Oxaziridine rearrangements in asymmetric synthesis

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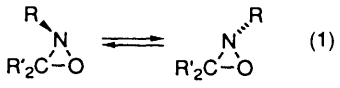
CHEMICAL SOCIETY REVIEWS

Oxaziridines undergo photochemical rearrangement reactions to afford chiral lactams with high levels of enantio- or regio-selectivity. This reaction was applied to the synthesis of targets such as carnitine, the yohimbine alkaloids, and several classes of peptidomimetics. In addition, single-electron transfer reactions can be elicited from oxaziridines using Cu^{I}. These reactions afford nitrogen and carbon radicals that add to an appended olefin, with the final products depending on both the substitution and stereochemistry of the starting oxaziridine.

1 Introduction to oxaziridines

The oxaziridine, that three-membered ring containing nitrogen, oxygen and carbon, has been of mechanistic and structural interest since its introduction in a classic paper by Emmons in 1957.[1] This paper not only describes the preparation and structural proof of a new heterocycle, it also contains the basis for most oxaziridine chemistry known to the present day, including a rich rearrangement chemistry and the decomposition of oxaziridines by low-valent metal salts.[2]

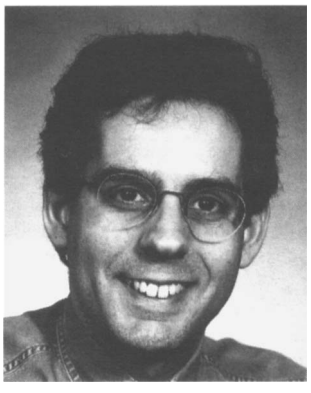
In the years that followed, the oxaziridine was mostly a curiosity that found little synthetic utility. This was despite significant efforts to devise nice methods for the synthesis of oxaziridines—ultimately settling on the oxidation of imines with peracids as the best method—and the attention of stereochemists interested in the configurational stabilization of a potential nitrogen stereocentre [eqn. (1)].[3] It turns out that the



(1)

combination of placing a nitrogen in a three-membered ring (which destabilizes the 120° angle of the sp^2-like transition state involved in pyramidal inversion) with attaching the electron-withdrawing oxygen atom (which opposes the increased s-orbital character of nitrogen during inversion) makes simple oxaziridines the most easily prepared and synthetically useful class of compounds containing a *bona fide* nitrogen stereogenic centre. More recently, *N*-sulfonyl oxaziridines ('Davis reagents') have become popular oxygen-transfer agents for the oxidation of olefins, sulfides and especially enolates. Asymmetric induction is often possible and practical in this chemistry.[2,4] A less-explored area that nonetheless has considerable promise is the use of oxaziridines as nitrogen-transfer reagents for the synthesis of aziridines and hydrazine derivatives.[5]

Our own interest in oxaziridines began with the rearrangement chemistry of *N*-alkyl oxaziridines, especially those containing chiral substituents. In particular, we wished to exploit the nitrogen stereocentre as a controlling feature in ring-expansion chemistry. This review will describe the development of ring-expansion reactions that proceed *via* oxaziridines and lead to the asymmetric synthesis of chiral lactams. This reaction has been used in the synthesis of a variety of interesting natural and unnatural products, including GABOB and carnitine, the yohimbine alkaloids, and several classes of peptidomimetics. In addition, we have recently become interested in the use of oxaziridines as precursors to nitrogen and carbon radicals, and our continuing efforts to develop useful synthetic techniques from this chemistry will be discussed.



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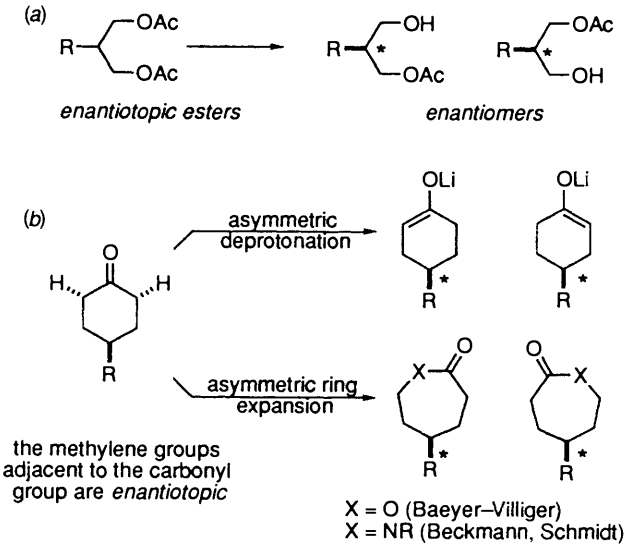
2 Stereoselective synthesis and rearrangements of chiral oxaziridines

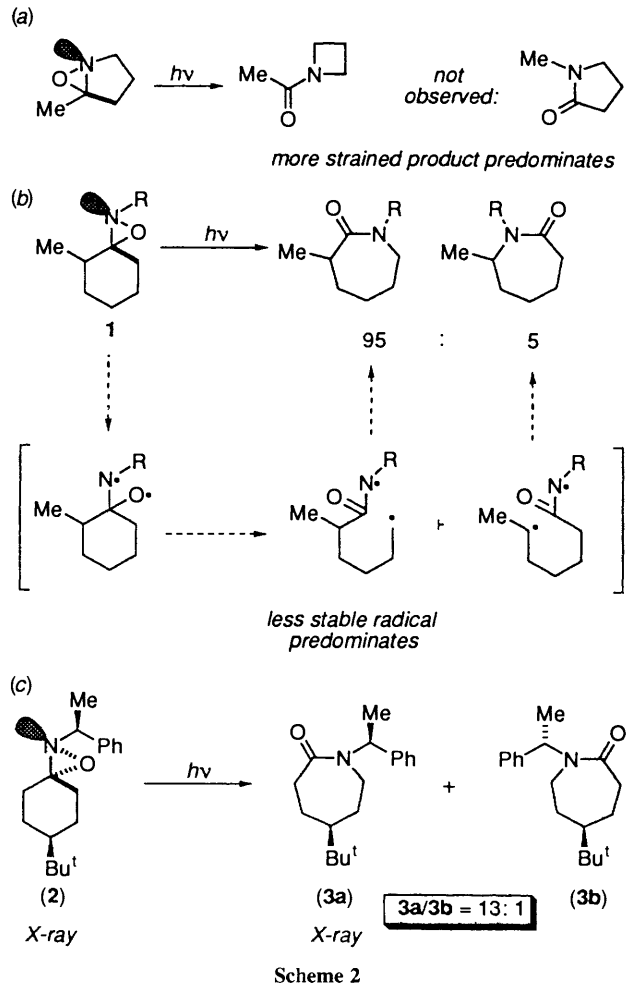
2.1 The concept of a group-selective ring expansion

