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Study on Oxaziridine With Reference To Properties

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Abstract - Oxaziridine are an important synthetic motif present in many natural products. α-hydroxyketones have been synthesized in many ways, including reduction of α-diketones, substitution of a hydroxyl for a leaving group and direct oxidation of an enolate. Oxodiperoxymolybdenum(pyridine)-(hexamethylphosphoric triamide) (MoOPH) and N-sulfonyloxaziridines are the most common electrophilic sources of oxygen implemented in this process. One advantage of using N-sulfonyloxaziridines is that higher chiral induction is almost invariably observed relative to MoOPH and other oxidants. High yield (77-91%) and dr (95:5 - 99:1) are reported for α-hydroxylation with the Evans' chiral auxiliary with N-sulfonyloxaziridine as the electrophile. Chiral induction has been demonstrated with many other chiral ketones and ketones with chiral auxiliaries, including SAMP and RAMP.

Key Words: Reduction, Hydroxyl, Electrophilic Sources, Chiral Auxiliaries, Chiral Ketones And Ketones.

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INTRODUCTION

An **oxaziridine** is an organic molecule that features a three-membered heterocycle containing oxygen, nitrogen, and carbon. Oxaziridne derivatives are commonly used as reagents in organic chemistry for a variety of oxidations, including alpha hydroxylation of enolates, epoxidation and aziridination of olefins, and other heteroatom transfer reactions. Oxaziridines are also synthetically useful as intermediates that undergo rearrangement to amides, as well as participate in [3+2] cycloadditions with various heterocumulenes to form substituted five remembered heterocycles. Chiral oxaziridine derivatives have also been developed in order to effect asymmetric oxygen transfer to prochiral enolates, as well as other substrates. Some oxaziridines also have the interesting property of a high barrier to inversion of the nitrogen, allowing for the possibility of chirality at the nitrogen atom.

REVIEW OF LITERATURE

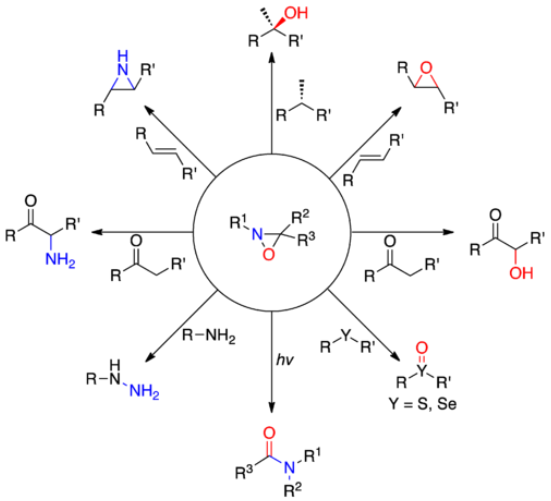
Oxaziridine derivatives were first synthesized in the mid-1950s by Emmons[2] and subsequently by Krimm[3] and Horner and Jürgens.[4] Whereas oxygen and nitrogen typically act as nucleophiles due to their high electronegativity, oxaziridines allow for electrophilic transfer of both heteroatoms. This unusual reactivity is due to the presence of the highly strained three membered ring and the relatively weak N-O bond. Nucleophiles tend to attack at the aziridine nitrogen when the nitrogen substituent is small (R^1= H), and at the oxygen atom when the nitrogen substituent has greater steric bulk. The unusual electronics of the oxaziridine system may be exploited to perform a number of oxygen and nitrogen transfer reactions including, but not limited to: α-hydroxylation of enolates, epoxidation of alkenes, selective oxidation of Sulphide s and selenides, amination of *N*-nucleophiles and *N*-acylamidation.

In the late 1970s and early 1980s F. A. Davis synthesized the first *N*-Sulfonyloxaziridines, which act exclusively as oxygen transfer reagents, and are the most predominantly used class of oxaziridines today.[6] While originally synthesized with mCPBA and the phase transfer catalyst benzyltrimethylammonium chloride, an improved synthesis using oxone as the oxidant is now most prevalent.

