CHEMICAL REVIEWS

Review

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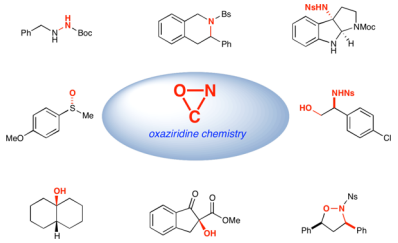
Advances in the Chemistry of Oxaziridines

Kevin S. Williamson,[†] David J. Michaelis,[‡] and Tehshik P. Yoon*

Department of Chemistry, University of Wisconsin—Madison, 1101 University Avenue, Madison, Wisconsin 53706, United States



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1. INTRODUCTION

Oxaziridines constitute a subset of a class of versatile oxidants whose characteristic feature is the presence of two electronegative heteroatoms within a strained three-membered ring (Figure 1). Other small organic heterocycles in this class include diaziridines[1] and dioxiranes,[2] which have been developed as reagents for a variety of oxidative transformations. η^2-Peroxo and η^2-hydroperoxy complexes of various transition metals are also members of this class,[3] and these structures are the active oxidizing species in a broad range of synthetically useful oxidative transformations, including the Sharpless asymmetric epoxidation,[4] $VO(acac)_2$-catalyzed epoxidations,[5] and $MeReO_3$-catalyzed hydroxylation of unactivated alkanes.[6] Peroxometal complexes are relevant in biological systems as well; dinuclear μ-η^2:η^2-peroxodicopper(II) complexes found within the active sites of metalloenzymes such as hemocyanin and tyrosinase have been extensively studied for their role in oxygen metabolism.[7]

Oxidants within this class are generally used in synthesis as atom-transfer reagents; oxidations and aminations of alkanes, alkenes, arenes, amines, sulfides, phosphines, and alkoxides are typical reactions observed.[8] Despite the diverse range of substrates oxidized in these transformations, the mechanisms involved are quite similar. These reactions generally involve a substantially concerted atom transfer from the oxidant to an organic substrate, driven by the release of ring strain and by the formation of a strong carbonyl, imine, or oxometal π-bond.[9] Consequently, reactions mediated by these oxidants have a propensity to be stereospecific, and the oxidations proceed without the generation of strongly acidic or basic byproducts. These features have generated considerable interest in the development of synthetic methods mediated by this class of heterocycles.

Oxaziridines, the subcategory consisting of oxygen−nitrogen−carbon heterocycles, were the first members of this class to be described. First reported by Emmons in 1957,[10] oxaziridines can be easily prepared by a variety of procedures on a multigram scale. Additionally, oxaziridines tend to be significantly more stable than analogous dioxirane and peroxometal complexes; most simple oxaziridines can be purified by standard chromatographic techniques or by recrystallization. They are also amenable to manipulation on the benchtop without precautions against air or moisture and can be stored indefinitely at reduced temperatures without noticeable decomposition.[11]

Research involving oxaziridines over the past five decades has been motivated by the unusual physical properties of these compounds as well as their distinctive reactivity. The most well characterized reactivity of oxaziridines is their ability to serve as electrophilic oxygen atom transfer reagents. Numerous excellent reviews focusing on this aspect of oxaziridine chemistry have been published,[12] and in deference to the comprehensiveness of these reviews, we focus largely upon

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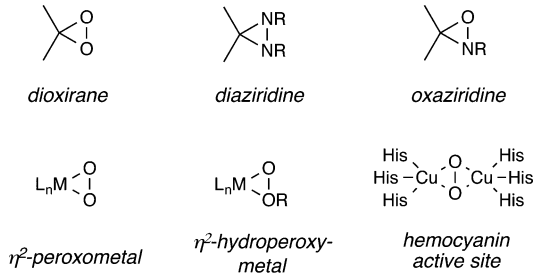


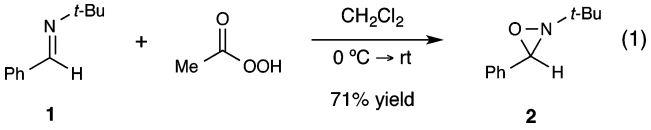
Figure 1. Representative oxidizing heterocycles with two electrophilic heteroatoms within a three-membered ring.

novel oxaziridine-mediated oxygen atom transfer reactions published within the last 20 years. Within the past decade, however, the chemistry of oxaziridines has been significantly expanded and now encompasses many diverse reaction types. In this review, we will provide a brief background on the synthesis and physical properties of different classes of oxaziridines, and then offer an evaluation of the growing body of new synthetic methods developed that exploit the unique chemistry of oxaziridines.

2. SYNTHESIS AND PHYSICAL PROPERTIES OF OXAZIRIDINES

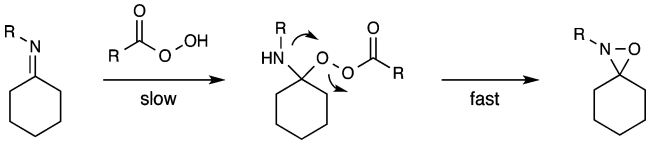
2.1. *N*-Alkyloxaziridines

Oxaziridines can be conveniently classified upon the basis of the identity of their *N*-substituent, which exerts a significant effect on their reactivity. The first class of oxaziridines to be reported were *N*-alkyl-substituted oxaziridines, initially synthesized by Emmons in 1957.[10] The standard method for their preparation involves the oxidation of an imine (e.g., **1**) to afford the corresponding oxaziridine (**2**). The use of peroxy acids,



particularly *m*-chloroperbenzoic acid (*m*CPBA), to oxidize imines as described in Emmons' initial report continues to be the most common method for oxaziridine synthesis. Experimental[13] and theoretical[14] studies support a two-step mechanism for imine oxidation (Scheme 1).

Scheme 1. Mechanism of Imine Oxidation by Peracids

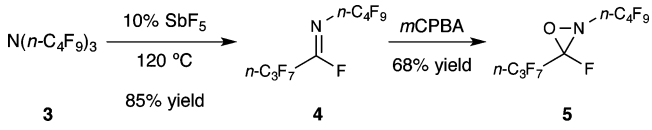


In addition to the use of peroxy acids, a range of other oxidation conditions has also been applied to transform *N*-alkyl imines to the corresponding oxaziridines. The use of cobalt/O_2,[15] urea–hydrogen peroxide,[16] in situ generated peroxyimidate,[17] and rhenium–peroxide[18] systems has been successful. Additionally, *N*-alkyloxaziridine structures can also be accessed via photochemical rearrangement of nitrones[19] or ozonolysis of Schiff bases,[20] albeit with lower yields.

Due to the inherent strain in the three-membered ring and the presence of an adjacent oxygen atom, the nitrogen stereocenter of *N*-alkyloxaziridines exhibits remarkable configurational stability,[21] with barriers of inversion ranging from 25 to 32 kcal/mol.[22] This high barrier of inversion allows the isolation of the cis and trans diastereomers of *N*-alkyloxaziridines as discrete entities at room temperature and has allowed the synthesis of optically active *N*-alkyloxaziridines chiral only at nitrogen.[23] Optically active *N*-alkyloxaziridines have also been prepared via photolysis of chiral inclusion complexes of nitrones in high ee.[24] Catalytic asymmetric approaches to *N*-alkyloxaziridines have been reported utilizing chiral α-bromonitriles and hydrogen peroxide, but the observed enantioselectivites are generally rather low.[25]

The synthesis of fluorinated *N*-alkyloxaziridines also generally relies on the use of *m*CPBA to oxidize the corresponding imine; however, the preparation of the starting imines is quite specific. Petrov and Resnati have reviewed synthetic approaches and applications of a wide variety of fluorinated oxaziridines.[12c] The most widely utilized perfluorinated oxaziridine, perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine **5**, is prepared by conversion of perfluorotributylamine to perfluoro-(*Z*)-4-aza-4-octene **4** by SbF_5 followed by oxidation with acid-free *m*CPBA (Scheme 2).[26] The barrier of nitrogen

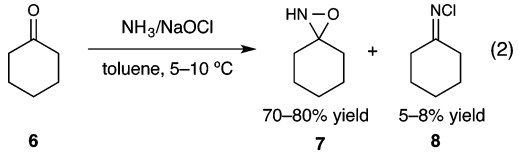
Scheme 2. Synthesis of Perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine



inversion in perfluoro-2,3-dialkyloxaziridines has not been reported; however, the lack of epimerization of these compounds at ambient or elevated temperature suggests that the barrier is higher than 25 kcal/mol.

2.2. *N*-H Oxaziridines

Oxaziridines bearing unsubstituted nitrogen atoms are generally not synthesized by standard peracid oxidation methods due to the instability of *N*-H imines. Schmitz et al. reported the preparation of oxaziridine **7** by reaction of cyclohexanone with ammonia and sodium hypochlorite.[27] A small amount of the *N*-chlorocyclohexanimine **8** is also formed in the reaction, but it does not affect typical synthetic applications of the *N*-H oxaziridine. *N*-Unsubstituted oxaziridines are highly reactive toward nucleophiles and are usually formed in situ in inert solvents and reacted further without additional purification. If chlorine-free solutions of oxaziridine **7** containing less unreacted cyclohexanone are required, the compound can be obtained from the reaction of hydroxylamine-*O*-sulfonic acid with cyclohexanone and sodium hydroxide.[28] In addition, *N*-H oxaziridines have also been obtained via photolysis of hydroxylamines,[29] oxidation of ketimines by peracid,[30] and ozonolysis in the presence of ammonia.[31]



Optically active *N*-H oxaziridines have been prepared from camphor and fenchone by Page and co-workers.[32] Due to the

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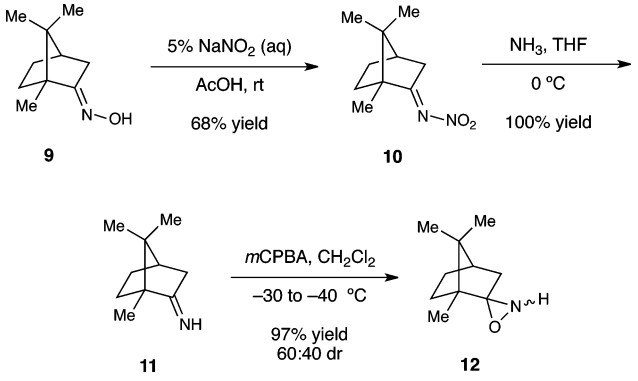
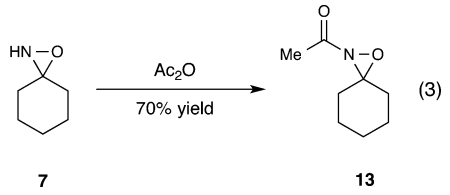
steric hindrance around the ketone moiety, the typical routes to access the *N*-H oxaziridine were unsuccessful. An alternative sequence involving nitrosation and rearrangement of oxime **9** followed by ammonolysis of the resulting nitromine provided access to the primary imine **11**. Oxidation from the endo face with *m*CPBA then afforded the *N*-H oxaziridine **12** as a 60:40 mixture of diastereomers at nitrogen. Derivatization studies were used to confirm the facial selectivity of the oxidation and the identity of the diastereomers. Unlike many *N*-H oxaziridines, compound **12** could be isolated in pure form and stored up to 6 months at 5 °C without noticeable decomposition (Scheme 3).

Scheme 3. Preparation of Chiral *N*−H Oxaziridine



2.3. *N*-Acyl- and *N*-(Alkoxycarbonyl)oxaziridines

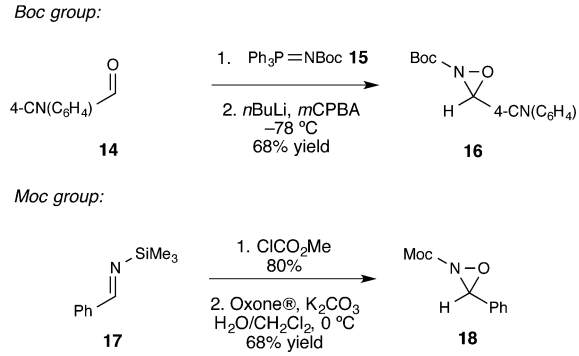
N-Acyloxaziridines are typically generated by acylation of the corresponding *N*-H oxaziridines (eq 3).[33] The application of



these compounds to organic synthesis has been limited; however, Jennings et al. used this class of oxaziridines to probe substituent effects on nitrogen inversion.[34] Although *N*-alkyloxaziridines exhibit a high barrier of inversion at the oxaziridine nitrogen (25−32 kcal/mol), the presence of an *N*-acyl group significantly lowers this barrier to 10.3 kcal/mol for oxaziridine **13**. This large effect is due to strong stabilizing π-conjugation in the transition state for nitrogen inversion and is a general phenomenon for *N*-substituents capable of conjugation; *N*-(alkoxycarbonyl)-, *N*-sulfonyl-, and *N*-phosphinoyloxaziridines also have lower barriers of inversion relative to *N*-alkyloxaziridines.

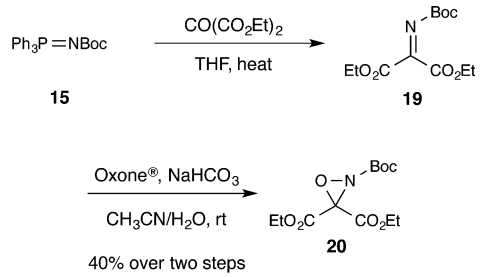
The preparation of *N*-(alkoxycarbonyl)oxaziridines can also be achieved starting from the corresponding imines. In the case of the *N*-Boc-oxaziridines, the most thoroughly investigated *N*-(alkoxycarbonyl)oxaziridines, the synthesis proceeds from an aza-Wittig reaction of the corresponding aldehyde to give an *N*-Boc imine. This imine can then be oxidized with basic buffered oxone, *m*CPBA, or the anhydrous *m*CPBA lithium salt. The related *N*-Moc- and *N*-Fmoc-oxaziridines are also prepared via oxidation of the corresponding imines, which can be prepared by acylation of *N*-silylimine **17** using the appropriate chloroformate (Scheme 4).[35]

Scheme 4. Synthesis of *N*-Carbamoyloxaziridines



Ketone-derived *N*-Boc-oxaziridines have also been reported.[36] Utilizing the aza-Wittig reagent **15**, diethyl ketomalonate can be converted to oxaziridine **20** in the standard two-step sequence. Additionally, the Armstrong group reported a route to the key aza-Wittig reagent **15** that avoids the use of the potentially hazardous Boc azide (Scheme 5).[37]

Scheme 5. Synthesis of Armstrong's *N*-Boc-oxaziridine



The barrier of inversion for *N*-Boc-oxaziridines has been calculated to be ∼18 kcal mol^{-1} at 27 °C. In solution, *N*-(alkoxycarbonyl)oxaziridines exist as a mixture of interconverting trans and cis conformers (∼80−93% trans depending on structure) with a conformer half-life of ∼3 s at 20 °C.[35c] Compared to the aforementioned *N*-alkyloxaziridines, this barrier is lower and the difference in energy is also generally rationalized by assuming that conjugation of the planar nitrogen with the alkoxycarbonyl group lowers the energy barrier of the transition state.