In the modern era of asymmetric synthesis, many methods for the stereodifferentiation of prochiral faces have been introduced. A fundamentally different mode of asymmetric induction involves the differentiation of enantio- or diastereo-topic groups. Many enzymes operate in just this way [Scheme 1(*a*)]. In this example, the two acetate esters present in the starting molecule are enantiotopic because they can be interchanged by a mirror-plane operation. Selective hydrolysis of this type of ester can be accomplished by a variety of different enzymes, including such popular 'reagents' as pig liver esterase or electric eel acetylcholinesterase. Inspired by nature, chemists have begun to develop abiotic reactions that can achieve this kind of selectivity; several processes particularly relevant to this review involve cyclic ketones containing a plane of symmetry [Scheme 1(*b*)]. Note, that the two methylene groups adjacent to the carbonyl moiety in a 4-alkylcyclohexanone are enantiotopic, as are the axially orientated hydrogen atoms shown. Stereodifferentiation of these protons can be accomplished by reaction with some external chiral reagent. For example, various chiral lithamide bases have been used to generate scalemic mixtures of axially dissymmetric enolates [Scheme 1(*b*)].[6]

We decided to explore another variation on this theme. The ring expansion of the 4-alkylcyclohexanone in Scheme 1(*b*) involves the insertion of a group X between the carbonyl and either enantiotopic methylene group; depending on which group migrates, one or another enantiomeric product results. This means that if a way could be found to differentiate these adjacent methylene groups in the migration step, it would be possible to enact an asymmetric synthesis of a seven-membered hetero- or carbo-cyclic product. Once again, enzymes have proved useful: Taschner and coworkers examined cyclohexanone oxygenase, which can effect enantioselective Baeyer–



Scheme 1



Scheme 2

Villiger chemistry over a range of symmetrical cyclohexanones.[7] Non-enzymatic methods of carrying out this reaction have been relatively slow in coming and do not yet approach the efficiency of the biochemical process.[8] In contrast, the possibility of a corresponding nitrogen insertion chemistry, *i.e.* asymmetric equivalents of the Beckmann or Schmidt rearrangement reactions, was recognized rather early but did not enter the synthetic mainstream until much later. Thus, Lyle and Lyle[9] and Toda[10] were able to resolve axially dissymmetric oximes and carry out their rearrangement to enantiomerically pure lactams, but neither a generally useful asymmetric nitrogen ring expansion chemistry nor its systematic application to problems in asymmetric synthesis were in place. It should also be noted that the case corresponding to Scheme 1(*b*) where X = CH_2 has received some recent attention as well.[11]

2.2 Synthetic methodology development

In the meantime, Lattes, Rivière, and coworkers at the University of Toulouse had been investigating the photochemical rearrangement reactions of oxaziridines to lactams.[12] A few examples are cited out of many because they demonstrate some puzzling aspects of the regiochemistry of this reaction (Scheme 2). In Scheme 2(*a*), ring-contraction to the azetidinone product shown was observed instead of migration of the methyl group, which would have led to a considerably less strained pyrrolidinone lactam. The outcome of the rearrangement of a spirocyclic oxaziridine derived from 2-methylcyclohexanone [**1**, Scheme 2(*b*)] highlights one of the most confusing aspects of the reaction mechanism as originally proposed. Photochemical promotion of the oxaziridine to a singlet excited state would afford an N/O diradical set up for subsequent C–C bond cleavage. Carbon–nitrogen bond formation would then afford lactam product. However, the main product of this reaction—favoured 95 : 5—results from migration of the less-substituted α-carbon, which corresponds to carbon–carbon cleavage affording the less stable carbon-centred radical intermediate. Lattes hypothesized that the bond antiperiplanar to the lone pair in each oxaziridine—signified by a bold bond in the Scheme 2—underwent preferential cleavage; this idea was convincingly demonstrated by the ingenious experiment shown in Scheme 2(*c*).[12]

In this case, the cleavage of either C–C bond of the oxaziridine ring would afford similarly substituted primary carbon radicals, presumably of nearly equal energy. Thus, photolysis of spirocyclic oxaziridine **2** afforded a single lactam **3a** in 70% yield after recrystallization. Since the complete structures of both oxaziridine and lactam were secured by X-ray crystallography, this experiment unambiguously demonstrated that the nitrogen stereocentre was responsible for the regiochemistry of the carbon–carbon cleavage event. Despite the utility of this observation and continued mechanistic interest,[13] many questions regarding the reasons for this selectivity and other details of oxaziridine photochemistry remain. In particular, the existence of radicals along this reaction pathway has still not been demonstrated.

Despite such nagging mechanistic issues, the stereoselective conversion of **2** → **3a** captured our imagination as a bona fide example of a group-selective nitrogen insertion reaction, especially considering that oxaziridines like **2** could be readily prepared from the corresponding substituted cyclohexanone. Before one could use this chemistry in asymmetric synthesis, it was necessary to quantitatively assess the level of stereochemical control possible for oxaziridine synthesis and rearrangement (recall that Lattes' experiments all involved recrystallized material, so that the actual diastereomeric ratios obtained in each reaction were unknown).

Oxaziridines derived from six-membered cyclic imines tend to form *via* equatorial attack[14] and are also subject to control by a chiral group on nitrogen substituent.[15] A useful way of applying these precepts to the second-order problem of inducing axial chirality is shown in Scheme 3. First, condensation of a 4-substituted cyclohexanone generates a mixture of diastereomeric imines. However, the imine oxidation step is generally considered to be a two-stage process, although this has never been rigorously proved.

