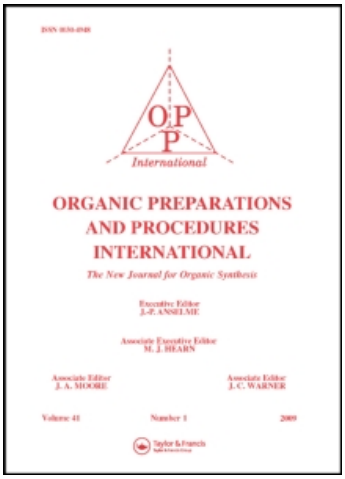

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Properties, Preparation and Synthetic Uses of Amine *N*-Oxides. An Update

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Introduction

This review covers practical aspects of the preparation, handling and use of all types of amine *N*-oxides. It aims to provide both an encyclopedic overview of the general chemistry of tertiary, heteroaromatic, and enamine *N*-oxides and focus particularly on more recent literature developments in the period *ca.* 2000 to early 2008. There have been several comprehensive reviews on the chemistry of aromatic and heterocyclic *N*-oxides[1–9] therefore this review focuses on more recent results with a special emphasis on *N*-oxides that do not fall into these categories.

I. Nomenclature: The *N*-Oxide Family

The term 'amine *N*-oxide' has been used in the literature to describe, more or less accurately, a broad range of structures with N–O bonds encompassing compounds where the nitrogen atom is either sp^3 or sp^2-hybridized **(1-3)**; the latter being more often encountered in the form of heterocyclic aromatic *N*-oxides. It is worth mentioning that occasionally in the literature, the use of the term '*N*-oxide' has been improperly extended to other N–O-bond containing compounds, such as nitrones **(4)**, nitrile oxides **(5)**, and substituted dialkylhydroxylamines **(6)** that are not the topics of this review (*Scheme 1*). Amine *N*-oxides possess a distinctive common fragment: an oxygen atom that is datively – rather than covalently – bonded to a nitrogen atom.

Over 100 years of literature define the area of '*N*-oxides'. While some of this has become 'textbook' material, certain areas have only come to the fore in the last few years (for example enamine *N*-oxides). Surprisingly, relatively few reviews have previously addressed this area, especially the *N*-oxides of sp^3 hybridized nitrogen. Previous reviews that we consider the most useful are summarized in *Table 1*. In our own summary, we

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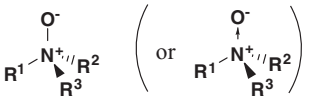
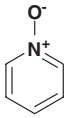
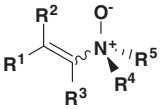


(**1**)
General structure of a tertiary amine *N*-oxide

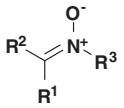


(**2**)
Pyridine *N*-oxide, the flagship of heteroaromatic *N*-oxides

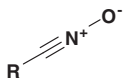


(**3**)
General structure of an enamine *N*-oxide

RELATED STRUCTURES
(Not covered in this review)



(**4**)
General structure of a nitrone



(**5**)
General structure of a nitrile *N*-oxide

(**6**)
N,*N*-Diethylhydroxylamine (DEHA, industrial polymerization inhibitor and antioxidant), sometimes improperly described as a "secondary amine *N*-oxide"

Scheme 1

have tried to provide an encyclopedic overview on useful synthetic procedures for attaining and characterising *N*-oxides supported by appropriate examples from the more modern literature (mainly 1980-2007) demonstrating their reactivity and concentrating more on sp^3 hybridized *N*-oxides.

While this review was in final preparation in 2008, an additional overview became available which is complimentary to the coverage here.[10]

II. Tertiary Amine *N*-Oxides

It is appropriate to first comment on some general properties of *N*-oxides. This coverage focuses on sp^3 hybridized *N*-oxides. However, the properties of heterocyclic *N*-oxides are largely analogous.

Table 1
Key Previous Reviews of the 'N-Oxide' Literature

Period Covered	Title/Topic	Ref.
1898–1991	Synthetic utility of amine *N*-oxides (coverage of both aliphatic and heterocyclic *N*-oxides)	1
ca. 1900–1990	Heterocyclic *N*-oxides (the most wide ranging book in this area, in terms of areas and years covered)	2
ca. 1900–1965	Heterocyclic *N*-oxides (coverage of the genesis of modern pyridine *N*-oxide chemistry and it early evolution)	3
ca. 1900–1970	Heterocyclic *N*-oxides (comprehensive cover within this period)	4
1950–1990	Mainly pyridine *N*-oxides (contains useful graphical summaries)	5
1990–2000	Synthesis and reactions of pyridine *N*-oxides (on-line resource)	6
1958–1988	Pyrimidine *N*-oxides (covers both 1- and 3- and some *bis* *N*-oxides)	7
1981–2006	Chiral *N*-oxides in asymmetric catalysis (recent developments in organocatalysis applications)	8, 9

1. Structural Features

The first report of an amine *N*-oxide was due to Pinner and Wolffenstein, and dates back to the end of the 19th century.[11] However, the tetrahedral nature of the arrangement of the oxygen and the three alkyl substituents around the central nitrogen atom remained unclear until the first X-ray structure of Me_3NO was published.[12] Contrary to amines, in tertiary amine *N*-oxides the tetrahedral arrangement of the substituents around the nitrogen atom prevents inversion, and therefore if the alkyl substituents are different this nitrogen atom becomes a stereogenic center. The N→O bond has been the object of much structural interest, and X-ray investigations suggest a bond length of 1.36 ± 0.03 Å for trimethylamine *N*-oxide.[12–22] Both theoretical and calorimetric investigations put the bond energy in the range 63-68 kcal mol^{-1}.[23, 24]

2. Physico-chemical Properties

Amine *N*-oxides possess a distinctive common fragment: an oxygen atom datively bonded to a nitrogen atom. This dative N→O bond shows one of the largest dipole moments of any functional group in organic chemistry; as demonstrated by the comparison in *Table 2*.

The unique physical properties of tertiary amine *N*-oxides are mainly due to the marked polarity of this functional group and include:

- Brönsted basicity
- Hydrogen-bonding acceptor character
- High hygroscopicity
- Solubility in water
- Lewis basicity and an aptitude to form complexes with metals

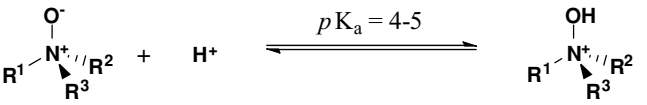
Table 2
Dipole Moments of the N→O Bond and Comparison with Some Other Organic Functional Groups

Compound	Dipole moment
DMF	3.82 D
N-Methyl-2-pyrrolidinone	4.09 D
DMSO	3.98-4.3 D
***N*-Methylmorpholine *N*-oxide**	**3.6–4.4 D (calcd.)[25]**
Sulfolane	4.69 D

These properties, which are often independent of the nitrogen hybridization (sp^3 or sp^2), will be addressed together here to avoid duplication in Sections III and IV. One consequence of the high dipole moment of *N*-oxides is their relative instability: the formation of more stable lower polarity products, is often the major thermodynamic driving-force of many rearrangements involving tertiary amine *N*-oxides.

a) Brönsted Basicity

Amine *N*-oxides are slightly basic, significantly less so than their parent amines. Combined with acids, they will readily form hydroxyammonium salts, the pKa of which being generally estimated at 4–5 (*Scheme 2*).[26] In cases where the parent *N*-oxide is unstable, the use of acidic reaction conditions can provide isolable salts—provided the issue of water solubility is addressed in the workup.

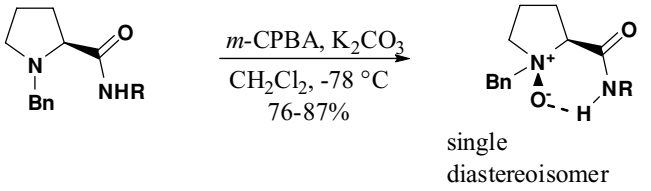


Scheme 2

b) Aptitude as Hydrogen-bonding Acceptors

Amine *N*-oxides are sometimes unstable compounds, but in these cases they can be stabilized by intermolecular H-bonds to water,[21] ethanol,[19] and *d*-α-bromo-*p*-camphorsulfonic acid.[27] Stabilization by intramolecular H-bonds was claimed with various hydrogen-bond-donors such as the hydroxyl groups of alcohols and carboxylic acids,[28, 29] the N-H part of primary amides and with the enols of some carbonyl derivatives,[30, 31] especially in cases where the hydrogen-bond becomes part of a 6-membered ring arrangement. X-ray investigations have provided evidence for both inter- and intramolecular H-bonds. For instance in *N,N*-dimethylethanolamine, intramolecular H-bonding is observed in the crystal structure.[32] The *N*-oxide is capable of forming two simultaneous H-bonds to two separate donors, as in combination of *N*-methylmorpholine *N*-oxide (NMO) and 1,2-cyclohexanediol.[16] Work by the O'Neil group has shown that intermolecular H-bonding to *N*-oxides can be used to control the conformation of proline-derived amide *N*-oxides, and that amine oxides

that are intramolecularly hydrogen bonded are usually stable and crystalline materials (*Scheme 3*).[28]



Scheme 3

c) Hygroscopicity

All amine *N*-oxides are often very hygroscopic due to their H-bonding acceptor nature. It has been shown that trimethylamine *N*-oxide (TMAO) absorbs water at a rate of approximately 1% water w/w per minute at 28°C and 80% relative humidity.[33] As often expected in a series of hygroscopic compounds, the hygroscopicity decreases as the considered amine *N*-oxides contain a larger number of carbon atoms in their structure. The introduction of lipophilic groups is strongly advantageous if standard organic preparative techniques are to be used.

d) Solubility

Due to the dipole moment of the N→O bond and the hydrogen-bonding capacity of the oxide, many amine *N*-oxides are highly soluble in water. This property is at the basis of the main industrial uses of tertiary amine *N*-oxides. Specifically: (i) *N*-Methylmorpholine *N*-oxide (NMO) is used on a ton-scale as a cosolvent for the extraction and dissolution of cellulose into water, for the "Lyocell" process,[34–36] aiming at the production of textile fibers (developed by two companies: Lenzing AG (Austria) and Courtaulds (US)). (ii) Long-chain *N,N*-dimethylalkylamine *N*-oxides, such as *N,N*-dimethyldecylamine, -dodecylamine, -tetradecylamine, -hexadecylamine, -heptadecylamine and -octadecylamine *N*-oxides, are used as non-denaturing zwitterionic surfactants to solubilize proteins and to study the conformation and molecular interactions of macromolecules.[37,38] More generally, amine *N*-oxides are also soluble in alcohols and dipolar aprotic solvents, but exhibit only limited solubility in non-polar organic solvents.[39]

e) Characterization

Suprisingly, one of the major difficulties in *N*-oxide chemistry is to identify with certainty the precise structure of the amine derivative formed during a given reaction. We focus here on differentiation between the parent tertiary amines, their hydrochloride salts, the tertiary amine *N*-oxides, and the common rearrangement by-products *N,N,O*-trialkylhydroxylamines ($R^1R^2N\text{-}OR^3$).

INFRARED

Zundel and co-workers have extensively studied the infrared properties of amine *N*-oxides,[40-46] and demonstrated that the N–O bond exhibits two characteristic absorptions:

1. a stretching mode at $\nu \approx 940\text{-}970\ cm^{-1}$ (for aromatic/heteroaromatic *N*-oxides, this band is shifted towards $1200\text{-}1300\ cm^{-1}$)
2. a vibrational mode at $\nu \approx 460\ cm^{-1}$ (in the far-infrared region, not of practical use)

Calculations have shown that, for *N*-propargylmorpholine *N*-oxide, the stretching mode could vary from $954\ cm^{-1}$ in media of aprotic or weakly hydrogen-bonding media ($CHCl_3$, CH_2Cl_2, *t*BuOH, *i*PrOH) to 960-965 cm^{-1} in hydrogen-bonding media (EtOH, MeOH, H_2O).[47]

The relatively low intensity of these absorptions limits somewhat their use for characterization purposes.

