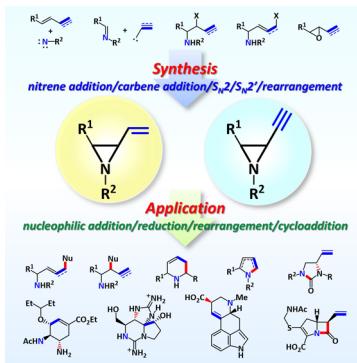


Synthesis and Applications of Vinylaziridines and Ethynylaziridines

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1. INTRODUCTION

Among the variously functionalized aziridines,¹ vinylaziridines and ethynylaziridines are increasingly being exploited as versatile building blocks in organic synthesis. Compounds of this particular type exhibit sufficient reactivity toward a large number of different transformations because of the ring strain associated with their three-membered ring, the electron-withdrawing nature of their nitrogen atom (especially when the nitrogen atom bears an electron-withdrawing group), and the presence of their carbon–carbon multiple bond, which can participate in reactions of the ring as well as stabilizing any positive/negative charges and radicals formed. In many cases, the reactions proceed in a highly stereoselective manner to give the ring-opening products. Vinylaziridines and ethynylaziridines are usually stable enough to be isolated and stored for periods of several months to several years, and this has allowed for aziridines to be widely used for stereoselective synthesis of biologically important compounds, including natural products. This review covers reports from the literature through mid-2013 concerning direct syntheses of vinylaziridines (section 2) and ethynylaziridines (section 3) as well as some of their most important and synthetically useful transformations, such as S_N2/S_N2' nucleophilic addition (section 4), reduction (section 5), rearrangement (section 6), and cycloaddition reactions (section 7). General comments on each reaction type will be described in the introductory part of each section.¹⁰

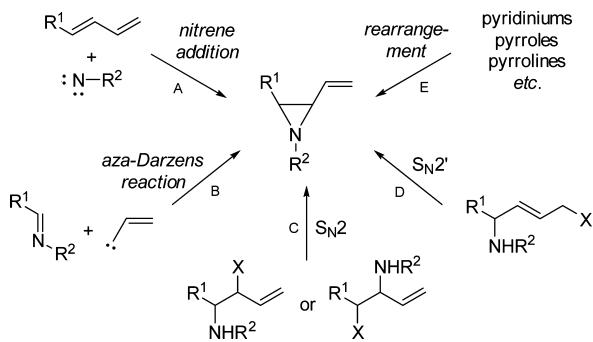
2. DIRECT SYNTHESIS OF VINYLAZIRIDINES

As shown in Scheme 1, vinylaziridines can be synthesized in a number of different ways, including (1) reaction of a nitrene equivalent with a conjugated diene (path A); (2) reaction of an allylic carbene equivalent (i.e., aza-Darzens-type/imino Corey–Chaykovsky reactions, path B); (3) S_N2 displacement of vinylated 1,2-amino alcohol derivatives and related compounds including vinyl epoxide-derived azides (path C); (4) S_N2' displacement of 4-aminobut-2-en-1-ol derivatives and related compounds (path D); and (5) rearrangement reactions of pyridinium salts, pyrroles, and pyrrolines (path E). This review

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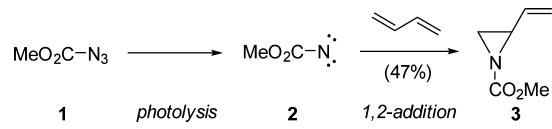
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Scheme 1. General Synthetic Routes to Vinylaziridines

is concerned primarily with providing a detailed discussion of the methods currently available for synthesis of vinylaziridines through construction of the aziridinyl moiety and not with general methods for the synthesis of aziridines, which have been well documented elsewhere. Vinylaziridines can be generally synthesized in two steps, with the vinyl group being constructed following formation of the aziridine ring. For example, Wittig olefination of aziridinyl aldehydes² and palladium-catalyzed cross-coupling of metalated aziridines with vinyl halides³ both provide access to vinylaziridines. Synthetic routes of this type, however, do not fall within the category of direct synthesis of vinylaziridines.

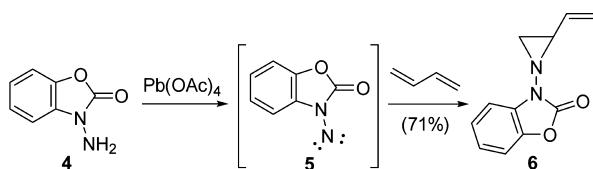
2.1. Addition of Nitrene Equivalents to Dienes

The addition of a nitrene equivalent to a conjugated diene is a traditional method for direct synthesis of aziridines.⁴ The synthesis of vinylaziridine 3 by 1,2-addition of alkoxy carbonylnitrene 2 to butadiene was reported in 1964 by Hafner et al.⁵ (Scheme 2). Nitrene 2 was generated by photolysis of the

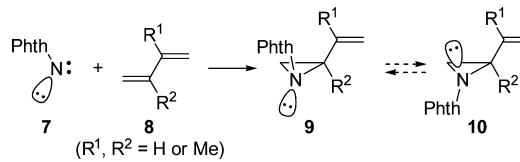
Scheme 2. 1,2-Addition of Methoxycarbonylnitrene 2 to 1,3-Butadiene

methoxycarbonyl azide 1, and the reaction of 2 with (*E*)- or (*Z*)-2-butene proceeded in a stereospecific manner to give the corresponding *trans*- or *cis*-dimethylaziridine. These results suggested that the nitrene reacted preferentially in its singlet state. Similar syntheses of vinylaziridines have also been reported by other research groups.⁶ Similarly, *N*-vinylaziridine was synthesized by reaction of a vinylazide with methyl acrylate or acrylonitrile.⁷

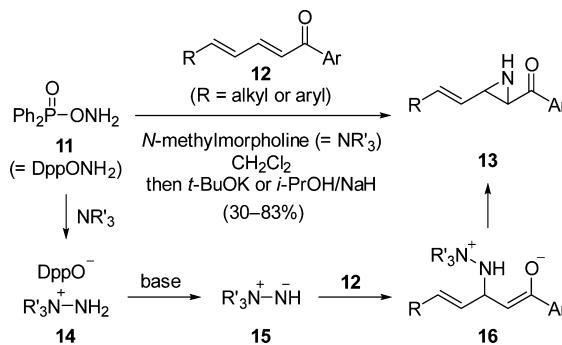
N-Aminobenzoxazolin-2-one 4 is also a useful nitrene precursor (Scheme 3). The 1,2-addition of nitrene 5, which was generated by oxidation of 4 with Pb(OAc)₄ in the presence of a conjugated diene, led to formation of vinylaziridine 6.⁸ It is

Scheme 3. 1,2-Addition of an Amino Nitrene to 1,3-Butadiene

worth mentioning that nitrene itself prefers to attack butadiene via a 1,4-addition.⁹ It is therefore important to use methoxycarbonylnitrene 2 (Scheme 2) or amino nitrene 5 (Scheme 3) for the selective synthesis of vinylaziridines by 1,2-addition. Since these reactions were stereospecific, even under high dilution conditions, it appeared that nitrene 5 was generated in a resonance-stabilized singlet state (probably the ground state).¹⁰ The stereochemical course of the nitrene addition was also investigated by Atkinson and Malpass.¹¹ Thus, nitrene 7, which was derived from 4 or *N*-aminophthalimide, afforded the invertomer 9 in a stereospecific manner at low temperatures (<-20 °C), where 9 contained a vinyl group that was *cis* to the nitrogen substituent (Scheme 4).

Scheme 4. Stereochemistry at Nitrogen following 1,2-Addition of Nitrene

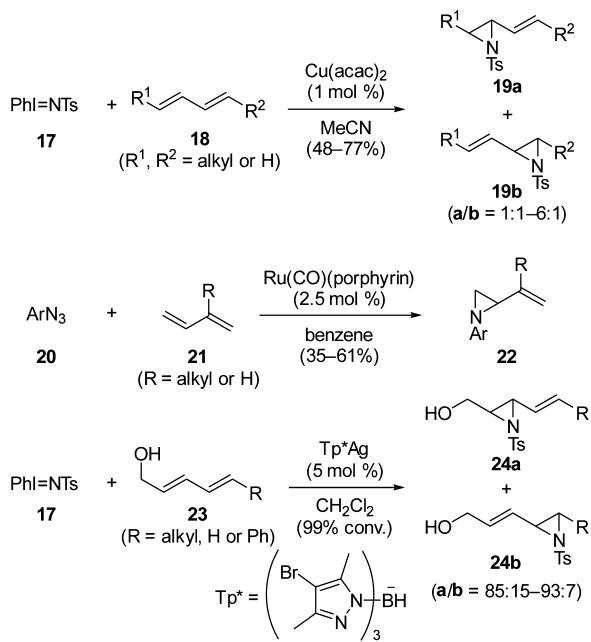
Synthesis of *N*-H vinylaziridines by use of *O*-diphenylphosphinyl hydroxylamine (DppONH₂, 11) as a nitrene precursor was recently reported (Scheme 5).¹² Regioselective aziridina-

Scheme 5. Aziridination of Dienes with Reagent Derived from Hydroxylamine

tion of 11 with conjugated dienones 12 was found to be promoted by *N*-methylmorpholine (NMM) and a strong base to give 2,3-*trans*-2-vinylaziridines 13 in a stereoselective manner. The authors of this particular report suggested that aminimine 15 was the reactive species in the reaction, which undergoes a 1,4-addition reaction to 12 followed by elimination of NMM to give the desired product vinylaziridine 13.

Transition metal complexes efficiently catalyze the aziridination reactions of conjugated dienes with nitrene equivalents. A novel method was developed in 1995 for aziridination of 1,3-dienes 18 using PhI=NTs 17 (Scheme 6)¹³ that was based on the pioneering works of Jacobsen and co-workers^{14a} and Evans et al.^{14b} on copper-catalyzed asymmetric aziridination of isolated alkenes.¹⁴ The regioselectivity of the aziridination toward unsymmetrical dienes was found to be dependent on the electronic and steric characteristics of the double bonds, with a mixture of regioisomers 19a and 19b being formed in different ratios (1:1–6:1). Aziridination of dienes with aryl azide 20 catalyzed by Ru(CO)(porphyrin) complexes has also been reported.¹⁵ In this case, the use of terminal unsymmetrical

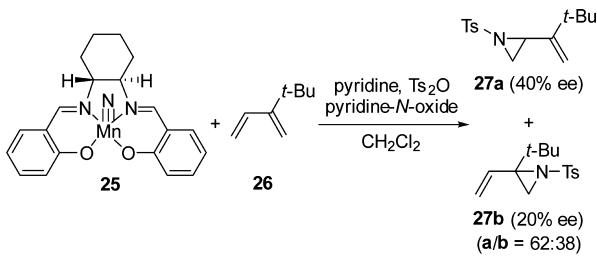
Scheme 6. Transition-Metal-Catalyzed Aziridination of Dienes with Nitrene Equivalents



dienes such as **21** allowed for the reaction to proceed in a regioselective manner. In 2010, Llaveria et al.¹⁶ reported the silver-catalyzed regio- and stereoselective aziridination of dienols such as **23**. The double bond of **23** that was proximal to the hydroxy group participated preferentially in the reaction, resulting in quantitative conversion of **23** to a mixture of vinylaziridines **24a** and **24b**.

The 1,2-addition of nitridomanganese complex **25** to dienes affords the corresponding vinylaziridines (Scheme 7).¹⁷ The

Scheme 7. Reagent-Controlled Asymmetric Synthesis of Vinylaziridines with a Conjugated Diene

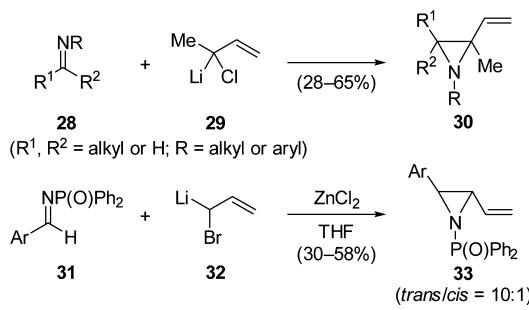


reagent-controlled asymmetric aziridination of conjugated dienes **26** was achieved by use of (*R,R*)-complex **25**, although the enantioselectivities of the reaction were low to moderate [20–40% enantiomeric excess (ee)].

2.2. Addition of Allylic Carbene Equivalents to Imines

The reaction of imines with carbene equivalents represents one of the most convenient and flexible methods for formation of aziridines,¹⁸ with halogenated organometallic reagents (e.g., aza-Darzens reaction) and sulfonium ylides (e.g., imino Corey–Chaykovsky reaction) regularly being used as the carbene equivalents. Synthesis of vinylaziridines according to the aza-Darzens-type reaction was first reported by Mauzé in 1980,¹⁹ where the reaction of aldimines/ketimines **28** with *gem*-chloro(methyl)allyllithium **29** gave highly substituted vinylaziridines **30** (Scheme 8). Sixteen years later, stereoselective

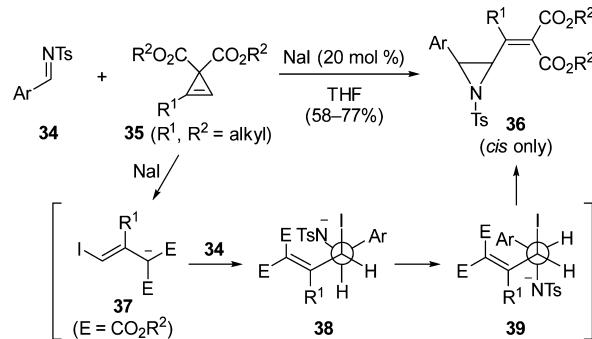
Scheme 8. Aza-Darzens Reaction of Imines with *gem*-Haloallyllithiums



synthesis of *2,3-trans*-*N*-diphenylphosphinyl-2-vinylaziridines **33** (*trans/cis* = 10:1) was reported by the reaction of *gem*-bromoallyllithium **32** with *N*-diphenylphosphinyl aldimines **31** in the presence of zinc chloride.²⁰

Interestingly, the treatment of mixture of imines **34** and cyclopropenes **35** with a catalytic amount of NaI gave the vinylaziridines **36** in a *cis*-selective manner (Scheme 9).²¹ This

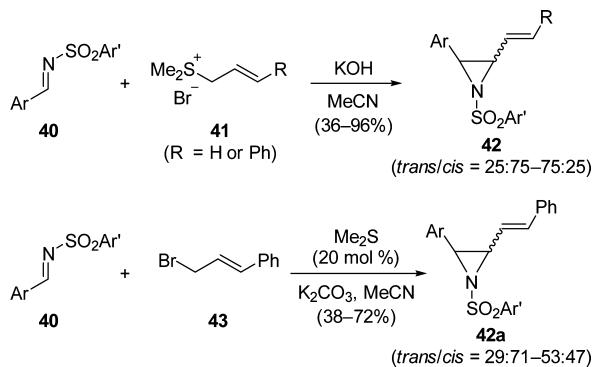
Scheme 9. NaI-Catalyzed *cis*-Selective Aziridination Using Cyclopropenes



reaction can be rationalized in terms of the regioselective nucleophilic attack of an iodide anion on cyclopropene **35** to form the allylic carbanion intermediate **37**. Subsequent stereoselective nucleophilic attack on imines **34** (vide infra, Scheme 11) followed by an anti cyclization process would give **36** and regenerate the iodide anion.

It is well-known that allylic sulfur ylides are weakly reactive compared with other sulfur ylides, such as dimethylsulfonium methylide, and that the formation of aziridines from allylic sulfur ylides and imines can be difficult. Dai and co-workers²² reported that activated imines **40** undergo aziridination with allylic sulfonium salts **41** under phase-transfer conditions (Scheme 10). Although these reactions were not stereoselective (*trans/cis* = 25:75–75:25), this work represents an important contribution to the synthesis of vinylaziridines by a route involving an ylide. The use of imines activated by a phosphinoyl group²³ or a Lewis acid (TMSCl or BF₃·OEt₂)²⁴ led to significant improvements in the stereoselectivity of the aziridination process. Stockman and co-workers²⁵ reported that it was possible to prepare 3-alkyl-2-vinylaziridines by use of a tetrahydrothiophene-derived sulfur ylide. Related imino Corey–Chaykovsky reactions involving the use of arsonium or telluronium salts have also been reported.²⁶ Dai and co-workers²⁷ have also shown that addition of a catalytic amount of dimethyl sulfide promoted the aziridination of arylsulfonyl

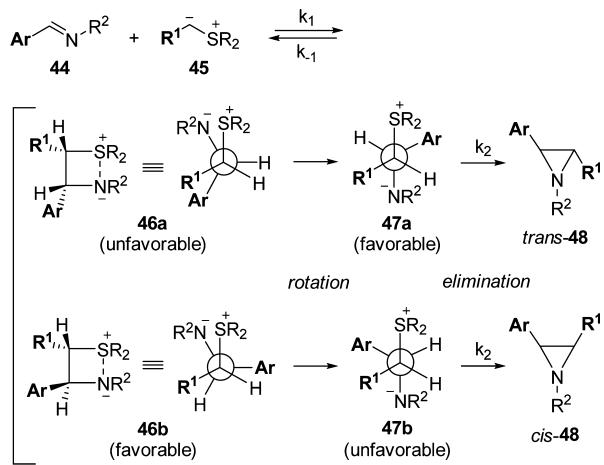
Scheme 10. Imino Corey–Chaykovsky Reaction of Activated Imines with Allylic Ylides



limines **40** with cinnamyl bromide **43** and K_2CO_3 by facilitating the regeneration of the sulfur ylide.

Generally, imines and ylides with lower reactivity favor the formation of *trans*-aziridines, whereas those with higher reactivity prefer to form *cis*-aziridines. A mechanistic study of ylide aziridination by Dai and Hou and co-workers²⁸ revealed that the reaction proceeded in two steps, including (1) addition of sulfonium ylide **45** to the imine **44** to form intermediates **46a** and **46b** (reversible process), which can rotate to form the conformers **47a** and **47b**, and (2) an *anti*-elimination pathway to yield the aziridines *trans*-**48** and *cis*-**48** (Scheme 11). Steric

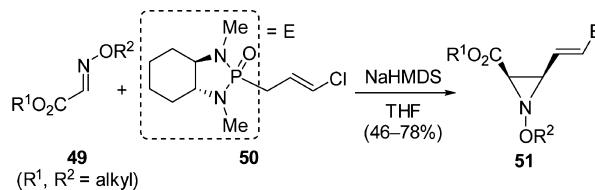
Scheme 11. Mechanism for Aziridination of Imines with Allylic Ylides



repulsion between the aryl and R^1 groups would destabilize **46a** and **47b** and therefore favor the intermediates **46b** and **47a**. Imines with high reactivity would have a large k_1 , and therefore promote the first addition step, as well as increasing the rate of the elimination step (k_2), which would ultimately favor the formation of *cis*-**48** because the highly reactive ylides would provide better leaving groups.

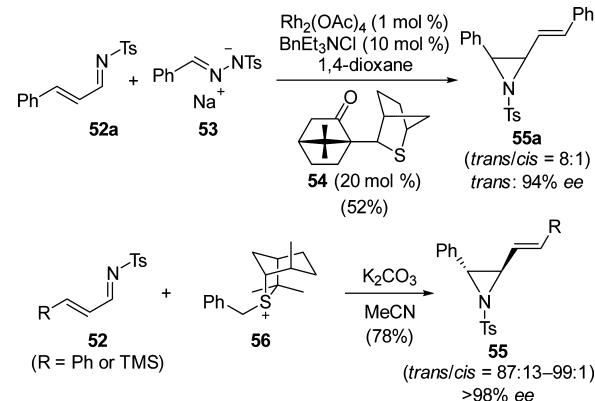
Reagent-controlled asymmetric induction for the synthesis of vinylaziridines was reported in 2000,²⁹ where the reaction of oximes **49** with a chloroallyl phosphonic diamide anion derived from **50** led to formation of *cis*-N-alkoxy-2-alkenylaziridines **51** in a enantiomerically pure form (Scheme 12). Shortly after this work, several asymmetric syntheses of vinylaziridine were reported involving the use of chiral sulfonium ylides, as shown below.

