INVESTIGATIONS INTO THE REACTIONS AND CHEMISTRY OF QUINUCLIDINE *N*-OXIDES AND RELATED MOLECULES

By

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Thesis submitted in accordance with the requirements of The University of Liverpool for the degree of Doctor in Philosophy

September 2001

To Dad, sadly missed

Publications arising from this thesis

Quinuclidine *N*-oxide: a potential replacement for HMPA. I. A. O'Neil, J. Y. Q. Lai and D. Wynn, *Chem. Commun.*, 1999, 59.

The synthesis and functionalisation of quinuclidine enamine *N*-oxide and borane complex. I. A. O'Neil, D. Wynn and J. Y. Q. Lai, *Tetrahedron Lett.*, 2000, **41**, 271.

Abstract

Hexamethyl phosphoramide (HMPA) is a dipolar, aprotic compound with a superb ability to form cation-ligand complexes and it can enhance the rates of a wide variety of main group organometallic reactions. In addition it can also influence the regio- and stereochemistry of key reactions such as enolate formation. Other reactions in which HMPA enhance activity include carbanion formation, carbanion reactivity, carbanion regioselectivity (1,2 vs 1,4 addition), ylide reactivity and anion reactivity. In essence it is thought that HMPA acts as a metal binding agent disrupting the aggregation states that enolates normally exist in.[206]

HMPA is a listed mutagen and as such does not find widespread use in either industry or academia. Several other substances, such as *N,N'*-dimethyl-*N*-*N'*-propylene urea (DMPU) have been used as replacements but all have their limitations.[173]

An amine oxide bears the same type of charge distribution as a phosphine oxide, but the dipole moment is much larger. Therefore an amine oxide would be expected to behave in a similar fashion to a reagent such as HMPA.

Therefore quinuclidine *N*-oxide (QNO) (**64**) was chosen to perform preliminary studies as a replacement for HMPA, since QNO is known to be stable in strongly basic conditions. Indeed, it can be deprotonated with *tert*-BuLi and the corresponding anion can be reacted with aldehydes and ketones.[80]

Four key reactions in which HMPA is known to play a vital role were chosen and the effect of replacing HMPA with QNO was investigated. The reactions examined were enolate alkylation,[207] 1,4 vs 1,2 addition,[208] diastereoselective nitroaldol reactions and epoxide opening.[173, 216]

Using 5 equivalents of QNO gave a similar result to using HMPA in the reaction. QNO also had an effect on the other types of reaction investigated, i.e. 1,4 vs 1,2 addition, diastereoselective nitroaldol reactions and epoxide opening, which were either similar or identical to when HMPA was used.

It has been demonstrated that QNO can act as a replacement of HMPA in a range of reactions. Moreover QNO was found to be negative in the bacterial reverse mutation test conducted on *Salmonella typhimurium* TA98, TA100 and TA 102 in the presence or absence of metabolic activation. Additionally it was also found to be negative in the test to evaluate its potential to induce micronuclei in Chinese hamster ovary cells using the cytokinesis block method in the presence or absence of metabolic activation.

However during the course of the investigation it was noted that QNO was sometimes partly insoluble in THF. Therefore in order to try and increase the solubility of the QNO it was decided to utilise the methodology developed by Barton and co-workers which treated QNO with strong base and formed an anion which was then reacted with aldehydes and ketones.[80] It was possible to form several *mono*-substituted analogues, two *bis*-substituted analogues and a *tris*-substituted QNO analogue.

The third part of the study into QNO and related molecules involved synthesising 1-azabicyclo[2.2.2]oct-2-ene *N*-oxide (**248**) and 1-azabicyclo[2.2.2]oct-2-ene *N*-borane complex (**267**). It was possible to remove the α-vinylic proton using *tert*-BuLi and react the newly formed anion with various electrophiles. It was hoped these newly formed substrates would be precursors to the formation of the *bis*-quinuclidine species.

Acknowledgements

I would like to thank my supervisor Dr. Ian A. O'Neil for his advice, support and enthusiasm over the past three years. I would like also to thank Dr. Justine Lai for her supervision and help in the three months I spent at RPR. I would also like to thank the EPSRC for their financial support.

Thanks also go to the technical staff of the University of Liverpool who provide an invaluable service.

Finally I would like to thank all my friends and colleagues from Liverpool and home; but most important of all many thanks go to my family and Kellie whose love and support means so much to me.

Abbreviations

Bn	Benzyl
BuLi	Butyllithium
CI	Chemical ionisation
CIDNP	Chemically Induced Dynamic Nuclear Polarization
CIP	Contact ion pairs
DBU	1,8-Diazibicyclo[4.3.0]non-5-ene
DCM	Dichloromethane
DEA	*N,N*-diethylacetamine
DIPT	Diisopropyl tartrate
DMDO	Dimethyldioxirane
DMPU	*N,N'*-dimethyl-*N*-*N'*-propylene urea
DMSO	Dimethylsulfoxide
EI	Electron Ionisation
Eq.	Equivalent
Equiv.	Equivalent
FAB	Fast Atom Bombardment
HMPA	Hexamethylphosphoramide
IR	*Infra* red
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilazide
m-CPBA	Meta-chloroperbenzoic acid
MMPP	Magnesium monoperoxyphthalate
Mol	Mole
NEP	1-Ethyl-2-pyrrolidinone
NMMO	*N*-methylmorpholine *N*-oxide
NMR	Nuclear Magnetic Resonance
Ph	Phenyl
ppm	Parts per million
QNB	Quinuclidine *N*-borane
QNO	Quinuclidine *N*-oxide
QNE	Quinuclidine enamine *N*-oxide
Sec	Secondary
SIP	Solvent-separated ion pairs

TBHP	*tertiary*-butylhydroperoxide
TEA	Triethylamine
TEAO	Triethylamine *N*-oxide
TES	*N,N,N,N*-Tetraethylsulphamide
Tert	Tertiary
TFAA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMAO	Trimethylamine *N*-oxide
TPAP	Tetra-*n*-propylammonium perruthenate
Ts	*para*-toluenesulfonyl

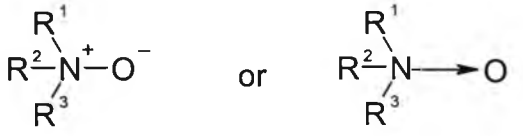
Contents

Chapter 1

Introduction

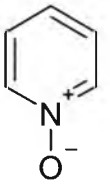
1 GENERAL INTRODUCTION.

Tertiary amine *N*-oxides possess a tetravalent nitrogen which is substituted with three alkyl or aryl groups and is datively bonded to an oxygen atom, see figure 1 for the general structure. The term 'amine *N*-oxide' is used through-out the literature to describe numerous chemical structures, however for the whole of this report it will generally refer to the gross structure where the tetravalent nitrogen is sp^3 hybridized and R is equal to an alkyl or aryl group ((**1**) or (**2**)). Aromatic sp^2 nitrogens which contain 2 R groups and a datively bonded oxygen, e.g. pyridine *N*-oxide (**3**), will also be discussed and referred to as an 'amine *N*-oxide' (Figure 2).



(1) (2)

Figure 1



(3)

Figure 2

Amine *N*-oxides were first reported in 1892 by Pinner and Wolffenstein,[1] However until relatively recently they have received little attention in organic chemistry and therefore only a small number of review articles have been published.[2-5] This

introduction will briefly describe the preparation, properties and the synthetic applications of the tertiary amine *N*-oxides reported in the literature.

The structure and some of the basic chemistry of amine *N*-oxides has been known since the turn of the century, the importance of their biological activity was not realised at that point and therefore the research did not take off until later.[6-12] So far, over a hundred naturally occurring tertiary amine *N*-oxides have been reported.[4]

Tertiary amine *N*-oxides have a number of rather unique characteristics. They are extremely polar compounds and contain one of the largest known dipoles in organic chemistry. Consequently tertiary amine *N*-oxides are very hygroscopic. Their hygroscopic nature is illustrated by the absorption of water by anhydrous trimethylamine *N*-oxide at circa 1% water/minute at 28°C @ 80% relative humidity.[13] In general tertiary amine *N*-oxides are readily soluble in water, alcohols and dipolar aprotic solvents. They have limited solubility in non-polar organic solvents.[14] As bases they tend to be weaker than their parent tertiary amines, but readily form stable hydroxyammonium salts with acids, the pKa of these salts generally estimated at somewhere in the region of 4-5.[15] The thermal stability of the amine *N*-oxides have in the past presented problems and their synthetic utility to the organic chemist has been limited. However, this problem has now been overcome with careful control of the molecular structure and chemical environment of the amine *N*-oxide.[16-18]

1.1 The general chemical structure of the tertiary amine N-oxides.

The physical structure of tertiary amine *N*-oxides was not confirmed until X-ray crystallography indicated the tetrahedral arrangement of the four substituents around the central nitrogen. In 1939 Lister and Sutton executed an electron diffraction study of trimethylamine *N*-oxide and they determined that the nitrogen-oxygen bond length of an amine *N*-oxide was actually 1.36 Å with a tolerance of 0.03 Å,[19] which correlates very closely to the N-O distances determined by numerous X-ray diffraction experiments. Several papers have been published discussing the N-O

bond length (as determined by X-ray crystallographic techniques) which suggest a minimum value of 1.336 to a maximum of 1.41Å.[20-30]

Amine oxides have been stabilised through intermolecular hydrogen bonds to water,[30] ethanol[28] and *d*-α-bromo-*p*-camphorsulphonic acid and evidence of this has been well supported by X-ray structures of these compounds published in the literature.[21] In the case of *N,N*-dimethylethanoline *N* -oxide,[27] an intramolecular hydrogen bond is observed in the X-ray crystal structure between the acidic hydrogen and the *N*-oxide oxygen. It has also been demonstrated through the X-ray structure of the complex formed between *N*-methylmorpholine *N*-oxide and 1,2-cyclohexanediol[23], that *N*-oxides are capable of forming two simultaneous hydrogen bonds to two separate hydrogen bond donors, in this case the two alcohol protons. This bis-hydrogen bonded system has been utilised by O'Neil and co-workers, to prepare β-turn mimics, to control the conformation of proline derived bis-amide *N*-oxides.[17] Both inter- and intramolecular hydrogen bonding results in a decrease in the N-O bond length by ~0.01-0.03 Å.

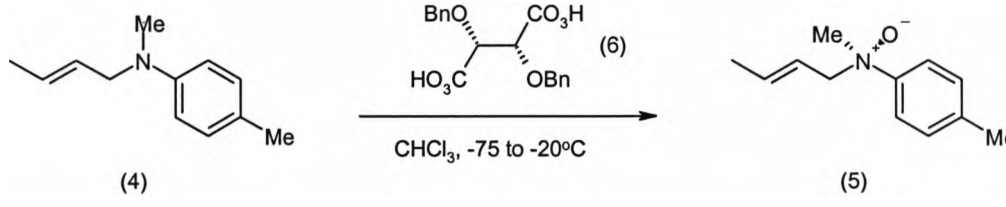
The structure of amine *N*-oxides has been eluded to further from the studies of their transition metal complexes.[31-33] These studies were performed using aliphatic and aromatic amine *N*-oxides as ligands in synthetic organic chemistry. Complexation of the metal to tertiary amine *N*-oxides has proved more difficult because they are less stable than their heteroatomic counterparts. Consequently full characterisation of transition metal complexes containing tertiary amine *N*-oxides are not well known. There have been reports of X-ray structures in which the amine *N*-oxide oxygen is complexed to copper (II),[22] manganese (III)[29,34] and dirhenium.[26] It was found that the only affect that such complexation had upon the structure of the amine *N*-oxide was a slight shortening of the N-O bond distance by ~0.02 Å.

Infra-red studies of tertiary amine *N*-oxides have been undertaken by Zundel and co-workers.[35-41] Their work demonstrated that the N-O bond exhibits a stretching mode at absorption ~940-970 cm^{-1} and a vibrational absorption at ~460 cm^{-1} in the infra-red and the far infra-red spectrum respectively.

1.1.1 CHIRAL TERTIARY AMINE *N*-OXIDES

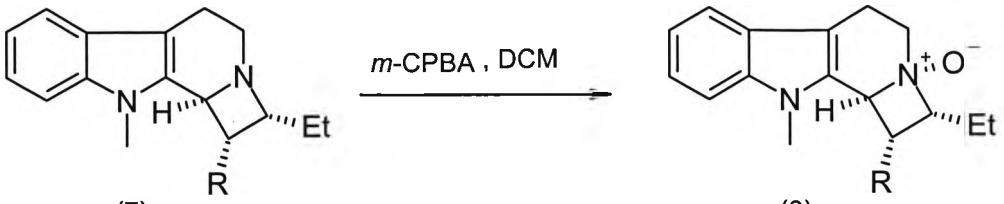
As stated earlier, tertiary amine *N*-oxides can exist in a tetravalent sp^3 hybridised structure and as such if the three alkyl groups are different the tertiary amine *N*-oxide can exist as two enantiomers. Traditionally the two enantiomers have been separated by recrystallization from racemic mixtures by forming a mixture of separable diasteromeric salts with a chiral acid, for example *d*-α-bromo-*p*-camphorsulphonic acid.[42] Preparation of optically pure or enriched, tertiary amine *N*-oxides by directly oxidizing the parent amine had until fairly recently met with only limited success. The most efficient procedure for the production of chiral amine *N*-oxides was *via* the reverse-Cope elimination,[43] which generally gives the amine *N*-oxide in a diastereomerically pure form.[30]

Chiral peracids have been used to oxidise tertiary amines yielding tertiary amine *N*-oxides with a low ee.[44] This was illustrated in scheme 1 which shows the *N*-oxidation of *trans*-*N*-crotyl-*N*-methyl-*p*-toluidine (**4**) with (*R,R*)-*O,O*-dibenzylpertartaric acid (**6**) in chloroform at -70°C gave the chiral amine *N*-oxide, *trans*-*N*-crotyl-*N*-methyl-*p*-toluidine-*N*-oxide (**5**) in 16% ee.[45]



Scheme 1

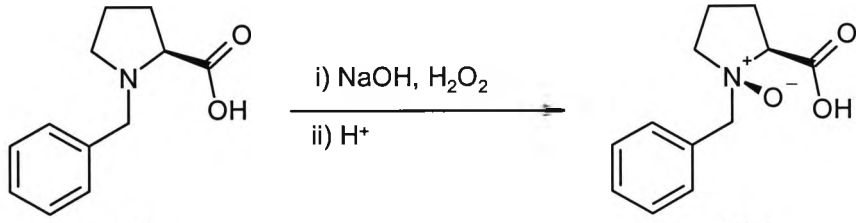
The formation of optically enriched amine *N*-oxides using non-chiral oxidizing agents has been reported on several occasions and has generally been due to attack of the oxidant at the less sterically hindered face of the tertiary amine substrate.[46] In the case of the oxidation of bicyclic fused azetidine (**7**) with *m*-CPBA (Scheme 2) by Kurihara, the diastereoselectivity observed was controlled by the 3-dimensional structure of the substrate.[47] However compound (**8**) was unstable and decomposed quite rapidly.



(7) (8)

Scheme 2

Siemion and co-workers found whilst investigating the *N*-oxidation of α-amino acid derivatives that the oxidation *N*-benzyl-L-proline (**9**) led to the formation of a single diastereoisomer of the amine *N*-oxide (**10**), *syn* to the carboxylic acid group (Scheme 3).[16]



(9) (10)

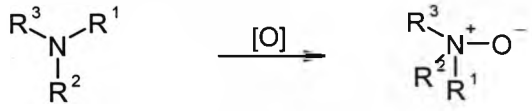
Scheme 3

1.2 PREPARATION OF TERTIARY AMINE N-OXIDES.

Tertiary amine oxides have been prepared in a number of ways. By far the most widespread is the oxidation of the parent tertiary amine.

1.2.1 Oxidation of tertiary amines.

The most common way of preparing tertiary amine *N*-oxides is the *N*-oxidation of the parent tertiary amine using a suitable oxidant (Scheme 4).

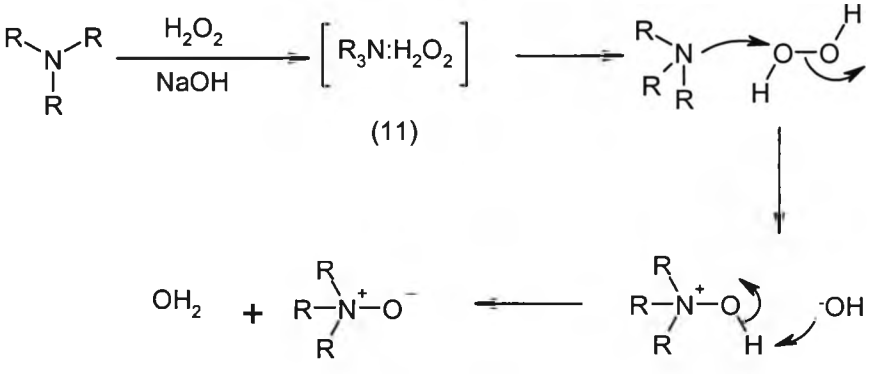


Scheme 4

There are a wide range of oxidants available for this purpose; however the most commonly used are hydrogen peroxide and *meta*-chloroperbenzoic acid (*m*-CPBA). Others which can be used are alkyl peroxides, oxaziridines, molecular oxygen and ozone, sodium periodate and selenoxides.

1.2.1.1 Hydrogen peroxide.

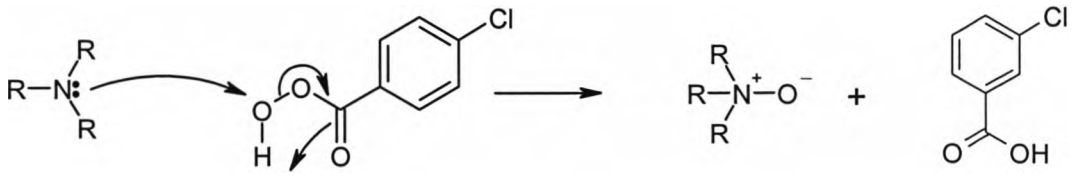
This is probably by far the most common method of *N*-oxidation available and is usually carried out in either aqueous or alcoholic solution. The mechanism of the reaction has been examined by Oswald and Guertin who demonstrated that the oxidation proceeds *via* a trialkylammonium complex (**11**).[48] The complex (**11**) decomposed giving the amine *N*-oxide followed by loss of water. A possible mechanism for this reaction is shown below (Scheme 5).



Scheme 5

1.2.1.2 Organic peracids.

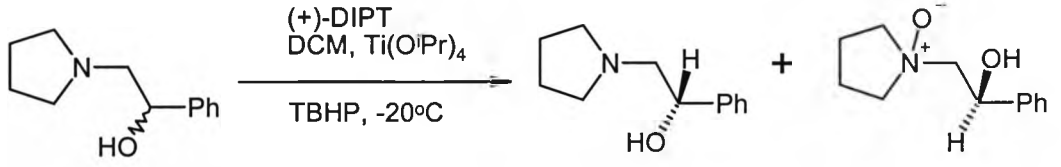
The most favoured peracid used is *meta*-chloroperbenzoic acid, however other acids can be used, such as peracetic and monophthalic for the conversion of the amine to the amine *N*-oxide. Craig and Prushothaman first reported the use of *m*-CPBA in 1970.[49] It was found that *m*-CPBA is tolerant of a wide range of functional groups and provides the amine *N*-oxide in reproducibly high yields in a range of organic solvents (Scheme 6).



Scheme 6

1.2.1.3 Alkyl peroxides.

Sharpless and co-workers developed a very effective procedure for the kinetic resolution of β-hydroxyamines *via* the formation of enantiomerically enriched amine *N*-oxides (Scheme 7).[50] Their worked further developed the work of Kuhnen who had initially employed *t*-butyl hydroperoxide (TBHP) and titanium alkoxide catalyst.[51] Using stipulated conditions the racemic alcohol (**12**) was treated with (+)-diisopropyl tartrate (DIPT) and $Ti(O^iPr)_4$ followed by TBHP. The faster reacting (*S*)-alcohol was converted to the amine *N*-oxide (**14**) leaving the less reactive enantiomeric (*R*)-alcohol (**13**) unchanged in 95% ee.

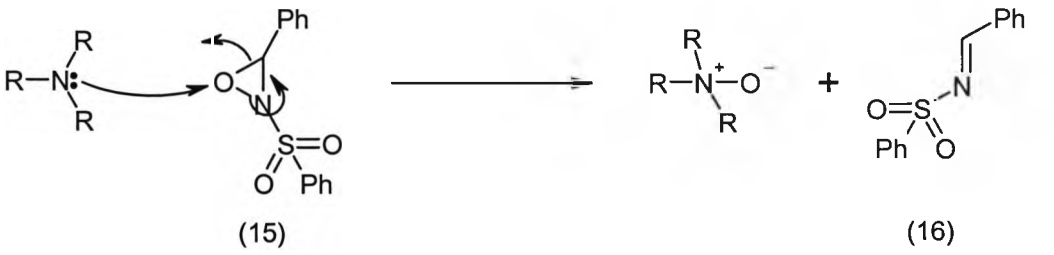


Scheme 7

1.2.1.4 Oxaziridines.

Davis's reagent, 2-phenylsulphonyl-3-phenyloxaziridine (**15**), has been shown by Zajac and co-workers to be efficient in the conversion of tertiary amines to amine *N*-oxides in good yields (Scheme 8).[52] It is worth noting that the amines were quite basic e.g. trimethylamine or *N*-methylpiperidine. The oxaziridine showed excellent

chemoselectivity in the presence of potentially sensitive functionality e.g. olefins, alcohols, hetroatomic tertiary amines.

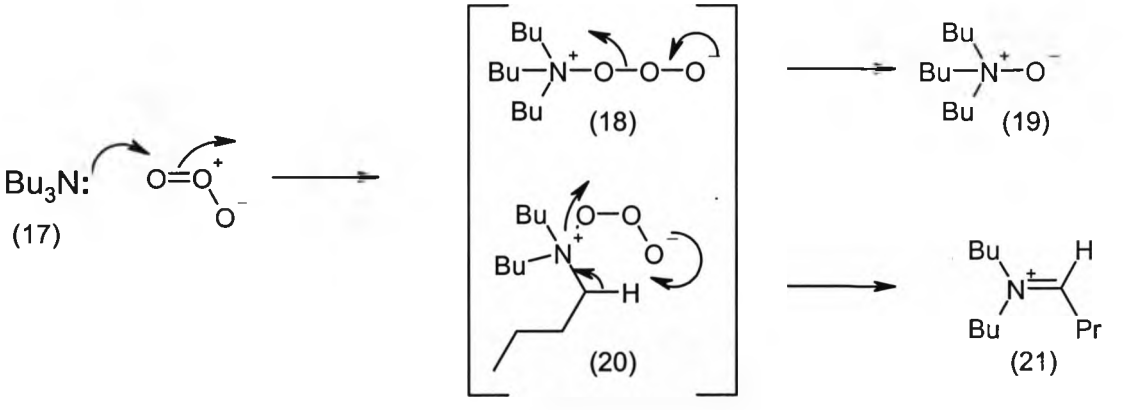


Scheme 8

1.2.1.5 Molecular oxygen and ozone.

Molecular oxygen is not synthetically used as a reagent for converting amines to amine *N*-oxides as it requires a transition metal catalyst and at high temperature and high pressure of oxygen.[53,54]

Amine *N*-oxides have been realised using ozone however there are complications due to the formation of side chain by-products.[55] A proposed reaction mechanism is shown below (Scheme 9).



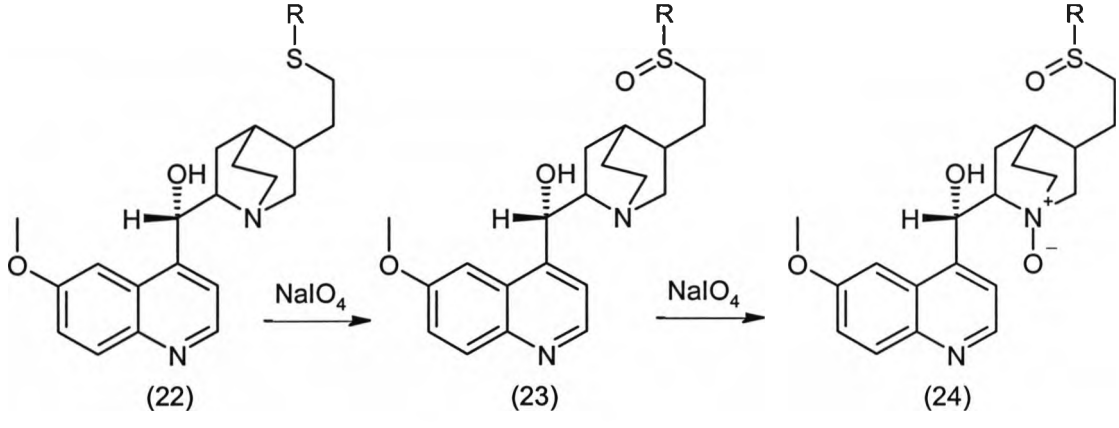
Scheme 9

The mechanism is thought to proceed through an initial nucleophilic attack of the terminal oxygen of ozone by the amine (**17**) lone pair. Decomposition of the resultant

zwitterionic species (**18**) gives the amine *N*-oxide (**19**) and molecular oxygen. However there are by-products and these are believed to be formed through a Polonovski-type reaction. The zwitterionic species (**20**) can undergo intramolecular deprotonation α to the charged nitrogen (Scheme 9), resulting in the formation of a highly reactive iminium ion (**21**), which decomposes to the various by-products observed. By-product formation can be limited by using protic solvents such as methanol.

1.2.1.6 Sodium periodate.

Kobayashi and co-workers noted during the oxidation of the cinchona alkaloid (**22**) (Scheme 10) with sodium periodate that a second more polar spot was formed.[56] They found that upon treatment with excess (1.5 equivalents) of sodium periodate that the *S,N*-dioxide (**24**) was formed in an approximately equimolar amount with the sulphoxide (**23**).



Scheme 10

1.2.1.7 Selenoxides.

The *N*-oxidation of tertiary amines such as strychnine, brucine, nicotinomide, trimethylamine and triethylamine *via* oxygen transfer from selenoxides e.g. dimethylselenoxide (**25**) was reported by Poje and co-workers in 1975 (Scheme 11).[57]

(25) (26)

Scheme 11

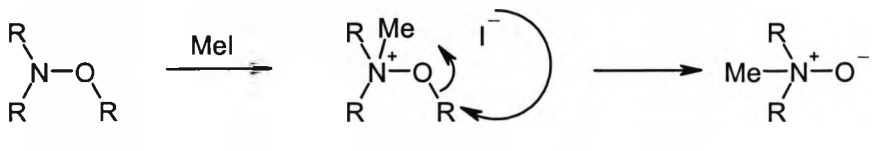
1.2.1.8 Other oxidizing reagents.

Recent work by Thomas and co-workers has shown the potential for the use of dimethyldioxirane (DMDO) as an oxidant for the conversion of tertiary amines to tertiary amine *N*-oxides.[58] Some work has been done within the O'Neil group using this as an oxidant.[59]

Magnesium monoperoxyphthalate (MMPP) has been reported to oxidize *N,N*-dimethylamine to the amine *N*-oxide in high yields.[60,61] The generality of this oxidant has not yet been investigated.

1.2.2 Alkylation of hydroxylamines.

The reaction of *N,N*-dialkyl-*O*-alkyl hydroxylamines with alkyl halides to give tertiary amine *N*-oxides was first reported by Dunston and Goulding in 1899.[6] A more recent example of this reaction was reported by Jones and Jones which showed that the yields of amine *N*-oxides through this type of reaction were variable.[62] The reaction is thought to proceed *via* a nucleophilic attack by the halide ion on an intermediary ammonium species (**28**) (Scheme 12).

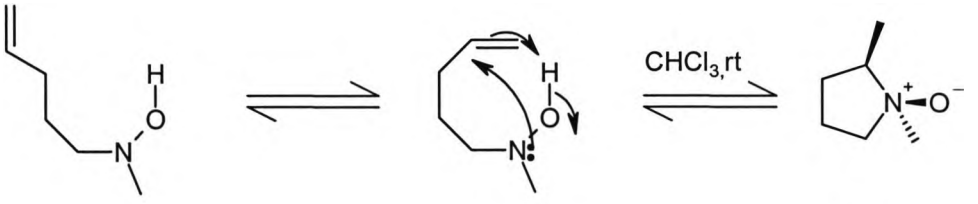


(27) (28) (29)

Scheme 12

1.2.3 The Reverse-Cope elimination.

The reverse-Cope elimination was first reported by Cope and co-workers in 1960 and is now widely used in the synthesis of amine *N*-oxides.[63] The reaction was further investigated by Laughlin and Ciganek and a mechanism for the reverse-Cope elimination has been established (Scheme 13).[30,64] For example, the cyclization of hydroxylamine (**30**) at room temperature yielded the amine *N*-oxide (**32**) as a single diastereoisomer in good yield.[30]



(30) (31) (32)

Scheme 13

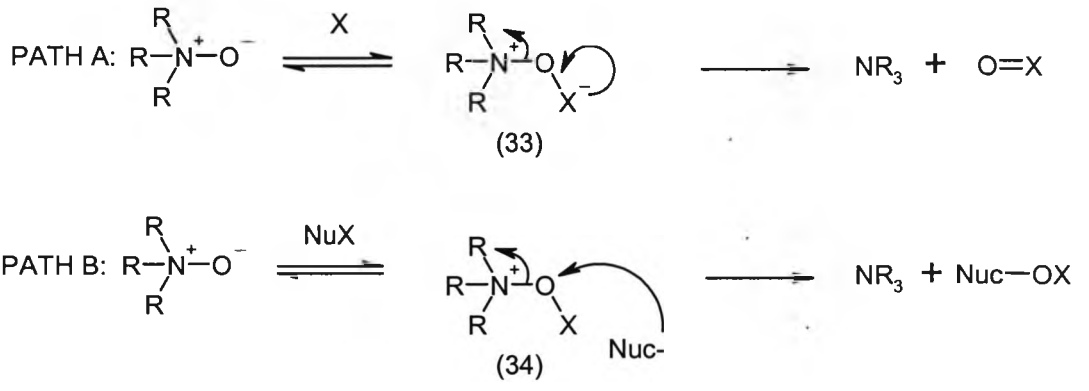
The major problem of the reverse-Cope elimination is the reversibility of it. Distillation of the amine *N*-oxide (**32**) resulted in the partial reversion to the hydroxylamine (**30**).

1.3 REACTIONS OF TERTIARY AMINE N-OXIDES.

1.3.1 Reduction of tertiary amine *N*-oxides.

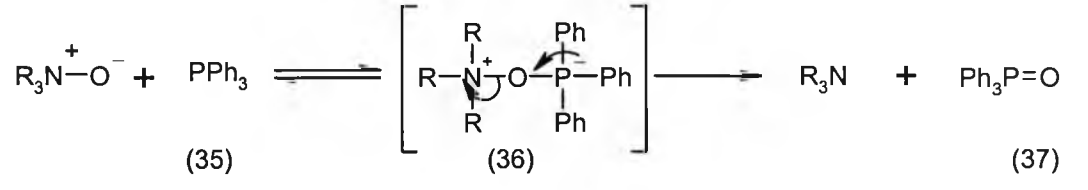
The reduction, or deoxygenation, of tertiary amine *N*-oxides has been classified into two groups, distinguished by the mechanism of the reductive process.[65] The first, path A, involves initial electrophilic attack of the reductant which forms a zwitterionic species (**33**) followed by the donation of the electron pair to the oxygen which in turn cleaves the N-O bond. The second, path B, involves co-ordination of

an electrophile to the amine *N*-oxide oxygen (**34**) followed by nucleophilic attack of the oxygen to, again, cleave the N-O bond (Scheme 14).



Scheme 14

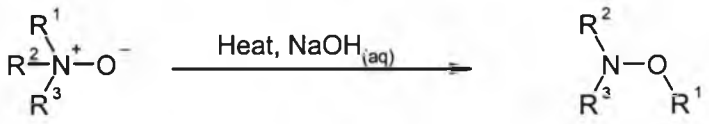
Common reducing agents used to cleave heteroatomic bonds have been shown to reduce amine *N*-oxides to their parent tertiary amines (e.g. lithium aluminium hydride, hydrogenation over palladium catalyst and zinc metal in acidic solution).[50,66] There was a need, however, to develop other reductive systems due to the lack of chemoselectivity of the above reagents. Of those developed trivalent phosphorus is probably the most commonly used particularly triphenylphosphine (**35**) (Scheme 15).[67,68]



Scheme 15

1.3.2 The Meisenheimer rearrangement.

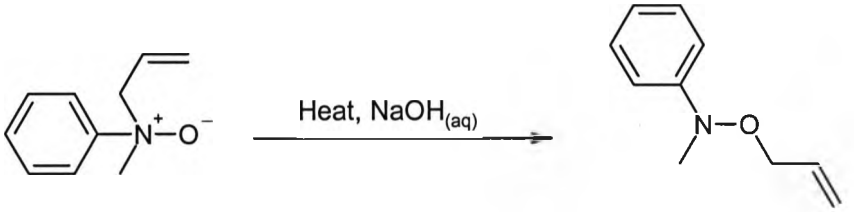
The Meisenheimer rearrangement is the thermal isomerization of a tertiary amine *N*-oxide (**38**) to a *N,N,O*-trisubstituted hydroxylamine (**39**) and is caused by the favourable conversion of a highly charged dipolar system to a more stable neutral hydroxylamine (Scheme 16).



(38) (39)

Scheme 16

The rearrangement was first reported by Meisenheimer when he found upon heating *N*-methyl-*N*-allylamine (**40**) in aqueous sodium hydroxide the isomeric hydroxylamine *O*-allyl-*N*-methyl-*N*-phenylhydroxylamine (**41**) was formed (Scheme 17).[69]



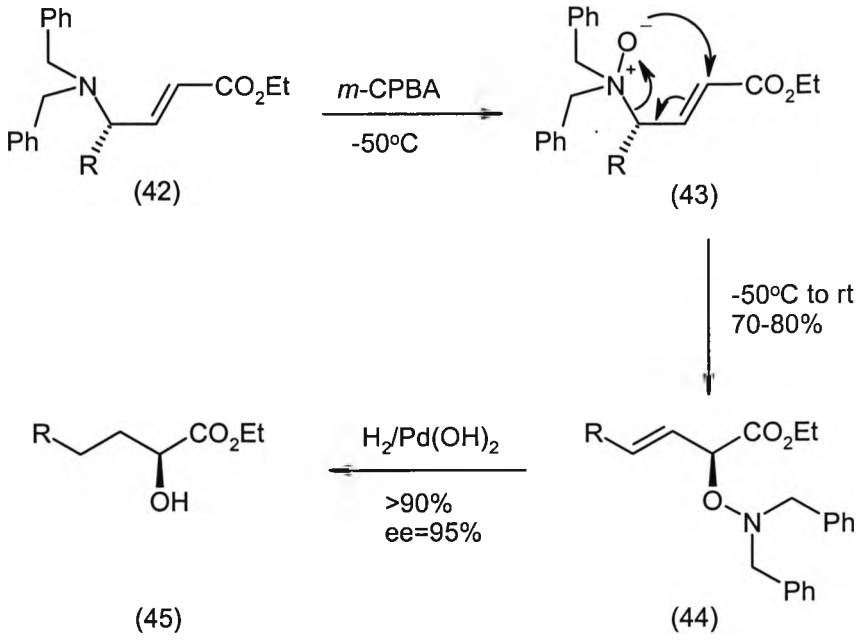
(40) (41)

Scheme 17

The Meisenheimer rearrangement can occur through two distinct mechanisms. When the tertiary amine is substituted with an allyl group a concerted [2,3]-sigmatropic rearrangement to give the *O*-allyl hydroxylamine prevails.[70] In the absence of a suitable allyl substituent, or at high temperature, The amine *N*-oxide will isomerize *via* a radical mediated [1,2]-rearrangement.

1.3.2.1 The [2,3]-Meisenheimer rearrangement.

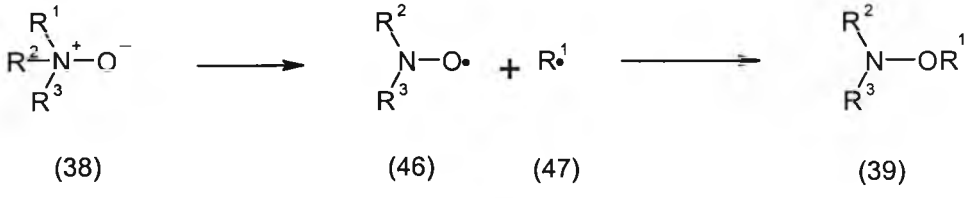
The [2,3]-Meisenheimer rearrangement mechanism is concerted (**43**) (Scheme 18) and in most cases transfer of all the chiral information to the resultant hydroxylamine occurs.[70,71] The rearrangement has been used by Reetz and co-workers in the preparation of enantiomerically pure α-hydroxy esters (**45**) from α-amino acids.[71]



Scheme 18

1.3.2.2 The [1,2]-Meisenheimer rearrangement.

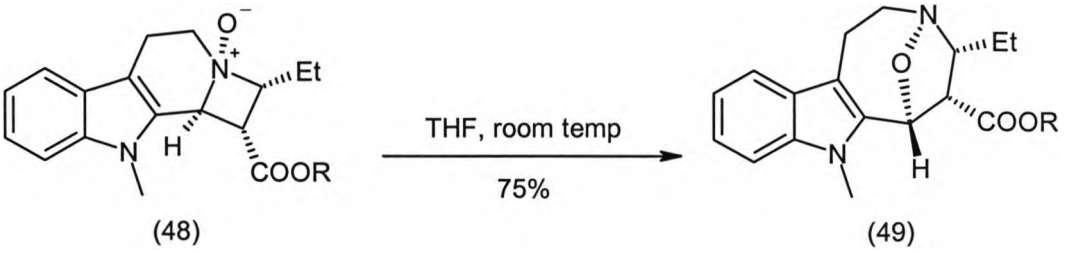
The [1,2]-Meisenheimer rearrangement is a radical mediated isomerization of a tertiary amine *N*-oxide to a trisubstituted hydroxylamine.[72] The first step of the reaction mechanism is homolytic cleavage of one of the C-N bonds. This produces a stable nitroxide radical (**46**) and a carbon centred radical (**47**) which recombine to form the hydroxylamine (**39**) (Scheme 19).



Scheme 19

This rearrangement has been used in the synthesis of 1,2-oxazaheterocycles[73] *via* the ring expansion of cyclic amine *N*-oxides and has been reported for the 4 to 10-membered cyclic *N*-oxides.[74-78] The azetopyridoindole *N*-oxide (**48**) rearranges

directly when formed upon treatment with a peracid of the amine at room temperature forming (**49**) as a single diastereoisomer in good yield (Scheme 20).[47,78]

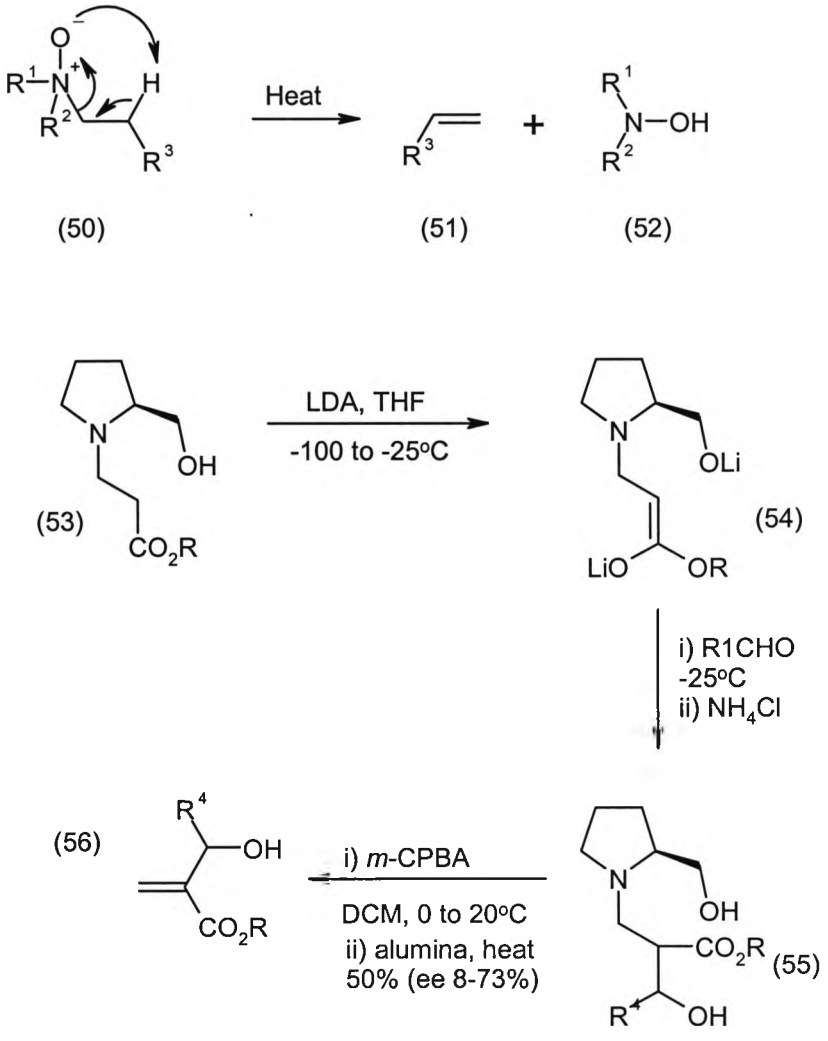


(48) (49)

Scheme 20

1.3.3 The Cope elimination.

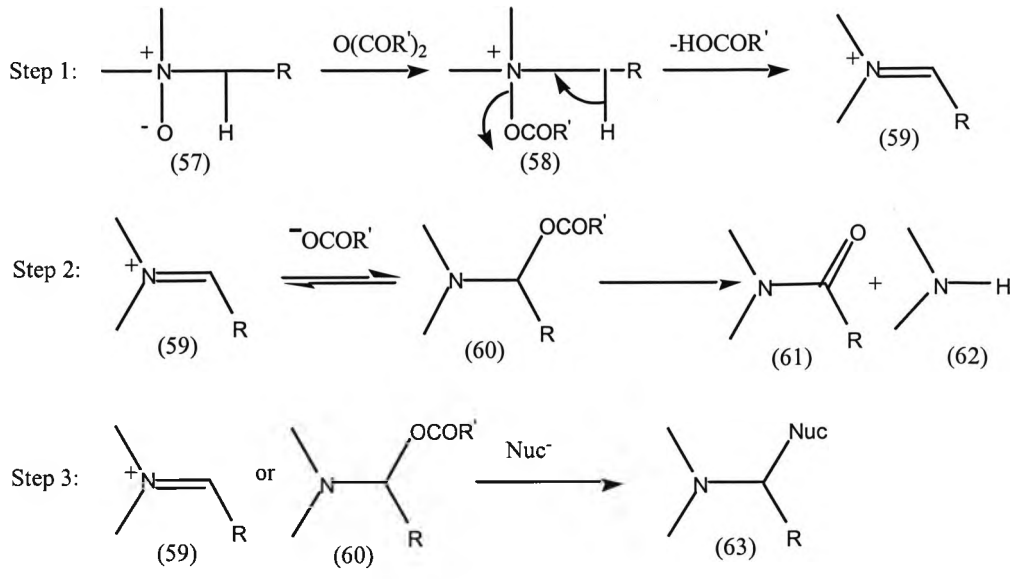
In the presence of suitably positioned β-hydrogen, tertiary amine *N*-oxides (**50**) decompose to generate an alkene (**51**) and a hydroxylamine (**52**), this is an example of a Cope elimination (Scheme 21).[76] The reaction has been used to good effect in the synthesis of chiral alkenes.[79] On treatment of amine (**55**) with *m*-CPBA and subsequent heating of the *N*-oxide whilst absorbed on alumina, the Cope elimination occurs to give the α-hydroxyalkylacrylates (**56**) (Scheme 21).