MASS SPECTRUM

Electron-impact mass spectrometry usually shows a large $[M\text{-}16]^{+\bullet}$ peak corresponding to the loss of the datively bonded oxygen atom, often this provides the base peak. As a result, electron-impact ionization does not necessarily allow one to differentiate between a tertiary amine and its corresponding *N*-oxide, but might in some cases allow one to distinguish between a tertiary amine *N*-oxide and a rearranged *N,N,O*-trialkylhydroxylamine. Using electrospray-ionization (and other 'soft' ionization techniques), no oxygen-loss is observed, making it *possible* to differentiate between *N*-oxides and their parent amines, but *not* between *N*-oxides and rearranged *N,N,O*-trialkylhydroxylamines.

NUCLEAR MAGNETIC RESONANCE

Comparative NMR data for *N*-oxides (vs. their parent amines and other derivatives, where possible) is given in *Table 3*.[48]

THIN LAYER CHROMOTOGRAPHY

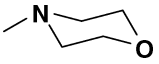
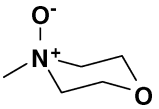
Due to their high polarity, amine *N*-oxides are only eluted by very polar mixtures (typical eluents are: (i) on Al_2O_3: AcOEt/MeOH 97:3-90:10; (ii) on SiO_2: AcOEt/MeOH 95:5-70:30). On TLC-plates their presence can be revealed:

- by dipping the plate into a ninhydrin (1 wt.-% in *i*PrOH) stain followed by heating, giving light brown to light pink spots;
- or by dipping into a TTC solution (5 wt.-% 2,3,5-triphenyltetrazolium chloride in *i*PrOH:H_2O = 4:1), gentle heating, and finally dipping into aqueous alkali (5 wt.-% aq. NaOH), giving reproducibly intense pink spots. This reagent also reveals nitrones and *N,N*-dialkylhydroxylamines.

Summary: As a result, the identification of a tertiary amine *N*-oxide must be confirmed by several analytical results:

- On TLC, a significant increase of polarity compared to the parent amine should be observed.
- The presence of the oxide must be confirmed by mass spectrometry, using Electrospray ionization (positive mode, $[M+H]^+$ should be observed). Electron impact can, in some instances, be used to distinguish between *N*-oxide ($[M]^{+\bullet}$ might be absent, but $[M\text{-}16]^{+\bullet}$ should be observed, and should be base peak) and rearranged *N,N,O*-trialkylhydroxylamines ($[M]^{+\bullet}$ should be observed, and $[M\text{-}16]^{+\bullet}$ should only be a very minor secondary ion).

Table 3
Comparative ^{1}H and ^{13}C NMR Data for tertiary Amine *N*-Oxides and Related Species

	^{1}H-NMR	**^{13}C-NMR**
Me_3N (SDBS No. 9568[a])	(300 MHz, CCl_4): $\delta = 2.12$	-[b]
$Me_3N \rightarrow O$ (SDBS No. 3643)	**(300 MHz, D_2O): $\delta = 3.26$ (300 MHz, DMSO-d_6): $\delta = 3.31$**	**(25 MHz, D_2O): $\delta = 60.4$ ($^{1}J^{14}_{N,C} = 3.0$ Hz) (25 MHz, DMSO-d_6): $\delta = 61.2$**
Me_3N·HCl (SDBS No. 3146)	(300 MHz, D_2O): $\delta = 2.91$	(100 MHz, DMSO-d_6): $\delta = 44.6$
$Me_4N^+ \cdot TsO^-$ (SDBS No. 5830)	(300 MHz, D_2O): $\delta = 3.13$	(15 MHz, D_2O): $\delta = 56.1$
Et_3N (SDBS No. 1288)	(300 MHz, CCl_4): $\delta = 2.43$ (1-H), 0.97 (2-H)	(15 MHz, $CDCl_3$): $\delta = 46.5$ (C-1), 11.8 (C-2)
$Et_3N \rightarrow O$	**(300 MHz, DMSO-d_6): $\delta =$ 3.01 (1-H), 1.10 (2-H)**	**(100 MHz, DMSO-d_6): $\delta =$ 58.5 (C-1), 8.1 (C-2)**
Et_3N·HCl (SDBS No. 3145)	(400 MHz, $CDCl_3$): $\delta =$ 3.26 (1-H), 1.43 (2-H)	(25 MHz, $CDCl_3$): $\delta = 46.2$ (C-1), 8.8 (C-2)
$Et_4N^+ \cdot BF_4^-$ (SDBS No. 15713)	(400 MHz, DMSO-d_6): $\delta =$ 3.20 (1-H), 1.16 (2-H)	(100 MHz, DMSO-d_6): $\delta = 51.3$ (C-1), 6.9 (C-2)
 (SDBS No. 2117)	(400 MHz, $CDCl_3$): $\delta = 3.72$ (2-H, 6-H), 2.36 (3-H, 5-H), 2.26 (CH_3)	(25 MHz, $CDCl_3$): $\delta = 66.9$ (C-2, C-6), 55.5 (C-3, C-5), 46.4 (CH_3)
 **(SDBS No. 22765)**	**(400 MHz, DMSO-d_6): $\delta = 4.07, 3.68$ (2-H, 6-H), 3.40, 2.93 (3-H, 5-H), 3.10 (CH_3)**	**(25 MHz, D_2O): $\delta = 61.0$ (C-2, C-6), 64.7 (C-3, C-5), 59.7 (CH_3)**

a) SDBS (Spectral Database for Organic Compounds) reference number given in parentheses; details for accessing this data are given in ref. 48.
b) Data not available in SDBS.

- For the alkyl groups that are directly bonded to the nitrogen, a variation of *ca* +1 ppm in ^{1}H NMR and +9 to +12 ppm in ^{13}C NMR compared to the parent amine must be observed.
- An absorption in the 940-970 cm^{-1} domain of the infrared spectrum should be observed (compared to 1200-1300 cm^{-1} in heteroaromatic *N*-oxide systems).

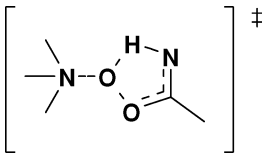
3. Preparation

a) N-Oxidation of tertiary Amines

i) Hydrogen Peroxide

For bulk quantities of amine oxides, hydrogen peroxide is almost certainly the most useful oxidant, being cheap and stable under standard conditions. It is best if the concentration of the hydrogen peroxide used is checked by readily available iodide-I_2 oxidation

methods before use.[49] Meisenheimer showed that H_2O_2 was efficient in oxidizing tertiary allylic *N*-oxides at temperatures of 25–60°C, the aqueous medium presumably slowing down rearrangements by hydrogen-bonding the *N*-oxide. However, the oxidation rate is usually highly dependent on the steric environment around the nitrogen atom and hindrance in this region dramatically slows the oxidation. The reaction can be accelerated by adding acetonitrile to the mixture, generating peroxyacetimidic acid *in situ* (*Scheme 4*).[50]

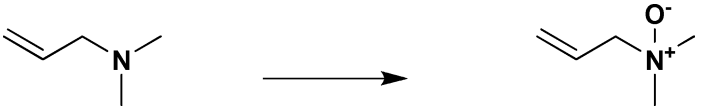


Scheme 4

In a number of cases, however, it has been shown that the use of hydrogen peroxide can lead to side-reactions, especially in substrates containing carbonyl-derived functional groups. For instance, Wenkert *et al.*[31] mentions that α-aminoamides can be oxidized cleanly to the *N*-oxides with *m*CPBA, while the use of hydrogen peroxide led to numerous side-products. The reaction rate as well as selectivity of these H_2O_2 *N*-oxidations can be enhanced by transition metal catalysts. The most useful appear to be:

- Aq. H_2O_2 + silica supported $(VSi_4O_{6.4})_n$ catalysts (acetonitrile, 80 °C)[51]
- Aq. H_2O_2 + layered double hydroxide WO_4^{2-} (20 °C)[52]
- Aq. H_2O_2 + manganese tetrakis(2,6-dichlorophenyl)porphyrin[53]

Representative Example of H_2O_2 N-Oxidation: Allyldimethylamine N-oxide[54]



Allyldimethylamine (20.0 g, 0.235 mol) was added slowly to 171 g (about 100% molar excess) of 10% aqueous H_2O_2 in a 500 mL flask fitted with a stirrer, dropping funnel, thermometer and reflux condenser. During the addition, the temperature of the mixture was maintained at 5–10 °C by cooling with an ice-bath. The turbid mixture became homogeneous after 2 h, and was allowed to warm to r.t. and stirred for 12 h. The solution was extracted with Et_2O (3 × 50 mL) to remove any unreacted amine. Approximately 12 cm^2 of platinum foil was added to the solution to catalyze the decomposition of the excess H_2O_2. The rate of evolution of oxygen decreased after 1.5 h, and the decomposition was allowed to continue for 24 h at r.t. The solution was decanted from the platinum into a solution of 53 g (0.24 mol) of picric acid in 1.57 L of water at 80°C. The solution was heated at 70–80°C for 15 min., cooled slowly and, after crystallization started, was placed in an ice-bath and stirred until the crystallization appeared to be complete. The yield of allyldimethylamine oxide picrate, m. p. 135–136°C, was 72.7 g (94%). [Reproduced with the permission of the American Chemical Society.]

ii) Carboxylic Peracids Generated in situ

Aqueous hydrogen peroxide has also been used to generate organic peracids from carboxylic acids or the corresponding anhydrides. When acids are used, the reaction medium

remains aqueous, whereas the use of an excess of anhydride allows for anhydrous reaction conditions.

