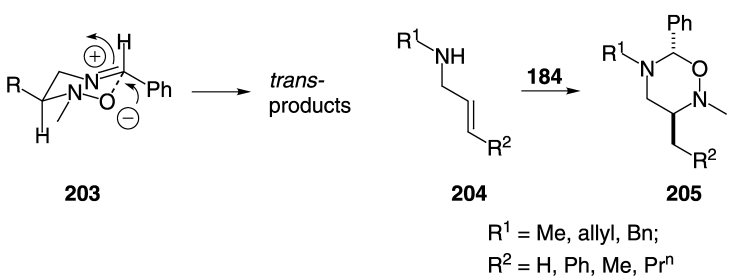



Scheme 54.

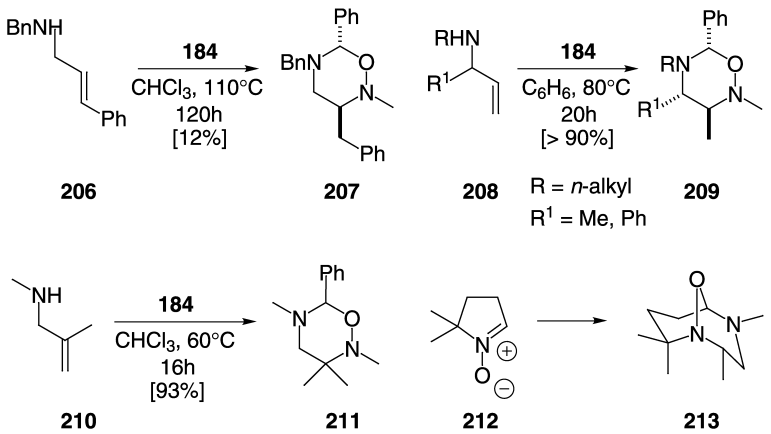
170 °C to achieve the same conversion into the dioxazinanes **192**, understandably in view of the less basic nature of the triggering oxygen.[39] Additionally consistent with the proposed mechanism was the finding that the reaction between the nitrone **184** and N-deuteriated allylamine gave only the 3-deuteriomethyl derivative **193** (Schemes 52, 53).[36] A typical feature of the reverse Cope cyclisation is that substitution at the terminus of the alkene function retards the reaction. This was reflected in the present chemistry: the reaction between the nitrone **184** and cinnamylamine **194** gave only a ca. 40% of the oxadiazinane **195**, along with a similar amount of the imine **196**, after a prolonged reaction time, while the corresponding crotyl derivative **197** gave only traces of the 3-ethyl analogue **198** (Scheme 51), along with much imine formation. Further substitution at the $sp^3$ centre in the allylamine did not, however, prevent the reaction: linalylamine **199** reacted to give largely the diastereoisomers **200** and **201**, together with a small amount of imine **202** (Scheme 54). Formation of diastereoisomer **200** is consistent with the previously-discussed transition state conformation of the reverse Cope cyclisation (Scheme 19). In general, imine formation presumably occurs by a simple exchange reaction between the allylamine and the nitrone, with expulsion of *N*-methylhydroxylamine. The 3,6-*trans*-stereocontrol is generated in the last ring closure step (Scheme 50), when the iminium species **188** adopts a chair-like conformation **203** in which the substituent(s) attached to the $sp^3$ carbon centres will assume equatorial positions (Scheme 55).

In order to prevent imine formation and possibly also to promote the whole sequence, we used, instead, the *N*-alkylallylamines **204** (Scheme 55).[36] Using unoptimised conditions (benzene or toluene, reflux, 20–120 h), we were able to secure good yields of the now-expected oxadiazinanes **205**, even when the reacting alkene was substituted at its terminus. While an *N*-allyl substituent did not appear to inhibit the sequence, an *N*-benzyl group certainly did: prolonged thermolysis of *N*-benzylcinnamylamine **206** with the nitrone **184** in chloroform gave only a 12% isolated yield of the oxadiazinane **207** (Scheme 56). The more positively allylically-substituted amines **208** gave essentially single diastereoisomers of the oxadiazinanes **209**; the vicinal *trans*-stereochemistry is presumably set during the reverse Cope cyclisation (Scheme 19), although the lack of information regarding the stereochemistry of the intermediate and non-isolable imidazolidine-*N*-oxide (Scheme 50) precludes detailed speculation as to the transition state conformation(s) involved. As illustrated previously (Schemes 14, 18, 20, 27 and 42), an internal methyl substituent on the alkene does not significantly inhibit the progress of the cyclisation; a further example is the efficient and relatively easy formation of the *gem*-dimethyl derivative **211** from allylamine **210** (Scheme 56). The somewhat unusual heterocycle **213** was similarly obtained from the pyrrolidine nitrone **212**, thus providing further evidence for the overall mechanism.

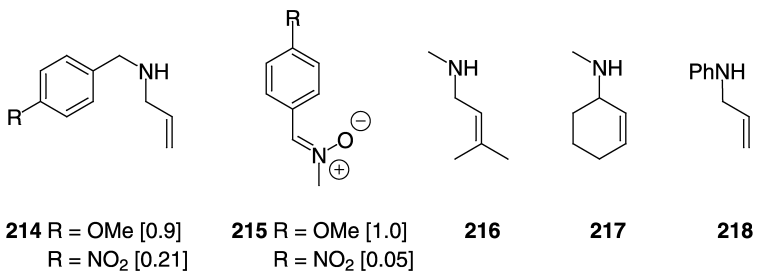
The multistep nature of the reaction and the probability of there being more than one rate-determining step were indicated by attempts to accelerate the sequence by using the amines **214** and the nitrones **215** having influential *para*-substituents. Two extremes are quoted (Scheme 57), along




Scheme 55.