Accordingly, addition of the peracid to either imine can afford products of equatorial attack or axial attack, with the former being favoured. At this point, the configuration of the imine has been lost and is no longer relevant. Now, N–O bond closure occurs such that the newly generated nitrogen stereo-

centre emerges with the unlike relative configuration when α-methylbenzylamine (α-MBA) was used for imine formation. The best results are usually obtained when a bulky peracid, like monoperoxycamphoric acid (MPCA), is used; for 4-phenylcyclohexanone, the ratio of the four possible products is 83 : 12 : 3 : 2 (87% combined yield).[16] Incidentally, the fact that the oxidant is chiral has no bearing because any given stereocentre on MPCA is too far away from the forming bonds to have an effect on the face selectivity of oxygen addition. So far, in fact, no generally useful reagent for the asymmetric synthesis of oxaziridines exists.

Taken together, the combination of the stereoselective synthesis of an oxaziridine (Scheme 3) with its regiospecific rearrangement reaction [Scheme 2(*b*)] results in the enantioselective synthesis of a lactam from a symmetrical ketone. Careful examination of both the oxaziridine-forming and -rearrangement steps established the efficiency of each reaction and the overall sequence. The proportion of the oxaziridine mixtures comprising equatorial/unlike product [*e.g.* **2** in Scheme 2(*c*)] was 59–91% when MPCA was used as the oxidant.[16] The best ratios were obtained in imines prepared from cyclohexanones containing bulky substituents, presumably due to their superior ability to prejudice the six-membered ring into one chair-like conformation over the other. Furthermore, photolysis of samples of all four purified oxaziridine diastereomers showed that the group *anti* to the nitrogen lone pair predominantly migrated in each case; ratios ranged from 7.3-24:1. [These experiments proved that the result in Scheme 2(*c*) was not just a fluke resulting from some unexpected stability of lactam **3a** over **3b**.] When one considered the entire sequence from ketone to lactam, however, the practical ratios of chiral lactams generally plateaued at *ca.* 7.3 : 1, although this was mitigated by the easy separability of the products. Although other amines have been investigated, α-MBA is preferred for simple ring-expansions due to its low cost and ease of removal under dissolving metal conditions.

As an aside, the structural determination of these spirocyclic oxaziridines has proved very difficult throughout our work because the quaternary and nitrogen stereocentres lack protons useful for coupling constant determinations. Accordingly, we have had to rely on NMR trends, chemical interconversions, and the occasional X-ray structure. A useful byproduct of all of this has been a greater appreciation for the solution state conformations of the spirocyclic oxaziridines (Fig. 1).[17] In this case, the axial hydrogen atom depicted is observed in the ^{1}H NMR spectrum at 0.22 ppm, a value consistent with a highly populated conformation in which the phenyl group is poised over the six-membered ring.

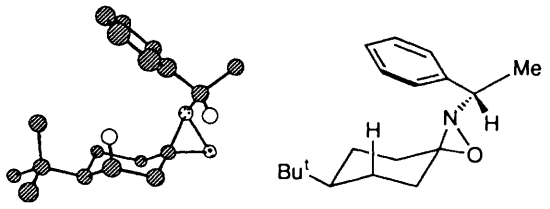
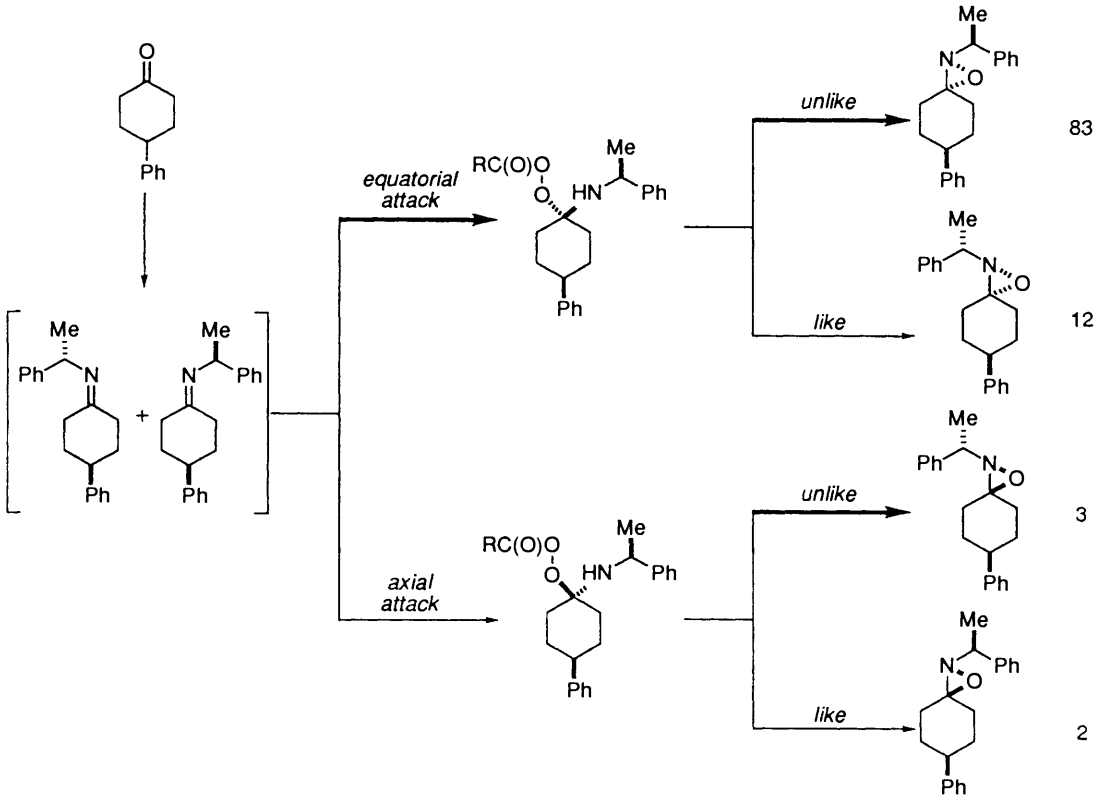


