

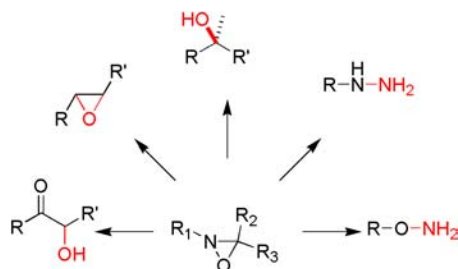
Oxaziridines as Heteroatom Transfer Reagents

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ABSTRACT



Oxaziridines have been utilized in organic synthesis as sources of both electrophilic oxygen and electrophilic nitrogen for a wide variety of nucleophiles. The predominance of one process over another can be affected by varying the substitution pattern on nitrogen. In general, oxaziridines with small groups on nitrogen (N, Me) act as aminating agents, whereas those with bulky or electron-withdrawing groups on nitrogen preferentially transfer the oxygen atom. Although other nitrogen and oxygen transfer reagents are known, oxaziridine-mediated processes are of interest due to the easy accessibility of the reagents and their potential for asymmetric induction.

Since the announcement of their discovery in 1956,¹ oxaziridines have been widely investigated, principally for two reasons. The presence of an inherently weak N-O bond in a strained ring promised a group of compounds of unusually high reactivity. In addition, this system possesses the structural elements that seem to be required to observe stereochemical isomerism at nitrogen: ring strain and an atom with unshared electron pairs attached to nitrogen. Since the discovery of oxaziridines, several reviews have appeared.² My intention in this review is to present a broad picture of this heterocyclic system with particular attention to their reactions and uses as heteroatom transfer reagents in synthetic organic chemistry.

Stereochemistry The stereochemistry of the oxaziridine ring has received considerable attention mainly due to the chirality of the nitrogen atom and the appreciable barrier to its inversion. This barrier to inversion was determined to be 25 – 32 kcal/mol in *N*-alkyl oxaziridines³. The transition state for thermal epimerization was shown to have increased ring strain,

thus providing the large barrier to nitrogen inversion (**Scheme 1**).⁴ Oxaziridines have also been shown to epimerize photochemically through a nitrene intermediate.⁵

While the inversion barrier is considerable in *N*-alkyl oxaziridines, when the *N*-substituent is capable of π -conjugation (or hyperconjugation) the inversion barriers are smaller. *N*-aryl as well as *N*-acyl oxaziridines both have inversion barriers near 20 kcal/mol^{6,7} due to their π -conjugation. *N*-sulfonyl oxaziridines also exhibit lower barriers to inversion due to the hyperconjugation present in the system.⁸

Preparation The first preparation of an oxaziridine, which continues today to be a favored method, was the oxidation of an imine with a peracid, commonly *meta*-chlorobenzoic acid (*m*-CPBA).⁹ Chiral oxaziridines can be

¹ Emmons, W. D. *J. Am. Chem. Soc.* **1956**, *78*, 6208.

² Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703.

³ Bjorgo, J.; Boyd, D. R. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1575.

⁴ Forni, A.; Garuti, G.; Moretti, I.; Torre, G.; Andreotti, G. D.; Bocelli, G.; Sagarabotto, P.; *J. Chem. Soc., Perkin Trans. 2* **1978**, 401.

⁵ Bjorgo, J.; Boyd, D. R.; Campbell, R. M.; Neill, D. C. *J. Chem. Soc., Chem. Commun.* **1976**, 162.

⁶ Ono, H.; Splitter, J. S.; Calvin, M. *Tetrahedron Lett.* **1973**, *42*, 4107.