2.4. *N*-Sulfonyloxaziridines

Soon after Davis et al. first described their synthesis in 1977,[38] *N*-sulfonyloxaziridines quickly became the most extensively utilized class of oxaziridine in organic synthesis because of their stability, ease of synthesis, and superior oxidizing ability compared to *N*-alkyloxaziridines. Now commonly referred to as "Davis' oxaziridines", *N*-sulfonyloxaziridines are generally prepared by oxidation of the corresponding *N*-sulfonyl imines, which in turn can be prepared by condensation of sulfonamides (RSO_2NH_2) with aromatic aldehydes using either Brønsted[39] or Lewis[40] acids. While the earliest reports described the oxidation of *N*-sulfonyl imines with *m*CPBA in the presence of a phase transfer catalyst,[39] the use of buffered potassium peroxymonosulfate (Oxone) provides a less expensive and more practical alternative.[41] This approach has also been applied to the synthesis Davis' oxaziridine on a large scale, which can provide over 100 g of the resulting oxaziridine in two steps from the corresponding aldehyde.[42] More challenging imine oxidations have also been reported using KOH/

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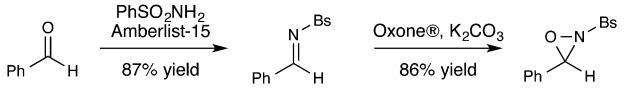
*m*CPBA[43] or peroxyimidate-mediated oxidations that utilize H_2O_2 as the stoichiometric oxidant.[17b] For example, the oxidation of polystyrene-supported *N*-sulfonyl aldimines required the use of KOH/*m*-CPBA, which produces solid-phase oxidants with reactivity comparable to that of soluble small-molecule oxaziridines of analogous structure.[44] Finally, while Davis' oxaziridines are most commonly derived from aldimines, several oxaziridines derived from ketimines have proven to be quite important reagents for organic synthesis (Scheme 6).[45,46]

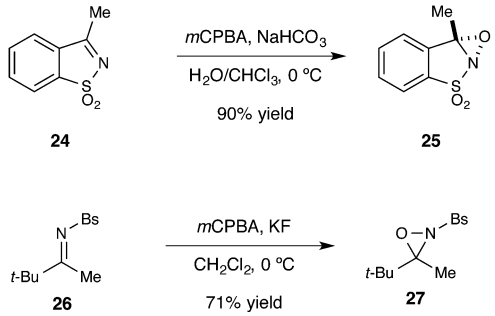
Scheme 6. Syntheses of *N*-Sulfonyloxaziridines

Large-scale synthesis of Davis' oxaziridine:



(performed by a 2nd year undergraduate)

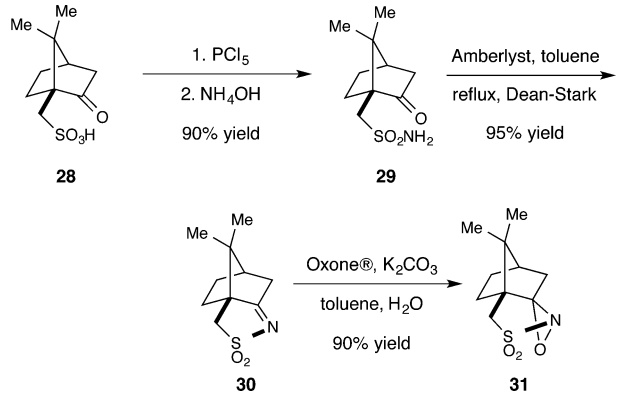
Ketimine derived N-sulfonyl oxaziridines:



In general, *N*-sulfonyloxaziridines are stable crystalline compounds that exist in a trans configuration. In order to determine whether this selectivity was the result of kinetic or thermodynamic product control, Jennings prepared a series of 3,3-disubstituted-2-sulfonyloxaziridines and measured the rate of nitrogen inversion by variable temperature NMR.[47] The barrier of inversion ($\Delta G^{\ddagger} \sim 20$ kcal/mol) measured for *N*-sulfonyloxaziridines is significantly lower than those of their *N*-alkyl counterparts ($\Delta G^{\ddagger} \sim 32$ kcal/mol),[22] which suggests that *N*-sulfonyloxaziridines can undergo spontaneous stereomutation at ambient temperature and that the high trans diastereoselectivity observed in the preparation of these oxaziridines is under thermodynamic control.

The earliest attempts to prepare optically active *N*-sulfonyloxaziridines relied on the use of a chiral camphor-based peracid;[48] however, this approach suffers from low selectivity, and repeated fractional recrystallizations are required to achieve high optical purity using this protocol. The first synthetically useful approach to chiral *N*-sulfonyloxaziridines was based on the synthesis of camphor sulfonic acid derived imine **30**, which can be selectively oxidized with oxone to give oxaziridine **31**.[49] The oxidation can only take place from the endo face of the C=N double bond due to the steric blocking of the exo-face, which results in a single oxaziridine isomer (Scheme 7). Davis and Chen have reviewed the use of this reagent in a number of asymmetric oxygen transfer reactions.[12b] An optically active *N*-sulfamyloxaziridine has also been reported.[50]

Scheme 7. Synthesis of Davis' Chiral Camphor-Derived Oxaziridine 31



Recently, several successful efforts to produce highly enantioenriched *N*-sulfonyloxaziridines via asymmetric catalysis have been reported in rapid succession (Scheme 8). The first catalytic enantioselective synthesis of oxaziridines was reported by Jørgensen and co-workers in 2011, which described the oxidation of *N*-tosyl imines utilizing a cinchona-alkaloid-based bifunctional phase-transfer catalyst.[51] The following year, a sulfonyl-directed oxidation of *N*-sulfonyl imines catalyzed by a chiral hafnium complex was reported by Yamamoto and co-workers.[52] Finally, Ooi and co-workers reported an asymmetric Payne-type oxidation of *N*-sulfonyl imines using chiral base **36** and trichloroacetonitrile.[53]

2.5. *N*-Phosphinoyloxaziridines

Oxaziridines bearing *N*-phosphinoyl groups were first synthesized by Boyd et al.[54] This class of oxaziridine is typically accessed via reaction of an aryl oxime with chlorodiphenylphosphine, followed by oxidation of the rearranged *N*-phosphinoyl imine with *m*CPBA (Scheme 9). These oxaziridines are stable compounds that have a low barrier to nitrogen inversion (~13 kcal/mol) and exist in the trans configuration. This barrier of inversion is lower than for the related *N*-sulfonyloxaziridines, which has been rationalized as the effect of a stronger conjugative interaction between nitrogen and phosphorus than between nitrogen and sulfur in the transition state for epimerization.[55,56]

Jennings et al. also synthesized optically active *N*-phosphinoyloxaziridines with a stereogenic phosphorus center.[57] Due to the potential of chlorophosphorus reagents to racemize by chloride exchange, the corresponding chiral *N*-phosphinoyl imines are prepared from the optically active phosphinic amides. For example, condensation of amide **40** and aryl aldehyde **41** proceeds cleanly in the presence of titanium(IV) chloride and triethylamine, and oxidation of the resulting *N*-phosphinoyl imine in situ with *m*CPBA/KF provides oxaziridine **42** as a 2.6:1 mixture of diastereomers (eq 4). Selective recrystallization can be used to access highly enantioenriched, diastereomerically pure oxaziridines.

2.6. *N*-Silyloxaziridines

Oxaziridines bearing an *N*-silyl group have been reported by Vidal and co-workers.[58] Due to the sensitivity of most *N*-silylamines to moisture and acid, only the *tert*-butyldiphenylsilyl (TBDPS) derivative has been successfully synthesized. The route involves silylation of benzylamine **43** to give the *N*-TBDPS amine **44**, which is oxidized to the imine in a two-step sequence involving chlorination of the amine with *tert*-butyl

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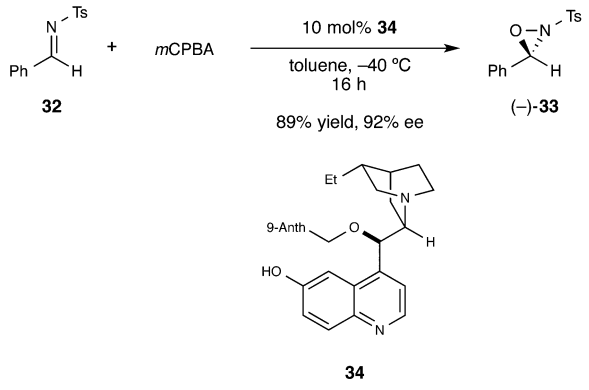
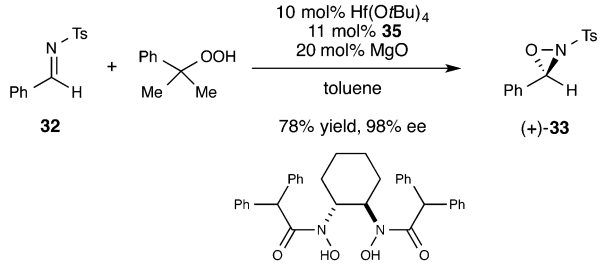
Scheme 8. Catalytic Enantioselective Routes to Chiral Oxaziridines

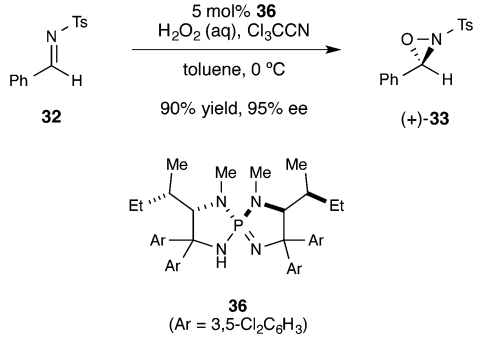
Jørgensen:



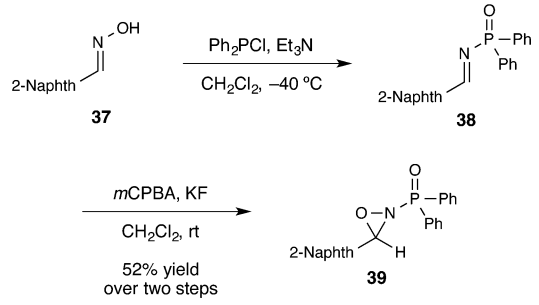
Yamamoto:



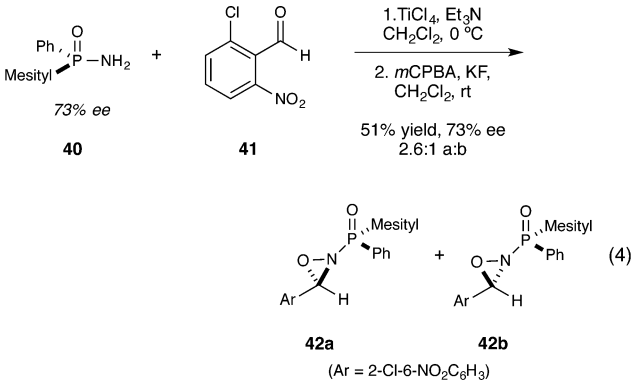
Ooi:



Scheme 9. Synthesis of *N*-Phosphinoyloxaziridines

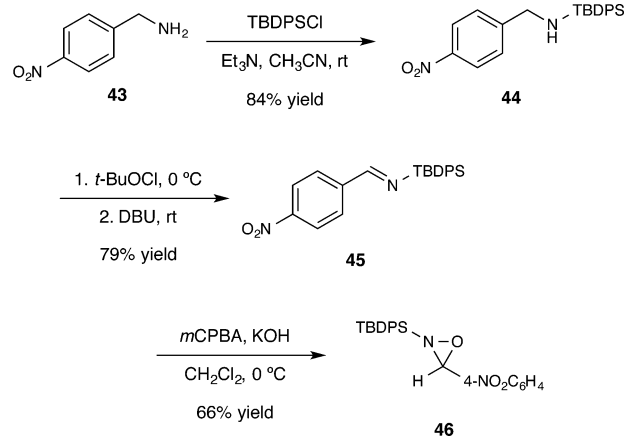


hypochlorite and elimination with DBU. Oxidation with *m*CPBA/KOH affords the *N*-silyloxaziridine **46** (Scheme 10). A more direct approach via derivatization of the corresponding



N-H oxaziridine was also investigated; however, the instability of the intermediates made this approach unviable.

Scheme 10. Synthesis of *N*-Silyloxaziridine



3. REACTIVITY OF OXAZIRIDINES

3.1. Oxygen Atom Transfer

Oxaziridines have been most commonly utilized in synthesis as electrophilic, aprotic sources of oxygen. In particular, *N*-sulfonyloxaziridines have been widely investigated for their ability to transfer oxygen to a range of nucleophiles. Oxygen atom transfer to sulfur,[59] phosphorus,[60] selenium,[61] nitrogen,[62] and carbon nucleophiles[63] produces the oxygenated products with the corresponding imine as a stoichiometric byproduct. Over the past 20 years, the majority of research on the chemistry of *N*-sulfonyloxaziridines has focused on the development of new oxaziridines with a broader synthetic scope, asymmetric induction in the oxaziridine-mediated oxidation of prochiral substrates, and the application of these reagents in total synthesis.