Fig. 1 Proposed predominant conformation of spirocyclic oxaziridines

2.3 Synthetic applications of the oxaziridine → lactam rearrangement reaction

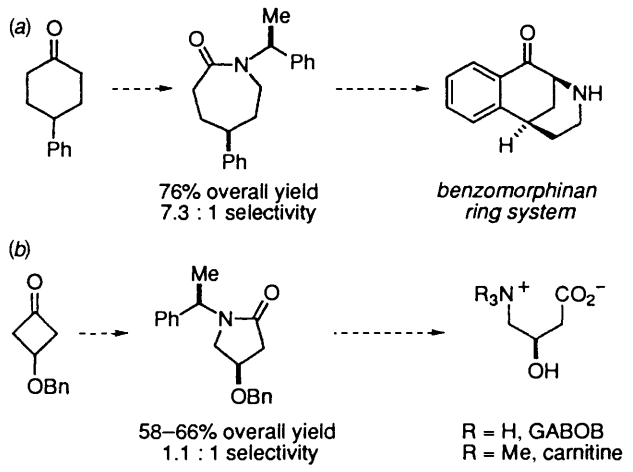
2.3.1 From amino acids to peptidomimetics

Our first synthetic goals were modest: directly apply the asymmetric ring expansion reaction to some simple precursors of biologically relevant heterocycles (Scheme 4). The ring expansion of the phenyl-substituted oxaziridines shown in Scheme 3 came with a ready-made application to morphinoid synthesis as racemic 5-phenylcaprolactam had been previously converted to the benzomorphinan ring system [Scheme 4(*a*)].[16,18] On the other hand, the application of oxaziridines to five-membered lactam synthesis was not selective, affording an equimolar mixture of lactams from 3-substituted cyclobutanones regardless of substitution.[19] Still, the alkoxy-substituted version shown in Scheme 4(*b*) was used in a very brief synthesis



Scheme 3

of enantiopure carnitine, an essential amino acid involved in fatty acid metabolism.[19]



Scheme 4

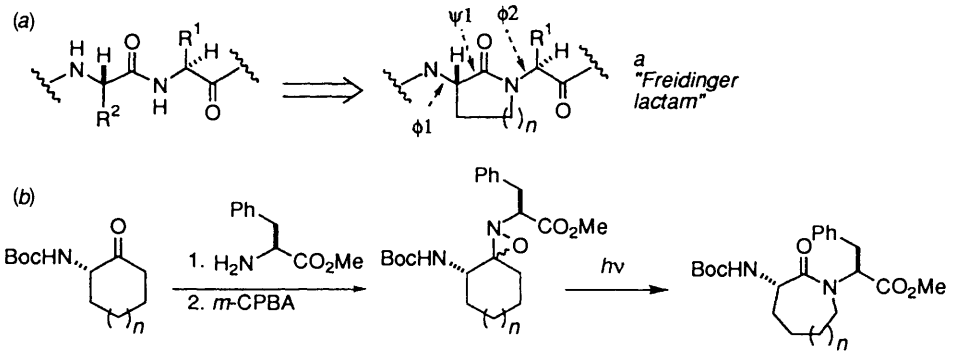
Another direct application of asymmetric synthesis has permitted the synthesis of a new and exciting class of peptidomimetics. Peptidomimetics have biological activity similar to naturally occurring peptides (*e.g.* hormones) but dissimilar chemical structures.[20] Lactams are especially good substructures for peptidomimetic design because the amide linkage is subject to a variety of conformational constraints imposed by the ring. Molecules in which the side chain of one amino acid is formally connected to the α-carbon of the next (going from N to C terminus) are colloquially called Freidinger lactams, after a key inventor of this strategy for peptide constraint [Scheme 5(*a*)].[21]

We have reported a new and potentially general synthesis of Freidinger lactams and applied it to the preparation of some inhibitors of angiotensin-converting enzyme.[22,23] Accordingly, 2-*N*-Boc-aminocycloalkanones varying from 5–7 membered rings were synthesized and converted to the corresponding oxaziridine by condensation with an amino ester like L-phenylalanine [Scheme 5(*b*)]. In this case, the face selectivity of the oxidation step is of little importance; instead, the key feature is the generally exclusive formation of the oxaziridine in which the group on nitrogen is *trans* to the more highly substituted carbon substituent. Photorearrangement in which the carbon *anti* to the lone pair on nitrogen predominates gives the desired peptidomimetic molecule. Note, that the issue is no longer stereoselectivity, but rather regioselectivity.

Typical Beckmann and Schmidt rearrangements occur so that the more substituted carbon migrates to nitrogen.[24] However, formation of the *trans* isomer coupled with the stereoelectronic preference of the photochemical rearrangement lead to migration of the less substituted carbon in Scheme 5(*b*). Thus, the Beckmann/Schmidt chemistry and oxaziridine chemistry complement one another (if the former worked at all: substrates containing α-heteroatoms often run into problems under normal Beckmann or Schmidt conditions). This is a general and most useful feature of oxaziridine chemistry.

An even trickier situation arises in unsymmetrical ketones where the substitution is not adjacent to the carbonyl group. For example, the two α-carbons of the bicyclic ketone in Scheme 6 have similar migratory aptitudes; in addition, there are no steric interactions that could be expected to lead to stereoselectivity in the derived oxime needed for Beckmann chemistry. However, since the ketones are (1) chiral and (2) give imines that should each undergo equatorial attack (*i.e.*, β-attack as drawn), one can use a chiral amine to direct the absolute configuration in the derived oxaziridines.[25] Thus, merely switching from (*S*)- to (*R*)-α-MBA in the imine-forming step, followed by *m*-CPBA oxidation, affords oxaziridines in which the nitrogen stereocentres are of opposite configuration. Photolysis and *N*-α-methylbenzyl reduction lead to regioisomeric lactams as shown. This strategy is one of very few in which a technique normally associated with asymmetric synthesis is coupled with reaction on an enantiomerically pure substrate to afford regioisomeric products. The need for enantiomerically pure starting materials arises from the fact that the racemic ketone would couple with enantiomerically pure amine to give an unavoidably 1 : 1 mixture of diastereomeric oxaziridines. In fact, racemic ketones can be 'resolved' into two lactams of opposite (1) regiochemistry and (2) absolute stereochemistry using this chemistry; the details of this are left to the interested reader as an exercise.[25,26]