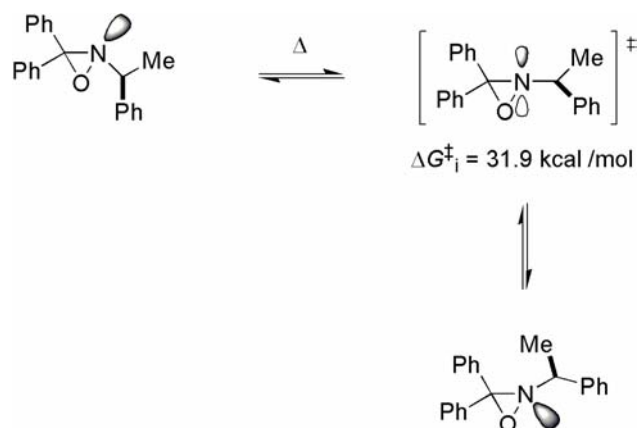
⁷ Jennings, W. B.; Watson, S. P.; Boyd, D. R. *J. Chem. Soc., Chem. Commun.* **1992**, 1078.

⁸ Jennings, W. B.; Watson, S. P.; Tolley, M. S. *J. Am. Chem. Soc.* **1987**, *109*, 8099.

⁹ Widmer, J.; Keller-Schierlein, W. *Helv. Chem. Acta* **1974**, *57*, 657.

produced via oxidation of a chiral imine,^{10,11} oxidation of an achiral imine with a chiral peracid or via separation of

Scheme 1. Thermal racemization of chiral oxaziridines proceeds through a very high barrier to nitrogen inversion.



diastereomeric oxaziridines produced from achiral peracid oxidation.⁹ The mechanism of peroxy oxidation has been studied and found to proceed through a two-step mechanism rather than a concerted oxygen transfer.^{12,13,14}

Other methods for the oxidation of imines have been developed. These efforts have come about due to ecological concerns over the mass use of *m*-CPBA and the difficulty that can occur when purifying the oxaziridine from the chlorobenzoic acid. Cobalt-mediated oxidation using molecular oxygen as the ultimate oxidant has recently been reported.¹⁵ Urea-hydrogen peroxide has also been used as an oxidant and was shown to produce the desired oxaziridine in very good yields.¹⁶

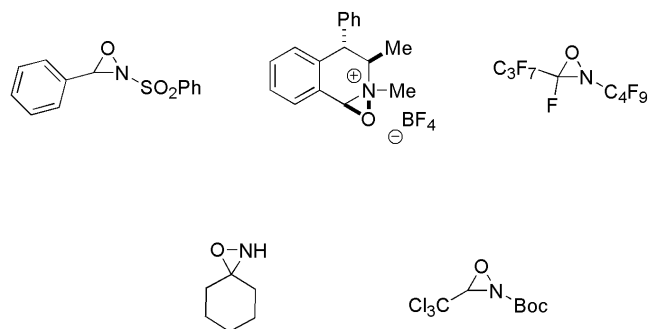
Oxaziridines have been prepared through a variety of other non-oxidative methods. The electrophilic amination of ketones has proved to be a versatile method to produce *N*-unsubstituted oxaziridines.¹⁷ The double 1,4 conjugate addition of hydroxamic acids to propiolates has also been shown to produce oxaziridines in good yields.¹⁸ Finally, the photolysis of nitrones can provide oxaziridines in good yield.¹⁹

Oxaziridines as Heteroatom Transfer Reagents

Oxaziridines can be used as both oxygenating and aminating agents in their reactions with a wide variety of nucleophiles. In spite of this reactive duality, the predominance of one process over another can be affected

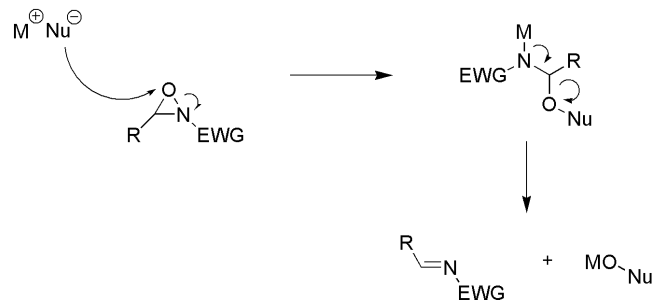
by varying the substitution pattern on nitrogen (**Figure 1**). In general, oxaziridines with small groups on nitrogen (N, Me) act as aminating agents, whereas those with bulky or electron-withdrawing groups on nitrogen preferentially transfer the oxygen atom. Although other nitrogen and oxygen transfer reagents are known, oxaziridine-mediated processes are of interest due to the easy accessibility of the reagents and their potential for asymmetric induction.