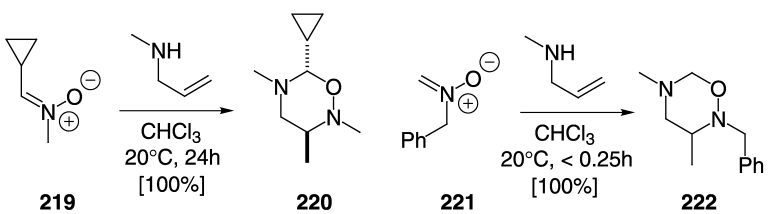



**Scheme 56.**

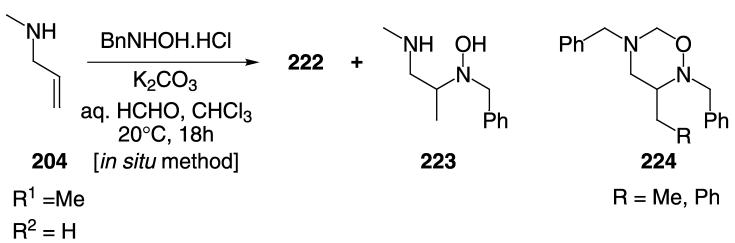



**Scheme 57.**

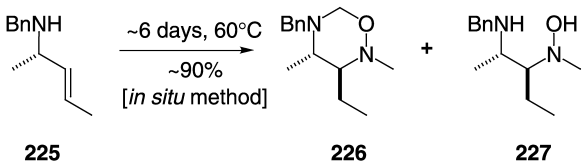
with rates relative to R=H. These and a number of related examples showed that the overall sequence was retarded by both electron-donating and, especially, electron-withdrawing substituents.[40] In line with many of the foregoing results, the allylamines **216**–**218** failed to form oxadiazinanes, probably due, respectively, to too much terminal substitution, an inability to adopt a planar transition state and a lack of amine nucleophilicity. The lengthy reaction times, together with some poor yields, then led us to use other nitrones, when we discovered that the phenyl group of the nitrone **184** engendered a significant overall rate retardation. For example, the *C*-cyclopropylnitrone **219** reacted smoothly with *N*-methylallylamine **204** ($R^1$=Me; $R^2$=H) at ambient temperature, to give a quantitative yield of the oxadiazinane **220** (Scheme 58).[36,40] The reaction even occurred during 3 days at −20 °C. Unfortunately, this enhanced reactivity was insufficient to overcome the rate retardation present in *N*-benzylcinnamylamine **206** (Scheme 56) at ambient temperature, while heating resulted in extensive decomposition. The next logical step was to dispense completely with the *C*-substituent of the nitrone. This proved to be a useful idea: the formaldehyde nitrone **221** reacted very rapidly (<0.25 h) at ambient temperature with *N*-methylallylamine **204** to give only the oxadiazinane **222**, despite the slight inhibiting effect of the *N*-benzyl group (Scheme 58).[40] The instability of the nitrone **221** led us to generate it in situ; after 18 h at ambient temperature, reaction with amine **204** gave the oxadiazinane **222** along with the amino-hydroxylamine **223** in 95% combined yield and in a ratio of 1.3:1 (Scheme 59). The latter compound



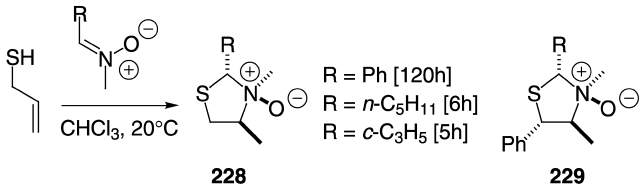

**Scheme 58.**




**Scheme 59.**




**Scheme 60.**



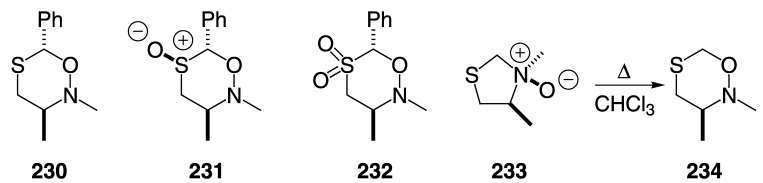

**Scheme 61.**

was presumably formed by interception of the Meisenheimer iminium salt intermediate (cf. Schemes 50 and 55) by water. Thus, although more convenient, the in situ method proceeded at a significantly slower rate than when using the isolated nitrone **221**. Despite this, very efficient if lengthy reactions (5–13 days) using the in situ method did deliver the products **224** derived from both *N*-benzylcinnamylamine **206** and *N*-benzylcrotylamine. While the reactions could be accelerated by heating, this advantage was offset by significant by-product formation, although an acceptable 90% yield of the expected products **226** and **227** (1.7:1) was obtained from amine **225** using the in situ method after 6 days at 60 °C (Scheme 60).[40]

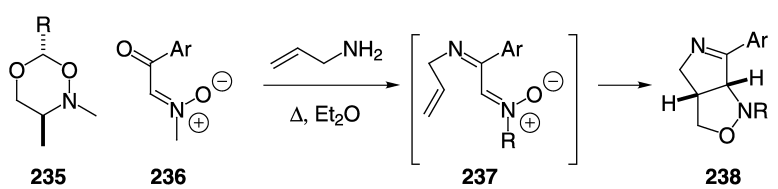
All of the foregoing trends were seen again in reactions between allylthiol and aldehyde-derived nitrones (Scheme 61).[41] These results also provided excellent evidence in support of the overall mechanism (Scheme 50), as the initial reverse Cope products, in this case the 1,3-thiazoline-*N*-oxides **228**, were isolated as the sole products. Again, the reaction was much faster when *C*-alkyl rather than *C*-aryl nitrones were used. Although more reactive, combinations of *C*-alkyl nitrones and terminally-substituted allylic thiols unfortunately did not undergo reverse Cope cyclisation at ambient temperature and gave a multitude of products when heated in chloroform. Reactions with 1-phenyl-2-propen-1-thiol gave the homologue **229**, although this chemistry may well be somewhat limited due to the relative instability of such thiols. This sequence therefore offers a unique opportunity to prepare thiazolidine-*N*-oxides (e.g. **228**), as oxidation of the parent system will always occur preferentially at sulfur. Indeed, if left in solution for a number of days, NMR evidence suggested that *N*- to *S*-oxygen transfer was occurring. The greater electronegativity of sulfur rendered the subsequent Meisenheimer rearrangement more difficult than when nitrogen acted as the trigger (Scheme 50). However, the *C*-phenyl nitrone product [**228**; R=Ph] did rearrange smoothly in refluxing chloroform to give a novel ring system, the 1,5,2-oxathiazinane **230** (Scheme 62). This compound was also obtained directly in ca. 90% yield from the precursor allylthiol and *C*-phenyl nitrone **184** by thermolysis in toluene at 70 °C in a sealed tube. Oxidation using *m*CPBA or $NaIO_4$ led to a single sulfoxide, assumed to have the stereochemistry shown [**231**], while use of $RuCl_3$–$NaIO_4$ led to the sulfone **232**. The in situ method (Scheme 59) with allylthiol delivered the thiazolidine-*N*-oxide **233**, which also underwent smooth rearrangement to the oxathiazinane **234**. Unfortunately, the related alkyl derivatives [**228**; R=alkyl] gave mixtures of products which, while containing the expected oxathiazinanes, also showed the presence of similar quantities of both thiazolidine- and oxathiazinane-*S*-oxides and unidentified elimination products.

Attempts to apply the same idea to allyl alcohol gave only trace amounts of dioxazinanes **235** (Scheme 63).[36,42] It is interesting to note that the foregoing sequences could have been discovered much earlier by Black's group. While investigating a neat idea for setting up intramolecular [1,3]-dipolar cycloaddition precursors by imine formation, it was found that attack of allylamine onto *C*-aroyl nitrones **236** occurred selectively at the carbonyl function to give the imines **237**, which then underwent smooth dipolar cycloaddition to give the hexahydro-pyrrolo[3,4-*c*]isoxazoles **238** (Scheme 63).[43] Had the addition occurred instead to the nitrone group, then presumably the chemistry reported above would have been uncovered!