MATERIAL AND METHOD

Chiral oxaziridine reagents have been developed, which allow for stereospecific transfer of heteroatoms. Chirality in oxaziridine compounds may be derived from the structure of the substituents on the oxaziridine, or from the conformationally locked nitrogen atom. Oxaziridines are unique in their exceptionally high inversion barrier for nitrogen to retain its stereochemical configuration. Chiral camphorsulfonyloxaziridines were synthesized by F. A. Davis in the 1970s have become a cornerstone of asymmetric synthesis. Among many prominent total syntheses employing oxaziridines, both the Holton Taxol total synthesis and the Wender Taxol total synthesis feature asymmetric α-hydroxylation with camphorsulfonyloxaziridine as a key step in the

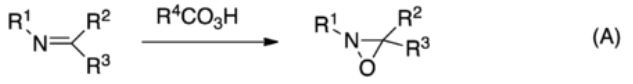
synthesis of Taxol, a complicated natural product marketed as a chemotherapy agent.

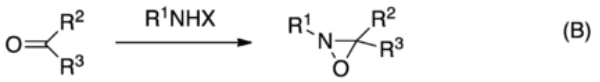


Synthesis

N-H, N-ALKYL, N-ARYLOXAZIRIDINES

The two main approaches to synthesis of N-H, N-Alkyl, and N-Aryloxaziridines are oxidation of imines with peracids (A) and amination of carbonyls (B).

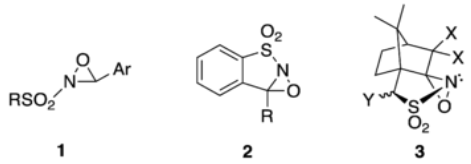


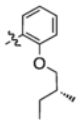


Additionally, oxidation of chiral imines and oxidation of imines with chiral peracids may yield enantiopure oxaziridines. Some oxaziridines have the unique property of configurationally stable nitrogen atoms at room temperature due to an inversion barrier of 24 to 31 kcal/mol. Enantiopure oxaziridines where stereochemistry is entirely due to configurationally stable nitrogen are reported.

N-SULFONYLOXAZIRIDINES

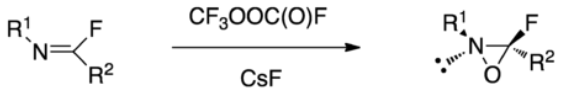
There are many N-sulfonyloxaziridines used today, each with slightly different properties and reactivity. A summary of some of these reagents may be found in the table below.



[O]	R	Ar	[O]	R	[O]	X	Y
1a	Ph	Ph	2a	Me	3a	H	H
1b	*p*-MePh	Ph	2b	Ph	3b	Cl	H
1c	*p*-MePh	*o*-MePh	2c		3c	MeO	H
1d		2-Cl-5-O_2NPH	2d		3d	H	MeO
1e		2-Cl-5-O_2NPH			3e	H	*p*-MeOBn
					3f	H	*p*-CF_3Bn

PERFLUORINATED OXAZIRIDINES

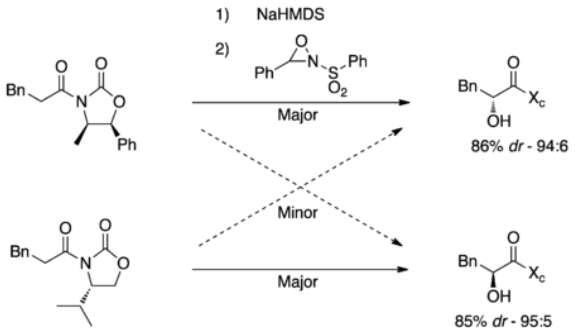
Perfluorinated oxaziridines display an interesting reactivity scheme unique from hydrocarbon based oxaziridines. The highly electron withdrawing perfluoroalkyl substituents cause oxaziridines of this class to have reactivity more similar to dioxiranes than typical oxaziridines. Notably, perfluoroalkyloxaziridines have the ability to hydroxylate certain C-H bonds with high selectivity. Perfluorinated oxaziridines may be synthesized by subjecting a perfluorinated imine to perfluoromethyl fluorocarbonyl peroxide and a metal fluoride to act as an HF scavenger.