Figure 1. Oxaziridines commonly used as heteroatom transfer reagents.



Oxaziridines as Oxygen Transfer Reagents Electron-deficient oxaziridines, such as *N*-sulfonyl oxaziridines, oxaziridinium salts, and perfluorinated oxaziridines have found extensive use as sources of electrophilic oxygen. The general mechanism involves nucleophilic attack on the oxaziridine oxygen with simultaneous N-O bond cleavage. The resultant hemiaminal undergoes breakdown to provide the oxygenated product and an imine byproduct (**Scheme 2**).

Scheme 2. General Mechanism of oxygenation of nucleophiles.



α -Hydroxy ketones have found use in organic synthesis as chiral synthons. Additionally, this functionality can be found in a wide variety of natural products. Their synthesis has been performed with a variety of methods, including substitution of a hydroxyl for a leaving group,

¹⁰ Davis, F. A.; Towson, J. C.; Weismiller, M. C.; Lai, S.; Carroll, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 8477.

¹¹ Kitagawa, O.; Vander Velde, D.; Dutta, D.; Morton, M.; Takusagawa, F.; Aube, J. *J. Am. Chem. Soc.* **1995**, *117*, 5169.

¹² Ogata, Y.; Sawaki, Y. *J. Am. Chem. Soc.* **1973**, *95*, 4687.

¹³ Azman, A.; Koller, J.; Plesnicar, B. *J. Am. Chem. Soc.* **1979**, *101*, 1107.

¹⁴ Wang, Y.; Chakalamannil, S.; Aube, J. *J. Org. Chem.* **2000**, *65*, 5120.

¹⁵ Lin, Y.; Miller, M. J. *J. Org. Chem.* **2001**, *66*, 8282.

¹⁶ Damavandi, J. A.; Karami, B.; Zolfigol *Synlett* **2002**, 933.

¹⁷ Andrae, S.; Schmitz, E. *Synthesis* **1991**, 327.

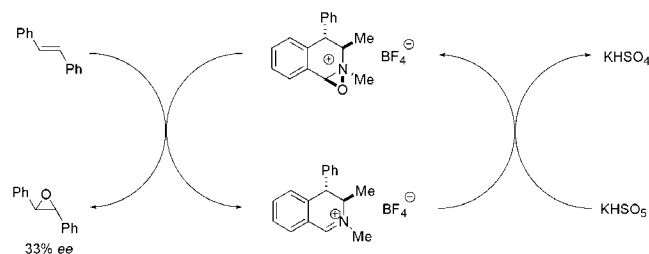
¹⁸ Zong, K.; Shin, S. I.; Ryu, E. K. *Tetrahedron Lett.* **1998**, *39*, 6227.

¹⁹ Toda, F.; Tanaka, K. *Chem. Lett.* **1987**, 2283.

homologation by addition of a carbocation, reduction of β -diketones and finally direct oxidation of an enolate. Direct oxidation of enolates is by far the most straightforward method of producing α -hydroxy ketones. Oxodiperoxymolybdenum(pyridine)-(hexamethylphosphoric triamide) (MoOPH) and *N*-sulfonyl oxaziridines have commonly been used as the electrophilic source of oxygen in the direct oxygenation of enolates.²⁰ Oxaziridines have several advantages including providing more efficient asymmetric induction, higher yields, easier preparation and the ability to perform oxygenations that MoOPH cannot (including the oxygenation of β -dicarbonyls).