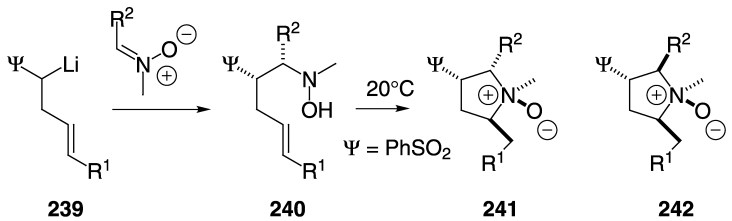
We then began to investigate if other carbon-based nucleophiles could be used to generate unsaturated hydroxylamines suitable for reverse Cope cyclisations. It was found that the lithiated sulfones **239** added very efficiently and stereoselectively to nitrones to give




**Scheme 62.**

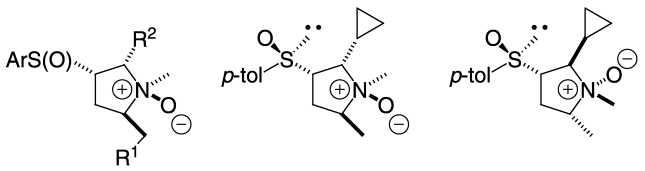



**Scheme 63.**



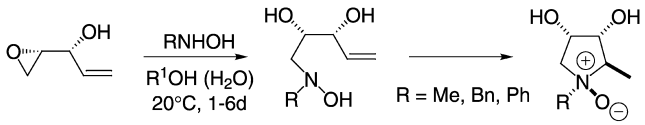

239 240 241 242

**Scheme 64.**




243 244 245

**Scheme 65.**



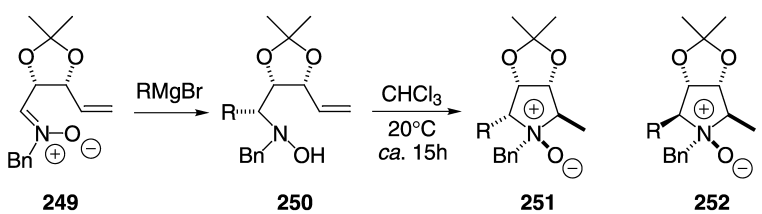

246 247 248

**Scheme 66.**

essentially single diastereoisomers of the hydroxylamines **240**, many of which cyclised at ambient temperature, a fortunate occurrence, as heating led to extensive decomposition (Scheme 64).[44] The resulting pyrrolidine-*N*-oxides were obtained with reasonably high levels of stereoselection (ca. 4–5:1) in favour of the 2,5-*trans* isomers **241**, but these underwent slow isomerization in chloroform solution to give mainly the corresponding and more thermodynamically stable 2,5-*cis* isomers **242** (cf. Scheme 23). Otherwise, the influence of the two substituents fell into a familiar pattern. When the alkene was unsubstituted [i.e. **240**; $R^1$=H], the cyclisations were completed during work-up of the initial condensation when $R^2$=alkyl or cyclopropyl. The rate retardation effect of a phenyl group was again in evidence as the unsubstituted hydroxylamine [**240**; $R^1$=H; $R^2$=Ph] in contrast took some 96 h to undergo complete cyclisation, while more substituted hydroxylamines [**240**; $R^1$=Ph, Me etc., $R^2$=Ph] failed to cyclise. However, such substituted hydroxylamines [i.e. **240**; $R^1$=Ph, Me; $R^2$=alkyl, cyclopropyl] did undergo smooth if slow (70–96 h) cyclisation at ambient temperature. The origins of the retardation effect of a phenyl group adjacent to the hydroxylamine are unclear. The fact that the isopropyl analogue [**240**; $R^1$=H; $R^2$=Pr$^i$) reacted very rapidly (ca. 0.5 h) suggests the effect is not steric; however, the styryl derivative [**240**; $R^1$=H; $R^2$=PhCH:CH] also cyclised very rapidly, indicating that any electronic effect is not transmitted by an olefinic linkage. One drawback to this method is the reduced yields obtained during the initial condensation step when using *C*-alkyl nitrones (i.e. $R^2$=*n*-alkyl), presumably due to competing deprotonation α- to the nitrone by the basic lithiated sulfone **239**.

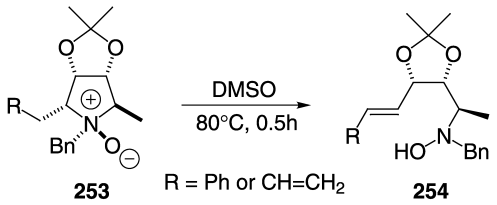
The slow isomerisation problem could be obviated by using the corresponding sulfoxides as nucleophiles, presumably due to their weaker electron-withdrawing effect. Otherwise, the characteristics of the reverse Cope cyclisations, which also occurred at ambient temperature, were much the same as with the foregoing sulfones **240** and delivered very largely the isomerically stable pyrrolidine-*N*-oxides **243** with ≥9:1 stereoselectivity, although the relative stereochemistry at sulfur was not determined (Scheme 65).[45] The use of a lithiated sulfoxide naturally gave the opportunity to prepare chiral, non-racemic products. Due to the lack of knowledge of the relative stereochemistry between the sulfoxide and the new adjacent stereogenic centre, a product from this sequence was either **244** or **245**, but which was obtained with >95% stereoselectivity. Although probably not all will be retained in subsequent synthetic transformations, it is interesting to note that this combination of two sequential reactions creates four additional stereogenic centres from a retained sulfoxide centre.

New methods for hydroxylamine synthesis are very welcome in this area. Both O'Neil[46] and Jäger[47] have used epoxide ring opening to secure suitable precursors for reverse Cope cyclisations leading to polyhydroxylated pyrrolidines (Scheme 66). Attack by *N*-methyl (or *N*-benzyl) hydroxylamine on the epoxide **246** is highly regioselective and cyclisations of the resulting hydroxylamines **247** are highly stereoselective at ambient temperature, giving excellent yields of the pyrrolidine-*N*-oxides **248**. Unusually in this area, methanol[46] or aqueous ethanol[47] proved to be the optimum solvents. Stereoselectivities were usually ≥9:1 in favour of the *N*-oxides **248** in these media. Similar cyclisations of the corresponding primary hydroxylamine were slower, as were those of the *N*-benzyl derivative, relative to the *N*-methyl analogues;[47] these are normal reverse Cope characteristics, despite the different solvent systems.