Scheme 12. Diastereoselective Synthesis of Vinylaziridines by Use of a Chiral Phosphonamide Reagent



In 2001, chiral sulfonium ylide-mediated enantioselective aziridination was independently reported by Aggarwal and co-workers³⁰ and Saito et al.³¹ Aggarwal et al.^{30a} developed a highly efficient catalytic method for the asymmetric aziridination of conjugated tosylimine **52a** using chiral sulfonium ylide **54** (20 mol %) through *in situ* generation of the diazo compound (Scheme 13). More recently, Aggarwal and co-

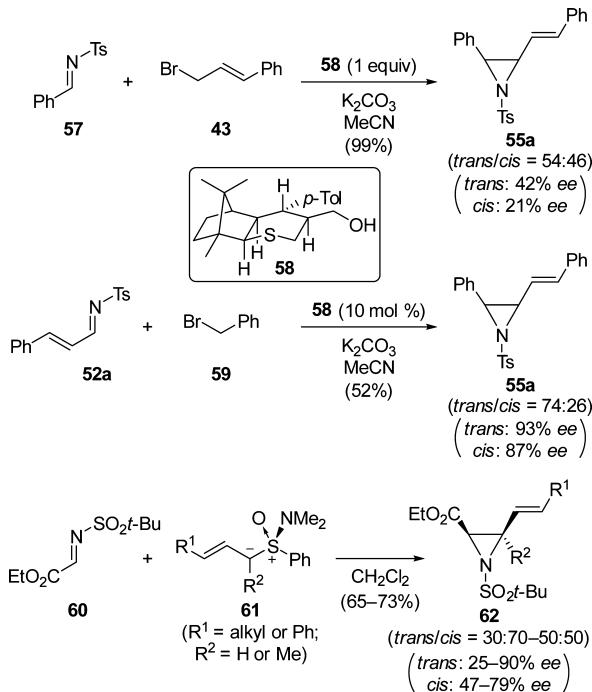
Scheme 13. Highly Efficient Asymmetric Synthesis of Vinylaziridines by Use of Sulfonium Ylides



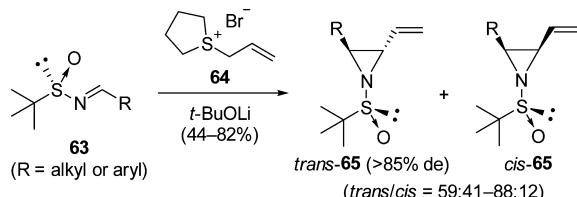
workers^{30b} found that a commercially available inexpensive sulfide (isothiocineole) derived sulfonium salt **56** afforded vinylaziridine **55** in >98% ee (Scheme 13). It is worth mentioning that the same report also described the asymmetric epoxidation of aldehydes using the corresponding allylic sulfur ylides in up to 98% ee. The camphor-derived chiral sulfide reagent **58** was used by Saito et al.³¹ to mediate the enantioselective aziridination reaction between *N*-tosylimine **57** and cinnamyl bromide **43** with moderate enantioselectivities (21–42% ee, Scheme 14). It is noteworthy that the formation of a vinylaziridine by reaction of the conjugated tosylimine **52a** with benzyl bromide **59** required only a catalytic amount (10 mol %) of sulfide **58** and afforded the same vinylaziridines **55a** with higher enantioselectivities (>87% ee).³¹ These results demonstrate that asymmetric induction with allylic sulfur ylides can be more difficult than using alkyl sulfide ylides. A related asymmetric formation of vinylaziridine based on the chiral allylic aminosulfoxonium ylide **61** was reported in 2007.³²

The final example from this section is a substrate-controlled asymmetric aziridination. Stockman and co-workers³³ reported that chiral *tert*-butylsulfinylimines **63** ($R =$ aryl or alkyl) underwent aziridination with the allylic sulfur ylide derived from *S*-allyl tetrahydrothiophenium bromide **64** to yield vinylaziridines **65** in moderate to good stereoselectivities [*trans/cis* = 59:41–88:12; 85–95% diastereomeric excess (de) for *trans*-**65**, Scheme 15]. The chiral sulfinyl group of **65** could then be readily removed by treatment with anhydrous HCl in dioxane to give the corresponding *N*-H vinylaziridines

Scheme 14. Asymmetric Synthesis of Vinylaziridines by Use of a Camphor-Derived Chiral Sulfonium Ylide and Related Reagents



Scheme 15. Asymmetric Synthesis of Vinylaziridines by Use of a Chiral Auxiliary

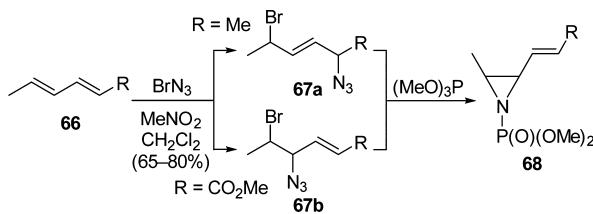


as hydrochloride salts in yields greater than 90%. It is worth mentioning that vinylaziridines can undergo ring-opening reactions in the presence of a strong acid (see section 4.4). Similarly, the *tert*-butylsulfinyl group can be particularly useful for asymmetric induction in the aziridination of ketimines,³⁴ telluronium salt-mediated reactions,³⁵ and aza-Darzens reactions of lithiated bromoacetates³⁶ and brominated allylzinc reagents.³⁷

2.3. S_N2 or S_N2' Displacement of Amino Alcohol Derivatives and Related Compounds

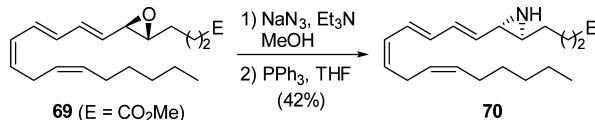
Cyclization of 1,2-amino alcohol derivatives is one of the most convenient and reliable methods for the synthesis of vinylaziridines, because a wide variety of enantiomerically enriched precursors including vinyloepoxides are readily available. The aziridination of dienes **66** with bromine azide was reported by Hassner and Keogh³⁸ in 1975 and is considered to be pioneering in terms of its contribution to the formation of vinylaziridines (Scheme 16). The addition of bromine azide proceeded under thermodynamic control to afford a mixture of the 1,4-adduct **67a** and the 1,2-adduct **67b**, with the ratio of the two adducts being dependent on the substituent R on the terminal carbon. Cyclization of the resulting brominated allylic azides **67** was effected by trimethyl phosphite.

Scheme 16. Synthesis of Vinylaziridines by Addition of Bromine Azide to Dienes



Similar conversion processes have also been reported³⁹ that start from alkenylepoxyde **69** (Scheme 17). According to the

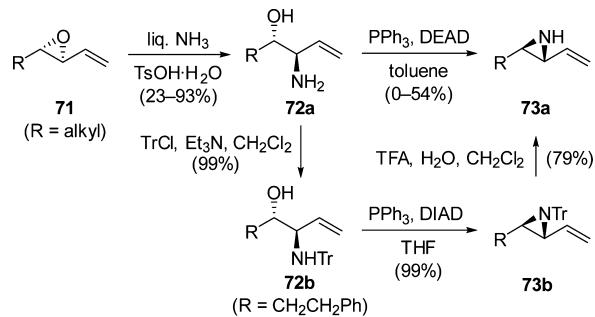
Scheme 17. NaN_3 -Mediated Ring-Opening Reaction of Alkenylepoxyde followed by Cyclization



two-step conversion of epoxides to aziridines developed by Ittah et al.,⁴⁰ regioselective ring-opening reaction at the allylic position with sodium azide gave the corresponding azide alcohol, which was treated with PPh_3 to give the N-H vinylaziridine **70** with inversion of configuration.

Lindström and Somfai⁴¹ developed a two-step process for the conversion of epoxides to N-H aziridines by aminolysis with liquid ammonia (Scheme 18). When vinyloepoxides **71** were

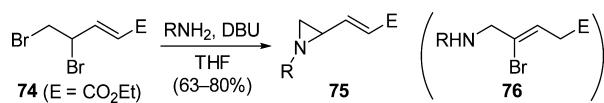
Scheme 18. Synthesis of Vinylaziridines by Aminolysis of Vinyloepoxides with Liquid Ammonia



subjected to these conditions in the presence of $\text{TsOH}\cdot\text{H}_2\text{O}$ (5 mol %), the amino alcohols **72a** were formed regioselectively. Subsequent cyclization of **72a** under Mitsunobu conditions gave N-H vinylaziridines **73a** in low to moderate yields (0–54%). It is worth mentioning that the use of sterically congested alcohols **72a** [i.e., $\text{R} = \text{c-Hex}$ or $\text{C}(\text{Me})_2\text{CH}_2\text{OBn}$] gave the corresponding ethyl carbamates under these conditions. As a more general approach to N-H vinylaziridines **73a**, the same group reported that use of a modified synthetic route involving protection of the nitrogen atom of **72a** with a trityl group, followed by sequential ring closure of **72b** and deprotection reactions, gave N-H vinylaziridines **73a**.⁴²

The Gabriel–Cromwell reaction of 4,5-dibromopent-2-enoates **74** is a convenient strategy for the synthesis of vinylaziridines (Scheme 19). The reaction of **74** with primary amines in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded the corresponding aziridines **75** in 63–80% yields.⁴³ The use of DBU was found to be essential for an

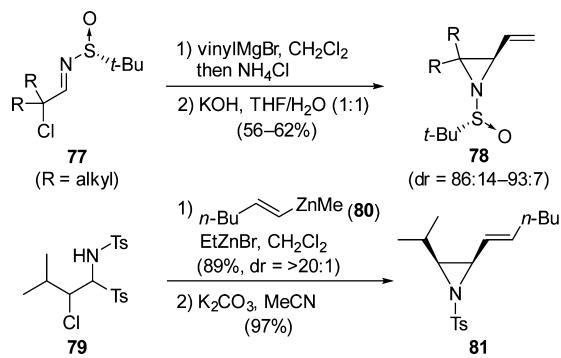
Scheme 19. Synthesis of Vinylaziridines by the Gabriel–Cromwell Reaction



efficient conversion because it facilitated olefin isomerization of the vinylbromide-type intermediate **76**.

Several stereoselective syntheses of vinylaziridines have been reported involving the substrate-controlled addition of alkenylmetal reagents to α -haloimines and their equivalents (Scheme 20). The addition of vinylmagnesium bromide to α -

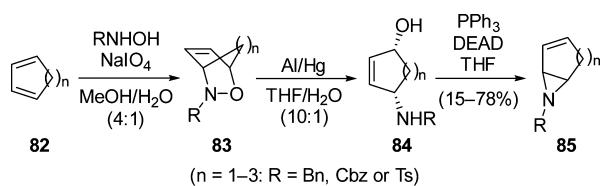
Scheme 20. Substrate-Controlled Stereoselective Syntheses of Vinylaziridines



chloroimines **77**, bearing a *tert*-butylsulfinyl group on their nitrogen atom as a chiral auxiliary, followed by treatment with base afforded vinylaziridines **78** stereoselectively [diastereomeric ratio (*dr*) = 86:14–93:7].⁴⁴ Chelation-controlled addition of the alkenylzinc reagent **80**, which can be prepared *in situ* by hydroboration of alkynes with HBCy₂ and Me₂Zn, to α -chloroaldimine **79** followed by cyclization, gave the *cis*-vinylaziridine **81** in 97% yield.⁴⁵

1,4-Amino alcohols are also good precursors of vinylaziridines. The *cis*-1,4-amino alcohols **84** were obtained by hetero Diels–Alder reaction of cyclic dienes **82** followed by reductive cleavage of the nitrogen–oxygen bond of the resulting bicyclic adducts **83**. These compounds underwent a *syn S_N2'*-type displacement reaction under Mitsunobu conditions to give cyclic vinylaziridines **85** (Scheme 21).⁴⁶

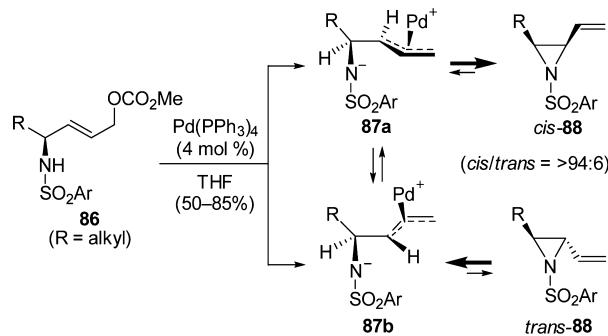
Scheme 21. Synthesis of Vinylaziridines from 1,4-Amino Alcohols



Palladium(0)-catalyzed aziridination of amino alcohol derivatives represents an efficient method for *cis*-stereoselective synthesis of vinylaziridines. Ibuka and co-workers⁴⁷ found that *trans*-2-vinylaziridines were thermodynamically less stable than the corresponding *cis* isomers. Furthermore, they succeeded in achieving the isomerization of *trans*-**88** to *cis*-**88** via the η^3 -allylpalladium(II) intermediates **87a** and **87b** by exposure to

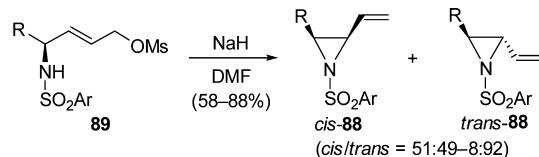
palladium(0) (vide infra, Scheme 107). On the basis of these findings, Ibuka and co-workers⁴⁸ reported the 2,3-*cis*-selective synthesis of aziridines from allylic carbonates **86** via the same intermediates **87** (Scheme 22).⁴⁹

Scheme 22. Palladium(0)-Catalyzed Aziridination of Allyl Carbonates



In contrast to thermodynamically controlled formation of aziridines from allylic carbonates (Scheme 22), base-mediated aziridination of allylic mesylates **89** proceeded under kinetic control (Scheme 23). Thus, the NaH-mediated reaction of **89**

Scheme 23. NaH-Mediated Aziridination of Allyl Mesylates



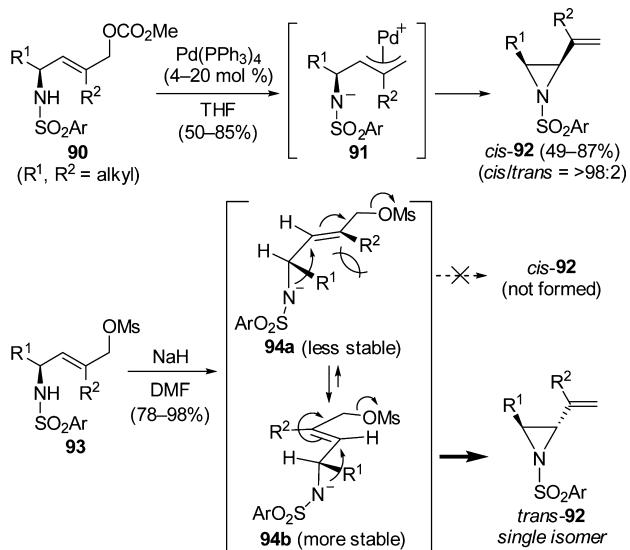
bearing an unbranched alkyl group as the R¹ substituent did not proceed in a stereoselective manner and gave a mixture of vinylaziridines **88** (cis:trans = 43:57–51:49).⁴⁸ In contrast, however, the reaction of **89**, bearing a branched group as the R¹ substituent, led predominantly to the formation of *trans*-**88** (up to 92:8). It is noteworthy that base-mediated cyclization of the corresponding (Z)-allylic mesylates gives 3-pyrrolines exclusively in high yields, whereas palladium(0)-catalyzed reaction of (Z)-carbonates predominantly afforded *cis*-vinylaziridines **88**, in a similar manner to (E)-carbonates **86**.⁵⁰

Ibuka and co-workers⁵¹ also reported a procedure for the highly stereodivergent synthesis of *cis*- and *trans*-alkenylaziridines **92** (Scheme 24). Exposure of methyl carbonates **90**, bearing an alkyl or bromo group as the R² substituent of their double bond, to a catalytic amount of Pd(PPh₃)₄ led predominantly to the corresponding thermodynamically more stable *cis*-**92** (up to 99:1). In contrast, treatment of the corresponding allylic mesylates **93** with NaH led exclusively to the thermodynamically less stable *trans*-**92** (>99:1). The trans-selectivity of base-mediated aziridination can be attributed to unfavorable steric interaction between the R¹ and R² groups in the conformation **94a** required for the formation of the *cis*-aziridine.

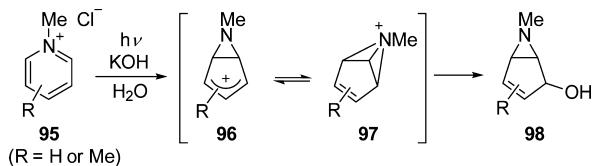
2.4. Rearrangement

In 1972, Kaplan et al.⁵² reported that the irradiation of N-methylpyridinium salts **95** with light in H₂O in the presence of KOH gave the bicyclic vinylaziridines **98** (Scheme 25). They proposed that the reaction proceeded through hydration of the interconverting cations **96** and **97**. This proposal was later

Scheme 24. Stereodivergent Synthesis of *cis*- and *trans*-2-Alkenylaziridines



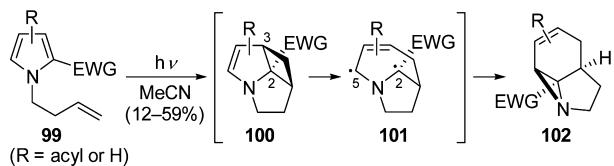
Scheme 25. Vinylaziridine Formation by Irradiation of Pyridinium Salts



supported by the work of Lüthi and co-workers⁵³ using computational investigations and deuterium experiments. Although this reaction ends with a nucleophilic addition, the vinylaziridine moiety was constructed by a rearrangement process. This vinylaziridine formation provides facile access to cyclopentenylamine derivatives.⁵⁴

The photoirradiation of *N*-homoallylpyrrole derivatives 99 leads to the formation of fused vinylaziridines 102 (Scheme 26).⁵⁵ In some cases, however, considerable amounts of

Scheme 26. Vinylaziridine Formation by Irradiation of Pyrrole Derivatives

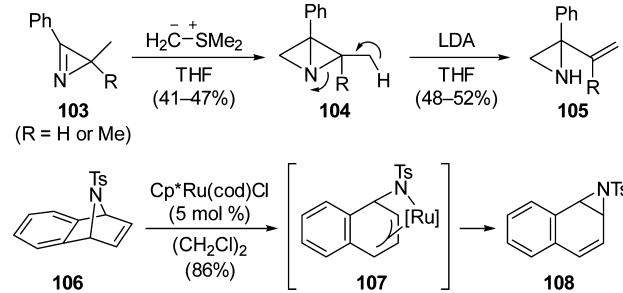


tricyclic cyclobutanes 100 were produced (0–44%) by a [2 + 2] cycloaddition reaction. Furthermore, it has been revealed that cyclobutanes 100 can be readily converted to vinylaziridines 102 under photoirradiation conditions and that the presence of an electron-withdrawing group (EWG) at the 2-position of the pyrrole is critical to the success of the reaction. Based on these results, a mechanism was proposed for the reaction involving C2–C3 fragmentation of [2 + 2] cycloadducts 100, followed by formation of a C2–C5 bond from the stabilized biradical intermediates 101.

The release of ring strain from the bicyclic ring systems provides the necessary driving force for formation of the

vinyiaziridine (Scheme 27). In 1974, Hortmann and Koo⁵⁶ reported lithium diisopropylamide (LDA)-mediated isomer-

Scheme 27. Isomerization of Strained Bicyclic Rings to Vinyiaziridines



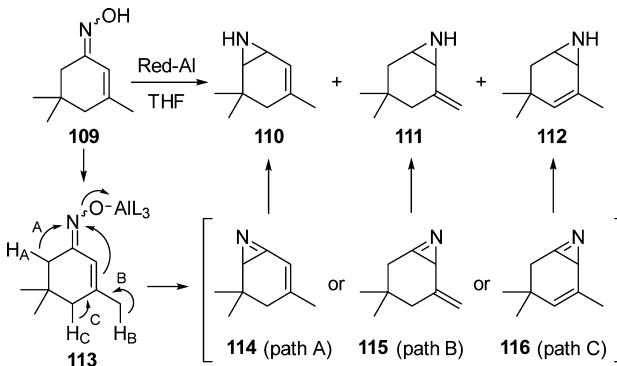
ization of azabicyclo[1.1.0]butane derivatives 104, which can be readily prepared by imino Corey–Chaykovsky reaction of azirines 103, to form vinyiaziridines 105. A ruthenium complex was used to catalyze the isomerization of 7-azabenzonorbornadiene 106 to the bicyclic vinyiaziridine 108, presumably by forming the η^3 -allylruthenium complex 107.⁵⁷

2.5. Miscellaneous

This section describes some of the other important contributions to the synthesis of vinyiaziridines that could not be categorized according to the reaction types described in sections 2.1–2.4.

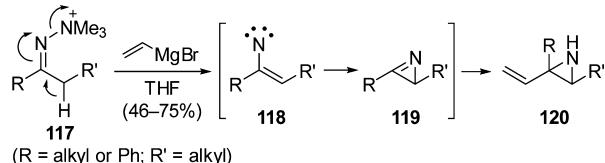
Vinyiaziridines can be obtained from unsaturated oximes and related compounds. The treatment of α,β -unsaturated oxime 109 with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) gave a mixture of vinyiaziridines 110–112, with the ratio being dependent on the *E/Z* ratio of the starting oxime 109 (Scheme 28).⁵⁸ The outcome of this reaction can be

Scheme 28. Reductive Aziridination of α,β -Unsaturated Oxime



explained in terms of the deprotonation of H_A, H_B, or H_C in intermediate 113, followed by sequential cyclization onto the nitrogen atom and reduction of the resulting azirines 114–116. The related synthesis of vinyiaziridines 120 by the reaction of hydrazone derivatives 117 with a Grignard reagent has also been reported (Scheme 29).⁵⁹ Nitrenes 118 have been suggested as plausible intermediates in this reaction, with the nitrenes themselves being converted to azirines 119, followed by addition of vinylmagnesium bromide to give the vinyiaziridines 120. Reaction pathways of this type involving a nitrene intermediate may also be used to rationalize the

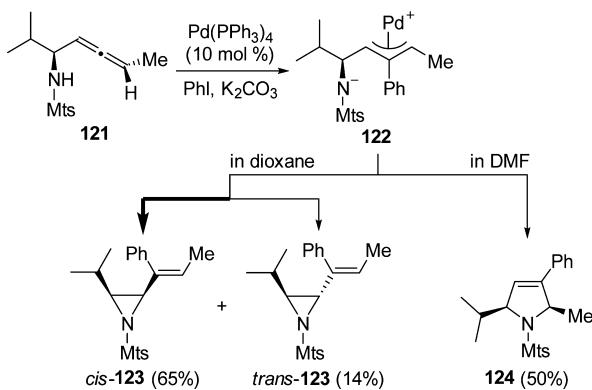
Scheme 29. Aziridination of Hydrazone Derivatives by Use of Vinylmagnesium Bromide



formation of vinylaziridines **110**–**112** from α,β -unsaturated oxime **109**.