It turned out that all of these techniques were needed for the preparation of a series of stereoisomeric β-turn mimics.[27] β-Turns [see Scheme 7(*a*) for an example of this type of peptide secondary structure, including a ball-and-stick model of a 'Type II' β-turn] are known to be involved in a wide variety of biologically important binding events; because of this, they have been some of the most studied archetypes for peptidomimetic design. We have been interested in making β-turn peptidomimetics by the straightforward strategy of constraining a dipeptide unit into a cyclic molecule using an aminocaproic acid linker [Scheme 7(*b*)].[27] We discovered that variously disubstituted linkers were able to bias the conformation of the macrocyclic peptidomimetics into different subclasses of β-turns. This study was made possible by preparing the appropriate aminocaproic acids in enantiomerically pure form and then coupling them to an appropriately protected dipeptide using standard chemistry [Scheme 7(*c*)]. For the *cis* (*meso*) isomers, application of our asymmetric ring expansion protocol gave the desired *syn*-dimethyl linker without incident (not shown). However, the *trans*-dimethylcyclohexanone starting material provided an opportunity to conduct a simultaneous ring expansion/resolution procedure [Scheme 7(*d*)]. Here, the *N*-α-methylbenzyl group permitted an easy chromatographic separation of the diastereomeric lactams prior to nitrogen 'deprotection'. An alternative route would have been to prepare *trans*-3,5-dimethylcyclohexanone in enantiomerically pure



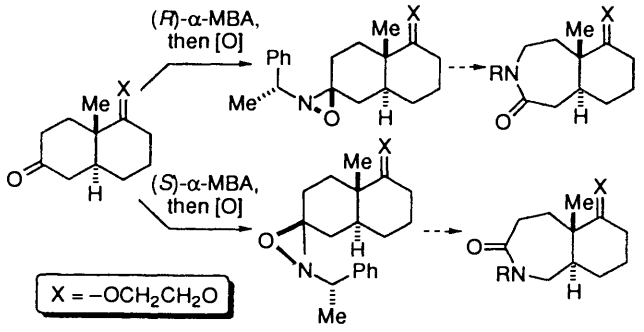
Scheme 5 *m*-CPBA = *m*-chloropenbenzoic acid

form and carry out a standard Beckmann rearrangement, recognizing that the two α-carbons are now identical.

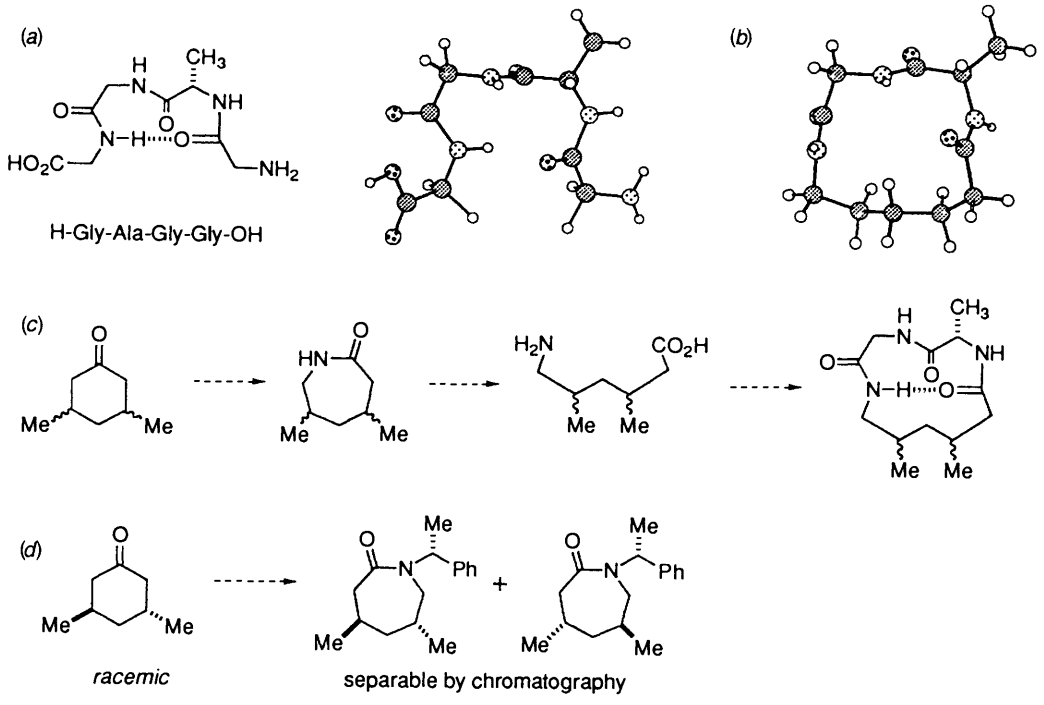
2.3.2 *Yohimbine alkaloids*

Some more sophisticated applications of the oxaziridine → lactam rearrangement reaction were carried out in the synthesis of several members of the yohimbine alkaloid family.[28,29] As shown in Scheme 8, we hoped to maximize the convergency of our syntheses by installing a nitrogen atom already bearing an indole group. An early route to alloyohimbane used α-MBA in the ring-expansion step; not only was this route poorly selective but several low-yielding steps were encountered between removing the *N*-α- methylbenzyl group and attaching the indole (sequence not shown). Here, the stereochemistry of the emerging oxaziridine would be controlled by the chiral amine, in direct analogy to the examples above, and by the tendency of *cis*-bicyclic ketones to undergo attack by oxidant from the less-hindered *exo* (convex) face of the molecule. In contrast, the normal yohimbine series has a *trans* C/D ring fusion, meaning that its synthesis can begin with a C_2 symmetrical ketone, in which the two α-carbons are rendered identical [Scheme 8(*b*].