249 250 251 252

**Scheme 67.**

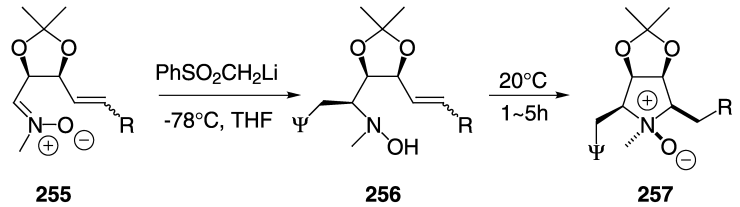



**Scheme 68.**

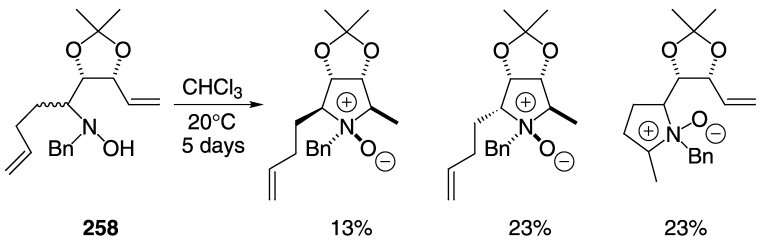
An alternative strategy for the preparation of similar, but protected, derivatives of the hydroxylamines **247** employs the addition of various organometallics to the nitrone **249** derived from D-ribose (Scheme 67).[48] The stereoselectivities of Grignard additions were quite variable, but had a tendency to favour the isomers **250**, as deduced from the predominant formation of the pyrrolidine-*N*-oxides **251** on leaving the intermediate hydroxylamines in chloroform overnight at ambient temperature. By contrast, additions of Grignard reagents modified by a Lewis acid ($Et_2AlCl$, $ZnCl_2{\cdot}OEt_2$) favoured the formation of the alternative epimer in which the new 'R' group is introduced on the opposite face to give a preponderance of the epimeric *N*-oxides **252**. These deductions seem reliable, as prolonged storage of the *N*-oxides **251** in chloroform did not lead to any isomerisation, indicating that these were indeed the initial reverse Cope products. Oddly, both the allyl and benzyl derivatives **253** underwent apparent Cope elimination, even at −25 °C, and in <0.5 h in DMSO at 80 °C, to give the alternative hydroxylamines **254** (Scheme 68). The stereochemistry of the *N*-oxides **253** suggests that this must be an inter- rather than an intramolecular process.

We investigated a similar strategy, using the alternative nitrones **255** also derived from D-ribose, based around the previously successful addition of lithiated sulfones (Scheme 64).[44] Thus, condensations between nitrones **255** and lithiated methyl phenyl sulfone gave very largely single isomers of the expected hydroxylamines **256**, the structures of which were deduced from those of the resulting pyrrolidine-*N*-oxides **257** which were all formed in good to excellent yields during 1–5 h in chloroform at ambient temperature (Scheme 69).[49] The relatively facile nature of these reverse Cope cyclisations, even with distally-substituted alkenes, strongly suggests that a significant activating effect is in operation which we had assumed, by design, to be the ring constraint provided by the *cis*-dioxolane ring. Further, the observed 'all-*cis*' geometry of the *N*-oxides **257** can be rationalised on the basis of a boat-like transition state in which the alkene and hydroxylamine groups are placed in close, planar proximity. However, the truth may be somewhat more subtle. In a competition experiment between the two unsubstituted alkene groups in the hydroxylamine **258**, three *N*-oxides were formed in fairly similar quantities (Scheme 70).[48] While the fact that hydroxylamine **258** was an epimeric mixture, which will influence transition state stabilities, clearly the *cis*-fused dioxolane ring did not provide complete control!

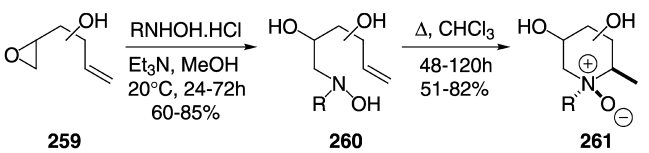
The preparation of hydroxylamines from epoxides (cf. Scheme 64)[46,47] was first highlighted by O'Neil in the context of reverse Cope chemistry in a neat approach to piperidine-*N*-oxides (Scheme 71).[50] Although reported in a limited way some 20 years previously, this very useful epoxide ring opening method seems to have escaped subsequent attention until this report. The optimum solvent for the initial ring openings of the epoxides **259** turned out to be methanol (use of THF or dichloromethane gave lower yields); subsequent prolonged reflux of the resulting hydroxylamines **260** in chloroform then delivered the piperidine-*N*-oxides **261** in respectable yields, as mixtures of diastereoisomers. Further studies of these reactions revealed that methanol might be an optimum solvent. Further, stereoselection was increased when sodium methoxide rather than triethylamine was used to liberate the initial hydroxylamine from its hydrochloride salt, suggesting that sodium ions may play a positive role in




**Scheme 69.**

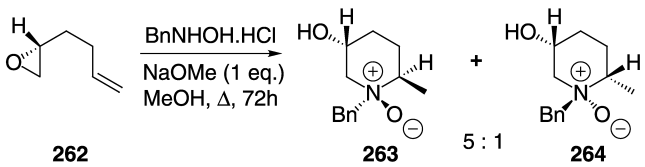



**Scheme 70.**



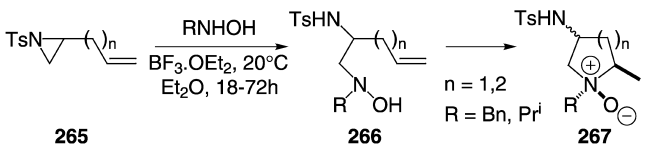

**Scheme 71.**

stereocontrol of the reverse Cope cyclisation.[51] Under these conditions, the reactions appear to be irreversible, perhaps due to hydrogen bonding between the solvent and the products. A combination of these observations resulted in a one-pot method for obtaining the piperidine-*N*-oxides **263** and **264** in a 5:1 ratio from the epoxide **262** (Scheme 72).[51] This idea has been successfully extended to similar and unprecedented ring openings of *N*-tosylaziridines **265** by hydroxylamines (Scheme 73).[52] The reaction requires boron trifluoride etherate as a trigger, when it occurs slowly at ambient temperature. In the context of reverse Cope cyclisations, both pyrrolidine- and piperidine-*N*-oxides **267** having *N*-tosylamino substituents have been prepared using this method. Pyrrolidine formation occurred at ambient temperature and hence the intermediate hydroxylamines [**266**; $n$=1] could not be isolated. In contrast, those leading to the piperidines [**267**; $n$=2] required heating in methanol for 48 h to complete the cyclisation and hence could be isolated. For future reference, it should be noted that substituted hydroxylamines can also readily be prepared by highly selective *cis*-Michael additions to α,β-unsaturated sulfones, nitriles and nitro compounds.[53] Interestingly, this stereochemical outcome, while it could be consistent with a Michael addition mechanism, suggests that an intermolecular reverse Cope cyclisation may be operating (Scheme 74), an idea supported by very recent theoretical studies.[54]