Scheme 21

1.3.4 The Polonovski reaction.

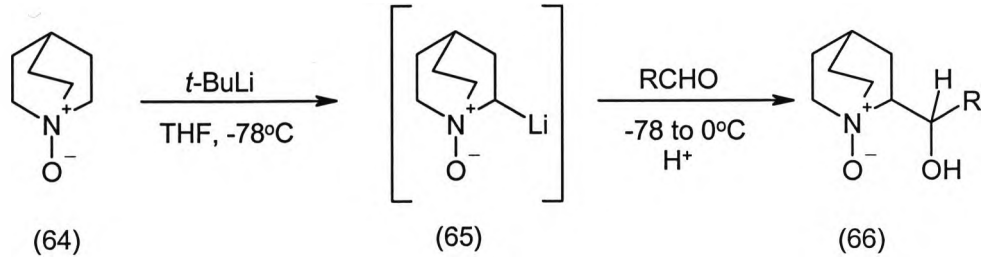
Amine *N*-oxides are easily *O*-acylated, but even at low temperatures the reaction will proceed further with deprotonation at the α-position and loss of acetate (*trans* elimination) to give the iminium ion (step 1 (**59**)) (Scheme 22).[9,20] Addition of the acetate ion (step 2 (**60**)) in the α-position and subsequent fragmentation of the N-C bond leads to the secondary amine (**62**) or the corresponding amide (**61**). In the presence of an external nucleophile, the iminium ion is trapped to yield the α-substituted tertiary amine (step3 (**63**)); alternatively the loss of a β-proton leads to the formation of an enamine.



Scheme 22

1.3.5 Deprotonation of tertiary amine *N*-oxides.

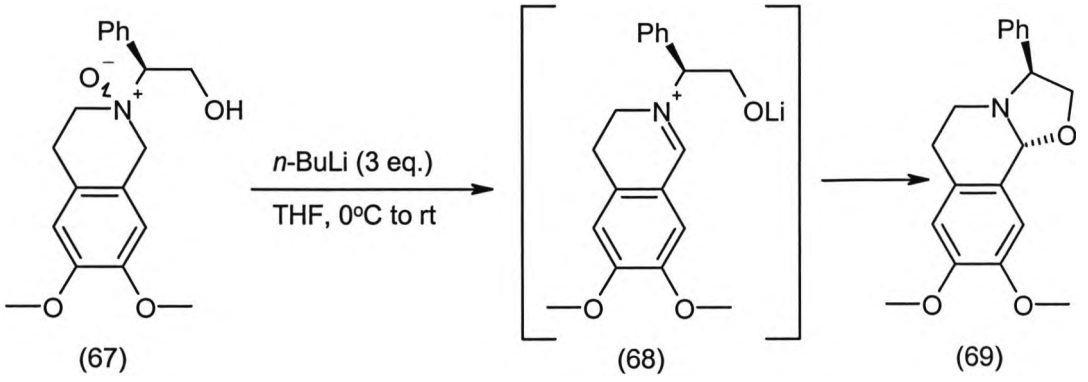
In 1978 Barton and co-workers deprotonated a tertiary amine *N*-oxide (**64**) using a strong base, *t*-butyllithium, which led to deprotonation at the α-position (**65**).[80] The lithiated species was treated with a range of electrophiles to yield various products an example of which is illustrated below (**66**) (Scheme 23).



Scheme 23

Deprotonation of tertiary amine *N*-oxides has also been used to synthesize aziridines,[81] and in [3+2]-dipolar cycloaddition reactions.[82] Oxazolidines have also been prepared by treatment of β-amino alcohol *N*-oxides with bases, for example treatment of amine *N*-oxide (**67**) with excess *n*-butyllithium at 0°C leads to

deprotonation and loss of Li_2O followed by an intramolecular cyclization and formation of a fused oxazolidine tricycle (**69**) as a single stereoisomer (Scheme 24).

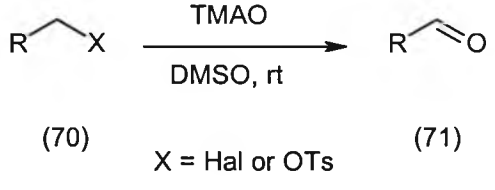


Scheme 24

1.4 TERTIARY AMINE N-OXIDE MEDIATED OXIDATIONS.

1.4.1 Oxidation of organic compounds.

Tertiary amine *N*-oxides have been used to oxidize several functionalities in synthetic organic chemistry, including the oxidation of primary alkyl bromides, iodides or tosylates (**70**) (*c.f.* the Kornblum oxidation[83]) to the corresponding aldehydes (**71**), first developed by Franzen and co-workers (Scheme 25).[84-87]



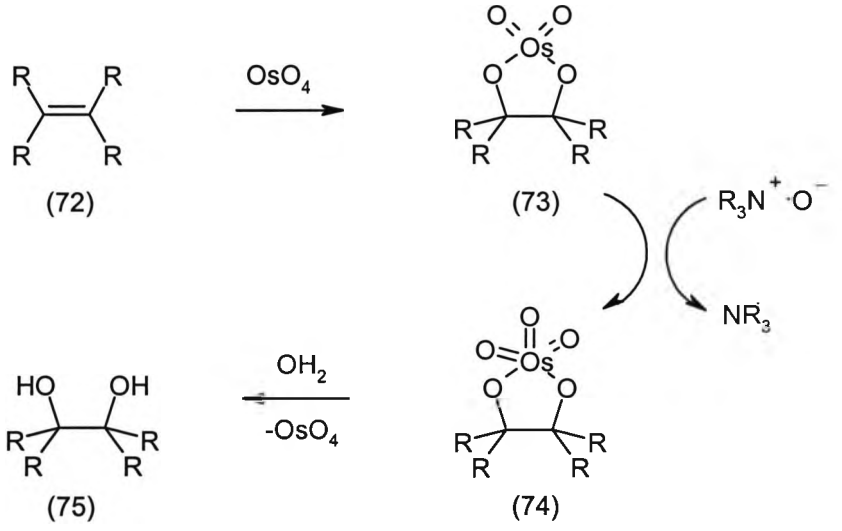
Scheme 25

Otera and co-workers has described the synthesis of α,β-unsaturated aldehydes from secondary chlorides, using an excess of trimethylamine *N*-oxide (TMAO) and a catalytic amount of copper (I) chloride.[86] The reaction gives almost exclusively the

trans alkene. Ganem and co-workers have also described the oxidation of primary amines to aldehydes utilising tertiary amine *N*-oxides.[88]

One of the most commonly used reactions in synthetic chemistry is the *syn*-dihydroxylation of alkenes with osmium (VIII) tetroxide. In order to reduce the amount of OsO_4 in the reaction a secondary oxidant, generally a tertiary amine *N*-oxides such as *N*-methylmorpholine-*N*-oxide (NMMO) is used stochiometrically in conjunction with a catalytic amount of the osmium reagent.

In a typical procedure[89] the alkene is added to a mixture of water/acetone/*t*-butyl alcohol containing 1 equivalent of TMAO and 0.5 mol. % of OsO_4.[89] Oxygen transfer from the amine *N*-oxide to the intermediary osmate ester (**73**) gives the osmium (VIII) species (**74**). Hydrolysis of (**74**) leads to 1,2-diol (**75**) formation and regeneration of the OsO_4 catalyst (Scheme 26).



Scheme 26

Sharpless and co-workers developed an asymmetric version of this oxidative system.[90] With the addition of a catalytic amount of a chiral ligand (usually a cinchona alkaloid) to the reaction, the *syn*-dihydroxylation proceeds at a much higher rate and in > 99% e.e. and excellent yields.

Ley and Griffith developed an extremely useful ruthenium (VII) catalyst, tetra-*n*-propylammonium perruthenate (TPAP),[91,92] which effects the oxidation of primary alcohols to aldehydes and secondary alcohols to ketones in the presence of 1 equivalent of the co-oxidant TMAO. The reaction conditions are very mild and tolerance is seen towards many potentially sensitive functional groups, *e.g.* halides. The yields of product are generally excellent and the chiral integrity is maintained in adjacent chiral centres.

Sharpless and co-workers have also reported the oxidation of primary and secondary alcohols using catalytic amounts of $RuCl_3$ and 1 equivalent of NMMO as the co-oxidant.[93] The reaction conditions are reasonably mild and yields of the product tend to be high.

Metalloporphyrins,[94] typically iron (III)[95,96] or manganese (III),[29,97] have been used as catalysts in the oxidation of alkenes to epoxides. The active oxidant is thought to be a highly reactive metal oxo species, generated by oxygen transfer from the tertiary amine *N*-oxide to the transition metal.

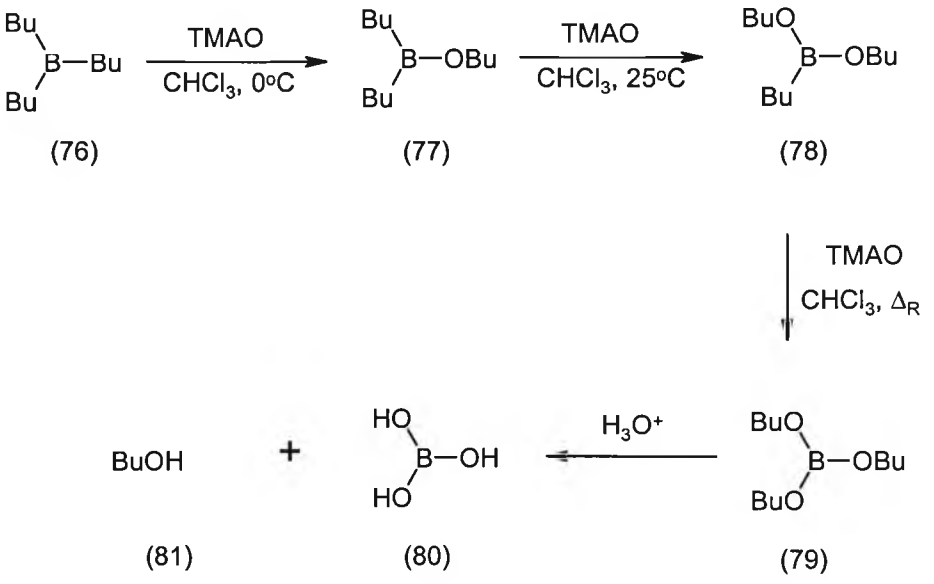
1.4.2 Oxidation of main group organometallics.

1.4.2.1 Organoboranes

Organoboranes are extremely versatile intermediates used widely in synthetic organic chemistry. Carbon-boron bonds are oxidized by a number of oxidizing agents, however in the presence of other sensitive functionality in a molecule complications may arise with unwanted by-products. Kostner and co-worker in 1969 found that the carbon-boron could be oxidized using TMAO, which with the mild conditions used, offers advantages over some other oxidative systems.[98,99,100]

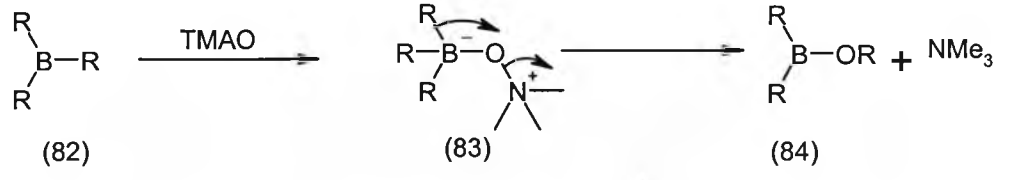
Treatment of a trialkylborane (**76**) with 3 equivalents of anhydrous TMAO gives the borate ester (**79**), which upon hydrolysis forms the corresponding alcohol (**81**) in

excellent yield. The oxidation occurs in a stepwise manner and the intermediate borinate (**77**) and boronate (**78**) can be isolated from the reaction (Scheme 27).[101]

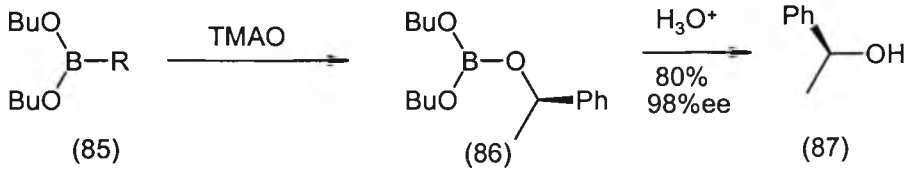


Scheme 27

Each oxidation is seen to be more difficult than the previous one. The temperature and also the substituents on the organoborane control the rate of oxidation. Studies have shown that the rate of oxidation is tertiary alkyl > cyclic secondary alkyl > acyclic secondary alkyl > *n*-primary alkyl > branched primary alkyl > vinyl.[102,103] The accepted mechanism for the TMAO oxidation of organoboranes is shown in Scheme 28. Nucleophilic attack on the trialkylborane (**82**) by the TMAO oxygen forms the betaine (**83**), and the trimethylamine group is believed to leave antiperiplanar to the migrating alkyl group (**83**) (Scheme 28). The oxidation proceeds with retention of configuration when the migrating group is chiral (Scheme 29).[104]



Scheme 28



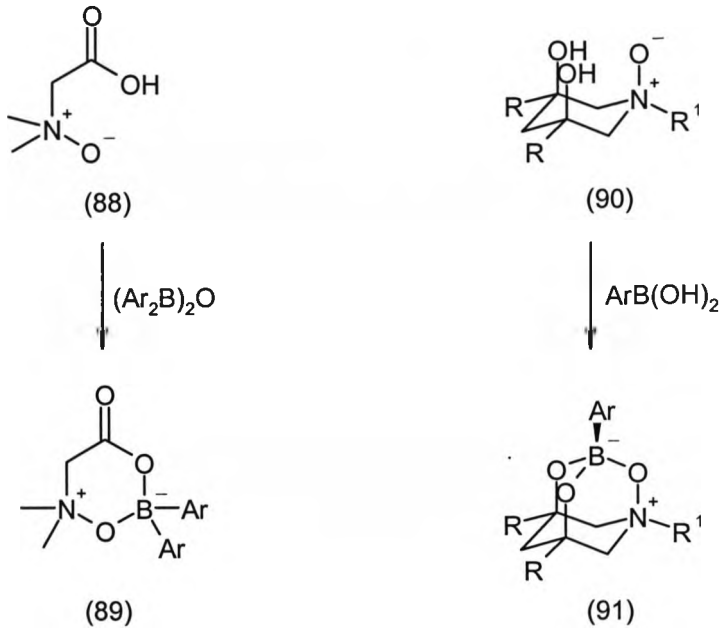
Scheme 29

Trialkyl- and triphenylaluminium compounds as well as dialkylhydroxysilanes are also efficiently oxidized to the alcohols using TMAO.[105,106] Insertion of two oxygen atoms into the Sn-Sn bond of distannanes has been observed,[107] as has oxygen transfer to phosphorus.[108] Amine oxides are readily deoxygenated by metal carbonyls and this method is often used for the 'activation' of metal complexes towards the substitution of a carbonyl with another ligand.[33,109] The metal carbonyl undergoes nucleophilic attack by the amine *N*-oxide liberating carbon dioxide and a coordinatively unsaturated metal complex; the entering ligand is either the tertiary amine or another molecule present.[110] This is also an important method for the liberation of organic ligands from metal complexes, particularly iron carbonyls.[111,112] The process is mild and often more effective than ligand exchange.

1.5 AMINE N-OXIDE METAL COMPLEXES.

1.5.1 Organoborane complexes.

The treatment of an organoborane with a tertiary amine *N*-oxide initially generates a zwitterionic betaine species (**83**). When the tertiary amine *N*-oxide possesses a suitably positioned second chelating functionality, *e.g.* an alcohol, then stable cyclic betaines can be formed (Scheme 30). Heterocyclic betaines can be isolated and a number of these betaines, formed by the reaction of arylboronic acids with tertiary amine *N*-oxides derived from the α-amino acid (**88**) or β-hydroxy amine (**90**), have been reported by Kliegel and co-workers (Scheme 30).[113-115]



Scheme 30

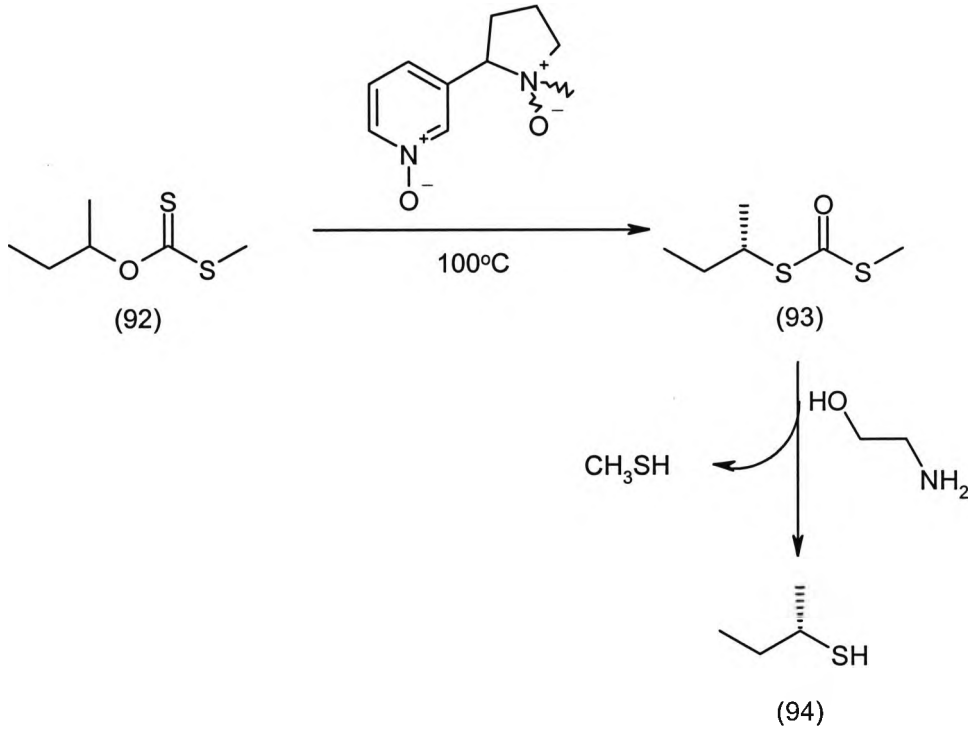
1.5.2 Transition metal and lanthanide complexes.

Tertiary amine *N*-oxides can form stable complexes with transition metals. Brown and co-workers have also reported a stable dirhenium heptacarbonyl trimethylamine *N*-oxide complex.[26] Other stable *N*-oxide complexes with nickel (II), copper (II) and cobalt (III) have also been reported in the literature.[116] Lehn and co-workers have developed several bis- and tetrakis-*N*-oxides, based on cyclic pyridal cryptates, which have been shown to coordinate to lanthanide metals (Eu (III), La (III) and Tb (III)).[117-119]

1.6 Amine Oxides as Catalysts of Organic Reactions.

Amine *N*-oxides have shown a catalytic effect on various reactions. A report by Marchetti and co-workers showed the enantioselective synthesis of thiols via a thione-thiol rearrangement catalyzed by optically active amine *N*-oxides.[120] The important step is the rearrangement of the racemic carbondithioic *O,S*-dialkyl ester (**92**) catalysed by 50 mol. % of *N*-oxide (**95**) at 100°C for 24 hours. The carbodithioic *S,S*-dialkyl ester (**93**) was formed in good yield (Scheme 31). Next (**93**) and 2-aminoethanol (1.5 eq.) were heated at 70°C for 10 minutes. Fractional distillation at

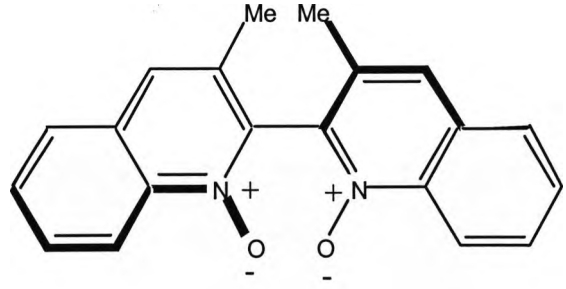
ambient pressure afforded (*S*)-(-)-butanethiol (**94**) in a yield of 95% with an ee of 37.7%.



(92) (93) (94)

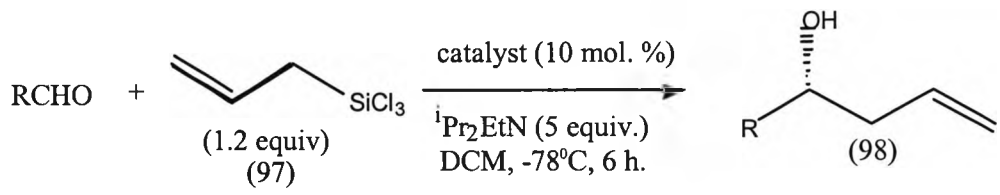
Scheme 31

Nakajima and co-workers recently reported an axially disymetric chiral ligand, (*R*)- or (*S*)-3,3'-dimethyl-2,2'-biquinoline *N,N'*-dioxide (Figure 3).[121] The catalyst has been used to prepare homoallylic alcohols (**98**) in up to 90% ee from aldehydes and allyltrichlorsilane (**97**) using 5 equivalents of diisopropylethylamine (Scheme 32). The use of diisopropylethylamine was found to accelerate the allylation reaction. The reaction was also catalyzed by isoquinoline *N*-oxide.



(96)

Figure 3


RCHO
+
SiCl3
(1.2 equiv)
(97)
catalyst (10 mol. %)
iPr2EtN (5 equiv.)
DCM, -78°C, 6 h.
OH
R
(98)

Scheme 32

Chapter 2

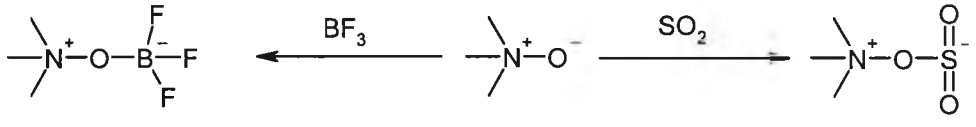
Results and Discussion

2 The Polar Nature of Amine Oxides.

As mentioned in Chapter 1, tertiary amine oxides are extremely polar in nature, possessing one of the largest permanent dipole moments in organic chemistry. With the exception of aromatic amine oxides, which have slightly lower dipole moments, *N*-oxides typically have a dipole moment within the region of 4.5 - 5.0 Debyes.[122,123] The dipole moment of similar polar bonds, e.g. phosphorus oxide (P-O) and sulfoxide (S-O) are much lower, typically around 3.2 D and 3.0 D respectively. The reason for this difference in polarity, stems from the ability of phosphorus and sulphur to partake in partial π orbital overlap with excess negative charge on the oxygen interacting with the empty d-orbital in the phosphorus and sulphur. The nitrogen atom of amine oxides, on the other hand, is unable to partake in such orbital overlap and hence the N-O bond exists in the highly polar single bond form.

The ability of amine oxides to form stable zwitterionic complexes provides strong evidence of the powerful electron donor or coordinating character of tertiary amine oxides (Scheme 33)

It has been shown that TMAO (**99**) reacts with sulphur dioxide and boron trifluoride to form the zwitterions shown (**100**) and (**101**).[124-126]



(100) (99) (101)

Scheme 33

It is known that HMPA coordinates lithium cation in a similar manner and we wondered if we could exploit the large dipole of the amine oxide and investigate whether it could be used in reactions as a potential replacement for HMPA.

2.1 Hexamethylphosphoramide (HMPA)

2.1.1 Physical Data

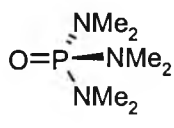
HMPA has a melting point of 7.2 °C and a boiling point of 230-232°C @ 740mmHg. Its density is 1.025 g cm^{-3} and it has a mild amine odour. HMPA is a colourless mobile liquid, which is miscible with water in all proportions. It is also miscible with many polar and nonpolar organic solvents, but not with saturated hydrocarbons.

HMPA has low to moderate acute toxicity in mammals; it has an LD = 6g/Kg for oral administration to rats.[127]

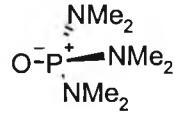
Inhalation exposure to HMPA has been shown to induce nasal tumours in rats,[128] and has been classified under ' Industrial Substances Suspect of Carcinogen Potential for Man'.[129] Adequate precautions must be taken to avoid all forms of exposure to HMPA.

2.1.2 Structure of HMPA

The HMPA (**102**) molecule is pyramidal in structure. The polar or double bond character of the P-O bond varies according to other substituents (Figure 14).[130,131]



(102)

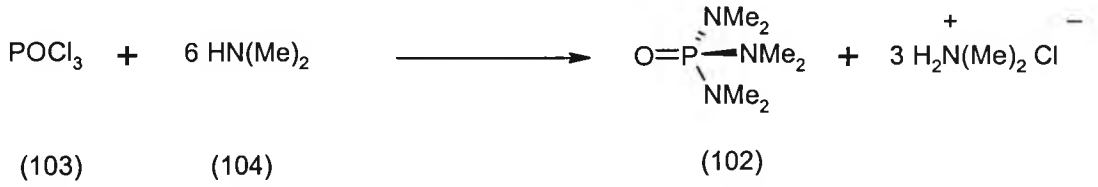


(102a)

Figure 14

2.1.3 Synthesis of HMPA

The first synthesis of hexamethylphosphoramide (**102**), HMPA, was reported by Michaelis in 1903.[132] It was prepared by the treatment of phosphorus oxychloride (**103**) with 6 equivalents of dimethylamine (**104**) giving HMPA. (Scheme 34)



Scheme 34

The chlorine atoms were replaced sequentially with increasing difficulty. The first replacement is rapid and strongly exothermic, while second and third proceed less rapidly and only on heating.

2.2 Reactions using HMPA.

2.2.1 Introduction

Hexamethylphosphoramide, HMPA, has been used extensively as an additive in organolithium chemistry.[133] It is among the strongest of electron pair donors and is superior to protic solvents as it solvates the cation much better than the anion which can dramatically affect the chemistry of the anion.[134,135] For instance, HMPA dramatically enhances the rates of a wide variety of organolithium reactions, as well as significantly influencing their regio- and/or stereochemistry. The reactivity or selectivity effects of HMPA are usually rationalised either in terms of changes in aggregation state or ion pair structure.[136,137] The breaking up of aggregates to form reactive monomers or solvent separated ion pairs is often implicated.

2.2.2 Solution Structure of Organolithium Reagents

HMPA may exert its reactivity effects by a combination of one or more of the following:

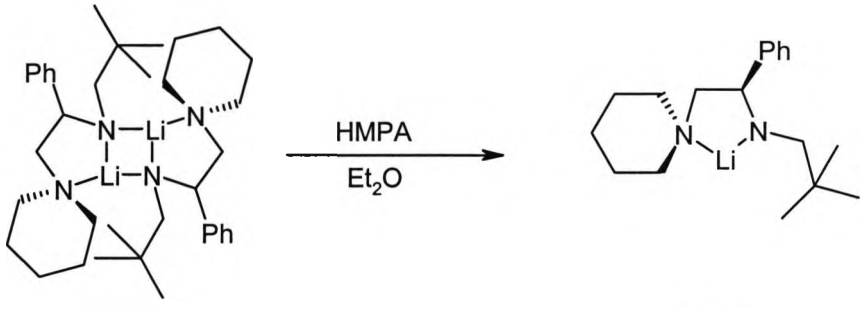
1. Lowering the degree of aggregation or forming separated ions.[138-141]

2. Increasing reactivity through cation coordination.[142]

3. Activating the aggregate through insertion into the aggregate site normally occupied by the anionic fragment.[143,144]

4. Promoting triple ion (ate complex) formation.[145]

For example the rate of metallation reactions with lithium diisopropylamide (LDA) as a base are significantly increased through the use of HMPA.[146-148] Treatment of LDA dimer with HMPA causes sequential solvation of the lithium cation, but no significant deaggregation.[146-149] A chiral bidentate lithium amide (**105**) was converted from a dimer to a monomer (**106**) by HMPA, with an increase in reactivity and enantioselectivity in deprotonation (Scheme 35).

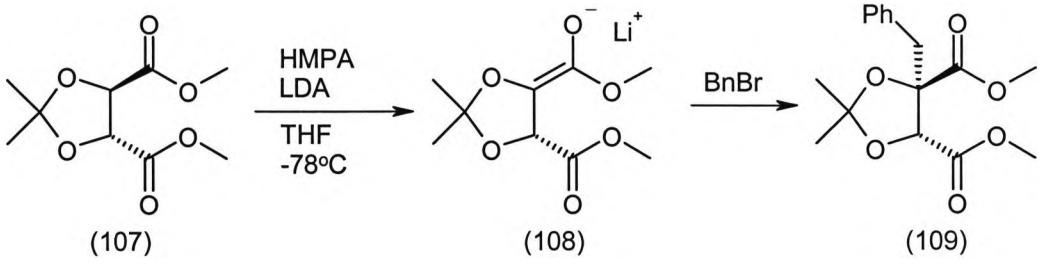


(105) (106)

Scheme 35

2.2.3 Enolate Formation

The formation of lithium enolates is one instance where the addition of HMPA can be advantageous.[150] The difficult generation of the dimethyl tartrate acetonide enolate (**108**) and subsequent benzylation (**109**) only become possible upon addition of HMPA (Scheme 36).[151]

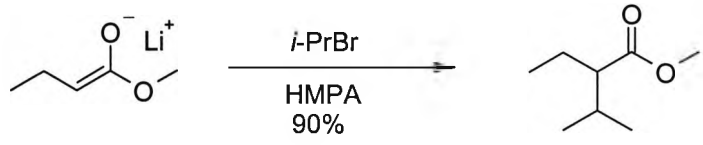


(107) (108) (109)

Scheme 36

2.2.4 Enolate Reactivity

Not only is HMPA necessary to generate certain enolates, it is often needed in the electrophilic trapping of enolates (**110**) (Scheme 37).[152-154] Studies of the electrophilic trapping of enolates have shown that substantial increases in reaction rates can be achieved through the use of polar aprotic solvents like HMPA.[134-135]



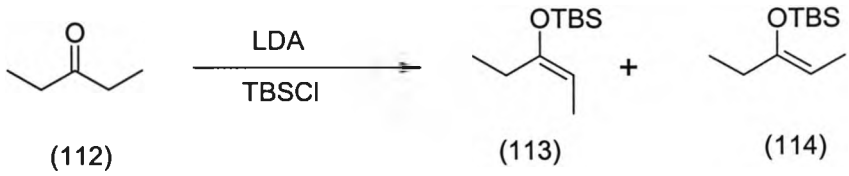
(110) (111)

Scheme 37

2.2.5 Enolate Stereochemistry

Stereochemical control of an ester enolate Claisen rearrangement was accomplished through stereoselective enolate formation.[155] The enolization of 3-pentanone (**112**)

with LDA in THF alone gave predominantly the (*E*)-enolate (**113**) whereas in THF-HMPA the (*Z*)-enolate (**114**) was preferentially formed. (Scheme 38)



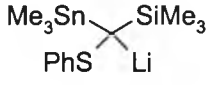
(112) (113) (114)

THF	77	:	33
THF:HMPA	5	:	95

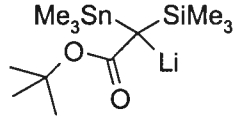
Scheme 38

2.2.6 Carbanion Formation

Often a substrate that cannot be metallated by LDA or *n*-BuLi in THF can be successfully deprotonated by adding HMPA as a cosolvent. Numerous other weakly acidic C-H acids, see Figure 2 below, can be successfully metallated in the presence of HMPA.[156-158] HMPA can also be used to aid the formation of dianions and increases the proton abstraction efficiency of sodium hydride.[159-169]



(118)



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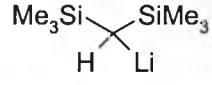

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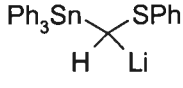
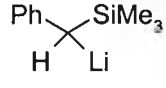


(121)



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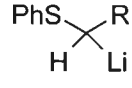
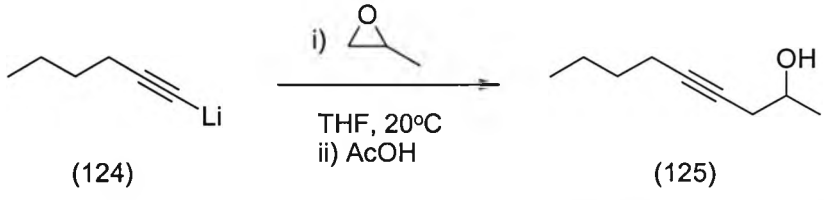


(123)

Figure 5

2.2.7 Carbanion Reactivity

An increase in reaction rate is observed for the reaction of alkyllithium reagents with alkyl halides and oxiranes (Scheme 39).[132, 161] It is assumed that the strongly coordinating HMPA complexes the lithium cation, thereby increasing the negative charge density on the carbon and creating a much more nucleophilic alkynyl anion. An example of this is shown in Scheme 39. The alkynyl anion (**124**) is unreactive to epoxides in THF alone however, the addition of HMPA results in the expected ring opening reaction giving the alcohol, non-4-yn-2-ol (**125**). A similar effect is seen for (trimethylstannyl)lithium, which does not react with oxiranes in THF but does so in THF-HMPA.[162]



(124) (125)

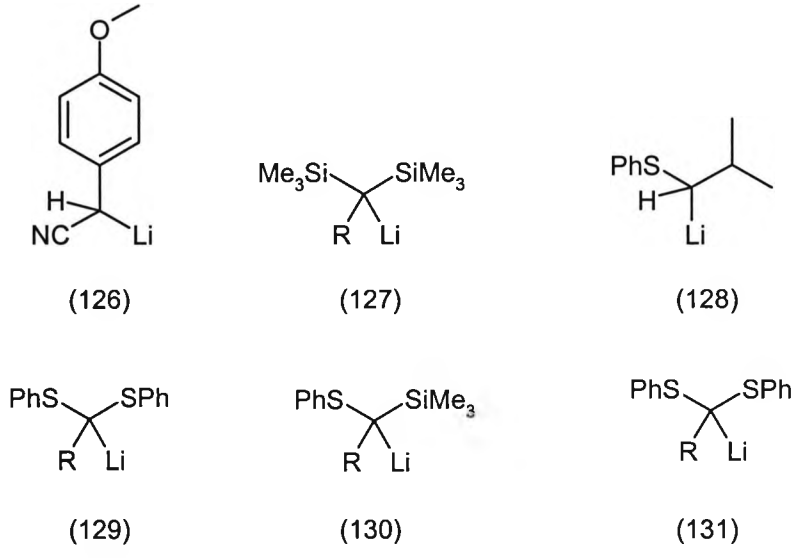
Cosolvent(% vol)	Yield(%)
-	<5
HMPA(17)	70
DMPU(50)	59

Scheme 39

HMPA is also the only dipolar aprotic solvent to be used extensively with organomagnesium compounds.[163] Large effects are observed when HMPA is used either as either a solvent or a cosolvent. This is illustrated in the addition of an allylic organomagnesium compound to aryl-substituted alkenes and addition of Grignards to carbon monoxide.[164,165]

2.2.8 Carbon Regioselectivity (1,2- vs. 1,4-addition)

The regioselectivity of addition of certain organolithium reagents to α,β–unsaturated carbonyl compounds is affected by the addition of HMPA. Examples of lithium reagents that exhibit kinetic 1,4-addition in HMPA are shown in Figure 6.

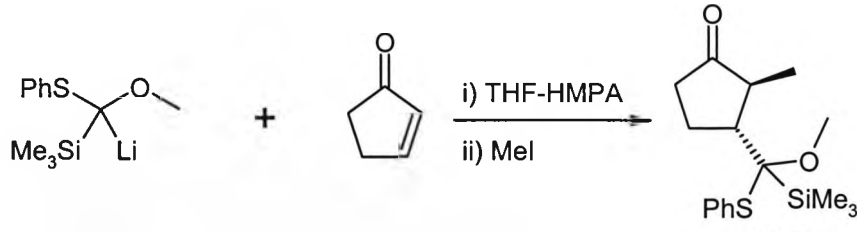


(126) (127) (128)

(129) (130) (131)

Figure 6

THE carboxy anion equivalent (**132**) in Scheme 40 was reported to undergo exclusive 1,2-addition in THF.[166,167] However repeating the reaction in the presence of 10 equivalents of HMPA gave the 1,4-addition product exclusively (**134**) (Scheme 40).

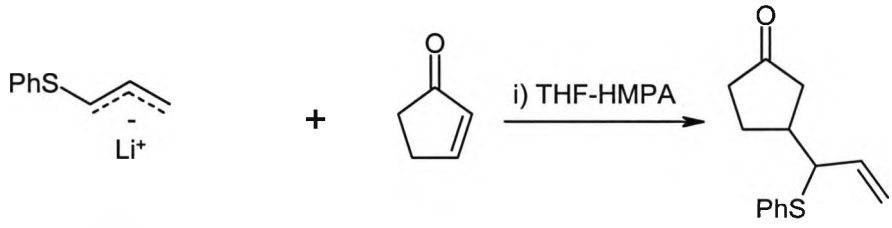


(132) (133) (134)

Scheme 40

Scheme 41 illustrates an example where the addition of HMPA not only affects the regiochemistry of the attack of the nucleophile, an allylic anion, (α- versus γ-alkylation) but also the position of attack on the electrophile (1,2 versus 1,4 attack on the enone).

Whereas HMPA can also promote 1,4 addition of alkyl and phenylthioallyl anions (**135**) to cyclopentanones (**133**) through the α-position in THF alone, irreversible 1,2-addition occurs with both α- and γ-attack.[168] The regioselectivities reported for the addition to cyclic enones of ketene dithioacetal anions and *t*-butyllithium are also influenced by HMPA.[169,170]

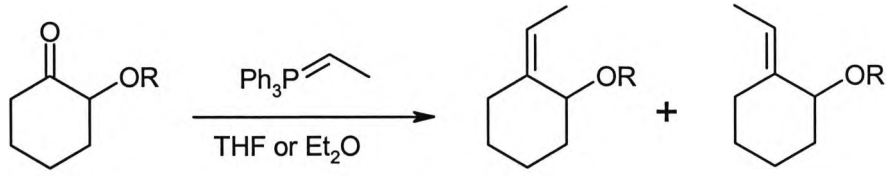


(135) (133)

Scheme 41

2.2.9 Ylide Reactivity

HMPA has been employed in the Wittig reaction to increase the reaction rate, yield and stereoselectivity. HMPA functions as a lithium cation-complexing agent and effectively removes LiBr by precipitation of the LiBr/HMPA complexes from diethyl ether.[171,172] It's perhaps the fact that the Wittig reaction mixture is then 'salt free' that is responsible for the high levels of *cis*-alkene observed in the reactions of nonstabilized ylides with aldehydes in THF or diethyl ether with added HMPA.[173-176] Similarly, increased (*Z*)-selectivity (**137**) is observed in the Wittig alkenation of α-oxygenated ketones (**136**) (Scheme 42) to generate protected (*Z*)- trisubstituted allylic alcohols.[177-179]



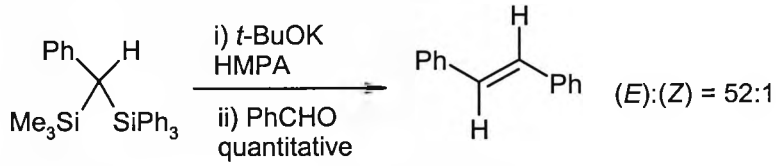
(136) (137) (138)

R	Cosolvent	Yield (%)	*E*:*Z*
Me	None	50	2.6:1
Ph	None	77	5:1
TBS	None	61	7.6:1
Bz	None	55	1.1:1
Me	HMPA	76	8:1
Ph	HMPA	84	10:1
TBS	HMPA	90	26:1
Bz	HMPA	86	36:1

Scheme 42

2.2.10 Anion Reactivity

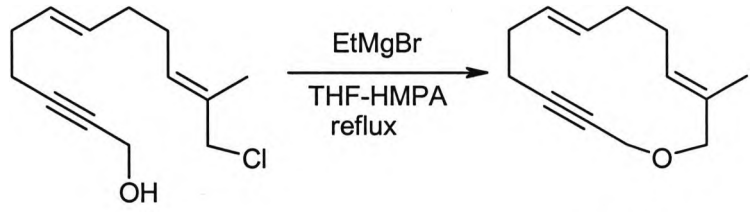
HMPA is one of the most potent electron pair donor solvents available for accelerating S_N2 reactions.[180] The formation, for example, of an α-silyl carbanion, formed from (**139**) and potassium *tert*-butoxide, for use in a Peterson alkenation reaction can be accomplished by the displacement of silicon using sodium methoxide or potassium *t*-butoxide in HMPA (Scheme 43).[181] The increased nucleophilicity of halide ions in the presence of HMPA is illustrated by the increased rate with fluoride ion induced silyl-protecting group removal.[182]



(139) (140)

Scheme 43

The increased nucleophilicity of a magnesium alkoxide has been demonstrated by the cyclization of chloro alcohol (**141**) to a 13-membered cyclic ether (**142**) upon treatment of the compound with ethylmagnesium bromide in refluxing THF/HMPA (Scheme 44).[183]

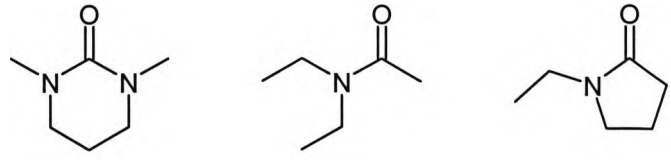


(141) (142)

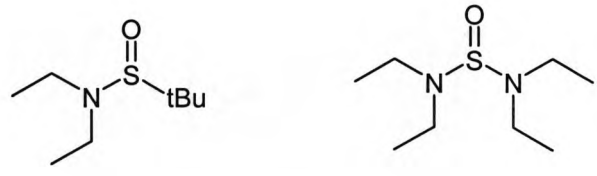
Scheme 44

2.3 HMPA Substitutes and Analogues

A number of researchers have searched for an alternative to HMPA. Such an additive/solvent must be stable to polar organometallic compounds and be comparable to HMPA in its many functions. Replacement solvents are typically useful in some applications but have limited value in others. Examples of some alternatives are shown below (Figure 7).[184-186]



(143) DMPU (144) DEA (145) NEP



(146) (147) TES

Figure 7

The above goes to illustrate the need to find a suitable replacement for HMPA. A cosolvent or additive would need to be compatible with highly nucleophilic and basic reagents, and could be employed at dry-ice temperature or below. In 1982 Mukhopadhyay and Seebach reported the use of *N,N'*-dimethyl-*N*-*N'*-propylene urea (DMPU) instead of HMPA in diverse types of reaction.[173]

2.4 N,N'-*dimethyl*-N-N'-*propylene urea (DMPU)*

DMPU (**143**) is hygroscopic and miscible with water in any ratio. It can be removed from a solution in hydrocarbons or ethers by washing with water.[187] Solvents such as chloroform and DCM, retain DMPU in the organic phase; in fact, DMPU can be recovered from water by extraction with these chlorinated solvents. The boiling point and polarities of DMPU (54°C/0.05 Torr, $\varepsilon = 36$, $\mu = 15 \cdot 10^{30}$cm) and HMPA (58°C/0.05 Torr, $\varepsilon = 30$, $\mu = 18 \cdot 10^{30}$cm) are remarkably similar, and both can be dried by distillation from calcium hydride.