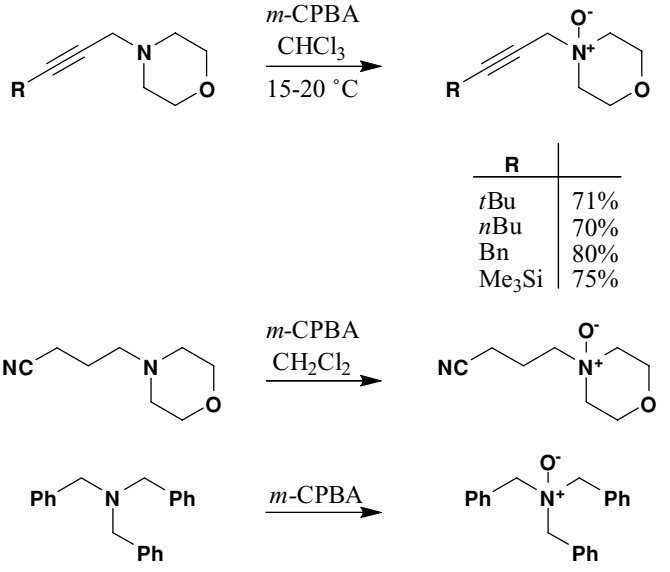
Permanganate, perborate[55] and percarbonate[56, 57] salts as well as urea-hydrogen peroxide adduct (UHP)[58] have been used as safer, greener or cheaper alternatives to hydrogen peroxide for the *in situ* generation of active peracids. However, in these methods the oxidation is accompanied by the release of a stoichiometric amount of water, which the hygroscopic nature of *N*-oxides makes difficult to remove. Alternatively, the combination of trifluoroacetic anhydride (TFAA) and urea-hydrogen peroxide complex (UHP) has been shown to efficiently oxidize electron deficient pyridines into their corresponding *N*-oxides, in formally anhydrous conditions.[59]

iii) Sulfonic Peracids Generated in situ

Schulz and co-workers showed that *p*-toluenesulfonic peracid, generated *in situ* from *p*TSA and basic aqueous hydrogen peroxide, was efficient in the chemoselective oxidation of nitrogen functionalities.[60] Recently, the Sain group reported that *in situ* oxidation of supported sulfonic acids (Nafion®-H^+) by aqueous hydrogen peroxide in a biphasic system catalytically generates a superior oxidant (presumably polyperoxysulfonic acids) for the conversion of tertiary amines into their corresponding *N*-oxides.[61]

iv) m-CPBA and Other Stable Carboxylic Peracids

Although magnesium monoperoxophthalate (MMPP) has long been shown to be a suitable reagent for *N*-oxidation (for instance of conchonine and cinchonidine,[62] or for the monooxidation of bipyridines[63,64]), its popularity has never come close to that of 3-chloroperbenzoic acid (*m*-CPBA) which remains the pre-eminent reagent in this area. Excellent texts are available describing the purification[65] and use of *m*-CPBA. Again, confirmation of the reagent's purity *via* redox titration[49] is vital to avoid competing over-oxidation. Under such selective conditions *N*-oxidation is possible (*Scheme 5*).[66–69]



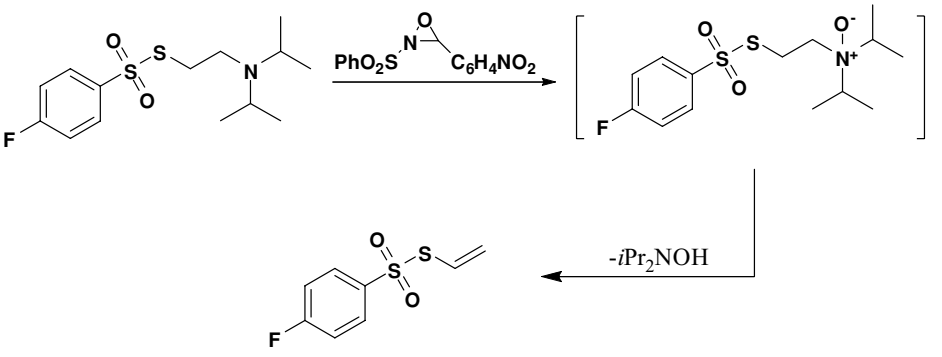
Scheme 5

v) Oxiranes

DMDO (dimethyldioxirane) has been shown to efficiently oxidise both tertiary amines and pyridines into the corresponding *N*-oxides quantitatively.[70] Kinetic parameters for the oxidation of variously substituted pyridines are available.[71] Theoretical investigations have provided interesting insight into the probable mechanism of these oxidations.[72]

vi) Oxaziridines

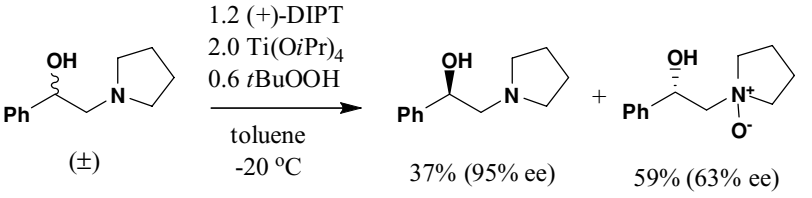
Davis has used oxaziridines as mild, selective oxidants for the formation of *N*-oxides.[73–75] For example, treatment of the amine appended thiosulfates results only in *N*-oxide formation; no *S*-oxidation is observed (*Scheme 6*). However, in this case the resultant *N*-oxide cannot be isolated as it undergoes Cope elimination at room temperature.



Scheme 6

vii) Titanium/tBuOOH (TBHP)

In attempts to extend the repertoire of the Ti(O*i*Pr)$_4$/(tartrate) catalysts, that had proved so useful on allylic alcohol epoxidation, the Sharpless lab reported the kinetic resolution of racemic β-hydroxy amines. The aim in this reaction was to use the tertiary amine capable of accepting an O-atom. As a by-product of the kinetic resolution significant yields of β-hydroxy-*N*-oxides were attained in moderate optical yield (*Scheme 7*).[76,77] No attempt was made to optimize the stereoselectivity of the process with respect to the *N*-oxide.

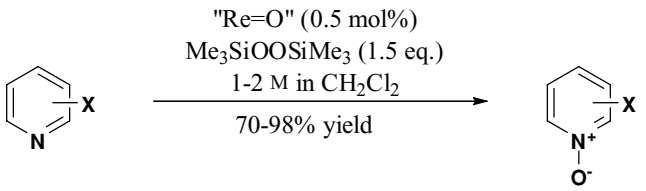


Scheme 7

viii) Rhenium-based Catalytic Oxidants

The use of rhenium-based catalytic systems in oxidation reactions has been reviewed.[78] Kinetic studies have provided more insight into the mechanism of the oxygen transfer reactions from oxo-rhenium oxidants.[79] Sharpless *et al.* reported an oxidation of pyridines and related amines using a combination of inorganic rhenium salts and

bis(trimethylsilyl)peroxide (*Scheme 8*).[80] The group of Sain recently reported another approach using catalytic amounts of methyl trioxorhenium (MTO) and acetic acid in the presence of sodium percarbonate (SPC) as a terminal co-oxidant.[81]



"Re=O": $MeReO_3$ (MTO), ReO_3, Re_2O_7 or $HOReO_3$

Scheme 8

ix) Molecular Oxygen

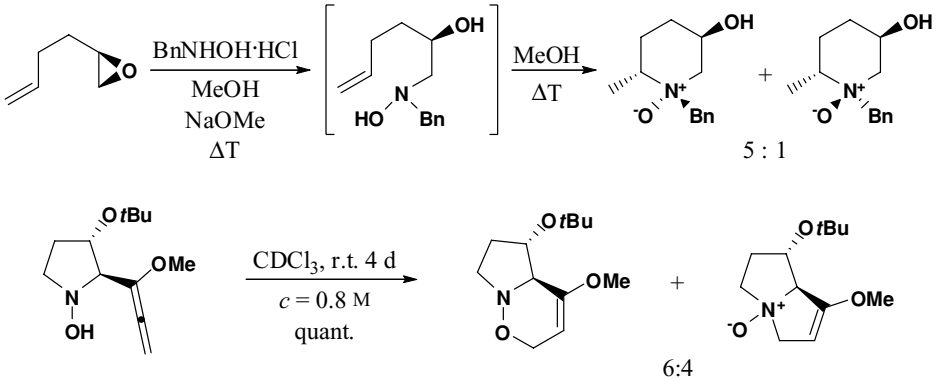
Molecular O_2 alone is not efficient for the *N*-oxidation of amines. Yet, in the presence of a ruthenium-based catalyst, it can be used to generate *in situ* better oxidants, such as ruthenium oxo-complexes.[82] Also branched aldehydes can be used as co-oxidants in this reaction, although the mechanism of this process is not yet fully understood.[83] Biomimetic approaches using molecular O_2 and flavin-based organocatalysts have also been successfully applied.[84,85]

x) Other Oxidants

In a process catalyzed by $RuCl_3$, bromamine-T (Na[4-$MeC_6H_4SO_2NBr$]) has been introduced as an *N*-oxidation system.[86]

b) By Cycloadditions

Formation of *N*-oxides can also be achieved by intramolecular cyclization of hydroxylamines to alkenes[87] or to an allene (*Scheme 9*).[88] Formally these are retro-Cope reactions (see the next section) and to attain a viable result for this reverse reaction intramolecular variants are normally required. In the formation of six-membered rings, complete control of relative stereochemistry can be difficult to attain.

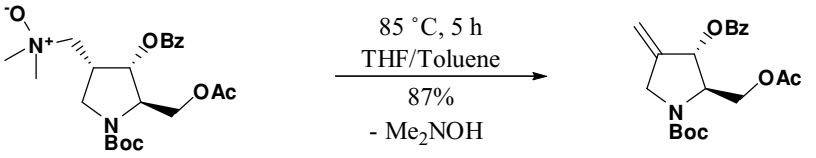


Scheme 9

4. Reactivity and Applications

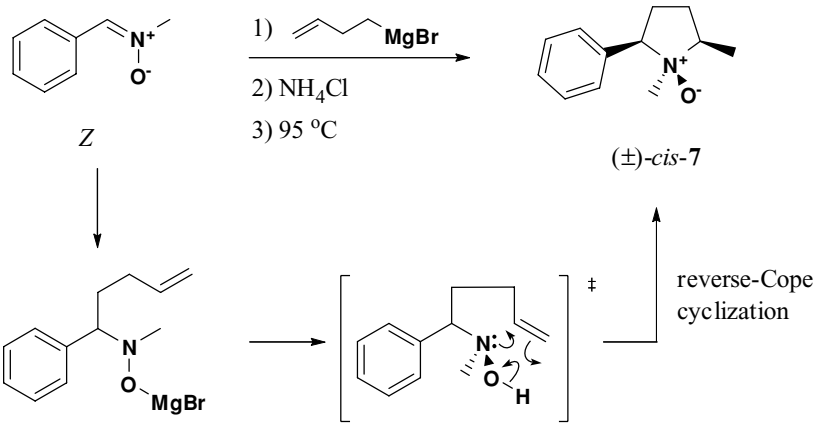
a) Cope Elimination

The pyrolysis of an amine *N*-oxide yields an olefin and a hydroxylamine.[89,90] In cases where the hydroxylamine co-product is lost to the reaction pool the procedure constitutes an effective route for the preparation of alkenes. A typical example of such a Cope elimination is shown in *Scheme 10*.[91] Early results and the basic features of the Cope elimination are summarized as part of the '*cis*-elimination review' of DePuy and King (literature 1949-60).[92]



Scheme 10

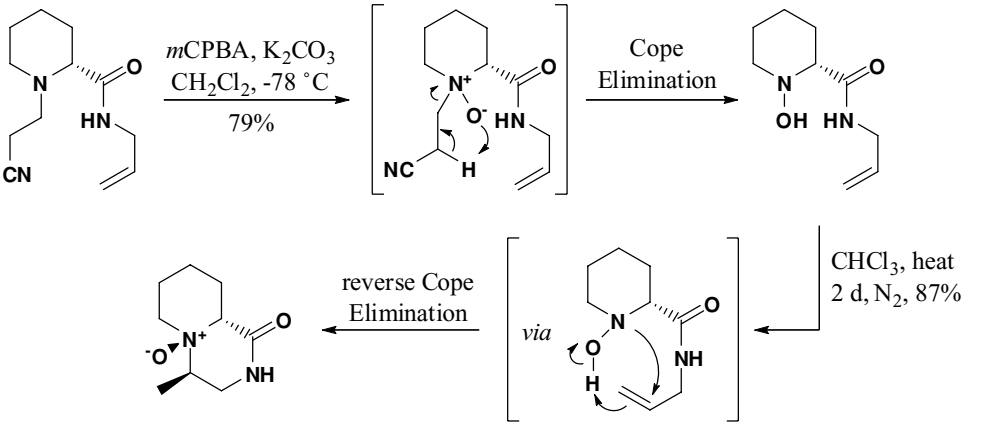
The Cope elimination normally proceeds under thermodynamical control due to the requirements for relatively high reaction temperatures. As alluded to above, if the substrates are appropriately engineered both forward and reverse reactions can be attained. The Cope reaction's reversibility can be seen in the many examples of reverse-Cope cyclizations, especially intramolecular variants.[22,93–95] Some of these lead to synthetically useful cyclic *N*-oxides, such as that of *Scheme 11* which proceeds with excellent control of the relative stereochemistry in **7**.[95] In recent work O'Neil has employed a Cope-retro Cope sequence to allow highly diastereoselective syntheses of six-membered cyclic hydroylamines (*Scheme 12*).[96]