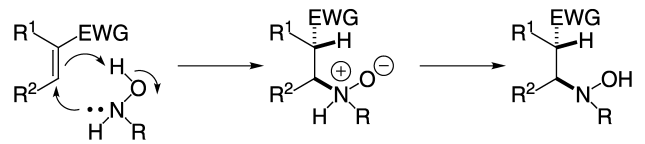

**262** **263** **264**

**Scheme 72.**




**265** **266** **267**

**Scheme 73.**

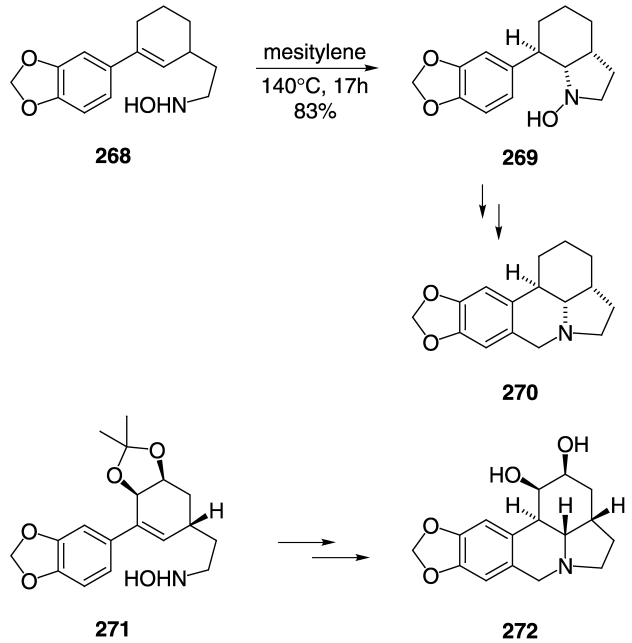



**Scheme 74.**

Finally, another useful way to convert secondary amines into the corresponding hydroxylamines involves sequential Michael addition to acrylonitrile, oxidation to the *N*-oxide level using *m*CPBA and lastly a Cope elimination of acrylonitrile.[55]

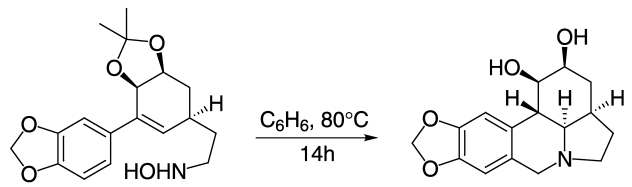
## 5. Applications in target synthesis

These have been slow to emerge, at least in the case of reverse Cope cyclisations onto alkenes. However, a very elegant use of the reaction is in Oppolzer's total syntheses of (±)-α-lycorane **270** and (+)-trianthine **272** (Scheme 75).[14] Although hardly activated in a reverse Cope sense, the primary hydroxylamine **268** underwent efficient conversion into the *N*-hydroxypyrrolidine **269** after harsh thermolysis in mesitylene. The synthesis of (±)-lycorane **270** was then completed by sequential N–O bond cleavage using Raney-nickel and a modified Pictet–Spengler ring closure ($CH_2$=$N^+Me_2$, THF, 40 °C, 15 h). Similarly, the more functionalized precursor **271**, obtained as a single enantiomer from (1*S*,2*S*)-3-chloro-cyclohexa-3,5-diene-1,2-diol, was converted into (+)-trianthine **272**. These elegant syntheses are remarkable examples of the reverse Cope methodology as a less reactive primary hydroxylamine is successfully cyclised onto a trisubstituted cycloalkene. It is also interesting to note that the epimer **273** of the trianthine precursor undergoes cyclisation in only 14 h in refluxing benzene to give the isomer **274** in 91% isolated yield (Scheme 76).[14] It is difficult to see a clear conformational reason for this; perhaps hydrogen bonding between the hydroxylamine hydroxyl and one of the now *syn*-dioxolane oxygens is responsible.




**268** **269** **270** **271** **272**

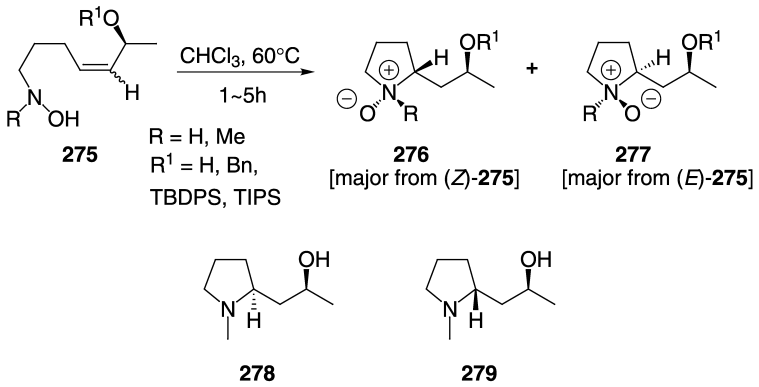
**Scheme 75.**




**273** **274**

**Scheme 76.**

An unexpected activating effect by oxygen was certainly observed in the recent syntheses of the alkaloids (−)-hygroline **278** and (+)-pseudohygroline **279** (Scheme 77).[56] Our original speculation was that the pendant oxygen group (as OH or OBn) should hydrogen bond with the



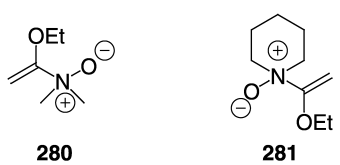

**Scheme 77.**

hydroxylamine function and hence provide a useful degree of stereocontrol. This proved not to be the case: the ratios of the two *N*-oxides [**276** and **277**; R=Me] were around 2–3:1 and were related to the alkene geometry, but relatively independent of the nature of the alcohol protecting group. However, the cyclisations proceeded with unexpected ease and even occurred at ambient temperature during 48–60 h. Even more surprising, in view of the failure of simple primary hydroxylamines having distal alkene substituents to cyclise (Scheme 18),[10] was the successful formation of the *N*-hydroxypyrrolidines derived from the initial products [**276** and **277**; R=H]. The sensitivity of the precursors [**275**; R=H] to heat proved no drawback, as these products were formed at ambient temperature during 3–8 h. It was concluded that this remarkable result was due to activation by the allylic oxygen atom. It may well be that this effect also benefited the foregoing trianthine synthesis (Scheme 73): while the simpler precursor **268** required heating to over 140 °C to effect cyclisation, the dioxolane derivatives [**271** and **273**] leading to trianthine underwent the same reaction at 80 °C, consistent with activation by the allylic oxygen present in the dioxolane ring. Further experiments will be necessary to confirm this conclusion; a few examples suggested that an internal allylic oxygen did not engender such an activation and, indeed, disfavoured cyclisation.[57]