Although the transition-metal-catalyzed cyclization of amino allenes to form five- and six-membered azacycles has been widely investigated,⁶⁰ the formation of aziridines according to this strategy remained unprecedented until 1999. Ibuka, Ohno, and co-workers⁶¹ reported that the palladium-catalyzed reaction of α -amino allene **121** with iodobenzene in the presence of K_2CO_3 in 1,4-dioxane afforded the corresponding vinylaziridines **123** bearing a phenyl group on the double bond exclusively (Scheme 30). Interestingly, when the reaction was

Scheme 30. Palladium(0)-Catalyzed Aziridination of α -Amino Allene

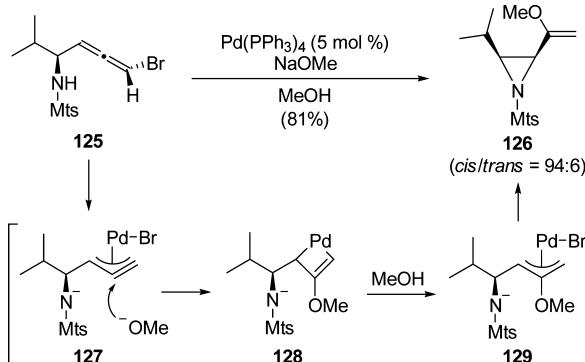


conducted in *N,N*-dimethylformamide (DMF), the corresponding 3-pyrroline derivative **124** was obtained as the sole isolable product. It was possible to introduce a variety of different aryl groups to the vinylaziridines in this way by use of the corresponding aryl halides in place of iodobenzene.

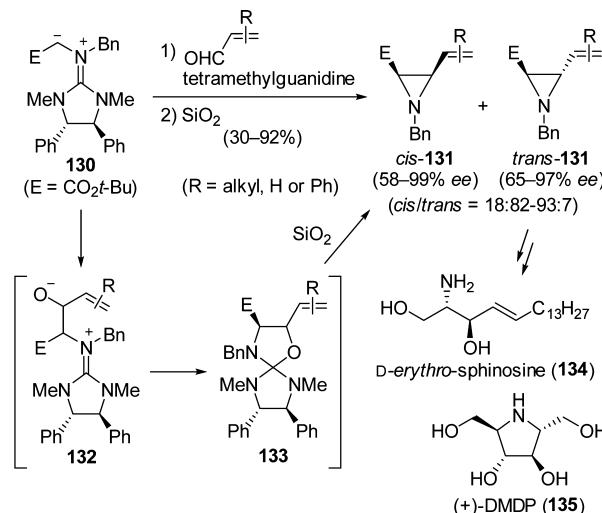
In 2003, Ohno et al.⁶² reported that *cis*-2-(1-methoxy)-vinylaziridine **126** (*cis/trans* = 94:6) could be obtained in a stereoselective manner by reaction of bromoallene **125** with $Pd(PPh_3)_4$ and $NaOMe$ in $MeOH$ (Scheme 31). This result strongly suggested that a η^3 -allylpalladium complex **129** bearing a methoxy group on its central carbon was being formed during the reaction to produce the thermodynamically more stable *cis* isomers.⁴⁷ It was therefore possible for two nucleophilic functionalities (i.e., amino and methoxy groups) to be introduced in this way to the three-carbon unit of the bromoallene moiety. This aziridination is believed to proceed through the oxidative addition of bromoallene **125** to palladium(0) to form the η^3 -propargylpalladium complex **127**. Subsequent intermolecular nucleophilic addition of a methoxide to the central carbon of the allylic moiety of **127**, followed by protonation and cyclization of the resulting palladacyclobutene **128**, would then give the vinylaziridine **126**.

The final example of this section is the guanidinium ylide-mediated enantioselective aziridination reported by Ishikawa and co-workers⁶³ (Scheme 32). From their asymmetric

Scheme 31. Palladium(0)-Catalyzed Aziridination of Bromoallene



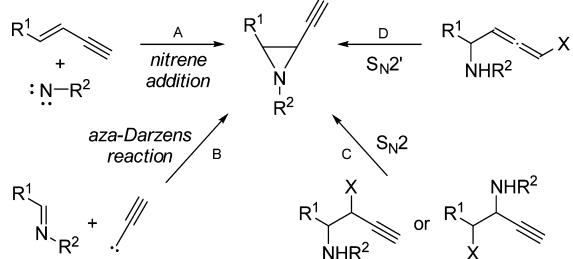
Scheme 32. Guanidinium Ylide-Mediated Enantioselective Aziridination



synthesis of arylaziridines using aryl aldehydes,⁶⁴ Ishikawa and co-workers obtained enantiomerically enriched vinylaziridines **131** with moderate to excellent enantioselectivities from acrolein derivatives. The same group also isolated a spirocyclic imidazolidine–oxazolidine of the general structure **133**, which was subsequently characterized by X-ray analysis and suggested as a plausible intermediate for the reaction.⁶⁵ This aziridination reaction was then applied to the asymmetric total syntheses of a range of biologically active compounds, including *D*-*erythro*-sphingosine **134** and (+)-DMDP (2,5-dihydroxymethyl-3,4-dihydroxypyrrrolidine, **135**).⁶³ Furthermore, this reaction was shown to be applicable to alkynyl aldehydes to produce enantiomerically enriched ethynylaziridines (91–98% ee).

3. DIRECT SYNTHESIS OF ETHYNYLAZIRIDINES

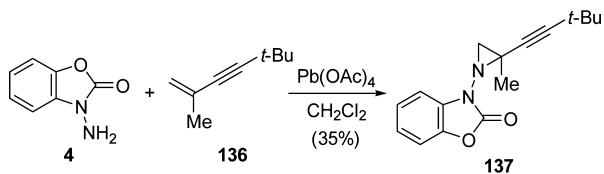
This section describes the synthesis of ethynylaziridines according to a system of classification similar to that used in section 2, including (1) ethynylaziridine syntheses based on the reaction of nitrene equivalents with conjugated enynes (Scheme 33, path A); (2) reactions of propargylic carbene equivalents (e.g., aza-Darzens-type/imino Corey–Chaykovsky reactions, path B); (3) S_N2' displacement of alkynylated 1,2-amino alcohol derivatives and related compounds (path C); and (4) S_N2' displacement of haloallene derivatives (path D). To the best of my knowledge, there have not been any reports in the literature to date concerning the synthesis of

Scheme 33. General Synthetic Routes to Ethynylaziridines

ethynylaziridines through rearrangement. Furthermore, reports describing the synthesis of ethynylaziridines via construction of the alkynyl group after the aziridine ring will not be discussed in this review.⁶⁶

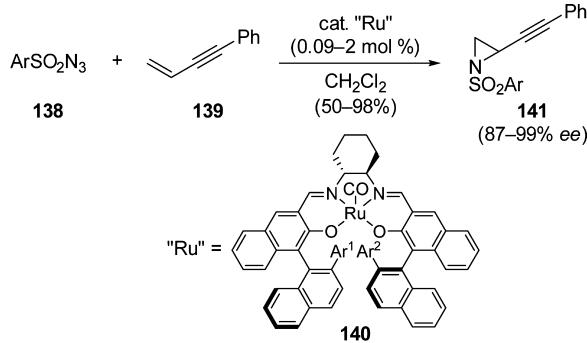
3.1. Addition of Nitrene Equivalents to Dienes

In 1973, while investigating the synthesis of azirines, Rees and co-workers⁶⁷ found that ethynylaziridine **136** was formed when conjugated enyne **135** was used as the alkyne component. Thus, the nitrenes generated by the treatment of *N*-amino-phthalimide **4** with $\text{Pb}(\text{OAc})_4$ reacted with the conjugated enyne **136** to give ethynylaziridine **137** in 35% yield (Scheme 34). Although this reaction was reported as an isolated example,

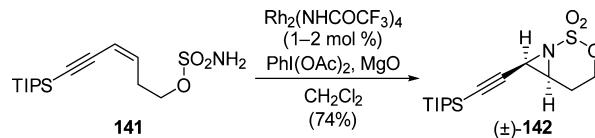
Scheme 34. 1,2-Addition of Amino Nitrene to 1,3-Enyne

it clearly demonstrated the potential of nitrene addition as a general strategy for the preparation of ethynylaziridines.

Katsuki and co-workers⁶⁸ reported the highly enantioselective ruthenium-catalyzed aziridination of enyne **139** with arylsulfonyl azide **138** (Scheme 35). This reaction could be

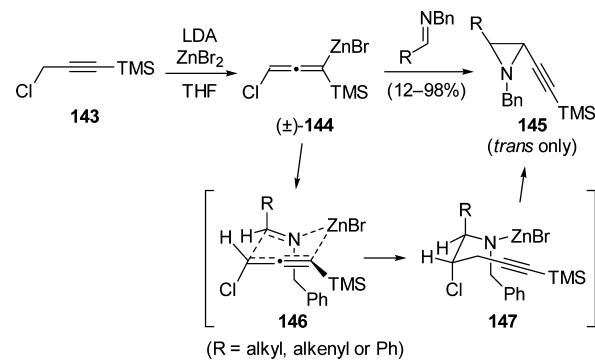
Scheme 35. Ruthenium-Catalyzed Asymmetric Aziridination of 1,3-Enyne with Arylsulfonyl Azides

useful for the synthesis of *N*-unprotected ethynylaziridines because 2-(trimethylsilyl)ethanesulfonyl azide (SESN_3) and *o*-/*p*-nitrobenzenesulfonyl azide (NsN_3) can also be used in the reaction to give the corresponding *N*-SES and *N*-Ns aziridines. The related rhodium(II)-catalyzed oxidative aziridination of unsaturated sulfamate **141** to produce **142** was reported by Du Bois and co-workers⁶⁹ (Scheme 36).

Scheme 36. Rhodium-Catalyzed Oxidative Aziridination of Enyne

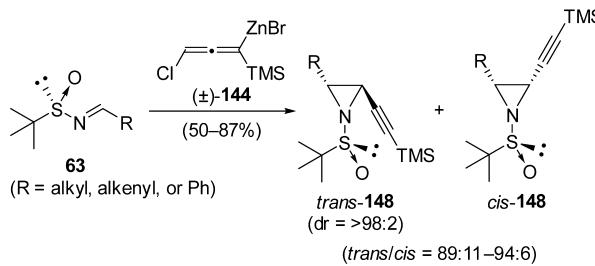
3.2. Addition of Propargylic Carbene Equivalents to Imines

Treatment of propargyl chloride **143** with LDA and ZnBr_2 affords the chlorinated allenylzinc reagent **144**, which can be added to imines to provide convenient access to *trans*-ethynylaziridines **145** (Scheme 37).^{70,71} The *trans* selectivity

Scheme 37. Stereoselective Addition of Allenylzinc Reagent to Imines

of this reaction is responsible for formation of the chelate transition state **146**, and the chelation model itself is supported by the low yields (27–41%) and low selectivities (*trans*:*cis* = 10:90–70:30) of the reaction with *N*-sulfonylimines.

On the basis of their discovery that the reaction proceeded with a high level of diastereoselectivity when it was conducted with *t*-butylsulfinimine,⁷² Chemla and Ferreira⁷³ extended the aziridination to the kinetic resolution of racemic allenylzinc reagents, and they used enantiomerically pure sulfinimines **63** to obtain enantiomerically pure *trans*-**148** (Scheme 38).

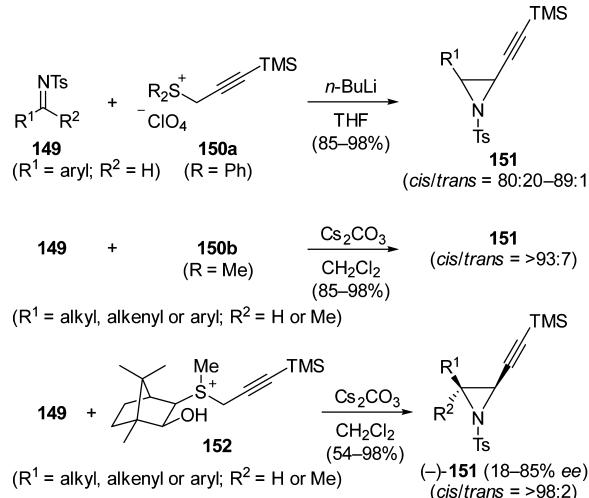
Scheme 38. Kinetic Resolution of Racemic Allenylzinc Reagent

Interestingly, the reaction gave *cis*-ethynylaziridines when it was conducted in the presence of excess hexamethylphosphoramide (HMPA, 60 equiv).⁷⁴ This change in the *cis*/*trans* selectivity was attributed to a change in the mode of addition, with the addition now occurring through a synclinal open transition state. This change was fully supported by density functional theory (DFT) calculations.

In 1997, Dai and co-workers⁷⁵ reported the synthesis of racemic 2-ethynylaziridines **151** by reaction of *N*-tosylimines

149 with propargylic diphenylsulfonium ylides derived from 150a ($R = \text{Ph}$, Scheme 39). Interestingly, the use of different

Scheme 39. Imino Corey–Chaykovsky Reaction of Activated Imines with Propargylic Ylides

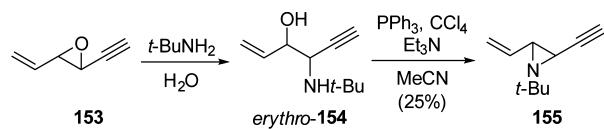


bases to generate the ylide had a significant impact on the outcome of this reaction. For example, the use of *n*-BuLi afforded the silylated aziridines 151 exclusively, whereas *t*-BuOK gave the corresponding desilylated aziridines. The cis selectivity of the reaction was improved by the use of the dimethylsulfonium salt 150b (cis:trans = >93:7). This report also included an asymmetric version of this reaction, with (−)-151 being obtained in low to good enantioselectivities (18–85% ee) from the camphor-derived sulfonium salt 152. In an interesting development of this chemistry, the synthesis of CF₃-containing ethynylaziridines by use of CF₃-substituted *N*-*tert*-butylsulfinyl ketimines has recently been reported.⁷⁶

3.3. S_N2 or S_N2' Displacement of Amino Alcohol Derivatives and Related Compounds

In a similar manner to vinylaziridines, ethynylaziridines can also be synthesized by the cyclization of 1,2-amino alcohols and related compounds, which can be readily prepared from the corresponding epoxides. In 1977, Manisse and Chuche⁷⁷ reported the preparation of 2-ethynyl-3-vinylaziridine 155 via the ring-opening reaction of epoxide 153 and the intramolecular cyclization of *erythro*-154 using PPh₃ and CCl₄ (Scheme 40). A related synthesis has also been reported

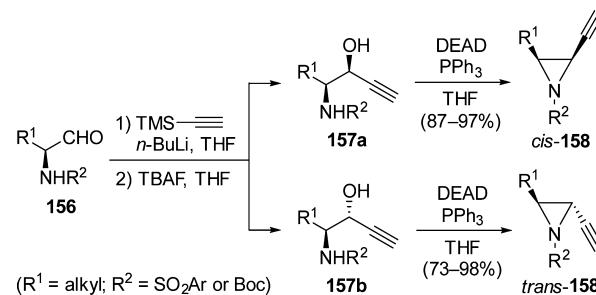
Scheme 40. Ring-Opening Reaction of Ethynylepoxyde Followed by Cyclization



involving the construction of ethynylaziridines from epoxides that do not possess a vinyl group.⁷⁸ Ethynylepoxydes can also be converted to ethynylaziridines through the corresponding azide alcohols.⁷⁹

One of the simplest methods for the synthesis of enantiomerically pure ethynylaziridines is the cyclization of propargyl alcohols 157 bearing an amino group (Scheme 41), which can themselves be readily prepared from α -amino acids.

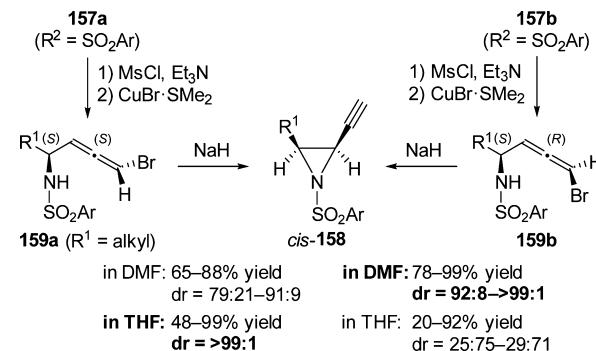
Scheme 41. Aziridination of Amino Acid-Derived Amino Alcohols under Mitsunobu Conditions



Ibuka, Ohno, and co-workers⁸⁰ prepared a variety of different ethynylaziridines via addition of lithium acetylides to amino-acid-derived aldehydes 156, followed by cyclization of the resulting amino alcohols under Mitsunobu conditions. The main drawback of this particular strategy is the low diastereoselectivity of the acetylidyne addition, with the syn- and anti-amino alcohols 157a and 157b, respectively, being obtained as a mixture in most cases.

Ohno and co-workers⁸¹ subsequently developed a way to overcome this problem in their cis-selective synthesis of ethynylaziridines via intramolecular amination of bromoallenes. Thus, the treatment of (*S,aR*)-bromoallenes 159b, which were derived from the corresponding amino alcohols 157b, with NaH in DMF afforded *cis*-158 with high levels of selectivity (cis:trans = 92:8–>99:1) (Scheme 42). Although the *cis*

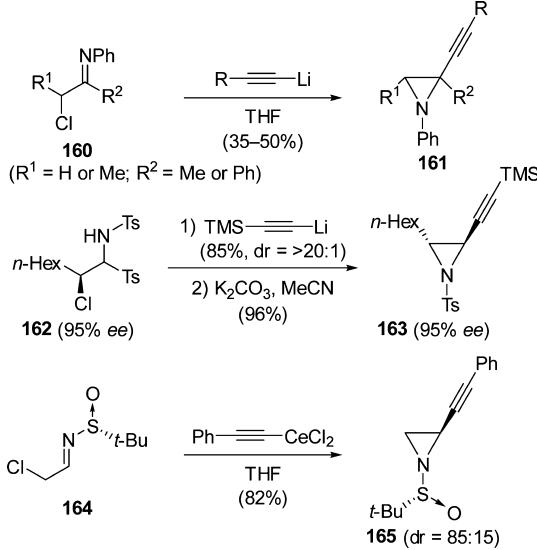
Scheme 42. NaH-Mediated Cis-Selective Aziridination of Bromoallenes



selectivities of the reactions of the (*S,aS*)-bromoallenes 159a with NaH/DMF were relatively low (79:21–91:9), they were improved to >99:1 when a less polar solvent such as tetrahydrofuran (THF) was used. These improvements were predicted by the B3LYP density functional calculations conducted by Ando and co-workers.^{81b}

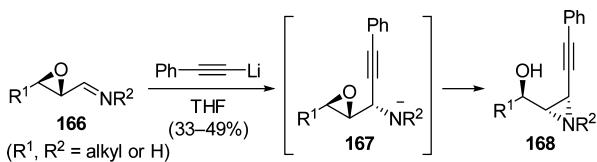
The addition of acetylides to α -haloimines also provides a convenient synthetic route to ethynylaziridines. For example, lithium acetylidyne adds to α -chloroimines 160 to afford ethynylaziridines 161 stereoselectively (Scheme 43).⁸² This strategy was used for the asymmetric synthesis of *trans*-ethynylaziridine 163 (95% ee) from the enantiomerically enriched 2-chloroalkan-1-amine derivative 162 bearing a sulfonyl group at the 1-position, which is a synthetic equivalent of α -chloroimine.⁸³ In a similar manner to the synthesis of vinylaziridines (Scheme 20), nucleophilic addition to *t*-butylsulfinimine 164 provided straightforward access to the enantiomerically pure ethynylaziridine 165.⁸⁴

Scheme 43. Stereocontrolled Synthesis of Ethynylaziridines via Alkylation of α -Chloroimines and Related Compounds



Epoxides can also effectively function as a leaving group at the α -position of imine as well as a stereocontrolling group for the alkynylation. The treatment of *trans*-oxiranylimines **166** with lithium acetylide gave *cis*-ethynylaziridines **168** stereoselectively.⁸⁵ (Scheme 44). This reaction can be rationalized by

Scheme 44. Synthesis of Ethynylaziridines via Aza-Payne Rearrangement



the stereospecific aza-Payne rearrangement⁸⁶ of the adduct **167** to form the aziridine ring. This pathway has been supported by ab initio calculations.