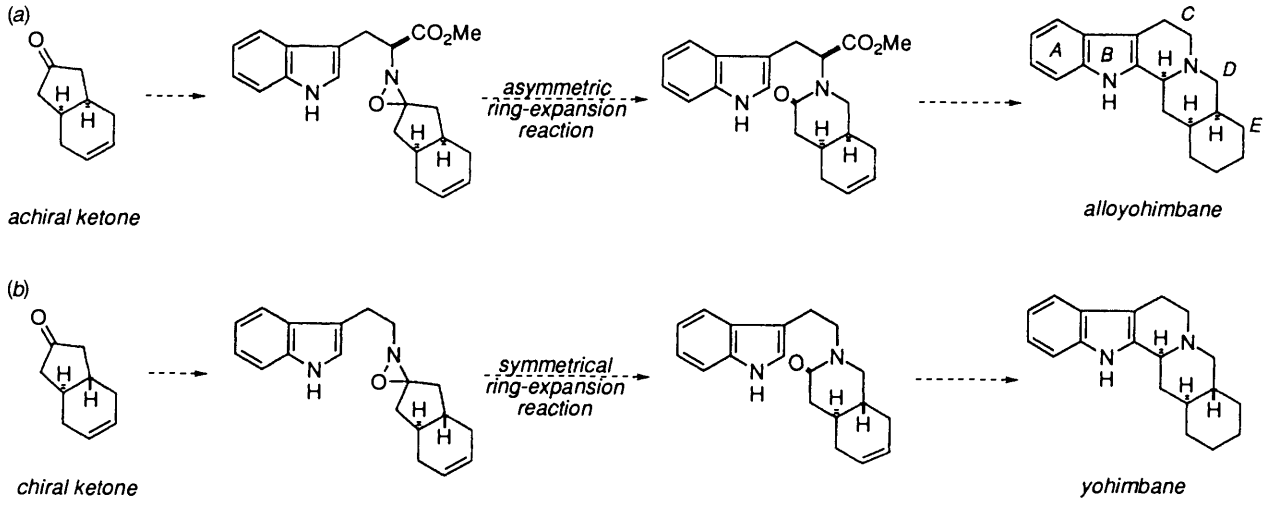
The direct use of a tryptophan ester in the oxaziridination was not much better in terms of selectivity—the lactam shown in Scheme 8(*a*) was obtained as a 2.2 : 1 mixture of stereoisomers—but the overall efficiency was much improved. (The survival of the oxidation-sensitive indole ring is itself noteworthy.) The conversion of the lactam to alloyohimbane



Scheme 6



Scheme 7



Scheme 8

entailed Bischler–Napieralski cyclization, isomer separation, and removal of the methoxycarbonyl group. For comparison, the chiral ketone in Scheme 8(*b*) (prepared in high enantiomeric purity using a sequence featuring an asymmetric Diels–Alder reaction) was readily converted to yohimbane in just six steps and 31% overall yield. The ability to directly introduce a substituted nitrogen is a real bonus of oxaziridine-based insertion chemistry as compared to classical reactions.

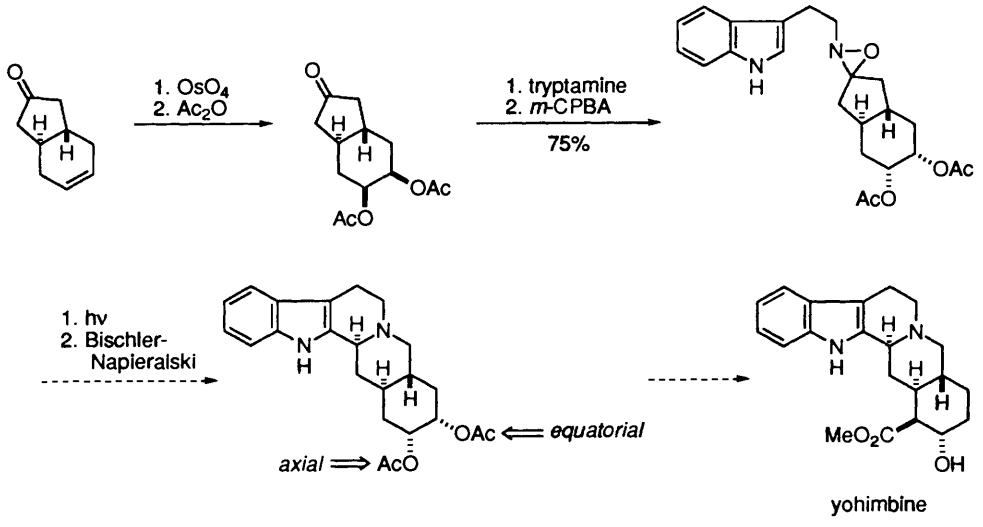
To date, the most ambitious synthesis that features an oxaziridine rearrangement reaction has been the total synthesis of (+)-yohimbine, the first non-formal asymmetric synthesis of this famous target (Scheme 9).[28] Of several possible approaches, we chose to begin with the same chiral ketone used for the yohimbane synthesis; osmylation and acetylation of its alkene installed a protected diol that would later be processed to the E-ring functionality of the natural product. Experimentally, it proved possible to prepare the oxaziridine shown as a complex mixture of stereoisomers that led to two isomeric lactams upon photolysis in 55 and 25% yields, respectively. The major lactam underwent Bischler–Napieralski cyclization to give a pentacyclic diacetate that was converted to yohimbine. Two points stand out. First, the conversion of the E-ring functionality to that of yohimbine was possible because of the rigid nature of this multicyclic compound and the fact the one ester occupied an equatorial position and the other was axial. Secondly, the minor isomer of the ring-expansion sequence, which is not shown, carried two β/*cis* acetoxy groups that could also have been differentiated in later chemistry and converted to yohimbine as well. Even if it did not really matter here (except in terms of convenience), the modest regioselectivity of the ring expansion (*ca.* 2.2 : 1) was remarkable given the distance between the imine and the resident acetoxy groups.