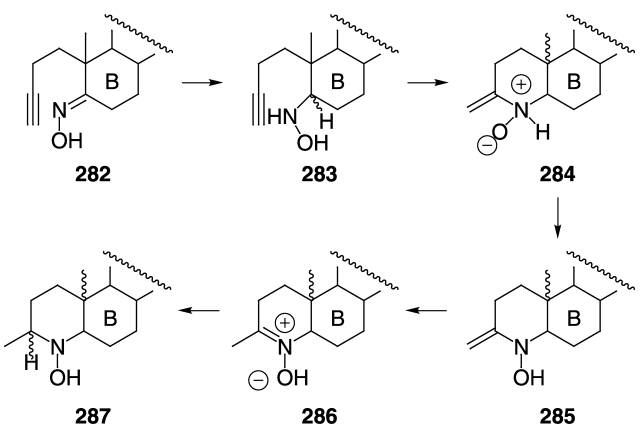
## 6. Cyclisation onto alkynes

The fact that hydroxylamines undergo intermolecular additions to alkynes has been established for some time.[58] While Michael additions to conjugated ynoates and ynones can be somewhat complicated, such chemistry can represent a very useful method for nitrone generation, especially if the latter are trapped intramolecularly.[59] Such nitrones are formed usually rapidly by isomerisation of the initial Michael adduct obtained by addition of an *N*-alkyl- or *N*-arylhydroxylamine. Clearly, such an isomerisation cannot occur in the case of an N,N-disubstituted hydroxylamine, exemplified by the isolation of excellent yields of the adducts **280** and **281** from ethoxyacetylene and *N*,*N*-dimethylhydroxylamine and *N*-hydroxypiperidine, respectively (Scheme 78).[4] In these cases, and possibly in the Michael additions, these are likely examples of intermolecular reverse Cope additions [cf. Schemes 3 and 74], although such reactions do not work with alkyl-substituted 1-alkynes.[59]

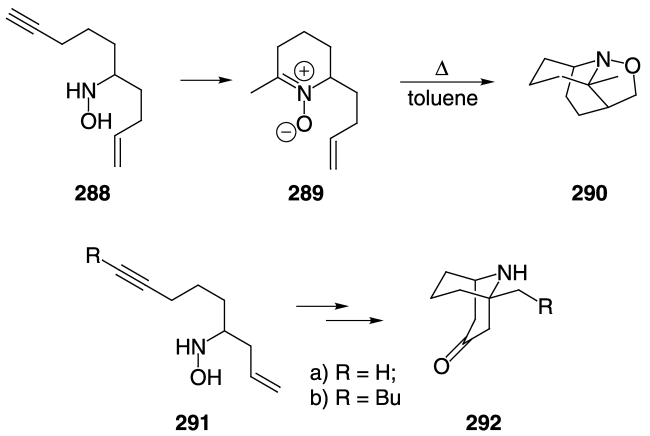
A possible example of an intramolecular reverse Cope cyclisation was reported in 1989 when the *N*-hydroxysteroid derivatives **287** were isolated from the reaction of the alkynyl oxime **282** with sodium borohydride in refluxing ethanol.[60] A plausible mechanism is outlined in Scheme 79: if an initial reduction gave the hydroxylamines **283**, subsequent reverse Cope cyclisation would then generate the *N*-oxides **284**. Rapid proton transfer and isomerisation (tautomerisation) of the resulting *N*-hydroxyenamines **285** to the nitrones **286** would allow final generation of the observed products **287** by hydride addition. True or not, such a sequence, at least at the reverse Cope stage, was certainly if unexpectedly observed during a preparation of the hydroxylamine **288** (Scheme 80).[61] Subsequent reaction with an aldehyde led not to the expected nitrone, but to the cyclic nitrone **289** without the anticipated incorporation of the aldehyde. The sequence of events presumably follows those detailed in Scheme 79; remarkably, no reverse Cope cyclisation onto the alkene group was observed, despite the fact that this would give an *N*-hydroxypyrrolidine.




**Scheme 78.**




**Scheme 79.**

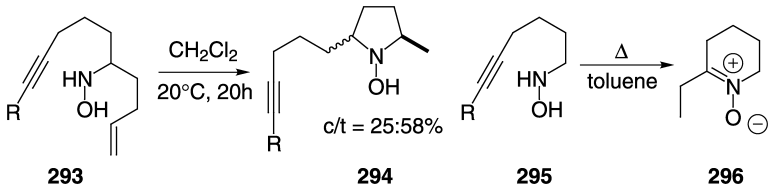



**Scheme 80.**

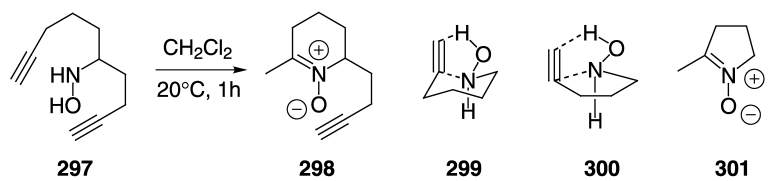
Preservation of the alkene function meant that a [1,3]-dipolar cycloaddition different to that originally planned could now be used to obtain the tricyclic product **290** in excellent overall yield. By using a faster work-up procedure, uncyclised nitrones derived from the hydroxylamine **288** could be obtained successfully without any intervention from the reverse Cope cyclisation.

Importantly, this version of the reverse Cope cyclisation is also successful for non-terminal alkynes (but see below) and also works well with the lower homologues **291**, leading to neat syntheses of the natural insect feeding deterrents (±)-euphococcinine **292a** and (±)-adaline **292b**.[62] In these examples, both the reverse Cope cyclisations and the subsequent [1,3]-dipolar cycloadditions were carried out in refluxing toluene for 9–12 h without nitrone isolation and in excellent overall yields of 71–76%. Despite this successful synthesis of adaline **292b**, no doubt substituted alkynes undergo cyclisation more reluctantly than do 1-alkynes; clearly, in the hydroxylamines **291**, reverse Cope cyclisation onto the alkene was precluded as this would give rise to a strained azetidine-*N*-oxide (cf. Scheme 31) This does not apply to 1-trialkylsilyl-1-alkynes: such a derivative of the hydroxylamine **288** undergoes rapid reverse Cope cyclisation to give cyclic nitrone **289** with loss of the silyl group after the reverse Cope step.[63,64] Remarkably, however, the hydroxylamine-alkene version of the reverse Cope cyclisation wins out in the case of the 2-alkyne analogue **293** of the terminal alkyne **288** (Scheme 81), with the isomeric pyrrolidines **294** being formed instead in a combined yield of 83%.[63,64] In the absence of a competing mode of cyclisation, internal alkynes will then undergo alkyne-hydroxylamine cyclisations successfully [cf. **291b**], a further example being the conversion of the simpler hydroxylamine **295** into nitrone **296**.[64] Clearly, more vigorous conditions are required with respect to the obviously favoured '5-*exo*' cyclisation of the hydroxylamine **293**, although the yield of nitrone remained excellent (94%). A final competitive experiment revealed an exclusive preference for six- rather than five-membered nitrone formation (Scheme 82). That the diynyl hydroxylamine **297** gave only the nitrone **298** can be understood by the lower strain energy inherent in the transition state **299** with respect to that [**300**] which would lead to the corresponding five-membered nitrone. Such nitrones [e.g. **301**] can be obtained using this chemistry, but their formation is clearly not especially favoured and hence the yields are rather lower from the more vigorous reaction conditions required. What is remarkable about these cyclisations is the often extreme ease with which they proceed, in the absence of activating substituent effects such as Thorpe–Ingold compression.