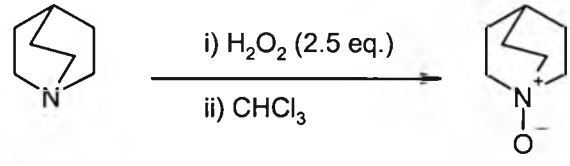
Lein and co-workers found that although DMPU contained a carbonyl it was quite unreactive. However, a vigorous, exothermic reaction takes place when a hexane solution of butyllithium is added to a (THF/DMPU)-mixture at -78°C (only a slow reaction was observed at -90°C). Fortunately, if a more reactive substrate was present in the solution, the DMPU cosolvent did not interfere. For example, at about -35°C or below, butyllithium deprotonates diisopropylamine quantitatively in a (2:1) (THF/DMPU) mixture, and the LDA formed is stable in this medium at temperatures between -78°C and -35°C for at least two to three hours. Of course, DMPU can also be added to a THF solution of a reagent generated under conventional metallation conditions, just prior to the reaction with an electrophile.

The results of their comparisons of the effects exerted by HMPA and DMPU are discussed in detail in section 2.6. It is fair to say that DMPU is not as efficient or general in its use as HMPA. For reasons discussed earlier we thought QNO would make an ideal replacement.

2.5 *Preparation and uses of quinuclidine N-oxide.*

Quinuclidine *N*-oxide (QNO) (**64**) was first prepared in 1968 by Mikhlina and co-workers.[188] Quinuclidine had been shown to be a stable chemical compound.[189-192] Mikhlina and co-workers assigned themselves the problem of synthesizing *N*-oxides of quinuclidine and its derivatives to study their thermal stability.

The *N*-oxides of quinuclidine (**64**) and its 3-substituted derivatives were obtained by oxidation of the parent amines (**148**) with a 25-30% aqueous solution of hydrogen peroxide at room temperature or above. Unfortunately, complete oxidation of quinuclidine under these conditions did not occur. It was necessary to extract the QNO (**64**) from the concentrated aqueous solution with chloroform. This also led to conversion of unreacted quinuclidine to its hydrochloride salt. The QNO was obtained in pure form in 42% yield after sublimation at reduced pressure (Scheme 45).



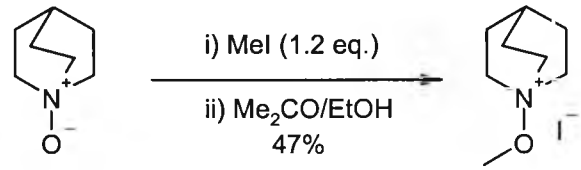
(148) (64)

Scheme 45

The thermal stability of QNO was studied by heating in dimethylformamide solution at 150°C and also without solvent up to 205-210°C. Unchanged QNO was recovered in the first case, while deoxygenation of QNO occurred in the second case, with sublimation of the quinuclidine formed. Cleavage of the quinuclidine molecule under these conditions was not observed.

This result indicated the stability of QNO to ring opening, which was evidently associated with the high symmetry of the quinuclidine molecule.

Treatment of QNO (**64**) with 1.2 equivalents of methyl iodide in acetone/ethanol (80:20) for 48 hours gave the 1-methoxyquinuclidinium iodide (**149**) in a 47% yield (Scheme 46).



(64) (149)

Scheme 46

The next report of QNO in the literature was by Kenyon and co-workers in 1976.[193] They were investigating the electron induced fragmentations and rearrangements of aliphatic and heterocyclic phosphine oxides. During the course of this study they wanted to compare the fragmentation patterns of phosphabicyclo[2.2.2]octane-1-oxide (**150**) and QNO (**64**).

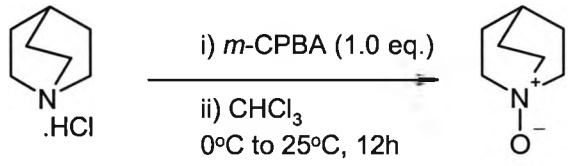
(150) (64)

Figure 8

Fragmentation of the bicyclic phosphine oxide (**150**) by electron ionisation gave a large fragment corresponding to M-28 (loss of C_2H_4) as well as a relatively large, unexpected fragment corresponding to M-15 (loss of CH_3). In order to examine the general loss of the CH_3 from the structures of this type, the electron impact spectra of both quinuclidine (**148**) and QNO (**64**) were examined.

During the study, they prepared QNO by treating quinuclidine hydrochloride (**151**) with one equivalent of 85% *m*-CPBA in chloroform initially at 0°C followed by stirring at room temperature for 12 hours (Scheme 47). This was followed by

purification by column chromatography with basic alumina eluting with 5%MeOH-$CHCl_3$ (v/v) to furnish QNO (**64**) in a yield of 68% as a hygroscopic solid, melting point of 120°C.



(151) (64)

Scheme 47

NMR analysis of the compound ($CDCl_3$) showed two signals at δ 2.03 (m, 7H, β and γ hydrogens) and 3.45 (m, 6H, α hydrogens).

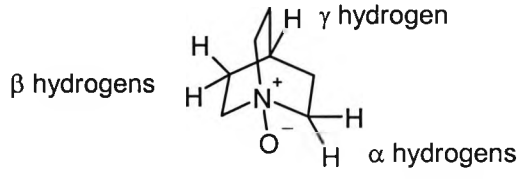
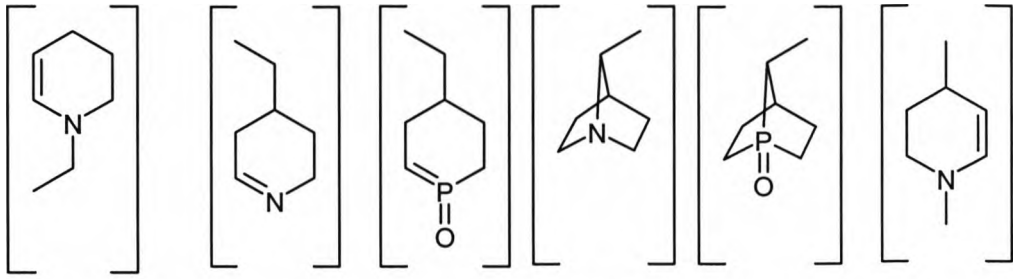


Figure 9

Although QNO and phosphabicyclo[2.2.2]octane-1-oxide (**150**) are isoelectronic their mass spectra are quite different. Loss of oxygen from the QNO, a phenomenon observed previously in the EI mass spectra of amine oxides,[194] was the predominant process. Consequently, a closer parallel to the character of fragmentation of the phosphine oxide (**150**) was seen in the fragmentation of quinuclidine (**148**) itself. Indeed many of the peaks observed in the EI mass spectrum of QNO may be shown to be coming from the molecular ion of quinuclidine which is formed from QNO by loss of oxygen. Significantly, to Keynon and co-workers, the mass spectrum of quinuclidine showed relatively large peaks corresponding to M^+-15 (18.9%), M^+-28 (29.4%) and M^+-29 (34.1%).

To account for these observations they presented the following possibility. The molecular ions of both phosphine oxide (**150**) and quinuclidine could be isomerizing via hydrogen shifts to one or more structures (Figure 10). By analogy the EI of

phosphine oxide **(150)** would be expected to show relatively large peaks corresponding to loss of C_2H_4 from 152a or 152b or the loss of CH_3 from 152d, 152e or 152f.



(152a) (152b) (152c) (152d) (152e) (152f)

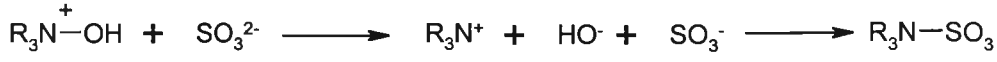
Figure 10

The possibility that the hypothetical rearrangements shown above are a thermal process, not induced by EI, was examined as follows. EI mass spectra for both phosphine oxide **(150)** and quinuclidine were examined as a function of inlet temperature. The relative ratios of peaks (e.g. M^+ vs. M^+-15) did not change appreciably over a wide temperature range. Thus, they decided that these processes were EI induced. In contrast, the ratio of $[M^+]/[M^+-16]$ in the case of QNO decreased continuously as the inlet temperature was raised confirming the idea that loss of oxygen for amine *N*-oxides is a thermal process.[195]

2.5.1 Reactions of QNO with Sulphur Dioxide.

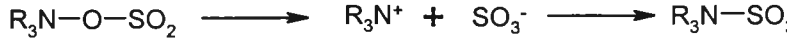
The reaction of amine oxides with sulphur dioxide has been studied sporadically and found to give products quite dependent on both the reaction conditions and the nature of the *N*-oxide.[196,197] For example, trimethylamine oxide and SO_2 in dry benzene gave the sulphitoamine, Me_3N-OSO_2, however the same in aqueous solution gave dimethylamine and formaldehyde; this was attributed to decomposition of the sulphitoamine intermediate *via* a Polonovski-type reaction.[198] Triethylamine oxide was shown to undergo a similar reaction with SO_2 in aqueous media, but, in dry benzene, triethylamine oxide-sulfur trioxide (Et_3N-OSO_3) was found to be a product.

In a third case strychnine *N*-oxide formed a sulphitoamine in dry benzene, however, in contrast to TMAO and TEAO, gave a strychnine-SO_3 complex upon SO_2 addition in cold aqueous solution. The reaction mechanism proposed for the formation of the latter, a sulphamic acid derivative, involved in the union of two radical ions according to equation 1.



Equation 1

The sulphitoamine was found to isomerise to strychnine-SO_3 in 24 h in boiling water according to the proposed mechanism also involving free radicals in equation 2.



Equation 2

α-Isosparteine *N*-oxide and sparteine *N*-oxide had also been found to yield amine-SO_3 complexes, and it was suggested that the rigidity to the ring systems made the Polonovski-type degradation followed by hydrolysis to secondary amine and aldehyde unfavourable.[199] In order to test the theory as well as to determine the feasibility of using certain structurally favourable amine oxides as SO_2 scavengers, Kubas and co-workers decided to systematically investigate the reaction of SO_2 with selected amine oxides, in particular QNO.[200] They wanted to ascertain if the amine oxide with a bridge head nitrogen were stable to Polonovski type reactions and subsequent degradation.

Their reasoning was that QNO, like strychnine and sparteine *N*-oxides, has a nitrogen at bridgehead position but has a much simpler, symmetric structure. X-ray crystal analysis of quinuclidine-SO_3 (QN-SO_3) showed that one of the products obtained from the SO_2 reaction, confirmed that the sulphur bonds directly to the nitrogen. They concluded that it did require amine oxides with a nitrogen at the bridgehead position to be stable against Polonovski-type degradation to secondary amines by SO_2. In aqueous media or undried organic solvents, the reactions of QNO with SO_2

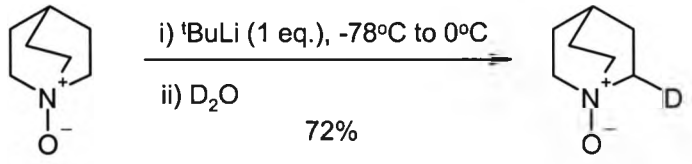
were quite comparable to those of strychnine *N*-oxide. In dry benzene, however, the observation that QN-OSO_3 is one of the products indicated that there was some similarity to the reaction of Et_3N-O with SO_2.

2.5.2 Metallation and anionic activity of the α-carbon of QNO

A seminal paper on the metallation and activity of the α-carbon of QNO was published by Barton and co-workers in 1978.[80] In their paper they described the deprotonation of QNO with *t*-BuLi to form the α-carbanion which was subsequently quenched with various electrophiles in order to ascertain if this was a viable route for the synthesis alkaloids such as quinine. Their previous efforts had involved many unsuccessful attempts to make either a carbocation or a radical in the α position.

This followed on from work in which the reverse of polarity, 'umpolung', which was first described by Seebach and Enders in 1975.[201] Seebach and Enders had described how inversion of polarity for primary and secondary amines had occurred in the form of isocyanates and *N*-nitroso compounds respectively. Barton and co-workers thought it might be possible for tertiary amines to show this property, umpulong, if they were quaternised as the *N*-oxide. However, it was known that treating quaternary ammonium salts with base led to rearrangement and elimination products.[202] So they explored the reactivity of QNO for which, at that point, there were very few examples in the literature.

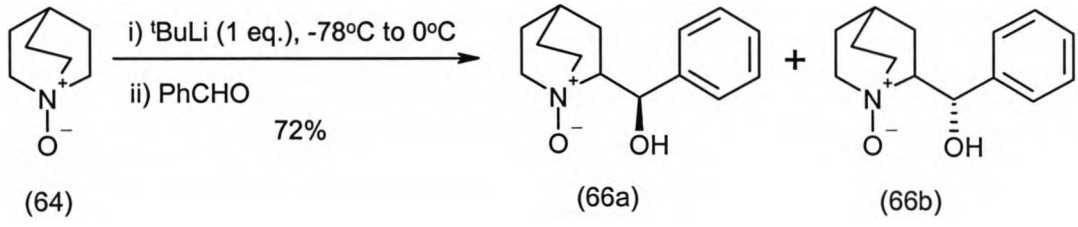
Their initial experiment was to treat a solution of QNO (**64**) in anhydrous THF at -78°C with 1 equivalent *t*-BuLi then, after a short while warm it to 0°C and add D_2O which gave the expected deuterated quinuclidine species (**153**) in a yield of 72%, confirming that an anion had been formed at the position α to the nitrogen (Scheme 48).



(64) (153)

Scheme 48

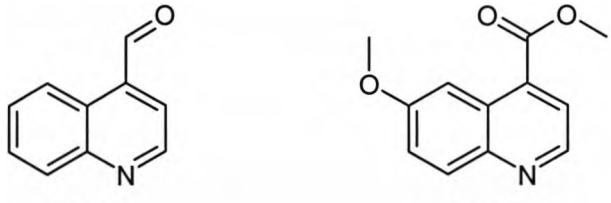
They had shown that QNO could be deprotonated in the α position and went on to lithiate QNO (**64**) and react it with other electrophiles. The first electrophile employed was benzaldehyde, which upon work up with saturated brine and ether gave a pair of diastereoisomers ((**66a**) and (**66b**)) in a combined yield of 50% (Scheme 49)



(64) (66a) (66b)

Scheme 49

They then went on to prepare a series of alkaloid analogues using the same methodology, this time reacting the anion with formyl-4'-quinoline (**154**) and carbomethoxy-4' methoxy-6'-quinoline (**155**) (illustrated in Figure 11) as electrophiles.



(154) (155)

Figure 11

The reaction with formyl-4'-quinoline gave the expected diastereomeric alcohols ((**156**) and (**157**)) in a combined yield of 35% whereas the reaction with

carbomethoxy-4' methoxy-6'-quinoline generated the ketone (**158**) in an unreported yield (Figure 12).

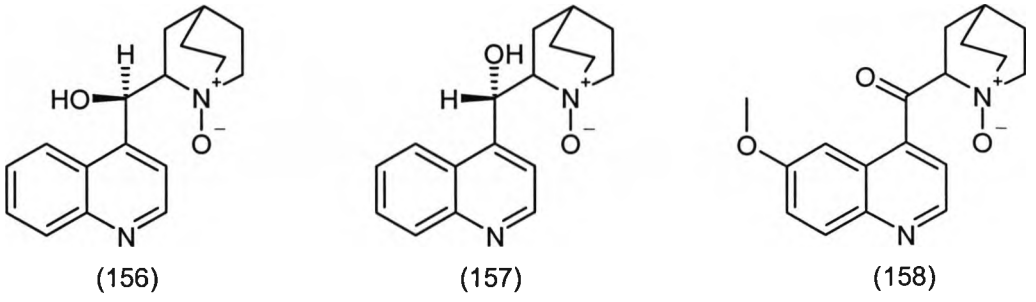


Figure 12

Barton and co-workers decided that in order for the above reaction to be synthetically useful the newly formed *N*-oxides had to be de-oxygenated. This was performed with hexachlorodisilane, forming the corresponding amines in good yield (Figure 13).[203]

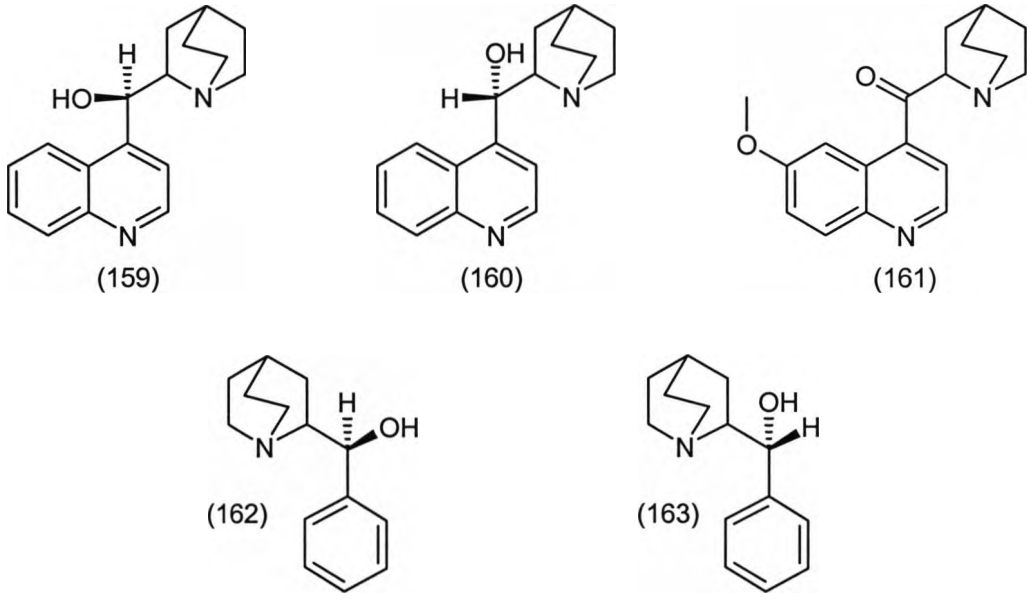
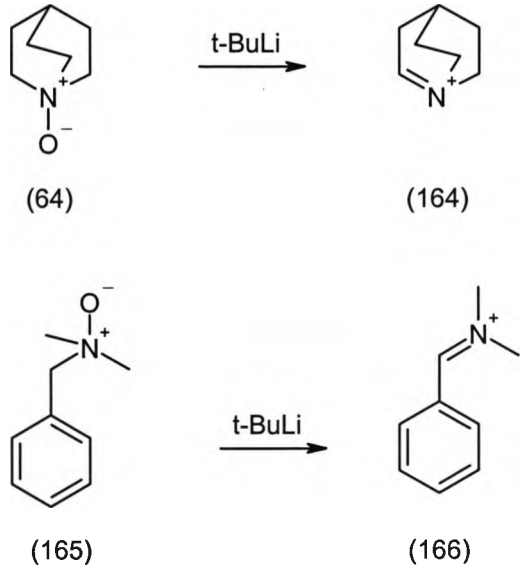


Figure 13

This elegant piece of work illustrated that QNO was stable to strong base and would not eliminate the oxygen *via* an OLi species. This elimination does occur in most *N*-oxides e.g. dimethyl benzyl amine *N*-oxide (**165**) which formed an iminium ion (**166**). In order for this elimination to occur with QNO a bridgehead iminium species

(**164**) would have to be formed which would violate Bredt's rules (Scheme 50) and does not seem to occur.

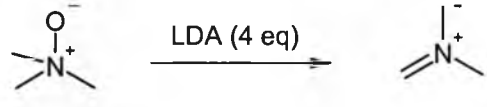


(64) (164)

(165) (166)

Scheme 50

The iminium ions formed by this method can react further, for example trimethylamine *N*-oxide (**167**) has been shown to form an azomethine ylide (**168**) upon treatment with 4 equivalents of LDA (Scheme 51), and QNO has been shown to be stable to strong base.[204] It was decided to investigate the chemistry of QNO.



(167) (168)

Scheme 51

2.6 The Chemistry of QNO

As previously mentioned there are numerous significant and important reactions in organic synthesis which require the addition of hexamethylphosphoramide, HMPA, to render them viable.[205] HMPA is a dipolar aprotic solvent with a superb ability to

form cation-ligand complexes and can enhance the rates of a wide variety of main group organometallic reactions. In addition, it can also influence the regio and stereochemistry of key reactions such as enolate formation. HMPA is a listed carcinogen and as such does not find widespread use either in industry or academia. Several other substances have been used as replacements but all have their limitations.[173] In essence, it is thought that HMPA acts as a metal binding agent, disrupting the normal aggregation states of organolithium compounds.[206]

An amine oxide bears a similar charge distribution to a phosphine oxide, except the dipole is larger. Therefore an amine oxide would be expected to behave in a similar fashion to a reagent such as HMPA. The major problem lies with the instability of most amine oxides towards strongly basic conditions, azomethine ylide formation being a common pathway (Scheme 51).

Preliminary studies employing quinuclidine *N*-oxide, showed it can be deprotonated with *t*-BuLi and the corresponding anion can be reacted with aldehydes and ketones.[80] The high stability of this amine oxide is explained by the fact that elimination of lithium oxide leads to an anti-Bredt bridgehead iminium ion (**164**) (Figure 14).

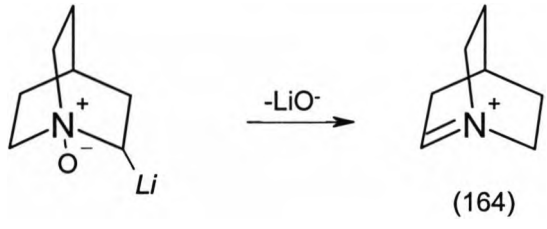


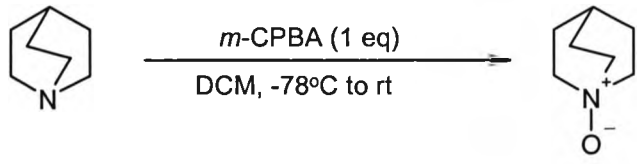
Figure 14

Therefore it was decided to synthesise QNO and use it as an additive instead of HMPA.

2.6.1 Preparation of QNO

QNO (148) was simply prepared by exposure of quinuclidine (**64**) to 1 equivalent of *m*-CPBA in CH_2Cl_2 at -78°C before warming to room temperature (Scheme 52).

Purification was by column chromatography on silica gel eluting with methanol/ethyl acetate (30/70).



(148) (64)

Scheme 52

After purification the QNO was an off white oil, due to strong H-bond formation between the *N*-oxide oxygen and water or methanol. The hydrogen bond donors are removed by storing the QNO over phosphorus pentoxide (P_2O_5) at high vacuum for several days. This gave the QNO as a white solid with yields typically in the region of 70-80%.

Another factor which aided the purification of the QNO was the use of purified *m*-CPBA. This was performed by washing Aldrich supplied 55-60% *m*-CPBA with a buffer solution which increased the purity to *circa* 95%.

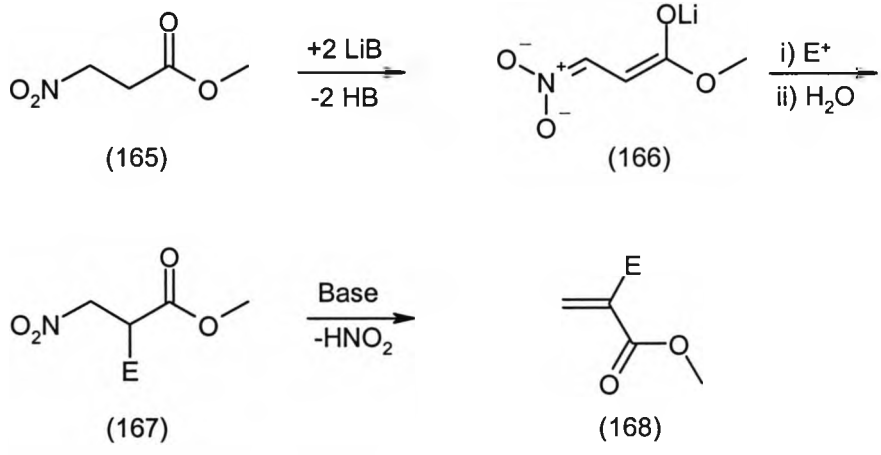
Having prepared the QNO we wanted to perform some initial experiments to ascertain if QNO would act as a substitute for HMPA. The first reaction we investigated was the alkylation of the dianion methyl 3-nitropropionate (**165**). It has previously been shown that this reaction requires HMPA (5.2 equivalents) or DMPU (10 equivalents) to proceed in reasonable yields.[207]

2.6.2 Lithiation of 3-methylnitropropionate and subsequent reaction with benzaldehyde

The functionalities of the nitro group (stronger acceptor, more acidifying, leaving group) and of the ester group (weaker acceptor, less acidifying, no leaving group) render the simple compounds of alkyl 3-nitropropanoate and -propanoate useful synthetic reagents. Seebach and co-workers demonstrated that 3-nitro propionic ester

could be used as an acrylic ester d^2-reagent (Scheme 53) through its dilithio derivative.

Their work described a three step synthetic sequence to convert methyl 3-nitropropanoate to the α-substituted acrylates. The procedure proceeded thus: (i) the double deprotonation of (**165**) to give (**166**), (ii) reaction with electrophiles leading to α-branched β-nitropropanoates of type (**167**), and (iii) elimination of HNO_2 to give (**168**) (Scheme 53).



Scheme 53

The structure of (**166**) is unknown; Seebach and co-workers believed that it was highly unlikely to exist as an ionic six atom-eight electron π-system (**169a**), a more reasonable structure was the Li-nitronate-Li-enolate structure (**169b**). Also possible was a bis(lithioxy)enamine form (**169c**) (Figure 11).

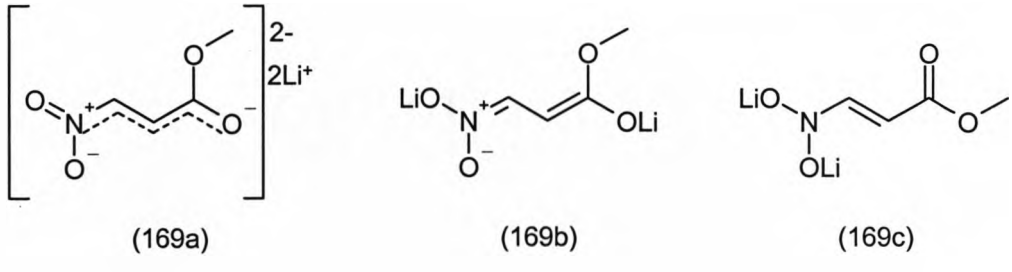
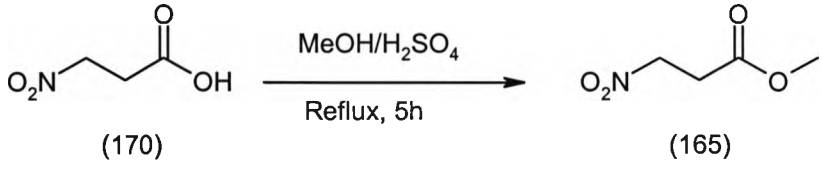


Figure 15

2.6.3 Preparation of THF solutions of reagent methyl 3-nitropropinate in the presence of co-solvents

Seebach and co-workers had treated methyl-3-nitropropionate with two equivalents of LDA in THF at -76°C, an immediate precipitation of a solid ensued. Unfortunately, subsequent addition of benzaldehyde did not lead to the isolation of the expected product. If, however, two equivalents of an LDA solution in THF/HMPA (5:1) at -76°C was treated with one equivalent of the nitro ester, an exothermic reaction lead to a clear, light yellow solution which was routinely stirred for 30-60 minutes before the addition of an electrophile. They found that the yield of the benzaldehyde adduct depended crucially upon the ratio in which the lithiated nitro species and the electrophile were employed; the best result was obtained using a 25% excess of the electrophile. We decided to use this as our first test reaction, using their reaction conditions but replacing HMPA with QNO.

Before the test reaction could be performed we had to prepare methyl 3-nitropropionate (**165**). This was achieved by heating 3-nitropropionic acid (**170**) in anhydrous methanol at reflux, in the presence of a catalytic quantity of sulphuric acid (Scheme 54). This gave methyl 3-nitropropionate (**165**) in a 91% yield, which was used in the subsequent reactions.

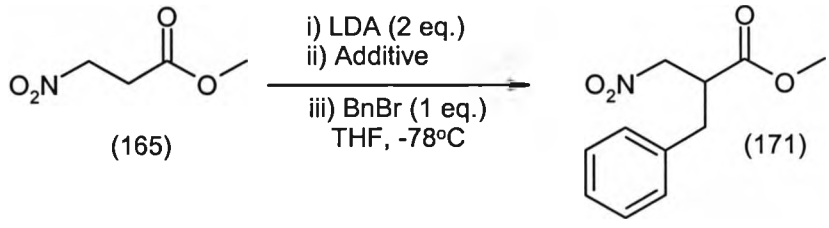


(170) (165)

Scheme 54

Now that the methyl 3-nitropropionate (**165**) had been prepared we could test our QNO (**64**) as a replacement for HMPA. The 2 equivalents of LDA were prepared by treating a cold (-35°C) THF/additive solution of diisopropylamine with *n*-BuLi. After stirring for 10 minutes at this temperature the solution was cooled to -78°C and methyl 3-nitropropionate added. Stirring was continued at this temperature for 30-60 minutes at which point double deprotonation was assumed to be quantitative. Benzyl

bromide, 1 equivalent, was added to the reaction mixture at -78°C and was stirred for a further 4 hours during which time the reaction mixture was allowed to warm to -25°C. The reaction was quenched, by adding acid, and the crude mixture purified to give the benzylated product (**171**). The results are shown in Table 1.



Scheme 55

Additive (equiv.)	Yield (%)
none	8
HMPA (5.2)	85
DMPU (10.)	85
QNO (1.4)	37
QNO (3.0)	47
QNO (5.0)	78

Table 1. Effect of additive on yield.

It is clear from the above results that the quinuclidine *N*-oxide has a considerable effect on the alkylation reaction, allowing the formation of the product in good yield. One very useful aspect of the reaction is that the *N*-oxide is highly soluble in water. Therefore when the water was added to the crude reaction mixture the organic product remains in the organic solvent while the *N*-oxide was found in the aqueous layer, from which it has been recovered. Once recovered and after purification and drying the *N*-oxide should be able to be reused in the reaction.

The above results indicate that quinuclidine *N*-oxide has a similar (presumably cation coordinating) effect on the reaction that HMPA exerts. After this promising result, we decided to screen this compound in a range of different reactions which are known to be effected by the presence of HMPA. These include enolate formation and geometry, enolate reactivity, carbanion formation and regioselectivity, ylide

reactivity and transition metal co-ordination. The effect on a range of different metals was also to be studied.

2.6.4 Regioselectivity of addition of organolithium reagents to 1,3-dithiane

Another example where HMPA has influenced the course of a reaction was reported by Brown.[208] The reaction investigated was the induced conjugate addition of a simple 2-lithio-1,3-dithiane to cyclic α,β-unsaturated ketones (Scheme 56). In sharp contrast to prior observations that 2-lithio-1,3-dithianes undergo only carbonyl (1,2-) additions to enones, the successful conjugate (1,4-) addition of the parent 2-lithio-1,3-dithiane and its simple derivatives was achieved by the addition of 1.0 - 2.0 equivalents of HMPA to the reaction mixture. After the previous success of QNO we decided to examine its effect on this reaction to see if we could induce similar selectivity in favour of the conjugate addition.

Metallation of the anion (**173**) was achieved in the usual manner, by the addition of *n*-butyl lithium to 1,3-dithiane (**172**) at -78°C in THF. After 1 hour the cyclohex-2-enone (Scheme 56) was added and the reaction quenched after 5 minutes by addition of saturated aqueous ammonium chloride. The sample was analysed by proton NMR and the ration of (**174**):(**175**) was found to be 8:92, in favour of the 1,2-addition product.

Brown and co-worker found that upon addition of 2 equivalents HMPA to the 2-lithio-1,3-dithiane (**173**) a yellow-orange colouration formed immediately, in the absence of HMPA it was colourless. Subsequent addition of cyclohex-2-enone to the solution resulted in a rapid discharge of the colour. Quenching of the mixture, (as described above), and subsequent analysis gave (**174**):(**175**) in a ratio of 95:5, this time in favour of the 1,4-addition product.

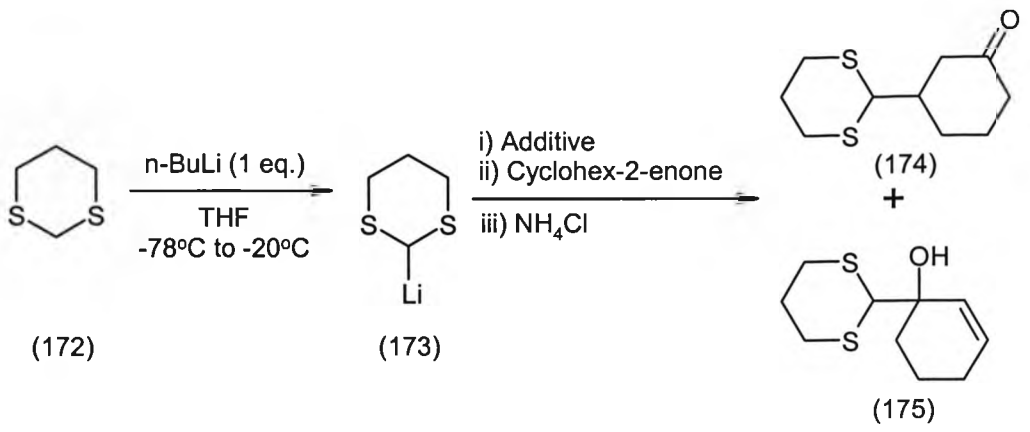


Table 2. Effect of additive on yield and ratio of **(174)**:**(175)**

Additive (equiv.)	Yield (%)	Ratio(174):(175)
none	90	8:92
HMPA (1)	50	88:12
HMPA (2)	80	95: 5
DMPU (2)	70	82:18
QNO (1)	27	88:12
QNO (2)	54	90:10

Scheme 56

We performed the same reaction replacing HMPA with 1 and then 2 equivalents of QNO. In both cases the major product was the 1,4-addition product **(174)**. The ratios of the products **(174)**:**(175)** were 88:12 and 90:10 for 1 equivalent and 2 equivalents of QNO respectively. The results are comparable to HMPA and an improvement upon DMPU in the regioselectivity of the reaction.

2.6.5 The Role of HMPA

Bryson and Cohen have proposed that the regioselectivity of addition is a function of the ion pair structure of the lithium reagent.[209,210] They postulated that contact ion pairs (CIP), with an intact C-Li association, gives 1,2-addition *via* a four centred transition state, whereas solvent-separated ion pairs (SIP) give predominantly 1,4-

addition. This hypothesis was based on the observations that the addition of HMPA and colder temperatures (conditions which favour SIP formation) kinetically favour 1,4-addition.[211-213] Their hypothesis could not be directly tested since no information about the solution structures of organolithium reagent-HMPA complexes was available. However, Reich has reported the use of a multinuclear NMR technique to quantify the quantity of separated ion in solution and correlate this with changes in the regioisomeric and diastereomeric product ratios.[214]

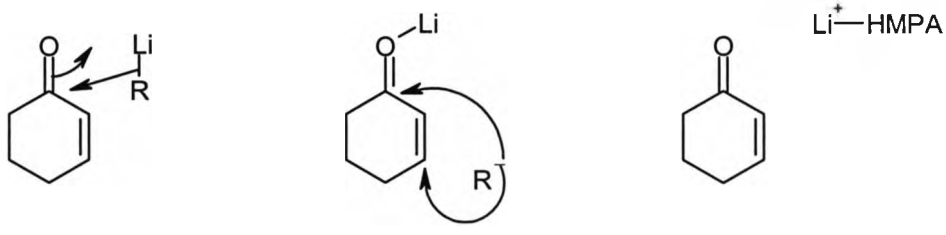
To simplify their analysis they studied stabilised organolithium reagents that were known or expected to be monomeric in THF. Their results demonstrated that the more HMPA was present, the greater the degree of ion pair separation, leading to the formation of 1,4 -addition product. However in each case the onset of 1,4-addition significantly preceded the appearance of the SIP. In the case of *bis*(phenylthio)methyllithium (**176**), which easily undergoes the CIP to SIP transition on addition of HMPA, over 50% 1,4-addition was observed even in the absence of HMPA. For 2-lithio-2-methyl-1,3-dithiane (**178**), which exhibited the tightest contact ion of the three, SIP's were not detectable until 1.5 equivalents of HMPA had been added, when 1,4 addition had already reached 90%. *Tert*-butylthio(methylthio)methyllithium (**177**) (Figure 16) showed intermediate behaviour.

(176) (177) (178)

Figure 16

It was hypothesised that if the CIP and the SIP interconverted more readily than they reacted with the enone then the product would not necessarily reflect the ground state CIP/SIP ratio measured in their NMR experiments. Its possible that minute quantities of the more reactive SIP would not be detected by NMR but could dominate the reaction, even though the CIP intermediate was the dominant ground-state structure.

By performing experiments using analogues of the above it was possible to determine that there was a dichotomy between the CIP-SIP ratio and the ratio of 1,2 vs 1,4 addition. They made the assumption that SIP is more reactive than CIP, therefore the simple ground state ratio was not solely responsible for the ratio of conjugate addition products. They also hypothesised that the rate retarding and conjugate addition effects of HMPA arose from the suppression of a lithium catalysed process. Scheme 57, represents the three processes they postulated for the reaction: (A) the CIP gives 1,2-addition; (B) reaction of the lithium-complexed enone with the free carbanion gives a mixture of products; and (C) the uncatalysed SIP process gives only 1,4-addition.



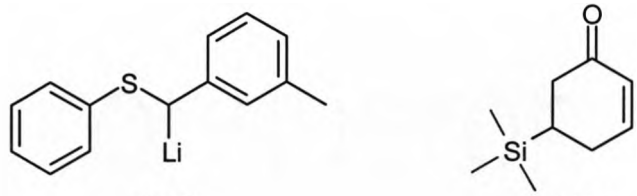
A. Contact Ion Pair
Lithium Assisted

B. Separated Ion Pair
Li^+ Catalysed

C. Separated Ion Pair
None Li^+ Catalysed

Scheme 57

These conclusions were supported by the use of diastereomeric products as 'fingerprints' to track the involvement of the CIP and SIP species. Reactions of phenylthio(3-methyl)benzyllithium (**179**), which is similar to bis(phenylthio)methyllithium (**176**) in its ion pair behaviour, with 5-trimethylsilyl-2-cyclohexene-1-one (**180**) were performed in diethyl ether with incremental amounts of THF added, followed by incremental amounts of HMPA.



(179) (180)

Figure 17

The most significant result was that the distribution of 1,4-diastereoisomers was essentially invariant as the THF was added to the ether, despite a change in the total amount of 1,4 addition from 0-65%. This suggested that 1,4-products are being produced by the same mechanism throughout. In the absence of THF, only 1,2-addition was observed, and they proposed that a CIP (A above) is the only reactive species. The addition of the THF to the diethyl ether solution increased and stabilised the small amounts of an SIP species which produced the 1,4-product through path B. Separated ions were not detected in the NMR experiment in the absence of HMPA.

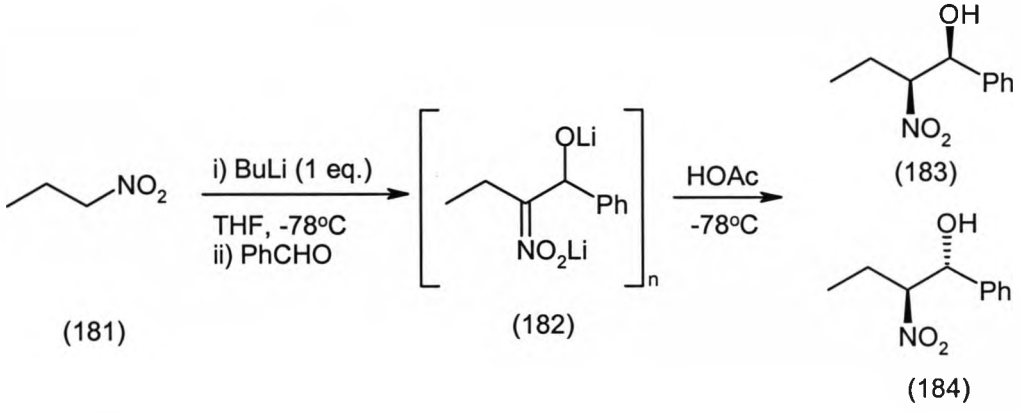
The addition of HMPA causes a dramatic change in the 1,4 diastereoisomer distribution. It seems HMPA affects the reaction beyond simply causing a greater degree to proceed thorough SIPs. They proposed that the change in the diastereoisomer ratios signalled the onset of an uncatalysed addition (Path C), a mechanism in which the lithium cation is inactive. These facts argued against the inhibition of 1,2-addition by a sterically encumbered HMPA-coordinated catalyst.

So we have seen that at least three mechanisms are required to explain their findings. The CIP produced exclusively 1,2-addition. However, the situation with the SIP is more complicated. In the presence of HMPA, only 1,4-addition by the SIP was observed for the anions tested. The absence of Li^+ catalysis is thought of as being an important factor in achieving clean 1,4-addition. For well stabilised anions in the absence of HMPA, when lithium catalysis is possible and SIPs are energetically accessible reactive intermediates, mixtures of 1,2- and 1,4-addition are observed.

Ultimately Reich and Sikorski demonstrated that sulphur-substituted organolithium reagents can be induced to add cleanly either 1,2 or 1,4 to enones. Lower temperatures and the addition of HMPA have been shown to favour 1,4-addition kinetically, only rarely was there an advantage to the use of more than 2 equivalents of HMPA. Conversely, clean 1,2-addition products were obtained when diethyl ether was used as the sole solvent, particularly at higher temperatures such as 0°C (which lead to improved solubility of the lithium reagent).

2.6.6 Addition of an electrophile to the anion of 3-nitropropane

The next reaction to be examined was one in which both HMPA and DMPU have demonstrated an effect on the stereochemical course of the reaction. Seebach reported that treatment of 1-nitropropane (**181**) with 2 equivalents of butyllithium followed by addition of an electrophile such as benzaldehyde followed by quenching with acetic acid gave 1:1 *erythro*:*threo* adducts in the absence of any additive.[173] However upon the addition of HMPA or DMPU there was a dramatic change in the ratio of products from 1:1 to 9:1 *threo*:*erythro*. We were extremely pleased to observe that on the addition of quinuclidine *N*-oxide (1.5 eq.) to the reaction the stereochemistry again favoured the formation of the *threo*- product (**183**).