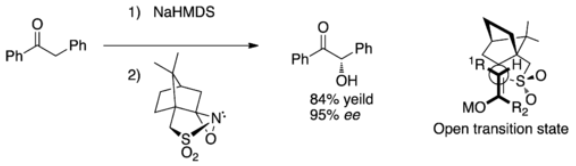
REACTIONS OF OXAZIRIDINES

α-Hydroxylation of enolates

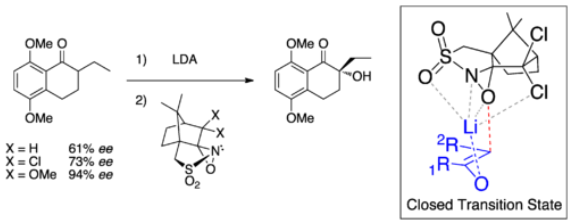
α-hydroxyketones, or acyloins, are an important synthetic motif present in many natural products. α-hydroxyketones have been synthesized in many ways, including reduction of α-diketones, substitution of a hydroxyl for a leaving group and direct oxidation of an enolate. Oxodiperoxymolybdenum(pyridine)-(hexamethylphosphoric triamide) (MoOPH) and *N*-sulfonyloxaziridines are the most common electrophilic sources of oxygen implemented in this process. One advantage of using *N*-sulfonyloxaziridines is that higher chiral induction is almost invariably observed relative to MoOPH and other oxidants. High yield (77-91%) and *dr* (95:5 - 99:1) are reported for α-hydroxylation with the Evans' chiral auxiliary with *N*-sulfonyloxaziridine as the electrophile.[18] Chiral induction has been demonstrated with many other chiral ketones and ketones with chiral auxiliaries, including SAMP and RAMP.



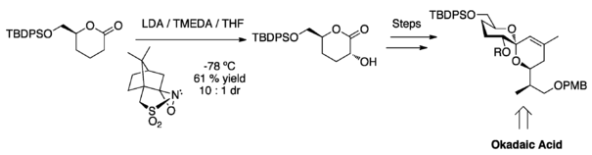
Davis has performed extensive work on asymmetric hydroxylation of prochiral enolates with camphorsulfonyloxaziridine derivatives, achieving moderate to high enantiomeric excess. The commonly accepted proposed transition state that justifies this stereochemical outcome involves an open transition state where the steric bulk of R^1 determines the face of approach.



Interestingly, the selectivity of some hydroxylations may be drastically improved in some cases with the addition of coordinating groups alpha to the oxaziridine ring as oxaziridines **3b** and **3c** in the table above. In these instances it is proposed that the reaction proceeds through a closed transition state where the metal oxyanion is stabilized by chelation from the sulfate and coordinating groups on the camphor skeleton.

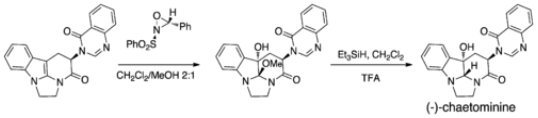


α-Hydroxylation with oxaziridines has been widely implemented in total synthesis. It is a key step in both the Holton Taxol total synthesis and the Wender Taxol total synthesis. Additionally, Forsyth implemented the transformation in his synthesis of the C3-C14 (Substituted 1,7-Dioxaspiro[5.5]undec-3-ene) System of Okadaic acid.



EPOXIDATION OF ALKENES

Epoxidation of alkenes is a versatile synthetic technique in organic synthesis. Epoxides may be derivatized to a number of useful functional groups and motifs. Classically, epoxidation is carried out with mCPBA or other peracids. Oxaziridines have been found to perform similar chemistry, and are useful for the formation of highly acid sensitive epoxides. Papeo et al. performed a synthesis of (-)-Chaetominine that utilized oxaziridine epoxidation as a late stage transformation as seen below.



CONCLUSION

Another transformation of high synthetic utility is asymmetric epoxidation. There exist a number of asymmetric epoxidations in the literature, including the Sharpless epoxidation, the Jacobsen-Katsuki epoxidation and the Juliá-Colonna Epoxidation. These methods have one major drawback in that they require very specific functionality in order to achieve selectivity. The Sharpless epoxidation is specific to allylic alcohols, the Jacobsen epoxidation requires *cis*-disubstituted aryl alkenes, and the Juliá epoxidation requires α-β unsaturated ketones. Epoxidation with asymmetric oxaziridine reagents is among a select few transformations that are stereospecific to unfunctionalized alkenes with sufficient asymmetric induction to provide steric differentiation between faces. It has even been shown to be possible to produce stereospecific epoxidation catalytic in the oxaziridine chiral unit. Further investigation into these reactions may be required before levels of enantiometic excess become practical for large scale synthesis. Lusinichi et al. have investigated asymmetric epoxidation with a chiral oxaziridinium salt using oxone as the stoichiometric oxidant seen below.

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