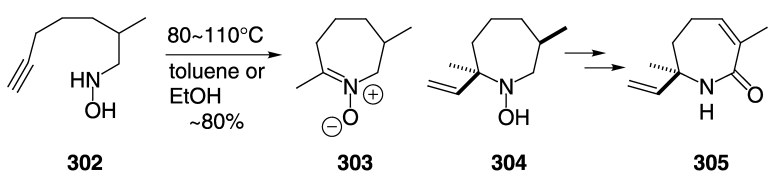
This type of cyclisation is also highly effective for the elaboration of azepines (Scheme 83).[64,65] Thus, thermolysis of the hydroxylamine **302** at 80–110 °C gave varying yields of the seven-membered nitrone **303**, with toluene or ethanol




**Scheme 81.**




**Scheme 82.**



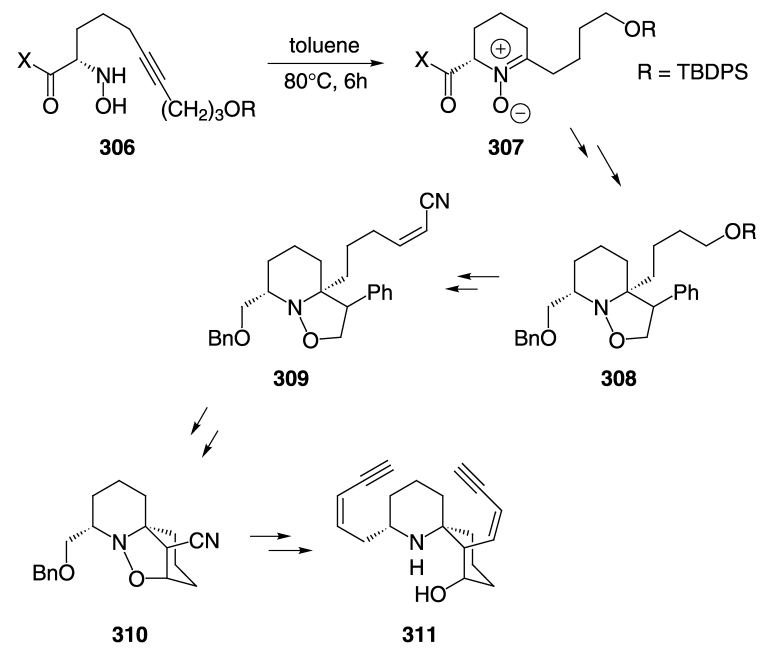

**Scheme 83.**

emerging as the optimum solvents; carbon tetrachloride or acetonitrile, while seemingly effective for the cyclisation step, proved to be too reactive and extensive decomposition resulted. Subsequent addition of vinylmagnesium bromide led exclusively to the *N*-hydroxyazepine **304** and thence to the proposed structure **305** for the natural product, acacialactam, which this work showed to be incorrect.

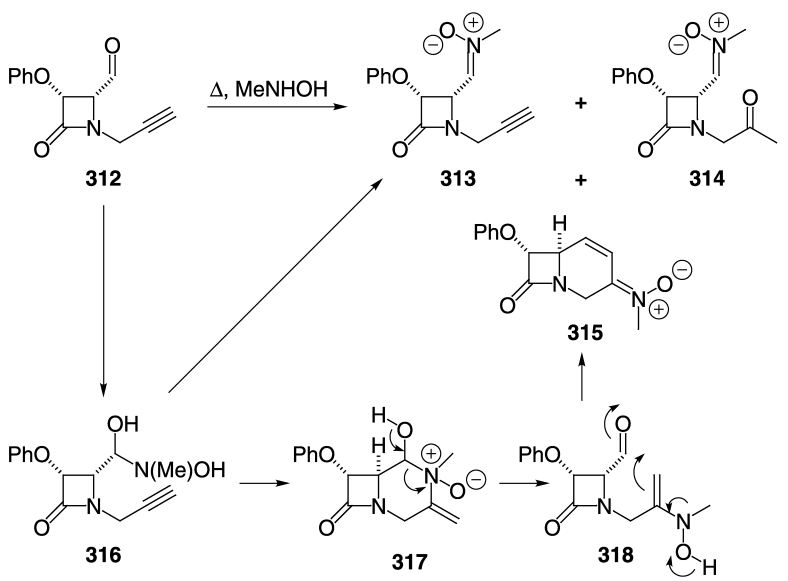
The Holmes group has subsequently applied this chemistry to a most notable total synthesis of (−)-histrionicotoxin **311** (Scheme 84).[66]

Reverse Cope alkyne–hydroxylamine cyclisation of the precursor **306**, obtained asymmetrically using Oppolzer sultam chemistry, proceeded smoothly in hot toluene to give the nitrone **307**, which was protected as its styrene adduct **308** while side-chain manipulations were carried out to give the (*Z*)-alkenylnitrile **309**. Thermolysis then resulted in a cycloreversion/cyclisation sequence of [1,3]-dipolar reactions to give the key tricyclic intermediate **310** and thence the target **311**, following relatively routine, but non-trivial, functional group manipulations and introduction of the side chains. Subsequently, similar tactics have been successfully applied to the elaboration of histrionicotoxins **259A**, **285C** and **285E**.[67]

This type of chemistry clearly has much potential but, in some cases, product control will need to be addressed. For example, treatment of the β-lactam aldehyde **312** with *N*-methylhydroxylamine gives rise to three products, the ratios of which depend very much on the exact reaction conditions (Scheme 85).[68] While the expected nitrone **313** is




**Scheme 84.**




**Scheme 85.**

formed, this can be accompanied by the ketone **314** and the annulated derivative **315**. An explanation of this chemistry echoes that described by Ciganek in one of his earliest studies of the reverse Cope cyclisation (Scheme 10)[4,12] and probably involves an alkyne-hydroxylamine cyclisation of the initial *N*-hydroxyaminal **316**, the competing dehydration of which leads to the expected nitrone **313**. The resulting heterocycle **317** can then fragment to give the *N*-hydroxy-enamine **318**, the precursor of both the ketone **314** following enamine hydrolysis and of the annulated derivative **315** formed by sequential ring closure and dehydration. Further heating of the nitrone **313** does not provide [1,3]-dipolar products (which would be highly strained 4/5 systems), although the corresponding *N*-4-pentynyl derivative was cyclised successfully in this manner.