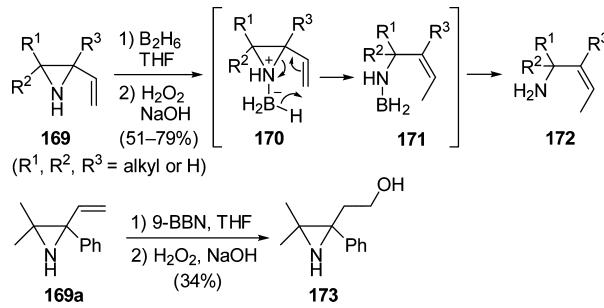
4. RING-OPENING REACTIONS WITH NUCLEOPHILES

The ring-opening reaction of vinyl- and ethynylaziridines can be affected by a variety of different carbon- and heteroatom-based nucleophiles to produce a variety of functionalized amine derivatives in a stereoselective manner.⁸⁷ In this section, the ring-opening reactions of vinyl- and ethynylaziridines with hydride, carbon nucleophiles (e.g., organocopper reagents), and heteronucleophiles (i.e., alcohols, water, and amines) will be discussed, together with some other nucleophiles such as radicals and metals.

4.1. Reaction with Hydrides

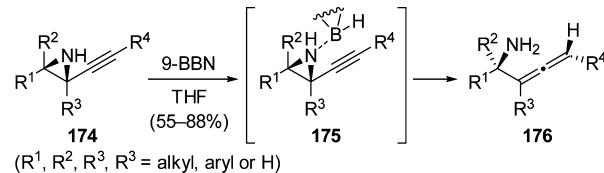
The first nucleophilic ring-opening reaction of vinylaziridines to be discussed in this section is diborane reduction of vinylaziridines, which was developed by Chaabouni and Laurent⁸⁸ in 1976 (Scheme 45). The treatment of *N*-H vinylaziridines **169** with B₂H₆ gave the corresponding allyl amine **172**, presumably via the intermediate **170**. In contrast, the same reaction with 9-BBN following an oxidative workup afforded 2-(hydroxyethyl)aziridines **173** without any of the ring-opened product being isolated.⁸⁹

Scheme 45. Borane-Mediated Reduction of Vinylaziridines



In 2010, He and Yudin^{66b} developed a reaction for the 9-BBN-mediated stereoselective ring-opening reduction of *N*-H ethynylaziridines **174** (Scheme 46), which were themselves

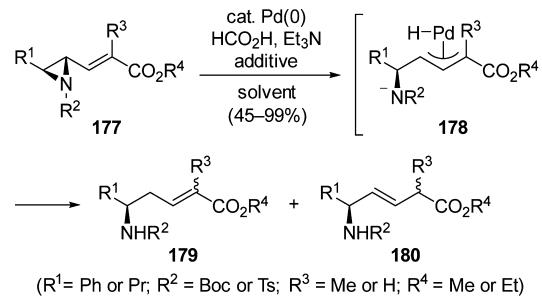
Scheme 46. Ring-Opening Reduction of *N*-H Ethynylaziridines with 9-BBN



obtained from the homologation of *N*-H aziridine aldehyde dimers by use of the Ohira–Bestmann reagent. In contrast to the organocupper-mediated ring-opening reaction of ethynylaziridines bearing an arylsulfonyl group (vide infra, Scheme 53), the hydride transfer proceeded in a *syn*-selective manner, presumably via the corresponding intermediates **175**, where the boron coordinates to the nitrogen atom of the aziridine.

The ring-opening reduction of vinylaziridines can be promoted by a palladium catalyst (Scheme 47).⁹⁰ The

Scheme 47. Palladium(0)-Catalyzed Reduction with Formic Acid

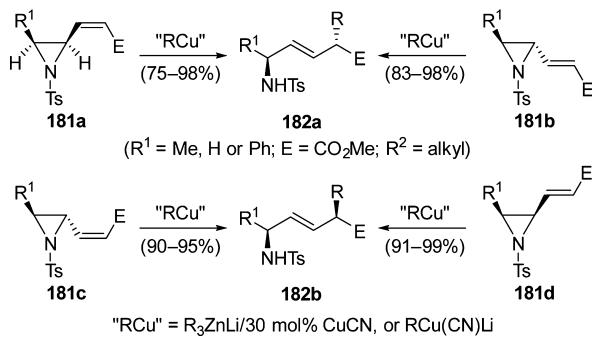


reduction of aziridines **177** bearing an α,β -unsaturated ester group with formic acid gave 1,2-reduction products **179** together with 1,4-products **180**. The ratios of the two products were found to be dependent on the reaction conditions (i.e., additive, solvent, and catalyst). The *E/Z* ratios of **179** and the diastereomeric ratios of **180** were strongly affected by the palladium-catalyzed isomerization of the vinylaziridines, which will be discussed later (Scheme 107). An efficient total synthesis of chamobutusin A was recently reported by Suzuki and Aoyagi,⁹¹ involving palladium-catalyzed reduction of a vinylaziridine with formic acid.

4.2. Reaction with Organocupre Reagents

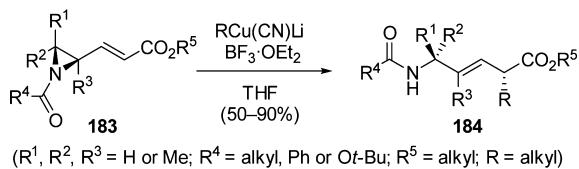
In 1994, three research groups (Ibuka and co-workers,⁹² Wipf and co-workers,⁹³ and Hudlicky and co-workers⁹⁴) independently reported the organocupre-mediated ring-opening reactions of vinylaziridines. In the stereospecific S_N2' alkylation reported by Ibuka and co-workers,⁹² where aziridinyl enoates **181** were converted to (*E*)-alkene dipeptide isosteres **182** (Scheme 48).⁹⁵ When these reactions were conducted with an

Scheme 48. Ring-Opening Reaction with Organocuprates Reported by Ibuka and Co-workers



organocupre such as $RCu(CN)Li$ or $R_3ZnLi/\text{cat. CuCN}$, they proceeded in a highly regio- and stereoselective manner to afford diastereomerically pure **182** and a small amount of the corresponding S_N2 product (<6% yield). A few months later, Wipf and co-workers⁹³ reported the closely related alkylative ring-opening reaction of aziridinyl enoates **183** with organocupre using $BF_3 \cdot OEt_2$ as an additive (Scheme 49). In some cases, these reaction also provided considerable amounts of the 1,4-reduction products (<24%) or S_N2 -alkylation products (<15% yield).

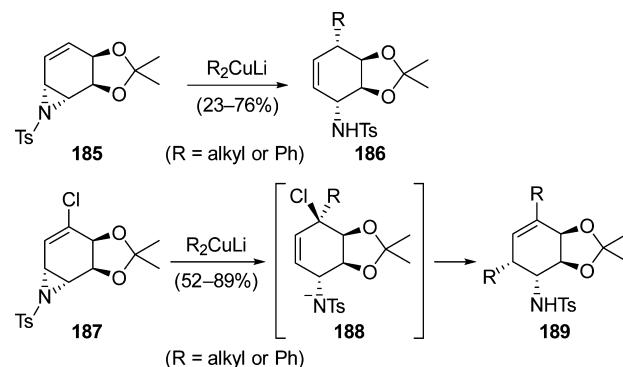
Scheme 49. Ring-Opening Reaction with Organocuprates Reported by Wipf and Co-workers



Hudlicky and co-workers⁹⁴ used bicyclic vinylaziridines **185** as the substrate, and the reaction of these compounds with organocupre of the type R_2CuLi proceeds in a highly syn-selective manner (Scheme 50).⁹⁶ The syn stereochemistry of the reaction was attributed to the effect of the acetonide group, which effectively blocked the approach of the copper reagent from the anti face of the aziridine ring. Interestingly, the reaction of cyclic (chlorovinyl)aziridine **187** afforded the dual adducts **189**, which were formed by sequential S_N2' displacements.^{94b} These products can be rationalized by assuming that the initial syn- S_N2' ring-opening reaction of **187** was followed by the anti- S_N2' displacement of the resulting allyl chloride intermediate **188**.

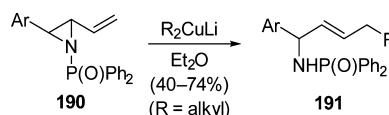
The organocupre-mediated ring-opening reactions of aziridines bearing an unsubstituted vinyl group afford the corresponding allylamines stereoselectively. Sweeney and co-workers²⁰ reported that the treatment of *trans*-vinylaziridines **190** with Gilman-type reagents gave the (*E*)-allylamines **191**

Scheme 50. Ring-Opening Reactions of Bicyclic Vinylaziridines Reported by Hudlicky and Co-workers



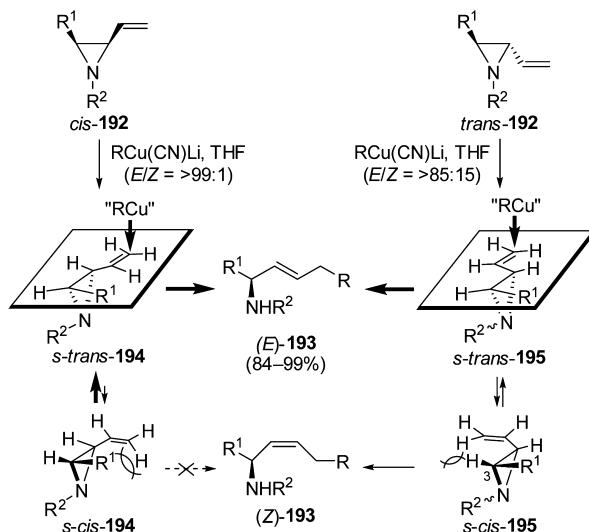
exclusively (Scheme 51). Ibuka and co-workers⁹⁷ reported the closely related reaction of a range of different 3-alkyl-2-

Scheme 51. Ring-Opening Reaction with Organocupre Reagents to Give (*E*)-Allylamines



vinyloaziridines and conducted a detailed investigation of the stereochemical course of the reaction (Scheme 52). Treatment

Scheme 52. Stereochemical Course of Ring-Opening Reaction with Organocupre Reagents

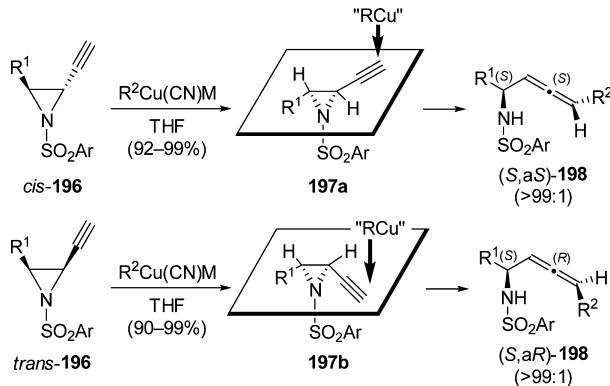


of *cis*-192 with organocupre reagents gave (*E*)-193 exclusively in high yields, whereas *trans*-192 afforded a mixture of (*E*)- and (*Z*)-193 (*E/Z* = >85:15). The exclusive formation of (*E*)-193 from *cis*-192 most likely occurred as a consequence of steric crowding of the disfavored conformer *s-cis*-194, which leads to (*Z*)-193. In contrast, the allylic 1,3-strain would be decreased in the conformer *s-trans*-194. Organocupre reagents therefore react with *cis*-192 by an anti- S_N2' reaction pathway from the favorable conformer *s-trans*-194 to yield (*E*)-193 exclusively. A relatively small steric repulsion effect from the vinyl group and the C-3 hydrogen in conformer *s-cis*-195 have been cited as the

major reasons for relatively low levels of (*E*)-selectivity (*E*:*Z* = >85:15) in the reaction of *trans*-192.

Organocupper-mediated ring-opening reactions of ethynylaziridines provide straightforward access to amino allene derivatives, which are attractive substrates for construction of many different types of azacycles. In 1999, Ibuka, Ohno, and co-workers⁹⁸ reported the stereoselective synthesis of chiral α -amino allenes 198 via $\text{RCu}(\text{CN})\text{M}$ -mediated anti- $S_{\text{N}}2'$ substitution of chiral 2-ethynylaziridines 196 (Scheme 53). In

Scheme 53. Synthesis of α -Amino Allenes by Ring-Opening Reaction of 2-Ethynylaziridines

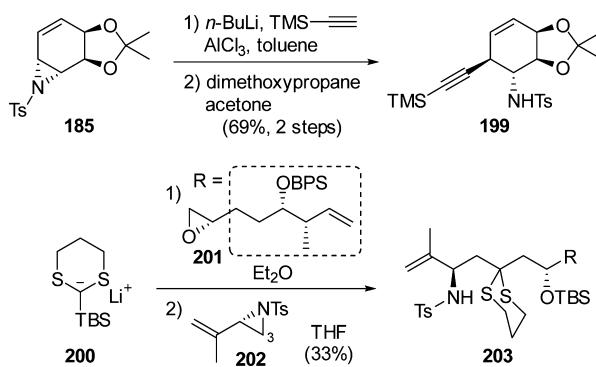


a similar manner to several other related substitution reactions involving propargylic compounds, the reaction of aziridines generally proceeded anti to the leaving nitrogen atom, as shown for 197a and 197b.

4.3. Reactions with Other Carbon Nucleophiles

The ring-opening reaction of vinylaziridines can be affected by other carbanions, including organolithiums and arenes. In their study on the synthesis of Amaryllidaceae-based analogues, Hudlicky and co-workers⁹⁹ observed that the $S_{\text{N}}2$ addition of lithium acetylide to bicyclic vinylaziridine 185 gave the ring-opened product 199 (Scheme 54). Smith and Kim¹⁰⁰

Scheme 54. Ring-Opening Reaction with Organolithium Reagents

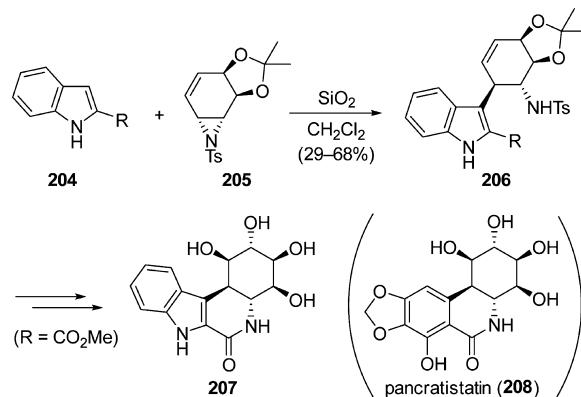


developed an interesting three-component coupling reaction, involving lithiated dithiane 200, epoxide 201, and vinylaziridine 202, which proceeded through a Brook rearrangement to give the ring-opened addition product 203, albeit in moderate yield (33%) (Scheme 54). It should be clearly noted that the ring-opening reaction of aziridine 202 occurred at the least hindered 3-position and not at the allylic position. The related ring-opening reaction of vinylaziridines at the allylic position by

sulfur-stabilized carbanions has also been reported.¹⁰¹ The ring-opening reaction of vinylaziridines in an $S_{\text{N}}2$ manner can also be promoted by Me_3Al .^{102,103}

The ring-opening reaction of vinylaziridines by hydroarylation with an indole was reported by Hudlicky and co-workers.¹⁰⁴ The silica-surface reaction of vinylaziridine 205 with indoles 204 provided tosylamides 206 (Scheme 55). One

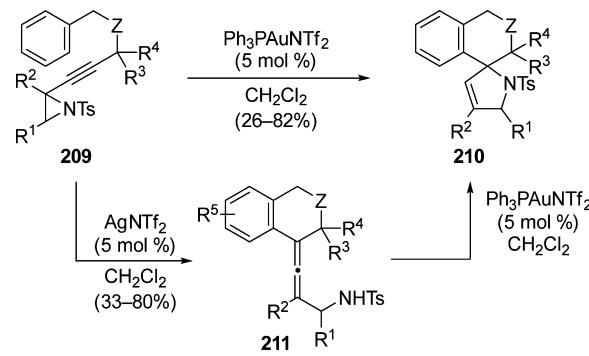
Scheme 55. Ring-Opening Reaction by $S_{\text{N}}2$ Hydroarylation with Indoles



of the products ($R = \text{CO}_2\text{Me}$) is an efficient precursor of the pancratistatin analogue 207, and the biological evaluation of this compound confirmed that it possessed borderline activity in a murine P388 lymphocytic leukemia assay.

Spirocyclization of ethynylaziridines via intramolecular hydroarylation have recently been developed.¹⁰⁵ Gold(I) complexes can be used to catalyze the Friedel–Crafts-type anti- $S_{\text{N}}2'$ hydroarylation of ethynylaziridines 209 bearing an aryl group, as well as intramolecular hydroamination of the resulting amino allene intermediates 211 to give tricyclic spirocycles 210 (Scheme 56). In contrast, the use of silver salts

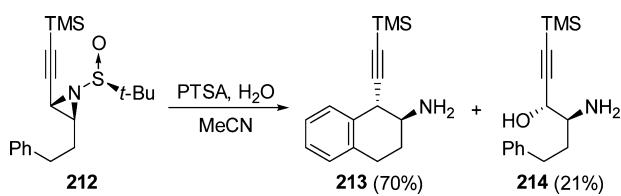
Scheme 56. Spirocyclization of Ethynylaziridines via Intramolecular $S_{\text{N}}2'$ Hydroarylation Followed by Hydroamination



$\text{R}^1, \text{R}^2 = \text{alkyl or H}; \text{R}^3, \text{R}^4 = \text{alkyl, aryl or H}; \text{Z} = \text{O}, \text{CH}_2 \text{ or NTs}$

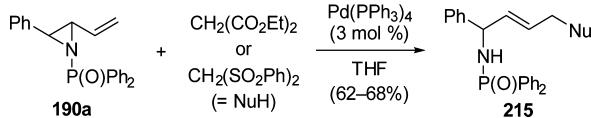
promoted only the first step to selectively afford the allenes 211, which were readily cyclized to 210 upon exposure to gold-catalyzed cyclization conditions. Ferreira and co-workers¹⁰⁶ obtained the anti- $S_{\text{N}}2$ arylation product 213 in 70% yield following acid treatment of ethynylaziridine 212 (Scheme 57) in their study on the hydrolysis of alkynylaziridines for the asymmetric synthesis of amino alcohols of type 214.

Scheme 57. Ring-Opening Reaction by S_N2' Hydroarylation with Phenyl Group



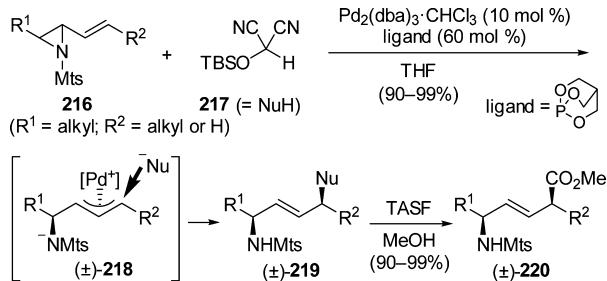
Palladium(0) catalysts efficiently promote ring-opening reactions with carbon nucleophiles to afford the corresponding allylic amine derivatives. In 1996, Sweeney and co-workers²⁰ reported their pioneering work on palladium-catalyzed ring-opening reaction of vinylaziridines. Reaction of 190a with diethyl malonate or bis(phenylsulfonyl)methane in the presence of catalytic Pd(PPh₃)₄ gave the (*E*)-allylic amines 215 stereoselectively (Scheme 58). More recently, a highly

Scheme 58. Palladium(0)-Catalyzed Ring-Opening Reaction by Use of Carbon Nucleophiles



regio- and stereoselective reaction was reported by Nemoto and co-workers¹⁰⁷ that used the silylated masked acyl cyanide reagent 217 (Scheme 59). This reaction was reported to

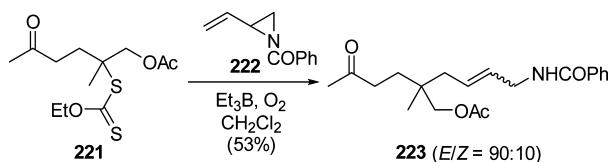
Scheme 59. Regio- and Stereoselective Ring-Opening Reaction with Masked Acyl Anion Reagent



proceed via a double inversion mechanism involving η^3 -allylpalladium intermediates 218, because it afforded the allylic amine derivatives 219 stereospecifically. Treatment of 219 with tris(dimethylamino)sulfonium difluorotrimethylsilylate (TASF) allowed for the masked acyl group to be readily converted to a methoxycarbonyl group to give 220. Aryl and alkenylboronic acids have also been reported as suitable carbon nucleophiles for this palladium-catalyzed ring-opening reaction.¹⁰⁸

The final example of this section is the radical reaction of xanthate with vinylaziridine (Scheme 60). In their study of the

Scheme 60. Radical Addition to Vinylaziridine

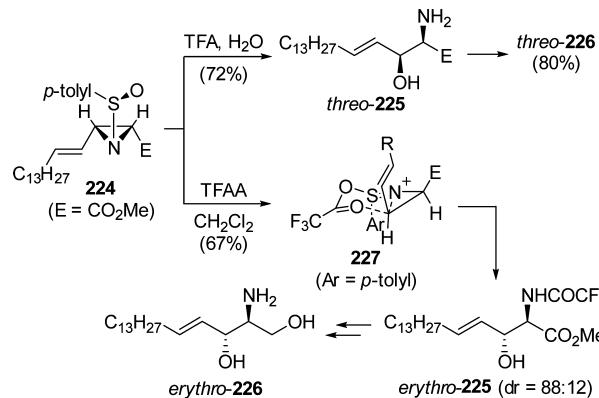


addition of radicals to vinyl- and ethynylepoxydes, Zard and co-workers¹⁰⁹ extended the reaction to vinylaziridine 221 and obtained the corresponding ring-opening product 223 in moderate yield. To the best of my knowledge, this report represents the only S_N2' addition of a radical to a vinylaziridine that has been reported to date.