3 Single-electron transfer reactions of oxaziridines: nitrogen and carbon radical generation

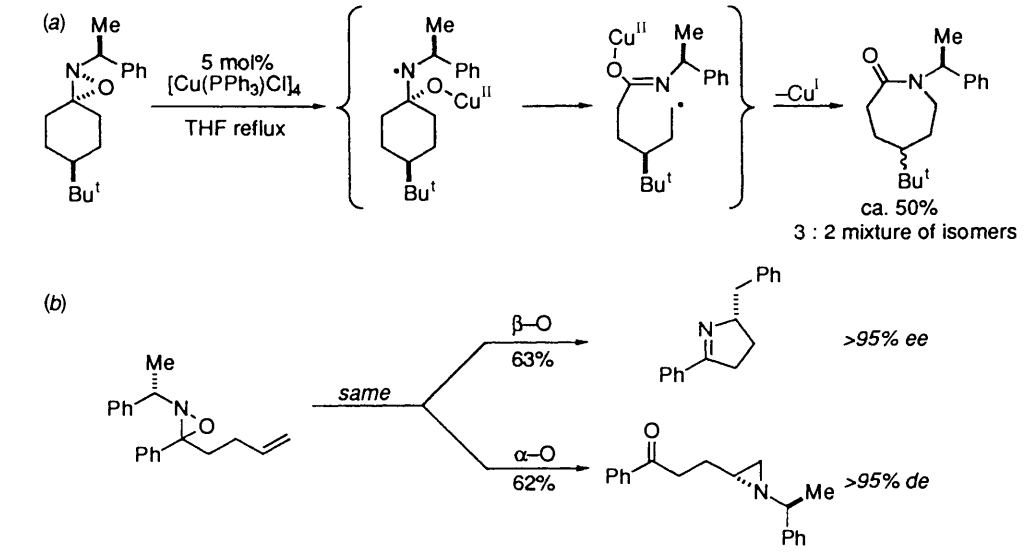
As the photochemical rearrangement reactions of oxaziridines were beginning to achieve some notoriety as a synthetic method, it occurred to us that it would be nice if we could replace the photochemical reaction conditions with another, preferably catalytic method. Recalling the early postulates regarding the mechanism of oxaziridine photochemical rearrangements, we wanted to compare the features of the light-induced reactions—especially regioselectivity—with 'real' radical conditions. Once again, it was only necessary to return to Emmons' original paper[1] to note that low-valent metal salts like Fe^{II} could reduce the oxaziridine ring *via* single-electron transfer (SET); these observations were later refined through important work by Minisci[30] and Black.[31] The resulting nitrogen radical–oxygen anion pairs could then lead to a variety of products depending on oxaziridine substitution. As applied to the present circumstance, a diastereomerically pure spirocyclic oxaziridine was converted to lactam by using $[Cu(PPh_3)Cl]_4$, an easily prepared form of Cu^I that is soluble in tetrahydrofuran (THF) [Scheme 10(*a*)]. However, although the reaction was reasonably efficient, this rearrangement method was not pursued because the reaction was poorly selective compared to the photochemical version described above. Other workers have since investigated SET-induced oxaziridine rearrangement chemistry,[32] but we were intrigued by the possibility that the putative nitrogen radical could undergo addition to an appended olefin and chose to briefly investigate that possibility.

To this end, the alkene-bearing oxaziridines shown in Scheme 10(*b*) were synthesized as a mixture of stereoisomers and separated by column chromatography. Each isomeric oxaziridine was individually submitted to the same conditions as used for the previous reaction.[33] We were unprepared for the products obtained in these experiments, and especially for the fact that two entirely different compounds were obtained from isomeric oxaziridines! The isomer in which the oxygen atom was β as drawn in Scheme 10(*b*) gave the pyrroline shown in 63% yield and, more interestingly, high enantiomeric purity. A change in the relative stereochemistry between the oxaziridine C-2 and N positions (such as the α-oxo isomer shown) resulted not in a stereoisomer of the pyrroline (as we expected) but rather an aziridine. After carrying out the appropriate experiments to completely ascertain the stereostructures of the products and to show that the aryl group was transferred intramolecularly, one possible explanation for these results was crafted (Scheme 11).

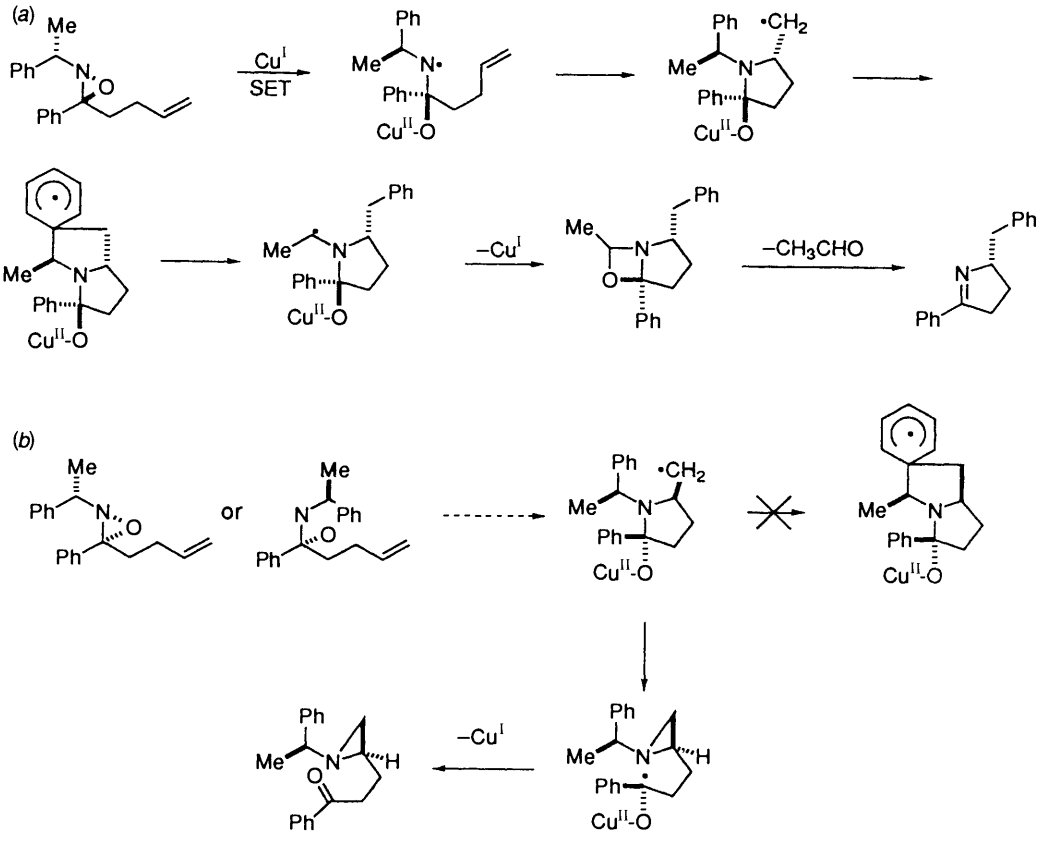
SET from the copper to the oxaziridine makes a nitrogen-centred radical that adds to the olefin as expected. In one case [Scheme 11(*a*)], the resulting radical attacks the aromatic ring, which is transferred, leaving behind a stabilized radical α to the nitrogen group. The formal loss of acetaldehyde now occurs; although several mechanisms to account for this are possible, we have been unable to obtain conclusive experimental evidence in favour of any one of these. The failure of some stereoisomeric oxaziridines to afford pyrroline was rationalized as shown in Scheme 11(*b*): the necessary conformation needed for radical attack on the aryl group leads to an unfavourable steric interaction between the α-methyl group and the phenyl substituent on the five-membered ring, and so the alternative path shown was taken, leading to aziridine. We have begun the considerable work of amassing experimental evidence pertaining to these mechanisms.