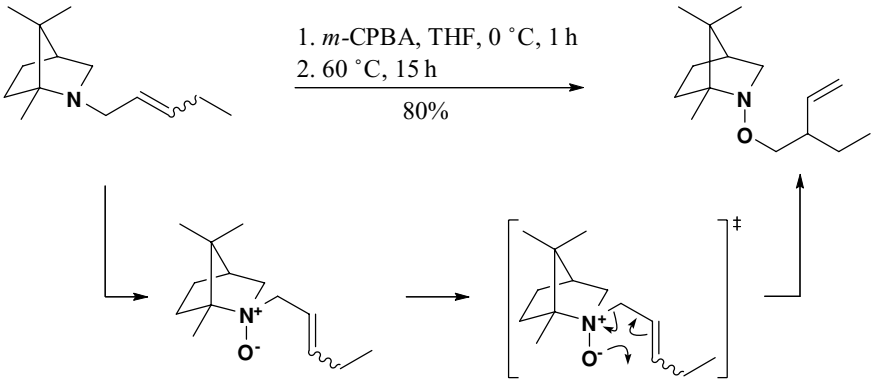
Scheme 11

b) [2,3]Meisenheimer Rearrangement

First described in 1919[97] for allylic amines, the [2,3] rearrangement results in concomitant breakage of the N→O bond with C-O bond formation γ to the nitrogen. A recent stereoselective variant of the process is given in *Scheme 13*.[98]



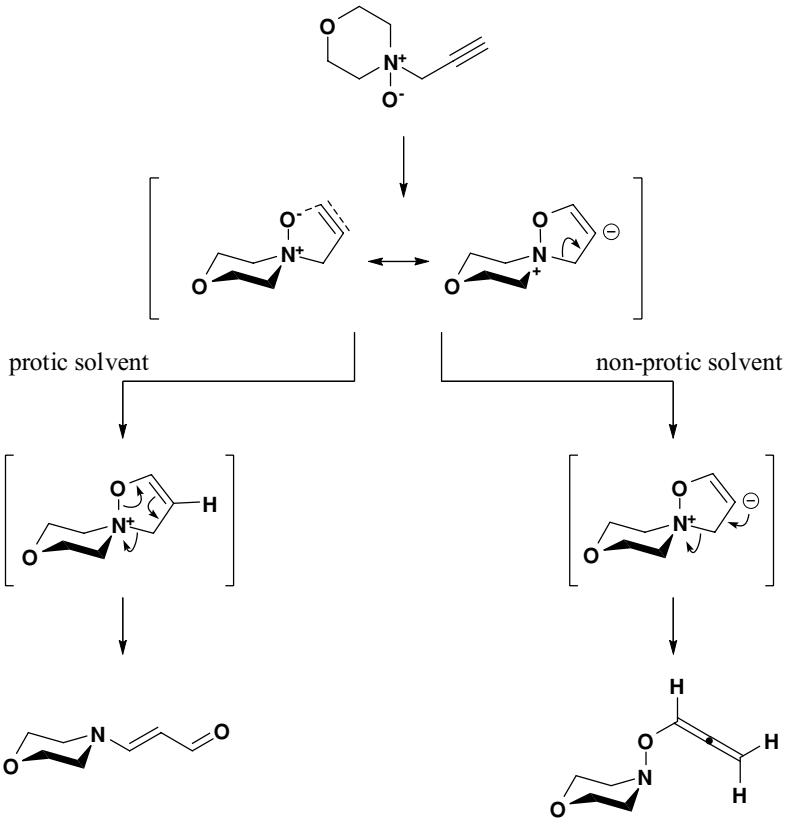
Scheme 12



Scheme 13

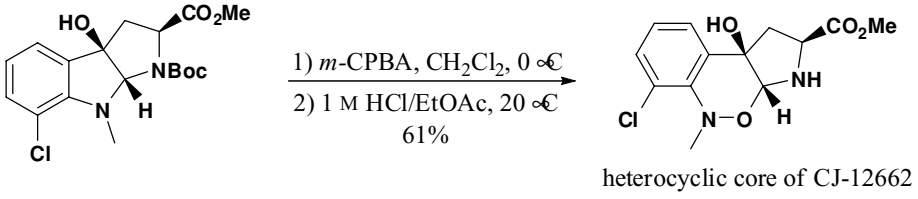
Early mechanistic studies by Wragg[99] are in accord with the [2,3]Meisenheimer rearrangement occurring by a concerted sigmatropic process. There are, however, only a few examples for the preparation of enantiomerically enriched allylic alcohols *via* chirality transfer from enantiopure *N*-oxides in the [2,3]Meisenheimer rearrangement and subsequent N-O bond cleavage. The diastereomeric excess (de) values achieved so far in these reactions presently seldom exceed 60–70%.[98,100–102] Various proposals have been put forward that may account for these observations: the reversibility of the rearrangement leading to product epimerization;[103] homolytic dissociation and recombination during the bond making/breaking processes;[104] and the presence of more than one reactive conformer during the rearrangement process.[105] Groups isolobal with the allyl fragment can take part in [2,3]Meisenheimer rearrangements;[106] perhaps the most interesting of these is the participation of propargylic amine systems that allow the preparation of allenic products under appropriate conditions (*Scheme 14*).[107]

In a wider sense the term 'Meisenheimer rearrangement' is also used to define any rearrangement that results in an *N* to *O* migration within a tertiary amine *N*-oxide including migration of alkyl and electron deficient aryl/heteroaryl groups.[106] However, in such cases clearly [2,3]-sigmatropic rearrangement processes do *not* operate. A recent example of



Scheme 14

such behavior is displayed in the synthesis of the potent anthelmintic pyrrolobenzoxazine terpenoid natural product CJ-12662 to establish the heterocyclic core (*Scheme 15*).



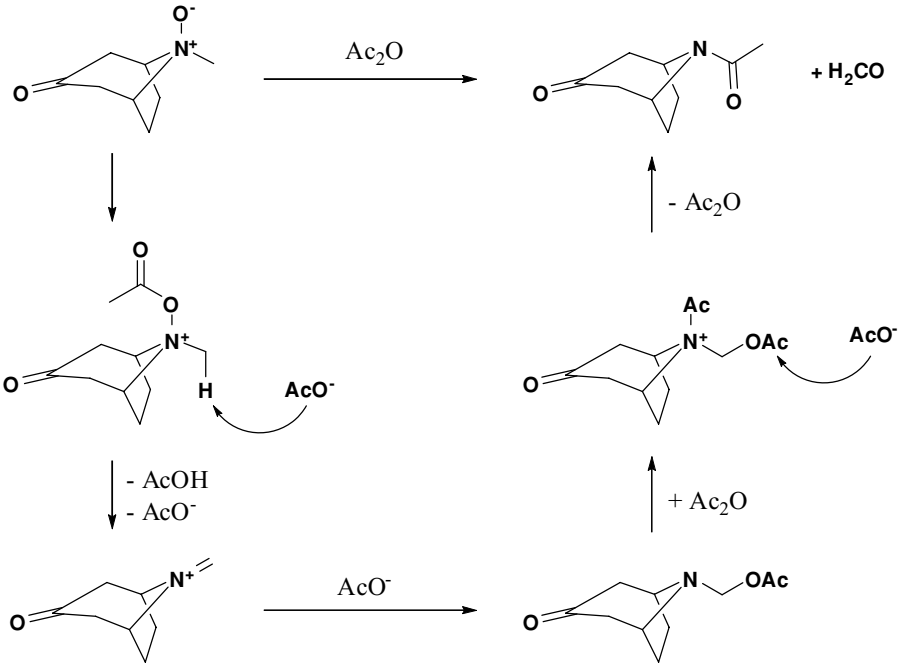
Scheme 15

Finally, as the energetic requirements of Cope and Meisenheimer rearrangements are broadly similar, care needs to be exercised in reaction design as the presence of competing processes from a single starting material is not unknown.[108]

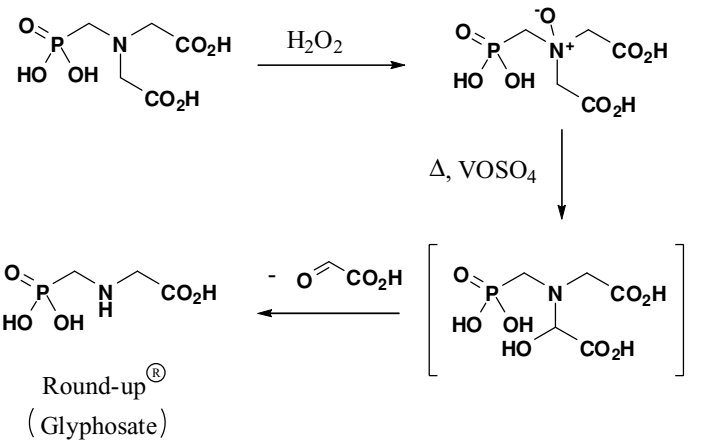
c) Polonovski Reaction and Related Intramolecular Red-Ox Reactions

The original Polonovski reaction consists formally of the demethylation of a *N,N,N*-dialkylmethylamine *N*-oxide. A typical example of the reaction's outcome and its

mechanistic pathway is presented in *Scheme 16*.[109] This reaction is thermodynamically driven by the formation of the stable amide bond, which largely compensates the loss of the rather weak N-O bond. A review by Grierson summarizes applications of this chemistry up to 1989.[110] The major current industrial use of this chemistry is in the BASF synthesis of the herbicide Round-Up® (*Scheme 17*). This relies on a vanadyl-catalyzed Polonovski-type degradation of a protected glycine.[111]



Scheme 16



Scheme 17

d) Tertiary N-Oxide Redox Chemistry with Metal Salts

Traditionally *N*-oxides are reduced to amines by either zinc in the presence of acetic acid, metal hydride reagents or phosphorus/sulfur species.[112–116] In the last decade, many metal species with accessible higher oxidation states have been shown to readily induce reduction of *N*-oxides including: Cp_2TiCl_2/In,[117] $ZrCl_4/NaBH_4$,[118] $MoCl_5$/NaI,[119] $TiCl_3$ under acidic conditions[120–122] and $FeCl_3 \cdot 6H_2O$/In.[123] In particular, the last two methods are attractive due to their mildness and apparent functional group tolerance. All of these methods rely on *in situ* generation of easily oxidized low valent metal species.

e) Tertiary N-Oxides as Ligands for Metal-Based Catalysts

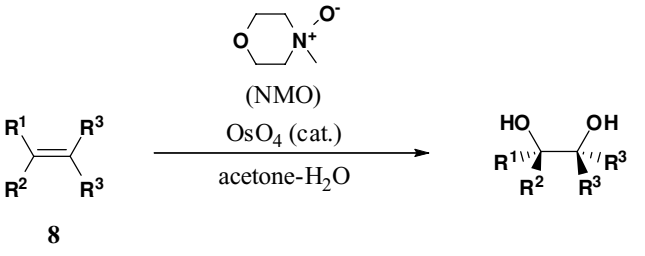
Due to the relative fragility of the *N*-oxide bond [D^o(N-O) $\sim$ 65 kcal mol^{-1}] complexes incorporating oxophilic metals either in lower oxidation states or those formed under reducing conditions are expected to be unstable (see Section d above). Thus far, relatively few examples of chiral, or other specialised ligand sets, for use in selective transition metal catalysis have been reported. To allow direct comparison these examples have been included with their heteroaromatic *N*-oxide analogues in Section III b.