Evans and co-workers found they could oxygenate these chiral enolates in good yield (77 – 91%) and good *dr* (95:5 – 99:1) using chiral auxiliaries based on oxazolidines.²⁰ The use of a chiral auxiliary afforded efficient asymmetric induction from a racemic oxaziridine. Prochiral enolates have been oxidized with chiral oxaziridines derived from camphor sulfonic acid.²¹ Davies recently reported that a chiral enolate could be generated in situ via conjugated addition of a chiral amide to an α,β unsaturated carbonyl followed by oxygenation with an oxaziridine.²²

Scheme 3. Catalytic asymmetric epoxidation using chiral iminium salts.

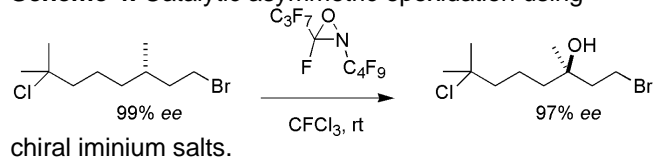


Epoxidation of alkenes has been a very widely used transformation in organic synthesis. It allows the easy conversion and incorporation of many functionalities from an olefin. Commonly, epoxides are formed in a racemic mixture via oxidation of the parent alkene with a peracid such as *m*-CPBA. Oxaziridines have also been shown to provide this useful transformation.²³ Oxaziridines have been employed in cases where the acid-sensitive epoxides are desired, as peracid epoxidations form acidic byproducts. Both experimental²⁴ and theoretical²⁵ evidence

have pointed to an asymmetric spiro transition for the oxygen transfer, as found in the more common peracid epoxidations.

Asymmetric epoxidation is also a desirable transformation. Several methods for the catalytic asymmetric epoxidation of olefins have been developed. These include the asymmetric epoxidation of allylic alcohols by the Sharpless Asymmetric Epoxidation (SAE), the Jacobsen-Katsuki epoxidation of aryl *cis*-disubstituted alkenes and chiral dioxirane epoxidations. Of these, only the chiral dioxirane epoxidations can be performed on unfunctionalized alkenes with asymmetric induction. Thus, chiral oxaziridines could be useful in developing methods toward the catalytic asymmetric epoxidations of alkenes. Oxaziridinium salts (methylated oxaziridines which can be oxidized stereospecifically), have been employed towards this goal (**Scheme 3**).²⁵ Catalytic amounts of ininium have been oxidized in situ to epoxidize unfunctionalized olefins in high yield and moderate *ee*.²⁶ Similar experiments have been performed with binaphthyl-derived oxaziridinium salts²⁷ and chiral amine derived oxaziridinium salts.²⁸

Scheme 4. Catalytic asymmetric epoxidation using



A large variety of nucleophiles can be oxygenated via oxaziridines. Oxidation of nitrogen nucleophiles has been shown to proceed in good yield while common oxidants (*m*-CPBA and magnesium monoperoxy phthalate) have failed to produce the desired compound.²⁹

The oxidation of C-H bonds is a conceptually simple, but pragmatically challenging route to oxygenated compounds. At the moment, efficient techniques for this transformation remain limited, and general and expedient techniques to accomplish it are highly sought. The Resnati group has shown that in a transformation of remarkable selectivity, perfluorinated oxaziridines are capable of oxygenating unactivated C-H bonds (**Scheme 4**).³⁰ The reaction proceeds selectively on tertiary hydrogens in the presence of a variety of functional groups. While the mechanism is currently not known, the transformation has

²⁵ Houk, K. N.; Liu, J.; DeMello, N. C.; Condroski, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10147.

²⁶ Bohe, L.; Hanquet, G.; Lusinch, M.; Lusinch, X. *Tetrahedron Lett.* **1993**, *34*, 7271.

²⁷ Aggarwal, V. K.; Wang, M. F. *J. Chem. Soc., Chem. Commun.* **1996**, 191.