Scheme 9



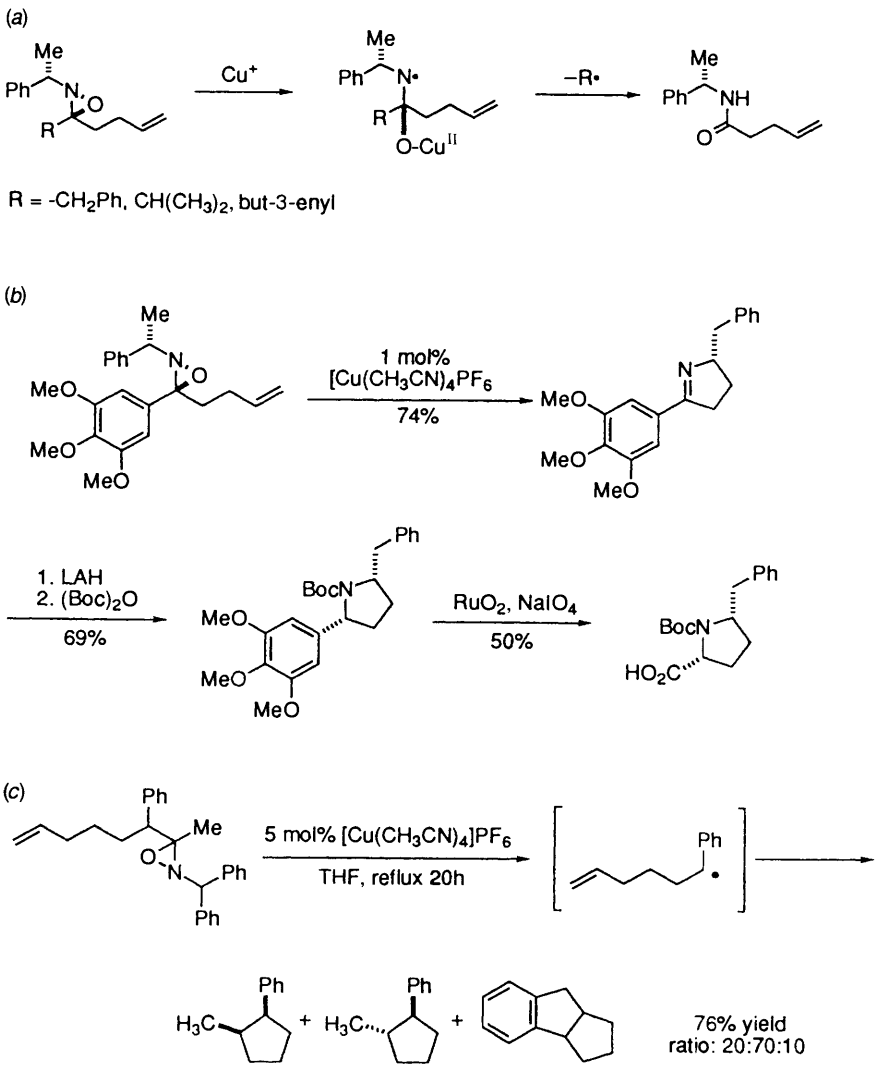
Scheme 10



Scheme 11

Still more complexity was introduced through the examination of alternative substrate types. It appears, for example, that an aromatic group on the oxaziridine is necessary for either of these reaction pathways to succeed [Scheme 12(*a*)]. Other groups, particularly ones that can readily form a relatively stable radical, undergo the cleavage reaction shown to afford amide. To circumvent this problem, an oxaziridine containing two chemically differentiable aromatic rings was subjected to the cyclization–aryl transfer protocol to afford a pyrroline in high enantiomeric purity and 74% yield [Scheme 12(*b*)]. Stereoselective reduction of the pyrroline and nitrogen protection was followed by the chemoselective oxidative degradation of the more electron-rich aromatic ring to afford the proline derivative shown.[34] Even more promising is the possibility that this cleavage reaction can be used to generate carbon-centred radicals under very mild conditions; the cyclization reaction shown in Scheme 12(*c*) is a preliminary indication of the potential of this chemistry.[35]

The mechanistic and stereochemical complexities of the reactions of oxaziridines with low-valent metal salts would seem to limit the synthetic utility of this reaction for the time being, but the same could once have been said about the photochemistry that has become such a recognized tool of substantial utility in nitrogen insertion chemistry. What is certain is that oxaziridine chemistry will continue to provide mechanistic and synthetic challenges for some time to come.



Scheme 12

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