4.4. Reaction with Oxygen Nucleophiles

Ring-opening reactions of vinylaziridines with oxygen nucleophiles generally require the presence of an acid to proceed, and they provide stereoselective access to 1,2-amino alcohol derivatives. In 1996, Davis and Reddy¹¹⁰ reported the stereodivergent synthesis of *threo*- and *erythro*-sphingosines 226 from the same *cis*-*N*-sulfinylaziridine starting material 224 (Scheme 61). Treatment of 224 with trifluoroacetic acid (TFA)

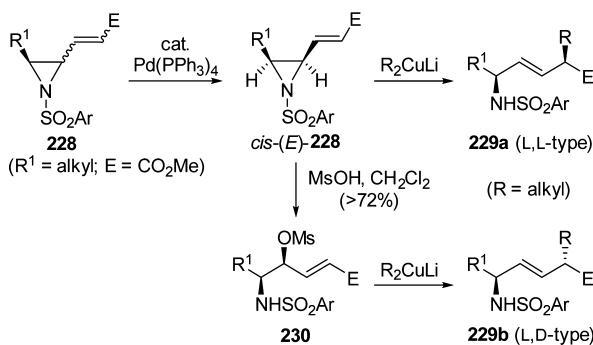
Scheme 61. Stereodivergent Synthesis of *threo*- and *erythro*-Sphingosines 226



in wet acetone gave *threo*-225 as a single isomer in 72% yield. Subsequent reduction of this material with LiBH₄ gave *L-threo*-sphingosine (*threo*-226). In contrast, treatment of the same aziridine 224 with trifluoroacetic anhydride (TFAA) in CH₂Cl₂ afforded *erythro*-225 as the major isomer (*erythro*:*threo* = 88:12). The *erythro*-225 was formed by nucleophilic attack from the same side as the departing amino group. This mode of reactivity was attributed to Pummerer-type rearrangement of the sulfoxide through 227, where the activated sulfoxide complex underwent a stereospecific [3,3]-sigmatropic rearrangement of the trifluoromethylacetoxyl group, which allowed for the syn-nucleophilic ring-opening reaction by the oxygen nucleophile. Hudlicky and co-workers¹¹¹ reported a ring-opening reaction with acetic acid (AcOH) in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) to produce O-acetylated 1,2-amino alcohols, which were used as intermediates for the asymmetric synthesis of (+)- and (-)-balanol. The stirring of vinyl- or ethynylaziridines in wet solvents (acetone or MeCN) in the presence of acid (TFA or *p*-toluenesulfonic acid, PTSA) can lead to the corresponding ring-opened products, where the ring-opening reactions have been affected by water.¹¹²

Fujii and co-workers¹¹³ reported the stereodivergent synthesis of (*E*)-alkene dipeptide isosteres using a combination of acid- and organocuprate-mediated ring-opening reactions of vinylaziridines (Scheme 62). Thus, aziridinyl enoates *cis*-(*E*)-228, which were readily obtained by palladium-catalyzed isomerization of isomeric mixtures of 228 followed by recrystallization, were subjected to ring-opening reaction with organocuprates to give *L,L*-type (*E*)-alkene dipeptide isosteres

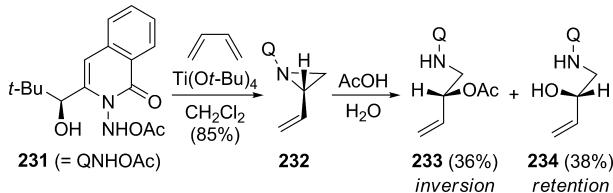
Scheme 62. Stereodivergent Synthesis of (*E*)-Alkene Dipeptide Isosteres



229a in a highly stereoselective manner. In contrast, methanesulfonic acid (MsOH)-mediated ring-opening reaction of *cis*-(*E*)-228 afforded the corresponding mesylates 230 with inversion of configuration. These compounds were subsequently converted to *L,D*-type dipeptide isosteres 229b by reaction with organocuprates. By use of organozinc-derived copper reagents and functionalized organocuprates, it is possible to synthesize dipeptide isosteres 229 bearing a functionalized side chain in good yields.¹¹⁴

The ring-opening reaction of vinylaziridine 232, which was prepared by aziridination of butadiene with enantiopure 3-acetoxyaminoquinazolinone 231,¹¹⁵ afforded the corresponding acetate 233 (36%) with inversion of configuration, as well as the retention product 234 (38%) (Scheme 63).¹¹⁶ The

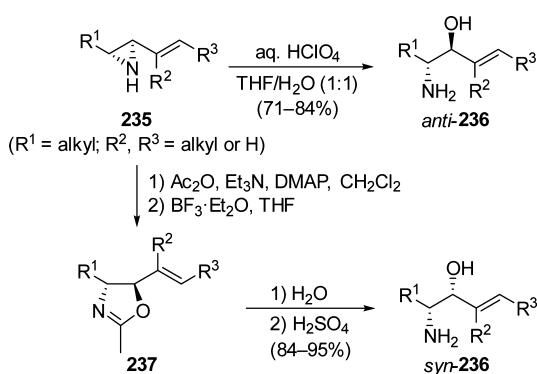
Scheme 63. Acetic Acid-Catalyzed Ring-Opening Reaction



formation of 234 in this case can be explained by the participation of the quinazolinone carbonyl oxygen, which causes the reaction to occur via an intramolecular *syn* nucleophilic substitution.

Somfai and co-workers¹¹⁷ reported the stereodivergent synthesis of 1,2-amino alcohols by the ring-opening reaction of N-H aziridines 235 with an acid (Scheme 64). Although 235

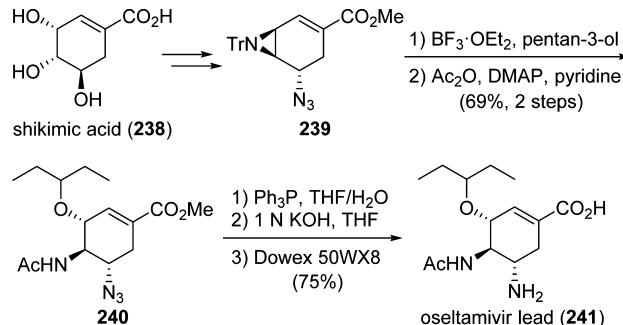
Scheme 64. Stereodivergent Synthesis of *Syn*- and *Anti*-Amino Alcohols



was regioselectively hydrolyzed to give *anti*-236 by treatment with HClO₄ in THF/H₂O, acetylation of 235 followed by treatment with BF₃·OEt gave the oxazoline derivatives 237 with retention of configuration. Sequential hydrolysis and deacetylation of 237 gave *syn*-236 in a stereospecific manner. This stereodivergent ring-opening reaction of 236 can be useful for the synthesis of D-*erythro*- and L-*threo*-sphingosines.¹¹⁸

Regioselective ring-opening reactions of vinyl- and ethynylaziridines with alcohols represent powerful strategies for the synthesis of biologically active compounds. In 1997, a group from Gilead Sciences Inc.¹¹⁹ developed a practical synthetic route to the oseltamivir lead (241) via the ring-opening reaction of vinylaziridine with pentan-3-ol (Scheme 65).

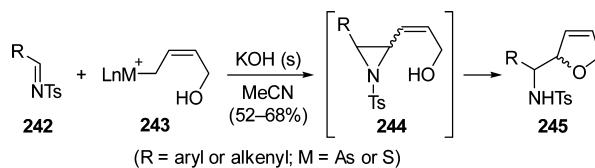
Scheme 65. Synthesis of Oseltamivir Lead via Ring-Opening Reaction of Vinylaziridine with Pentan-3-ol



Starting from shikimic acid (238), the bicyclic vinylaziridine 239 was prepared as a single enantiomer and subjected to a ring-opening reaction with pentan-3-ol in the presence of BF₃·OEt₂. Subsequent acetylation of the resulting amine gave 240, which is a good precursor of oseltamivir lead compound (241). This type of ring-opening reaction currently represents one of the most reliable approaches to oseltamivir (ethyl ester of 241).¹²⁰

The intramolecular reaction of oxygen nucleophiles to give 2,5-dihydrofuran derivatives 245 is shown in Scheme 66. In this

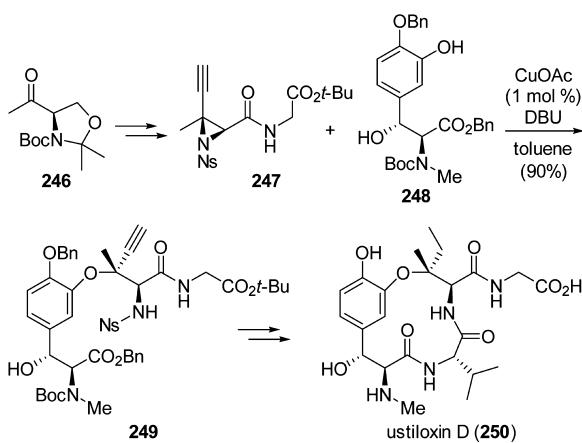
Scheme 66. Intramolecular Reaction with an Oxygen Nucleophile



case, vinylaziridines were generated *in situ* by reaction of imines 242 with the ylide formed from 243,¹²¹ with the ylide itself formally behaving as a 2,5-dihydrofuran anion equivalent.

Ethyynylaziridines are efficient building block for stereoselective construction of tertiary alkyl aryl ethers. From their original copper(I)-catalyzed ring-opening reaction of ethynylaziridines with phenols,¹²² Joullié and co-workers¹²³ went on to report the successful total synthesis of ustiloxin D (250), as well as several related macropeptides (Scheme 67). Starting from the D-serine-derived methyl ketone 246, aziridine 247 was prepared through alkynylation with ethynylmagnesium bromide, followed by sequential coupling with glycine ester and aziridination under Mitsunobu conditions. The ring-opening reaction of 247 with phenol 248 proceeded efficiently in an

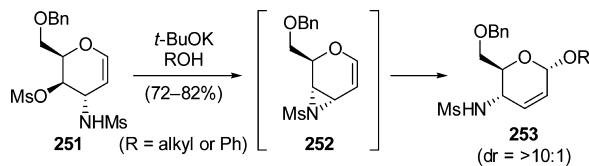
Scheme 67. Total Synthesis of Ustiloxin D via Ring-Opening Reaction with Phenol



anti-selective manner to give the tertiary ether **249** in 90% yield. The total synthesis of **250** was accomplished following several additional manipulations, including removal of the Ns group followed by condensation of the resulting amine with Z-Val-OH and subsequent macrocyclization. This chemistry allowed for the total synthesis of a related macropeptide, phomopsin B.¹²⁴ In some cases, the ring-opening reaction was found to be promoted to a greater extent by 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD).¹²²

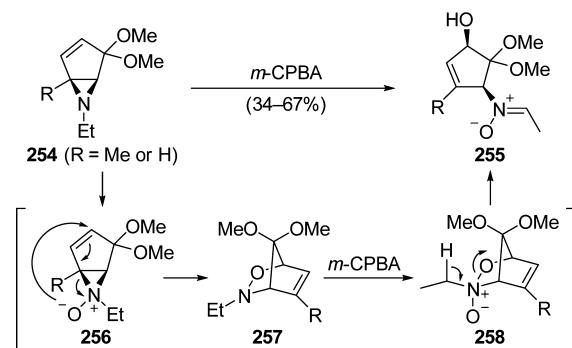
$S_{N}2'$ reactions with oxygen nucleophiles proceed only in a very limited number of cases. Glycosylation of alcohols by the $S_{N}2'$ -type ring-opening reaction of in situ-generated fused vinylaziridines **252** has been reported (Scheme 68).¹²⁵ In this case, $S_{N}2'$ displacement of **252** would be activated by the oxygen atom directly bound to the vinyl group.

Scheme 68. Glycosylation of Alcohols with Vinylaziridines



An interesting $S_{N}2'$ -type oxidative ring-opening reaction is shown in Scheme 69. Oxidation of vinylaziridines **254** with *m*-chloroperoxybenzoic acid (*m*-CPBA) gave **255** via a [2,3] Meisenheimer rearrangement of intermediate *N*-oxide **256**,

Scheme 69. Oxidative $S_{N}2'$ -type Ring-Opening Reaction of Vinylaziridines

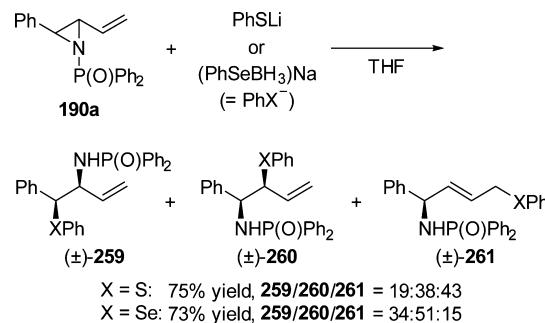


followed by further oxidation to **258** and subsequent cleavage of the N–O bond.¹²⁶

4.5. Reaction with Sulfur and Selenium Nucleophiles

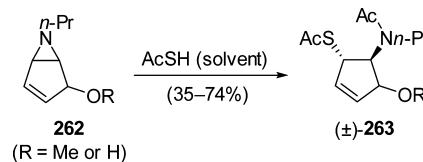
Ring-opening reactions of vinyl- and ethynylaziridines with chalcogenide nucleophiles other than oxygen are relatively rare. In 1996, two research groups independently reported ring-opening reactions of vinylaziridines with sulfur nucleophiles. Sweeney and co-workers²⁰ reported ring-opening reactions with thiolate and selenolate nucleophiles, with the corresponding $S_{N}2$ (**259** and **260**) and $S_{N}2'$ (**261**) ring-opened products being formed with low selectivities (Scheme 70).^{20b} In contrast,

Scheme 70. Ring-Opening Reaction with Thiolate and Selenolate Nucleophiles



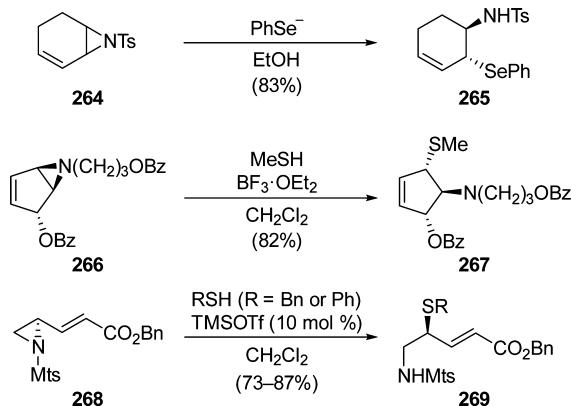
Mariano and co-workers^{52b} reported the ring-opening reaction of bicyclic aziridines **262** with thioacetic acid (AcSH) proceeded in a regioselective manner to give the $S_{N}2$ products **263** (Scheme 71).

Scheme 71. Ring-Opening Reaction with Thioacetic Acid



Some of the other regioselective reactions involving sulfur and selenium nucleophiles are shown in Scheme 72. In a similar manner to the reaction of **262** with AcSH, the bicyclic vinylaziridine **264** underwent a ring-opening reaction with

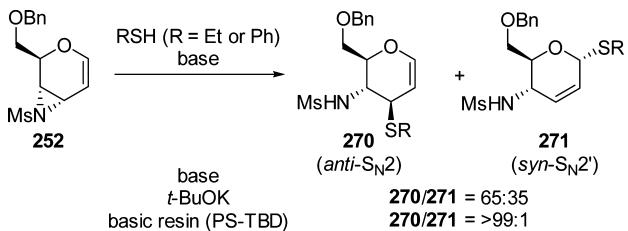
Scheme 72. Regio- and Stereoselective Ring-Opening Reactions with Sulfur and Selenium Nucleophiles



selenolate in EtOH to give **265** in good yield.¹²⁷ Acid-mediated reactions with thiols (i.e., BF₃-promoted reactions of **266**¹²⁸ and TMSOTf-catalyzed reaction of **268**¹²⁹) proceeded in a regio- and stereoselective manner to afford the corresponding products **267** and **269**, respectively.

In a recent study, Di Bussolo et al.¹³⁰ reported some interesting observations concerning the impact of base on the regioselective outcome of the ring-opening reaction of sugar-derived bicyclic vinylaziridines **252** (Scheme 73). In this study,

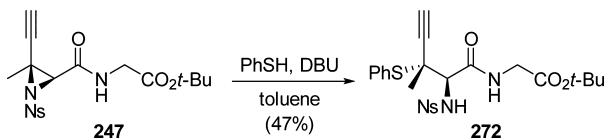
Scheme 73. Effect of Base on Regioselectivity in Reaction with Thiols



the use of *t*-BuOK as the base afforded a mixture of anti- S_N2 (**270**) and syn- S_N2' (**271**) products, whereas the use of polystyrene-bound 1,5,7-triazabicyclo[4.4.0]dec-5-ene (PS-TBD) gave the anti- S_N2 (**270**) products exclusively. These results strongly suggested that the syn- S_N2' products were formed by coordination of the mesylamido group in **252** to the metal of the thiolate anion, which enabled the nucleophilic attack to occur from the syn face to the aziridine nitrogen.

The only reported example, to date, of a ring-opening reaction of an ethynylaziridine with a sulfur nucleophile is the DBU-mediated ring-opening reaction with thiophenol (PhSH, Scheme 74). The reaction of **247** proceeded in a regio- and stereoselective manner to give the S_N2 product **272** bearing a tertiary alkyl aryl thioether moiety.^{122b}

Scheme 74. Reaction of Ethynylaziridine with PhSH

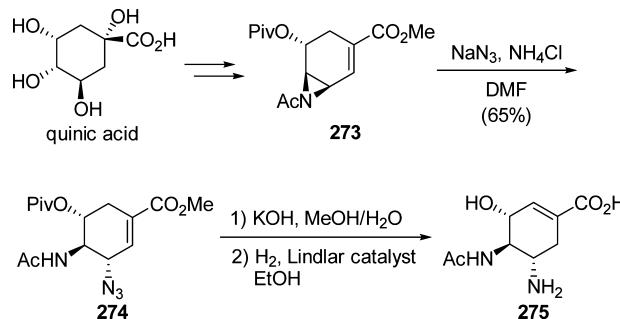


4.6. Reaction with Nitrogen Nucleophiles

Ring-opening reactions of vinylaziridines with nitrogen nucleophiles can provide convenient and efficient access to the 1,2-diamine structures found in many natural products and biologically active compounds. In 1997, a group from Gilead Sciences Inc.¹¹⁹ reported the use of this type of reaction in their work toward the identification of oseltamivir. As shown in Scheme 75, the ring-opening reaction of bicyclic aziridine **273** with NaN₃ in the presence of NH₄Cl proceeded in a regioselective manner to give the corresponding azide **274**, which was subsequently converted to the anti-influenza candidate **275**. Several total syntheses of oseltamivir and related compounds have been reported based on similar ring-opening reactions involving NaN₃ or diphenylphosphoryl azide (DPPA).¹³¹ The ring-opening azidation of vinylaziridines can also be efficiently promoted by trimethylsilyl azide (TMSN₃).¹³²

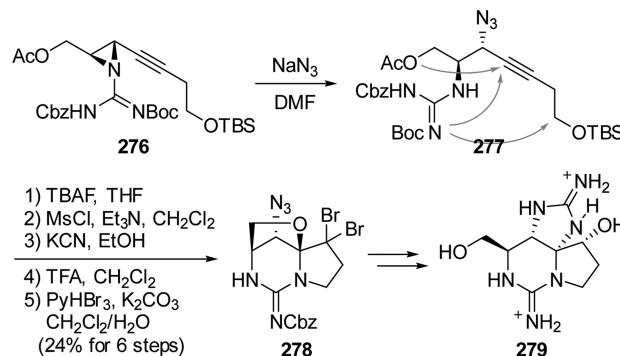
The ring-opening azidation reaction can also be applied to ethynylaziridines. Sawayama and Nishikawa¹³³ used this

Scheme 75. Reaction of Vinylaziridine with NaN₃



methodology for construction of the saxitoxin skeleton (Scheme 76). Aziridine **276** efficiently underwent a ring-

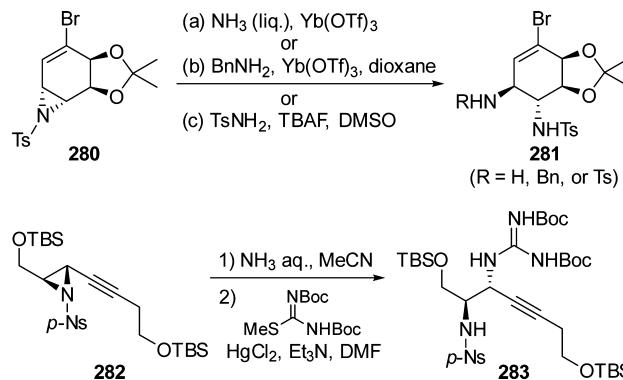
Scheme 76. Reaction of Ethynylaziridine with NaN₃



opening reaction with NaN₃ in DMF to produce the propargylic azide **277**. This compound was used as a good precursor of the substrate for a cascade PyHBr₃-mediated bromocyclization, which provided an elegant strategy for construction of the core structure of decarbamoyl α -saxitoxinol (**279**).