f) Use of N-Oxides as Oxidation Promoters

As *N*-oxides display the characteristic reactivity above with various transition metal complexes they have been extensively investigated as benign, nonexplosive, terminal oxidants. In particular, *N*-oxides such as *N*-methylmorpholine-*N*-oxide (NMO) or Me_3NO are preferred stoichiometric oxidants for a number of transition metal-catalyzed oxidations. Both of these species are commercially available and are easily handled. For example, NMO monohydrate has a melting point of 70°C, and is stable under normal conditions. It is soluble in polar solvents, especially water.

i) Upjohn and Sharpless Dihydroxylations

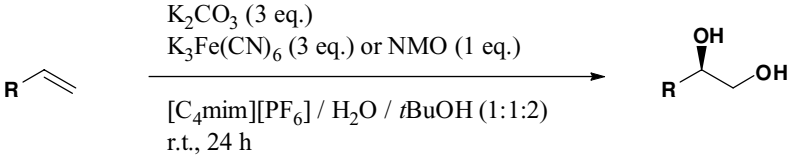
From the earliest inception of osmium-catalyzed dihydroxylation, NMO has proved an extremely effective terminal oxidant (*Scheme 18*).[124] In cases where the reaction is slow, its rate can be increased by addition of quinuclidine.[125] The efficiency of the reaction allows even demanding or unusual substrates to participate. For example, the use of **8** ($R^1 = (CH_2)_nBF_3K$) allowed *cis*-dihydroxylation of olefin-containing potassium alkyl- and aryltrifluoroborates in moderate to excellent yields. The resulting diols are efficient coupling partners in Suzuki-Miyaura-type reactions with both alkenyl and aryl bromides.[126]



8

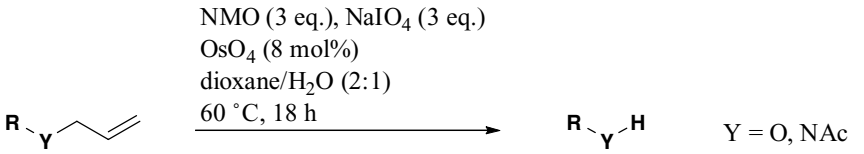
Scheme 18

The use of NMO in asymmetric Sharpless dihydroxylation processes is not favored as the enantioselectivities realized are not as high as with $K_3Fe(CN)_6$ in *t*BuOH-water systems.[127] However, recent developments include the use of an ionic liquid based solvent system. A systematic study on the use of ionic liquids as cosolvents in asymmetric dihydroxylation clearly demonstrates that among various ionic liquids, $[C_4mim][PF_6]$ and $[C_8mim][PF_6]$ gave yields and enantioselectivities that were comparable or higher than those of the conventional H_2O/*t*BuOH solvent system (*Scheme 19*).



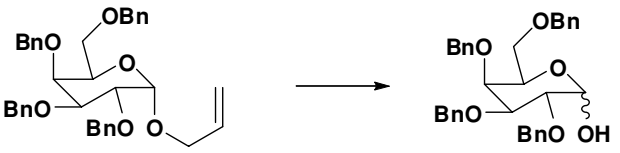
Scheme 19

Resin-based OsO_4 dihydroxylation catalysts are claimed as very efficient catalysts for the dihydroxylation of various olefins to afford vicinal diols with high yields irrespective of the cooxidant used. Resin-OsO_4 is recovered quantitatively by a simple filtration and reused for a number of cycles with consistent activity. The high binding ability of the heterogeneous osmium catalysts enables the use of an equimolar ratio of a chiral ligand such as $(DHQD)_2PHAL$ to osmium to give excellent enantioselectives in the asymmetric dihydroxylation.[128] In a related approach, *in situ* polymerization gave osmium tetroxide encapsulated in a polyurea matrix. The use of these microcapsules as reusable catalysts in dihydroxylation and oxidative cleavage of olefins has been described.[129] A new, one-pot method is described for the removal of *O*- and *N*-allyl protecting groups under oxidative conditions at near neutral pH. The allyl group undergoes hydroxylation and subsequent periodate scission of the vicinal diol. Repetition of this reaction sequence on the enol tautomer of the aldehyde intermediate releases the deprotected functional group (*Scheme 20*).[130]



Scheme 20

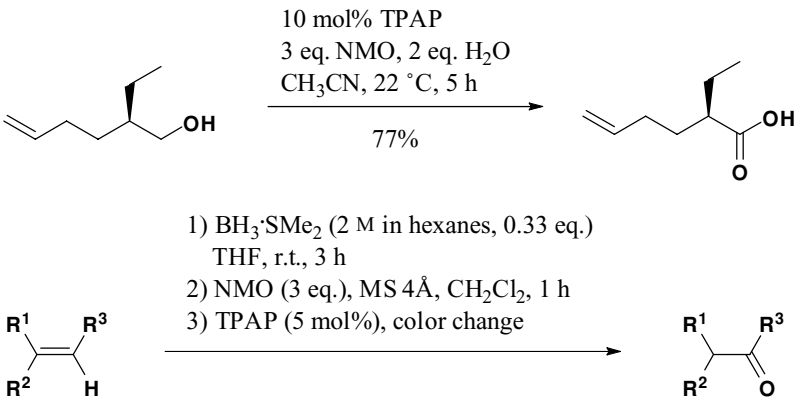
Representative Example of N-Oxide Use: Preparation of 2,3,4,6-tetra-O-benzyl-D-galactopyranose by Oxidative Deallylation[131]



To a solution of allyl 2,3,4,6-tetra-O-benzyl-α-D-galactopyranoside (585 mg, 1.01 mmol) in dioxane (5 mL) and water (0.5 mL) was added a mixture of 4-methylmorpholine N-oxide (3 equiv, 354 mg) and OsO_4 (0.2 mL, 100 mg/mL solution in t-BuOH) followed by addition of a suspension of $NaIO_4$ (3 equiv, 646 mg) in water (2 mL). The mixture was stirred at 60°C for 18 h and then diluted with brine and extracted with dichloromethane. Chromatography on silica gel with hexanes−ethyl acetate (8:2−6:4) gave the target 2,3,4,6-tetra-O-benzyl-D-galactopyranose (335 mg, 60%) and traces of its formyl analogue. [Reproduced with the permission of the American Chemical Society.]

ii) Ley-Griffith Type Oxidations

The well-known combination of tetrapropylammonium perruthenate (TPAP) and NMO is used in the preparation of aldehydes from primary alcohols, wherein the water produced must be taken up by molecular sieves.[131] The presence of water fosters an equilibrium concentration of the aldehyde hydrate, which can undergo further oxidation to the carboxylic acid (*Scheme 21*). The diversity of the process can be extended to other oxidations. For example, an efficient method for the oxidation of an olefin to the less substituted carbonyl compound is known. This one pot conversion involves hydroboration with borane dimethyl sulfide (BDMS), followed by oxidation of the resulting alkylboranes with TPAP and NMO. Conveniently, this reaction is self indicating (*Scheme 21*).[132]



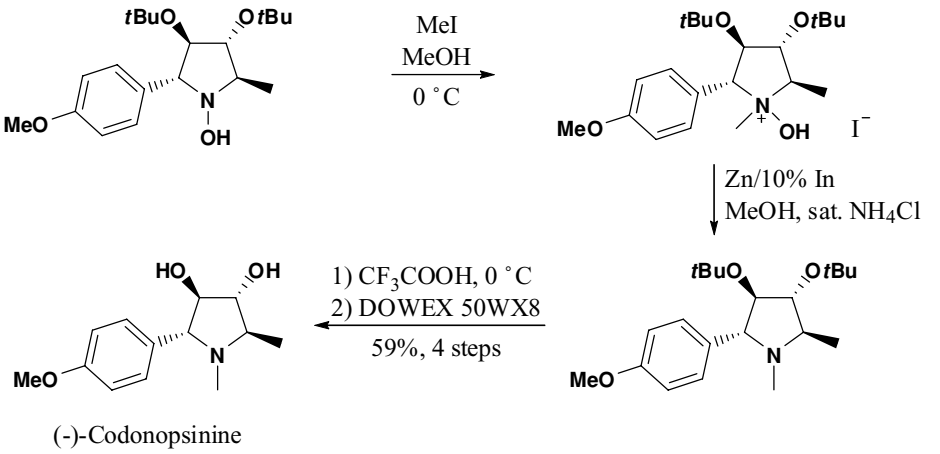
Scheme 21

iii) Other Processes Using Me_3NO

Copper(II)-catalyzed oxidation of benzylic alcohols by Me_3NO has been reported.[133] Related oxidation of RCH_2Br to RCHO is known as the Kornblum oxidation when sulfoxides are used as the terminal oxidants. The equivalent reaction with Me_3NO is known and, in this case, referred to as the Ganem oxidation.[134]

g) Tertiary Amine N-Oxides in Target Synthesis

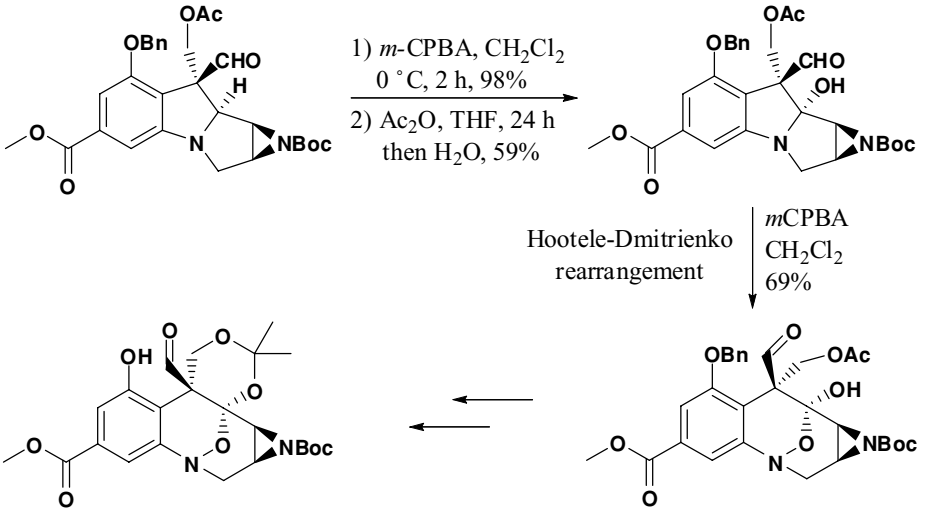
The synthesis of (−)-codonopsinine was achieved by Goti *et al.* (*Scheme 22*).[135] Methylation of a hydroxylamine to the corresponding *N*-oxide and subsequent reduction was used to convert a hydroxylamine to the methylamine.