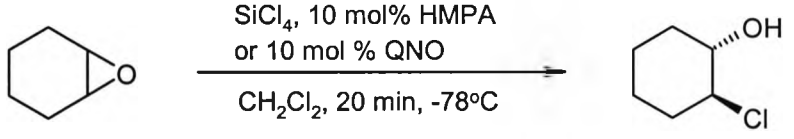
Additive (equiv.)	Yield (%) (183)	Yield (%) (184)
HMPA (5)	90	10
QNO (1.5)	81	19
QNO (3.0)	79	21

Scheme 58

2.6.7 Ring opening of epoxides using silicon tetrachloride in the presence of a Lewis acid.

The facile ring opening of epoxides makes them highly versatile intermediates in organic synthesis.[215]

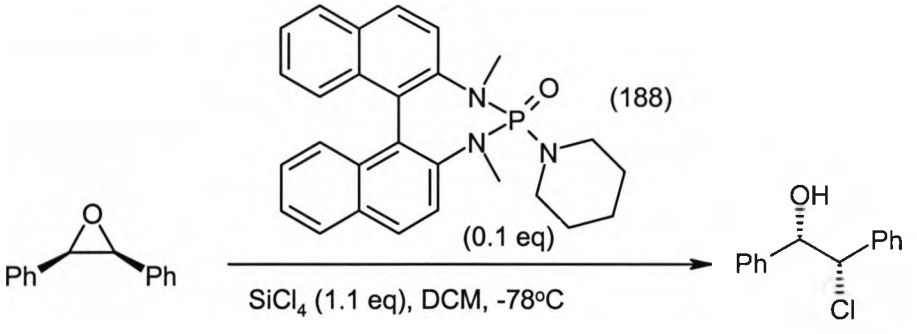
Recently, Denmark and co-workers have reported the use of catalytic quantities of HMPA with $SiCl_4$ to open epoxides to yield chlorohydrins (Scheme 59).[216] For example, the opening of cyclohexene oxide (**185**) with HMPA and $SiCl_4$ gave the chlorohydrin (**186**) in 89%, and the yield was identical when QNO was employed in the reaction (Scheme 59). Their studies showed that $SiCl_4$ alone, when HCl free, did not lead to ring opened products.



(185) (186)

Scheme 59

Moreover, Denmark has developed a chiral phosphoramide (**188**) which cleaves *meso* epoxides (**187**) to give enantiomerically enriched chlorohydrins (**189**), the best result being 93.5/6.5 (87% ee)for reaction shown in Scheme 60.



(187) (+)-(189)

Scheme 60

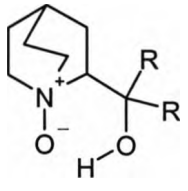
We have now seen that QNO has a similar effect on lithiation reaction as HMPA and DMPU giving comparable results. However, during the course of our study it was noted that when QNO was used in large excess it was sometimes partially insoluble

in THF. This might limit the effectiveness of QNO. We decided to investigate ways of improving the solubility of QNO.

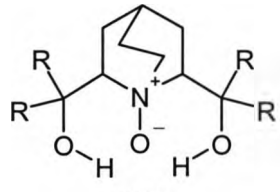
2.7 Functionalisation of QNO

In an attempt to overcome the problem of solubility and to try and enhance the metal binding properties it was decided to utilise the chemistry first reported by Barton and co-workers in 1978.[80] They demonstrated that QNO was stable to treatment with a strong base, *t*-BuLi forming the α-anion which they reacted with electrophiles, for example aromatic aldehydes, to form alcohols which were used to synthesise quinine and quinidine analogues (1.3.5). It is noteworthy that *N*-oxides are not generally stable to strong base, decomposing *via* a Polonovski type pathway that is unavailable to QNO. (See 1.3.4)

Therefore it was decided to extend the scope of the previous study in order to increase the number of heteroatoms around the QNO core. We thought that the addition of a lipophilic group and the resulting hydrogen bonding, shown in Figure 18, would lead to an increase in solubility and the metal binding properties of the new molecules.



(190)



(191)

Figure 18

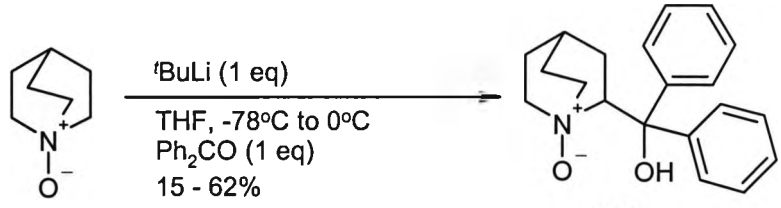
2.7.1 Mono-substitution of QNO with benzophenone

After a little consideration we decided to employ benzophenone as the electrophile to react with the α-anion. In order to achieve this QNO was prepared in the usual manner then rigorously dried over P_2O_5 at high vacuum to remove the final traces of

water and methanol. The α-anion of QNO was formed by its exposure, under, nitrogen, to *t*-BuLi in cold THF (-78°C). To ensure complete anion formation the reaction mixture was warmed to 0°C before recooling to -78°C at which point the electrophile (in this case benzophenone) was added. The mixture was stirred at -78°C for 15 minutes before being allowed to warm to 0°C when the reaction was quenched with acetic acid (Scheme 60) and was partitioned between ethyl acetate and water. The organic layer was collected, dried over $MgSO_4$ and the solvent was removed under vacuum. The desired compound, 1-oxy-1-azabicyclo[2.2.2]oct-2-yl diphenylmethanol (**192**) was isolated in a 15% yield after column chromatography.

Although the desired compound had been prepared, the yield was disappointing. We thought the reason for this might have been the aqueous work up, it is likely that the substituted quinuclidine product was water-soluble. We decided to repeat the reaction without the aqueous work up.

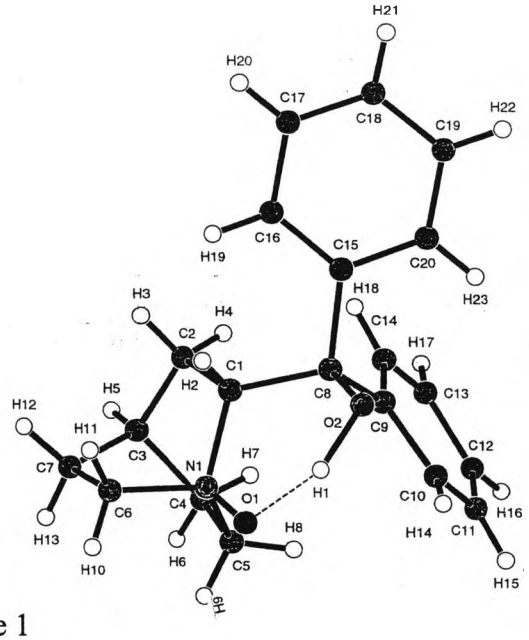
The reaction was repeated as before but without the addition of water. Instead, once the reaction had reached room temperature the solvent was removed at reduced pressure and the crude product absorbed onto silica gel then purified by column chromatography eluting with methanol/ethyl acetate (30:70). This improved the yield of the reaction, forming the *mono* substituted product (**192**) in a pleasing 62% yield.



(64) (192)

Scheme 61

Recrystallisation of the newly formed compound from DCM gave crystals which were suitable for an X-ray structure analysis. The structure clearly shows the hydrogen bond between the *N*-oxide oxygen and the hydrogen of the hydroxyl as we had hoped (X-ray structure 1).



X-ray structure 1

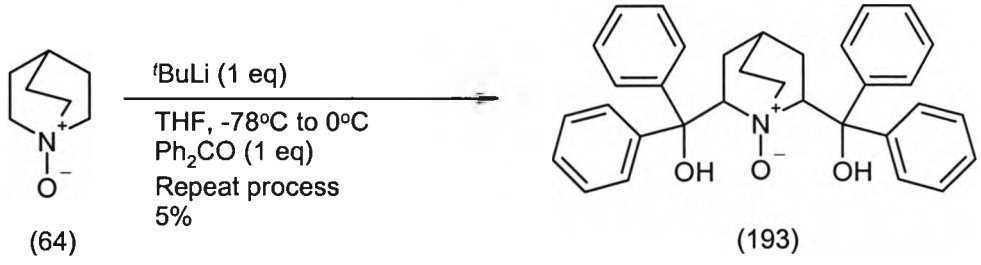
As expected, the hydrogen at the newly formed centre is quite distinct from the other 4 α-hydrogens. It undergoes a downfield shift from 3.40 ppm to appear as a triplet at δH 4.36ppm. The addition of the benzophenone moiety to the QNO core also helps distinguish the other protons around the quinuclidine ring.

2.7.2 *Bis*-substitution of QNO with benzophenone

The promising result from the formation of the *mono* adduct, 1-oxy-1-azabicyclo[2.2.2]oct-2-yl diphenylmethanol (**192**), prompted us to wonder what would happen if we installed another H-bonding moiety. We felt that we could repeat the Barton protocol to add further functionality to the QNO core. For reasons of structural simplicity we decided to use benzophenone derived alcohol in order to assess the H-bonding, solubility and polarity properties of the compound.

Our first attempt was a two step, one pot procedure in which we tried to install both benzophenone units starting from QNO itself. QNO was dissolved in THF, cooled to -78°C and was treated with 1 equivalent of *t*-BuLi. After 1 hour 1 equivalents of benzophenone was added. The reaction mixture was stirred for 1 hour at -78°C followed by the addition of 1 equivalent of *t*-BuLi, after 1 hour a second equivalent of benzophenone was added. The mixture was allowed to warm to 0°C. After the

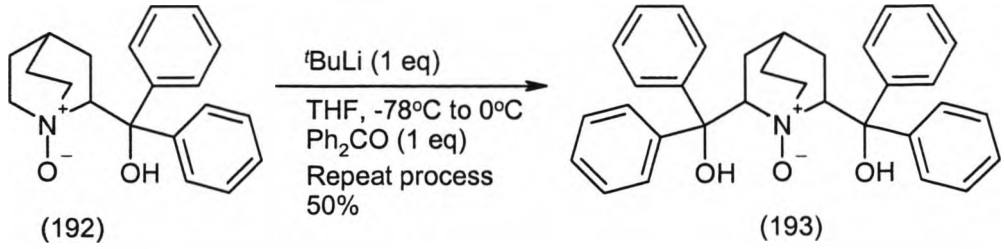
reaction mixture had warmed to 0°C it was quenched with 2M acetic acid. Then it was partitioned between brine and diethyl ether. The organic layer was collected and dried ($MgSO_4$), filtered and the volatiles removed at reduced pressure. The residue was purified by flash chromatography eluting with ethyl acetate/methanol (100:0 up to 70:30) which gave 1-oxy-1-azabicyclo[2.2.2]oct-2-yl diphenylmethanol (**192**) and the desired bis-substituted product, [6-hydroxydiphenylmethyl)-1-oxy-1-azabicyclo[2.2.2]oct-2-yl]diphenylmethanol (**193**) in yields of 18 and 5% respectively (Scheme 62)



(64) (193)

Scheme 62

Clearly we were not too impressed with a 5% yield so we took a less "gung ho" approach. This time 1-oxy-1-azabicyclo[2.2.2]oct-2-yl diphenylmethanol (**192**) was employed, rather then QNO (**64**) itself. The mono adduct was treated with 2 equivalents of *t*-BuLi. The first equivalent removes the hydrogen of the OH group leaving the second to remove one of the α-hydrogens. As usual the reaction mixture was warmed to 0°C then cooled to -78°C before the addition of 1 equivalent of benzophenone (Scheme 61). The reaction was quenched with acetic acid and the volatiles removed at reduced pressure. The crude reaction mixture was dissolved in the minimum quantity of DCM and absorbed onto silica before being purified by flash chromatography eluting with ethyl acetate to give the *bis* adduct, [6-hydroxydiphenylmethyl)-1-oxy-1-azabicyclo[2.2.2]oct-2-yl]diphenylmethanol (**193**) as a white solid in a 50% yield.



Scheme 63

Once again, we were able to grow crystals suitable for x-ray analysis and the structure was determined (Appendix). Inspection of the x-ray structure clearly shows the two OH groups hydrogen bonding to the oxygen of the *N*-oxide. Analysis of the proton NMR shows signals for the two hydrogens α to the benzophenone derived moiety as triplets at δH 4.32 and 4.43ppm. The x-rays also illustrates that the two electrophiles had added *trans* to one another as depicted in Figure 19.

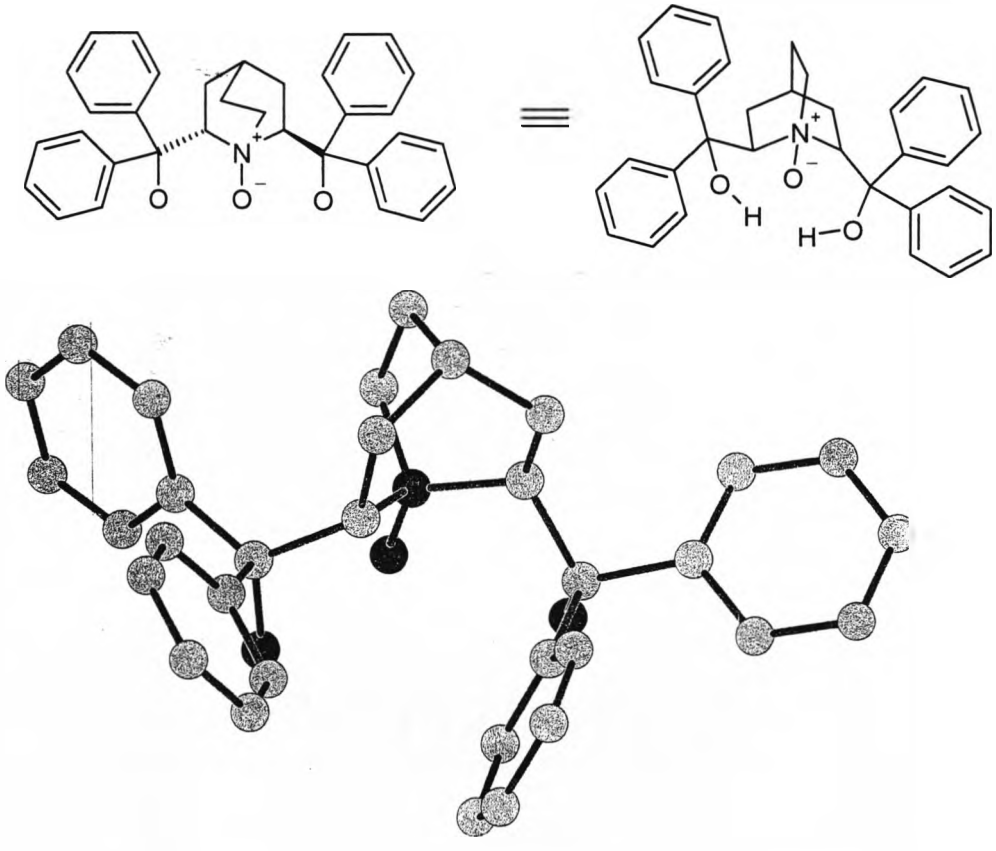
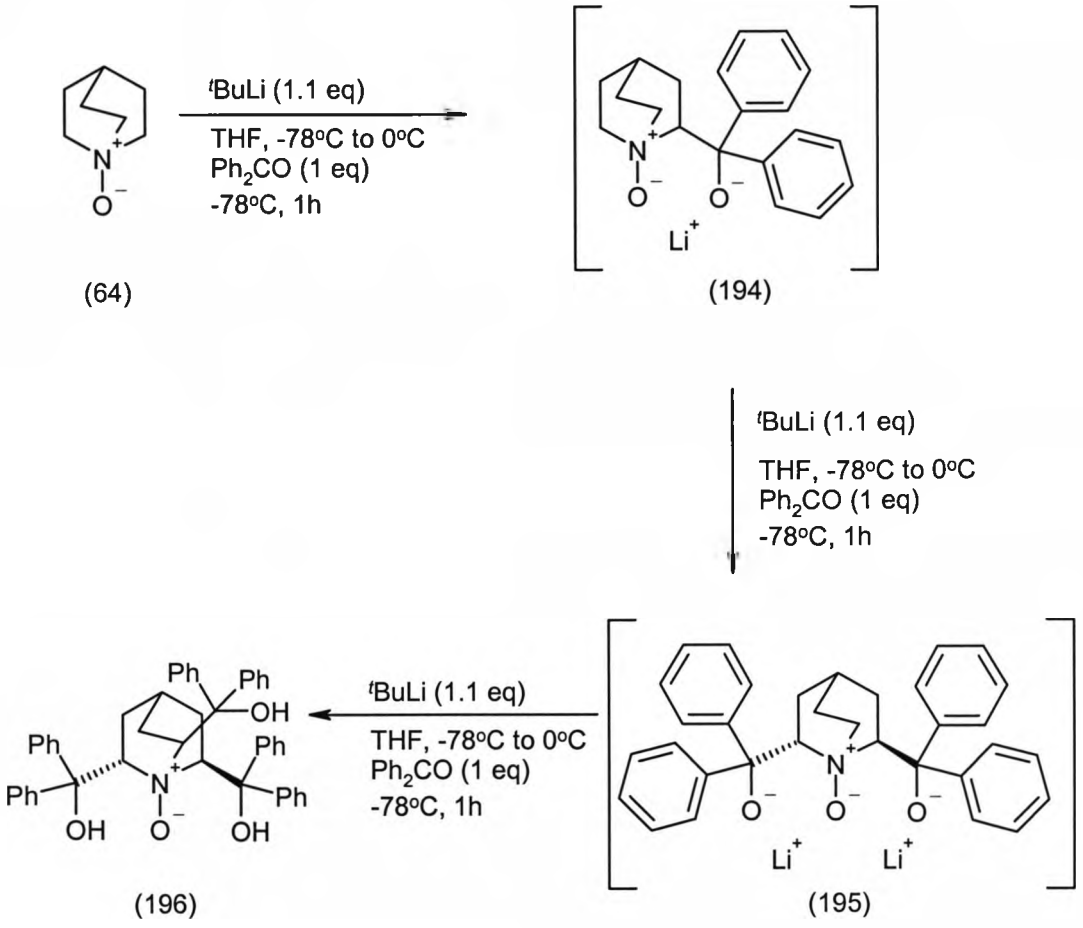


Figure 19

The *trans* addition of the two groups was very interesting. It suggested that the addition of the first electrophile determines the stereochemical outcome of subsequent additions. This gave us an impetus to add another benzophenone moiety. Again we wanted to address the solubility, etc. properties of this *tris* adduct, along with the stereochemistry of the addition.

2.7.3 Tris-substitution of QNO with benzophenone

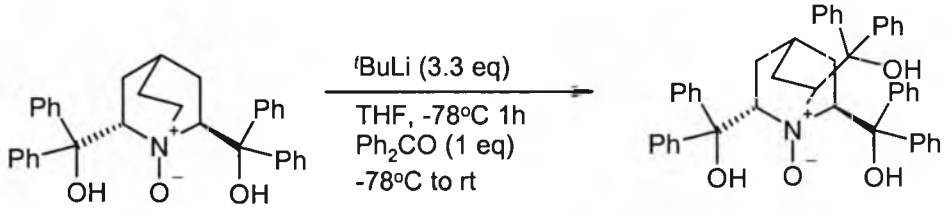
In an attempt to minimise the number of synthetic steps and purifications involved in the synthesis of the tri-substituted analogue we decided to try and add three electrophiles to the QNO (**64**) *in-situ*. We hoped was that by taking QNO (**64**) and performing the deprotonation and addition of the electrophile in the usual way, but without quenching the reaction it might be possible to perform subsequent deprotonations and electrophile additions. The sequence followed was to perform the initial deprotonation and addition of electrophile to form species (**194**). Subsequent deprotonation with another equivalent of *t*-BuLi followed by the addition of benzophenone should form species (**195**). The final step was to deprotonate again with one equivalent of *t*-BuLi and add a final equivalent of benzophenone to form [6,7-bis(hydroxyphenylmethyl)-1-oxy-1-azabicyclo[2.2.2]oct-2-yl]diphenylmethanol (**196**) which was quenched with acetic acid (Scheme 64).



Scheme 64

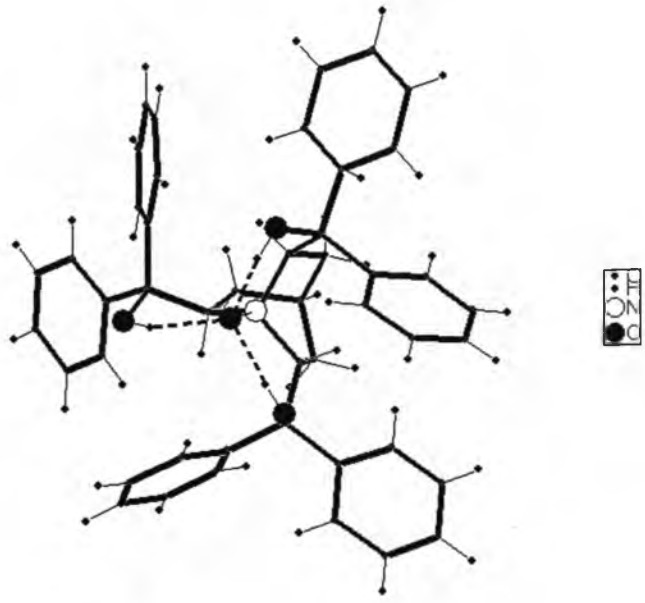
Unfortunately, after work up, TLC analysis of the crude reaction mixture indicated a large number of products had been formed. Inspection of the crude mass spectrum indicated that some of the desired *tris*-substituted compound, [6,7-bis(hydroxyphenylmethyl)-1-oxy-1-azabicyclo[2.2.2]oct-2-yl]diphenylmethanol (**196**) had been formed. After column chromatography on silica, eluting with ethyl acetate/petroleum ether (70:30) it was possible to isolate enough material for a very weak, but promising ^{1}H NMR spectrum.

In order to confirm the structure and improve the yield we decided to attempt the synthesis of [6,7-bis(hydroxyphenylmethyl)-1-oxy-1-azabicyclo[2.2.2]oct-2-yl]diphenylmethanol (**196**) in a sequential manner. We treated (rigorously dried) *bis* adduct [(6-hydroxydiphenylmethyl)-1-oxy-1-azabicyclo[2.2.2]oct-2-yl]-diphenylmethanol (**193**) (prepared as before) with 3.3 equivalents of *t*-BuLi in dry THF, after warming to 0°C then recooling to -78°C the final equivalent of benzophenone was added (Scheme 65). This gave a much cleaner TLC of the crude reaction mixture and by careful flash chromatography on silica eluting with petroleum ether it was possible to isolate [6,7-bis(hydroxyphenylmethyl)-1-oxy-1-azabicyclo[2.2.2]oct-2-yl]diphenylmethanol (**196**), albeit in a very low 2% yield.



Scheme 65

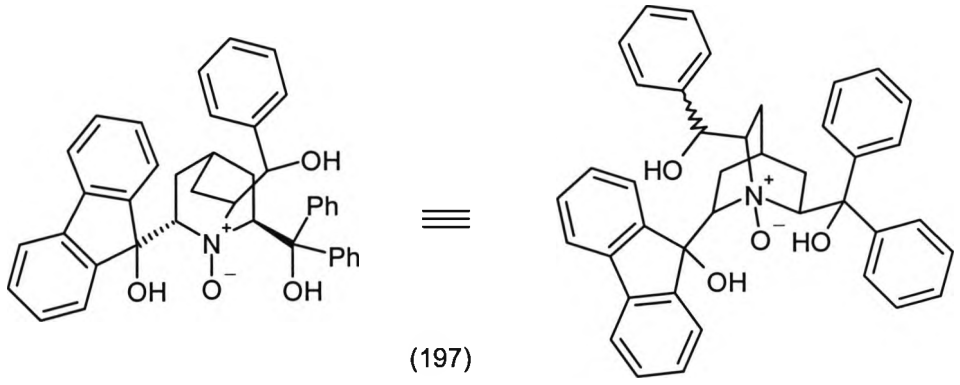
Once again, we were able to grow crystals suitable for X-ray analysis and the structure was determined (X-ray structure 2). Inspection of the X-ray structure clearly shows the three OH groups hydrogen bonding to the oxygen of the *N*-oxide. As far as we are aware this is the first example of a system in which there are three intramolecular H-bonds to a single heteroatom! It was also gratifying to observe that the three benzophenone groups have added *trans* with respect to one another. It is also worth noting that when the crude reaction mixture was analysed by mass spectroscopy there was a parent ion which suggested that a fourth benzophenone molecule had added to the system.



X-ray structure 2

2.7.4 Tris-substitution of QNO with three different electrophiles

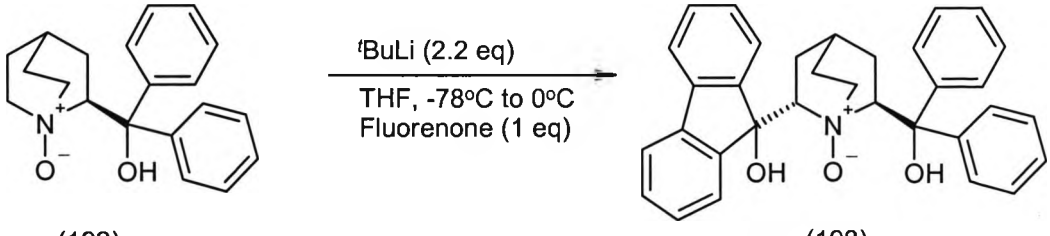
Having shown we could prepare the symmetrical *tris* substituted QNO, [6,7-bis(hydroxyphenylmethyl)-1-oxy-1-azabicyclo[2.2.2]oct-2-yl]diphenylmethanol (**196**) we wanted to prepare an unsymmetrical system. We suspected that with the addition of the third electrophile to the QNO core was low yielding for steric reasons. It was hoped that by using three different electrophiles it would be possible to add a smaller, third electrophile to the QNO core. Our idea was to follow the same, successful sequential alkylation procedure but to employ three different electrophiles. The electrophiles chosen were: benzophenone, fluorenone and benzaldehyde. Benzophenone was chosen because we knew it reacted well with the α-lithiated QNO (**65**). Fluorenone was picked because it is similar to benzophenone but conformationally locked. Benzaldehyde was picked because it is a relatively small electrophile. The target molecule (**197**) is illustrated below (Figure 20).



(197)

Figure 20

To start the synthesis of 9-[6-(hydroxydiphenylmethyl)-7-(hydroxyphenylmethyl)-1-oxy-1-aza-bicyclo[2.2.2]oct-2-yl]-9H-fluoren-9-ol (**197**) QNO was deprotonated in the usual manner and the resultant anion reacted with one equivalent of benzophenone. The reaction was quenched, worked up, purified and dried as previously described to give the *mono* substituted QNO, 1-oxy-1-azabicyclo[2.2.2]oct-2-yl diphenylmethanol (**192**) in a 62% yield as a white solid. Incorporation of the second electrophile was achieved by deprotonation with 2.2 equivalents of *t*-BuLi followed by the addition of 1 equivalent of fluorenone. After the usual work up and purification the desired product, 9-[6-(hydroxydiphenylmethyl)-1-oxy-1-azabicyclo[2.2.2]oct-2-yl]-9H-fluorene-9-ol (**198**) as a yellow solid in 36% yield (Scheme 66).



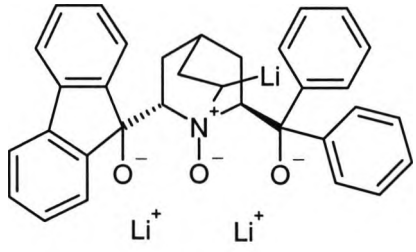
(192) (198)

Scheme 66

It is noteworthy that if the synthetic sequence is reversed i.e. the first alkylation employs fluorenone, attempts to add a second electrophile result in drastically reduced yields, typically in the order of 16%. We do not have a complete explanation

for this observation but attempts to install a third electrophile on to the *bis* substituted QNO do shed some light on a possible explanation.

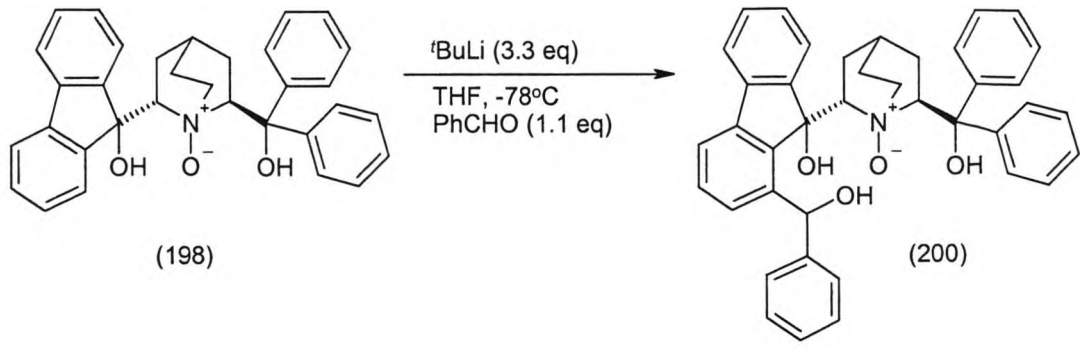
When we attempted the triple deprotonation of 9-[6-(hydroxydiphenylmethyl)-1-oxy-1-azabicyclo[2.2.2]oct-2-yl]-9H-fluorene-9-ol (**198**) using 3.3 equivalents of *t*-BuLi, this, it was hoped, would form the *tris* lithio species (**199**) (Figure 21) to which we would add one equivalent of freshly distilled benzaldehyde to form the *tris* substituted QNO, 9-[6-(hydroxydiphenylmethyl)-7-(hydroxyphenylmethyl)-1-oxy-1-aza-bicyclo[2.2.2]oct-2-yl]-9H-fluoren-9-ol (**197**) (Figure 20).



(199)

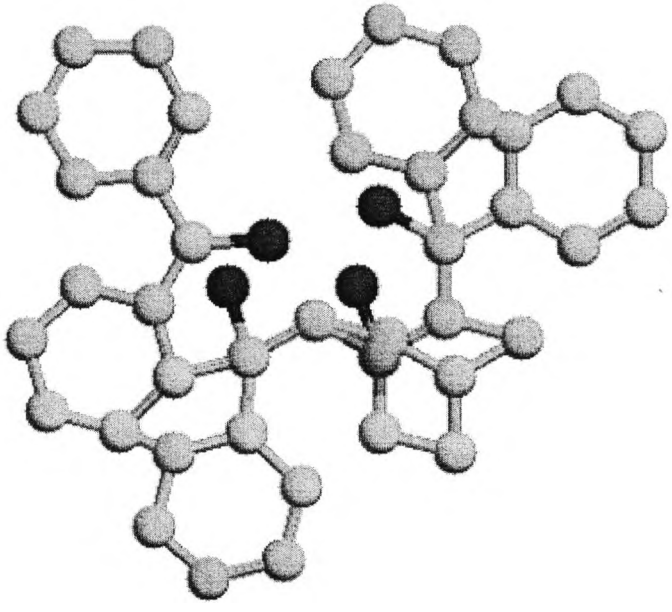
Figure 21

The reaction appeared to proceed as normal and after purification the ^{1}H NMR and mass spectral analysis looked promising. In particular, the mass spectrum had a signal corresponding to the expected parent ion. However, a crystal of 9-[6-(hydroxydiphenylmethyl)-1-oxy-1-azabicyclo[2.2.2]oct-2-yl]-1-(hydroxyphenylmethyl)-9H-fluoren-9-ol (**200**) was obtained and the X-ray structure painted a different picture. The third deprotonation had not taken place α to the *N*-oxide but had occurred on the fluorenone ring presumably *via* an *ortho*-lithiation process. Reaction of the anion with benzaldehyde then formed the compound shown in Scheme 67.



(198) (200)

Scheme 67



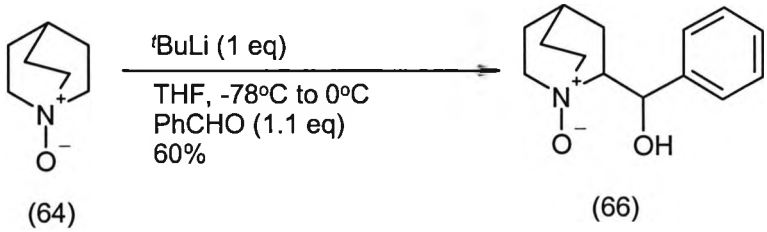
X-ray structure 3

This result was not too surprising given that *ortho*-lithiation can readily occur on such substrates. One group which has exploited *ortho*-lithiations is Snieckus and co-workers.[217]

2.7.5 Reaction of QNO anion with benzaldehyde

In order to check that there was not a problem using benzaldehyde as a general electrophile we decided to react the anion of QNO (**64**) with benzaldehyde. The α-deprotonation was performed using the standard conditions with subsequent addition

of 1.1 equivalents of freshly distilled benzaldehyde. After work up and column chromatography on silica gel eluting with methanol/ethyl acetate (20:80) the mono-substituted product, 1-oxy-1-azabicyclo[2.2.2]oct-2-yl)-phenylmethanol (**66**) was isolated in a 60% yield as white solid (Scheme 68). Unfortunately, we were unable to separate the two diastereoisomers by flash chromatography.



(64) (66)

Scheme 68

As expected, this indicated that the fluorenone was probably causing the problem in the reaction rather than the benzaldehyde.

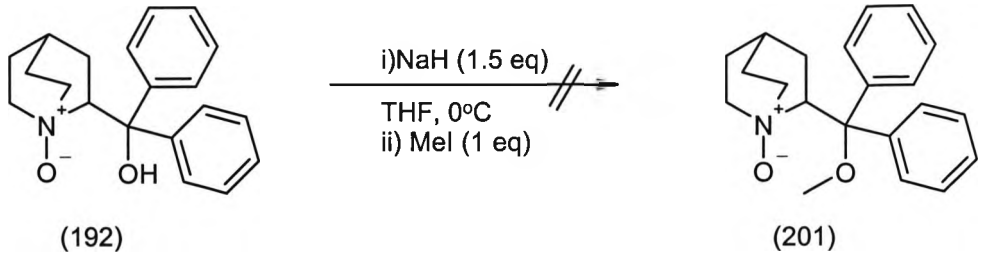
2.7.6 Functionalisation of the hydroxy groups of modified QNO derivatives

We wanted to use these QNO derivatives as a replacement for HMPA. The reactions involved the use of strong bases, clearly something three hydroxy groups are incompatible with. Therefore, we decide to protect the hydroxy groups making the QNO derivatives suitable for use with a strong base as well as, hopefully, making them more soluble in THF.

2.7.7 Formation of the methyl ether

The first ether we attempted to prepare was the methyl ether of the mono substituted QNO, 1-oxy-1-azabicyclo[2.2.2]oct-2-yl diphenylmethanol (**192**). The anion was formed by treatment with 1.5 equivalents of sodium hydride in dry THF under a nitrogen atmosphere at 0°C. One equivalent of iodomethane was added and the reaction mixture allowed to warm to room temperature (Scheme 69) However upon

work up and purification the spectral data indicated none of the desired material (**201**) had been formed.



(192) (201)

Scheme 69

There are a number of possible explanations for this lack of success: i) the iodomethane was too volatile; ii) the hydroxyl proton was not removed and the anion was not formed; iii) the anion had formed but was too hard to react with iodomethane, iv) that the metal was bound very tightly to the two oxygen atoms (Figure 22).

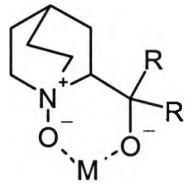
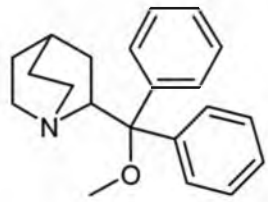


Figure 22

In order to test out the first hypothesis the reaction was repeated, again treating (**192**) with 1.5 equivalents of sodium hydride but this time adding 2 equivalents of iodomethane. The reaction mixture was stirred at 0°C for one hour then allowed to warm to room temperature. Again after purification by column chromatography eluting with methanol/ethyl acetate (30:70) none of the desired product (**201**) was isolated. However the mass spectrum indicated that there was a molecular ion where the methyl ether had formed but the *N*-oxide had been reduced, i.e. $[M+H]^+$-16 (**202**).

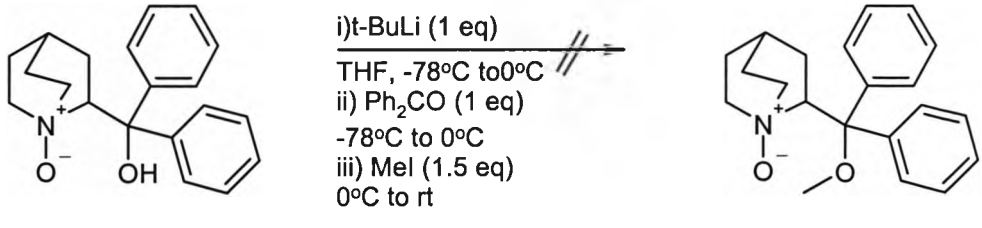


(202)

Figure 23

The third method to be attempted in order to form the methyl ether was by forming the anion in the usual way and adding a harder source of "Me^{+}", we used dimethyl sulphate. Again, (**192**) was treated with base in the usual way followed by addition of 1.1 equivalents of dimethyl sulphate (Scheme 70). After purification by column chromatography eluting with methanol/ethyl acetate (30:70) none of the desired product (**201**) was isolated.

We thought that perhaps the sodium counter ion was not helping the reaction. We decided to employ a different counter ion, this time lithium. The advantage of choosing lithium was that the lithium counter ion is generated when the benzophenone is added to the α-anion of QNO. Therefore rather than quenching the reaction with acid it was decided to add 1.5 equivalents of iodomethane (Scheme 40).



(192) (201)

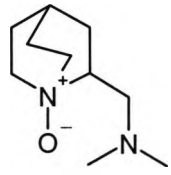
Scheme 70

Once again this strategy proved unsuccessful and we were unable to isolate any of the desired methylated product. We think that this might be due to the metal being tightly bound to the oxygen atoms.

2.8 Functionalisation of QNO with other electrophiles

2.8.1 Reaction of QNO anion with Eschenmoser's salt

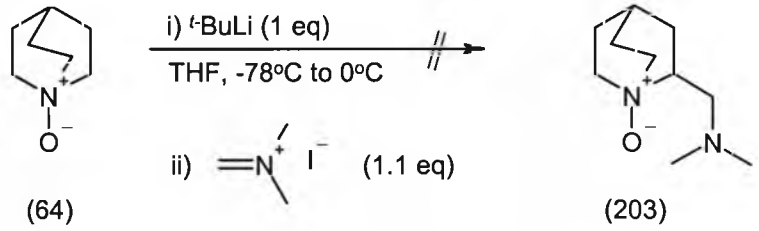
In order to assess the metal binding properties of incorporating other heteroatoms around the QNO nucleus we decided to react the QNO lithio-anion with Eschenmoser's salt. This would give dimethyl-(1-oxy-1-azabicyclo[2.2.2]oct-2-ylmethylamine (**203**) shown in Figure 24 with both the *N*-oxide oxygen and the nitrogen able to bind to a metal cation.



(203)

Figure 24

Our first attempt to prepare dimethyl-(1-oxy-1-azabicyclo[2.2.2]oct-2-ylmethylamine (**203**) involved the standard deprotonation of QNO followed by the addition of 1.1 equivalents of, *N,N*-dimethyl(methylene)ammonium iodide (Eschenmoser's salt) at -78°C under a nitrogen atmosphere. The reaction mixture was stirred at this temperature for 15 minutes before being allowed to warm to room temperature (Scheme 71). The TLC of the reaction mixture indicated a new more polar compound had been formed. Unfortunately, after work up and column chromatography on silica gel none of the desired product (**203**) was isolated. Only QNO was recovered.



(64) (203)

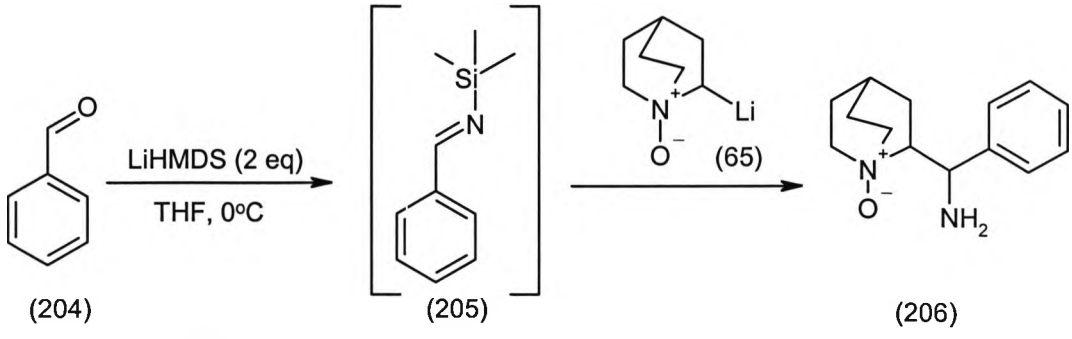
Scheme 71

Our initial attempt may have failed due to the poor quality of the Eschenmoser's salt from a previously used bottle. The reaction was repeated using a new batch of Eschenmoser's salt (Scheme 71). Unfortunately this was unsuccessful and once again, none of the desired material could be isolated.

It was thought that the low solubility of Eschenmoser's salt in THF could be causing the lack of reaction.

2.8.2 Reaction of QNO anion with the *N*-TMS imine of benzaldehyde.

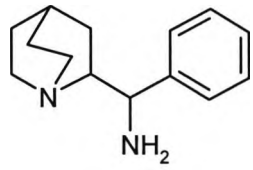
In another attempt to add another nitrogen around the QNO (**64**) nucleus we decided to employ an imine rather than an iminium salt as the electrophile. The imine (**205**) was formed by reacting freshly distilled benzaldehyde (**204**) with two equivalents of lithium hexamethyldisilazide (LiHMDS) in THF at 0°C. Meanwhile the QNO anion (**65**) was prepared in the usual way and added *via* cannula to the solution of the imine (**205**) and the reaction was stirred at 0°C. The reaction was worked up and purified by flash chromatography over silica gel to give a solid in a yield of 33% (Scheme 72).



Scheme 72

However, analysis of the spectroscopic data was a little misleading. The NMR spectrum appeared to correspond to the expected compound C-(1-oxy-1-azabicyclo[2.2.2]oct-2-yl)-C-phenylmethylamine (**206**) but the mass spectrum

indicated a parent ion of $[M+H]^+$-16 which suggested loss of an oxygen atom C-(1-azabicyclo[2.2.2]oct-2-yl)-C-phenylmethylamine (**207**) (Figure 25).



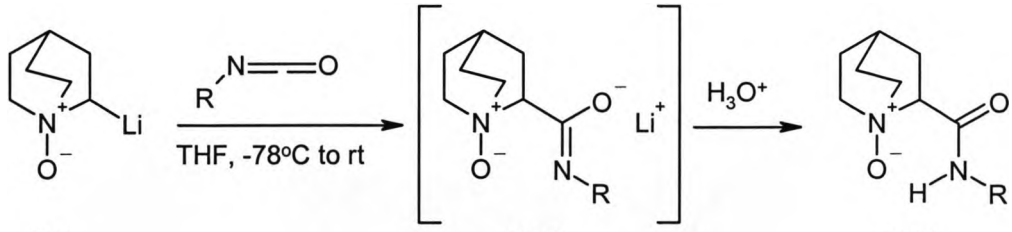
(207)

Figure 25

There are two possible reasons for this. Firstly, that the conditions used to generate the mass spectrum result in the loss of oxygen. The second effect could be due to LiHMDS or another silicon containing group deoxygenating the molecule. For example, it has been shown that $Me_3SiSiMe_3$ can be employed to reduce *N*-oxides.