Some ring-opening reactions involving other nitrogen nucleophiles are shown in Scheme 77. Hudlicky and co-

Scheme 77. Reaction with Amine Derivatives

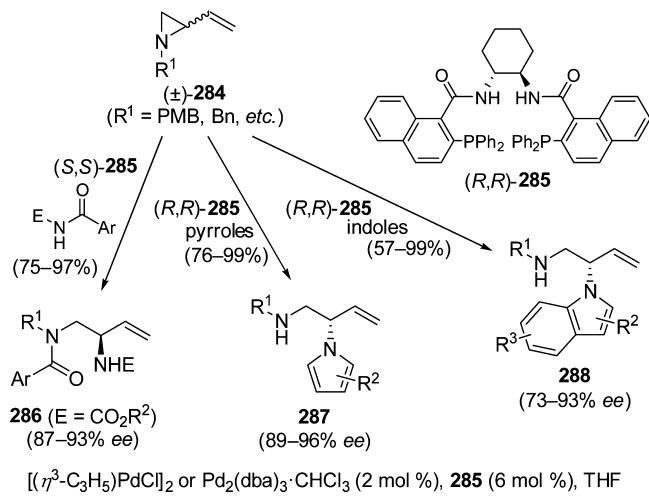


workers¹³⁴ found that ring-opening reaction of bicyclic aziridine **280** with NH₃ or BnNH₂ was efficiently catalyzed by Yb(OTf)₃. For the reaction with *p*-toluenesulfonamide (TsNH₂), tetra-*n*-butylammonium fluoride (TBAF) was found to be an appropriate promoter. The ring-opening reaction of highly activated *N*-nosylaziridine **282** with aqueous NH₃ proceeded in a regioselective manner to afford **283**.

following a guanidinylation reaction with di-Boc-methylisothiourea in the presence of $HgCl_2$.¹³⁵ Related ring-opening reactions involving the use of $NH_3/MeOH$ ¹³⁶ and $ArNH_2/LiClO_4$,¹³⁷ as well as the use of amines without a promoting reagent (for N-Ns ethynylaziridines)¹³⁸ have also been reported.

On the basis of their powerful palladium-catalyzed asymmetric allylic alkylation (AAA) using chiral diphosphine ligands such as **285**, Trost et al.¹³⁹ developed a highly efficient process for the dynamic kinetic asymmetric transformations of vinylaziridines **284** (Scheme 78). Palladium-catalyzed reaction

Scheme 78. Dynamic Kinetic Asymmetric Reactions with Nitrogen Nucleophiles



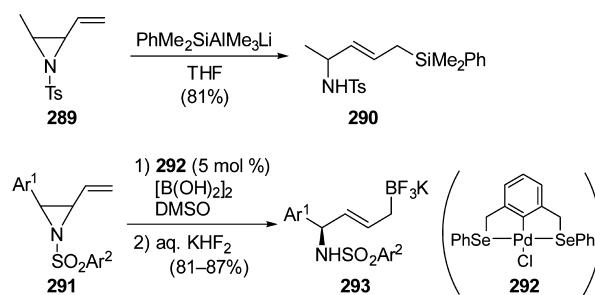
of **284** with imides in the presence of diphosphine ligand (*S,S*)-**285** gave the protected 1,2-diamine derivatives **286** in 87–93% ee via an asymmetric allylic amination followed by acyl migration.^{139a} Pyrroles and indoles were also used as nitrogen nucleophiles and gave the corresponding N-allylation products **287** (89–96% ee) and **288** (73–93% ee), respectively.^{139b} These dynamic kinetic asymmetric transformations are related in some respects to the palladium-catalyzed isomerization reactions of vinylaziridines reported by Ibuka and co-workers⁴⁷ (vide infra, Scheme 107).

4.7. Reaction with Other Nucleophiles

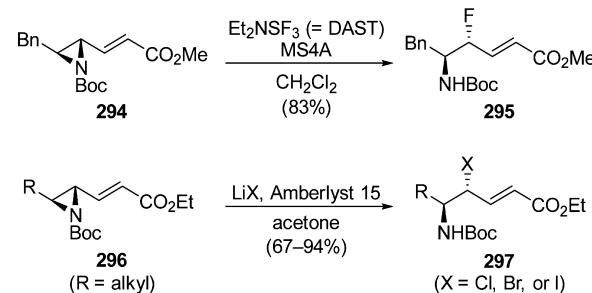
Reports describing the introduction of atoms other than hydrogen, carbon, oxygen, sulfur/sele-nium, and nitrogen by the ring-opening reaction of vinyl- and ethynylaziridines are scarce. In 1987, Oshima et al.¹⁴⁰ reported the preparation of allylsilanes such as **290** by the S_N2' -type ring-opening reaction of three-membered rings including aziridines **289** with silylaluminum reagents (Scheme 79). Interestingly, the use of dienylaziridines instead of vinylaziridines allowed silylation to occur at the terminal position to give the corresponding dienylsilanes. In a related publication, Szabó and co-workers¹⁴¹ reported the preparation of allyl trifluoroborates **293** by use of the palladium pincer complex **292** as a catalyst.¹⁴²

Halogen atoms can be stereoselectively introduced by the ring-opening reaction of aziridinyl enoates (Scheme 80). Reaction of **294** with diethylaminosulfur trifluoride (DAST) resulted in stereospecific ring-opening of the aziridine to give the fluorinated derivative **295**.¹⁴³ In a related report, lithium halide was used in the presence of Amberlyst 15 to facilitate stereoselective conversion of **296** to the allyl halides **297**.¹⁴⁴ It

Scheme 79. Synthesis of Allylic Silanes and Borates by Ring-Opening Reaction



Scheme 80. Ring-Opening Reactions with Halogen Nucleophiles



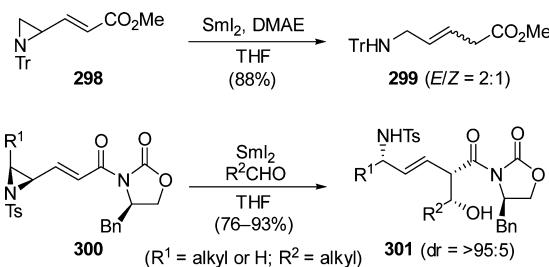
should be noted that chlorination of vinylaziridines by use of HCl was reported earlier by Atkinson et al.¹⁴⁵ and Fujii and co-workers.^{95,114}

5. REDUCTIVE RING-OPENING REACTIONS

This section provides a summary of ring-opening reactions that are promoted by electron transfer to vinylaziridines to afford the allyl amine derivatives. Reductive ring-opening reactions by hydride transfer have already been described above as nucleophilic ring-opening reactions with hydrides (section 4.1).

Molander and Stengel¹⁴⁶ reported that the reaction of **298** with $SmI_2/DMAE$ (*N,N*-dimethylaminoethanol) afforded the allyl amine **299** as a mixture of isomers (*E/Z* = 2:1) in 88% yield (Scheme 81). In 2005, Mukaiyama and co-workers¹⁴⁷

Scheme 81. Ring-Opening Reactions by SmI_2

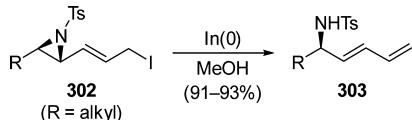


found that reaction of **300**, bearing a chiral oxazolidinone auxiliary, with SmI_2 in the presence of an aldehyde effectively promoted the asymmetric aldol reaction of in situ-generated samarium enolates to give the addition products **301** in a highly diastereoselective manner. This reaction can be considered as an umpolung of vinylaziridines (see also Schemes 83 and 84).

Another example of electron transfer to aziridines is the indium(0)-mediated reduction of **302** bearing an allyl iodide moiety, where treatment of **302** with indium(0) in refluxing

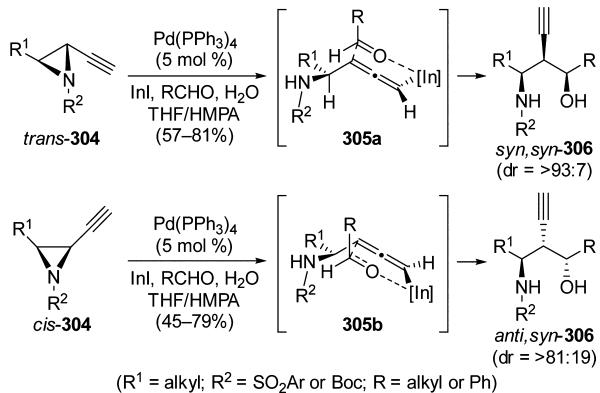
MeOH gave the corresponding (*E*)-dienylamines **303** in excellent yields (Scheme 82).¹⁴⁸ Indium was found to be more effective than several other metals such as zinc, samarium, and yttrium for this particular transformation.

Scheme 82. Indium(0)-Mediated Reduction of 2-(Iodoprop-1-en-1-yl)aziridines



In 2000, Ohno et al.¹⁴⁹ reported the umpolung of chiral 2-ethynylaziridines by indium(I), followed by stereoselective addition of the resulting allenylindium reagents to aldehydes (Scheme 83). In many cases, the reaction proceeded with high

Scheme 83. Indium(I)-Mediated Umpolung of Ethynylaziridines and Their Addition to Aldehydes

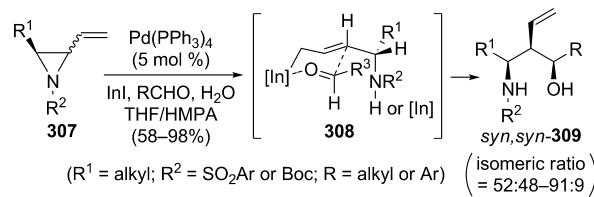


levels of stereoselectivity (>98:2) to give *syn,syn*-306 (from *trans*-304) and *anti,syn*-306 (from *cis*-304) possessing three contiguous chiral centers. In contrast, when the reaction was conducted with sterically less hindered aziridines ($R^1 = \text{Me}$) and acetaldehyde ($R = \text{Me}$), the corresponding adducts were formed with relatively lower selectivities ($\text{dr} = 81:19\text{--}93:7$). The differences in the stereochemical outcomes of these reactions can be understood as follows: the attack of palladium(0) to 304 from the opposite side of the aziridine ring would give the allenylpalladium(II) intermediate, which would be converted into 305a or 305b with retention of configuration by transmetalation with InI. Coordination of the indium atom to the carbonyl oxygen of the aldehyde would allow for the aldehyde to approach from the same side of the indium atom.

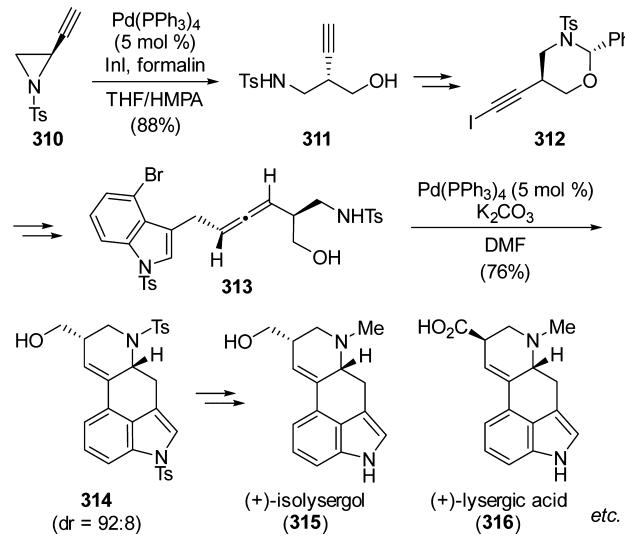
Almost at the same time (in 2001), the umpolung of vinylaziridines with indium(I) iodide was reported by Take-moto and co-workers¹⁵⁰ (Scheme 84). This reaction allowed for the stereoselective formation of *syn,syn*-amino alcohols **309**. The stereoselectivity of this reaction can be explained in terms of formation of a preferred cyclic transition state such as **308**. From these observations, vinyl- and ethynylaziridines can be used as chiral nucleophiles in carbon–carbon bond-forming reactions.

On the basis of the chemistry of the indium(I)-mediated umpolung of ethynylaziridines, Inuki, Ohno, and co-workers¹⁵¹ accomplished the total synthesis of (+)-lysergic acid as well as several related alkaloids (Scheme 85). The chiral 1,3-amino

Scheme 84. Indium(I)-Mediated Umpolung of Vinylaziridines and Their Addition to Aldehydes



Scheme 85. Total Synthesis of Lysergic Acid and Related Alkaloids via Indium(I)-Mediated Umpolung of Ethynylaziridine



alcohol 311, which was used as a precursor for the Nozaki–Hiyama–Kishi (NHK) reaction, was prepared by the palladium(0)- and indium(I)-mediated reductive coupling reaction between L-serine-derived 2-ethynylaziridine 310 and formaldehyde. Palladium(0)-catalyzed cascade cyclization of the amino allene 313 bearing a bromoindolyl group allowed for direct construction of the core structure of the ergot alkaloid skeleton as well as creation of the C5 stereogenic center with transfer of the allenic axial chirality.

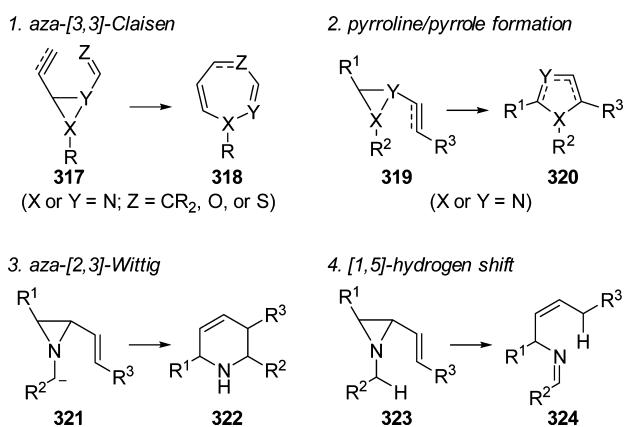
6. REARRANGEMENT AND ISOMERIZATION

The rearrangement and isomerization processes of vinyl- and ethynylaziridines are used extensively in organic synthesis, and four of these rearrangement reactions are shown in Scheme 86, including (1) formation of seven-membered rings by the aza-[3,3]-Claisen rearrangement of 1,2-divinyl or 2,3-divinylaziridines and their ethynyl congeners 317 (section 6.1); (2) formation of pyrrolines and pyrroles from 319 (section 6.2); (3) aza-[2,3]-Wittig rearrangement of anionic species 321 (section 6.3); and (4) hydrogen shift from 323 (section 6.4). Miscellaneous reactions including epimerization processes will be presented in section 6.5.

6.1. Aza-[3,3]-Claisen Rearrangement

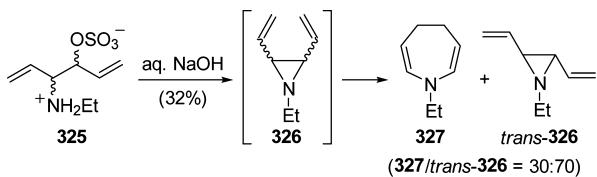
The formation of azepine derivatives by the aza-[3,3]-Claisen rearrangement was first reported by Stogryn and Brois¹⁵² in 1965. In this study, an isomeric mixture of 2,3-divinylaziridines 326 was formed following treatment of sulfonate 325 with aqueous NaOH, and this mixture was subsequently converted

Scheme 86. Rearrangement Reactions of Vinyl- and Ethynylaziridines



into azepine 327 by steam distillation (Scheme 87), with the unchanged *trans*-326 also being isolated with the product

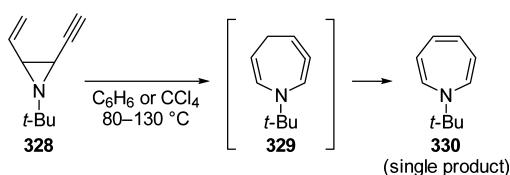
Scheme 87. Pioneering Work on Rearrangement of 2,3-Divinylaziridine to Dihydroazepine



(327:*trans*-326 = 30:70). A similar reaction involving formation of azepines from pure *cis*-2,3-divinylaziridine has also been reported.¹⁵³

Thermal rearrangement of *cis*-2-ethynyl-3-vinylaziridine 328 affords the 1*H*-azepine 330 (Scheme 88). This reaction

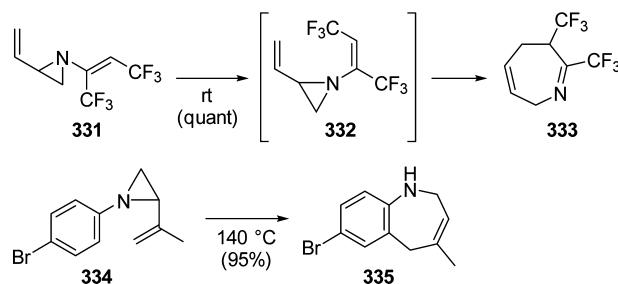
Scheme 88. Formation of 1*H*-Azepine from 2-Ethynyl-3-vinylaziridine



proceeds through an aza-[3,3]-Claisen rearrangement followed by a hydrogen shift from the cyclic allenene intermediate 329.¹⁵⁴ The corresponding *trans*-aziridine also yielded the same azepine 330, presumably via thermal isomerization of *trans*-328 to the corresponding *cis* isomer through cleavage of the carbon–carbon bond followed by aziridination.⁷⁷

Pioneering research studies toward the construction of azepines from 1,2-divinylaziridine-type substrates were independently reported by two research groups in 1967 (Scheme 89). Stogryn and Brois¹⁵⁵ reported that 1,2-divinylaziridine 331 was formed by low-temperature addition of *N*-H 2-vinylaziridines to hexafluorobut-2-yne. This aziridine subsequently isomerized, on standing at ambient temperature overnight, to azepine 333 via the 1,2-*cis* isomer 332. Almost at the same time, Scheiner¹⁵⁶ reported that heating of the *N*-phenylvinylaziridine derivative 334 led to a clean rearrangement process to give the fused ring product 335. A series of studies,

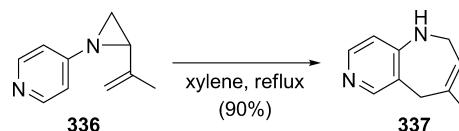
Scheme 89. Pioneering Research on Isomerization of 1,2-Divinylaziridine Derivatives to Dihydroazepines



involving rearrangement reactions of [2-(aziridin-1-yl)alkenyl]-triphenylphosphonium bromides¹⁵⁷ and 1,2-divinylaziridines,¹⁵⁸ which were prepared by addition of *N*-H aziridines to electrophilic carbon–carbon multiple bonds such as acrylonitrile, were reported later.

Thermal isomerization processes of *N*-heteroaryl-2-vinylaziridines such as 336 have been reported to yield the corresponding pyrido-, isothiazolo-, and thienoazepine compounds, as shown in Scheme 90.¹⁵⁹ Since the isomerization of

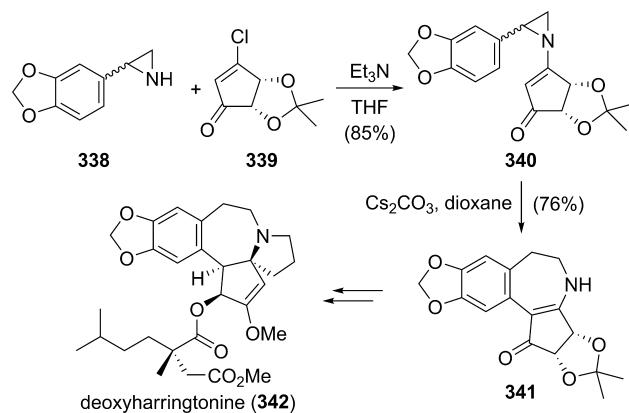
Scheme 90. Formation of Pyridoazepine by Aza-[3,3]-Claisen Rearrangement



N-pyridinyl-2-vinylaziridines to the corresponding azepine shows substituent effects that are completely analogous to those observed in the related benzenic O-Claisen rearrangement, the ring-expansion reaction of divinylaziridines can be classified as a concerted [3,3]-sigmatropic rearrangement.¹⁶⁰ Recent DFT calculations have provided a rationale for the aza-[3,3]-Claisen rearrangement of *N*-aryl-2-vinylaziridines to benzazepines.¹⁶¹ The isomerization of 4-(2-vinylaziridino)-5-methoxy-1,2-benzoquinones to bicyclic benzoquinones has also been reported.¹⁶²

On the basis of the [3,3]-Claisen rearrangement, Gin and co-workers¹⁶³ successfully achieved total synthesis of the anti-leukemia alkaloid (−)-deoxyharringtonine (342) (Scheme 91).