(-)-Codonopsinine

Scheme 22

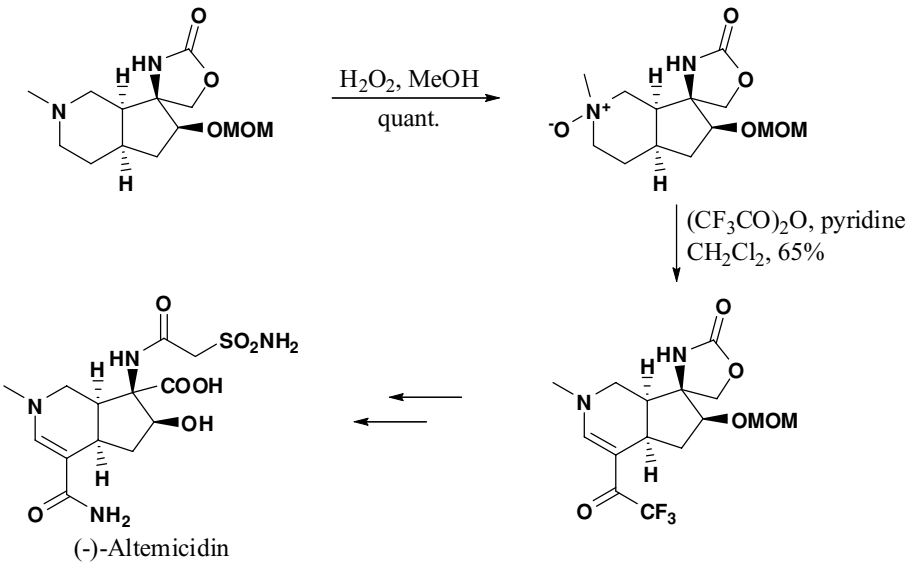
The Polonovski reaction has been deployed in several total syntheses in the last two decades. For example, in the synthesis of the core nucleus of FR900482 a Polonovski sequence has been used by Ziegler (*Scheme 23*).[136] Trost used the same strategy in the synthesis of *epi*-(+)-FR900482.[137] Both FR900482 and *epi*-(+)-FR900482 show anticancer activity.



Core nucleus of FR900482

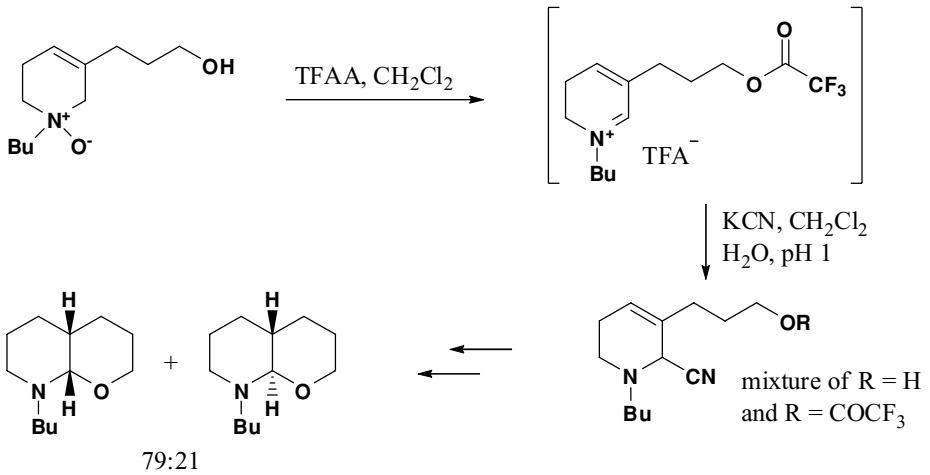
Scheme 23

The carbamoyl-enamine moiety in the total synthesis of (-)-altemicidin by Kende was established *via* a modified Polonovski-Portier rearrangement using $(CF_3CO)_2O$ (*Scheme 24*).[138] The better leaving group ability of the trifluoroacetate group engendered elimination of TFA generating an enamine that captured further TFAA.



Scheme 24

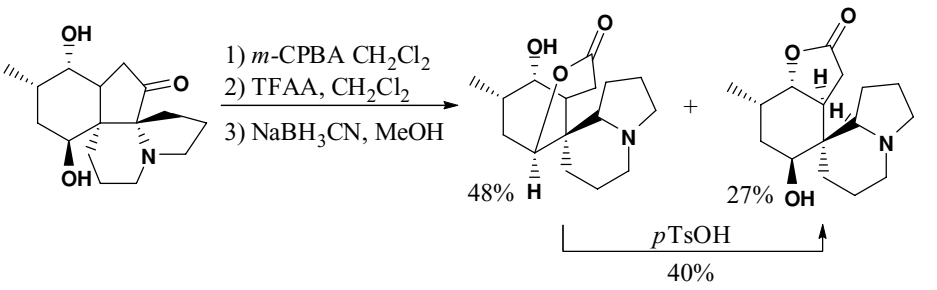
In the synthesis of the octahydropyranol[2,3-*b*]pyridine ring system of 'upenamide, the *N*-oxide was transformed into the aminonitrile *via* Polonovski-Portier reaction and subsequent trapping of the intermediate dihydropyridinium salt with potassium cyanide (*Scheme 25*).[139]



Scheme 25

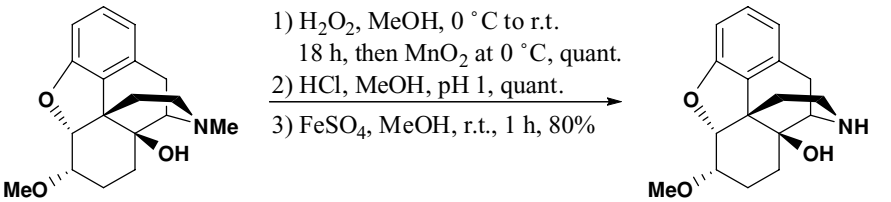
The biomimetic transformation of serratinine into serratezomine A through a modified Polonovski reaction is shown in *Scheme 26*.[140]

N-Demethylation of several opiate alkaloids in up to 80% yield was carried out *via* hydrogen peroxide oxidation to the *N*-oxide followed by nonclassical Polonovski reaction



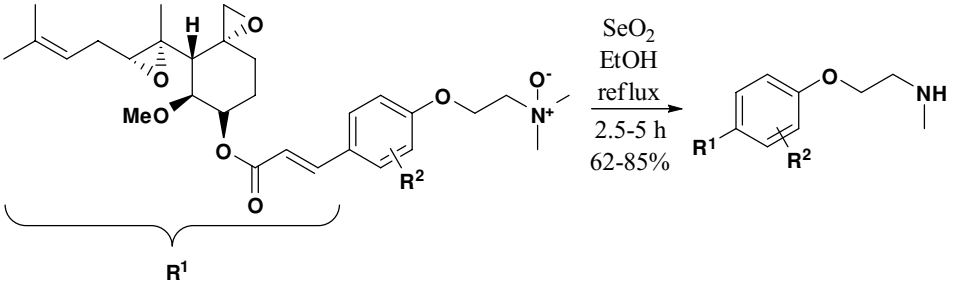
Scheme 26

using iron(II) sulfate (*Scheme 27*).[141] The workup and purification of the nor-opiates were complicated due to the presence of the iron-salts. These problems were solved by evaporating the reaction solvent and dissolving the crude product in 0.1 M EDTA solution basified to pH 10 prior to chloroform extraction.



Scheme 27

A series of fumagillol derivatives was demethylated with SeO_2 in ethanol giving the corresponding secondary amines in 62–85% yield (*Scheme 28*).[142] Both the epoxides and the unsaturated ester 'survived' this potentially demanding transformation! Aminofumagillol derivatives are antiangiogenesis inhibitors.



Scheme 28

III. Heteroaromatic Amine *N*-Oxides

1. Preparation

Preparations of heterocyclic *N*-oxides are normally attained by procedures that are often related to their tertiary aliphatic cousins. Additionally, as there are already highly extensive

Table 4
Average Bonding Modes for N-oxide Metal Complexes

No. of examples	Bonding Type	Ave. Distance (M-O)/Å	Ave. M-O-N angle/°
12	I: Binding of $Me_3N\rightarrow O$ to 1st row transition metals and lighter elements	1.90 ± 0.05	~125
>200	II: Binding of pyridine *N*-oxide to 1st row transition metals and lighter elements	2.00 ± 0.05	124 ± 6
>100	III: Binding of pyridine *N*-oxide to 2nd row transition metals and heavier elements	2.00 ± 0.05	124 ± 6

reviews detailing 'classical approaches' describing heteroaromatic *N*-oxide formation (see *Table 1*), duplication here is not helpful.

2. Reactivity and Applications

a) Heteroaromatic N-Oxides as Ligands and Reagents in Metal-Based Catalysts

i) Ligands and Catalysts

About 400 discrete metal complexes of sp^3 and sp^2 *N*-oxides are reported in the Cambridge Crystallographic Database;[143] the latter sp^2 derivatives being by far the most common. The bonding parameters of these species group conveniently into three categories (*Table 4*). The presence of significant steric crowding or Jahn-Teller distortions can however result in significant lengthening of the M-O bond (towards the values in Bonding Type III) but in general the N→O-M bond angle is not significantly altered.

Metal coordination of *N*-oxides has proved an effective method for improving the efficiency of manganese salen-based catalysts.[144] The binding of a single *N*-oxide is thought to prolonging the lifespan of the active Mn(V) oxo species (*Scheme 29*). These Mn . . . O interactions are rather weak: a binding constant of 0.19 M^{-1} has been determined for the equilibrium between JCl and $[JL_2]^+$.[145] No measurement for the formation of $[JL]^+$ has been reported.

Aside from their use by Jacobsen, application of *N*-oxide ligated transition metal complexes represents a burgeoning area for selective catalysis dating only from 1999. The apparent reason for this paucity are that many transition metals are active catalysts for *N*-oxide reduction in the presence of suitable O-acceptors. Recent examples of *N*-oxide based catalysts (*Scheme 30*) have had their applications collected together in *Table 5* for convenience.

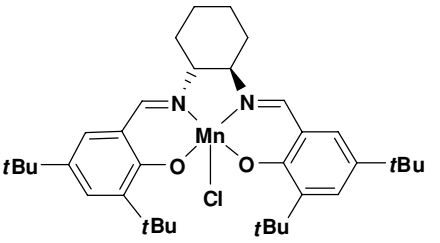
ii) Use as Oxygen-atom Transfer Reagents

Due to the relative weakness of the N→O dative bond (~65 kcal mol^{-1}) heteroaromatic *N*-oxides have potential as mild, safe, oxidants. The intrinsic limitation of this approach is that after O-atom transfer to a metal catalyst (forming $L_nM{=}O$) the free amine is released. The latter often binds the catalyst more strongly preventing catalyst turnover. The use of 2,6-lutidine-*N*-oxide overcomes this issue.[152] Apparently such competitive amine binding

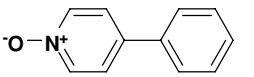
Table 5
Selective Catalytic Syntheses using N-oxide Ligated Complexes

Complex	Process (starting materials)	Selectivity	Ref.
9	Cyclopropanation (styrene and N_2CHCO_2Et)	*cis*-1,2-cyclopropane (21% ee); *trans* (15% ee)	146
10	*ortho* C-H activation of *N*-oxides (pyridine *N*-oxide and Ar-H)	Only substitution at 2,6 positions of pyridine *N*-oxide; mono:di substitution 3:1 to 20:1	147
10	*ortho* C-H activation of *N*-oxides (pyridine *N*-oxide and alkenes)	Only substitution at the 2 positions of pyridine *N*-oxide	147
11	Ethylene polmerization (CH_2=CH_2 plus organoaluminium promoter)	Flory-Schulz distribution; polydispersivity 1.2-1.7	148
12	Ketone allylation (PhC(=O)Me + $Sn(CH_2CH=CH_2)_4$)	70–83% ee	149
13	Henry reaction (ArCHO + $MeNO_2$)	85–98% ee	150
5	Hetero Diels-Alder (Danishefsky diene and imine)	71–89% ee	151

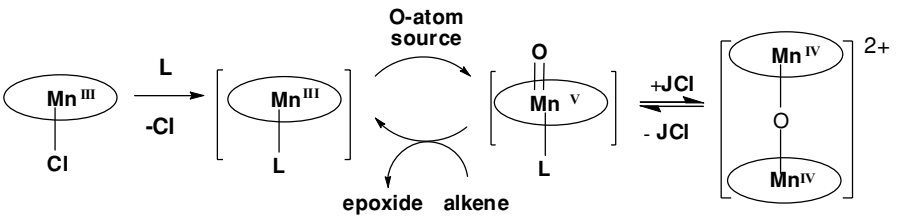
a) Ligand **12** + $InBr_3$ used *in situ*.
b) Ligand **13** + CuOTf used *in situ*.
c) Ligand **5** + $Sc(OTf)_3$ used *in situ*.