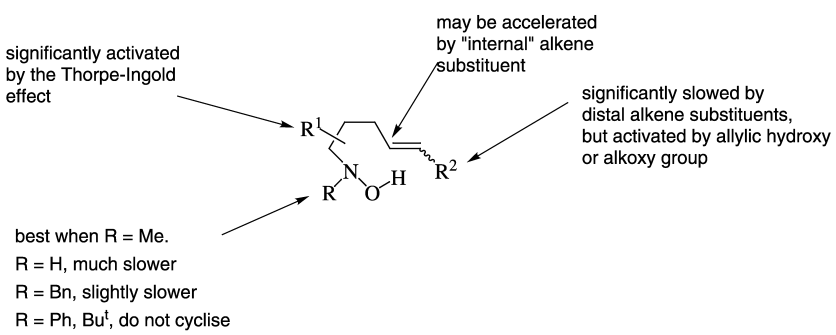
## 7. Conclusions—the salient features of the reverse Cope cyclisation

The conclusions and trends identified below are, in some cases, based on too few examples to be promulgated with any great certainty and, for sure, exceptions to these statements are likely to be discovered in future research. These should therefore be regarded as no more than guidelines that should be used with some caution, especially if applied in a negative sense to a new application of the reverse Cope cyclisation.

1. The optimum solvents are often chloroform or methanol, but hydrocarbons can be used to simply provide an inert diluent for thermolysis.
2. The cyclisation is retarded by distal alkene substituents, more so by alkyl than phenyl groups; recalcitrant substrates tend to undergo decomposition before cyclisation on increased heating, the hydroxylamine group usually being the weak point. Piperidine formation, which is more difficult than the comparable pyrrolidine syntheses, is currently restricted to α-methyl examples; as yet, no example of piperidine formation by cyclisation onto a distally-substituted alkene has been reported.
3. In contrast, an internal substituent (methyl groups only, thus far) does not retard and may even favour cyclisation.
4. The cyclisation is significantly accelerated by steric compression (the Thorpe–Ingold effect), especially when caused by geminal substituents or a fused ring in the chain connecting the two reacting functions. This may also facilitate transannular versions of the cyclisation.
5. Substituents at nitrogen are very influential: in general, *N*-methylhydroxylamines react significantly faster than primary hydroxylamines. *N*-benzyl groups, which are of course more easily removed, may slightly retard the cyclisation, but *N*-allyl groups (or other linear alkyls) may not; as yet, meaningful comparisons have not been reported. *N*-phenyl and *t*-butyl groups usually prevent cyclisation.
6. Allylic oxygen groups (OH, $OSiR_3$, OBn) strongly accelerate the cyclisation when positioned externally, but not when internal to the reacting alkene.
7. Alkyne-hydroxylamine cyclisations strongly favour the formation of six-membered cyclic nitrones at the expense of comparable five-membered rings. When in direct competition, cyclisation of a primary hydroxylamine completely favours reaction with a 1-alkene rather than a 1-alkyne when both modes would lead to a five-membered ring. Substituents at the alkyne terminus (alkyl groups) retard the cyclisation (e.g. a 1-alkyne cyclises at 20 °C, while an 'internal' alkyne requires heating in refluxing toluene). Seven-membered nitrones, however, can be efficiently obtained using this chemistry in contrast to hydroxylamine-alkene cyclisations
8. All cyclisations require a planar transition state geometry, which explains some of the failures but which can be used to deduce the expected kinetic stereochemical outcome of a particular cyclisation. Isomerisation to a more thermodynamically stable isomer can subsequently occur, however.

Many of the features, at least for pyrrolidine formation, are summarised in Scheme 86.

Overall, the reverse Cope cyclisation represents a useful method for C–N bond formation involving an unactivated alkene or alkyne. This places it firmly in the class of 1,3-azaprotio cyclotransfer reactions, as defined and exploited so well by the Grigg group.[69] It also resembles an ene reaction, but with the key difference that the latter is a $2\pi+2\sigma+2\pi$ process featuring a six-membered transition state, while the reverse Cope cyclisation constitutes a $2\pi+2\sigma+2n$ reaction which involves a five-membered transition state. In this respect, it resembles similar thermally-induced intramolecular additions of oximes to unactivated alkenes and alkynes and therefore represents a most useful 'disconnection' for the elaboration of azaheterocycles. No doubt, the reverse Cope cyclisation




**Scheme 86.**

has much potential in synthesis and many exciting and useful developments can be expected in the future.

## Acknowledgements

Thanks are due to Herbert House and Wolfgang Oppolzer for having the wit to spot the first reported reverse Cope cyclisations, to Engelbert Ciganek for defining many of its basic features and to Andy Holmes for identifying alkynes as alternative reaction partners. Previous members of the Knight group are thanked for their contributions—Steve Thornton, who initiated the entire project, which was then continued with skill and enthusiasm by Andy Wheildon, Kathy White (née Bell), Mike Coogan, Jane Hanrahan and Rhys Salter. D.W.K. also thanks his Siberian colleague, Alexey Tkachev, both for helpful discussions and for suggesting the title of this review. Helpful advice and support from our industrial colleagues Mike Gravestock, Angela Currie and James Muir is also gratefully acknowledged, as is financial support from AstraZeneca and the EPSRC. Finally, we thank Horace Walpole for coining the splendid word serendipity, which so aptly describes most of the initial discoveries made in this fascinating area.

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**Biographical sketch**

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**Professor David W. Knight** was born in Northampton in 1951 and gained his BSc degree from Nottingham University in 1972 and his PhD from the same Institution in 1975, for studies of the synthesis of natural butenolides, under the supervision of Professor Gerry Pattenden. He then secured a lectureship at University College, Cardiff in 1976 before returning to Nottingham University in 1980 as a lecturer and later (1989) a Reader in Organic Chemistry. 1995 was a good year, during which he was granted a Leverhulme Senior Research Fellowship and also a Chair of Synthetic Organic Chemistry at Cardiff University. His research interests are currently focussed in three main areas: novel aspects of benzyne chemistry, the development and applications of 5-*endo* cyclisations for the synthesis of saturated, semi-saturated and aromatic heterocycles and new versions and applications of the reverse Cope cyclisation.