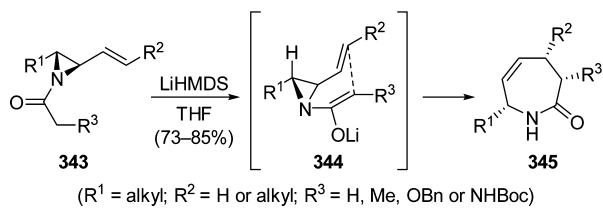
Scheme 91. Total Synthesis of (−)-Deoxyharringtonine via [3,3]-Claisen Rearrangement of *N*-Alkenyl-2-arylaziridine



The conjugate addition–elimination reaction of racemic aziridine 338 to 339 provided *N*-alkenyl-2-arylaziridine 340 as a 1:1 mixture of diastereomers. Subsequent thermal activation (100 °C) of 340 in the presence of Cs₂CO₃ promoted the [3,3]-rearrangement process to provide benzazepine 341 bearing the tetracyclic core of (−)-342 in 76% yield.

In 1997, Somfai and co-workers¹⁶⁴ reported the aza-[3,3]-Claisen enolate rearrangement of vinylaziridines 343 (Scheme 92). Treatment of *N*-acyl-2-vinylaziridines 343 with lithium

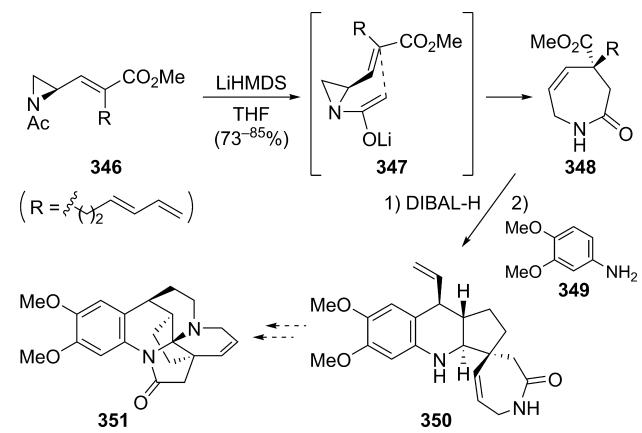
Scheme 92. Aza-Claisen Enolate Rearrangement of *N*-Acyl-2-vinylaziridines



hexamethyldisilylamide (LiHMDS) in THF gave the corresponding aziridinyl enolates, which underwent a stereoselective 3,3-rearrangement to form seven-membered lactams 345, presumably through a boatlike transition state 344.

The synthetic application of the aza-[3,3]-Claisen rearrangement has recently been reported (Scheme 93). *N*-Acetylaziridine

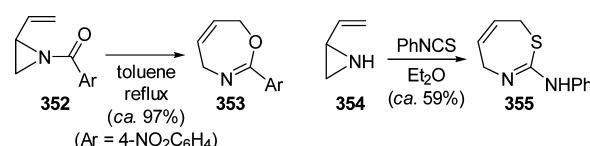
Scheme 93. Approach to Synthesis of Isoschizogamine via Aza-Claisen Rearrangement



idine 346, which was easily prepared via Wittig reaction of the enantiomerically pure aziridine aldehyde, was stereoselectively converted to the seven-membered lactam 348 by the aza-Claisen rearrangement.¹⁶⁵ Reduction of ester with diisobutylaluminium hydride (DIBAL-H) followed by a formal hetero-Diels–Alder reaction using aniline 349 gave the highly functionalized tetrahydroquinoline derivative 350, which is an advanced intermediate for the synthesis of isoschizogamine (351).¹⁶⁶

Reactions involving the formation of a seven-membered ring via the 3,3-Claisen rearrangement of substrates including a carbonyl or thiocarbonyl group are shown in Scheme 94. Thermolysis of 352 in refluxing toluene afforded 4,7-dihydro-1,3-oxazepine 353 in good yield.¹⁶⁷ Similarly, treatment of *N*-vinylaziridine 354 with phenyl isothiocyanate in ether at 0 °C

Scheme 94. Rearrangement of 2-Vinylaziridines Bearing a Carbonyl or Thiocarbonyl Group

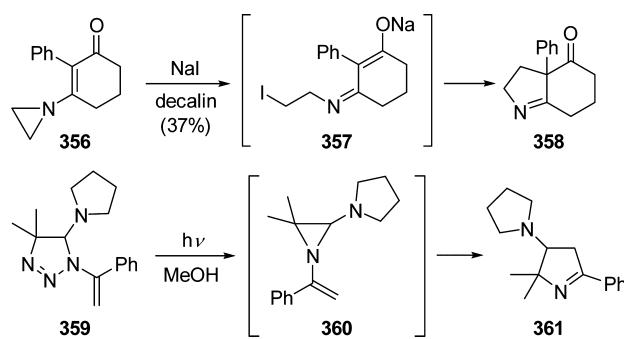


gave the seven-membered ring product 355 via a 2-vinylaziridine-*N*-carbothioamide intermediate.¹⁶⁸

6.2. Pyrroline/Pyrrole Formation

Rearrangement reactions of vinylaziridines can be promoted by heat, photoirradiation, or a Lewis acid/base to give the corresponding 1-, 2-, and/or 3-pyrrolines, depending on the substrate structures and reaction conditions. Formation of pyrrolines from vinylaziridines was first reported by Whitlock and Smith¹⁶⁹ for *N*-vinylaziridine (Scheme 95). The sodium

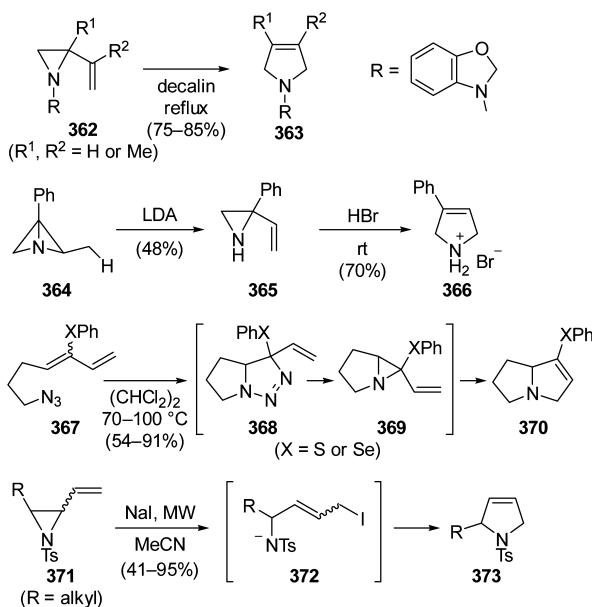
Scheme 95. Rearrangement of *N*-Vinylaziridines to 1-Pyrrolines



iodide-mediated ring-opening reaction of 356 was followed by formation of a five-membered ring from enolate intermediate 357 to give the bicyclic 1-pyrroline 358 in 37% yield. The related conversion of *N*-vinylaziridine 360, which was generated by photolysis of *N*-vinyl-1,2,3-triazole 359, has also been reported.¹⁷⁰

Thermal- and acid-mediated rearrangement reactions of 2-vinylaziridines usually afford 3-pyrrolines. When aziridines of general structure 362 were heated in decalin at 180 °C, 3-pyrroline products 363 were formed in yields of 75–85% (Scheme 96).¹⁷¹ A similar rearrangement reaction has also been reported by Lwowski and co-workers.⁶ Rearrangement reactions of this type can effectively be promoted by an acid at lower temperatures. For example, treatment of 2-vinylaziridines 365, which were prepared by LDA-induced ring-opening of 1-azabicyclobutane 364, with 48% HBr at room temperature gave the 3-pyrroline 366 as the hydrobromide salt.^{56a} In contrast, heating of 365 in decalin at 175–180 °C led to decomposition of 365, with none of the desired pyrrolines 366 being detected. Bicyclic vinylaziridines 369 have been suggested as plausible intermediates in the intramolecular reaction of azides 367 with electron-rich 1,3-dienes (substituted by SPh or SePh group) to form bicyclic 3-pyrrolines 370.¹⁷² Rearrangement reactions of related substrates can be efficiently promoted by trimethylsilyl iodide (TMSI).¹⁷³ NaI-mediated rearrangement of vinylaziridines 371 to 3-pyrrolines 373 via allyl iodides 372 at 200 °C under microwave irradiation, as well as application of this reaction to the formal total synthesis of (−)-anisomycin, has also been reported.¹⁷⁴ A process

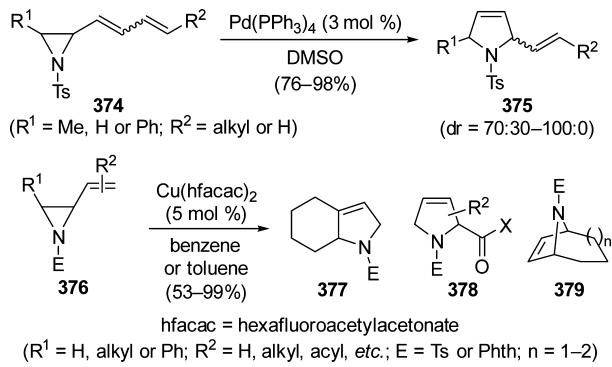
Scheme 96. Rearrangement of 2-Vinylaziridines to 3-Pyrrolines



describing the combination of vinylaziridine formation and spontaneous rearrangement reactions was recently developed as a convenient strategy for synthesis of 3-pyrrolines.¹⁷⁵

Transition-metal-mediated reactions can also be used to provide convenient access to 3-pyrrolines under mild conditions. For example, Oshima and co-workers¹⁷⁶ reported palladium(0)-catalyzed isomerization of 2-dienylaziridines 374 to 3-pyrrolines 375 (Scheme 97). This isomerization occurred

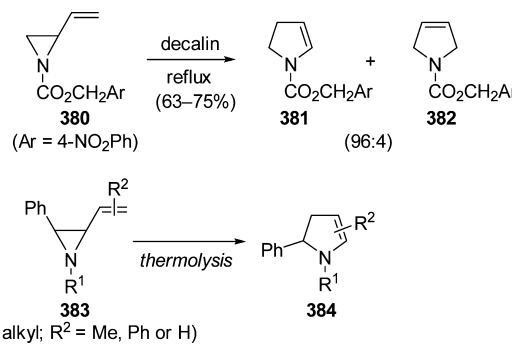
Scheme 97. Transition-Metal-Catalyzed Rearrangement of 2-Vinylaziridines to 3-Pyrrolines



in striking contrast to the palladium-catalyzed isomerization reported by Ibuka and co-workers,⁴⁷ which gave *cis*-vinylaziridines from the corresponding 2,3-*trans* isomers (Scheme 107). A highly efficient process for copper(II)-catalyzed ring expansion of vinylaziridines 376 was recently reported.¹⁷⁷ This reaction was also highly stereospecific¹⁷⁸ and applicable to a wide range of vinylaziridines to give the corresponding 3-pyrrolines, including bicyclic ones, such as 377, 378, and 379.

Thermal rearrangement of 2-vinylaziridine 380 bearing an electron-withdrawing group on its nitrogen atom in refluxing decalin afforded 2-pyrroline 381 as the major product, along with a small amount of 3-pyrroline derivative 382 (Scheme 98).¹⁷⁹ A similar reaction has also been reported involving *N*-alkyl-2-phenyl-3-vinylaziridines 383.¹⁸⁰ On the basis of these

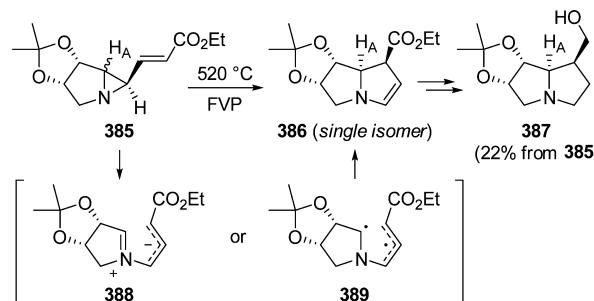
Scheme 98. Thermal Rearrangement of Vinylaziridines to 2-Pyrrolines



reports, it is clear that the nature of products formed from these reactions is dependent on the nature of substituents on the aziridine ring as well as reaction conditions.

Hudlicky et al.¹⁸¹ also reported a related process for formation of 2-pyrrolines involving flash vacuum pyrolysis of vinylaziridines such as 385 (Scheme 99). The resulting bicyclic

Scheme 99. Pyrolysis of Fused Vinylaziridine to 2-Pyrroline



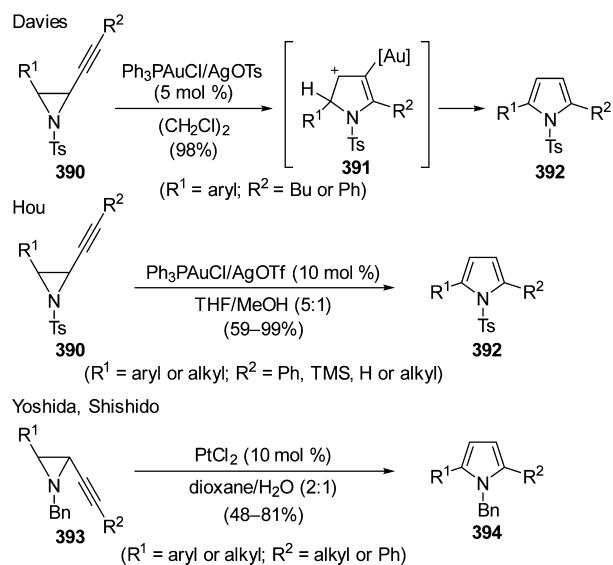
2-pyrroline 386 represents a useful building block for synthesis of pyrrolizidine alkaloids and their derivatives, including the protected (+)-trihydroxyheliotridane 387. Given that pyrolysis of the two different diastereomers of 385 furnished the cyclized product 386 as the single isomer, the authors of the report proposed that the reaction proceeded through a zwitterionic or biradical intermediate (388 or 389, respectively).

Cycloisomerization of ethynylaziridines provides access to pyrroles. In 2009, three research groups—Davies and Martin,¹⁸² Hou and co-workers,¹⁸³ and Yoshida and co-workers¹⁸⁴—independently reported their methods for transition-metal-catalyzed synthesis of pyrroles by rearrangement of ethynylaziridines (Scheme 100). Davies' method, in particular, involved the use of Ph₃PAuCl/AgOTs (5 mol %) in dichloroethane to give the corresponding pyrroles 392 in excellent yields. Following on from these reports, several groups have reported the development of similar gold(I)-catalyzed reactions for formation of pyrroles.¹⁸⁵ Furthermore, in 2009, Yoshida et al.¹⁸⁶ developed a process involving iodine-mediated rearrangement of ethynylaziridines to form 3-iodopyrroles.

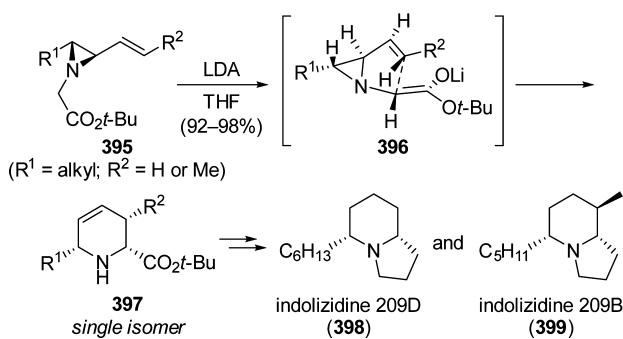
6.3. Aza-[2,3]-Wittig Rearrangement

Aza-[2,3]-Wittig rearrangement of vinylaziridines was originally reported by Åhman and Somfai in 1994¹⁸⁷ (Scheme 101), where reaction of *N*-*tert*-butyl (vinylaziridinyl)acetates 395 with LDA afforded the corresponding *cis*-tetrahydropyridines 397 as single isomers. A concerted mechanism proceeding through

Scheme 100. Transition-Metal-Catalyzed Isomerization of Ethynylaziridines to Pyrroles



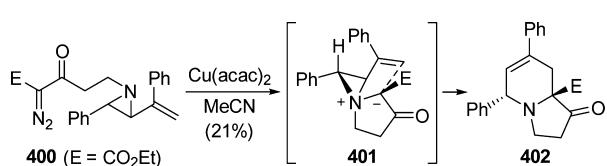
Scheme 101. Aza-[2,3]-Wittig Rearrangement of Vinylaziridines



396 was suggested to account for the observed stereochemical outcome of the rearrangement. This type of reaction can also be applied to *N*-propargyl-2-vinylaziridines.¹⁸⁸ The same group also applied this chemistry to the total syntheses of some indolizidine alkaloids, including indolizidines 209D (398) and 209B (399).¹⁸⁹ In 1995, Coldham et al.¹⁹⁰ reported a similar transformation involving rearrangement of aziridines bearing a 1-phenylvinyl group.

Aza-[2,3]-Wittig rearrangement of vinylaziridine-derived quaternary aziridinium ylides 401 has been reported (Scheme 102),¹⁹¹ and this transformation can also be categorized as a [2,3]-Stevens rearrangement. The aziridinium ylide 401 was generated by intramolecular reaction of a copper carbenoid tethered to a vinylaziridine.

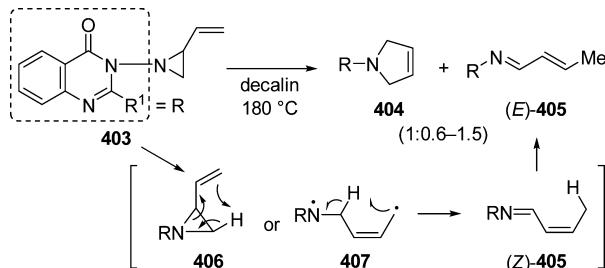
Scheme 102. [2,3]-Stevens Rearrangement of Vinylaziridine-Derived Ammonium Ylide



6.4. Hydrogen Shift

Hydrogen shift reactions are generally observed during thermal isomerization of vinylaziridines and sometimes represent an undesired transformation. Heating of 403 at 180 °C led to a mixture of 3-pyrrolines 404 and hydrazones (*E*)-405 (Scheme 103).¹⁹² The formation of (*E*)-405 in this case was rationalized

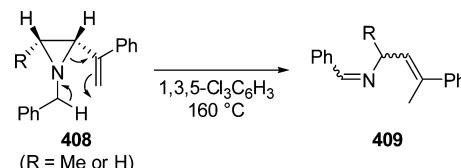
Scheme 103. Imine Formation by Hydrogen Shift



in terms of a concerted hydrogen shift through 406 or the biradical intermediate 407, with both of these intermediates resulting ultimately in the formation of (*Z*)-405. The (*Z*)-carbon–carbon double bond of this product would subsequently undergo a thermal isomerization reaction to give (*E*)-405. A similar isomerization process has also been reported involving the use of a nickel catalyst.¹⁹³

A hydrogen shift from the nitrogen substituent of *N*-benzyl-2-vinylaziridine 408 was observed when the material was heated at 160 °C (Scheme 104).^{180b} Similar [1,5]-hydrogen shifts were

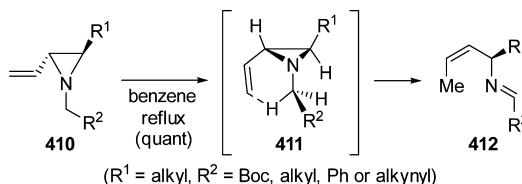
Scheme 104. [1,5]-Hydrogen Shift of *N*-Benzyl-2-vinylaziridines



also reported by Pearson et al.¹⁷² in their study on thermal isomerization of bicyclic vinylaziridines 369 (Scheme 96). Similar observations have also been reported by several other research groups.¹⁹⁴

Somfai and co-workers¹⁹⁵ investigated thermal isomerization of vinylaziridines 410 and found that reaction of 410 gave the allylic imines 412 in a stereoselective manner and quantitative yields by the [1,5]-hydrogen shift, with the transformation presumably progressing through 411 (Scheme 105). This reaction occurred in striking contrast to LDA-mediated isomerization of 410 bearing a *t*-butyl acetate moiety (*R*²=CO₂*t*-Bu), which afforded tetrahydropyridines through an aza-[2,3]-Wittig rearrangement (Scheme 101).¹⁸⁷

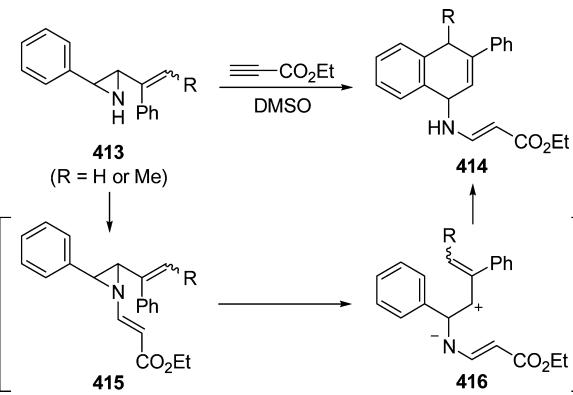
Scheme 105. Stereoselective [1,5]-Hydrogen Shift



6.5. Miscellaneous

An interesting reaction involving the rearrangement of 1,3-divinyl-2-phenylaziridines is shown in Scheme 106. The

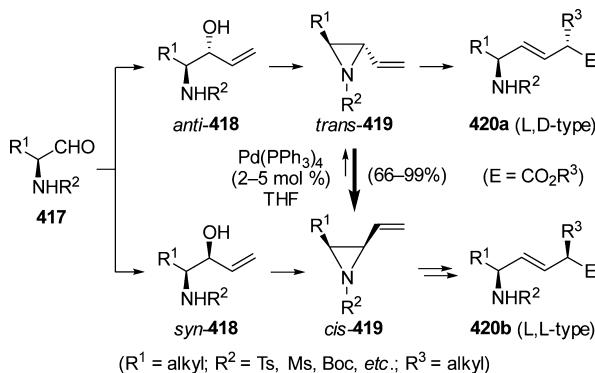
Scheme 106. Arylative Rearrangement of 2-Phenyl-N-vinylaziridines



addition of *N*-H aziridines 413 to ethyl propiolate gave 1,3-divinylaziridines 415, which underwent a rearrangement process to afford 1,4-dihydronaphthalenes 414.¹⁹⁶ Heterolytic cleavage of the carbon–nitrogen bond to form the zwitterionic intermediates 416 was proposed as a possible mechanism. To date, this transformation represents the only example of a process involving rearrangement of a 2-vinylaziridine bearing an aryl group on the aziridine carbon. The related reactions of *N*-aryl-2-vinylaziridines have already been shown in section 6.1 (Schemes 89 and 90).