2.8.3 Reaction of QNO anion with phenyl isocyanate

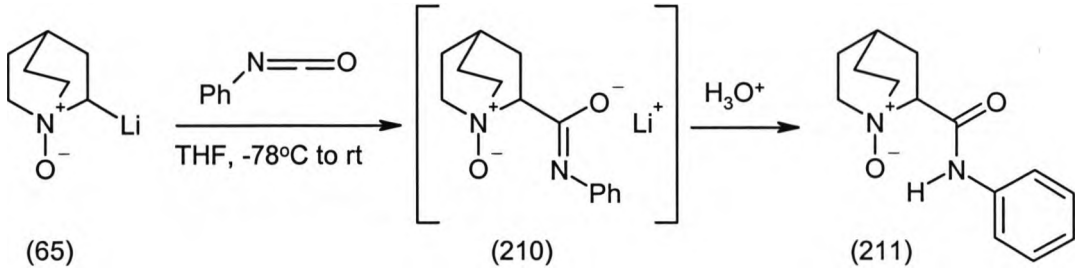
We have previously seen the QNO anion (**65**) reacts with ketones, aldehydes and imines. We wondered if we could employ another type of electrophile, namely, isocyanates. If the reaction had been successful, it would incorporate an amide, adding further heteroatoms around the QNO core (**209**) and presumably alter its metal binding ability (Figure 26).



(65) (208) (209)

Figure 26

The QNO anion (**65**) was prepared in the usual way by treatment with *t*-BuLi in dry THF at -78°C. One equivalent of commercial phenyl isocyanate was added at -78°C and the reaction stirred for 15 minutes before it was allowed to warm to room temperature. Once the reaction mixture had reached room temperature it was quenched with 2M hydrochloric acid. Following work up the crude reaction mixture was purified by flash column chromatography on silica gel eluting with methanol/ethyl acetate (20:80) to give the desired amide, 1-oxy-1-azabicyclo[2.2.2]octane-2-carboxylic acid phenylamide (**211**) as a white crystalline solid in a 50% yield (Scheme 73)



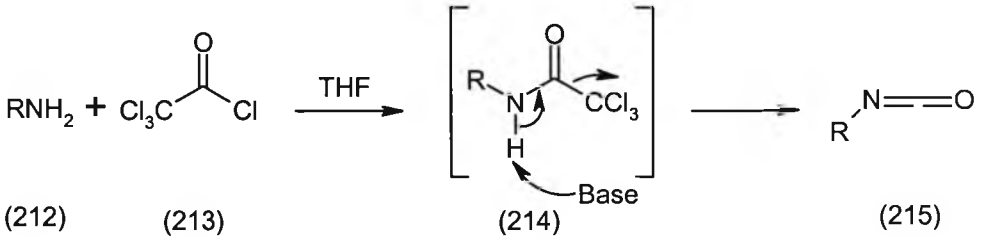
Scheme 73

The product, 1-oxy-1-azabicyclo[2.2.2]octane-2-carboxylic acid phenylamide (**211**) is drawn hinting at a hydrogen bond between the amide hydrogen and the oxygen of the *N*-oxide. A clear indication of this is the large downfield shift of NH proton in the ^{1}H NMR, the proton resonates at δ13.29 ppm. Following the success of the reaction with phenyl isocyanate we decided to attempt reactions with other isocyanates. The first task was to prepare a number of isocyanates *in situ* and then react them with the QNO anion.

2.8.4 *In situ* preparation of isocyanates

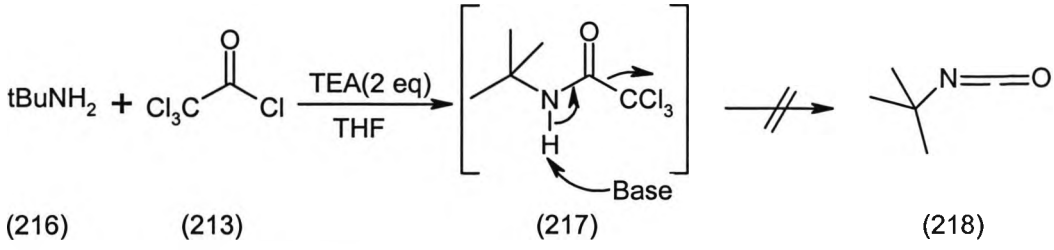
The route chosen to prepare the isocyanates was to react a variety of amines with trichloroacetyl chloride (**213**) in the presence of 2 equivalents of base in THF (Scheme 74). The amine attacks the carbonyl group to form the trichloroacetyl amide (**214**) and HCl which forms the salt with the first equivalent of base. The second

equivalent of base promotes the elimination of chloroform ($CHCl_3$) to form the isocyanate (**215**) as shown in Scheme 74.



Scheme 74

The first amine we chose was *t*-butylamine, it is known to work well in this chemistry, the base we chose was triethylamine (TEA). The *t*-butylamine (**216**) was dissolved in THF and cooled to 0°C under a nitrogen atmosphere. One equivalent of trichloroacetyl chloride (**213**) and 2 equivalents of TEA were added and the reaction was stirred at 0°C for one hour then warmed to room temperature (Scheme 75). To assess if the reaction had been successful, a small amount of the crude reaction mixture was removed and the volatiles removed at reduced pressure. NMR analysis indicated the reaction had not been successful and only *t*-butylamine was present. The reason for the failure of the experiment was put down to the base, TEA, not being strong enough to remove the second amine hydrogen.



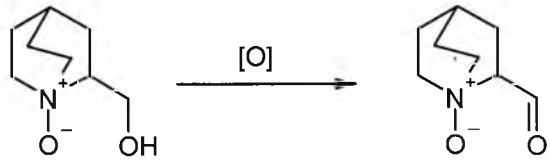
Scheme 75

To try and encourage the reaction we decided to employ a stronger base, this time DBU. The reaction was repeated replacing the two equivalents of TEA with two equivalents of DBU. Rather than isolate the isocyanate the QNO lithio-anion was

added directly *via* cannula. Unfortunately the only materials recovered upon work up were QNO and *t*-butylamine.

2.8.5 Reaction of QNO anion with monomeric formaldehyde

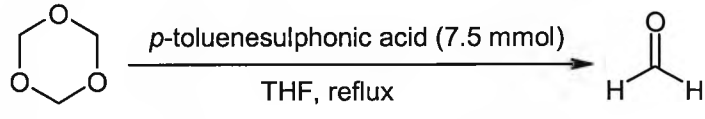
We thought the product of the reaction between QNO anion and monomeric formaldehyde would be a useful intermediate. The α-methyl alcohol, (1-oxy-1-azabicyclo[2.2.2]oct-2-yl)-methanol (**219**) itself could be interesting but it could also be oxidised to the aldehyde (**220**) which could serve as a precursor to a number of other interesting analogues (Scheme 76).



(219) (220)

Scheme 76

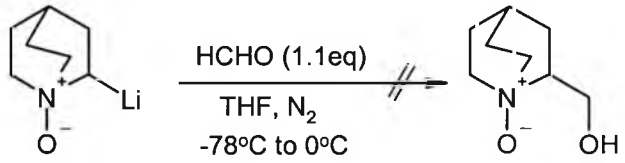
We decided to use the method developed by Schlosser and co-workers to crack paraformaldehyde (**221**) to generate the monomeric form (**222**).[218] Paraformaldehyde (**221**) and a small amount of *p*-toluenesulphonic acid were dissolved in THF under an inert atmosphere and a gentle distillation was performed. The distillate was collected and this was assumed to be monomeric formaldehyde (**222**) at a concentration of *circa.* 0.5M in THF (Scheme 77). The monomeric solution formaldehyde was stored under a nitrogen atmosphere in a freezer.



(221) (222)

Scheme 77

The QNO anion (**65**) was prepared in the usual way by treatment with *t*-BuLi in dry THF at -78°C. One equivalent of monomeric formaldehyde was added at -78°C and the reaction stirred for 15 minutes before it was allowed to warm to room temperature. Following work up the crude reaction mixture was analysed by ^1H NMR and the reaction had not been successful with only starting material present (Scheme 78).

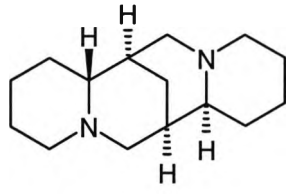


(65) (219)

Scheme 78

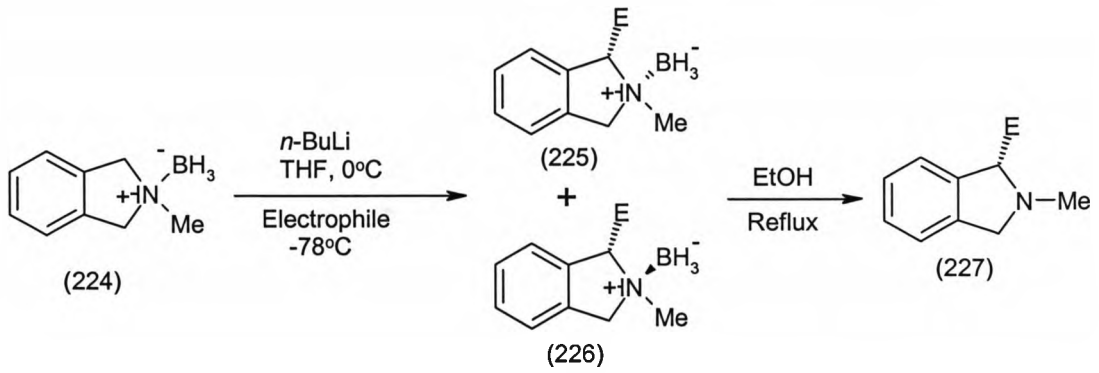
2.9 Deprotonation of QNO using a chiral base

Simpkins and co-workers have employed (-)-sparteine (**223**) (Figure 27)/*sec*-BuLi to obtain diasteroselective and enantioselective substitution reactions of isoindoline-borane complexes.[219] The alkylation of *N*-methylisoindoline-borane complex (**224**) was diastereoselective, with the substitution occurring predominantly *syn* (**225**) to the borane group in a ratio of up to 25:1 (*syn*:*anti*) (Scheme 79).



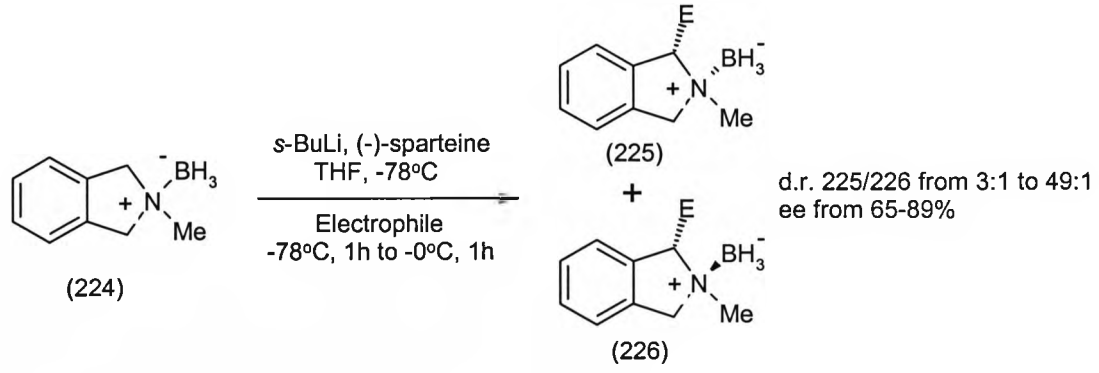
(223)

Figure 27



Scheme 79

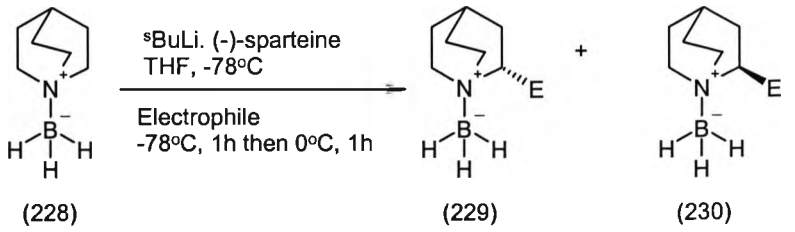
The use of *sec*-BuLi/(-)-sparteine mixture resulted in the enantioselective deprotonation in the alkylation of isoindoline-borane complexes in up to 89% ee (Scheme 80). Both the relative and absolute configuration of the alkylation products were established by X-ray structural analysis. These results prompted us to prepare the quinuclidine-borane complex.



Scheme 80

2.10 Preparation of quinuclidine-borane complex

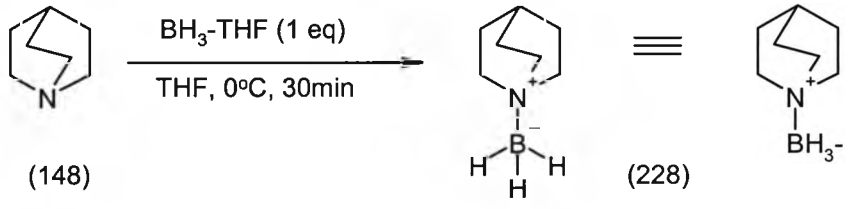
It was hoped that by forming the borane complex of quinuclidine (**228**) it would be possible to selectively remove one of the enantiotopic α hydrogens, react the resultant anion in the presence of (-)-sparteine with an electrophile to give an increased yield of one of the enantiomers (**229**) or (**230**) (Scheme 81).



(228) (229) (230)

Scheme 81

The quinuclidine borane complex (QNB) (**228**) was prepared by adding 1 equivalent of BH_3.THF to a solution of quinuclidine (**148**) in anhydrous THF at 0°C under an inert atmosphere. After stirring for 30 minutes at 0°C (Scheme 82), TLC indicated that all the quinuclidine had reacted, forming a new, less polar compound. The solvent was removed at reduced pressure and the material was purified by flash column chromatography eluting with ethyl acetate to give the QNB as a white semi-crystalline solid in 90% yield. The QNB was dried and stored over P_2O_5 at reduced pressure.



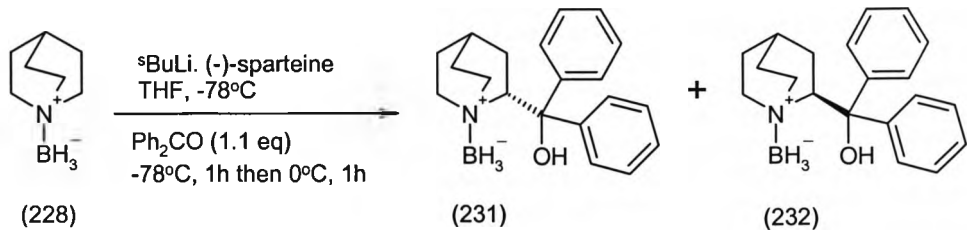
(148) (228)

Scheme 82

2.10.1 Deprotonation of QNB using (-)-sparteine (**223**)

A solution of QNB in THF at -78°C was added a mixture of 1 equivalent of *sec*-BuLi and (-)-sparteine *via* cannula. The mixture was stirred for one hour at -78°C when 1 equivalent of benzophenone was added and stirring continued at -78°C for 30 minutes, before being allowed to warm to room temperature (Scheme 83). After work up the crude product was purified by chromatography on silica to give a dark green solid which was analysed by ^{1}H NMR. It appeared to be the same as the ^{1}H NMR of the product when no chiral base was used. The two products would be

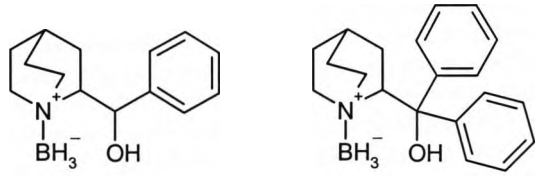
distinguishable only by HPLC using chiral chromatography which was not a facility open to us at the time of doing this work.



(228) (231) (232)

Scheme 83

We did go on to perform deprotonations of QNB (**228**) using *t*-BuLi as the base as we would for QNO. We used two electrophiles, benzaldehyde and benzophenone and after the usual work up and column chromatography eluting with we managed to isolate the two desired products, 1-azabicyclo[2.2.2]oct-2-yl-phenylmethanol *N*-borane complex (**233**) and 1-azabicyclo[2.2.2]oct-2-yl-diphenylmethanol *N*-borane complex (**234**) as white solids in yields of 38% and 35% respectively (Figure 28).



(233) (234)

Figure 28

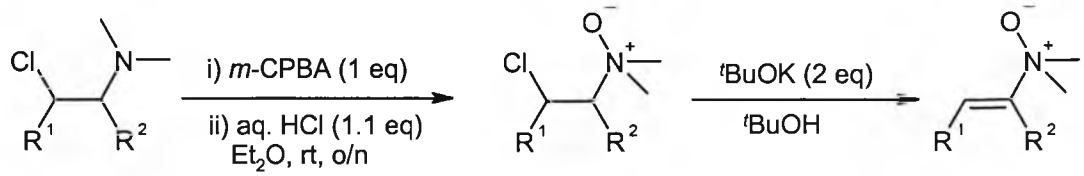
In summary, we have demonstrated that it is possible to treat both QNO (**64**) and QNB (**228**) with strong base and that it is possible to functionalise in the α-position by adding various electrophiles to add more heteroatoms around the quinuclidine core in the hope that it will increase the metal binding properties and the solubility of quinuclidine based molecules.

2.11 Preparation of Enamine N-Oxides

Previous to 1978 enamine *N*-oxides (α,β-unsaturated amine *N*-oxides) were an unreported class of tertiary amine oxides. Krouwer and Richmond were the first to report a general synthetic route to enamine oxides, as well as investigating their chemistry.[220] Their evidence suggested that direct oxidation of an enamine was not a viable route to this class of *N*-oxide.[221] They showed that pyrolysis of *trans*-2,3-bis(dimethylamino)norborane *N,N*-dioxide gave 2-dimethylaminonorborane *N*-oxide,[222] but unfortunately further investigations into other systems revealed that this was not a general route.[223]

As an extension to the facile synthesis of vinylammonium salts from 2-haloalkylammonium salts *via* elimination of HCl with alcoholic potassium hydroxide Renshaw and co-worker proposed that 2-haloamine *N*-oxides might be prepared in a similar manner.[224] Rate studies on the dimerization of 2-chloro- and 2-bromoalkylamines suggested that it would be more convenient to work with the chlorides.[225] Dimethylamine derivatives were chosen so as to exclude complications from the Cope elimination reaction.

Thus *N,N*-dimethyl-2-chlorocyclohexylamine *N*-oxide (**236a**), *N,N*-dimethyl-2-chloropropylamine *N*-oxide (**236b**), and *N,N*- dimethyl-2-chloroethylamine *N*-oxide (**236c**) were prepared as the stable hydrochloride salts from the corresponding amines 134a-c in 54-66% yield by oxidation with *m*-CPBA.[226] Elimination of freshly dried *N*-oxide hydrochlorides was achieved by treatment with potassium *tert*-butoxide in *tert*-butyl alcohol to give *N,N*- dimethyl-1-cyclohexenylamine *N*-oxide (**237a**), *N,N*-dimethyl-*trans*-propenylamine *N*-oxide (**237b**), and *N,N*- dimethylvinylamine *N*-oxide (**237c**) respectively. The solutions were aliquoted under argon and could be reacted directly or lyophilised and sublimed under argon to give crystalline enamine *N*-oxides (**237a-c**) in 45-60% yield. (Scheme 84)



(235)	(236)	(237)
235a $R^1R^2 = -(CH_2)_4-$	236a 54%	237a 60%
235b $R^1 = Me$, $R^2 = H$	236b 65%	237b 45%
235c $R^1 = R^2 = H$	236c 66%	237c 52%

Scheme 84

As expected enamine *N*-oxides (**237a-c**) were extremely hygroscopic, white crystalline solids. They are stable for months when stored at 0°C in anhydrous conditions under argon either as crystals or in solution. However, if the crystals are allowed to oil in air, the resultant hydrates decompose within a few hours.

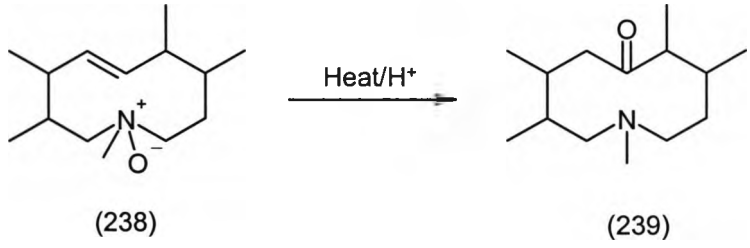
Cyclohexenylamine *N*-oxide (**237a**), with the largest alkyl residue, was the only enamine *N*-oxide of the three which was soluble in benzene and carbon tetrachloride. Likewise, (**237a**) is the most thermally stable *N*-oxide of the three, it also withstands acidification and basification at 60°C, whereas the acid salts of (**237b**) and (**237c**) rapidly decompose. For these reasons they decided to study the chemistry of (**237c**) further.

2.11.1 Reactions of *N,N*- dimethyl-1-cyclohexenylamine *N*-oxide (**237a**)

N,N-dimethyl-1-cyclohexenylamine *N*-oxide (**237a**) was chosen as a model for study of the reactions of the enamine *N*-oxide system. The reactions were performed either on an aliquot of (**237a**) in *tert*-butyl alcohol or on freshly sublimed (**237a**). After aqueous hydrolysis, yields were determined by VPC.

2.11.2 VPC Decomposition of *N,N*- dimethyl-1-cyclohexenylamine *N*-oxide (**237a**)

Injection of a benzene solution of *N,N*-dimethyl-1-cyclohexenylamine *N*-oxide (**237a**) into the VPC instrument at injection port temperatures from 170 to 260°C gave cyclohexanone (6%), *N,N*- dimethyl-1-cyclohexenylamine (20%), and 2-dimethylaminocyclohexanone (13%) as the major products. Similar rearrangement has been reported by Perkin and co-worker.[227] When cyclic 1,4,5,8,9-pentamethyl-3,4,5,8,9,10-hexahydro-2H-azecine *N*-oxide (**238**) was heated in acidic medium, it gave aminoketone, 1,3,4,7,8-pentamethyl-azecan-6-one (**239**). In another example of *o*- and *p*-dimethylaminophenols were formed by pyrolyzing dimethylaniline *N*-oxide (Scheme 85).[228]

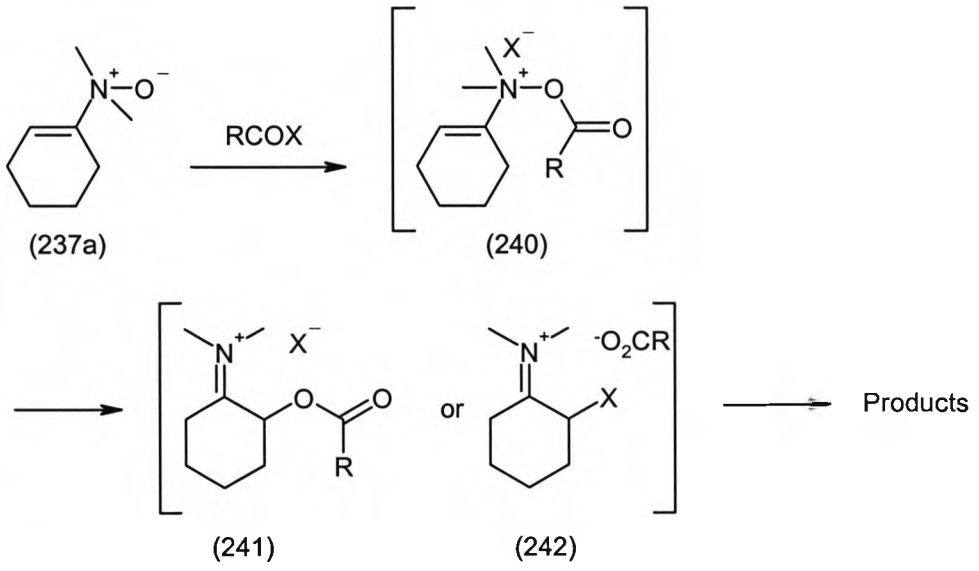


(238) (239)

Scheme 85

2.11.3 Reactions of *N,N*- dimethyl-1-cyclohexenylamine *N*-oxide (**237a**) with Acylating Agents.

The products obtained from the reactions of *N,N*-dimethyl-1-cyclohexenylamine *N*-oxide (**237a**) with acetic anhydride, benzoyl chloride, and diketene indicate that one reaction pathway predominates when these amine oxides are reacted with electrophiles (Scheme 86). Attack of the negatively charged oxygen on the electrophile generates acyloxyeneammonium salt (**240**). Subsequent [3,3] rearrangement gives intermediate (**241**) which may react with an external nucleophile (e.g. Cl^- in the case of PhCOCl) to form intermediate (**242**). Upon work up either of these intermediates form the observed 2-substituted cyclohexanones.



Scheme 86

A range of products can be formed depending on the external nucleophile employed. In the case of benzoyl chloride, the products and their respective yields are shown in Figure 29. (You will note the yields add up to >100%, they are as reported in the literature)

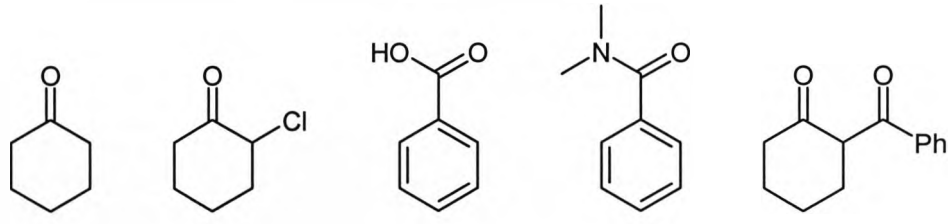


Figure 29

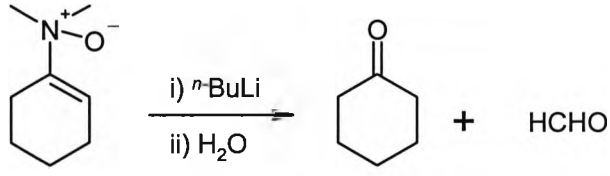
The detailed mechanism of the [3,3] rearrangement of **(240)** to **(241)** is open to speculation. No CIDNP signals were observed when the reactions were initiated in the probe of an NMR instrument, although this result does not completely exclude a radical mechanism. Another product, cyclohexanone, is probably the result of deoxygenation followed by hydrolysis. It appears that demethylation does not occur

as one would expect to find monomethylamides in the product distribution but none were observed.

Potier and co-workers have studied the Polonovski type intermediates of saturated amine oxides and have found that reaction with trifluoroacetic acid (TFAA) gave iminium trifluoroacetates.[229] This pathway is not available to the enamine *N*-oxide and treatment with. In a number of examples they found that the intermediate acyloxyammonium salts decomposed to give imonium trifluoroacetates as the final products. However the reaction of *N,N*-dimethyl-1-cyclohexenylamine *N*-oxide (**237a**) with TFAA gave, after hydrolysis, 2-trifluoroacetoxycyclohexanone (32%) and cyclohexanone (18%) as the major products, a result consistent with other reactions of (**237a**) with acylating agents (Scheme 86). Before aqueous hydrolysis, the reaction mixtures were investigated by NMR but none of the vinylammonium salts corresponding to those of Potier and co-workers were observed.

2.11.4 Other reactions of (237a)

The reaction of (**237a**) with *n*-butyllithium gave, after hydrolysis, cyclohexanone (**243**) (48%) and formaldehyde, present in an undetermined amount in the aqueous phase (Scheme 87).



(237a) (243)

Scheme 87

The formaldehyde was presumably derived from one of the methyl groups of (**237a**), in a reaction similar to those of *N,N*-dimethylaniline *N*-oxides with *n*-butyllithium and phenyllithium where monomethylanilines were the major products.[230]

The following reagents did not react with *N,N*-dimethyl-1-cyclohexenylamine *N*-oxide (**237a**): methyl acrylate, 2-cyclohexenone, *m*-CPBA, cyclopentadiene and diazomethane.

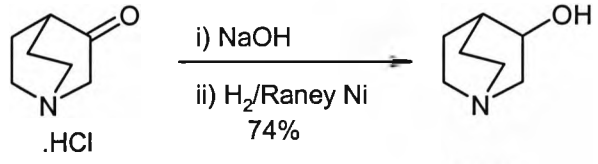
2.11.5 1-Azabicyclo[2.2.2]oct-2-ene (Quinuclidine enamine (QEN))

During our work concerning QNO (**64**) as a possible replacement for HMPA we wondered what the properties of the unusual enamine *N*-oxide, 1-azabicyclo[2.2.2]oct-2-ene *N*-oxide (**248**) would be. A search of the literature showed that although this compound had not previously been reported, the parent enamine, 1-azabicyclo[2.2.2]oct-2-ene (**249**) (QEN) had been prepared first by Grob 1957 (Figure 30).[231]

(248) (249)

Figure 30

Grob prepared the 1-azabicyclo[2.2.2]oct-2-ene (**249**) by the dehydration of the corresponding 3-hydroxyquinuclidine (**251**) which in turn was made from 3-quinuclidinone (**249**) (Scheme 88)

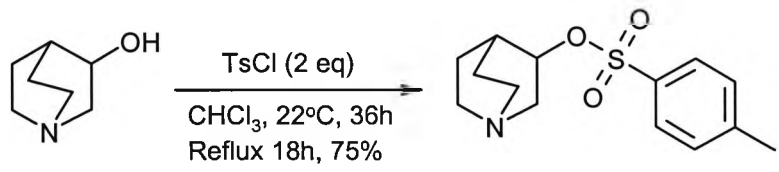


(250) (251)

Scheme 88

Exposure of 3-hydroxyquinuclidine (**251**) to 2 equivalents of *p*-toluenesulfonyl chloride in alcohol free chloroform at room temperature for 36 hours, followed by

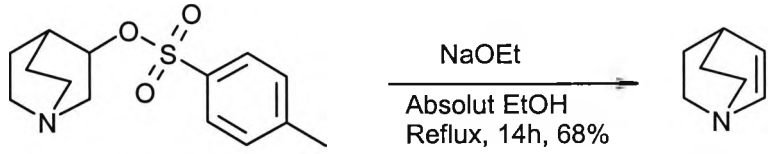
heating at reflux for 18 hours gave the expected 3-tosyloxyquinuclidine (**252**) in a 75% yield (Scheme 89).



(251) (252)

Scheme 89

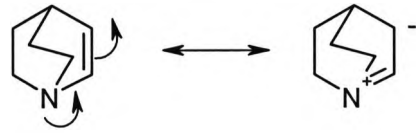
The 1-azabicyclo[2.2.2]oct-2-ene (**249**) was then formed by treatment of 3-tosyloxyquinuclidine (**252**) with sodium ethoxide in ethanol, heating at reflux for 14 hours which gave the desired enamine in 68% yield (Scheme 90).



(252) (249)

Scheme 90

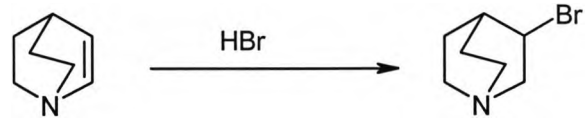
We expected the chemistry of this enamine to be different from other enamines on account of the violation of Bredt's rule required to form the mesomeric iminium form e.g.



(249)

Doering and co-workers investigated the reactivity of enamines and discussed how their reactivity towards electrophiles is dependent upon the production of planar iminium ions as intermediates.[232] Grob and co-workers have reported some interesting reactions that imply that QEN is unable to form the bridgehead iminium.[231] For example , 1-azabicyclo[2.2.2]oct-2-ene (**249**) reacts with hydrogen bromide at 160°C, not to give 2-bromoquinuclidine or its decomposition product as

expected from normal enamines, but rather 3-bromoquinuclidine (**253**) (Scheme 91). In a second example they showed 3-phenyl-1-azabicyclo[2.2.2]oct-2-ene does not react with nitric acid in acetic anhydride to give the expected ring-opened products of an iminium ion but instead gave a mixture of 3-phenyl- and 3-*p*-nitrophenyl-3-nitro-1-azabicyclo[2.2.2]oct-2-ene. This led them to believe that QEN could not and did not behave like a conventional enamine because the intermediate bridgehead iminium ion could not be formed.



(249) (253)

Scheme 91

A different synthetic route was employed by Ripoll and co-workers.[233] Their synthesis started with 3-chloroquinuclidine (**254**). Treatment with potassium *tert*-butoxide in DMSO at 60°C for 24 hours gave 1-azabicyclo[2.2.2]oct-2-ene (**249**) in a rather low 30% (Scheme 92). Subsequent thermolysis of 1-azabicyclo[2.2.2]oct-2-ene (**249**) at 520°C and 5 x 10^{-7} torr formed 5,6-dihydropyridine (**255**) in an unreported yield.

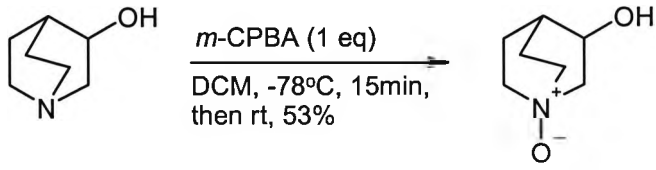
(254) (249) (255)

Scheme 92

To summarise we were pleased that both the published routes to the desired enamine 1-azabicyclo[2.2.2]oct-2-ene (**249**) should be adaptable to the chemistry developed by Richmond used to generate enamine *N*-oxides.

Due to the availability of 3-hydroxyquinuclidine (**251**) this was to serve as our initial precursor. Unfortunately, the initial attempt to synthesise the 1-azabicyclo[2.2.2]oct-

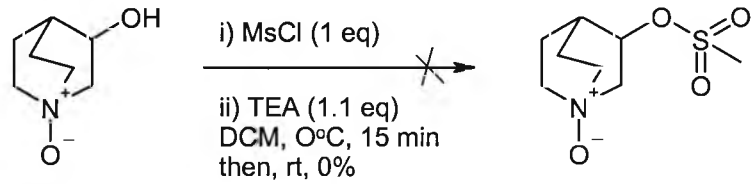
2-ene (**249**) was unsuccessful due to the order of the reactions sequence. Our initial attempt commenced with the oxidation of 3-hydroxyquinuclidine (**251**) using one equivalent of *m*-CPBA in DCM at -78°C which gave the expected *N*-oxide, 1-oxy-1-azabicyclo[2.2.2]-octane-3-ol (**256**) in a 53% yield as a hygroscopic, off white solid (Scheme 93).



(251) (256)

Scheme 93

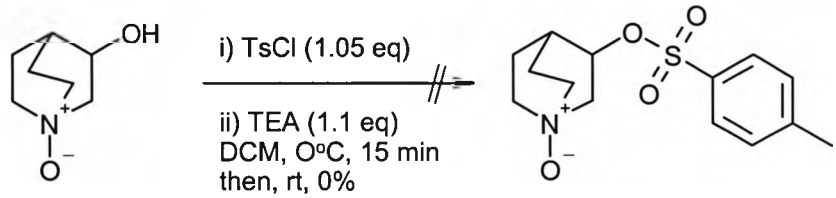
The next step in the synthesis was activation of the hydroxy group by forming a mesylate (**257**) which would hopefully lend itself to the elimination step. The mesylation of (**256**) was attempted under standard conditions (Scheme 94). Unfortunately, none of the desired product was isolated. Presumably, this was due to the *N*-oxide reacting with the mesyl chloride in preference to the hydroxyl moiety.



(256) (257)

Scheme 94

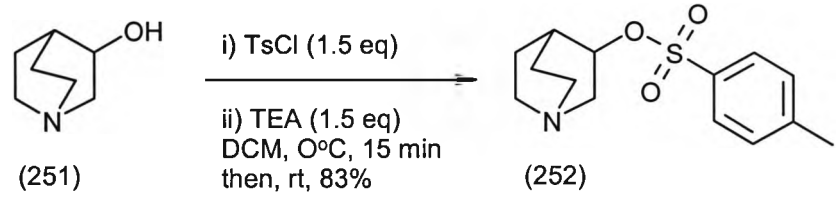
In an attempt to form the 3-tosyloxyquinuclidine *N*-oxide (**258**) a similar reaction was performed replacing the mesyl chloride with tosyl chloride (Scheme 95), again the reaction was unsuccessful.



(256) (258)

Scheme 95

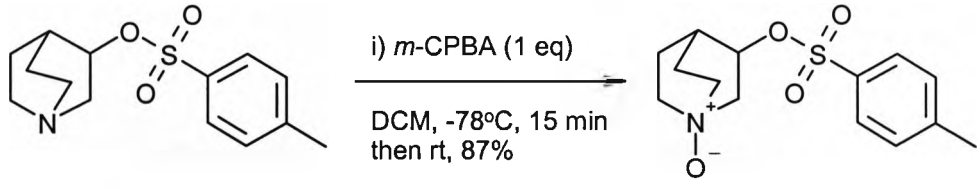
This prompted us to revise our strategy, the second approach involved tosylation prior to *N*-oxidation. To this end, 3-hydroxyquinuclidine (**251**) was treated with tosyl chloride and triethylamine 1.5 equivalents of each and allowed to warm from 0°C to room temperature (Scheme 96). The mixture was separated by column chromatography over silica gel eluting with methanol/ethyl acetate (30:70) giving 3-oxytosyl quinuclidine (**252**) in a 83% yield as an orange solid/oil.



(251) (252)

Scheme 96

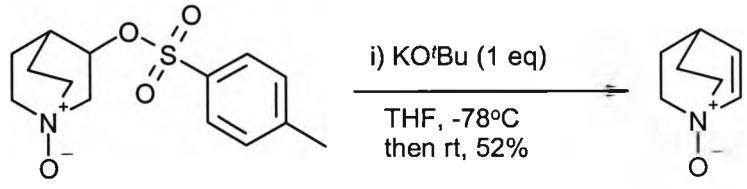
Oxidation of the nitrogen was achieved by treatment with *m*-CPBA at low temperature to form the desired amine *N*-oxide, 3-tosyloxyquinuclidine *N*-oxide (**258**) in 87% yield as a white solid (Scheme 97).



(252) (258)

Scheme 97

The final step of the synthesis was the elimination to form the enamine *N*-oxide. Exposure of 3-tosyloxyquinuclidine (**258**) to one equivalent of potassium *tert*-butoxide in anhydrous THF gave 1-azabicyclo[2.2.2]oct-2-ene *N*-oxide (**248**) in a 52% yield as an off white solid (Scheme 98).



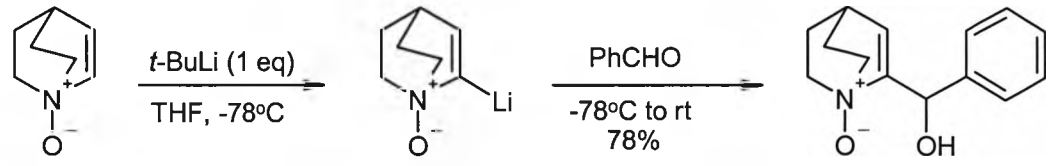
(258) (248)

Scheme 98

The formation of the new product, 1-azabicyclo[2.2.2]oct-2-ene *N*-oxide (**248**), is clearly illustrated in the ^{1}H NMR spectrum in which the two signals corresponding to the vinylic protons resonate at δH 6.70 and 6. 49 (doublet and triplet respectively). The low chemical shift of these protons indicating the powerful inductive electron withdrawing effect of the nitrogen.

2.11.6 Reactions of Quinuclidine Enamine *N*-Oxide (QEO)

We have seen previously (2.11) that Richmond and co-workers reported that when *N,N*-dimethyl-1-cyclohexenylamine *N*-oxide (**237a**) was treated with *n*-BuLi it gave cyclohexanone.[220] In stark contrast, when the quinuclidine derived 1-azabicyclo[2.2.2]oct-2-ene (**248**) was treated with *t*-BuLi the stable lithio anion (**259**) was formed which was trapped with benzaldehyde and gave alcohol, (1-azabicylclo[2.2.2]oct-2-en-2-yl)-phenylmethanol *N*-oxide (**260**) in a 78% yield as a white solid (Scheme 99). Presumably the difference in reactivity can be attributed to the inability to form anti Bredt iminium ion.



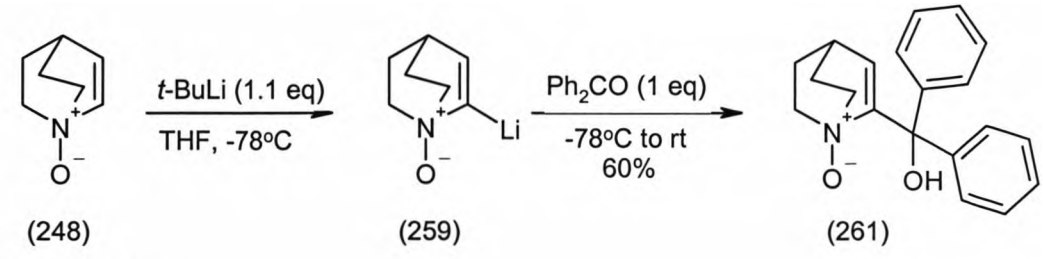
(248) (259) (260)

Scheme 99

Analysis of the ^{1}H NMR spectrum of the new compound showed a change in the vinylic region. The starting material (**248**) had two vinylic protons at δH 6.70 and 6. 49 (doublet and triplet respectively) whereas in the product (**260**) there is only one vinylic signal, a doublet at δH 5.65.

We wondered how the anion (**259**) would react with other electrophiles. Due to the success of benzophenone in the chemistry of QNO this was to be our next electrophile.

The enamine was treated in anhydrous THF under a nitrogen atmosphere with 1.1 equivalents of *t*-BuLi under a nitrogen atmosphere at -78°C. After one hour, one equivalent of benzophenone was added to the reaction mixture at -78°C, allowed to warm to room temperature. This reaction gave the expected alcohol, (1-azabicylclo[2.2.2]oct-2-en-2-yl)-diphenylmethanol *N*-oxide (**261**) in a yield of 60% as a white solid (Scheme 100)

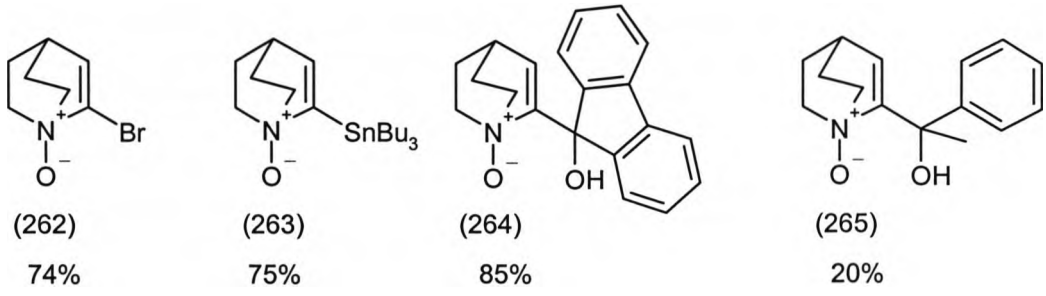


(248) (259) (261)

Scheme 100

The new alcohol was clearly identifiable from the ^{1}H NMR spectrum with the vinylic signal, a doublet at δH 5.77.

Now we had a reliable protocol for the deprotonation of the enamine had been established, we explored a range of other electrophiles. The electrophiles chosen were bromine, tributyltin chloride, fluorenone and acetophenone, the products of these reactions, along with the yields are illustrated in Figure 31.