²⁸ Page, P. C. B.; Rassias, G. A.; Bethell, D.; Schilling, M. B. *J. Org. Chem.* **1998**, *63*, 2774.

²⁹ Paleo, M. R.; Aurrecoechea, N.; Jung, K. J.; Rapoport, H. *J. Org. Chem.* **2003**, *68*, 130.

³⁰ Arnone, A.; Foletto, S.; Metrangolo, P.; Pregnotato, M.; Resnati, G. *Org. Lett.* **1999**, *1*, 281.

²⁰ Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346.

²¹ Davis, F. A.; Sheppard, A. C.; Chen, B. C.; Haque, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6679.

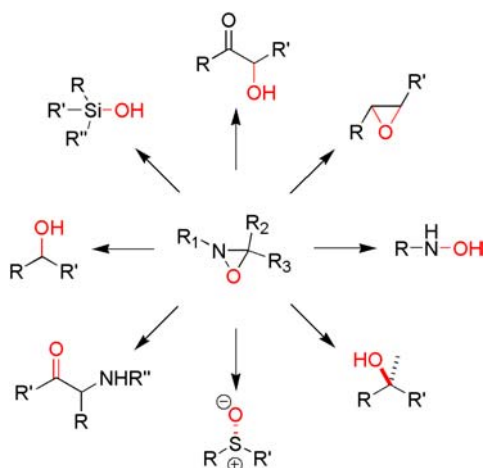
²² Davies, S. G.; Epstein, S. W.; Garner, A. C.; Ichihara, O.; Smith, A. D. *Tetrahedron: Asymmetry* **2002**, *13*, 1555.

²³ Davis, F. A.; Adul-Malik, N. F.; Awad, S. B.; Harakal, M. E. *Tetrahedron Lett.* **1981**, *22*, 917.

²⁴ Anderson, D. R.; Woods, K. W.; Beak, P. *Org. Lett.* **1999**, *1*, 1415.

been utilized on steroid backbones to selectively oxygenate tertiary protons at *cis* ring junctions.³¹

Figure 2. Oxaziridines have been used as an electrophilic source of oxygen in many transformations.



Along with direct oxidation of enolates, the epoxidation of alkenes, nitrogen oxidation and oxygenation of unactivated C-H bonds, oxaziridines have found a variety of uses as electrophilic source of oxygen (Figure 2). Thioethers can be oxidized to chiral sulfoxides,^{32,33} enamines,³⁴ organometallic reagents,³⁵ and tertiary Si-H bonds³⁶ can be oxygenated.

Oxaziridines as Nitrogen Transfer Reagents *N*-Unsubstituted and *N*-acyl substituted oxaziridines have found extensive use as sources of electrophilic nitrogen. As with the electrophilic oxygenation of nucleophiles via oxaziridines, nitrogen-transfer via oxaziridines can provide a plethora of synthetically useful transformations.

Hydrazino acids (amino acids in which the amide functionality is replaced by a hydrazone) have found considerable use in the field of peptidomimetics. In addition, hydrazines are of great utility in a wide array of organic transformations. Hydrazines are popularly synthesized via an electrophilic amination of a nucleophilic nitrogen using chloramine or hydroxylamine-*O*-sulfonic acid. These methods have limitations; residual chlorine functionality resulting from the use of chloramine can be disadvantageous and hydroxylamine-*O*-sulfonic acid is not soluble in anhydrous organic solvents.

³¹ Arnone, A.; Cavicchioli, M.; Montanari, V.; Resnati, G. *J. Org. Chem.* **1994**, *59*, 5511.

³² Betchell, D.; Page, P. C. B.; Vahedi, H. *J. Org. Chem.* **2000**, *65*, 6756.

³³ Sandrinelli, F.; Perrio, S.; Averbuch-Pouchot, M. T. *Org. Lett.* **2002**, *4*, 3619.

³⁴ Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703.