3.1.1. Olefin Epoxidation. At elevated temperatures, Davis' oxaziridines can be utilized to synthesize epoxides from alkenes.[64] Experimentally, the transition state for the transfer of oxygen from *N*-sulfonyloxaziridines to alkenes has been investigated using the endocyclic restriction test.[65] By evaluating a number of substrates containing an oxaziridine and an alkene, Beak and co-workers concluded that the transition state of oxygen transfer from an *N*-sulfonyloxaziridine to a corresponding nucleophile is one in which N–O bond cleavage is more advanced than C–O bond cleavage (Figure 2, **47**). Houk et al. also performed computational studies that probe

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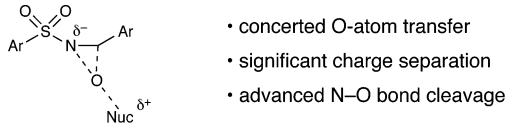

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Figure 2. Asynchronous transition state for oxygen atom transfer reactions of *N*-sulfonyloxaziridines.

the transfer of oxygen from oxaziridines to alkenes. These calculations similarly indicate a concerted, asynchronous process; advanced cleavage of the N−O bond is accompanied by significant buildup of partial negative charge at nitrogen.[66] Thus, to a first approximation, oxaziridines can be considered electrophilic oxidants, and factors that stabilize the incipient negative charge at nitrogen are expected to increase the reactivity of oxaziridines.

Indeed, substitution of oxaziridines with electron-withdrawing groups significantly increases their reactivity toward oxygen transfer. For example, epoxidation of monosubstituted olefins fails to proceed with *N*-(benzenesulfonyl)oxaziridine **23**, even at elevated temperatures.[64] Upon using a more electrophilic perfluoroalkyloxaziridine **5**, however, 1-octene is efficiently epoxidized in less than 1 h at −40 °C (Figure 3).[67]

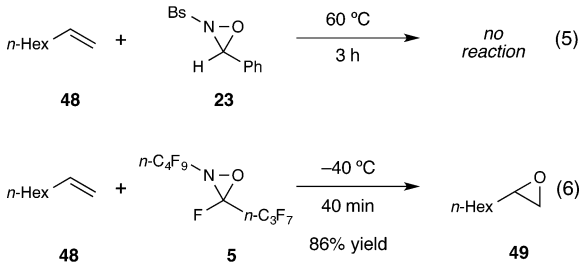
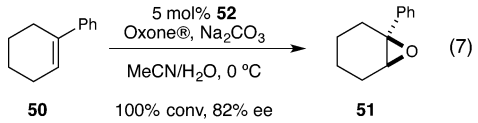
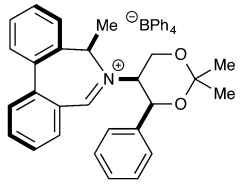


Figure 3. Electronic influence on oxaziridine reactivity.

Quaternized oxaziridinium salts, first investigated by Lusinchi and co-workers,[68] have also been explored in oxygen transfer reactions to alkenes.[69] Consistent with the general trend that electron-deficient oxaziridines tend to be more powerful oxygen atom-transfer reagents, these positively charged oxaziridinium salts efficiently epoxidize alkenes at ambient temperatures. These reagents can be generated catalytically from the corresponding iminium salt in the presence of a stoichiometric oxidant, typically Oxone. Chiral iminium salts have thus been used in catalytic asymmetric epoxidation reactions with moderate to excellent enantioselectivities (eq 7).[70]





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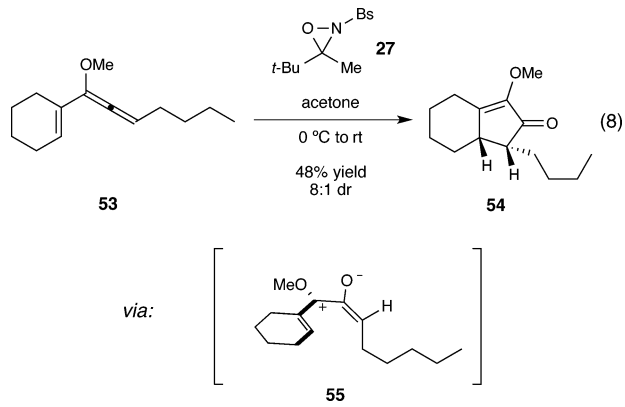
The Frontier group reported an elegant cascade reaction initiated by oxaziridine-mediated oxidation of an allene (eq 8).



Vinyl allene **53** smoothly reacts with *N*-sulfonyloxaziridine **27**, and the resulting putative dienyl cation is poised to undergo a subsequent Nazarov cyclization.[71] When more reactive oxidants such as dimethyldioxirane are used, the reaction proceeds with lower selectivity.

3.1.2. Sulfur Oxidation. The ability of *N*-sulfonyloxaziridines to oxidize sulfides to sulfoxides has been widely explored.[72] In general, sulfides can be quantitatively oxidized to sulfoxides in minutes with minimal overoxidation to the corresponding sulfone. Catalytic systems in which Oxone oxidation of a substoichiometric amount of sulfonimine to generate a reactive oxaziridine in situ have also been disclosed. Mechanistically, these atom transfer reactions are considered to proceed via an S_N2 attack on the oxaziridine oxygen with concomitant displacement of the imine as a leaving group.[73]

The asymmetric synthesis of chiral sulfoxides with optically active oxaziridines has been an area of considerable continuing interest.[74] Early investigations involving chiral *N*-sulfamyl-,[50] *N*-sulfonyl-,[75] and *N*-phosphinoyloxaziridines[57] demonstrated the feasibility of chirality transfer from oxaziridines to a wide range of sulfoxides. Despite generally rather modest and substrate-dependent levels of enantioselectivity, these reactions can be convenient and readily scalable, and in certain cases the stereoselectivities have been optimized to quite high levels. For example, a kilogram-scale synthesis of the proton pump inhibitor rabeprazole (**57**) has been reported, in which the key step involved sulfoxidation of **56** mediated by camphor-derived oxaziridine **31** (Scheme 11).[74a]

A method for catalytic sulfoxidation was reported by Page and co-workers. This system utilizes a chiral saccharin-based imine as the catalyst and hydrogen peroxide as the stoichiometric oxidant.[76] The authors were able to confirm catalytic turnover in sulfoxidation reactions of the chiral imine, but enantiomeric excesses were low. Additionally, the use of stoichiometric oxaziridine in these reactions led to different levels of enantioselectivity, thus indicating that different species may be contributing to the selectivity observed in the catalytic system (eq 9).

The use of exogenous additives for the asymmetric oxidation of sulfides with chiral *N*-alkyloxaziridines has also been investigated. While *N*-(perfluoroalkyl)oxaziridine analogues rapidly oxidize sulfides to the corresponding sulfoxide or sulfone depending on the equivalents of oxidant,[77] normal *N*-alkyloxaziridines are generally insufficiently reactive to participate in oxygen transfer unless forcing high-pressure conditions are used.[78] Bohé et al. observed that the addition of exogeneous

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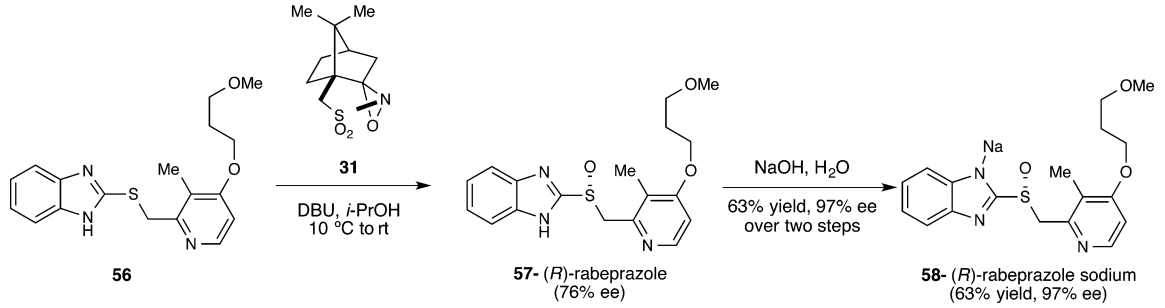
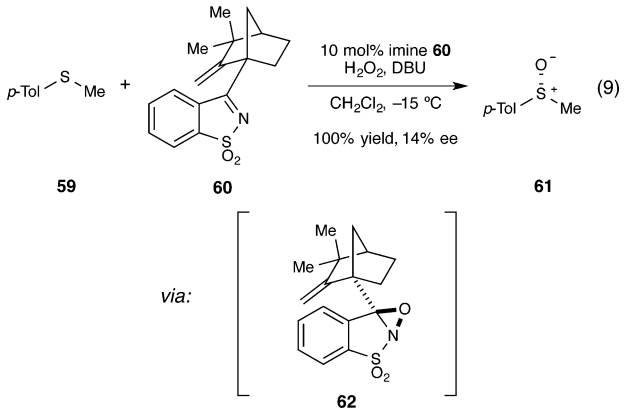
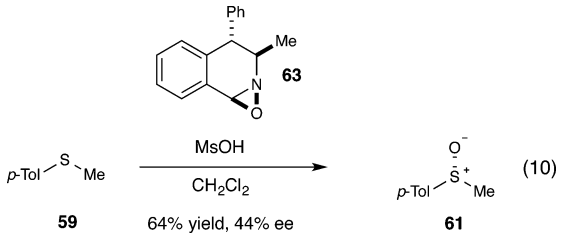
Scheme 11. Synthesis of Rabeprazole Using Camphor-Derived Oxaziridine 31





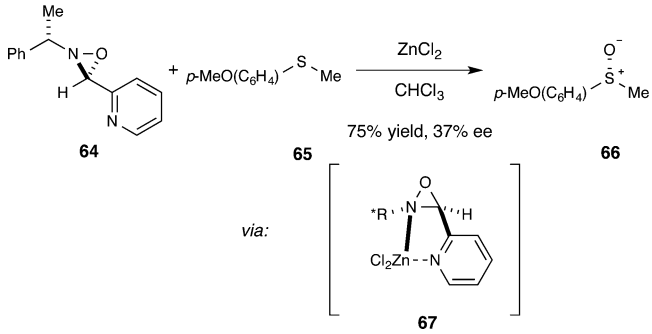
acid additives promotes sulfide oxidation by oxaziridine **63** in modest enantioselectivity (eq 10).[79] The rate acceleration is proposed to be a result of protonation of the basic nitrogen to give the corresponding oxaziridinium in situ.



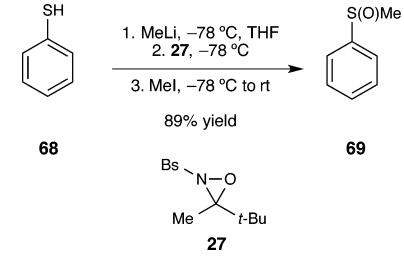
Fontecave and co-workers also reported Lewis acid mediated activation of chiral *N*-alkyloxaziridines using $ZnCl_2$.[80] Oxidation of **65** with (*S*)-1-phenylethylamine-derived 3-pyridyloxaziridine **64** resulted in the formation of sulfoxide **66** with modest enantioselectivity. The necessity of a heteroaromatic substitutent on the oxaziridine led the authors to propose that Lewis acid activated intermediate **67** is the active oxidizing species. Coordination of the Lewis acid to the nitrogen atom of the oxaziridine is believed to increase the electron deficiency of the oxygen atom, thus enhancing its electrophilicity (Scheme 12).

The ability of *N*-sulfonyloxaziridines to oxidize thiols has also been investigated. The reaction between thiols and *N*-sulfonyloxaziridines typically results in the production of sulfinic acids. Davis and Billmers demonstrated that sulfenic acids are intermediates in this process[81] and that the rate of sulfenic acid oxidation outcompetes thiol oxidation even when a large excess of thiol is used. Perrio and co-workers subsequently investigated chemoselective thiol functionalizations with pinacolone-derived *N*-sulfonyloxaziridine **27**. The oxidation of aromatic thiols to sulfoxides has been reported in a

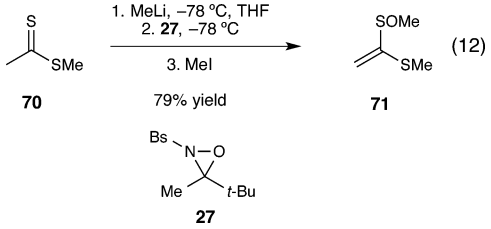
Scheme 12. Lewis Acid Activation of Chiral *N*-Alkyloxaziridines



three-step, one-pot procedure involving deprotonation of the thiol, oxidation with oxaziridine **27**, and trapping of the sulfenate anion with an alkyl halide (eq 11).[82,83] Notably, this sequence proceeds without disulfide formation or *O*-alkylation.