(262) 74%

(263) 75%

(264) 85%

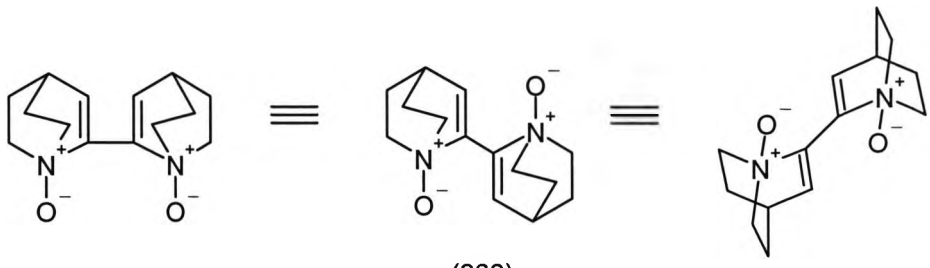
(265) 20%

Figure 31

As can be seen from Figure 31 the yields for the anion formation and trapping are good. The exception being acetophenone, which is enolisable, it is this presumably which accounts for the low yield of 1-(1-oxy-1-azabicyclo[2.2.2]oct-2-en-2-yl)-1-phenylethanol (**265**).

Clearly, the chemistry of the quinuclidine enamine *N*-oxide is very different to the conventional enamines *N*-oxide investigated by Krouwer and Richmond. It is possible to form a stable anion at the α position to the nitrogen and react it with electrophiles.

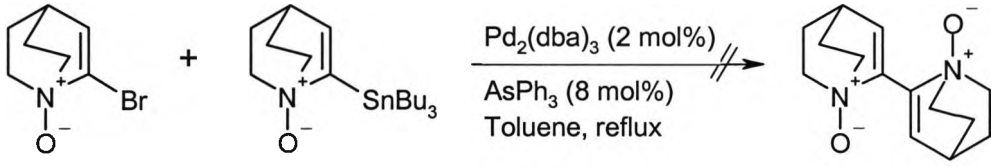
One motivation for the choice of electrophile was to generate the two partners for a sp^2-sp^2 palladium catalysed coupling between α-bromo, 2-bromo-1-azabicyclo[2.2.2]oct-2-ene *N*-oxide (**262**) and 2-Tributylstannyl-1-azabicyclo[2.2.2]oct-2-ene *N*-oxide (**263**) analogues. If successful we would generate a *bis* *N*-oxide species, [2,2']bi[1[aza-bicyclo[2.2.2]octyl]-2,2'-diene 1,1'-dioxide (**266**) (Figure 32).



(266)

Figure 32

In an attempt to synthesise [2,2']bi[1[aza-bicyclo[2.2.2]octyl]-2,2'-diene 1,1'-dioxide (**266**) we attempted a Stille coupling using a palladium (0) catalyst to join the α-bromo (**262**) and tributyl tin (**263**) analogues.[234] Therefore, one equivalent of bromo (**262**) and the tributyl tin analogue (**263**) were dissolved in toluene and cooled to -78°C and allowed to warm to room temperature while attached to a vacuum pump to remove any gaseous oxygen. The freeze-thaw procedure was performed twice more. The solution was placed under a nitrogen atmosphere and tris(dibenzylideneacetone)Pd(0), ($Pd_2(dba)_3$), 2 mol %, was added followed with triphenylarsine, 8 mol%. The reaction mixture was stirred at -78°C for one hour and then allowed to warm to room temperature (Scheme 101).



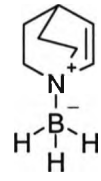
(262) (263) (266)

Scheme 101

Unfortunately the reaction was unsuccessful. The reasons for this could be the oxygen of the *N*-oxide was interfering with the palladium catalyst or the reaction solvent was not fully deoxygenated during the freeze-thaw process.

We thought that it was the *N*-oxide oxygen of either (**262**) or (**263**) might be interfering with the palladium catalyst used to perform the Stille coupling it was

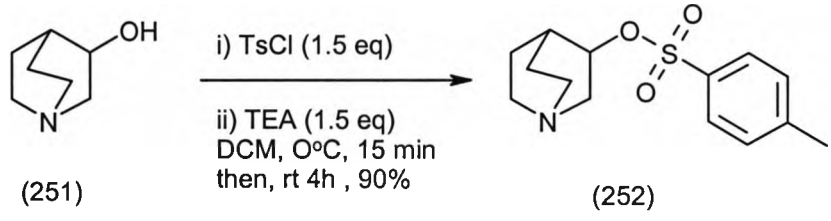
decided to try and prepare enamine-borane complex of quinuclidine (**267**) (Figure 33).



(267)

Figure 33

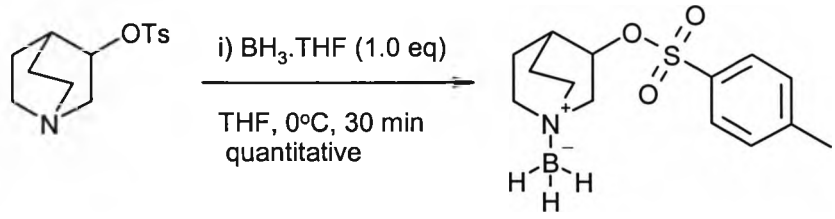
The first step in the preparation of the enamine-borane complex (**267**) was to add a tosyl group to 3-quinuclidinol. This was done by adding sequentially 1.5 equivalents of TsCl and 1.5 equivalents of TEA to one equivalent of 3-quinuclidinol in DCM at 0°C (Scheme 102). The reaction mixture was stirred for 15 minutes then allowed to warm to room temperature, the reaction mixture was flittered and the crude mixture purified by column chromatography over silica gel to give the desired product (**252**) in a yield of 90% as a white solid.



(251) (252)

Scheme 102

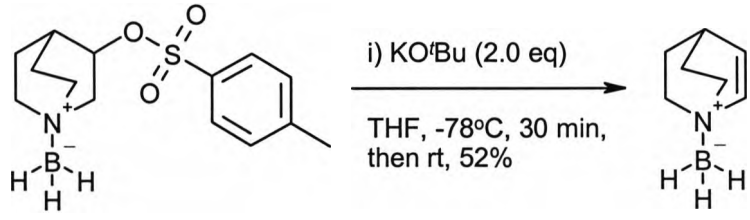
(**252**) was then treated with one equivalent of borane-THF complex in THF at 0°C for 30 minutes under a nitrogen atmosphere. A tlc of the reaction mixture indicated there was no starting material present and the reaction had gone quantitatively to one spot giving (**268**) (Scheme 103).



(252) (268)

Scheme 103

The final step in the preparation of the enamine-borane complex was the treatment of (**268**) with 2 equivalents of KO^{t}Bu starting the reaction at -78°C and after 30 minutes allow it to warm to room temperature to give the desired enamine (**267**) in a yield of 52% (Scheme 104).

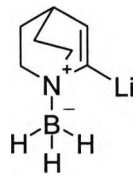


(268) (267)

Scheme 104

The vinylic hydrogens were clearly identifiable in the ^{1}H NMR spectrum at δH 6.53 as a triplet and 6.39 as a doublet, it was also possible to identify the three hydrogens of the BH_3 moiety as a very broad singlet δH 2.12 to 1.32.

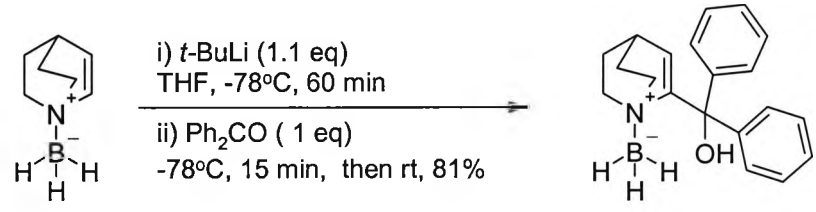
Now we had prepared enamine-borane complex (**267**) we reacted it with 1.1 equivalents of *t*-BuLi in an analogues manner to the quinuclidine borane complex (**228**). The resultant lithio-anion species (**269**) (Figure 34) was quenched with various electrophiles.



(269)

Figure 34

It was decided to utilise the now well established protocol to form the α-anion (**269**). The enamine borane complex was treated with 1.1 equivalents of *t*-BuLi at -78°C in THF under a nitrogen atmosphere. After one hour one equivalent of benzophenone was added, the solution was stirred at -78°C for 15 minutes and then allowed to warm to room temperature. The solvent was removed under reduced pressure and the residue was purified by column chromatography to give the desired product, 1-azabicyclo[2.2.2]oct-2-en-yl-diphenylmethanol *N*-borane complex (**270**) in a yield of 81% (Scheme 105).

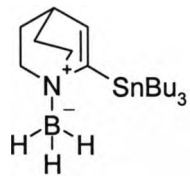


(267) (270)

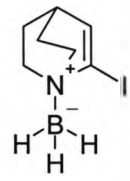
Scheme 105

The reaction product was clearly identifiable from the ^{1}H NMR, as one would expect the doublet and triplet had disappeared leaving only one vinylic proton present at δH 5.77 as a doublet.

The above procedure was repeated using different electrophiles; the electrophiles used were iodine, tributyltin chloride. The products of the reaction, with yields in parentheses, are illustrated below in Figure 35.



(271)(56%)

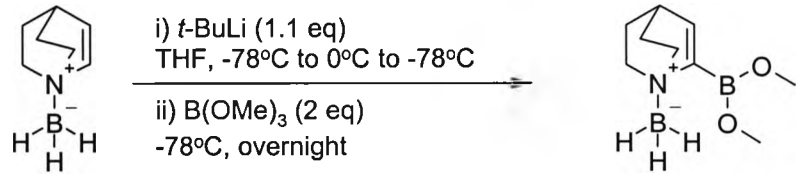


(272)(86%)

Figure 35

The two analogues illustrated in Figure 35 would lend themselves to a Stille coupling reaction. However the Stille reaction was not performed. It was decided to attempt a Suzuki coupling reaction.[235]

In order to perform a Suzuki type coupling reaction the vinylboronic acid, or ester, needed to be prepared. This was done by forming the lithio-anion of the enamine borane complex (**269**) and adding two equivalents of trimethyl borate to form the boronic ester species (**273**) (Scheme 106).[236]

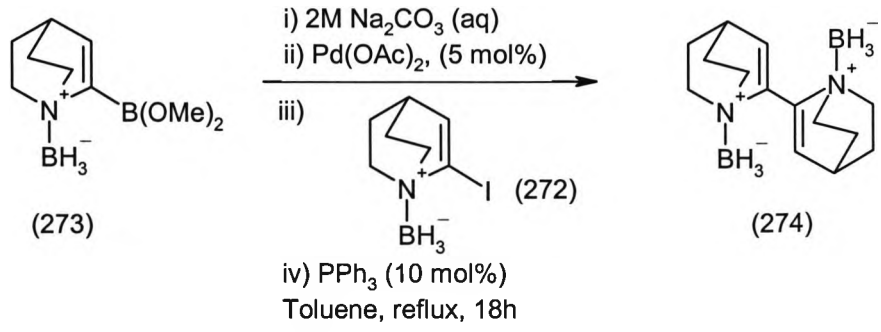


(267) (273)

Scheme 106

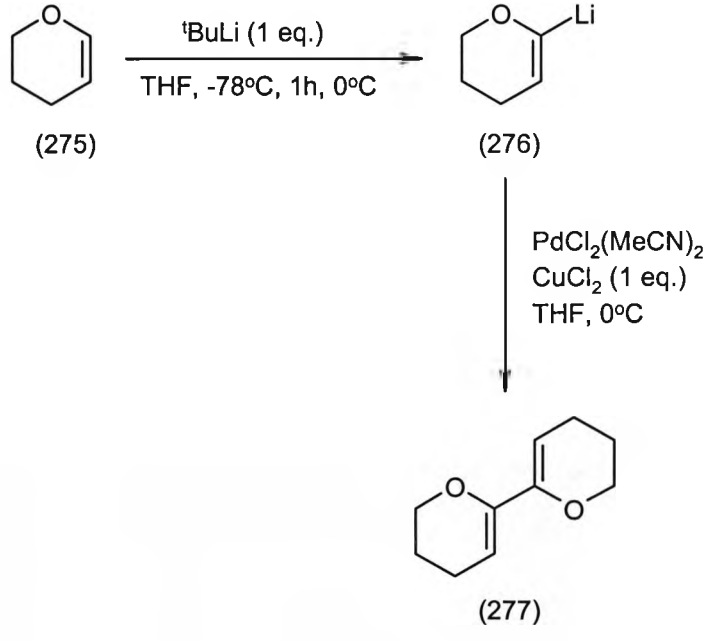
The boronic ester (**273**) was not isolated and was used directly in the next step. The boronic ester (**273**) was dissolved in dry toluene (15 ml) and had 2M sodium carbonate (4 ml) added to it followed by 5 mol% palladium acetate ($Pd(OAc)_2$. The iodo species (**272**) was dissolved in toluene (5 ml) and was added to the reaction mixture followed by triphenyl phosphine. The solution was heated under reflux for 18 hours (Scheme 107). After an aqueous work up washing with water, copper sulphate and brine the solvent was dried over magnesium sulphate and filtered. The solvent was removed at reduced pressure to give a yellow/brown solid. The material

was analysed by ^{1}H NMR and mass spectrometry. Unfortunately none of the desired product (**274**) was found.



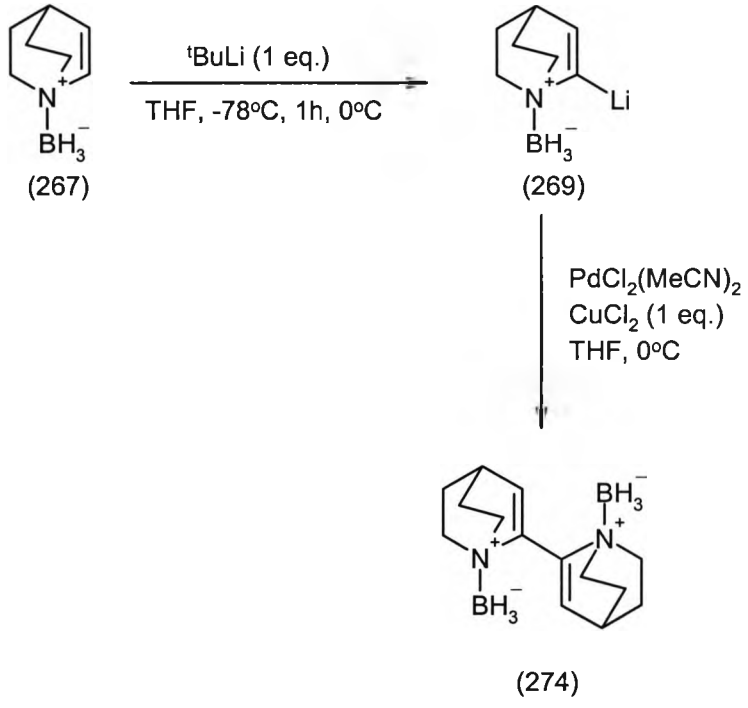
Scheme 107

The next approach taken was to use coupling chemistry developed by Ley and coworkers.[237] 2,3-dihydropyran (**275**) was exposed to one equivalent of *t*-BuLi at -78°C for one hour before being warmed to 0°C under a nitrogen atmosphere. Concurrently a flask was charged with nitrogen, the palladium catalyst (palladium chloride *bis* acetonitrile) and one equivalent of copper (II) chloride was stirred in THF at 0°C (Scheme 108). After purification it gave the dimer (**277**).



Scheme 108

It was decided to use the same approach as Ley and co-workers to see if it would be possible to perform a similar coupling of (**267**) to form the dimer (**274**). The enamine borane complex (**267**) was dissolved in anhydrous THF (30 ml) and treated with one equivalent of *t*-BuLi under a nitrogen atmosphere at -78°C for one hour before being warmed to 0°C. Concurrently a flask was charged with nitrogen and the palladium catalyst (palladium chloride *bis* acetonitrile) and one equivalent of copper (II) chloride was stirred in THF at 0°C (Scheme 109). The reaction was stirred at 0°C for 6 hours. The reaction mixture was filtered through celite and the solvent was removed under reduced pressure. Column chromatography eluting with petroleum ether (40-60) purified the mixture. This gave an off white solid in a yield of 34%.



Scheme 109

The compound was analysed by ^{1}H and ^{13}C NMR and this was quite promising. However, the mass spectral analysis was not consistent with what was required. It was possible to grow a crystal suitable for X-ray analysis but this proved impossible to resolve.

We have seen it is possible to form 1-azabicyclo[2.2.2]oct-2-ene *N*-oxide (**248**) and 1-azabicyclo[2.2.2]oct-2-ene *N*-borane complex (**267**). Once formed it has been

possible to treat 1-azabicyclo[2.2.2]oct-2-ene *N*-oxide (**248**) and 1-azabicyclo[2.2.2]oct-2-ene *N*-borane complex (**267**) with *tert*-BuLi and react the newly formed anion with various electrophiles. We attempted to form a *bis*-quinuclidine dimer (274) *via* a palladium catalysed carbon-carbon bond forming reaction but this proved unsuccessful.

2.12 Summary

Firstly, we have seen the QNO can be used in reactions in which HMPA is known to play a vital role. The reactions examined were enolate alkylation,[207] 1,4 vs 1,2 addition,[208] diastereoselective nitroaldol reactions and epoxide opening.[173, 216]

It has been demonstrated that QNO can act as a replacement of HMPA in a range of reactions. Moreover QNO was found to be negative in the bacterial reverse mutation test conducted on *Salmonella typhimurium* TA98, TA100 and TA 102 in the presence or absence of metabolic activation. Additionally it was also found to be negative in the test to evaluate its potential to induce micronuclei in Chinese hamster ovary cells using the cytokinesis block method in the presence or absence of metabolic activation. This *in-vitro* testing was performed by Rhone-Poulenc Rorer.

Secondly, it has been demonstrated that it is possibly to functionalise the QNO core with many different electrophiles and it is possible to repeat the process and add up to three electrophiles to the QNO care, one electrophile to each α-carbon.

The third part of the study into QNO and related molecules involved synthesising 1-azabicyclo[2.2.2]oct-2-ene *N*-oxide (**248**) and 1-azabicyclo[2.2.2]oct-2-ene *N*-borane complex (**267**). It was possible to remove the α-vinylic proton using *tert*-BuLi and react the newly formed anion with various electrophiles.

Chapter 3

Experimental

REAGENTS AND GENERAL TECHNIQUES.

i) ANALYTICAL THIN LAYER CHROMATOGRAPHY (tlc)

Thin layer chromatography was performed on pre-coated UV_{254} sensitive silica gel plates using various solvent systems. The developing chromatograms were visualised by irradiation with a UV lamp. Compounds were visualised by staining with powdered iodine or by coating with *p*-anisaldehyde, vanillin or CAM (see reagents) and developed by heating the plate to 150°C for 1 min.

ii) FLASH COLUMN CHROMATOGRAPHY

Columns were packed with dry silica (silica gel 60 H, unless otherwise stated) on a bed of sand and the packed column was eluted with the desired solvent creating a homogenous slurry. The crude material was subsequently applied in a small volume of eluent, as an oil or as a powder having been pre-absorbed onto silica. The product was covered by a layer of sand and eluted with further eluent. The fractions were collected in vials or test tubes (10-50 ml) and were analysed by tlc.

iii) SOLVENTS

Analytical grade solvents were used for reactions involving semi-aqueous media, anhydrous solvents were obtained as follows:

DICHLOROMETHANE - Distilled from calcium hydride immediately before use.

DIETHYL ETHER - Distilled from sodium and benzophenone immediately before use.

***N*,*N*-DIMETHYL FORMAMIDE (DMF)** - Sure-seal^{TM} anhydrous solvent purchased from Aldrich Chemical company and used directly from the bottle.

DIMETHYLSULFOXIDE (DMSO) - Sure-seal^{TM} anhydrous solvent purchased from Aldrich Chemical company and used directly from the bottle.

ETHYL ACETATE - Distilled from phosphorus pentoxide immediately before use.

METHANOL - Analytical grade methanol was distilled from calcium hydride immediately before use.

PETROLEUM ETHER (40-60) - Distilled immediately before use.

PYRIDINE - Distilled from calcium hydride immediately before use.

TOLUENE - Distilled from calcium hydride immediately before use.

TETRAHYDROFURAN (THF) - Distilled from sodium and benzophenone immediately before use.

iv) REAGENTS

***P*-ANISALDEHYDE DIP** - Produced from ethanol (90 ml), concentrated sulphuric acid (0.5 ml), glacial acetic acid (0.5 ml) and *p*-anisaldehyde (9 ml).

All other reagents employed were commercially available, of general purpose grade and stored in a refrigerator until use.

(v) EQUIPMENT & TECHNIQUES

ELEMENTAL ANALYSIS - Obtained by the Microanalytical Laboratory technical staff at The University of Liverpool.

HPLC - Conducted using a Varian Star 9010 liquid chromatograph equipped with a Varian star 9050 variable wavelength UV-VIS detector recording at 260 nm. Absorbance was plotted using a Varian 4400 integrator.

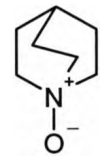
IR SPECTROSCOPY - Samples of liquids were recorded as films using sodium chloride cells, and liquid paraffin (nujol) was used to dilute solid samples (recorded as nujol mulls). Spectra were recorded in the range 4000-600 cm^{-1} using a Perkin Elmer Paragon 1000 FT-IR spectrometer with a polystyrene reference.

MASS SPECTROMETRY - Performed on a VG analytical 7070E mass spectrometer operating with a PDP11/250 data system. FAB spectra were obtained using an Ion Tech FAB ion gun working at 8Kv using 3-nitrobenzyl alcohol (3-NOBA) as the matrix. Acrylate derivatives were recorded using either electronic ionisation (EI) or Chemical ionisation (CI) with ammonia as the carrier gas.

MELTING POINTS - Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected.

NMR SPECTROSCOPY – ^{1}H and ^{13}C spectra were recorded on a Bruker AC200 (200 MHz, 50.4 MHz), Varian Gemini 300 (300 MHz, 75.5 MHz) or Bruker AMX400 (400 MHz, 101.6 MHz). An internal standard of tetramethylsilane (TMS) was used for ^{1}H and ^{13}C.

Preparation of quinuclidine-*N*-oxide (64).



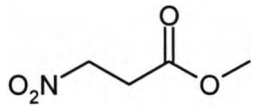
To a solution of quinuclidine (2.23g, 0.02 mol) in dry DCM (25ml) at -78°C (CO_2/ acetone) was added ~90% *m*-CPBA (3.48g, 0.02 mol) under an inert atmosphere. The solution was stirred for six hours during which time it was allowed to warm up to room temperature. The resulting suspension was filtered and the solvent removed *in vacuo* and the solid was purified by flash chromatography on silica using a graduated eluent MeOH/EtOAc (1:19) to MeOH/EtOAc (3:7). The *N*-oxide was dried over P_2O_5 at high vacuum until a constant weight was achieved in a yield of 80%, 2.04 g.

NMR δH (300MHz, $CDCl_3$) 3.44-3.24 (m, 6H), 2.10-1.90 (m, 7H). δC (75MHz, $CDCl_3$) 20.0 (1C, C-H), 26.5 (3C, β-CH_2), 63.2 (3C, α-CH_2).

MS$[M+H]^+$ 128.2.

IR (Nujol mull, cm^{-1}), 951, 420

Preparation of methyl 3-nitropropanoate (165).[207]

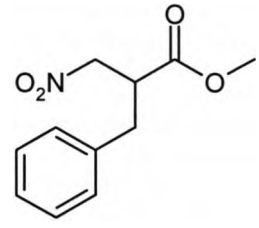


To a solution of 3-nitropropionic acid (2.2g, 0.018 mol) in dry methanol (32ml) was added concentrated sulphuric acid (0.5ml). The reaction mixture was refluxed for eight hours. The reaction mixture was cooled and *circa* half the solvent was removed *in vacuo*. Ether (60 ml) was added and the organic washed with water (3x30ml). The organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo*. This gave a pale yellow oil in a yield of 91%, 2.18 g.

NMR δH (200MHz, $CDCl_3$.) 4.67 (2H, t, *J* 6.0 -O_2N-*CH_2*), 3.75 (3H, s, -O*Me*), 3.00 (2H, t, *J* 6.0, *CH_2*-CO-).

IR(film): 1741(C=O), 1560 (-NO_2), 1378 (-NO_2).

Preparation of methyl 2-benzyl -3-nitropropanoate (171).[207]



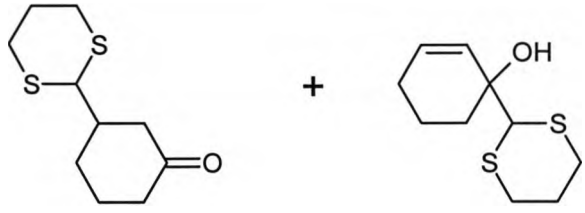
A solution of diisopropylamine (0.9ml, 6.3 mmol) and quinuclidine *N*-oxide (x mmol) in dry THF (40 - 200 ml) was cooled to -78°C. To this solution was added *n*-BuLi (4.0 ml, 1.6M in Hexane, 6.3 mmol). The solution was stirred for thirty minutes, and then methyl 3-nitropropanoate (0.3ml, 2.8 mmol) was added. After stirring for a further sixty minutes benzyl bromide (0.4ml, 3.5 mmol) was added. The solution was stirred for five hours. Acetic acid (1.0ml, 2.8 mmol) was added followed fifteen minutes later by distilled water (5.0 ml). The solution warmed to room temperature and water (50 ml) was added. Diethyl ether (50 ml) was added, the organic layer separated and the aqueous layer was extracted with diethyl ether (3 x 50 ml). The combined organic layers washed with water (100 ml), and dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude reaction mixture was purified by flash chromatography on silica gel eluting with 10% EtOAc/ Pet. Ether (40-60) to give the desired product (R_f = 0.54).

NMR (200MHz, $CDCl_3$): 7.37-7.11 (5H, m, *Ph*), 4.72-4.30 (2H, m, -CH_2-NO_2), 3.73 (3H, s, O*Me*), 3.54-3.39 (1H, m, *H*-βNO_2), 3.19-2.76 (2H, m, CH_2-Ph)

IR: 1737 (C=O), 1555 (-NO_2), 1378 (-NO_2)

M.S(C.I) $[M+NH_4^+]^+ = 241.1$.

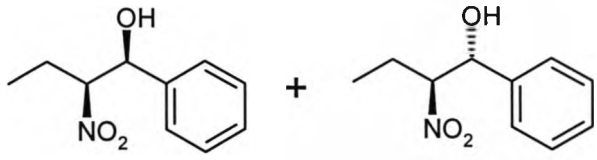
Preparation of *3*-(*1,3*-dithan-*2*-yl)-*1*-cyclo-hexanone (174) and *1*-(*1,3*-dithian-*2*-yl)-*2*-cyclohexen-*1*-ol (175).[208]



To a solution of 1,3-dithiane (0.6 ml, 6 mmol) in THF (13 ml) was added *n*-BuLi (3.15 ml, 5 mmol) at -78°C. After stirring for 15 minutes the CO_2/acetone bath was replaced with an ice bath and the reaction mixture was stirred for 1 hour then cooled to -78°C. After 10 minutes cyclohex-*2*-en-*1*-one was added and stirred for 15 minutes followed by addition saturated ammonium chloride solution (2.5 ml). The reaction mixture was allowed to warm to room temperature at which point distilled water (10 ml) and diethyl ether (10 ml) were added. The aqueous layer was washed with more ether (3 x 10 ml). The combined organic layers were washed with water (5 x 10 ml), dried over $MgSO_4$ and the solvent was removed *in vacuo*. The two products ((174) and (175)) were separated on silica gel (Pet. Ether. 40-60) ($R_f = 0.15$).

NMR (300 MHz, $CDCl_3$) δH of (174) - 4.09 (1H, d, *J* 5, S*CH*S); 2.94-2.81 (4H, m, 2 SCH_2); 1.57-2.59 (11 H, m, 9 cyclohexane H-atoms and CH_2CH_2S). δH of (175)- 6.06-5.94 (1H, m, *H-C*(3)); 5.77 (1H, d, *J* 12, *H-C*(2)); 4.25 (1H, s, S*CH*S); 2.94-2.81 (4H, m, 2 SCH_2); 2.15-1.66 (8H, m, $(CH_2)_3$ of cyclohexene and CH_2CH_2S).

Preparation of *2*-nitro-*1*-phenyl-*1*-butanol ((183) and (184)).[207]

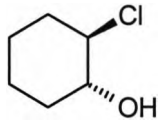


(183) (184)

To a slurry of quinuclidine *N*-oxide (0.98 g, 0.0077 mol) in THF (60 ml) at -78°C was added sequentially *n*-BuLi (6.2 ml, 10 mmol.) and *1*-nitropropane (0.45 ml, 5 mmol.). The reaction mixture was stirred at -78°C for 1 hour, after which time benzaldehyde (0.50 ml, 5 mmol.) was added. The reaction mixture was stirred at -78°C for 2 hours before quenching with *glacial* acetic acid (1.5 ml, 25 mmol.) then warming to room temperature. Distilled water (80 ml) was added and the aqueous layer was washed with diethyl ether (2 x 100 ml). The organic layer was washed with water (5 x 50 ml) then dried over $MgSO_4$. The solvent was removed *in vacuo* and the mixture separated on silica gel (10% EtOAc/90% PE (40-60)) (R_f - 0.40).

NMR (300 MHz, $CDCl_3$) δH of (183) and (184) - 7.40-7.20 (5H, m, aromatic); 5.17 and 5.02 (2 H, *J* 5 and 9 diastereoisomers (183) and (184) in a ratio of 19:81 respectively.); 4.61 (1H, d x t, *J* 4 and 10, *H-C*(2)); 2.70 (1H, s, *OH*); 2.10-1.01 (2H, m, 2*H-C*(3)); 0.86 (3H, t, *J* 4.5, *CH3*).

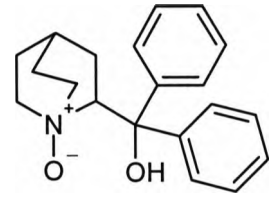
Preparation of *trans-2*-chloro-cyclohexan-*1*-ol (186).[216]



To a solution of cyclohexene oxide (0.49 g, 5 mmol) in DCM (50 ml) was added quinuclidine *N*-oxide (64 mgs, 0.5 mmol). The reaction mixture was cooled to –78°C. Freshly distilled silicon tetrachloride (0.63 ml, 5.5 mmol) was added to the reaction mixture and stirred for 20 minutes at which point AcOH (0.4 ml, 6 mmol.) was added and the reaction mixture was allowed to warm to room temperature. Distilled water (50 ml) was added and DCM (50 ml). The aqueous layer was washed with DCM (2 x 50 ml). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. This gave the desired product in a yield of 89%, 0.60 g.

NMR (300 MHz, $CDCl_3$) δH: 3.79-3.71 (1H, m), 3.66-3.45 (1H, m), 2.65 (1H, s), 2.30-2.01 (2H, m), 1.80-1.55 (3H, m) 1.40-1.22 (3H, m). (75 MHz, $CDCl_3$) δC: 23.9, 25.6, 33.1, 35.1, 67.5, 75.3.

Preparation of 1-oxy-1-azabicyclo[2.2.2]oct-2-yl diphenylmethanol (192).



Method (1)

To a solution of quinuclidine *N*-oxide (0.38g, 0.003 mol) in dry THF (50ml) at –78°C was added 1.7M *tert*-butyllithium (1.8ml, 0.003 mol) followed by benzophenone (0.60g, 0.0033 mol). The reaction mixture was warmed to room temperature over a period of three hours and then washed with saturated brine (100ml), diethyl ether (6 x 50ml). The ethereal layer was dried over magnesium sulphate and the solvent was removed *in vacuo*. The mixture was purified by flash chromatography on silica gel eluting with 30%MeOH / EtOAc to give the desired product in a 16% yield, 148 mg. (R_f 0.30).

IR (nujol mull/ cm^{-1}) 3387 (O-H), 2924 (C-H), 2853 (C-H)

δH (300 MHz $CDCl_3$) 7.84-7.80 (2H, m, aromatics) 7.42-7.20 (8H, m, aromatics), 4.35 (1H, t *J* 9 N-*CH*-CH_2), 3.55 (1H, t *J* 9, N-*CH_2*-CH_2), 3.31 (1H, t *J* 9, N-*CH_2*-CH_2) , 2.89-2.72 (2H, m, N-*CH_2*-CH_2), 2.23-2.01 (5H, m), 1.71-1.60 (1H, m,), 1.47-1.37 (1H, m,). δC (75 MHz $CDCl_3$) 21.5, 26.2, 26.5, 59.3, 69.2, 74.1, 80.5, 127.5, 127.6, 129.6, 142.1

M.S(C.I) $[M+H]^+$ requires 310. 18070, found 310.18026

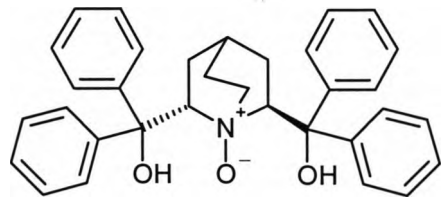
M. Pt., 200-202°C.

Anal calcd. for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.16; H, 7.55; N, 4.42.

Method (2)

To a solution of quinuclidine *N*-oxide (0.38g, 0.003 mol) in dry THF (50ml) at -78°C was added 1.7M *tert*-butyllithium (1.8ml, 0.003 mol) followed by benzophenone (0.60g, 0.0033mol). The reaction mixture was warmed to room temperature over a period of three hours and then the solvent was removed *in vacuo*. The residue was dissolved in methanol then absorbed onto silica gel. The mixture was purified by column chromatography over silica gel eluting with 30% MeOH / EtOAC to give the desired product in a yield of 62%, 575 mg. (R_f 0.30).

Preparation of [6-hydroxydiphenylmethyl)-1-oxy-1-azabicyclo[2.2.2]oct-2-yl]diphenylmethanol (193).



Method (1)

To a solution of quinuclidine *N*-oxide (1.48 g, 0.012 mol) in dry THF (150 ml) at -78°C was added 1.7M *tert*-butyllithium (7.0 ml, 0.012 mol), the solution was warmed to 0°C then recooled to -78°C followed by addition of benzophenone (2.18g, 0.012 mol). The process was repeated then the reaction mixture was warmed to room temperature and then washed with saturated brine (100 ml), diethyl ether (6 x 50 ml). The ethereal layer was dried over magnesium sulphate and the solvent was removed at reduced pressure. The mixture was purified by flash chromatography on silica gel eluting with 30%MeOH / 70%EtOAC to give the desired product in a yield of 5%, 287 mg. (R_f 0.30).

IR(nujol mull/ cm^{-1}) 3387(O-H), 2924(C-H), 2853(C-H)

δH (300 MHz $CDCl_3$) 10.24 (1H, s, OH), 9.63 (1H, s, OH), 7.93-6.75 (20H, m, aromatics), 4.46 (1H, t, *J* 10 N-*CH*-CH_2), 4.30 (1H, t *J* 10 N-*CH*-CH_2), 2.97 (2H, t *J* 9, N-*CH*$_2$-CH_2), 2.25 (1H, t *J* 12, CH_2-*CH*-CH_2) , 2.08-2.00 (1H, m, N-*CH*$_2$-CH_2), 1.93-1.72 (3H, m), 1.63-1.53 (2H, m). δC (75 MHz, $CDCl_3$) 22.5, 26.0, 29.7, 30.0, 30.3, 64.0, 68.2, 79.4, 80.2, 127.4, 127.6, 127.8, 128.3, 128.4, 129.5, 129.6, 142.4, 143.6

M.S (FAB) $[M+H]^+$ found 492.64072 $C_{33}H_{34}NO_3$ requires 492.25387.

Anal calcd. For $C_{33}H_{33}NO_3$: C, 80.62; H, 6.77; N, 2.85. Found C, 80.35; H, 7.00; N, 2.84.

M.Pt., 210-212°C.

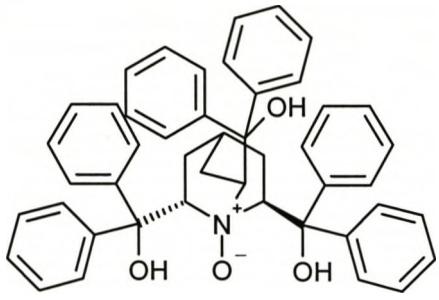
Method (2)

To a solution of mono substituted quinuclidine *N*-oxide (192) (0.62 g, 0.002 mol) in dry THF (100 ml) at -78°C was added 1.7M *tert*-butyllithium (2.5 ml, 0.004 mol), the straw coloured solution was warmed to 0°C then recooled to -78°C followed by addition of benzophenone (0.37 g, 0.002 mol). After 15 minutes the cooling bath was removed and the purple mixture allowed to warm to room temperature. The solvent was removed under vacuum and the residue dissolved in methanol before being adsorbed onto silica gel. The mixture was purified by flash chromatography on silica gel eluting with 10% MeOH / EtOAC up to 30% MeOH/ EtOAc to give the desired product in a yield of 50%, 493 mg. (R_f 0.30).

Method (3)

To a solution of quinuclidine *N*-oxide (0.38 g, 0.003 mol) in dry THF (50 ml) at -78°C was added 1.7M *tert*-butyllithium (1.8 ml, 0.003 mol), the straw coloured solution was warmed to 0°C then recooled to -78°C followed by addition of benzophenone (0.60 g, 0.0033 mol) and the reaction mixture became blue in colour. The process was repeated then the reaction mixture was warmed to room temperature. The solvent was removed *in vacuo*. and the residue was dissolved in methanol then adsorbed onto silica gel. The mixture was purified by flash chromatography over silica gel eluting with 30% MeOH / EtOAC to give the desired product in a yield of 23%, 340mg. (R_f 0.30).

Preparation of [6,7-bis(hydroxyphenylmethyl)-1-oxy-1-azabicyclo[2.2.2]oct-2-yl]diphenylmethanol (196).



Method (1)

To a solution of quinuclidine *N*-oxide (0.38 g, 0.003 mol) in dry THF (50 ml) at -78°C was added 1.7.M *tert*-butyllithium (1.8 ml, 0.003 mol), the straw coloured solution was warmed to 0°C then recooled to –78°C followed by addition of benzophenone (0.60 g, 0.0033 mol) and the reaction mixture became blue in colour. The process was repeated twice more. After the second addition of benzophenone the solution was purple and the third addition it was green. Then the reaction mixture was warmed to room temperature. The solvent was removed *in vacuo* and the residue was dissolved in methanol then adsorbed onto silica gel. The mixture was purified by flash chromatography over silica gel eluting with EtOAC to give the desired product.(R_f 0.30) .

IR(nujol mull/ cm^{-1}) 3387(O-H), 2924(C-H), 2853(C-H)

δH (300 MHz $CDCl_3$) 7.85-6.87 (30H, m, aromatics), 5.72 (1H, t *J* 9 N-*CH*-CH_2) 5.10 (1H, t *J* 9 N-*CH*-CH_2), 4.50 (1H, t *J* 9 N-*CH*-CH_2) 3.45(1H, m *CH*), 3.31 (2H, t *J* 9, N-*CH_2*-CH_2) , 2.09-1.55 (6H, m, N-CH_2-*CH_2*), δC (75 MHz $CDCl_3$) 23.0, 26.3, 30.6, 64.9, 72.9, 79.1, 81.6, 83.3, 126.2, 128.2, 130.4, 132.8, 141.5, 143.3, 148.4, 151.8.

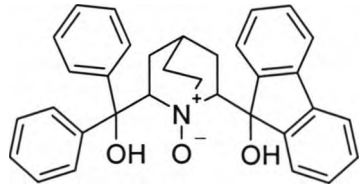
M.S(FAB) $[M+H]^+$ found 674.32811, $C_{46}H_{44}NO_4$. requires 674.32703.

M. Pt, 220-222°C.

Method 2.

To a solution of *bis* substituted quinuclidine *N*-oxide (97) (0.24 g, 0.5 mmol) in dry THF (10 ml) at -78°C was added 1.7M *tert*-butyllithium (1.0 ml, 1.7 mmol), the straw coloured solution was warmed to 0°C then recooled to -78°C followed by addition of benzophenone (0.092 g, 0.5 mmol). After 15 minutes the cooling bath was removed and the purple mixture allowed to warm to room temperature. The solvent was removed under vacuum and the residue dissolved in methanol before being absorbed onto silica gel. The mixture was purified by flash chromatography on silica gel eluting with petroleum ether to give the desired product as a white solid in a yield of 2%, 7 mg. (R_f 0.30) .

Preparation of 9-[6-(hydroxydiphenylmethyl)-1-oxy-1-azabicyclo[2.2.2]oct-2-yl]-9H-fluorene-9-ol (198)



To a solution of 1-oxy-1-azabicyclo[2.2.2]oct-2-yl diphenylmethanol (192) (0.62 g, 0.002 mol) in dry THF (100 ml) at -78°C was added 1.7M *tert*-butyllithium (3.0 ml, 0.005 mol), the straw coloured solution was warmed to 0°C then recooled to -78°C followed by addition of fluorenone (0.36g, 0.002 mol). After 15 minutes the cooling bath was removed and the purple mixture allowed to warm to room temperature. The solvent was removed under vacuum and the residue dissolved in methanol before being absorbed onto silica gel. The mixture was purified by flash chromatography on silica gel eluting with 10% MeOH / EtOAC up to 30%MeOH/ EtOAc to give the desired product in a yield of 36%, 353 mg, (R_f 0.30).

IR(nujol mull/ cm^{-1}) 3381(O-H), 2920(C-H), 2851(C-H)

δH (300 MHz $CDCl_3$) 11.72 (1H, s, OH), 10.38 (1H, s, OH), 8.74-7.11 (18H, m, aromatics), 5.25 (1H, t *J* 9 N-*CH*-CH_2), 3.89 (1H, t *J* 9 N-*CH*-CH_2), 2.95 (2H, t *J* 8, N-*CH*$_2$-CH_2), 2.86 (1H, t *J* 9, CH_2-*CH*-CH_2), 2.13-2.02 (1H, m, N-*CH*-CH_2), 1.93-

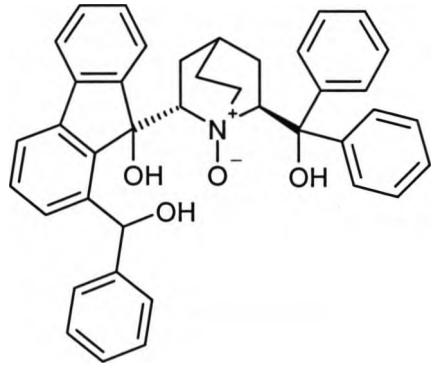
1.72 (3H, m), 1.68-1.53 (2H, m). δ C(75 MHz $CDCl_3$) 21.6, 25.1, 27.9, 63.5, 66.0, 75.1, 88.4, 127.0, 127.6, 128.1, 128.7, 129.6, 144.3

Anal. Calcd. For $C_{33}H_{32}NO_3$ requires C, 80.95; H, 6.38; N, 2.86; found C, 80.79; H, 6.58; N, 2.85.

M.S(FAB) $[M+H]^+$ found 490.23834, $C_{33}H_{32}NO_3$ requires 490.23822.