JCl

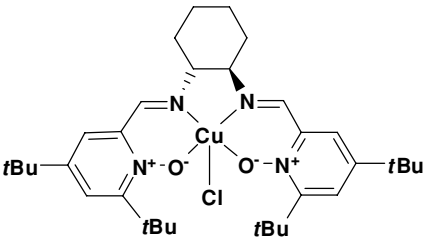


L

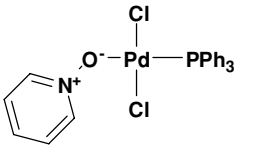


JCl **[J(L)]$^+$** **[J(=O)(L)]$^+$** **[J$_2$(O)]$^{2+}$**

Scheme 29



9



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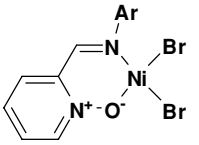
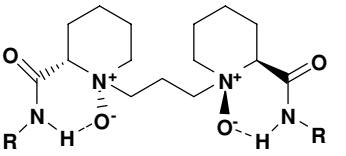


11



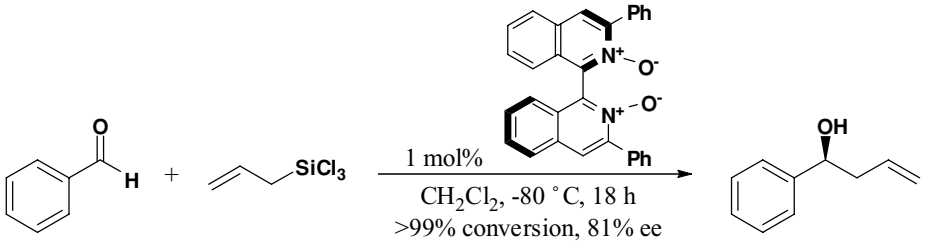
12 R = Ph
13 R = cC$_5$H$_9$

Scheme 30

is not an issue in related O-atom transfers to aliphatic amines from pyridine-*N*-oxides under palladium catalysis.[153]

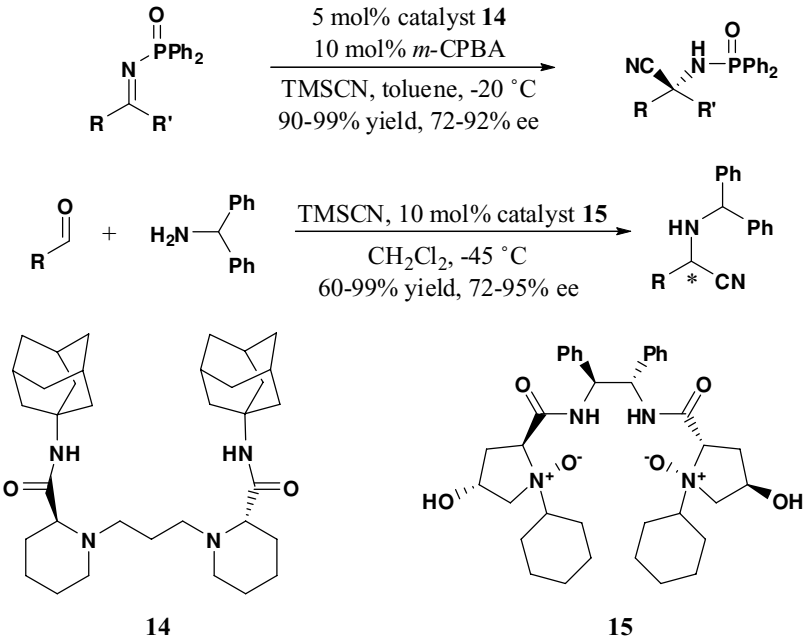
b) Heteroaromatic Amine N-Oxides as Organocatalysts

A microreview[8] by Malkov and Kočovský from 2007 on chiral *N*-oxides as catalysts in asymmetric synthesis covers: allylation, propargylation and allenylation of aldehydes, asymmetric aldol reactions, asymmetric opening of *meso*-epoxides and cyanosilation of aldehydes/aldimines (metal-free reactions), cyanosilylation of ketones and Michael additions from the inception of this field (see *Table 1*). It also details other, so far less successful, metal catalyzed reactions (asymmetric cyclopropanation, reduction of ketones and addition of Et_2Zn to ketones. See also Section 2a herein).[154] The asymmetric allylation has established itself as the most important area of utility in *N*-oxide organocatalysis. Investigations on the mechanism of this reaction have been done by Kočovský with enantiomeric excess (ee) values up to 98%.[155] Only a few new catalysts have been developed since the Kočovský review.[156–158] A representative example is shown in *Scheme 31*.[158]



Scheme 31

Aside from allylation reactions, significant advances have been attained in asymmetric epoxidation of α,β-unsaturated ketones[159] where ee values up to 82% were achieved. However, in this case a yield of only 26% was attained. In cases where the conversion and yield was allowed to maximize at 75%, the selectivity fell to just 30% ee. Enantioselective Strecker reactions of phosphinoyl ketoimines are also catalysed by the *in situ* prepared chiral *N*,*N*-dioxides, for example catalyst **14**. Related asymmetric three-component Strecker reactions catalysed by hydroxy-L-proline derived *N*,*N*-dioxides, for example catalyst **15**, have also been reported recently (*Scheme 32*).[160,161]

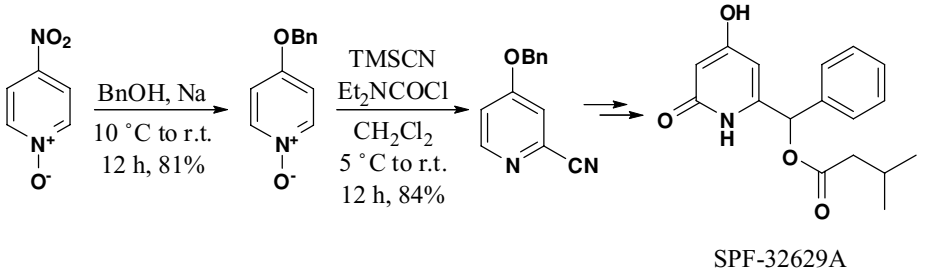


14 **15**

Scheme 32

c) Heteroaromatic N-Oxides in Target Synthesis

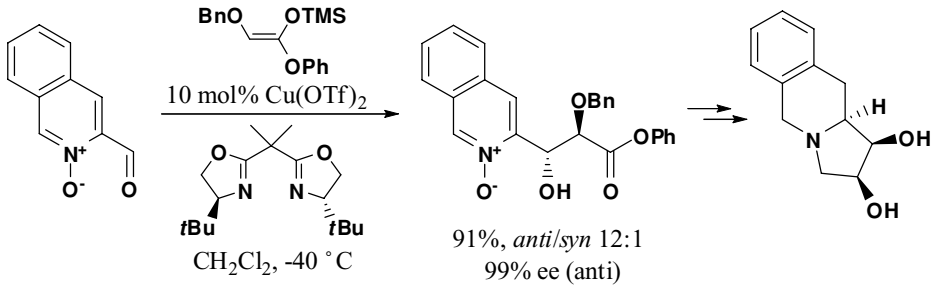
Vegi *et al.* used 4-nitropyridine *N*-oxide (commercially available) as starting material in their synthesis of the human chymase inhibitor SPF-32629A (*Scheme 33*).[162] The formation of the 2-cyano compound is analogous to well known chlorinations of *N*-oxides using phosphorous oxychloride and related reagents.



SPF-32629A

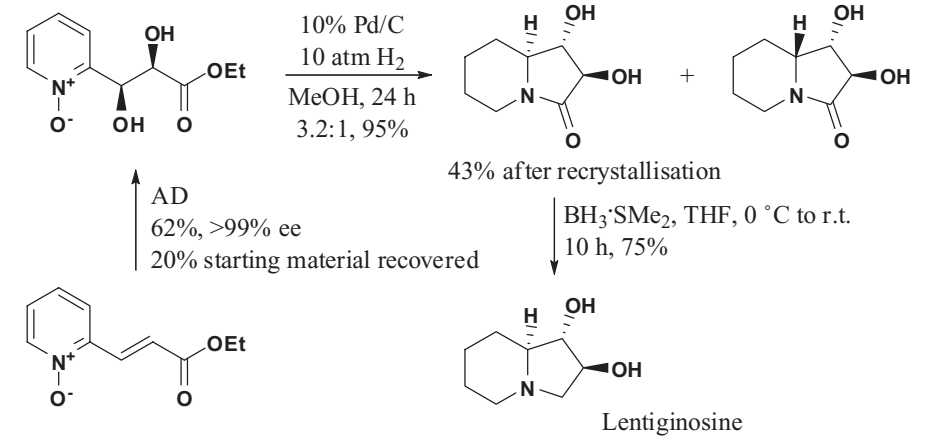
Scheme 33

bis(Oxazoline) Lewis acid catalyzed aldol reactions of pyridine *N*-oxide aldehydes was employed in the synthesis of an indolizidine alkaloid by Jørgensen (*Scheme 34*).[163] The ee in this reaction was up to 99%, whereas similar pyridine derivatives gave racemic products.



Scheme 34

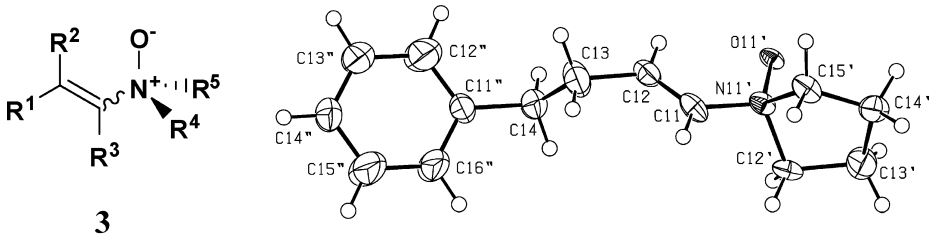
In the total synthesis of (+)-lentiginosine by Zhou the *N*-oxide works as a protecting group for the pyridine moiety in the asymmetric dihydroxylation step (*Scheme 35*).[164] Asymmetric dihydroxylation of the corresponding pyridine derivative was "not successful" presumably because the pyridine moiety reacts as an accelerating ligand and is thus competing with the chiral ligand. This would lead to a very low product ee.