The scope of oxidation reactions with oxaziridine **27** has also been extended beyond aromatic thiols. Dithioester-based enethiolates can be chemoselectively oxidized with oxaziridine **27** to afford the ketene dithioacetal *S*-oxide in good yield (eq 12).[46a] Additionally, the base-induced fragmentation of 4-



substituted 1,2,3-thiadiazoles produces acetylenic thiolates that can be oxidized and alkylated to provide 1-alkynyl sulfenates (eq 13).[46b] Aliphatic thiols have also been converted to sulfones using 2 equiv of the oxidant.[84]

The ability of oxaziridine **27** to act as a weak oxidant has also been exploited for the selective oxidation of sulfur-containing

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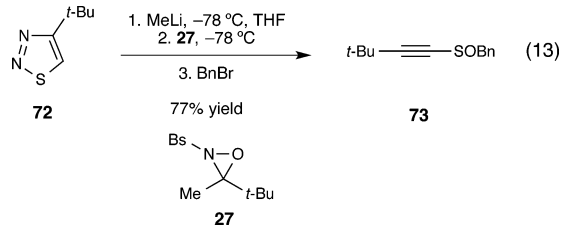
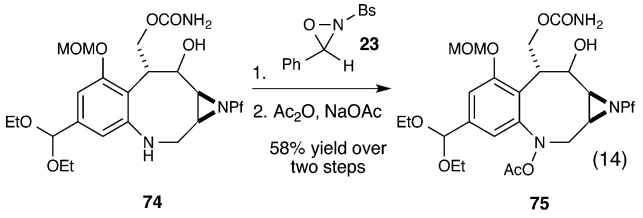


ligands. Alves de Sousa and Artaud demonstrated that careful control of reagent stoichiometry can allow the generation of mixed sulfonate/thioether and mixed sulfonate/sulfoxide compounds that were investigated for their ability to bind metal cations.[85] Additionally, Kovacs and co-workers utilized a selective oxidation of an iron thiolate complex to investigate how the addition of an oxygen atom affected the properties of Fe−nitrile hydratase analogues.[86]

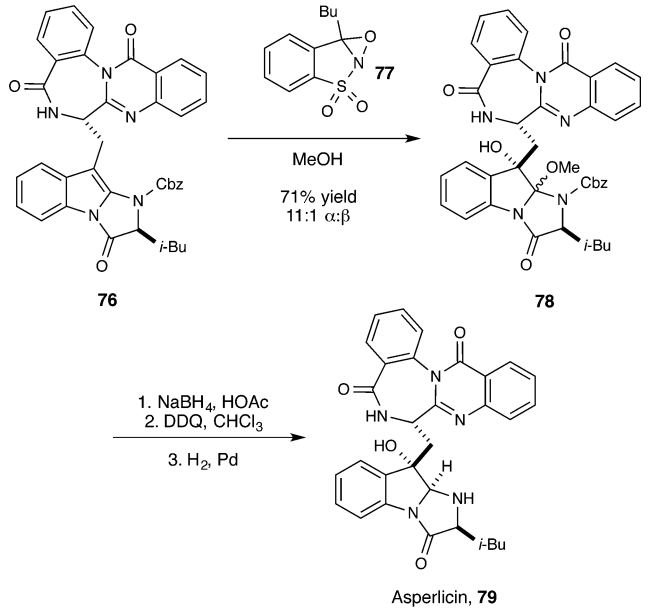
3.1.3. Amine Oxidation. A well-established mode of reactivity for Davis' oxaziridines is the transfer of oxygen to secondary amines to yield hydroxylamines.[61] Rapoport and co-workers applied this process toward the enantioselective formal synthesis of (+)-FR900482.[87] In the route, intermediate **74** was oxidized with Davis' oxaziridine and subsequently protected to give acetoxyamine **75** in good yield. Notably, the use of more common oxidants like *m*CPBA and MMPP led to lower yields, which highlights the ability of *N*-sulfonyloxaziridines to act as a mild aprotic, electrophilic source of oxygen (eq 14).



3.1.4. Enamine Oxidation. Davis also investigated the oxidation of enamines by *N*-sulfonyloxaziridines. Disubstituted and trisubstituted enamines are rapidly oxidized to α-amino and α-hydroxy ketones, respectively.[88] A mechanism involving initial oxidation to an α-amino epoxide was proposed to account for the product distributions. The oxaziridine-mediated oxidation of indoles has proven to be particularly useful in the synthesis of a variety of structurally complex alkaloids. For example, the Snider group exploited an oxaziridine-mediated indole oxidation as a key step of their synthesis of asperlicin and asperlicin C (Scheme 13).[89] The advanced indole **76** was oxidized with oxaziridine **77** in methanol to give a 71% yield of an 11:1 mixture favoring the α-alcohol after ring-opening of the epoxide. Directed reduction of the C-2 position, reoxidation of the dihydroquinazolinone, and hydrogenolysis of the Cbz group then gave the natural product **79**. Similar recent applications of indole oxidation in alkaloid synthesis include the Snider syntheses of the fumiquinazoline natural products[90] and Williams' synthesis of versicolamide B.[91]

In 2011, Movassaghi and co-workers demonstrated the utility of camphor-derived (+)-((8,8-dichlorocamphoryl)sulfonyl)-oxaziridine in their synthesis of the trigonoliimine natural product family.[92] Oxidation of bistryptamine **80** with oxaziridine **81** provided hydroxyindolenines **82a** and **82b** with excellent yield and enantioselectivity. These isomeric hydroxyindolenines served as a useful branching point to access

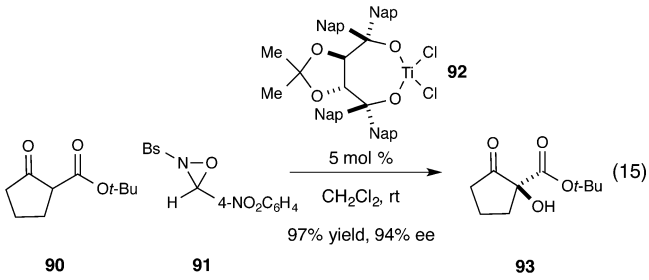
Scheme 13. Oxaziridine-Mediated Indole Oxidation in the Synthesis of Asperlicin



each member of the trigonoliimine family by judicious choice of synthetic sequence (Scheme 14).

3.1.5. Enolate Oxidations. The oxidation of enolates to α-hydroxycarbonyl compounds is arguably the most widely utilized reaction of oxaziridines. The products of these reactions are valuable intermediates in organic synthesis and key structural motifs in many biologically active natural products; several recently completed targets whose syntheses feature oxazirdine-mediated enolate oxidations are featured in Figure 4.[93] Prior reviews have detailed early approaches to generating these bonds with facial selectivity utilizing both chiral auxiliaries approaches[94] and optically active oxaziridines.[95] Much of the contemporary interest in this area has focused on catalytic asymmetric α-oxidations of carbonyl compounds using *N*-sulfonyloxaziridines as terminal oxidants.

Mezzetti, Togni, and co-workers described an asymmetric hydroxylation of β-keto esters catalyzed by a chiral titanium-(IV) TADDOLate complex (eq 15).[96] The authors suggest that



coordination of the Lewis acid catalyst to the β-keto ester substrate results in the formation of a chiral titanium enolate. This enolate then reacts with *N*-sulfonyloxaziridine **91** to give α-hydroxylated products with up to 94% ee; however, the selectivity is generally modest if the ester substituent is less sterically demanding than a *tert*-butyl group. A copper(I)-catalyzed asymmetric α-hydroxylation of β-keto esters has also been reported utilizing a phosphine-Schiff base ligand, but observed enantioselectivities were generally somewhat modest.[97]

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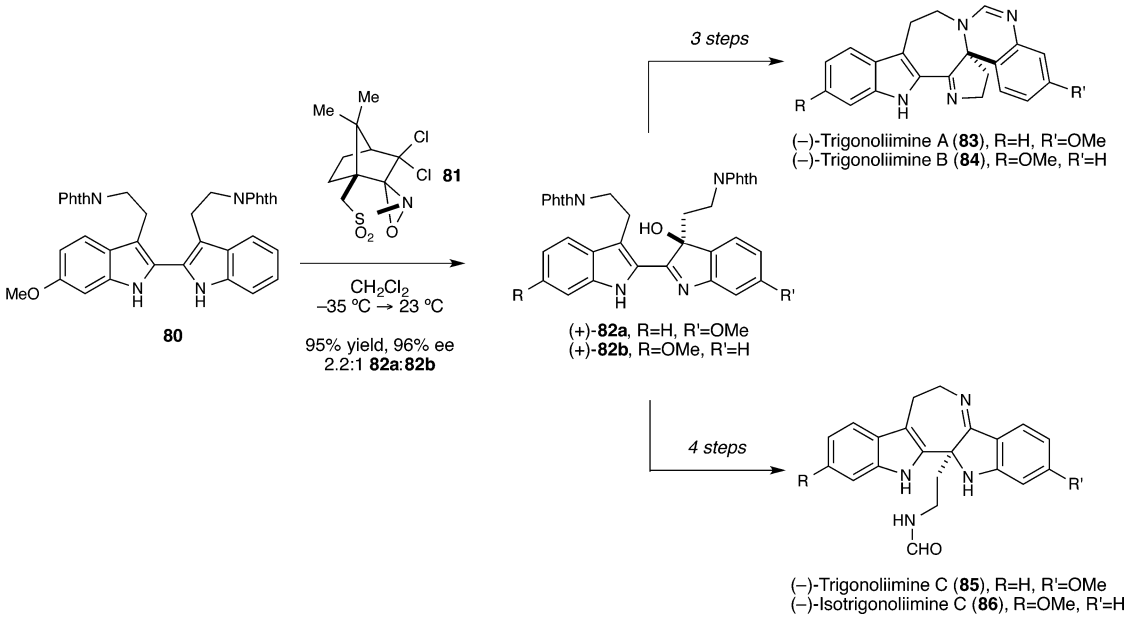
Scheme 14. Asymmetric Indole Oxidation in the Synthesis of Trigonoliimine Natural Products



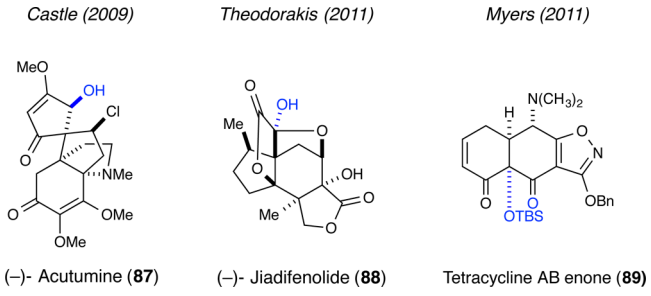
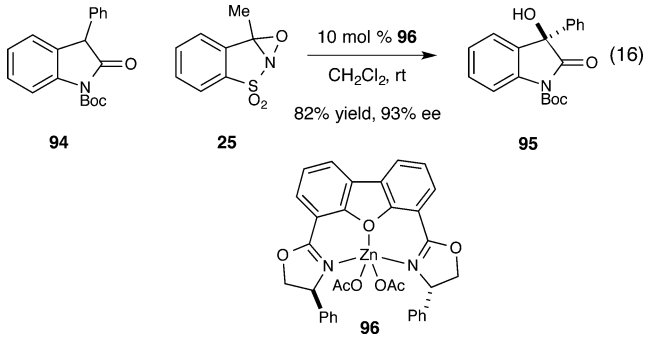


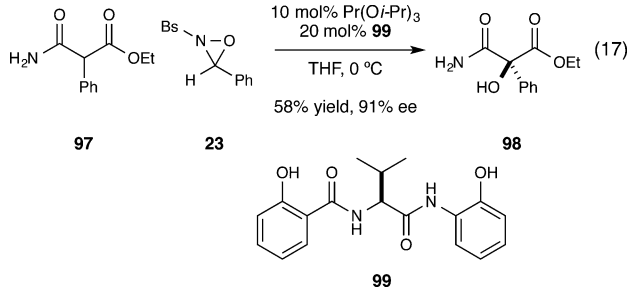
Figure 4. Target molecules synthesized using oxaziridine-mediated α-hydroxylation.

Conceptually similar Lewis acid-catalyzed enantioselective α-hydroxylations of other classes of enolates have also been reported. Shibata, Toru, and co-workers recently reported that zinc(II) DBFOX complex **96** catalyzes the highly enantioselective hydroxylation of 3-aryl-2-oxindoles, which they propose proceeds by a similar mechanism involving Lewis acid-promoted enolization of the oxindole substrate (eq 16).[98]

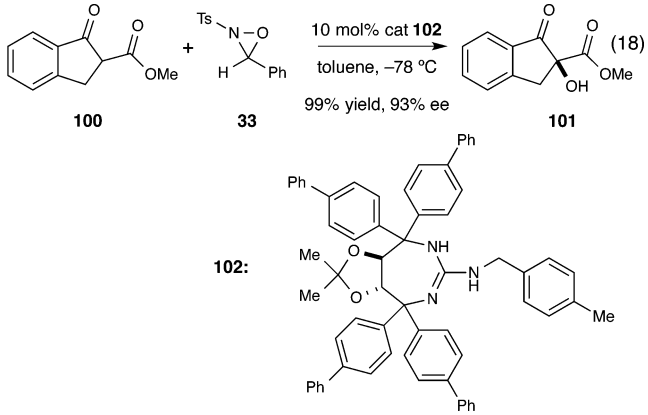


Additionally, Shibasaki and co-workers demonstrated a highly stereoselective α-hydroxylation of α-substituted α-alkoxycarbonyl amides using a praseodynium/amide **99**-based catalyst system and Davis' oxaziridine **23** (eq 17).[99]

In addition to Lewis acid-mediated approaches to catalytic enantioselective α-hydroxylation, there have been a number of



highly enantioselective organocatalytic routes to α-hydroxylated carbonyl compounds involving oxaziridine as oxidants.[100] Utilizing the L-tartrate-derived chiral guanidine **102**, Zou et al. developed the α-hydroxylation of β-keto ester and β-dicarbonyl substrates with exceptional yields and enantioselectivities (eq 18). *N*-Tosyloxaziridine **33** proved to be much more selective than the other sources of electrophilic oxygen investigated.



3.1.6. C–H Functionalization. Oxaziridines have also been used to achieve the selective oxyfunctionalization of C–H bonds. Due to the oxidizing power required to achieve this type of transformation, most of the early reports of this reactivity

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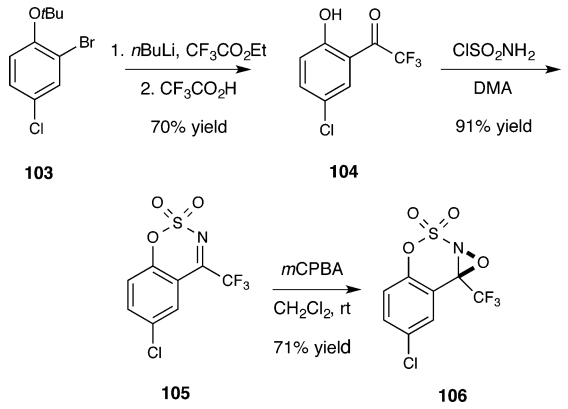
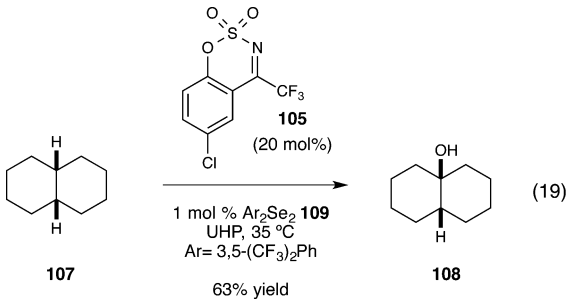
involved the use of highly electron-deficient perfluorinated oxaziridines in order to convert alkane C−H bonds to alcohols under ambient conditions.[101] The use of perfluorinated oxaziridines in C−H functionalization reactions has been the subject of a previous review[12c] and will not be covered here.