M. Pt, 204-207°C.

Preparation of 9-[6-(hydroxydiphenylmethyl)-1-oxy-1-azabicyclo[2.2.2]oct-2-yl]-1-(hydroxyphenylmethyl)-9H-fluoren-9-ol (200)



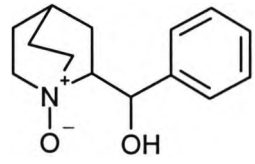
To a solution of [6-hydroxydiphenylmethyl)-1-oxy-1-azabicyclo[2.2.2]oct-2-yl]diphenylmethanol (198) (0.24 g, 0.5 mmol) in dry THF (10ml) at -78°C was added 1.7M *tert*-butyllithium (1.0 ml, 1.7 mmol), the straw coloured solution was warmed to 0°C then recooled to -78°C followed by addition of benzaldehyde (0.092 g, 5 mmol). After 15 minutes the cooling bath was removed and the purple mixture allowed to warm to room temperature. The solvent was removed under vacuum and the residue dissolved in methanol before being adsorbed onto silica gel. The mixture was purified by flash chromatography on silica gel eluting with petroleum ether to give the desired product as a white solid in a yield of 2%, 6 mg, (R_f 0.50).

IR(nujol mull/ cm^{-1}) 3387(O-H), 2924(C-H), 2853(C-H)

δH (300 MHz $CDCl_3$) 11.72 (1H, s, OH), 10.38 (1H, s, OH), 8.74-7.11 (18H, m, aromatics), 5.25 (1H, t *J* 9 N-*CH*-CH_2), 3.89 (1H, t *J* 9 N-*CH*-CH_2), 2.95 (2H, t *J* 8, N-*CH*$_2$-CH_2), 2.86 (1H, t *J* 9, CH_2-*CH*-CH_2), 2.13-2.02 (1H, m, N-*CH*-CH_2), 1.93-

1.72 (3H, m), 1.68-1.53 (2H, m). δC (75 MHz $CDCl_3$) 21.6, 25.1, 27.9, 63.5, 66.0, 75.1, 88.4, 127.0, 127.6, 128.1, 128.7, 129.6, 144.3
M.S(FAB) $[M+H^+]$ $C_{40}H_{38}NO_4$ requires 596.28008. Found 596.27870,
Anal calcd. For $C_{40}H_{37}NO_4$: C, 80.65; H, 6.26; N, 2.35. Found C, 80.71; H, 6.21; N, 2.34.

Preparation of (1-oxy-1-azabicyclo[2.2.2]oct-2-yl)-phenylmethanol (66)



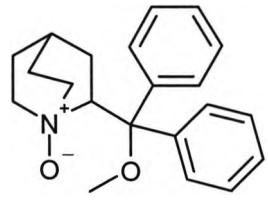
To a solution of quinuclidine *N*-oxide (0.50 g, 3.9 mmol) in dry THF (60 ml) at -78°C was added 1.7M *tert*-butyllithium (2.5ml, 4.2 mmol) followed after 1 hour by benzaldehyde (0.42 g, 0.004 mol). The reaction mixture was allowed to warm to room temperature. The solvent was removed under reduced pressure. The residue was dissolved in methanol then absorbed onto silica gel and eluted with 20% methanol/80% ethyl acetate. This yielded 0.55g (60%) of the desired product as a white solid.

δH(200 MHz $CDCl_3$) 7.45-7.18 (5H, m, aromatics), 6.12 (1H, s Ar-*OH*), 5.66 (1H, d *J* 6, *H-C*(9)), 3.97-3.75 (1H, m, C2-H), 3.70-3.31 (4H, m 2 x N-*CH_2*-CH_2) , 2.77 (1H, m ,*H-C*(4)), 2.13-1.55 (4H, m, N-$(CH_2)_2$-(*CH_2*)2).
δC (50 MHz $CDCl_3$) 21.3, 26.5, 26.6, 59.5, 65.9, 67.1, 74.7, 126.4, 126.7, 128.1, 128.4, 128.6, 143.3.
MS(FAB)$[M+H]^+$ found 234.14985 $C_{14}H_{20}NO_2$ requires 234.141940.

Anal calcd. For $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found C, 72.22; H, 8.27; N, 5.93.

M. Pt, 182-184°C.

Attempted preparation of 2-(methoxydiphenylmethyl)-1-azabicyclo[2.2.2]octane-1-oxide (201)



Method 1

To a solution of (192) (0.50 g, 0.0016 mol) in THF at 0°C under a nitrogen atmosphere was added 1.5 equivalents of 60% sodium hydride (0.10 g, 0.0024 mol). The reaction mixture was stirred at 0°C for 1 hour followed by addition of 1.0 equivalent of iodomethane (0.33 g, 0.0016 mol). The reaction was allowed to warm to room temperature. A precipitate had formed which was removed by filtration and the solvent was removed under reduced pressure to yield a pale yellow solid.

Method 2

To a solution of (192) (0.50 g, 0.0016 mol) in THF at 0°C under a nitrogen atmosphere was added 1.5 equivalents of 60% sodium hydride (0.10 g, 0.0024mol). The reaction mixture was stirred at 0°C for 1 hour followed by addition of 2.0 equivalents of iodomethane (0.66 g, 0.0016mol). The reaction was stirred at 0°C then allowed to warm to room temperature. A precipitate had formed which was removed by filtration and the solvent was removed under reduced pressure to yield an pale yellow solid.

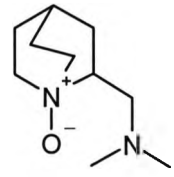
Method 3

To a solution of (193) (0.50 g, 0.0016 mol) in THF at 0°C under a nitrogen atmosphere was added 1.5 equivalents of 60% sodium hydride (0.10 g, 0.0024 mol). The reaction mixture was stirred at 0°C for 1 hour followed by addition of 1.0 equivalent of dimethylsulphate (0.20 g, 0.0016 mol). The reaction was allowed to room temperature. The solvent was removed at reduced pressure to yield a pale yellow solid.

Method 4

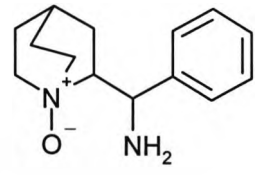
To a solution of quinuclidine *N*-oxide (0.50g, 0.004 mol) in dry THF (50ml) at -78°C was added 1.7M *tert*-butyllithium (2.5 ml, 0.0042 mol) followed by benzophenone (0.72 g, 0.0039 mol). After 15 minutes the reaction mixture was warmed to 0°C and 2 equivalents of iodomethane (0.50 ml, 0.008 mol) to room temperature. The precipitate which had formed was removed by filtration and the solvent was removed under reduced pressure. The residue was dissolved in methanol then adsorbed onto silica gel and purified by column chromatography to yield a yellow solid.

Preparation of Dimethyl-(1-oxy-1-azabicyclo[2.2.2]oct-2-ylmethylamine (203)



To a solution of quinuclidine N-oxide (0.47 g, 0.0032 mol) in dry THF (40 ml) at -78°C was added 1.7M *tert*-butyllithium (2.5 ml, 0.0042 mol) followed after 1 hour by Eschenmoser's salt (0.74 g, 0.004 mol). The reaction mixture was allowed to warm to room temperature. The white precipitate which formed was removed by filtration and then the solvent was removed under reduced pressure. The residue was dissolved in methanol then absorbed onto silica gel and column chromatography eluting with metanol/ethyl acetate (2:8) purified the compound. None of the desired material was formed.

Preparation of C-(1-oxy-1-azabicyclo[2.2.2]oct-2-yl)-C-phenylmethylamine (206)



To a solution of freshly distilled benzaldehyde (0.254 , 0.0024 mol) in THF (20 ml) was added 4.8 ml of LiHMDS (1M solution in THF) at 0°C under a nitrogen atmosphere. To a solution of QNO (0.30 g, 0.0024 mol) in THF (30 ml) at -78°C under a nitrogen atmosphere was added 1.7M *t*-BuLi (1.4 ml, 0.0024 mol) after 1 hour the reaction mixture was warmed to 0°C and added to the solution of (112). The

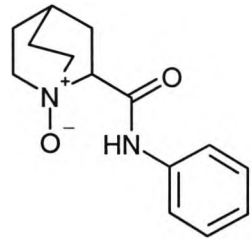
ice bath was removed and the mixture was stirred at room temperature for 4 hours. The solvent was removed under reduced pressure and the mixture was purified by column chromatography eluting with methanol/ethyl acetate (30:70) to give a brown solid in a yield of 33%.

δH (300 MHz $CDCl_3$) 7.64-7.01 (5H, m, aromatics), 3.89-3.83 (2H, m), 3.55-3.50 (1H, m) 3.39-3.34 (4H, m), 3.20-3.15 (5H, m)

δC (75 MHz $CDCl_3$) 23.2, 26.2, 29.7, 45.2, 46.5, 47.8, 60.4, 68.1, 126.7, 127.6, 128.9, 129.2, 132.3, 136.8.

Anal calcd. For $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found C, 46.67; H, 6.72; N, 6.81.

Preparation of 1-oxy-1-azabicyclo[2.2.2]octane-2-carboxylic acid phenylamide (211)



To a solution of quinuclidine *N*-oxide (1.0g, 7.9 mmol) in dry THF (80 ml) at -78°C was added 1.7M *tert*-butyllithium (5.1 ml, 8.7 mmol) followed after 1 hour by phenyl isocyanate (0.94g, 7.9 mmol). The reaction mixture was allowed to warm to room temperature and was quenched with 2M hydrochloric acid (4ml, 8 mmol). The solvent was removed at reduced pressure. The residue was dissolved in methanol then adsorbed onto silica gel and eluted with methanol/ethyl acetate (3:7). This yielded 0.97 g (50%) of the desired product (211).

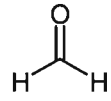
δH (300 MHz, $CDCl_3$) 13.29 (1H, s, NH), 7.64-7.60 (2H, m, Ar), 7.36-7.28 (2H, m, Ar), 7.10-7.06 (1H, m, Ar), 4.00-3.96 (1H, m) 3.86-3.64 (2H, m) 3.60-3.46 (2H, m), 3.43-3.24 (2H, m), 2.90-2.85 (1H, m) 2.10-1.88 (4H, m)

δC (75 MHz, $CDCl_3$) 19.8, 25.5, 26.4, 49.6, 59.2, 65.8, 70.1, 119.9, 123.8, 128.6, 137.8, 164.5

M Pt 180-182°C

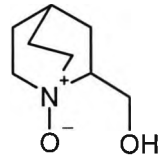
Anal calcd. For $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37;N, 11.37. Found C, 68.39; H, 7.45; N, 11.30.

Preparation of monomeric formaldehyde in ethereal solution.[218]



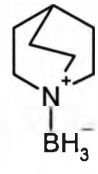
Paraformaldehyde (15g, 1.0mol) and *p*-toluenesulphonic acid (2.45g, 7.5mmol) were placed in a three necked flask and THF (500ml) was added. The mixture was heated to gentle reflux. The literature procedure followed stated the concentration was in the 0.6-0.8M range. It was assumed it was *circa* 0.5M concentration.

Preparation of (1-oxy-1-azabicyclo[2.2.2]oct-2-yl)-methanol (219)



To a solution of quinuclidine N-oxide (0.76g, 0.006 mol) in dry THF (90ml) at -78°C was added 1.7M *tert*-butyllithium (3.5ml, 0.006 mol) followed after 1 hour by monomeric formaldehyde (1.0ml, ~0.006 mol). The reaction mixture was allowed to warm to room temperature. The solvent was removed at reduced pressure. The solvent was removed at reduced pressure and the crude mixture was analysed by ^1H NMR. None of the desired material was present.

Preparation of quinuclidine *N*-borane complex (228)



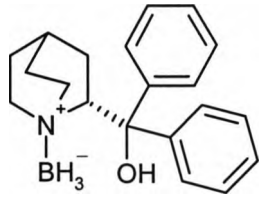
To a solution of quinuclidine (2.2g 0.02mol) in dry THF (30ml) at 0°C under a nitrogen atmosphere was added 1M borane-THF complex (20ml, 0.02mol). The reaction mixture was stirred for one hour. The solvent was removed under reduced pressure to give the desired product in a quantitative yield, 2.48 g, as a white solid.

δH (200 MHz $CDCl_3$) 3.03-2.98 (6H, m, N(*CH2*)3), 2.02-1.99 (1H, m, *CH*), 1.79-1.69 (6H, m, N-CH_2-*CH2*). 2.03-1.05 (3H, s (vbr), BH_3)
δC (75MHz, $CDCl_3$) 20.3 (1C, C-H), 25.3 (3C, β-CH_2), 53.6 (3C, α-CH_2).

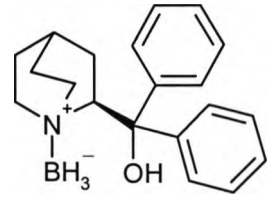
IR (KBr) 2979, 2962, 2934, 2356 (B-H), 2311 (B-H), 2268 (B-H), 1461, 1170, 1042

M. Pt, 140-142°C

Preparation of 1-azabicyclo[2.2.2]oct-2-yl-diphenylmethanol *N*-borane complexes (231 and 232)



(231)

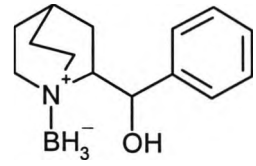


(232)

To a solution of quinuclidine borane complex (0.42g, 0.0034 mol) in anhydrous THF (30ml) was added 1.7 M *sec*-BuLi (2.0ml, 0.0034 mol) and (-)-sparteine at -78°C under a nitrogen atmosphere. After 1 hour 1 equivalent of benzophenone (0.62g, 0.0034 mol) and the mixture was stirred at -78°C for 15 minutes and then allowed to warm to room temperature. The solvent was removed at reduced pressure and purified by column chromatography eluting with ethyl acetate/petroleum ether (20:80) to give a white solid in a yield of 35%.
δH (300 MHz $CDCl_3$) 7.80-7.18 (10H, aromatic), 3.71-3.20 (6H, m), 2.15-2.10 (1H, m), 1.92-1.81 (6H, m). δC (75MHz $CDCl_3$) 20.3, 25.1, 63.6, 126.6, 127.6, 128.3, 128.5, 130.1, 132.4, 137.7.

M. Pt. 187-189°C

Preparation of 1-azabicyclo[2.2.2]oct-2-yl-phenylmethanol *N*-borane complex (233)



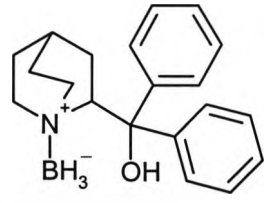
To a solution of quinuclidine borane complex (136) (0.42g, 3.4 mmol) in anhydrous THF (30 ml) was added 1.7 M *t*-BuLi (2.0ml, 3.4 mmol) at -78°C under a nitrogen atmosphere. After 1 hour 1 equivalent of benzaldehyde (0.35ml, 3.4 mmol) was added and the mixture was stirred at -78°C for 15 minutes and then allowed to warm to room temperature. The solvent was removed at reduced pressure and purified by column chromatography eluting with ethyl acetate/petroleum ether (20:80) to give a white solid in a yield of 298 mg, 38%.

M. Pt. 166-168°C

δH (200 MHz $CDCl_3$) 7.45-7.18 (5H, m, aromatics), 6.12 (1H, s, Ar-*CH*), 5.61 (1H, d, *J* 5, *H-C*(3)), 3.70-3.31 (4H, m, 2 x N-CH_2-CH_2), 2.77 (1H, m, *H-C* (4)), 2.20-1.40 (3H, vbr, B-H) 2.13-1.55 (4H, m, N-CH_2-CH_2)). δC (75MHz $CDCl_3$) 20.8, 25.2, 63.8, 126.6, 127.6, 128.5, 128.7, 130.1, 132.4.

IR (KBr) 2962, 2934, 2357 (B-H), 2311 (B-H), 2268 (B-H), 1464

Preparation of 1-azabicyclo[2.2.2]oct-2-yl-diphenylmethanol *N*-borane complex (234)



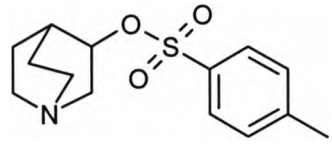
To a solution of quinuclidine borane complex (0.42g, 3.4 mmol) in anhydrous THF (30 ml) was added 1.7 M *t*-BuLi (2.0ml, 3.4 mmol) at -78°C under a nitrogen atmosphere. After 1 hour 1 equivalent of benzophenone (0.62g, 3.4 mol) and the mixture was stirred at -78°C for 15 minutes and then allowed to warm to room temperature. The solvent was removed at reduced pressure and purified by column

chromatography eluting with ethyl acetate/petroleum ether (20:80) to give a white solid in a yield of 366 mg, 35%.
δH (300 MHz $CDCl_3$) 7.80-7.18 (10H, aromatic), 3.71-3.20 (6H, m), 2.15-2.10 (1H, m), 1.92-1.81 (6H, m). δC (75MHz $CDCl_3$) 20.3, 25.1, 63.6, 126.6, 127.6, 128.3, 128.5, 130.1, 132.4, 137.7.

IR (KBr) 2962, 2934, 2357 (B-H), 2311 (B-H), 2268 (B-H), 1464

M. Pt. 187-189°C

Preparation of 3-oxytosyl quinuclidine (252).



To a solution of quinuclidinol (0.50 g, 3.5 mmol.) in dry THF (50 ml) was added at 0°C toluene sulphonyl chloride (1.00 g, 5 mmol.) followed by TEA (0.75 ml, 5 mmol.). The mixture was allowed to warm to room temperature and was stirred for 16 hours. The solvent was removed *in vacuo and* the mixture was purified by flash chromatography on silica gel (70% MeOH/30% EtOAc (R_f 0.22)) to give a white solid a yield of 748 mg, 76%

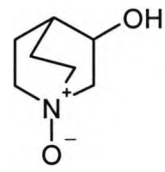
IR(nujol mull, cm^{-1}) 1190 (-SO_2-), 1095 (-SO_2-).

δH (300 MHz $CDCl_3$) 7.81-7.34 (4H, m, aromatics), 4.69 (1H, m, -CH_2-*CH*-OTs), 3.11 (1H, m, CH-*CH*-(CH_2)2), 2.90-2,55 (6H, m, N-(*CH_2*)3) , 2.45 (3H, s, *CH_3*-Ph), 2.00-1.30 (4H,m, N-(CH_2)2-(*CH_2*)*2*.). δC (75 MHz $CDCl_3$): 17.1, 21.3, 21.7, 25.5, 45.4, 46.5, 53.3, 74.1, 127.7, 130.3.

MS(CI) found 281.10857. $C_{14}H_{19}NO_3S$ requires 281. 10855.

M. Pt. 166-168°C
Anal calcd. for $C_{14}H_{19}NO_3S$: C, 59.76; H, 6.81; N, 4.98. Found C, 59.42; H, 6.77; N, 4.93.

Preparation of 1-oxy-1-azabicyclo[2.2.2]-octane-3-ol (256)

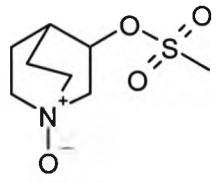


To a solution of 3-hydroxyquinuclidine (2.0 g, 0.016 mol) in DCM (50ml) at -78°C was added *m*-CPBA (3.40 g, 0.018 mol). The reaction was stirred under a nitrogen atmosphere for 2 hours before being allowed to warm to room temperature. The crude mixture was purified by column chromatography eluting with methanol/ethyl acetate (30:70) to give the desired product (256) as a waxy solid in a yield of 1.21 g, 53%.

δH (300 MHz $CDCl_3$) 4.35-4.26 (1H, m), 3.70-3.10 (6H, m), 2.57-2.47 (1H, m), 2.11-1.68 (4H, m) δC (200 MHz $CDCl_3$) 20.5, 23.3, 27.1, 61.9, 62.9, 66.0, 72.7

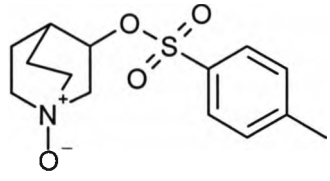
M. Pt. 86-90°C

Preparation of methanesulfonic acid 1-oxy-1-azabicyclo[2.2.2]-oct-3-yl ester (257)



To a solution of 1-oxy-1-azabicyclo[2.2.2]-octane-3-ol (**256**) (1.00 g, 0.007 mol) in DCM at 0°C was added sequentially mesyl chloride (1.40 g, 0.007 mol) and triethylamine under a nitrogen atmosphere. The ice bath was removed and the reaction mixture was allowed to warm to ambient temperature and stirred for 4 hours. The reaction mixture was filtered and the solvent removed at reduced pressure to yield a white solid. Analysis by NMR showed only starting material was present.

Preparation of 3-oxytosyl quinuclidine *N*-oxide (258).



Method 1

To a solution of 1-oxy-1-azabicyclo[2.2.2]-octane-3-ol (**256**) (1.00 g, 0.007 mol) in DCM at 0°C was added sequentially *p*-toluene sulphonyl chloride (1.40 g, 0.007 mol) and triethylamine under a nitrogen atmosphere. The ice bath was removed and the reaction mixture was allowed to warm to ambient temperature and stirred for 4 hours. The reaction mixture was filtered and the solvent removed at reduced pressure to yield a yellow solid. A ^{1}H NMR revealed that none of the desired material had been formed, it showed only TEA.HCl.

Method 2

To a solution of 3-oxytosyl quinuclidine (0.50 g, 0.0018 mol) in DCM (50 ml) stirred at -78°C (CO_2/acetone) was added *m*-CPBA (0.33 g, 0.0018 mol). The reaction mixture was stirred for one hour then allowed to warm to room temperature. After five hours the solvent was removed at reduced pressure and the mixture purified by

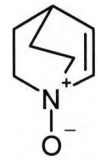
flash chromatography on silica gel eluting with 30% MeOH/70% EtOAc to give an off white solid in a yield of, 466 mg, 87 %.(R_f 0.22).

IR(nujol mull, cm^{-1}) 1190 (-SO_2-), 1095 (-SO_2-).

δH (300 MHz $CDCl_3$) 7.82-7.37 (4H, m, aromatics), 4.93-4.87 (1H, m, -CH_2-*CH*-OTs), 3.62-3.50 (1H, m, CH-*CH*-(CH_2)2), 3.40-3.20 (6H, m, N-(*CH_2*)3) , 2.47 (3H, s, *CH_3*-Ph), 2.18-1.84 (4H,m, N-(CH_2)2-(*CH_2*)2). δC (75 MHz $CDCl_3$): 130.3, 127.6, 76.8, 75.6, 69.1, 63.0, 62.0, 25.5, 22.7, 21.5, 20.5.
MS(CI) $[M+H]^+$ @ m/z 298.11065, $C_{14}H_{19}NO_4S$ requires 298.11131 .
Anal calcd. For $C_{14}H_{18}NO_4S$: C, 56.55; H, 6.44;N, 4.71. Found C, 56.50; H, 6.41; N, 4.65.

M. Pt. 184-186°C

Preparation of 1-azabicyclo[2.2.2]oct-2-ene *N*-oxide (248).

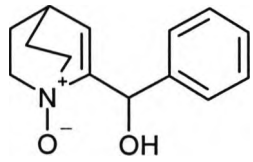


To a solution of 3-oxytosyl quinuclidine *N*-oxide (**258**) (200 mg, 0.67 mmol) in dry THF (50 ml) stirred at -78°C (CO_2/acetone) was added potassium *tert*-butoxide (1.5 eq.). The reaction mixture was allowed to warm to room temperature and was stirred for 16 hours. The resulting mixture was filtered and the solvent was removed at reduced pressure and the mixture purified by flash chromatography over silica gel eluting with methanol/ethyl acetate (30:70) (R_f 0.17) to give a white solid in a yield of 44 mg, 52%.

δH (300 MHz, $CDCl_3$) 6.71(1H, d, *J* 6, N-*CH*=CH), 6.48 (1H, t, *J* 6, CH=*CH*-CH) 3.56 (2H, m, N-*CH_2*), 3.30(2H, m, N-*CH_2*), 2.85 (1H, CH=*CH*), 1.99 (2H, m, N-CH_2-*CH_2*), 1.83 (2H, m, N-*CH_2*). δC (75 MHz, $CDCl_3$) 151 (N-*CH*=CH), 134 (N-CH=*CH*), 70 (N-(*C*H_2)2), 31 (N-(CH_2)2-(*C*H_2)2).

MS(CI) $[M+H]^+$ $C_7H_{12}NO$ requires 126.09189. Found 126.09167,

Preparation of (1-azabicylclo[2.2.2]oct-2-en-2-yl)-phenylmethanol *N*-oxide (260).



To a solution of enamine *N*-oxide (**248**) (0.25g, 0.002 mol) in dry THF (30ml) at -78°C was added 1.7M *tert*-butyllithium (1.2ml, 0.002 mol), the mixture was placed in an ice bath for 1 hour then cooled again to -78°C followed by addition of benzaldehyde (0.210ml, 0.0022 mol). The reaction mixture was warmed to room temperature over a period of three hours and then 10 %AcOH (1 ml) was added. The solvent was removed *in vacuo* and the reaction mixture was purified by flash chromatography on silica gel eluting with 30%MeOH / EtOAC to give the desired product as a white solid in a yield of 360 mg, 78% (R_f 0.30).

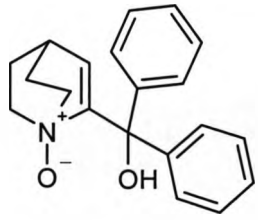
δH (300 MHz $CDCl_3$) 7.29-7.40 (5H, m, aromatics), 5.76 (1H, s Ar-*CH*), 5.66 (1H, d*J* 5, *H-C* (3)), 3.70-3.31 (4H, m, 2 x N-*CH_2*-CH_2, 2.77 (1H, m, H-*C* (4)), 2.13-1.55 (4H, m, 2 N-CH_2-(*CH_2*). δC (75 MHz $CDCl_3$) 25.9, 26.2, 26.3, 66.1, 67.3, 126.0, 127.4, 127.9, 128.3, 138.8, 154.9.

MS (FAB) $[M+H]^+$ $C_{14}H_{18}NO_2$ requires 232.13375. Found 232.13362

Anal.calcd. For $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found C, 72.82; H, 7.38; N, 6.01.

M. Pt. 155-158°C

Preparation of (1-azabicylclo[2.2.2]oct-2-en-2-yl)-diphenylmethanol *N*-oxide (261)



To a solution of enamine *N*-oxide (**248**) (0.30 g, 2.4 mmol) in dry THF (60 ml) at –78°C was added 1.7M *tert*-butyllithium (1.6 ml, 2.7 mmol), the mixture was placed in an ice bath for 1 hour then cooled again to -78°C followed by addition of

benzophenone (0.44 g, 2.4 mmol). The reaction mixture was warmed to room temperature over a period of three hours and then 10 %AcOH (1 ml) was added. The solvent was removed under reduced pressure and the reaction mixture was purified by flash chromatography on silica gel eluting with 30%MeOH / EtOAC to give the desired product as a white solid in a yield of 443 mg, 60% (R_f 0.32).

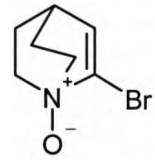
δH (300 MHz $CDCl_3$) 7.41-7.23 (10H, m, aromatics), 5.77 (1H, d =*CH* , *J* 4) 3.81-3.72 (2H, m N-*CH*$_2$-), 3.49-3.40 (2H, m N-*CH*$_2$-), 2.82 (1H, m ,*H-C*(4)), 2.03-1.97 (2H, m, N-(CH_2)-(*CH*$_2$)), 1.86-1.80 (2H, m, N-(CH_2)-(*CH*$_2$))., δC (75 MHz $CDCl_3$): 25.8, 26.6, 66.9, 81.1, 127.3 127.4, 128.0, 128.5, 143.9

MS(FAB) $[M+H]^+$ $C_{20}H_{22}NO_2$ requires 308.16505. Found 308.16496

Anal calcd. For $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.55. Found C, 78.10; H, 6.74; N, 4.53.

M. Pt. 172-174°C

Preparation of 2-bromo-1-azabicyclo[2.2.2]oct-2-ene *N*-oxide (262).



Method 1

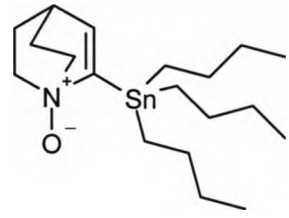
To a solution of enamine *N*-oxide (**248**) (0.25 g, 2 mmol) in dry THF (30 ml) at -78°C was added 1.7M *tert*-butyllithium (1.2 ml, 2 mmol), the mixture was placed in an ice bath for 1 hour then cooled again to -78°C followed by addition of *N*-bromo succinimide (0.400 g, 2.2 mmol). The reaction mixture was warmed to room temperature over a period of three hours, then the solvent was then removed *in vacuo* and the reaction mixture was purified by flash chromatography over silica gel eluting with 30% MeOH /70% EtOAC to give the desired product.(R_f 0.36). δH (200 MHz $CDCl_3$) 7.09 (1H, d, *H-C*(3)), 4.33 (2H, m N-*(CH*$_2$*)*$_2$-CH_2) , 3.63 (2H, m N-*(CH*$_2$*)*$_2$-CH_2) 3.17 (1H, m ,*H-C*(4)), 2.35 (2H, m, N-(CH_2)$_2$-*(CH*$_2$ *)*$_2$)) ,2.03 (2H, m, N-(CH_2)$_2$-(*CH*$_2$)$_2$))

MS(FAB) $[M+H]^+$ $C_7H_{11}NOBr$ requires 204.00240 found 204.00194

Method 2

To a solution of enamine *N*-oxide (**248**) (0.25 g, 2 mmol) in dry THF (30 ml) at -78°C was added *tert*-butyllithium (1.2 ml, 2 mmol), the mixture was placed in an ice bath for 1 hour then cooled again to -78°C followed by addition of bromine (0.13 g, 2.2 mmol). The reaction mixture was warmed to room temperature over a period of three hours, then the solvent was removed *in vacuo* and the reaction mixture was purified by flash chromatography over silica gel eluting with MeOH/EtOAC (3:7) to give the desired product in a yield of 302 mg, 74% (R_f 0.36).

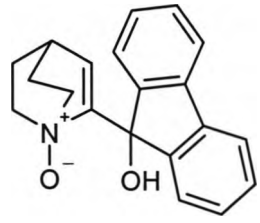
Preparation of 2-Tributylstannyl-1-azabicyclo[2.2.2]oct-2-ene *N*-oxide (263)



To a solution of enamine *N*-oxide (**248**) (0.15 g, 1.2 mmol) in dry THF (50 ml) at -78°C was added 1.7M *tert*-butyllithium (1.0 ml, 1.7 mmol), the mixture was placed in an ice bath for 30 minutes then cooled again to –78°C followed by addition of *n*-tributyltin chloride (0.36 ml, 1.3 mol). The reaction mixture was stirred at -78°C for 90 minutes then warmed to room temperature and stirred overnight. The solvent was removed at reduced pressure to give an off white solid in a yield of 373 mg, 75%.

δH (200 MHz $CDCl_3$): 6.56 (1H, d, *J* 8), 4.92-4.58 (2 H, m), 4.34-4.06 (2H, m), 2.87-2.71 (1H, m)2.19-1.96 (2H, m), 1.85-1.68 (2H, m), 1.58-1.025 (12H, m), 0.93-0.81 (15H, m)

Preparation of 9-(1-oxy-1-azabicyclo[2.2.2]oct-2-en-yl)-9H-fluoren-9-ol (264)



To a solution of enamine *N*-oxide (**248**) (0.30 g, 2.4 mmol) in dry THF (30 ml) at -78°C was added 1.7M *tert*-butyllithium (1.6 ml, 2.7 mmol), the mixture was placed in an ice bath for 1 hour then cooled again to -78°C followed by addition of fluorenone (0.47 g, 2.6 mmol). The reaction mixture was warmed to room temperature over a period of three hours and then 10 %AcOH (1.4 ml) was added. The solvent was removed *in vacuo* and the reaction mixture was purified by flash chromatography on silica gel eluting with 30% MeOH / EtOAC to give the desired product in a yield of 623 mg, 85% (R_f 0.26).

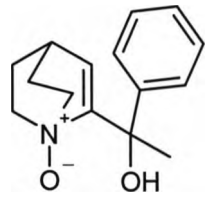
δH (300 MHz $CDCl_3$) 8.01-7.29 (8H, m, aromatics), 5.81 (1H, d, =*CH*, *J* 4) 4.11-3.92 (2H, m, N-*CH*$_2$-), 3.61-3.46 (2H, m, N-*CH*$_2$-), 2.62 (1H, m, H-*C*(4)), 2.13-1.85 (2H, m, N-(CH$_2$)-(*CH*$_2$)), 1.80-1.67 (2H, m, N-(CH$_2$)-(*CH*$_2$))., δC (75 MHz $CDCl_3$): 25.8, 26.0, 26.6, 67.1, 68.0, 120.1, 126.3, 128.2, 128.3, 139.9, 147.4

MS(FAB). $C_{20}H_{20}NO_2$ requires: 306.14940. Found: 306.14916

Anal calcd. For $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.57. Found C, 78.20; H, 6.36; N, 4.49.

M. Pt. 166-168°C

Preparation of 1-(1-oxy-1-azabicyclo[2.2.2]oct-2-en-2-yl)-1-phenylethanol (265)

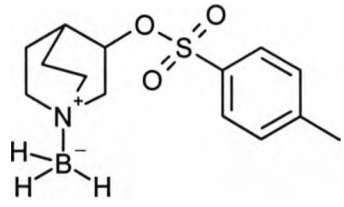


To a solution of enamine *N*-oxide (**248**) (0.30 g, 2.4 mmol) in dry THF (60 ml) at -78°C was added *tert*-butyllithium(1.7 ml, 2.7 mmol), the mixture was placed in an ice bath for 1 hour then cooled again to -78°C followed by addition of acetophenone (0.30 ml, 2.6 mmol). The reaction mixture was warmed to room temperature over a period of three hours and then 10 %AcOH (1.4 ml) was added. The solvent was removed *in vacuo* and the reaction mixture was purified by flash chromatography over silica gel eluting with MeOH / EtOAC (3:7) to give the desired product as an oil in a yield of 118 mg, 20% (R_f 0.20).

δH(300 MHz $CDCl_3$) 7.47-7.13 (5H, m, aromatics), 6.49 (1H, d, =*CH* , *J* 4) 3.98-3.82 (2H, m, N-*CH_2*-), 3.78-3.65 (2H, m N-*CH_2*-), 3.60-3.45 (1H, m ,*H-C*(4)), 3.03-2.91 (2H, m, N-(CH_2)-(*CH_2*)), 2.06-1.78 (2H, m, N-(CH_2)-(*CH_2*)), 1.64 (3H, s, Ph(C)*CH_3*), δC(75 MHz $CDCl_3$): 21.6, 26.8, 67.2, 81.7, 127.3, 127.4, 128.6, 143.9.

MS(FAB) $[M+H]^+$ $C_{15}H_{20}NO_2$ requires 246.14940. Found 246.14983.
Anal. calcd. For $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81;N, 5.71. Found C, 72.96; H, 7.77; N, 5.47.

Preparation of 3-tosyloxy-*N*-borane quinuclidine complex (268)



To a solution of 3-tosyloxy quinuclidine (5.0g, 17.7 mmol) was in THF (100 ml) was added 18ml of 1M borane THF complex (18 mmol) at 0°C under a nitrogen atmosphere. The ice bath was removed and the reaction mixture allowed to warm to room temperature. After 30 minutes the reaction had gone to completion by tlc. The solvent removed under vacuum and the solid was dissolved in DCM and preadsorbed

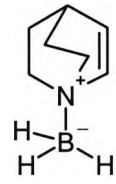
onto silica gel. The mixture was purified on silica gel eluting with ethyl acetate to give a white solid in a yield 5.22 g, 99%.

IR (Nujol) 2921, 2853, 2368 (B-H), 2319 (B-H), 2275 (B-H)

δH (300 MHz $CDCl_3$) 7.80-7.35 (4H, m, aromatics), 4.68 (1H, m, N-CH_2-*CH*-OTs), 3.62-3.50 (1H, m, CH-*CH*-$(CH_2)_2$), 3.40-3.20 (6H, m, N-$(CH_2)_3$) , 2.46 (3H, s, CH_3-Ph), 2.18-1.84 (4H,m, 2 x N-CH_2-CH_2), 1.10-1.85 (3H, s, vbr, BH_3) , δC (75 MHz $CDCl_3$): 130.30, 127.63, 75.65, 59.81, 53.40, 52.34, 25.89, 22.68, 21.69, 18.55.

Anal. calcd. for $C_{14}H_{22}BNO_3S$: C, 56.96; H, 7.51; N, 4.74. Found C, 56.88; H, 7.55; N, 4.71.

Preparation of 1-azabicyclo[2.2.2]oct-2-ene *N*-borane complex (267)



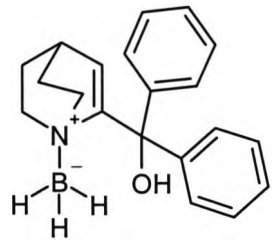
To a solution of 3-tosyloxy-*N*-borane quinuclidine complex (**268**) (1.27 g, 4.3 mmol) in THF (60 ml) at 0°C was added 2 equivalents of potassium *tert*-butoxide (1.01 g 8.6 mmol) under a nitrogen atmosphere. The ice bath was removed and the reaction mixture was allowed to warm to room temperature. The reaction was monitored by tlc and after two hours more KO^tBu was added and the mixture was heated to reflux. After 1 hour the reaction had gone to completion by tlc. The reaction mixture was filtered and the solid was washed with fresh THF. The filtrate was reduced in volume to dryness to yield the azabicyclo[2.2.2]oct-2-ene *N*-borane complex (**267**) as a white solid in a yield of 278 mg, 52%.

IR (Nujol) 2995, 2924, 2370 (B-H), 2319 (B-H), 2275 (B-H)

δH (400 MHz $CDCl_3$) 6.52(1H, t, *J* 8, N-CH=*CH*), 6.39 (1H, d, *J* 8, N-*CH*=CH)) 3.17(2H, m, N-CH_2), 2.82(2H, m, N-CH_2), 2.85 (1H, CH=*CH*-$(CH_2)_2$), 1.84 (2H, m, N-CH_2-CH_2), (2H, m, N-CH_2), 2.12 - 1.70 (3H, s (vbr), BH_3).
δC (100 MHz, $CDCl_3$) 140.5 (N-*C*H=CH), 133.5 (N-CH=*C*H), 57.3 (N-$(CH_2)_2$-$(CH_2)_2$), 27.3 (N-$(CH_2)_2$-$(CH_2)_2$, 26.2 (*C*H)

Anal calcd. For $C_7H_{14}BN$: C, 68.35; H, 11.47; N, 11.39. Found C, 68.38; H, 11.46; N, 11.35.

Preparation of 1-azabicyclo[2.2.2]oct-2-en-yl-diphenylmethanol *N*-borane complex (270)



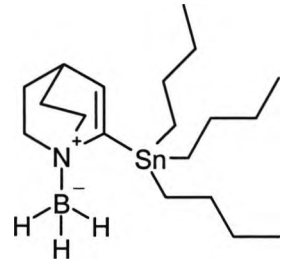
To a solution of enamine *N*-borane complex (**267**) (0.25g, 2 mmol) in dry THF (30 ml) at -78°C was added 1.7M *tert*-butyllithium (1.2 ml, 2 mmol), the mixture was warmed to 0°C for 1 hour then cooled again to -78°C followed by addition of 1 equivalent of benzophenone (0.36 g, 2 mmol). The reaction mixture was stirred at -78°C for 15 minutes before being warmed to room temperature. After 1 hour the solvent was removed at reduced pressure to give an off white solid. The crude material was purified by silica gel chromatography giving 1-azabicyclo[2.2.2]oct-2-en-yl-diphenylmethanol *N*-borane complex (**270**) as a white solid in a yield of 494 mg, 81%.

IR (Nujol neat, cm^{-1}), 2374 (B-H), 2319 (B-H), 2775 (B-H),

δH (200 MHz, $CDCl_3$): 7.43-7.22 (10H, m, aromatics), 5.77 (1H, d, C=*CH*, *J* 6), 3.41-3.32 (2H, m N-*CH*$_2$-), 3.19-3.10 (2H, m N-*CH*$_2$-), 2.74 (1H, m , *H*-*C*(4)), 1.93-1.86 (2H, m, N-(CH_2)-(*CH*$_2$)), 1.84-1.72 (2H, m, N-(CH_2)-(*CH*$_2$)). δC (75 MHz $CDCl_3$): 148.7, 145.5, 129.1, 128.5, 127.9, 127.6, 82.5, 66.8, 26.7, 26.1

M. Pt. 134-138°C

Preparation of 2-tributylstannyl-1-azabicyclo[2.2.2]oct-2-ene *N*-borane complex (271)

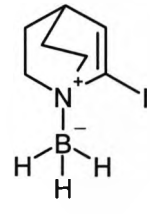


To a solution of eneamine *N*-borane complex (**267**) (0.25 g, 2 mmol) in dry THF (30 ml) at -78°C was added 1.7M *tert*-butyllithium (1.2 ml, 2 mmol), the mixture was warmed to 0°C for 1 hour then cooled again to -78°C followed by addition of 1 equivalent of *n*-tributyltin chloride (0.36 g, 2 mmol). The reaction mixture was stirred at -78°C for 15 minutes before being warmed to room temperature. After 1 hour the solvent was removed at reduced pressure to give an off white solid. The crude material was purified by silica gel chromatography giving 2-tributylstannyl-1-azabicyclo[2.2.2]oct-2-ene *N*-borane complex (**271**) as an oil in a yield of 461 mg, 56%.

IR (Nujol neat, cm^{-1}), 2995, 2924, 2871, 2852, 2374 (B-H), 2319 (B-H), 2775 (B-H), 1458, 1169

δH (400 MHz, $CDCl_3$): 6.66 (1H, d, *J* 8), 3.21-3.12 (2 H, m), 2.77-2.65 (3H, m), 1.82-1.73 (2H, m) 1.69-1.46 (10H, m), 1.39-1.26 (8H, m), 1.05-1.00 (4H, m), 0.93-0.85 (12H, m). δC (100 MHz, $CDCl_3$): 160.0, 145.3, 55.8, 30.8, 29.4, 29.1, 28.9, 27.3, 26.8, 13.7, 12.3

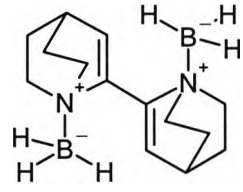
Preparation of 2-iodo-1-azabicyclo[2.2.2]oct-2-ene *N*-borane complex (272)



To a solution of eneamine *N*-borane complex (267) (0.25g, 2 mmol) in dry THF (30 ml) at -78°C was added 1.7M *tert*-butyllithium (1.2 ml, 2 mmol), the mixture was warmed to 0°C for 1 hour then cooled again to -78°C followed by addition of 1 equivalent of iodine (0.51 g, 2 mmol). The reaction mixture was stirred at -78°C for 15 minutes before being warmed to room temperature. After 1 hour the solvent was removed at reduced pressure to give an off white solid. The crude material was purified by silica gel chromatography giving 2-iodo-1-azabicyclo[2.2.2]oct-2-ene *N*-borane complex (**272**) as an orange oil in a yield of 428 mg, 86%.