³⁵ Davis, F. A.; Wei, J.; Sheppard, A. C.; Gubernick, S. *Tetrahedron Lett.* **1987**, *28*, 5115.

³⁶ Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992**, *92*, 919.

Oxaziridines can serve as a simple, one-step aminating process in the production of hydrazines from amines.³⁷ Amination of a variety of nucleophilic nitrogen compounds (including amino acids) was shown to be a facile transformation using *N*-unsubstituted oxaziridines.¹⁷ In a reaction unique to oxaziridines, direct *N*-acyl transfer as a method of protected hydrazine synthesis has also been shown to proceed in good yield with a wide variety of substrates.^{38,39,40}

O-Alkyl oximes are important in the synthesis of semisynthetic biopolymers and are present in various drug candidates as well. The oximes are prepared by the direct condensation of an aldehyde or ketone with an alkoxyamine. Alkoxyamines have traditionally been obtained by a two-step sequence: attack of a protected hydroxylamine on an electrophilic carbon and subsequent deprotection. Nitrogen transfer reagents like chloramine have also been used to aminate simple alkoxides with limited success. Ellman and co-workers have produced a one-step, high-turnover reaction that pairs a nucleophilic alkoxide ion with an *N*-unsubstituted oxaziridine.⁴¹ As with protected hydrazine formation, alkoxides can be converted to protected alkoxy amines via *N*-acyl transfer from *N*-acyl oxaziridines.⁴²

Aside from the synthesis of hydrazines and alkoxy amines, oxaziridines have proved themselves very useful in the electrophilic amination of a wide variety of nucleophiles. Among the notable uses are: C-H acidic functionalities can be aminated,^{17,43,44} thioethers can be aminated to generate sulfimide functionalities,⁴⁵ enolates can be smoothly converted into α -amino carbonyl compounds,^{39,45} and aryl substituted olefins can be epaminated to generate aziridines.⁴⁶

Conclusions We have seen oxaziridines used in a variety of unique transformations. Their ease of synthesis via a number of synthetic methods enables their widespread use. Further, the nitrogen inversion barrier in oxaziridines is high enough to allow for the preparation (or separation) of chiral oxaziridines. *N*-Sulfonyl oxaziridines are widely used as reagents in the oxygenation of enolates. Oxaziridinium salts are very promising for the catalytic asymmetric epoxidation of alkenes. Perfluorinated oxaziridines are powerful oxidants, and can oxidize electron deficient olefins and unactivated C-H bonds. New syntheses of hydrazines and alkoxyamines have relied upon the use of *N*-H and *N*-acyl as facile electrophilic aminating agents.

³⁷ Andrae, S.; Schmitz, E.; Sonnenschein, H. *J. Prakt. Chemie.* **1985**, *327*, 445.

³⁸ Schmitz, E.; Fechner-Simon, H.; Schramm, S. *Liebigs Ann. Chem.* **1969**, *725*, 1.

³⁹ Vidal, J.; Guy, L.; Sterin, S.; Collet, A. *J. Org. Chem.* **1993**, *58*, 4791.

⁴⁰ Vidal, J.; Hannachi, J. C.; Hourdin, G.; Mulatier, J. C.; Collet, A. *Tetrahedron Lett.* **1998**, *39*, 8845.

⁴¹ Choong, I. C.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 6528.

⁴² Foot, O. F.; Knight, D. W. *J. Chem. Soc., Chem. Commun.* **2000**, 975.

⁴³ Andrae, S.; Schmitz, E. *Synthesis* **1991**, 327.

⁴⁴ Enders, D.; Poisez, C.; Joseph, R. *Tetrahedron: Asymmetry* **1998**, *9*, 3709.

⁴⁵ Armstrong, A.; Cooker, R. S. *J. Chem. Soc., Chem. Commun.* **2002**, 904.

⁴⁶ Schmitz, E.; Jahnisch, K. *J. Geterozykl. Soedin.* **1974**, *12*, 1629.