The Du Bois group developed a catalytic system for C−H hydroxylation utilizing a fluorine-containing benzoxathiazine-based oxaziridine.[102] The authors used DFT calculations to design the highly electron-deficient oxaziridine **106**, which they predicted would be a viable oxidant for C−H functionalization. This reagent can be prepared in a four-step sequence in gram quantities from the corresponding aryl bromide **103** (Scheme 15) and was shown to be a viable reagent for the oxidation of C−H bonds.

Scheme 15. Du Bois' Fluorinated Benzoxathiazine-Based Oxaziridine



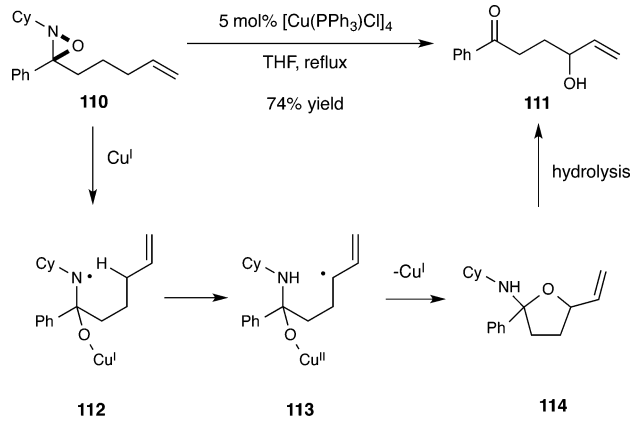
In addition to using oxaziridine **106** as a stoichiometric reagent for C−H functionalization, Du Bois and co-workers demonstrated that the imine **105** can also be used in catalytic quantities in the presence of urea−hydrogen peroxide (UHP) as the stoichiometric oxidant to generate oxaziridine **106** in situ (eq 19). Their reaction design involved two cocatalytic



components. First, catalytic diselenide **109** [Ar = 3,5-bis(trifluoromethyl)phenyl] reacts with stoichiometric H_2O_2 to produce perselenimic acid in situ. This oxidant then reacts with benzoxathiazine-derived imine **105** to produce the active oxaziridine. Under these conditions, a number of unactivated C−H bonds could be smoothly oxidized. In 2009, a redesigned benzoxathiazine-based oxaziridine was reported for selective tertiary C−H bond oxidation under aqueous acetic acid/H_2O_2 conditions.[103]

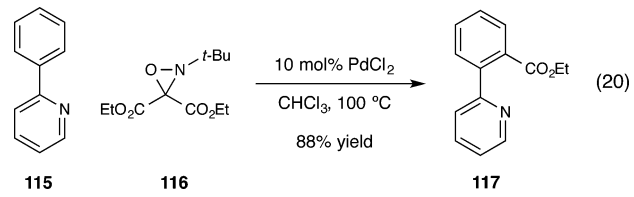
Recently, the Aubé group reported the Cu(I)-catalyzed formal insertion of the oxygen atom of an oxaziridine into activated C−H bonds (Scheme 16).[104] The authors proposed

Scheme 16. Cu(I)-Catalyzed C−H Oxidation



that Cu(I)-promoted homolysis of *N*-cyclohexyloxaziridine **110** resulted in Cu(II)-stabilized radical/anion pair **112**. Subsequent 1,5-hydrogen atom abstraction by the reactive nitrogen-centered radical affords allylic radical **113**, which can then undergo radical recombination with the copper(II) alkoxide to regenerate the Cu(I) catalyst and liberate 2-aminotetrohydrofuran **114**. This intermediate undergoes hydrolysis to produce the observed keto alcohol product **111**. Benzylic and propargylic C−H bonds could also be oxidized in modest to good yield.

Shi and co-workers reported an unusual example of a C−H functionalization reaction in which an oxaziridine transfers a carbon-centered functional group (eq 20).[105] This reaction



presumably involves the metallocycle that arises from Pd(II)-catalyzed C−H activation of 2-phenylpyridine, which then reacts with oxaziridine **116** in a novel alkoxycarbonylation reaction to afford ester **117** in high yield. While the mechanistic details of this reaction await further interrogation, this is an unusual example of a reaction in which an oxaziridine oxidant participates in a reaction by transferring a moiety other than oxygen or nitrogen.

3.2. Nitrogen Atom Transfer

Oxaziridines can act as sources of electrophilic nitrogen when the *N*-substituent is small. For many years, the reagents of choice for these transformations were *N*-H oxaziridines, particularly 1-oxa-2-azaspiro[2.5]octane **7**. This work was largely pioneered by Schmitz and co-workers, and an account detailing many of the synthetic applications of oxaziridines in this class has been compiled.[12d] Given the high reactivity of these reagents, however, the broader application of Schmitz-type oxaziridines in synthesis has been somewhat limited due to the requirement that they should be prepared in situ. This has led to continued interest in designing oxaziridine reagents that can act as electrophilic sources of nitrogen with improved practicality.

3.2.1. Amination of Nitrogen Nucleophiles. Collet and co-workers designed *N*-carbamoyloxaziridine **16** to address the

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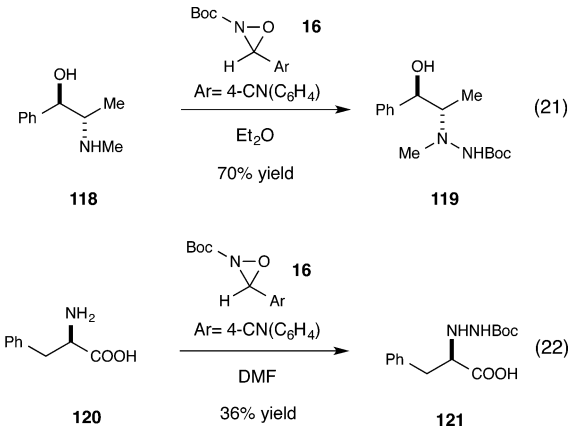
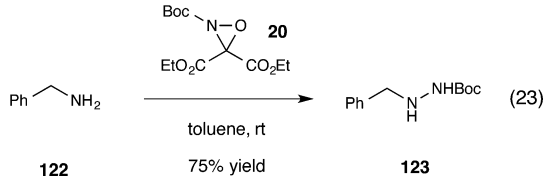
challenges outlined above (Scheme 17). In addition to being an isolable and stable crystalline solid, the ability of oxaziridine **16**

Scheme 17. Amination of Amines with Oxaziridine

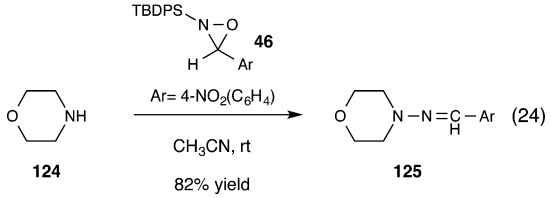


to transfer nitrogen in protected form is highly attractive. Due to the Collet group's interest in hydrazido peptides, the authors investigated the amination of various amines to produce *N*-Boc-hydrazides.[35] Both secondary (eq 21) and primary amines (eq 22) react to give products in good yield; however, competitive Schiff base formation with the 4-cyanobenzaldehyde byproduct can be problematic and leads to reduced yields with some primary amine substrates. Nevertheless, a number of research groups have utilized these *N*-Boc-hydrazines as building blocks for molecules of biological interest.[106]

Armstrong et al. attempted to address the problematic side reactions of the aldehyde byproduct generated from nitrogen transfer reactions with oxaziridine **20**.[37] Utilizing the diethyl ketomalonate-derived *N*-Boc-oxaziridine **20**, a number of primary amines were aminated to *N*-Boc-hydrazides (**123**) in good yield without a significant amount of deleterious imine formation (eq 23). The authors also applied this methodology to a one-pot synthesis of 1,3,5-trisubstituted pyrazoles.

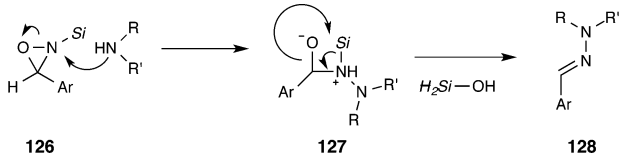


Vidal and co-workers also reported an intriguing amination of amines with *N*-silyloxaziridine **46**. Primary and secondary amines react to give the corresponding hydrazine in moderate to good yield (eq 24).[58] Unlike other *N*-substituted aminating



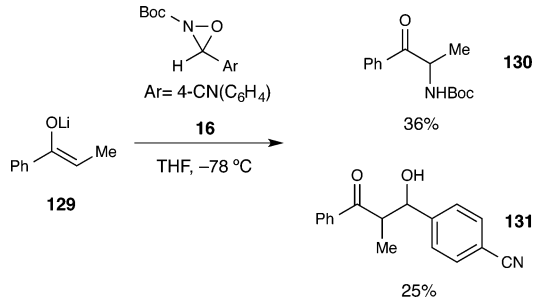
oxaziridines, however, the *N*-silyl variant does not transfer the nitrogen-protecting group to the observed products. The authors propose that the reaction proceeds via **127**, an aza-analogue of the β-hydroxysilane intermediate in Peterson olefination, to account for the observed hydrazine (Scheme 18).

Scheme 18. Rationale for Divergent Reactivity of *N*-Silyloxaziridine 46



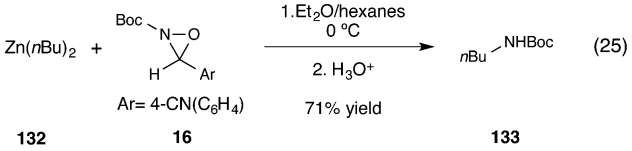
3.2.2. Amination of Carbon Nucleophiles. *N*-(Alkoxycarbonyl)oxaziridines can also react with carbon nucleophiles. Oxaziridine **16** reacts with various enolates to give electrophilic amination products, albeit in modest yield (Scheme 19).[35] Competitive aldol condensation between the

Scheme 19. Amination of Enolates with *N*-Boc-oxaziridine 16



released 4-cyanobenzaldehyde and the enolate results in a loss of overall reaction efficiency. Amide and ester enolates also react in similar yields; however, silyl enol ethers are epoxidized to give the α-hydroxy ketone product. Enders exploited the nitrogen atom transfer reactivity of *N*-Boc-oxaziridines in the asymmetric synthesis of α-amino ketones using chiral α'-silyl ketones.[107]

Ghoraf and Vidal demonstrated that *N*-Boc-oxaziridines also transfer nitrogen to organometallic species. After surveying different classes of organozinc reagents, the authors found that diorganozinc compounds are optimal for reactions with oxaziridine **16** to give a variety of *N*-Boc-protected primary amines (eq 25).[108] To rationalize the selectivity of nitrogen



transfer over oxygen transfer, the authors propose that the oxygen atom of oxaziridine **16** acts as a Lewis base to form a zincate complex. This activates attack of the electrophilic nitrogen by the organozinc compound, which leads to observed product after acidic workup.

3.2.3. Amination of Sulfides. Collet and co-workers have also investigated the use of oxaziridine **16** for the amination of sulfides; however, competitive oxygen transfer leads to complex product mixtures and low yields.[35] Armstrong and Cooke demonstrated that higher levels of selective amidation can be achieved using the diethyl ketomalonate-derived *N*-Boc-

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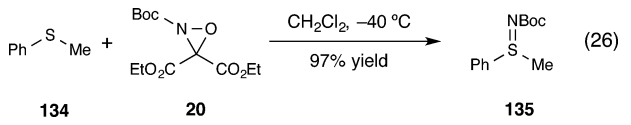
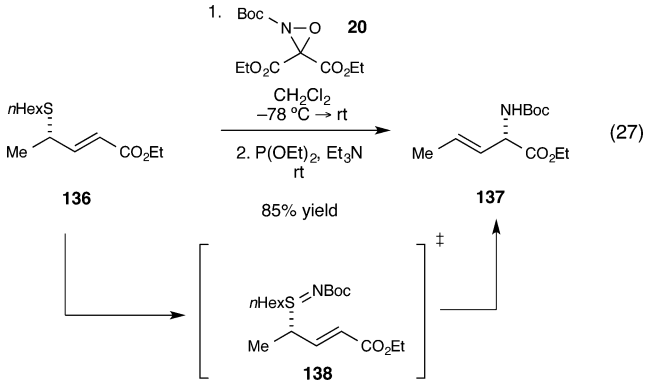
oxaziridine **20** (eq 26).[36] While the reasons for the higher chemoselectivity are unclear, it was hypothesized that steric

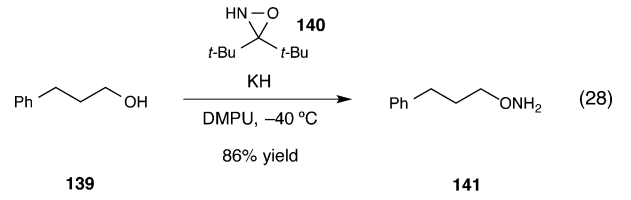


interactions between the *N*-alkoxycarbonyl group and the ester substituents might disfavor oxygen transfer.