IR (Nujol neat, cm^{-1}), 2934, 2874, 2853, 2374 (B-H), 2317 (B-H), 2774 (B-H)
δH (200 MHz, $CDCl_3$): 6.89 (1H, d, *J* 5), 3.15-2.77 (4H, vbr, m), 2.60-2.55 (1H, m, C4H), 1.92-1.56 (4H, m) 2.20-1.40 (3H, vbr, B-H)
δC (100 MHz, $CDCl_3$): 146.8, 145.9, 58.3, 57.0, 48.9, 31.0, 28.5, 26.3

Attempted dimerisation of 1-azabicyclo[2.2.2]oct-2-ene *N*-borane complex (274)



Method 1

The enamine borane complex (267) (0.28 g 2.3 mmol) was dissolve in THF under a nitrogen atmosphere at -78°C to which was added 1.7M *t*-BuLi (1.5ml, 2.5 mmol). After one hour two equivalents of trimethyl borate (0.52 ml, 4.6 mmol) was added dropwise to form the boronic ester species (273).The boronic ester (273) was not isolated and was used directly in the next step. The boronic ester (273) was dissolved in dry toluene (15 ml) and had 2M sodium carbonate (4 ml) added to it followed by 5 mol% palladium acetate ($Pd(OAc)_2$) (25 mg, 0.1 mmol). The iodo species (272) (0.49 g, 2 mmol) was dissolved in toluene (5 ml) was added to the reaction mixture followed by triphenylphosphine (50 mg, 0.2 mmol) and the solution was heated under reflux for 18 hours. After an aqueous work up washing with water (30ml), 10% aqueous copper sulphate (30 ml) and brine (30 ml) the solvent was dried over

magnesium sulphate and filtered. The solvent was removed at reduced pressure to give a yellow/brown solid.

Method 2

Preparation of solution A

To a solution of azabicyclo[2.2.2]oct-2-ene *N*-borane complex (0.5 g, 4.1 mmol) in THF (20 ml) at -78°C was added 1.7M ^{t}BuLi (2.4ml, 4.1 mmol) under a nitrogen atmosphere. The solution was stirred at -78°C then allowed to warm to 0°C.

Preparation of solution B

A suspension of palladium dichloride(*bis*-acetonitrile) (0.08 g, 0.31 mmol) and copper(II)chloride (0.55g, 4.1 mmol) was stirred in THF (30 ml) at 0°C under a nitrogen atmosphere.

Solution B was added by cannula to solution A and the reaction was stirred at 0°C for 6 hours. The crude reaction mixture was filtered through celite, the filtrate collected and the solvent was removed under reduced pressure. The mixture was purified by column chromatography eluting with petroleum ether (40-60). This gave an off white solid in a yield of 34%.

δH(400 MHz $CDCl_3$) 6.67(2H, dd, N-CH=*CH*), 3.27-3.21(4H, m, N-*CH_2*), 2.99-2.91(4H, m, N-*CH_2*), 2.85-2.75 (2H, m, C=*CH*-$(CH_2)_2$), 1.92-1.88 (2H, m, N-CH_2-*CH_2*), 2.20-0.97 (3H, *vbr*, *B-H*), 1.70-1.64 (2H, m, N-*CH_2*), 1.70 (1H, s, *B-H*)., δC(100 MHz CDCl3) 137.0 (N-*C*H=CH), 134.2 (N-CH=*C*H), 54.1 (N-(*CH_2*)2), 26.3 (N-$(CH_2)_2$-(*CH_2*)2). 26.2 (CH)

Bibliography

1. A.Pinner and R. Wolffenstein, *Ber. Der. Dtsch. Chem. Ges.*, 1892, **25**, 1428.
2. C. C. Culvenor, *Review of Pure and Applied Chemistry*. 1953, **3**, 83.
3. J. S. Roberts, *Comprehensive Organic Chemistry, Pergamon, New York*, 1979, **2**, 185.
4. A. Albini, *Heterocycles*, 1992, **34,** 1973.
5. A. Albini, *Synlett,,* 1993, 263.
6. Dunstan and Goulding, *J. Chem. Soc.*, 1899, 794.
7. A. Hanztch and W. Hiland, *Ber. Der. Dtsch. Chem. Ges.*, 1898, **31**, 2058.
8. J. Meisenheimer, *Ber. Der. Dtsch. Chem. Ges.*, 1919, **52**, 1667.
9. M. Polonovski and M. Polonovski, *Bull. Chim. Soc. Fr.*, 1927, **41**, 1190.
10. J. A. Lovern, *Chem. Ind.*, 1952, 948
11. G. Clemo and H. McIlwain, *J. Chem. Soc.*, 1938, 479.
12. E. C. White and J. H. Hill, *J. Bacteriol.*, 1943, 433.
13. J.A. Sonderquist and C. L. Anderson, *Tetrahedron Lett.*, 1986, **27**, 3961.
14. R. Koster and R. Morita, *Leibigs. Ann. Chem.*, 1967, **704**, 70.
15. P. Nylon, *Cham. Abstr.*, 1938, **32**, 8888.
16. I. Z. Siemon, K. Marks and A. Sucharada-Sobczyk, *Buletin of the Polish Academy of Sciences*, 1983, **31**, 1.
17. I. A. O'Neil, N. D. Miller, J.Peake, J. V. Berkley, C. M. R. Low and S. B. Kalindjian, *Synlett*, 1993, 515.
18. I. A. O'Neil, N. D. Miller, J. V. Berkley, C. M. R. Low and S. B. Kalindjian, *Synlett*, 1993, 617 and 619.
19. W.M. Lister and L. E. Sutton, *Faraday. Soc.*, 1939, **35**, 495.
20. R. T. Lalonde, E. Auer, C. F. Wong and V. P. Muralidharan, *J. Am. Chem. Soc.*, 1971, **93**, 2501.
21. W.H. Pirkle, R.L. Muntz and I. C. Paul, *J. Am. Chem. Soc.*, 1971, **93**, 2817.
22. A. Pajunen and M. Nasakkala, *Acta. Cryst, B*, 1980, **B36**, 1650.
23. E. Maia, A. Peguy and S. Perez, *Acta. Cryst, B*, 1981, **B37**, 1858.
24. E. Maia and S. Perez, *Acta. Cryst, B*, 1982, **B38**, 849.
25. H. Chanzy, E. Maia and S. Perez, *Acta. Cryst, B*, 1982, **B38**. 852.
26. P. O. Nubel, S. R. Wilson and T. L. Brown, *Organometallics*, 1983, **2**, 515.
27. E. Maia, A. Peggy and S. Perez, *Can. J. Chem.*, 1984, **62**, 6.

28. M. W. Berdenkemp, A. Wiechers and P. H. van Rooyen, *Tetrahedron Lett.*, 1985, **26**, 929.
29. R. B. Brown. Jr., M. M. Wiliamson and C. L. Hill, *Inorg. Chem.*, 1987, **26**, 1602.
30. E. Ciganek, *J. Org. Chem.*, 1990, **55**, 3007.
31. S. Kida and T. Oniki, *Bull. Chem. Soc. Japan*, 1972, **45**, 1078.
32. K. Alshaikh-Kadir and P. F. Holt, *Makromol. Chem.*, 1977, **178**, 329.
33. T. Y. Luh, *Coord. Chem. Rev.*, 1984, **60**, 255.
34. C. L. Hill and M. M. Williamson, *Inorg. Chem.*, 1985, **24**, 3024.
35. U. Bohner and G. Zundel, *J. Phys. Chem.*, 1986, **90**, 964.
36. S. Oh, A. Rabold and G. Zundel, *J. Chem. Soc. Faraday. Trans.*, 1993, **89**, 1733.
37. B. Brezenski and G. Zundel, *Chem. Phys. Letts.*, 1980, **75**, 500.
38. B. Brezenski and G. Zundel, *Can. J. Chem.*, 1981, **59**, 786.
39. B. Brezenski and G. Zundel, *J. Phys.Chem.*, 1982, **86**, 5133.
40. B. Brezenski B. BrychiG. Zundel and T. Kiel, *J. Phys.Chem.*, 1991, **95**, 8598.
41. T, Keil, B. Brezenski and G. Zundel, *J. Phys.Chem.*, 1992, **96**, 4421.
42. J. Meisenheimer, *Liebigs. Ann. Chem.*, 1926, **449**, 188.
43. A. C. Cope, C. L. Gardener and E. E. Schweizer, *J. Am. Chem. Soc.*, 1957, **79**, 4729.
44. K. Long, *diss Abstr. Int. B.*, 1971, **31**, 3926.
45. M. Moriwaki, Y. Yamamoto, J. Oda and Y. Inouye, *J. Org. Chem.*, 1976, **41**, 300.
46. Y. Shvo and E. Kaufman, *J. Org. Chem.*, 1982, **46**, 2148.
47. T. Kurihara, Y. Sakamoto, M. Takai, K. Ohuchi, S. Harusawa and R. Yoneda, *Chem. Pharm. Bull.*, 1993, **41**, 1221.
48. A. A. Oswald and D. L. Guertin, *J. Org. Chem.*, 1963, **28**, 65.
49. J. C. Craig and K. K. Purushothaman, *J. Org. Chem.*, 1970, **35**, 1721.
50. S. Miyano, L. Lu, S. Viti and K. B. Sharpless, *J. Org. Chem.*, 1985, **50**, 4350.
51. L. Kuhnen, *Chem. Ber.*, 1966, **99**, 3384.
52. W. W. Zajac, T. R. Walters and M. G. Darcy, *J. Org. Chem.*, 1988, **53**, 5856.
53. D. P. Riley, *J. Chem. Soc. Chem. Commun.*, 1983, 1530.
54. D. P. Riley and P. E. Correa, *J. Org. Chem.*, 1985, **50**, 1563.

55. P. S. Bailey, *Ozonation in Organic Chemistry, Academic Press, New York*, 1982, **vol II**, 156.

56. N Kobayashi and K. Iwai, *J. Polymer. Science, Polymer. Letts. Ed.*, 1982, **20**, 85.

57. M. Poje and K. Balenovic, *Chem. Abstr.*, 1975, **83**, 4358u.

58. P. W. N. Christian, R. Gil, K. Muniz-Fernandez, S. E. Thomas and A. T. Wierzchleyski, *J. Chem. Soc. Chem. Commun.*, 1994, 1569.

59. I. A. O'Neil, C.D. Turner and J. C. Woolley, unpublished results.

60. H. Heaney, *Aldrichimica. Acta.*, 1993, **26**, 35.

61. T. Balasubramanian and K. K. Balasubramanian, *J. Chem. Soc. Chem. Commun.*, 1994, 1237.

62. L. W. Jones and R. T. Jones, *J. Am. Chem. Soc.*, 1928, **50**, 2742.

63. A. C. Cope and N. A. LeBel, *J. Am. Chem. Soc.*, 1960, **82**, 4656.

64. R. G. Laughlin, *J. Am. Chem. Soc.*, 1973, **95**, 3295.

65. T. Yoshimura, K. asada and S. Oae, *Bull. chem. Soc, Japan.*, 1982, **55**, 3000.

66. Y. Langolis, L. Konopski, N. Van Bac, A. Chiaroni and C. Riche, *Tetrahedron Lett.*, 1990, **31**, 1865.

67. E. Howard Jr. and W. F. Olszewski, *J. Am. Chem. Soc.*, 1959, **81**, 1483.

68. M. Hamana, *Chem. Abstr.*, 1956, 1817.

69. J. Meisenheimer, *Ber. Der. Dtsch. Chem. Ges.*, 1919, **52**, 1667.

70. R. F. Kleinschmidt and A. C. Cope, *J. Am. Chem. Soc.*, 1944, **66**, 1929.

71. M. T. Reetz and E. H. Lauterbach, *Tetrahedron Lett.*, 1991, **32**, 4481.

72. U. Schollkopf, U. Ludwig, M. Patsch and W. Franken, *Liebigs. Ann. Chem.*, 1967, **703**, 77.

73. L. D. Quin and F. A. Shelbourne, *J. Org. Chem.*, 1965, **30**, 3135.

74. R. T.LaLonde, J. T. Woolever, E. Auer and C. F. Wong, *Tetrahedron Lett.*, 1972, **15**, 1503.

75. B. Gozler and M. Shamma, *J. Chem. Soc. Perkin .Trans. 1.*, 1983, 2341.

76. A.C. Cope and E. R. Turnbell, *Org. React.*, 1960, **11**, 362.

77. H. Ronsch and A. Preiss, *Heterocycles*, 1987, **26**, 109.

78. T. Kurihara, K. Ohuchi, M. Kawamoto, S. Harusawa and R. Yoneda, *Chem Letts.*, 1991, 1781.

79. M. Brand, S. E. Drewes, G. Loizou and G. H. P. Roos, *Synth. Commun.*, 1987, **17**, 795.

80. D. H. R. Barton, R. Beugelmans and R. N. Young, *Nouv. J. Chem.*, 1978, **2**, 363.
81. H. Takayama and T. Nomoto, *J. Chem Soc. Chem. Commun.*, 1982, 408.
82. R. Beugelmans, G. Negron, and G. Roussi, *J. Chem Soc. Chem. Commun.*, 1983, 31.
83. N Kornblum, W. J. Jones and G. J. anderson, *J. Am. Chem. Soc.*, 1959, **81**, 4113.
84. V. Franzen and S. Otto, *Chem. Ber.*, 1961, **94**, 1360.
85. A. G. Godfrey and B. Ganem, *Tetrahedron Lett.*, 1990, **31**, 4825.
86. S. Suzuki, T. Onishi, Y. Fujita, H. Misawa and J. Otera, *Bull. Chem Soc. Japan*, 1986, **59**, 3287.
87. D. Barby and P. Champagne, *Tetrahedron Lett.*, 1996, **37**, 7725.
88. N. Nikolaides, A. G. Godfrey and B. Ganem, *Tetrahedron Lett.*, 1990, **31**, 6009.
89. V. VanRheenen, R. C. Kelly and D. Cha, *Tetrahedron Lett.*, 1976, 1973.
90. E. N. Jacobsen, I. Marko, W. S. Mungall, W. S. Schroder and K. B. Sharpless, *J. Am. Chem. Soc.*, 1988, **110**, 1968.
91. W. P. Griffith, S. V. Ley, G. P. Whitcombe and A. D. White, *J. Chem. Soc. Chem. Commun.*, 1987, 1625.
92. S. V. Ley, J. Norman, W. P. Griffith and S. P. Marsden, *Synthesis*, 1994, 639.
93. K. B. Sharpless, K. Akashi and K. Oshima, *Tetrahedron Lett.*, 1976, 2503.
94. L. C. Luan, T. S. Calderwood and T. C. Brucie, *J. Am. Chem. Soc.*, 1985, **107**, 8273.
95. C. M. Dicken, F-L Lu, M. W. Lee and T. C, Brucie, *J. Am. Chem. Soc.*, 1985, **107**, 5776.
96. C. M. Dicken, T. C. Woon and T. C, Brucie, *J. Am. Chem. Soc.*, 1986, **108**, 1636.
97. M. F. Powell, E. F. Pai and T. C, Brucie, *J. Am. Chem. Soc.*, 1984, **106**, 3277.
98. R. Koster and Y. Morita, *Angew Chem. Int. Ed.*, 1966, **5**, 580.
99. R. Koster, S. Arora and P. Binger, *Angew Chem. Int. Ed.*, 1969, **8**, 205.
100. R. W. Hoffman, K. Ditrich and S. Froch, *Liebigs. Ann. Chem.*, 1987, 977.
101. J. A. Soderquist and M. R. Najafi, *J. Org. Chem.*, 1986, **51**, 1330.
102. G. W. Kabalka and H. C. Hedgecock, *J. Org. Chem.*, 1975, **40**, 1776.

103. G. W. Kabalka and S. W. Slayden, *J. Organomet. Chem.*, 1977, **125**, 273.
104. A. G. Davies and B. P. Roberts, *J. Chem. Soc. (C),*, 1968, 1474.
105. G. W. Kabalka and R. J. Newton, *J. Organomet. Chem.*, 1978, **156**, 65.
106. H. Sakurai, M. Ando, N. Kawada, K. Sato and A. Hosomi, *TetrAhedron. Lett.*, 1986, **27**, 75.
107. M. A. Edelman, P. B. Hitchcock and M. f. Lappert, *J. Chem. Soc. Chem. Comun.*, 1990, 1116.
108. F. Bouvier, J. M. Dupart, A. Grand and J. G. Reiss, *Inorg. Chem.*, 1987, **26**, 2090.
109. Y Shvo and E. Hazam, *J. Chem. Soc. Chem. Comun.*, 1975, 829.
110. J-K. Shen, Y-C. Gao, Q-Z. Shi and F. Basolo, *Organometallics*, 1989, **8**, 2144.
111. L. A. Paquette, G. A. O'Doherty, B. L. Miller, D. R. Rogers, A. L. Rheingold and S. L. Geib, *Organometallics*, 1989, **8**, 2167.
112. M. Frank-Neumann, C. Dietrich-Bucherer and A. K. Kheimiss, *J. Organomet. Chem.*, 1982, **224**, 133.
113 W. Kliegel and E. Ahlenstiel, *Chem. Ber.*, 1977, **110**, 1623.
114. W. Kliegel and J. Gauman, *Liebigs. Ann. Chem.*, 1983, 950.
115. W. Kliegel and E. Ahlenstiel, *Chem. Ber.*, 1976, **109**, 3547.
116. S. Kida and T. Onika, *Bull. Chem. Soc. Japan.*, 1972, **45**, 1078.
117. J-M. Lehen, M. Pietraszkiewicz and J. Karpurik, *Helv. Chim. Acta.*, 1990, **73**, 106.
118. J-M. Lehn and C. O. Roth, *Helv. Chim. Acta.*, 1991, **74**, 572.
119. C. O. Paul-Roth, J-M. Lehn, J. Guilhem and C. Pascard, *Helv. Chim. Acta.*, 1995, **78**, 1895.
120. M. B. Diana, M. Marchetti and G. Melloni, *Tetrahedron Asymmetry*, 1995, **6**, 1175.
121. M. Nakajama, M. Saito, M. Shiro and S-I. Hashimoto, *J. Am. Chem. Soc.*, 1998, **120**, 6419.
122. E. P. Lipton, *J. Am. Chem. Soc.*, 1940, **62**, 1945.
123. M. J. Cook, A. R. Hatritzhy and M. M. Manas, *J. Chem. Soc. (B)*, 1971, **30**, 1330.
124. A. B. Bury, *J. Am. Chem. Soc.*, 1943, **65**, 1629.
125. J. C. Craig and K. K. Purushothaman, *Tetrahedron Lett.*, 1969, **60**, 5305.

126. A. B. Bury and J. H. Bickerton, *J. Am. Chem. Soc.*, 1945, **67**, 2261.

127. L. Robert, *Chim. et Ind.*, 1967, **97,** 337.

128. *J. Natl. Cancer Inst.*, 1982, **68,** 157.

129. C. P. Mihail, Jr. *Am. Ind. Hyg. Assoc. J.*, 1987, **48**, 997.

130. J.W. Bell, J. Heisler, H. Tannenbaum and J. Goldensen, *J. Am. Chem. Soc.*, 1954, **76**, 5185.

131. L. Larson, Svensk Kem. Tidskr, 1959, **71**, 336.

132. A. Michaelis, *Liebigs Ann. Chem.*, 1903, **326**, 129.

133. H. Normant, *Angew. Chem. Int. Ed.*, 1967, **6**, 1046.

134. J. C. Stowell, *Carbanions in Organic Synthesis*, Wiley: New York, 1979

135. H. O. House *Modern Synthetic Reactions*, 2nd ed., Benjamin, New York 1972.

136. M. Newcomb, T. R. Varick and S-H Gosh, *J. Am. Chem. Soc.*, 1979, **6**, 5186. ,

137. D. Seebach, R. Amstutz and J. D. Dunitz, *Helv. Chim. Acta.*, 1981, **64**, 2622.

138. L. M. Jackman, L. M. Scarmoutzos and W. Porter, *J. Am. Chem. Soc.*, 1987, **109**, 6524.,

130. R. R. Fraser and T. S. Mansour, *Tetrahedron Lett.*, 1986, **27**, 331.

140. L. M. Jackman and B. Lange, *J. Am. Chem. Soc.*, 1981, **103**, 4494.

141. J. Corset, F. Forment, M-F. Lautie, N. Ratovelomanana, J. Seyden-Penne, T. Strzalko and M-C. Roux-Schmitt, *J. Am. Chem. Soc.*, 1993, **115**, 1684.

142. L. M. Jackman and B. Lange, *J. Am. Chem. Soc.*, 1981, **103**, 4494.

143. C. Reichardt, *Solvent and Solvent Effects in Organic Chemistry*, VCH, Germany, 1988, p.17

144. N. S. Nudelman, N. E. Lewkowicz and J. J. P. Furlong, *J. Org. Chem.*, 1993, **58**, 1847.

145. L. M. Jackman, L. M. Scarmoutzos and W.Porter, *J. Am. Chem. Soc.*, 1987, **109**, 6524.)

146. F.E. Romsburg, J. H. Gilchrist, A. T. Harrison, D. J. Fuller and D. B. Collum, *J. Am. Chem. Soc.*, 1991, **113**, 5751.

147. F.E. Romsburg and D. B. Collum, *J. Am. Chem. Soc.*, 1992, **114**, 2112.

148. F.E. Romsburg, M. P. Bernstein, J. H. Gilchrist, A. T. Harrison, D. J. Fuller and D. B. Collum, *J. Am. Chem. Soc.*, 1993, **115**, 3475., F.E.

149. S. A. Galiano-Roth and D. B. Collum, *J. Am. Chem. Soc.*, 1989, **111**, 6772.

150. K. Tsushima, K. Araki and A. Murai, *Chemistry Lett.*, 1989, 1313.

151. R. Naef and D. Seebach, *Angew. Chem. Int. Ed.*, 1981, **20**, 1030.

152. E. Piers and H. L. A. Tse, *Tetrahedron Lett.*, 1984, 3155. ,

153. R. J. Cregee, J. L. Hermann, C. S. Lee, L. E. Richman and R. H. Schlessinger, *Tetrahedron Lett.*, 1973, 2425.

154. P. E. Pfeffer and L. S. Silbert, *J. Org. Chem.*, 1970, **35**, 262.

155. R. E. Ireland, R. H. Mueller and A. K. Willard, *J. Am. Chem. Soc.*, 1976, **98**, 2868.

156. T. H. Chan and E. Chang, *J. Org. Chem.*, 1974, **39**, 3264.

157. T. H. Chan and E. Chang, E. Vinokur, *Tetrahedron Lett.*, 1970, 1137.

158. T. M. Dolak and T. A. Bryson, *Tetrahedron Lett*, 1977, 1961.

159. T. A. Bryson, G. A. Roth, L. Jing-hau, and T. A. Bryson, *Tetrahedron Lett.*, 1986, **27**, 3685.

160. P. Caubre, *Angew. Chem. Int. Ed.*, 1983, **22**, 599.

161. Y. L Merrer, C. Gravier-Pelletier, D. Micas-Languin, F. Mestre, A. Dureault and J-C. Depezay, *J. Org. Chem.*, 1989, **54**, 2409.

162. E. Murayama, T. Kikuchi, K. Sasaki, N. Sootome and T. Sato, *Chem. Letters.*, 1984, 1897.)

163. S. Marczak and J. Wicha, *Tetrahedron Lett.*, 1993, **34**, 6627.

164. G. F. Luteri and W. T. Fork, *J. Org. Chem.*, 1977, **42**, 820.

165. W. J. J. M. Sprangers and R. Louw, *J. Che, Soc., Perkins 2.*, 1976, 1895.

166. S. Hackett and T. Livingstone, *J. Org. Chem.*, 1986, **51**, 879.

167. J. Otera, Y. Niibo and H. Nozaki, *J. Org. Chem.*, 1989, **54**, 5003.

168. M. R. Binns, R. K. Haynes, R. G. Katsifis, P. A. Schober and S. C. Vonwiller, *J. Am. Chem. Soc.*, 1988, **110**, 5411.

169. F. E. Ziegler, J-M. Tang and C. C. Tam, *J. Am. Chem. Soc.*, 1982, **104**, 7174.

170. W. C. Still and A. Mitara, *Tetrahedron Lett.*, 1978, 2659.

171. G. Magnusson, *Tetrahedron Lett.*, 1977, 2713.

172. D. Barr, M. J. Doyle, R. E. Mulvey, P. R. Raithby, D. Reed, R. Snaith and D. S. Wright, *J. Chem. Soc., Chem. Commun.*, 1989, 318.

173. T. Mukhopadhyay and D. Seebach, *Helv. Chim. Acta.*, 1982, **65**, 385.

174. E. J. Corey, D. A. Clark, G. Goto, A. Marfat, C. Mioskowski, B. Samuelsson and S. Hammarstrom, *J. Am. Chem. Soc.*, 1980, **102**, 1436.

175. D. Wernic, J. DiMaio, J. Adams, *J. Org. Chem.*, 1989, **54**, 3635.

176. P, Yadagiri, S. Lumin, J. R. Flack, A. Karara and J. Capdevila, *Tetrahedron Lett.*, 1989, **30**, 429.
177. C. Sreekumar, K. P. Darst and W. C. Still, *J. Org. Chem.*, 1980, **45**, 4260.
178. M. Koreeda, P. D. Patel and L. Brown, *J. Org. Chem.*, 1985, **50**, 5910.
179. E. Cereda, M. Attolini, E. Bellora and A. Donnetti, *Tetrahedron Lett.*, 1982, 23.
180. G. F. Lutteri, W. T. Fork, . *J. Org. Chem.*, 1977, **42**, 820.
181. D. J. Ager, *Organic Reactions*, 1990, **38**, 1.
182. J. R. Falck and P. Yadagiri, *J. Org. Chem.*, 1989, **54**, 5851.
183. J. A. Marshall, J. Lebreton, B. S. DeHoff and T. M. Jenson, *J. Org. Chem.*, 1987, **52**, 3883.
184. H. G. Richey Jr., and J. Farkas Jr., *J. Org. Chem.*, 1987, **52**, 479.
185. S. Marczak and J. Wicha, *Tetrahedron Lett.*, 1993, **34**, 6627.
186. A. F. Sowinski and G. M. Whitesides, *J. Org. Chem.*, 1979, **44,** 2369.
187. E. J. Lien and W. D, Kumler, *J. Am. Chem. Soc*, 1961, **83**, 214.
188. E. E. Mikhlina, V. Ya. Vorob'eva, S. S. Bobyleve and L. N. Yakhontov, *Pharm. Chem. J. (Engl. Transl.)*, 1969, **3**, 134.
189. I. Maisenheimer, *Justus Liebigs Ann. Chem.*, 1920, **420**, 190.
190. R. Lukes, *Collect. Czech. Chem. Commun.*, 1949, **14**, 655.
191. T. Perrine, *J. Org. Chem.*, 1957, **22**, 1484.
192. V. Prelog and K. Balenovic, *Chem Ber.*, 1941, **74**, 1508.
193. G. L. Kenyon, D. H. Eargle and C. W. Koch, *J. Org. Chem.*, 1976, **41**, 2417.
194. R. Rabinowitz, *J. Org. Chem.*, 1963, **228**, 2975.
195. F.Dagne and N. Castagnoli, *J. Med.Chem.*, 1972, **15**, 840.
196. J. T. Edwards and J. Whiting, *Can. J. Chem.*, 1971, **49**, 3502.
197. A. B. Burg, *J. Am. Chem. Soc.*, 1943, **65**, 1629.
198. H. Z. Lecher and W. B. Hardy, *J. Am. Chem. Soc.*, 1948, **70**, 3789.
199. M. Wiewiorosky and P. Baranowski, *Bull. Acad. Pol., Sci. Chim.*, 1962, **10**, 549.
200. G. J. Kubas, A. C. Larson and R. R. Ryan, *J. Org. Chem.*, 1979, **44**, 3867.
201. D. Seebach and D. Enders, *Ang. Chem. Int. Ed.*, 1975, **14**, 15.
202. R. D. Bach and D. Andrzewski, *J. Am. Chem. Soc.*, 1971, **93**, 7118.
203. K Nauman, G. Zon and K. Mislow, *J. Am. Chem. Soc.*, 1969, **91**, 7012.

204. R. Beugelmans, L. Benadjila-Iguertsira and G. Roussi, *J. Chem. Soc., Chem. Commun.*, 1982, 544.

205. R. R. Dykstra, *Enctclopedia of Organic Reagents*, ed. L. Paquette, 1995, **4.**, 2668.

206. D. Seebach, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1624.

207. D Seebach, R. Henning and T. Mukhopadhyay, *Chem. Ber.*, 1982, **115**, 1705.

208. C A. Brown and A. Yamaichi, *J. Chem. Soc., Chem. Commun.*, 1975, 100.

209. T. M. Dolak and T. A. Bryson, *Tetrahedron Lett.*, 1977, 1961.

210. T. Cohan, W. D. Abraham and M. Myers, *J. Am Chem. Soc.*, 1987, **109**, 7923.

211. T. E. Hogan-Esch and J. Schmid, *J. Am Chem. Soc.*, 1966, **88**, 307.

212. T. E. Hogan-Esch, *Adv. Phys. Org. Chem.*, 1977, **15**, 153.

213. T. E. Hogan-Esch and J. Schmid, *J. Am Chem. Soc.*, 1966, **88**, 318.

214. H. J. Reich and W. H. Sikorski, *J. Org. Chem.*, 1999, **64**, 14.

215. Erden I, *Comprehensive Heterocyclic Chemistry*, 2nd. Ed., Editor, A. Padawa, Pergamon Press: Oxford, 1996, Vol. 1A, Chapter 1.03.

216. S.E. Denmark, P. A. Barsanti, K-T Wong and R. A. Stavenger, *J. Org. Chem.*, 1998, **63**, 2428.

217. B. Miao, M. Tinki and V, Snieckus, *Tetrahedron Lett.*, 1999, **40**, 2449.

218. M .Schlosser, T. Jenny and Y. Guggisberg, *Synlett*, 1990, 704.

219. A. J. Blake, M. R. Ebden, D. N. A. Fox, W-S Li and N. S. Simpkins, *Synlett*, 1998, 189.

220. J.S. Krouwer and J.P. Richmond, *J. Org. Chem.*, 1978, **43**, 2464.

221. "Enamines: Synthesis, Structure, and Reactions", A.G. Cook, ed., Marcel Dekkar, New York, N.Y., 1969.

222 E.M. Volker, M.S. Thesis, M.I.T., Cambridge, Mass., 1967.

223. F.L. Lam and G.A. Berchtold, unpublished results.

224. R.R. Renshaw and J.C. Ware, *J. Am. Chem. Soc.*, 1925, **47**, 2989.

225. B. Hansen, *Acta Chem. Scand.*, 1963, **17**, 1483.

226. The preparation of **2c** from **1c** with peracetic acid had been reported by Y. Sakura and M. Izumi, *Pharm. Bull.*, 1953, **1**, 297.

227. R.D. Haworth and W.H. Perkin, *J. Chem. Soc.*, 1926, 1769.

228. E. Bamberger and P. Leyden, *Ber.*, 1901, **34**, 12.

229. A. Ahond, A. Cave, C. Kan-Fan, H.P. Husson, J. De Rostolan and P. Potier, *J. Am. Chem. Soc.*, 1968, **90**, 5622.

230. M.L. Loeb, Ph.D. Thesis, M.I.T., Cambridge, Mass., 1969.

231. C.A. Grob, A. Kaiser and E. Renk, *Helv. Chem. Acta.*, 1957, **40**, 2170.

232 W. von E. Doering, L. Birladeanu, D.W. Andrews and M. Pagnotta, *J. Am. Chem. Soc.*, 1985, **107,** 428.

233. M-C. Lanse, J-L. Ripoll, J-C. Guillemin and J-M. Denis, *Tetrahedron Lett.*, 1984, **35**, 3847.

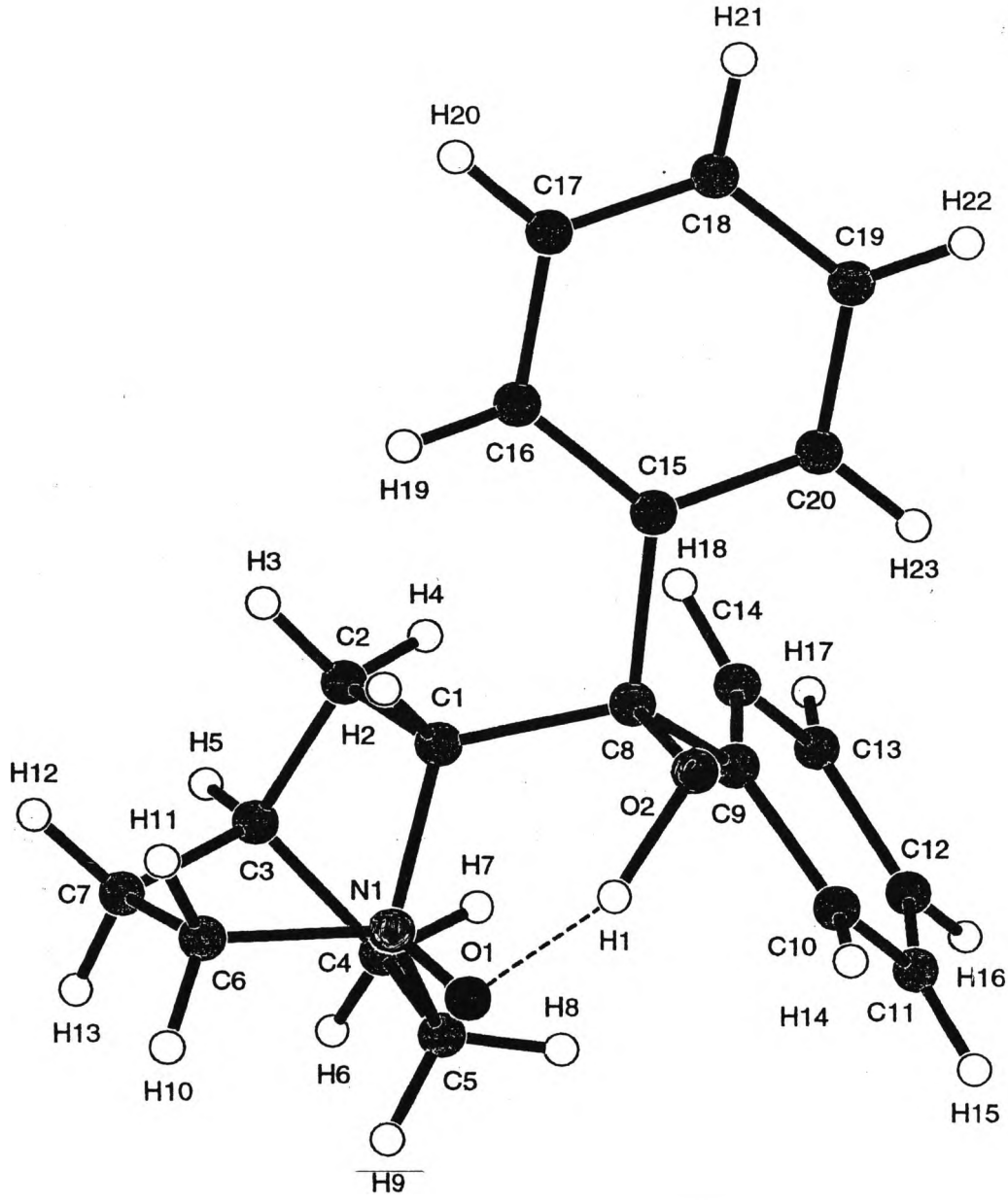
234. D. Milstein and J. K. Stille, *J. Am. Chem. Soc.*, 1979, **101**, 4992.

235. N. Miyaura, K. Yamada, and A. Suzuki, *Tetrahedron Lett.*, 1979, **20,** 3437.

236. H. Zhang, F. Y. Kwong, Y. Tian and K. S. Chan, *J. Org. Chem.*, 1998, **63**, 6886.

237. S. V. Ley, H. M. Osborn, H. W. Priepke and S. L. Warriner, *Organic Synthesis*, 1998, **75**, 170.

Appendix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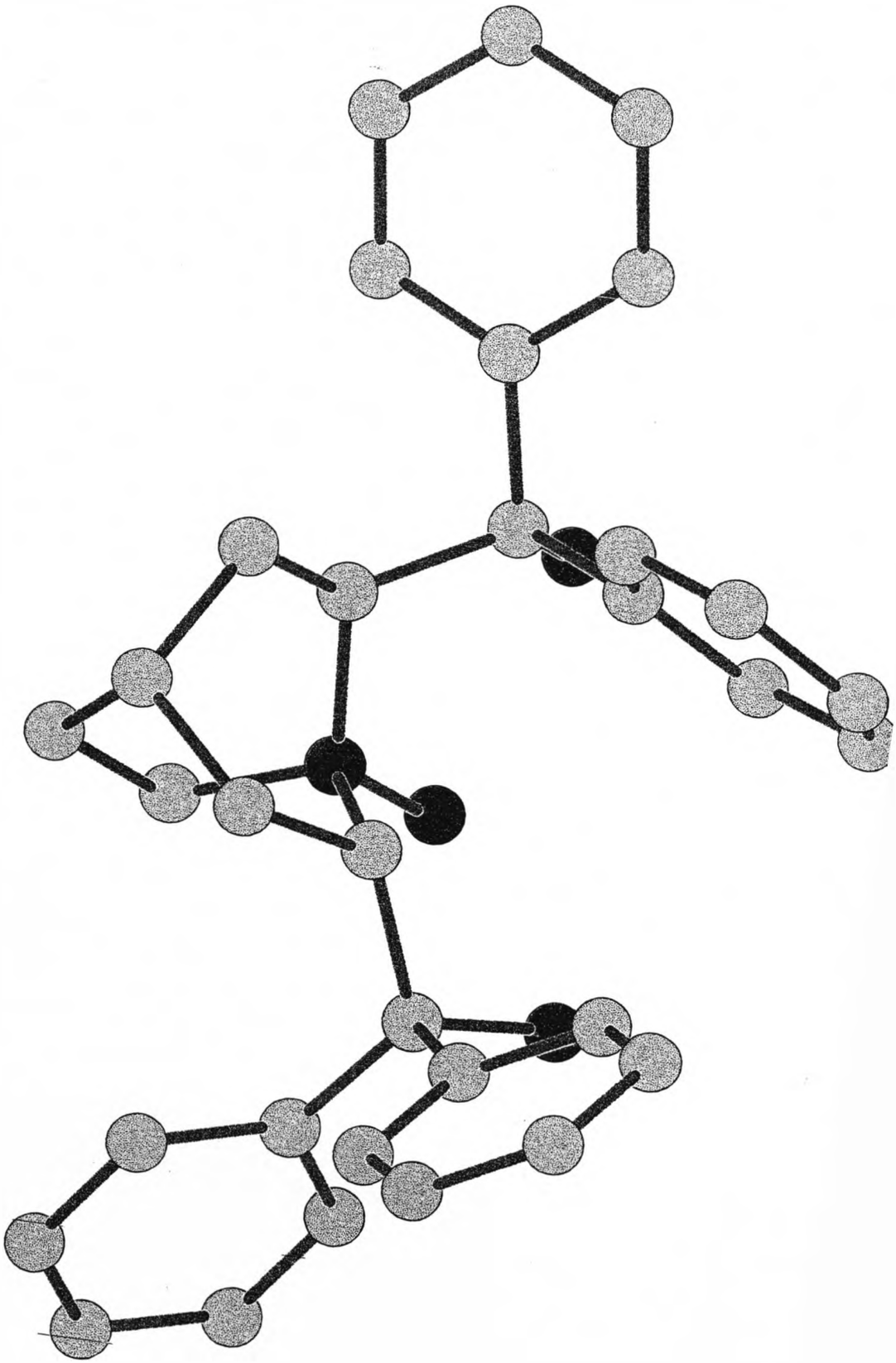

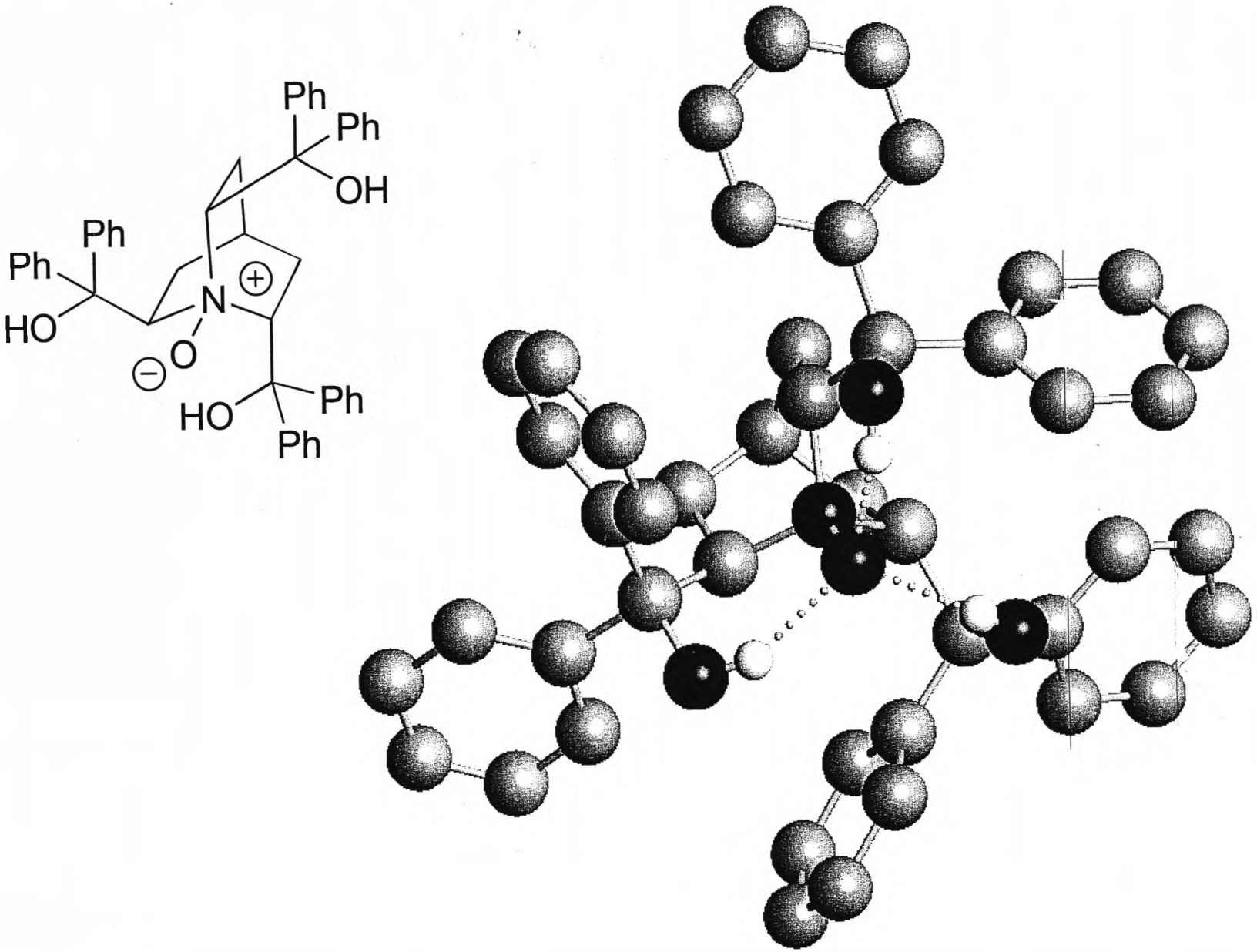
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