Scheme 35

IV. Enamine *N*-Oxides

Enamine *N*-oxides of general structure **3** constitute the least abundant members of the *N*-oxide family. This is, in part, due to the problems associated with the direct synthesis of molecules of this class rather than any intrinsic thermodynamic instability. For example, compound **3** $R^1 = CH_2CH_2Ph$; R^2,$R^3 = H$; R^4,$R^5 = (CH_2)_4$ is recovered unchanged after at least one year at $-25°C$ when stored under a protective atmosphere. The physical and structural properties of enamine *N*-oxides are akin to their heteroaromatic analogues and in one case an X-ray structure has been attained (*Figure 1*).[165]



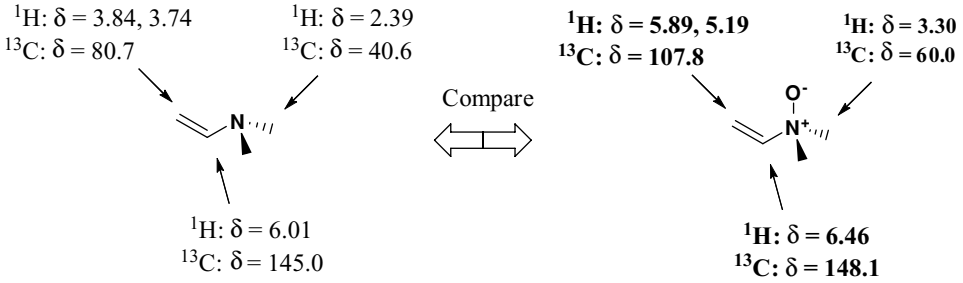
3

Molecular Structure of a Representative Enamine-*N*-Oxide **3** ($R^1 = CH_2CH_2Ph$; R^2,R^3 = H; R^4,$R^5 = (CH_2)_4$).

Figure 1

Selected intramolecular distances and angles for an example of **3**. N(11′)-O(11′) 1.390(3); N(11′)-C(12′) 1.508(5); N(11′)-C(15′) 1.513(5); N(11′)-C(11) 1.468(5); C(11)-C(12) 1.303(6) Å. C(12′)-N(11′)-C(15′) 101.3(3); C(11)-N(11′)-C(12′) 110.7(4); C(11)-N(11′)-C(15′) 111.0(3); O(11′)-N(11′)-C(11) 113.1(3); N(11′)-C(11)-C(12) 123.0(4)°. C(12)H(12C)···O11′ 2.35 Å. (Figure 1 is reproduced with the permission of the American Chemical Society.)

Due to the presence of their highly electron rich C=C bond, direct *N*-oxidation of enamines cannot be used for the preparation of **3**. Such attempted oxidations usually lead instead to complex reaction mixtures, comprised mainly of amides, α-amino ketones and, in some cases, unstable aminoepoxides. Due to this issue, the double bond in **3** has to be installed by alternative procedures. Enamine *N*-oxides **3** are best identified by their ^{1}H and ^{13}C NMR spectra as the substituents α and β to the N→O core show characteristic shift ranges compared to their nominal enamine progenitors (*Scheme 36*).



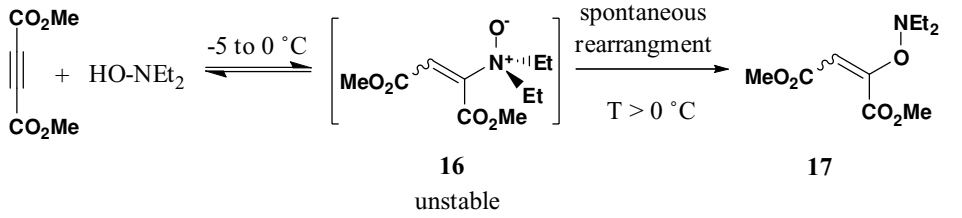
Scheme 36

1. Preparation

a) Retro-Cope Approaches

The proximity of the β-placed =CH and the *N*-oxide in Figure 1 (2.35 Å) suggests that such motifs ought to be accessible through retro-Cope addition of hydroxylamines to suitably activated alkynes. Indeed, the first to claim a synthesis of an enamine *N*-oxide was Winterfelt[166] who pursued such an approach in 1969 (*Scheme 37*). Unfortunately, the derived *N*-addition product **16** was *not* isolable; above 0 °C, the reaction's reversibility allows rapid conversion to the thermodynamically more stable *O*-addition product **17**. Later Hwu and

co-workers confirmed this observation through NMR studies.[167] The formation of rearranged products (*e. g.* **17**) is best evidenced by the observation of a low frequency, 'enol ether-like' β-carbon at 80–85 ppm in a low polarity product compared to that expected for an *N*-oxide product. Such N/O-rearrangement processes may constitute a common decomposition process in all enamine-*N*-oxides provided high enough temperatures are supplied.



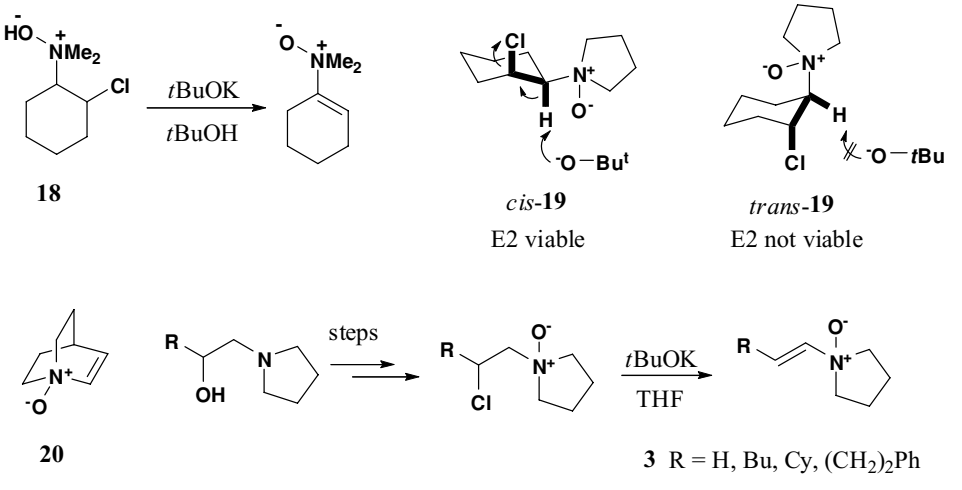
16
unstable

17

Scheme 37

b) HX Elimination from β-Substituted N-Oxides

The first systematic approach to the preparation of enamine-*N*-oxides was by Richmond and Krouwer in 1978 (*Scheme 38*).[168] They employed HCl elimination from **18** under strongly basic conditions. It would appear that these eliminations proceed *via* an E2 mechanism. In the original literature the relative stereochemistry of **18** had not been specified. However, Bernier was able to show that closely related *cis*-**19** smoothly eliminated with *t*BuOK to form the desired enamine *N*-oxide but that no reaction occurred from the equivalent *trans* isomer. In another rare example, O'Neil prepared **20** by an equivalent process (elimination of HOTs) from quinuclidinol tosylate *N*-oxide.[169,170] A further range of acyclic pyrrolidine-based compounds was prepared by Bernier.[165] The prerequisite β-chloro *N*-oxides were attained from epoxide derived amino alcohols after chlorination and *N*-oxidation with *m*CPBA.



18

cis-**19**
E2 viable

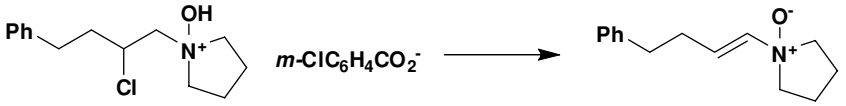
trans-**19**
E2 not viable

20

3 R = H, Bu, Cy, $(CH_2)_2Ph$

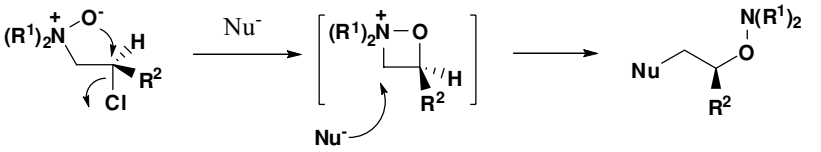
Scheme 38

Representative Preparation of an Enamine N-Oxide: N-(4-Phenylbuten-1-yl)pyrrolidine N-oxide[165]



A solution of the m-chlorobenzoic acid salt of β-chloroamine N-oxide (13.3 g, 28.8 mmol) in THF (0.2 M) was added dropwise to an ice-cold suspension of KOtBu (10.0 g, 3 eq.) in THF (0.6 M). The mixture was stirred and allowed to warm up to room temperature. After 7 h, the THF was removed in vacuo. The resulting solid was triturated under CH_2Cl_2/MeOH (80/20) and filtered through a short plug of neutral alumina. Concentration in vacuo and chromatography (SiO_2, CH_2Cl_2/MeOH from 95/5 to 70/30) afforded the enamine N-oxide (3.91 g, 67%) as a crystalline solid, that became oily if exposed to atmospheric moisture. [Reproduced with the permission of the American Chemical Society.]

The HX elimination approach of *Scheme 38* is often complicated by competing rearrangement chemistry. 'Naked' *N*-oxides are relatively nucleophilic and unless the desired β-elimination is more rapid than intramolecular formation of an unstable oxazetidinium that can be opened by a range of *in situ* nucleophiles (*Scheme 39*). As the former ring-closure occurs in a stereospecific manner, this approach can form the basis for a useful preparation of substituted hydroxylamines.



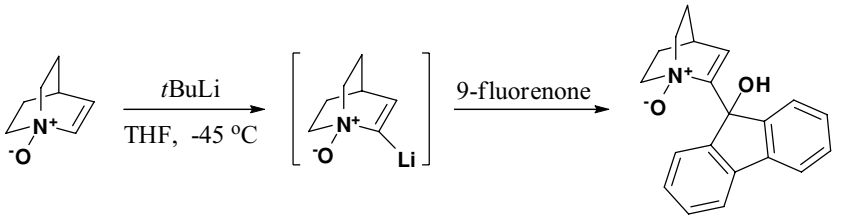
Scheme 39

2. Reactivity

The chemistry of enamine-*N*-oxides remains little explored at present due in part to the small number of members of this compound class. As judged by the published ^{13}C NMR data the C=C bond has a similar electron density to that of a simple terminal alkene (δ_α = 137–148; δ_β = 108–139). However, the α-carbon is clearly electron deficient relative to the carbon β to the *N*-oxide.

a) Lithiation

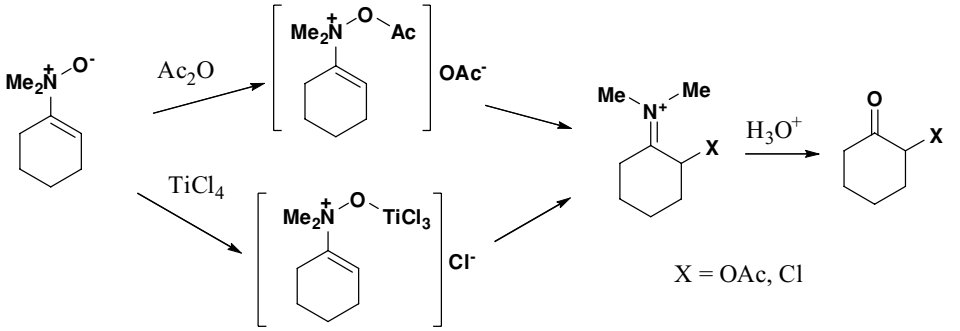
The presence of the electron withdrawing *N*-oxide, together with its properties as a Li^+ directing group, allows deprotonation at acidic C-H positions as demonstrated by O'Neil through trapping with 9-fluorenone (*Scheme 40*).[169,170] Richmond reacted the enamine-*N*-oxide derived from **18** with *n*BuLi but in this case the intermediate was quenched only with protons resulting in production of cyclohexanone.[168]



Scheme 40

b) Other Reactions

The other main reported reaction manifold for enamine-*N*-oxides arises from interaction of the oxide with 'hard' oxophilic electrophiles. Cleavage of the N-O bond apparently results in the unmasking of a transient iminium species which intercepts any available nucleophile. *Scheme 41* gives two representative examples from the chemistry of Richmond.[168]



Scheme 41

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