The Armstrong group also developed a clever application of this sulfide amination using allylic[36] and propargylic[109] sulfides. Upon amidation of the sulfur moiety, the intermediate sulfimides undergo rapid [2,3]-sigmatropic rearrangement to yield allylic and allenic amines, respectively. When applied to chiral allylic sulfides, the reactions proceed with complete transfer of chirality.[110] Desulfurization of these compounds with triethyl phosphite results in (*E*)-vinylglycine derivatives. Due to the mildness of the reaction conditions, a one-pot amination/rearrangement/N–S bond cleavage sequence can be performed in good overall yield (eq 27).[111]

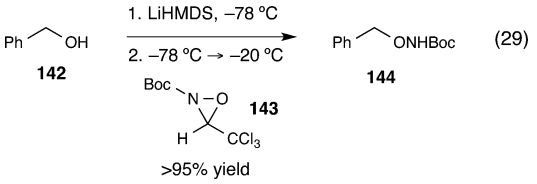


3.2.4. Amination of Alkoxides. Both *N*-H and *N*-Boc-oxaziridines have been applied to the amination of alkoxides to give alkoxyamines. Choong and Elmann demonstrated that 3,3-di-*tert*-butyloxaziridine **140** can be used for the amination of a variety of primary and secondary alcohols in good yield (eq 28).[112] Unlike the highly reactive, base-sensitive cyclohexanes-



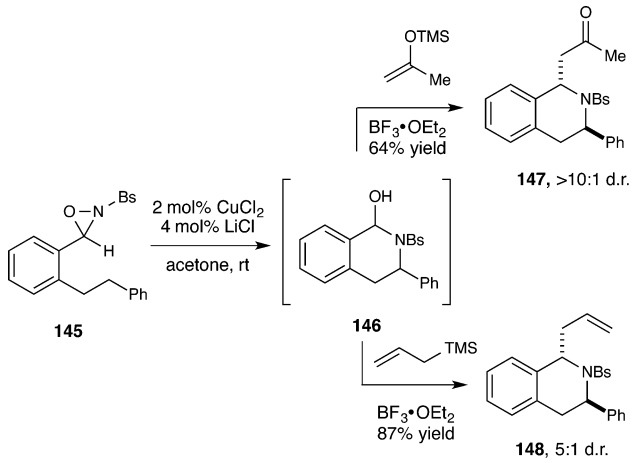
piro-3′-oxaziridine **7**, the increased steric hindrance of oxaziridine **140** adds significant stability. Oxaziridine **140** can be isolated in pure form and stored at room temperature for months without decomposition. Additionally, the steric hindrance of the 2,2,4,4-tetramethyl-3-pentanone byproduct prevents condensation with the desired alkoxyamine product. As one might expect, this steric encumbrance does limit substrate scope; tertiary alcohol products were isolated in low yield.

Foot and Knight also developed a mild method for the electrophilic amination of alkoxides utilizing chloral-based oxaziridine **143** (eq 29).[113] Primary, secondary, tertiary, allylic, propargylic, and phenolic alkoxides can be aminated in moderate to excellent yields.



3.2.5. C–H Amination. Few examples of formal nitrogen atom transfer reactions from *N*-sulfonyloxaziridines have been documented. The Yoon laboratory demonstrated that treatment of oxaziridine **145** with $CuCl_2$ in the presence of LiCl results in the regioselective net insertion of the oxaziridine nitrogen into an sp^3-hybridized C–H bond with exclusive formation of a six-membered ring (Scheme 20).[114] No trace of

Scheme 20. Copper Catalyzed C–H Amination with *N*-Sulfonyloxaziridines



insertion into the other possible alkane position was observed. Indeed, the regioselectivity for functionalization of the δ position is high, even when the reacting methylene position is unactivated (i.e., when Ph = alkyl). The aminal intermediates are amenable to further synthetic manipulations (e.g., to **147**, **148**), which enables the rapid synthesis of piperidine-containing structures that are common features of a variety of potent bioactive alkaloids.

3.3. Transition-Metal-Promoted Rearrangements

Oxaziridines participate in a remarkably broad variety of rearrangement reactions when exposed to exogenous chemical and photochemical stimuli. Acid-mediated rearrangements to hydroxylamines,[115] base-catalyzed eliminations,[116] thermal rearrangements to nitrones,[117] and photochemical isomerizations[118] have all been extensively studied and reviewed.[119] In addition, the Aubé group elegantly demonstrated the synthetic utility of photochemical isomerizations of oxaziridines in their synthesis of the yohimbine alkaloids.[120]

Recent investigations of reactions involving rearrangements of oxaziridines have focused on activation by redox-active transition metals. The ability of oxaziridine rearrangements to be initiated by single-electron transfer is consistent with many of their other properties. For example, theoretical calculations probing the epoxidation of ethylene by oxaziridine indicate a substantial buildup of radical spin density at the reacting carbon

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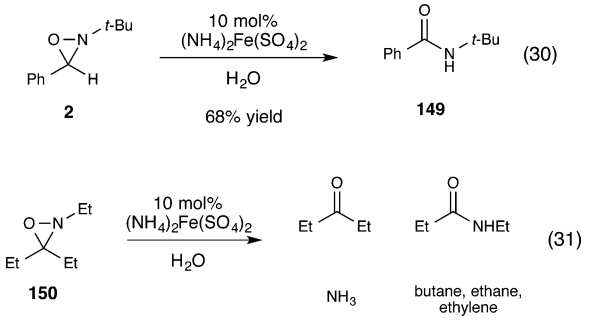
of the olefin and on the nitrogen of the oxaziridine.[66] The concerted atom transfer reactions of oxaziridines can therefore be considered to have significant diradical character.

The first report of transition-metal-catalyzed rearrangement of oxaziridines to amides dates to the earliest papers detailing the synthesis and isolation of oxaziridines. In 1957, Emmons reported that treatment of oxaziridine **2** with catalytic ammonium iron(II) sulfate in water generated *N*-*tert*-butylbenzamide **149** in 68% yield (Scheme 21, eq 30).[10]

Scheme 21. Iron-Catalyzed Rearrangement of *N*-Alkyloxaziridines

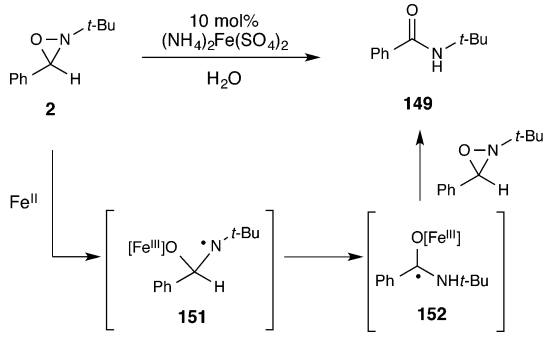


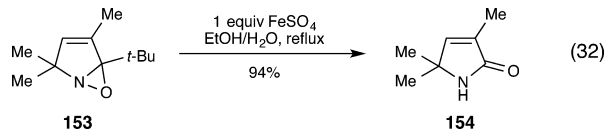
When ketone derived oxaziridines are subjected to the reaction conditions, radical cleavage products resulting from β-scission processes predominate. For example, treatment of triethyloxaziridine **150** with iron sulfate leads to diethyl ketone (50%), *N*-ethylpropionamide (32%), ammonia (55%), and a mixture of butane, ethane, and ethylene gases (Scheme 21, eq 31).

Minisci and co-workers investigated the mechanism for the transition-metal-catalyzed rearrangement of oxaziridines to amides.[121] They suggested that formation of the more stable nitrogen-centered radical rather than an oxygen-centered radical was the favored pathway for decomposition of the oxaziridine. Thus, one-electron reduction of an oxaziridine by a redox-active transition metal generates a nitrogen-centered radical, which can either undergo 1,2-hydrogen atom migration with a chain-propagating one-electron oxidation by another equivalent of oxaziridine or undergo radical cleavage (Scheme 22).

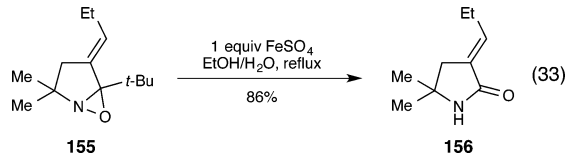
Several groups have recognized that the ability to oxidize an imine to an amide via an intermediate oxaziridine is a synthetically valuable process. Black et al.[122] demonstrated that stoichiometric iron(II) sulfate can effect the rearrangement of a series of oxaziridines such as **153** to the corresponding pyrrolin-2-ones **154** (eq 32). In this case, amide formation

Scheme 22. Proposed Mechanism of Iron-Catalyzed Rearrangement to Amides



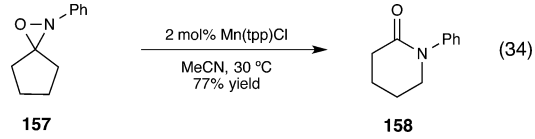


proceeds by loss of a stable *tert*-butyl radical via β-scission of the nitrogen-centered radical. This methodology was also extended to formation of 3-alkylidenepyrrolin-2-ones (**156**) by rearrangement of the corresponding oxaziridines (**155**) (eq 33). Although the authors reported that the reaction proceeds

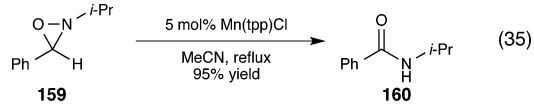


with catalytic iron(II) sulfate, stoichiometric iron(II) salts led to shorter reaction times and fewer byproducts. Presumably, since the rearrangement can proceed under catalytic conditions, the *tert*-butyl radical can act as a radical initiator for rearrangement of the oxaziridine to the amide.

More recent investigations into the transition-metal-catalyzed rearrangement of oxaziridines to amides have sought to improve the practicality and efficiency of the transformation. In 1994, Suda[123] reported a manganese-catalyzed rearrangement of *N*-phenylspirooxaziridine **157** to lactam **158** through a ring expansion. The reaction proceeds in high yield using 2 mol % of a manganese(III) tetraphenylporphyrin catalyst (eq 34).



Importantly, a range of lactam ring sizes could be generated in high yield using this catalytic method simply by changing the nature of the starting oxaziridine. Although the authors suggest that this transformation may proceed by an ionic and not electron transfer mechanism, the mechanism was not studied in detail. In a similar report, Eisenstein and co-workers[124] reported that cyclic, 3-arlyoxaziridines such as **159** could be converted to the corresponding amide **160** using the same manganese catalyst, albeit under more forcing reaction conditions (eq 35).



Transition-metal catalyzed rearrangements of oxaziridines are not limited to the formation of amides. Catalytic reactions that take advantage of the formation of a nitrogen-centered radical for intramolecular cyclizations and fragmentations have also been developed. Aubé and co-workers studied intramolecular radical cyclizations with oxaziridines and found that product distributions are heavily dependent on oxaziridine substitution.[125] For instance, each diastereomer of alkene-bearing oxaziridine **161** forms a different product when treated with catalytic amounts of a copper(I) salt (Scheme 21).[126] The authors proposed that treatment of diastereomer **161a** with 5 mol % of a copper(I) catalyst generates the nitrogen-centered

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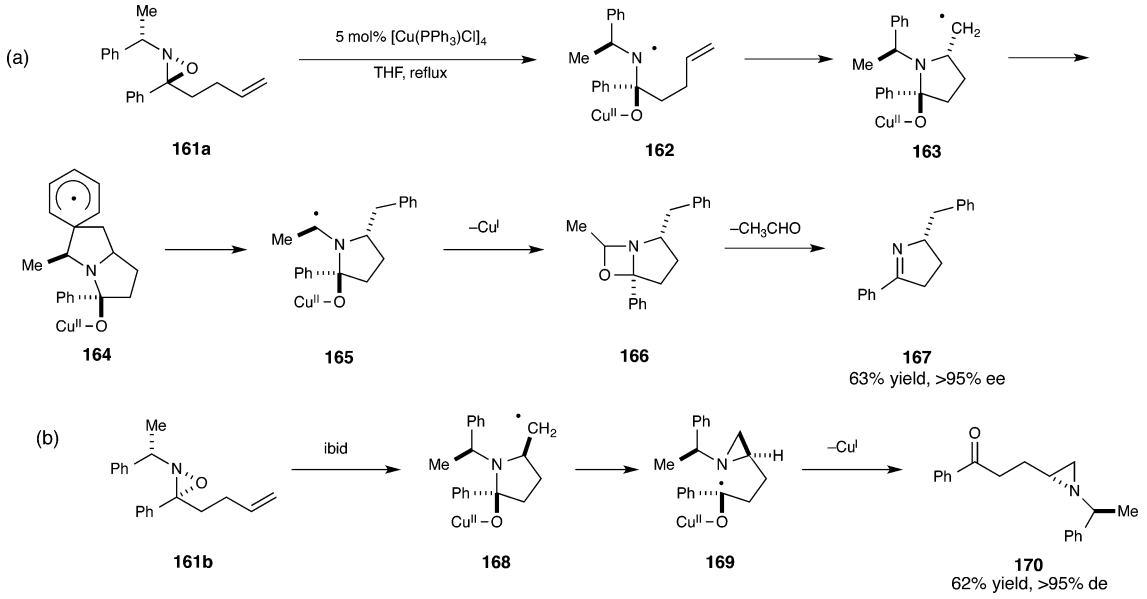
Scheme 23. Intramolecular Radical Amine Cyclizations with Oxaziridines



radical, which can undergo intramolecular cyclization with the olefin to generate primary radical **163** (Scheme 23a). The carbon-centered radical in **163** can then attack the aromatic ring, which is transferred, generating a stabilized radical α to the amine. After regeneration of the copper(I) salt and loss of acetaldehyde, pyrroline **167** is formed. For diastereomer **161b**, however, the authors suggest that radical **168** is incapable of reacting with the aryl ring due to geometrical constraints. As a result, aziridine **170** is the favored product (Scheme 23b).