As described in section 4.2, vinylaziridines are versatile intermediates for the stereoselective synthesis of (*E*)-alkene dipeptide isosteres. One of the simplest methods for synthesis of alkene isosteres 420 involves organocopper-mediated ring-opening reaction of aziridine enoates derived from 419 (Scheme 107). These aziridines can be readily prepared from

Scheme 107. Palladium(0)-Catalyzed Isomerization of Vinylaziridines and Application of This Strategy to Synthesis of L,L-type (*E*)-Alkene Dipeptide Isosteres 420b

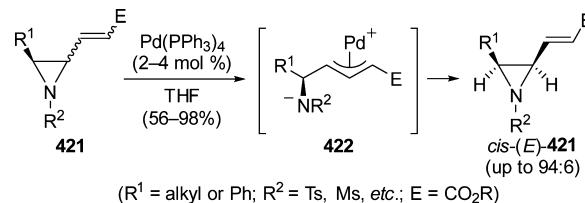


chiral *anti*- and *syn*-amino alcohols 418, which can themselves be derived from chiral amino aldehydes 417. However, the reaction of amino aldehydes 417 with organometallic reagents such as vinylmagnesium bromide generally results in formation of a mixture of *anti*- and *syn*-amino alcohols 418. Ibuka and co-workers⁴⁷ overcame this difficulty by developing a useful method for the epimerization of vinylaziridines, where

treatment of *trans*-419 with a catalytic amount of palladium(0) afforded the thermodynamically more stable *cis*-419 as the major product (*cis:trans* = >94:6) through the η^3 -allylpalladium intermediate. These results were in agreement with ab initio calculations. This epimerization represents a useful strategy for the highly stereoselective synthesis of L,L-type (*E*)-alkene dipeptide isosteres 420b through mixtures of *trans*- and *cis*-2-vinylaziridines 419. Rhodium and iridium complexes can also be used to catalyze this epimerization process.¹⁹⁷

A related process for palladium(0)-catalyzed epimerization of aziridinyl enoates was also reported by Ibuka et al.¹⁹⁸ (Scheme 108). Treatment of either isomer of 421 with a catalytic

Scheme 108. Palladium(0)-Catalyzed Isomerization of Aziridinyl Enoates



(R¹ = alkyl or Ph; R² = Ts, Ms, etc.; E = CO₂R)

amount of Pd(PPh₃)₄ in THF yielded an equilibrated mixture, where *cis*-(*E*)-421 with the desired configuration was formed as the major product [*cis*-(*E*):other isomers = 85:15–94:6]. In most cases, it was possible for *cis*-(*E*)-421 to be easily separated from the diastereomeric mixture by a single recrystallization. The organocupper-mediated ring-opening reaction of *cis*-(*E*)-421 afforded the L,L-type (*E*)-alkene dipeptide isosteres 420b directly (Scheme 107). Palladium(0)-catalyzed isomerization has also been used for the *cis*-selective synthesis of bicyclic vinylaziridines in combination with sulfur ylide-mediated aziridination.¹⁹⁹

7. CYCLOADDITION

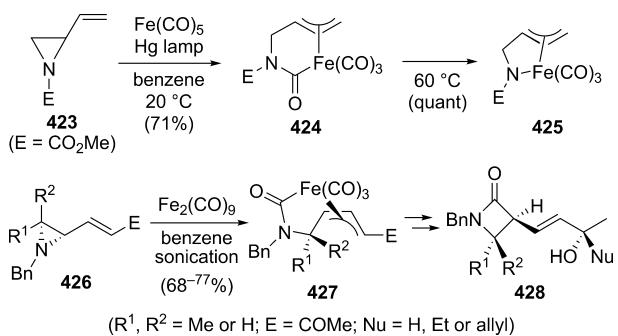
Vinylaziridines readily undergo cycloaddition reactions with carbon monoxide, carbon dioxide (and its equivalents), heterocumulenes (isocyanates, isothiocyanates, and carbodiimides), and alkenes to afford β -lactams, cyclic carbonates, cyclic carbamates, and other five- and seven-membered heterocycles. Palladium complexes can sometimes be used to promote cycloaddition reactions of this type by forming η^3 -allylpalladium intermediates. Important contributions to this area, as well as some early research toward ethynylaziridine cycloaddition chemistry, have been summarized here in the final section of this review.

7.1. Carbonylative Ring Expansion to Lactams

Ring expansion of vinylaziridines with carbon monoxide is a useful method for preparation of β -lactams. In 1974, Aumann et al.²⁰⁰ reported the light-induced reaction of vinylaziridine 423 with Fe(CO)₅ to give η^3 -allyltricarbonyliron lactam complex 424, which was shown to decompose at 60 °C with the loss of 1 equiv of CO to form 425 (Scheme 109). Ley and Middleton²⁰¹ synthesized ketone-functionalized lactam complexes 427 by reaction of vinylaziridines 426 with Fe₂(CO)₉ under sonication conditions in benzene. These lactam complexes 427 were readily converted to the corresponding β -lactams 428 by stereoselective addition of nucleophiles to the carbonyl group followed by decomplexation with Me₃NO.

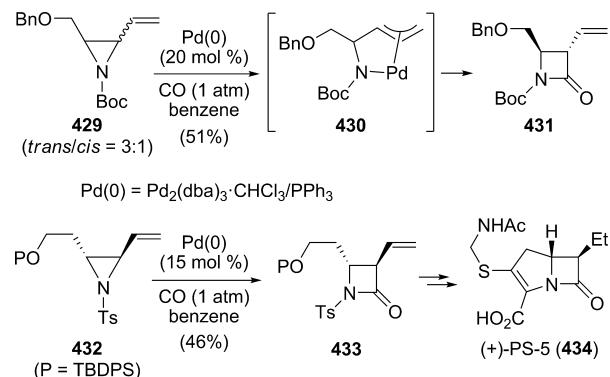
In 1991, Ohfune and co-workers²⁰² reported palladium(0)-catalyzed carbonylation of vinylaziridines 429 with carbon

Scheme 109. Formation of η^3 -Allyltricarbonyliron Lactam Complexes



monoxide (1 atm) in benzene (Scheme 110). Interestingly, this procedure allowed for a diastereomeric mixture of *trans*- and

Scheme 110. Palladium(0)-Catalyzed Carbonylative Ring Expansion to β -Lactams

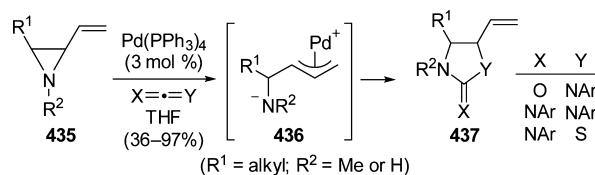


cis-vinylaziridines 429 (3:1) to be converted to *trans*-azetidinone 431. Tanner and Somfai²⁰³ used palladium(0)-catalyzed *trans*-selective β -lactam formation to synthesize (+)-PS-5 (434). The generality of these reactions, as well as the effects of aziridine substituents and reaction conditions (i.e., temperature, CO pressure, and Pd concentration) on the course of the reaction, has been thoroughly investigated by Aggarwal and co-workers²⁰⁴

7.2. Cycloaddition with Isocyanates and Related Compounds

Cycloaddition reactions of vinylaziridines with isocyanates and related heterocumulenes were reported by Alper and co-workers²⁰⁵ in 2000. On the basis of their previous study on cycloaddition reactions of vinyl epoxides and alkylaziridines, they investigated the cycloaddition reaction of vinylaziridines 435 and found that isocyanates, carbodiimides, and isothiocyanates represented good reaction partners for the transformation, with the corresponding five-membered ring products 437 being obtained in good yields (Scheme 111). When 3-substituted-2-vinylaziridine 435 ($R^1 = Me$) was subjected to reaction conditions, a 2:1 mixture of *cis*- and *trans*-five-membered rings 437 was obtained. In this process, the palladium catalyst activates the vinylaziridines by forming η^3 -allylpalladium intermediates 436, in a similar manner to the isomerization of vinylaziridines⁴⁷ (Scheme 107). The related palladium-catalyzed reaction with CO_2 as a heterocumulene was recently reported.²⁰⁶ A separate report revealed that when $ClCO_2Me$ was used as the coupling partner or the reaction was

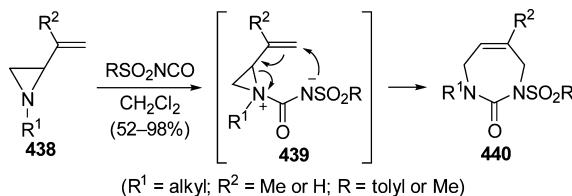
Scheme 111. Palladium(0)-Catalyzed [3 + 2] Cycloaddition with Heterocumulenes



conducted at a higher temperature, the cycloaddition reaction proceeded efficiently in the absence of palladium catalyst.²⁰⁷

Interestingly, the catalyst-free cycloaddition reaction of *N*-alkyl-2-vinylaziridines 438 with *N*-sulfonylisocyanates in CH_2Cl_2 afforded seven-membered ureas 440 selectively (Scheme 112).²⁰⁸ The mechanism proposed to account for

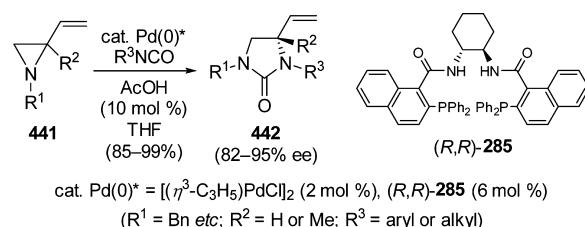
Scheme 112. Catalyst-Free [5 + 2] Cycloaddition with Sulfonyl Isocyanates



the outcome of this reaction involves S_N2' intramolecular nucleophilic attack of a zwitterionic species 439. The reaction in DMF gave [3 + 2] adducts of type 437, which could be explained in terms of S_N1 ring closure through the linear intermediate derived from 439.

An asymmetric version of the cycloaddition of isocyanates to vinylaziridines was reported by Trost and Fandrick²⁰⁹ (Scheme 113). Treatment of racemic vinylaziridine 441 with isocyanates

Scheme 113. Dynamic Kinetic Asymmetric Cycloaddition with Isocyanates

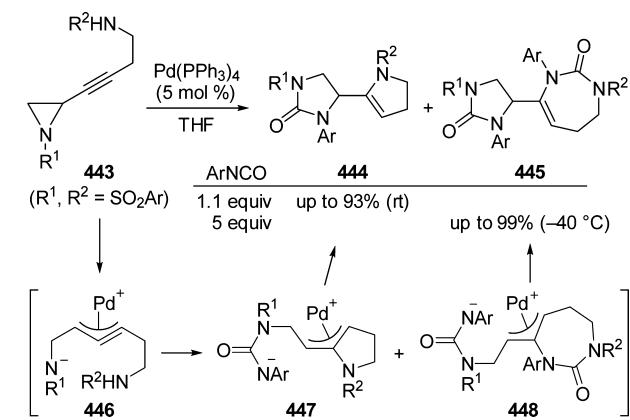


in the presence of $(\eta^3-C_3H_5PdCl_2)_2$ (2 mol %) and the chiral ligand $(R,R)-285$ (6 mol %) gave the corresponding chiral imidazolidinones 442 in up to 95% ee via a dynamic kinetic asymmetric transformation involving η^3 - η^1 - η^3 interconversion. The resulting imidazolidinones 441 were readily converted to the corresponding chiral diamines by successive treatment with $LiAlH_4$ and $H_2NOH \cdot H_2O$. Dong and Alper²¹⁰ reported a similar $CeCl_3$ -promoted asymmetric cycloaddition reaction using (*S*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (BINAP) and $Pd_2(dba)_3 \cdot CHCl_3$ that gave ee values of up to 83%.

It is well-known that the palladium(0)-catalyzed reactions of propargylic compounds developed by Tsuji and co-workers²¹¹ represent efficient methodologies not only for introduction of two nucleophiles into a substrate but also for construction of a variety of different heterocyclic compounds. Ohno and co-

workers²¹² used ethynylaziridines as propargylic substrates in one of these palladium-catalyzed reactions and succeeded in achieving the cascade cyclization of aziridines **443** bearing another nucleophilic nitrogen group (Scheme 114). Treatment

Scheme 114. Cascade Cyclization of Ethynylaziridines via Cycloaddition with Isocyanates

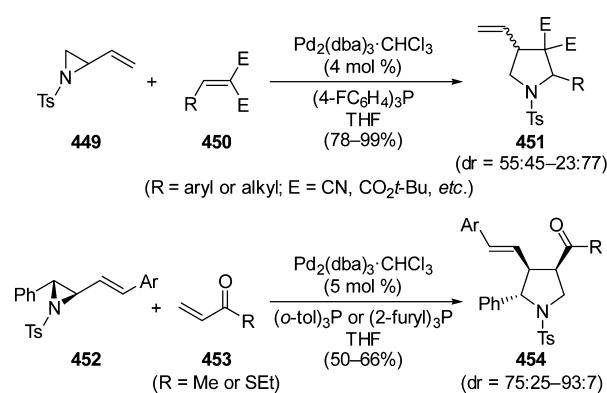


of **443** with a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$ and an aryl isocyanate in THF at room temperature afforded **444** in good yields. Interestingly, bis-adducts **445** were obtained selectively when an excess of isocyanate was used (5 equiv) at a lower reaction temperature. These two linked nitrogen heterocycles would have been derived from the η^3 -allylpalladium intermediates **447** and **448**, respectively, which would have been formed by the first cyclization reaction from η^3 -propargylpalladium intermediates **446**.

7.3. Cycloaddition with a Carbon–Carbon Multiple Bond

Yamamoto and co-workers²¹³ developed a cycloaddition reaction, based on their three-component aminoallylation reaction, involving the reaction of activated olefins with vinylaziridines **449** in the presence of palladium(0) catalyst, with the corresponding 4-vinylpyrrolidines **451** being obtained as a mixture of diastereomers (*cis:trans* = 55:45–23:77) (Scheme 115). Aggarwal and co-workers²¹⁴ improved the stereoselectivity of the reaction for vinylaziridines **452** by tuning the reaction conditions and the type of Michael acceptor **453**. The resulting pyrrolidine **454** ($\text{Ar} = \text{Ph}$, $\text{R} = \text{Me}$) was easily converted to (–)-kainic acid in several steps. More recently, intramolecular cycloaddition of vinylaziridines bearing

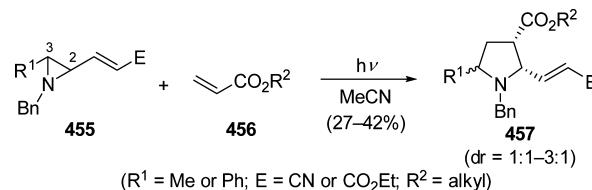
Scheme 115. Palladium-Catalyzed [2 + 3] Cycloaddition with Activated Olefins



an unactivated olefin moiety via a gold/palladium dual activation has been reported.²¹⁵

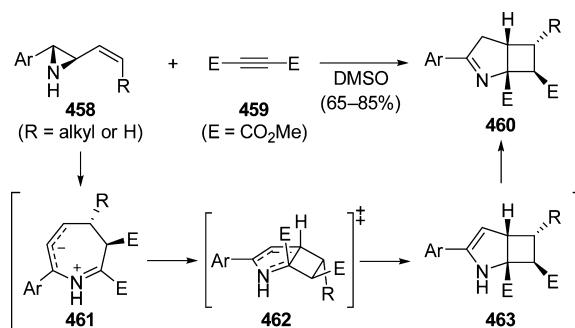
In contrast to the palladium-catalyzed reactions shown in Scheme 115, photochemical cycloaddition reaction of aziridinyl nitriles/enoates **455** with acrylates **456** gave pyrrolidines **457** bearing an alkenyl group at the 2-position (Scheme 116).²¹⁶ The formation of **457** can be understood in terms of photoinduced homolytic cleavage of the carbon–carbon ($\text{C}_2\text{–C}_3$) bond of aziridines **455**.

Scheme 116. Photoinduced [2 + 3] Cycloaddition with Activated Olefins



The final example discussed in this review is the formal [5 + 2] cycloaddition of *N*-H vinylaziridines **458** with dimethyl acetylenedicarboxylate (DMAD), which was reported by Yudin and co-workers²¹⁷ (Scheme 117). The *N*-H aziridines **458** were

Scheme 117. Formal Cycloaddition of *N*-H Vinylaziridines with Dimethyl Acetylenedicarboxylate



prepared by Wittig-type reaction of the corresponding *N*-H aziridine aldehyde dimers. The reaction with DMAD proceeded via nucleophilic attack of the aziridine nitrogen onto the alkyne carbon of DMAD, followed by aza-Claisen-type rearrangement (Scheme 89) of the intermediate to an azepine. Electrocyclization of the zwitterionic intermediates **461** through the boatlike transition state **462** was suggested to account for the observed stereochemistry, which was supported by DFT calculations.

8. CONCLUSION

Vinylaziridines and ethynylaziridines are versatile intermediates for the construction of many different kinds of compounds containing a nitrogen atom. A number of new and useful methodologies for the synthesis of these compounds including asymmetric reactions have been developed, which will further improve the synthetic utility of vinyl- and ethynylaziridines. The strained aziridine ring at the reactive allylic/propargylic position provides efficient levels of reactivity toward a range of transformations, including stereoselective nucleophilic ring-opening reactions, as well as rearrangement and cycloaddition reactions to yield a variety of nitrogen-containing molecules. Given the increasing levels of interest in nitrogen heterocycles,

as well as amine-containing compounds from organic and medicinal chemistry, vinyl- and ethynylaziridines will become increasingly useful and important compound classes that will continue to fascinate organic chemists. Development of new efficient methods for asymmetric syntheses of vinyl- and ethynylaziridines, as well as pioneering of their unknown reactivities, will offer further opportunities for the expansion of their synthetic utility. I look forward to the contributions that will be disclosed in the near future.

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Notes

The authors declare no competing financial interest.

Biography



Hiroaki Ohno was born in 1973 and grew up in Kushiro, Hokkaido, Japan. He graduated with a B.Sc. in Pharmaceutical Sciences from Kyoto University in 1996. Following his doctoral work at the same university (1996–1999; as a Japan Society for the Promotion of Science [JSPS] Research Fellow during 1999) under the direction of Professor Toshiro Ibuka, he joined the research group of Professor Tetsuaki Tanaka at Osaka University as a Research Associate in 1999. He received his Ph.D. from Kyoto University (2002) and the Pharmaceutical Society of Japan Award for Young Scientists (2005). He began his work as an Associate Professor at Kyoto University (Professor Nobutaka Fujii's research group) in 2005. Quite recently, he received the Banyu Chemist Award (BCA) 2013. His research interests include the development of transition-metal-catalyzed cascade reactions, as well as the synthesis of biologically active compounds and their application to drug discovery.

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ABBREVIATIONS

Dpp	diphenylphosphinyl
DMAD	dimethyl acetylenedicarboxylate
DPPA	diphenylphosphoryl azide
NMM	<i>N</i> -methylmorpholine
PTSA	<i>p</i> -toluenesulfonic acid
Py	pyridine

SES	2-(trimethylsilyl)ethanesulfonyl
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilylate

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