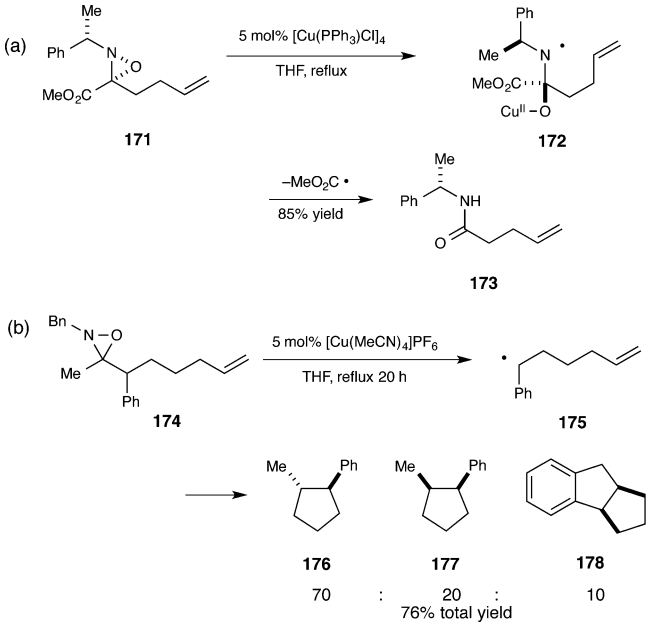
Aubé et al. also studied single-electron transfer reactions of oxaziridines other than nitrogen radical cyclizations. For example, oxaziridines bearing substituents β to the nitrogen that readily form a stabilized radical (e.g., **171**) can undergo β-scission to generate a carbon-centered radical and the corresponding amide **173** (Scheme 24a).[127] Aubé and co-workers also recognized that the carbon radical generated by β-scission from the nitrogen radical could be utilized in subsequent rearrangement reactions.[128] Treatment of oxaziridine **174** with catalytic copper(I) salts favors formation of a benzylic stabilized radical that can subsequently cyclize to form products **176**–**178** (Scheme 24b).

Other groups have recognized the synthetic potential of intramolecular radical cyclizations for generating complex molecules in a stereodefined manner. Black and co-workers used diastereomerically pure oxaziridines such as **179** to generate bicyclic amide **180** in high yield (Scheme 25).[129] In this transformation, the initially formed nitrogen-centered radical cyclizes onto the olefin, followed by attack at the phenyl ring. Subsequent amide formation gives the product and regenerates the copper(I) catalyst. This rearrangement was used to generate [5,5]-, [5,6]-, and [5,7]-bicyclic ring alkaloids by changing the length of the tethered olefin in the starting material.

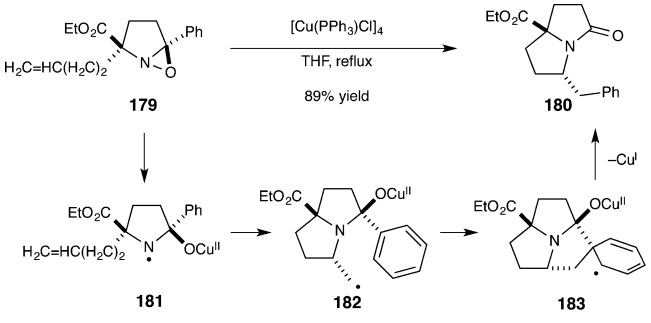
3.4. Cycloadditions

The central ring of an oxaziridine is composed of three different types of bonds; in principle, formal cycloaddition reactions involving cleavage of the C–O, C–N, and N–O bonds are all feasible and would lead to different classes of heterocyclic products. Much of the literature involving cycloadditions of

Scheme 24. Transition-Metal-Catalyzed β-Scission Reactions of Oxaziridines



Scheme 25. Alkaloid Synthesis by Transition-Metal-Catalyzed Oxaziridine Rearrangement



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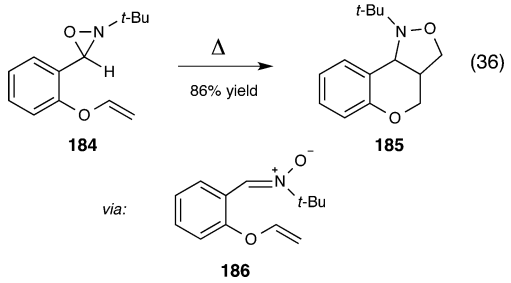
oxaziridines focuses on cleavage of the C−O bond, primarily because the propensity of oxaziridines to rearrange to nitrones under Brønsted and Lewis acidic conditions has been recognized since Emmons' original description of these compounds.[10] Many early reports focus on cycloaddition reactions with heterocumulenes.[130] Recently, however, methods to promote synthetically useful cycloadditions involving cleavage of the C−N and N−O bonds of oxaziridines have also been reported.

3.4.1. Dipolar Cycloadditions. The thermal rearrangement of oxaziridines to nitrones has been the subject of extensive investigation.[117] Given the numerous synthetic applications of 1,3-dipolar cycloaddition reactions, there has been considerable interest in the design of tandem rearrangement−dipolar cycloaddition reactions that begin with oxaziridine substrates. In 1986, Padwa and co-workers described the intramolecular 1,3-dipolar cycloaddition of a nitrone generated from an oxaziridine bearing a tethered alkene.[131] In this reaction, oxaziridine **184** was heated to generate the putative nitrone **186**, which was trapped by the pendant alkene to yield isoxazolidine **185** in 86% yield (eq 36). The same product



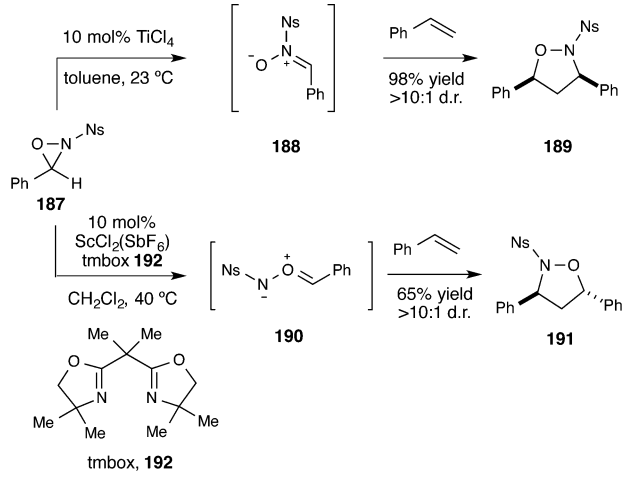
(36)

could also be formed in high yield from the independently prepared nitrone **186**, thus supporting its role as an intermediate. The authors also established that intermolecular cycloadditions were possible with electron-deficient alkenes to give 5-substituted isoxazolidines.

Davis et al. also postulated that nitrones might be intermediates in the thermal decomposition of *N*-sulfonyloxaziridines, but due to their instability, *N*-sulfonyl nitrones generated by thermal rearrangements of oxaziridines have not been trapped via dipolar cycloaddition reactions. The Yoon laboratory, on the other hand, discovered that *N*-nosyloxaziridine (nosyl = 4-nitrobenzenesulfonamide) **187** undergoes efficient rearrangement in the presence of catalytic $TiCl_4$ (Scheme 26).[40] Under these mild conditions, the highly electrophilic *N*-nosyl nitrone **188** reacts productively with electron-rich dipolarophiles to yield 1,2-isoxazolidine **189** with high cis selectivity.

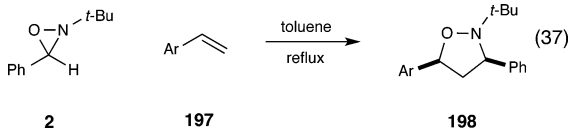
The isoelectronic rearrangement of oxaziridines that involves cleavage of the C−N bond would result in the formation of an unusual class of 1,3-dipoles called carbonyl imines, the chemistry of which has not been extensively explored. Huisgen predicted the existence of these dipoles in 1963,[132] in analogy to nitrones and carbonyl oxides. The first experimental validation of the ability of these compounds to undergo dipolar cycloaddition reactions was reported by the Yoon laboratory in 2010. *N*-Nosyloxaziridine **187** rearranges to carbonyl imine **190** in the presence of the bulky scandium complex [Sc(tmbox)-Cl_2]SbF_6; cycloaddition with a range of π systems results in the formation of 1,2-isoxazolines (**191**) with high trans selectivity.[133] Together with the $TiCl_4$-catalyzed nitrone rearrangement, these cycloadditions provide straightforward access to

Scheme 26. Complementary Dipole Formation from *N*-Sulfonyloxaziridines



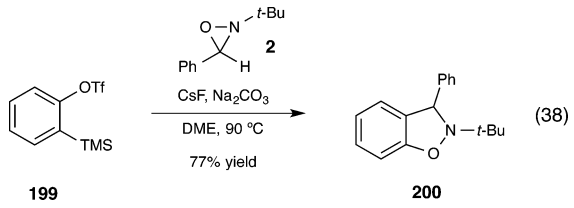
either cis- or trans-substituted *N*-nosylisoxazolidines. Selective cleavage of the N−O bond or removal of the *N*-nosyl moiety can be accomplished under orthogonal conditions (Scheme 27).

A number of cycloadditions have also been reported utilizing *N*-*tert*-butyl-3-phenyloxaziridine **2** that involve insertion of a π-unsaturated system into the C−O bond of the oxaziridine to yield heterocyclic products. Troisi and co-workers demonstrated that electron-rich alkenes react with oxaziridine **2** to give 3,5-diarylisoxazoline **198** with moderate to excellent cis selectivity (eq 37).[134] Aryl[135] and aliphatic[136] terminal alkynes



(37)

are also competent reaction partners; however, product distributions are highly variable, depending on the substrate. Internal alkynes and benzonitriles[137] have also been utilized to yield 5-acylisoxazolines and 2,3-dihydro-1,2,4-oxadizole products, respectively. Kivrak and Larock demonstrated that benzynes can insert into the C−O bond of a range of *N*-alkyl-3-aryloxaziridines to yield dihydrobenzisoazoles (eq 38).[138]



(38)

3.4.2. Oxyaminations. Cycloaddition reactions involving the cleavage of the N−O bond of an oxaziridine have received increasing attention in the past several years. When the reaction partner involved in the cycloaddition is an alkene, the product is a 1,3-oxazolidine that can be considered to be a protected amino alcohol. However, direct, uncatalyzed oxyamination reactions between oxaziridines and olefinic substrates are quite rare. Desmarteau reported that electron-deficient 1,1-difluoroalkenes react with perfluoro oxaziridine **202** to furnish 1,3-

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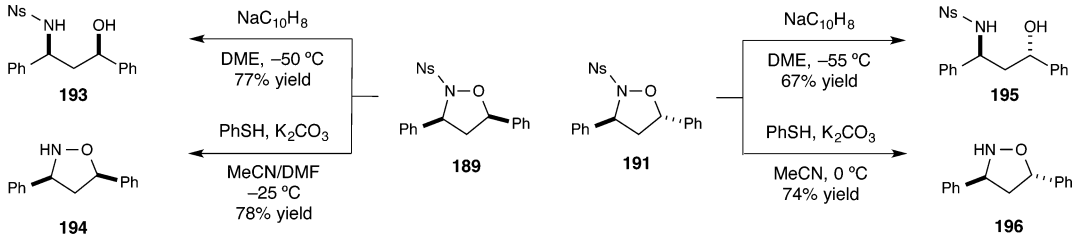
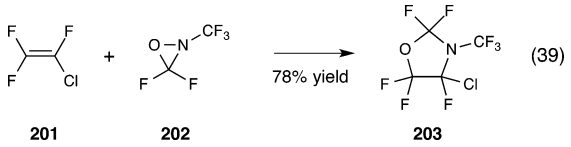
Scheme 27. Orthogonal Isoxazolidine Deprotection

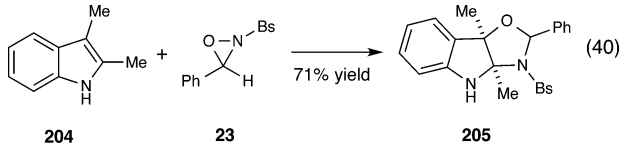


oxazolidine **203** in good yield (eq 39),[139] but only electron-deficient alkenes undergo this unusual aminohydroxylation.



(39)

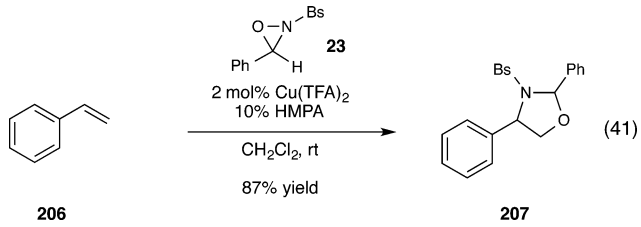
Simple olefins react with **202** to give epoxides, which is an example of the oxygen transfer typically associated with these oxaziridines. More recently, Dmitrienko observed the unexpected formation of aminal **205** upon reaction of *N*-sulfonyloxaziridine **23** and 2,3-dimethylindole during a model study toward the total synthesis of the antitumor alkaloid FR900482 (eq 40).[140] The scope of this reaction is also limited



(40)

to a very narrow substrate range; only extremely electron-rich 2,3-dialkylindoles were reported to give the aminohydroxylation product.

In 2007, the Yoon laboratory reported that copper(II) complexes catalyze the oxyamination of a range of alkenes using *N*-sulfonyloxaziridines as the terminal oxidant. A range of olefins, including styrenes, allylsilanes, enol ethers, and 1,3-dienes, were found to be excellent substrates, and the aminal products are formed with complete regioselectivity in each case (eq 41).[141] Reactions involving unsymmetrical 1,3-dienes

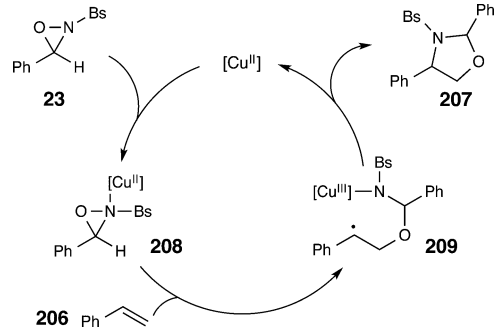


(41)

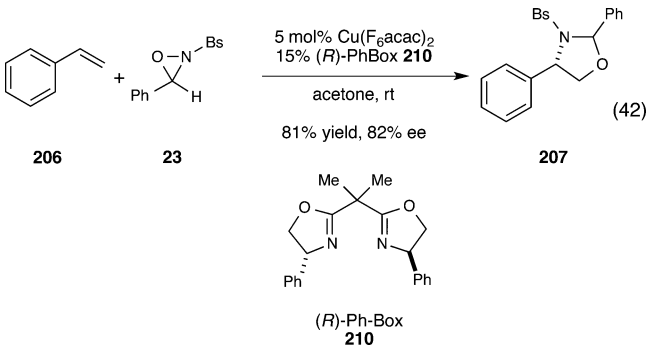
proceed with good to excellent olefin selectivity, and only mono-oxyamination is observed. The resulting allylic 1,2-amino alcohols can be easily elaborated to a variety of synthetically useful complex amine-containing compounds.[142]

Yoon proposed the mechanism for this transformation as shown in Scheme 28. Upon coordination to a copper catalyst, oxaziridine **23** becomes activated toward substrate-induced homolysis of the N—O bond. Thus, attack of the olefin onto the copper-activated oxaziridine gives intermediate **209** with a benzylic radical and copper(III)-stabilized sulfonamide. Cyclization of the Cu(III)—sulfonamide then forms the aminal product **207** and regenerates the copper catalyst.[143]

Scheme 28. Proposed Mechanism of Oxaziridine-Mediated Oxyamination



An enantioselective version of this reaction catalyzed by a chiral bis(oxazoline)copper(II) complex has been reported. Oxyamination of a variety of styrenes proceeded in good yield and modest to good enantioselectivity in the presence of commercially available copper(II) hexafluoroacetylacetonate [Cu(F_6acac)$_2$)] and (*R*,*R*)-Ph-Box 210 (eq 42).[144] The amino



(42)

alcohol products that result from this protocol are highly crystalline, and very highly enantioenriched amino alcohols can easily be prepared by recrystallization. Thus, while the stereocontrol available from this method are lower than those generally observed in the Sharpless aminohydroxylation reaction,[145] the regioselectivity is much higher for styrenes.

The addition of exogenous halide salts to the copper(II)—aminooxygenation reaction greatly enhances reaction rates.[143] Yoon et al. have hypothesized that the addition of chloride anion results in the formation of an anionic halocuprate(II) complex in situ, which may be better able to stabilize the copper(III) intermediate invoked in Scheme 28. The greater reactivity available using these conditions enables the oxyamination of less reactive substrates with higher yields and shorter reactions times. The use of a halocuprate(II) catalyst also allows the use of the less reactive symmetrical 3,3-

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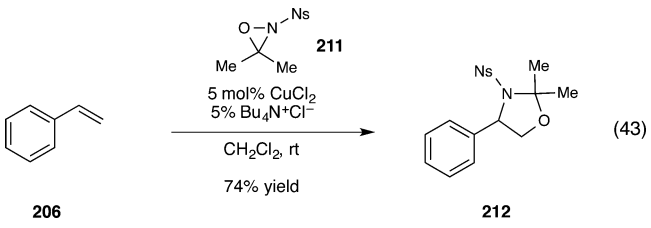
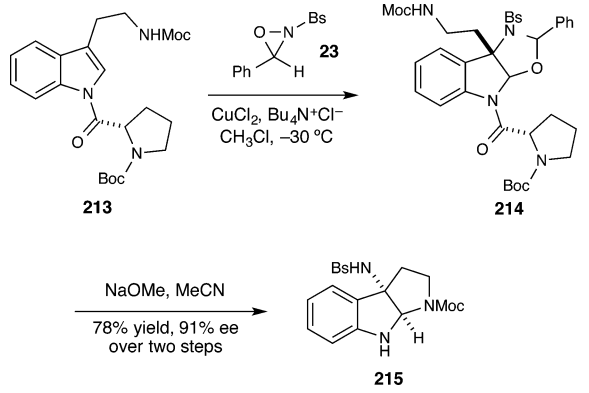
dimethyloxaziridine **211** (eq 43), which circumvents some of the difficulties associated with purification and analysis of the



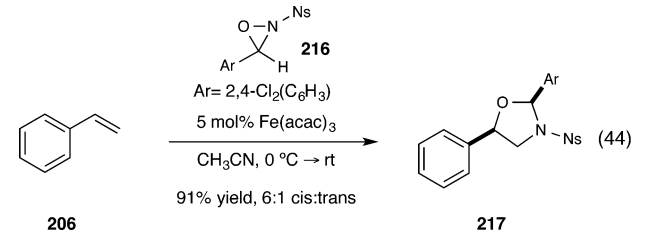
(43)

diastereomeric aminal products previously reported. These halocuprate conditions have been applied to the oxyamination of tryptamine derivatives as an efficient route to enantiomerically enriched 3-aminopyrroloindolines,[146] a common functional motif present in numerous biologically active indole alkaloids (Scheme 29).

Scheme 29. Synthesis of Enantioenriched 3-Aminopyrroloindolines

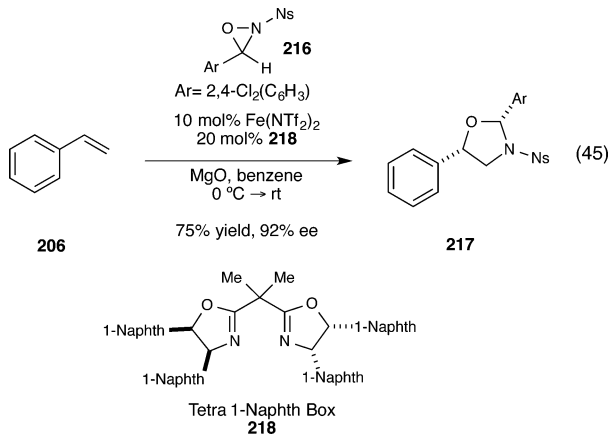


The Yoon laboratory later discovered that iron salts are also effective catalysts for the intermolecular addition of the N–O bond of the oxaziridine across a range of styrenes, dienes, and aliphatic olefins.[147] However, the regiochemical outcome of this reaction is opposite that observed in copper-catalyzed reactions; oxazolidine **217**, which bears the amino functionality on the less-substituted carbon, is the exclusive regioisomer formed (eq 44).



(44)

A highly enantioselective iron-catalyzed oxyamination using this strategy was reported in 2012. Utilizing a combination of a highly electron-deficient iron(II) triflimide salt and bis(oxazoline) ligand **218**, the oxazoline product **217** was produced in good yield and exceptional enantioselectivity (eq 45).[148] Notably, this allows complementary access to enantioenriched chiral amino alcohols utilizing copper and iron bis(oxazoline) catalysts and is also a rare example of a highly enantioselective oxidative iron-catalyzed reaction.

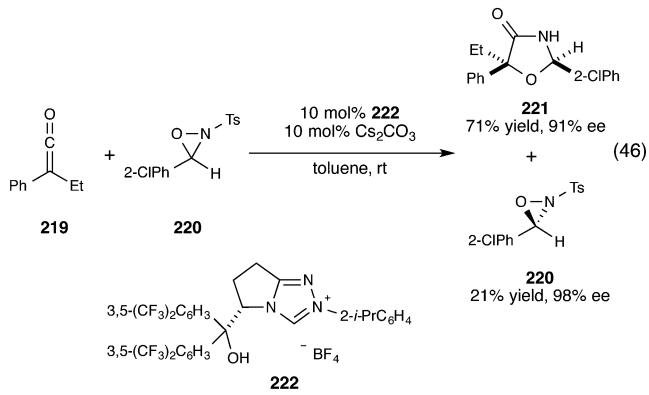


(45)

Lewis base catalysts have also been utilized to achieve formal [3 + 2]-cycloaddition reactions of *N*-sulfonyloxaziridines to yield oxazolin-4-ones via N–O bond cleavage. Lui, Feng, and co-workers demonstrated that chiral *N*-heterocyclic carbene **222** can be used to generate reactive zwitterionic enolates from disubstituted ketenes to produce the oxazolin-4-one **221** in high yield and ee (Scheme 30, eq 46).[149] The oxaziridine is also resolved over the course of the reaction and can be recovered in varying levels of enantioselectivity depending on the substrate. The authors propose a mechanism that involves addition of the

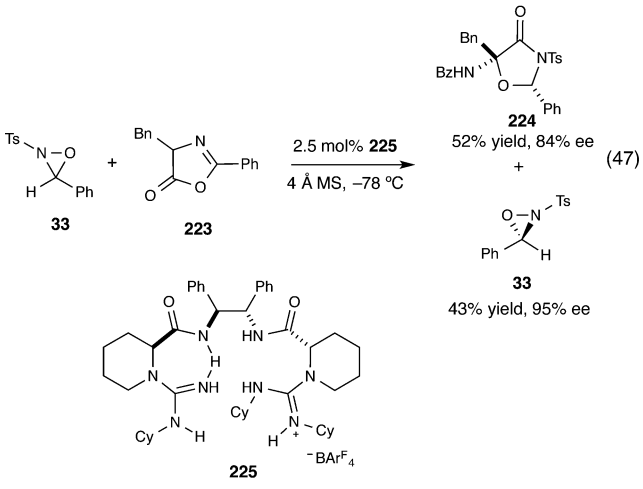
Scheme 30. Chiral Lewis Base-Catalyzed Cycloadditions

Ye (2010):



(46)

Lui and Feng (2013)



(47)

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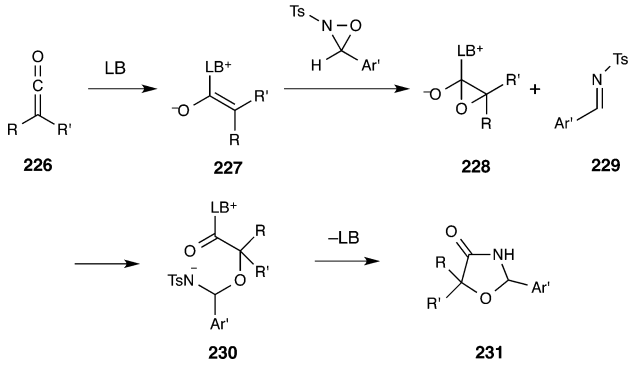
zwitterionic enolate **227** to the electrophilic oxygen of the oxaziridine to give intermediate **228** and the imine **229**, which can subsequently react to form the cyclic product and regenerate the catalyst (Scheme 31). More recently, Dong et

Scheme 31. Mechanistic Proposal for Lewis Base-Catalyzed Cycloaddition



al. reported the oxyaminations of azlactones with oxaziridines utilizing a chiral bis-guanidinium salt.[150] The reaction affords oxazolin-4-ones with exceptional enantioselectivities and results in the kinetic resolution of a range of oxaziridines with high *S* factors (Scheme 30, eq 47).

4. CONCLUDING REMARKS

The chemistry of oxaziridines has developed in many diverse and unexpected directions over the past 6 decades. Initial interest in the unique structural and physical properties of these strained heterocyclic ring compounds became overshadowed in the 1980s by the recognition that electron-deficient oxaziridines could be convenient, bench-stable, neutral sources of electrophilic oxygen. The use of oxaziridines in oxygen atom transfer reactions continues to be the most broadly appreciated application of oxaziridine chemistry. However, many of the most recent new methods involving oxaziridines have shown that their reactivity can be perturbed in order to achieve reactions involving nitrogen atom transfer, oxyamination, cycloaddition reactions, and skeletal rearrangement reactions. The use of exogenous catalysts to control the stereoselectivity, regiochemistry, and chemoselectivity of these reactions will inevitably continue to be a focus of innovation in this area.

One reasonable conclusion that can be drawn from the fact that such a broad diversity of new oxaziridine-mediated reactions has been discovered in the past few decades is that the synthetic potential of oxaziridine chemistry has yet to be fully revealed. The subtle sensitivity of oxaziridines toward the steric and electronic properties of their substituents suggests that structurally modified oxaziridines with different chemoselectivity profiles or superior rates of reactivity with organic substrates may yet be discovered. The success that theoretical computation has enjoyed in rationalizing and predicting the reactions of oxaziridines will be particularly useful in these efforts. Thus, a combination of rational mechanistic investigation and empirical serendipitous discovery will continue to be important as interest in the chemistry of these intriguing heterocycles continues to grow.

AUTHOR INFORMATION

Corresponding Author

*E-mail: tyoon@chem.wisc.edu.

Present Addresses

[†]Department of Chemistry, Columbia University, 3000 Broadway, New York, NY 10027.

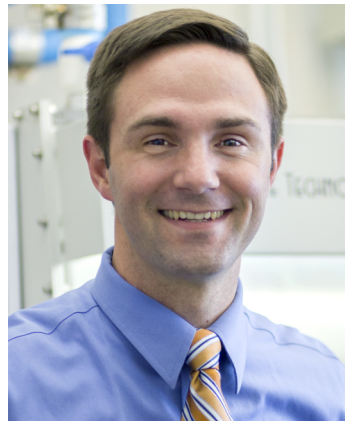
[‡]Department of Chemistry and Biochemistry, Brigham Young University, Provo, UT 84602.

Notes

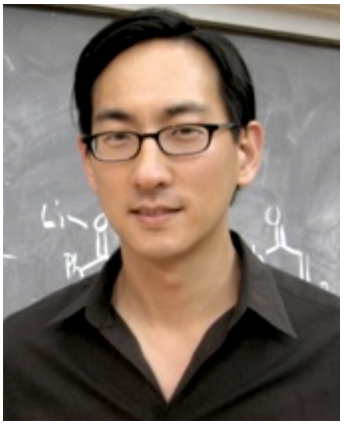
The authors declare no competing financial interest.

Biographies

Kevin S. Williamson received his bachelor's degree at the University of Texas—Austin in 2007 and his Ph.D. under Prof. Tehshik Yoon at the University of Wisconsin—Madison in 2013. He is currently an American Cancer Society postdoctoral fellow at Columbia University with Prof. James Leighton.



David J. Michaelis is an Assistant Professor of Chemistry at Brigham Young University. He received his Ph.D. from the University of Wisconsin—Madison in 2009, where he performed research in the Yoon laboratory. He then pursued postdoctoral studies under the direction of Barry M. Trost at Stanford University as an NIH fellow. In 2013, he began his independent career at Brigham Young, where his research spans the areas of organic synthesis, inorganic chemistry, and catalysis.



Tehshik P. Yoon is a Professor of Chemistry at the University of Wisconsin—Madison. He received his Ph.D. from Caltech working with Prof. David MacMillan, first at Berkeley and then at Caltech. After finishing graduate school in 2002, he became an NIH postdoctoral fellow in the laboratory of Prof. Eric Jacobsen at Harvard. In 2005, he joined the faculty at UW—Madison, where his research has focused on the development of new catalytic methods for organic synthesis.

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