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# Ring Expansions of Vinyloxiranes, -thiiranes, and -aziridines: Synthetic Approaches, Challenges, and Catalytic Success Stories

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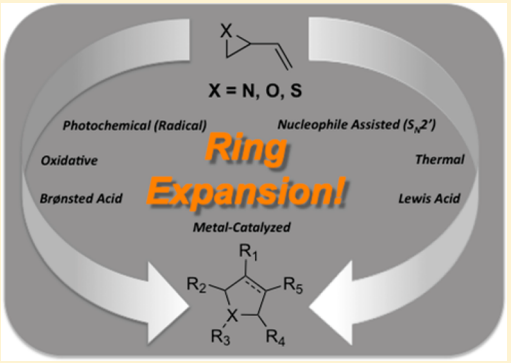
**ABSTRACT:** Ring expansion reactions of strained vinylic heterocyclic substrates have attracted the attention of the synthetic community for decades. Strategic manipulations of these organic architectures enable access to many useful synthetic intermediates. This paper highlights various methods for the ring expansion of vinyloxiranes, -thiiranes, and -aziridines described in the literature from 1964 to 2013.




Vinyl substituted oxiranes, thiiranes, and aziridines are intriguing classes of heterocyclic compounds that have widespread efficacy. The strained nature and conjugation to an olefin provide opportunities for application in both curious and effective ways using the vast arsenal of organic chemistry activation modes. This paper discusses strategies for the ring expansion of vinyloxiranes, -thiiranes, and -aziridines disclosed over the last 50 years. We chose to focus on the diversity of ring-expansion methods, at the expense of highlighting each individually. Our presentation is divided into seven parts, each based on the activating approach (reaction conditions) used to facilitate the ring expansion; and categorized as follows: (1) thermal, (2) photochemical (radical), (3) Brønsted acid, (4) Lewis acid, (5) metal-catalyzed, (6) nucleophile assisted ($S_N2'$), and (7) oxidative.

## THERMAL RING EXPANSIONS

The majority of early ring-expansion methods were focused on thermal behavior. Stogryn and Brois reported that a *cis*-divinyloxirane and a *cis*-divinylaziridine could be thermally ring expanded to afford 4,5-dihydrooxepine[1] and 1-ethyl-4,5-dihydro-1*H*-azepine,[2] respectively, in high yields (Scheme 1a). Stogryn noted that upon exposure to thermal/basic conditions, the corresponding *trans*-divinylaziridine was unreactive. It was revealed that the *cis*-thiirane analogue behaved differently when thermolyzed, generating three major products, one being acyclic.[3] Competing desulfurization and radical pathways were proposed as the reason for this divergence.

Vogel demonstrated that a *trans*-divinyloxirane required twice the thermal input as compared to a *cis*-divinyloxirane in order to ring expand (Scheme 1b).[4] The ring expansion generated two products, with 2-vinyl-2,3-dihydrofuran as the major. This product suggested that the reaction was proceeding via an oxonium ylide intermediate. Paladini determined that vinyloxirane substrates containing a phenyl group in the 1-position could be ring expanded in excellent yields to 2,3-dihydrofuran products at high temperatures.[5] Hudlicky established the significance of carefully controlling the temperature when performing flash vacuum pyrolysis (FVP) vinyloxirane ring-expansion reactions.[6] For example, one vinyloxirane was converted to either a 4,5-dihydrooxepine (lower temperature) or 2,3-dihydrofuran (higher temperature) product. Hudlicky[7] and Pearson[8] both distinctively designed one-pot FVP procedures for forming and ring expanding vinylaziridines from azido-tethered diene precursors. The intermediate vinylaziridine produced a mixture of three compounds, with the undesirable imine elimination product in higher yield than the expected [3.3.0]azabicyclic ring-expansion product.

Explorations of thermal vinylaziridine ring expansions exposed that the nature of the nitrogen substituent was critical for reaction success. Rees[9] and Lwowski[10] reported that the thermolysis of *N*-substituted vinylaziridines at high temperatures yielded 3-pyrroline products (Scheme 2a). Heine[11] demonstrated that a *p*-nitrobenzyl carbamate substituted aziridine afforded a 2-pyrroline product, presumably proceeding through an ylide intermediate. Heine also disclosed that alternate acyl groups (benzoyl[12] and thiourea[12]) resulted in strain-assisted aza-Claisen rearrangements to form seven-membered ring products. Scheiner[13] and Stogryn[14] independently revealed that *N*-aryl- and *N*-vinyl-substituted aziridines both underwent a thermal Claisen rearrangement to form azepine structures. Aziridine *N*-groups like 1-(3,4-dihydro-4-oxoquinazolin-3-yl)[15] result in ring-opened acyclic products.

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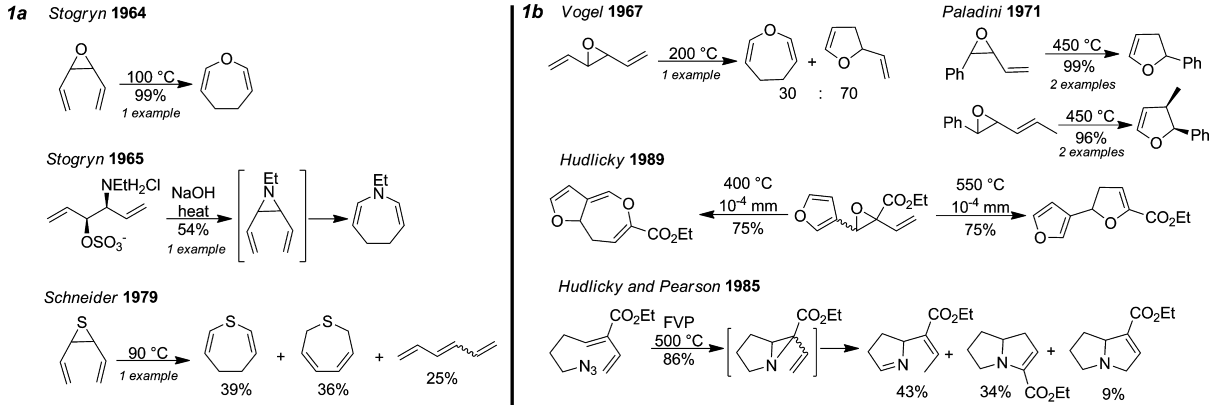
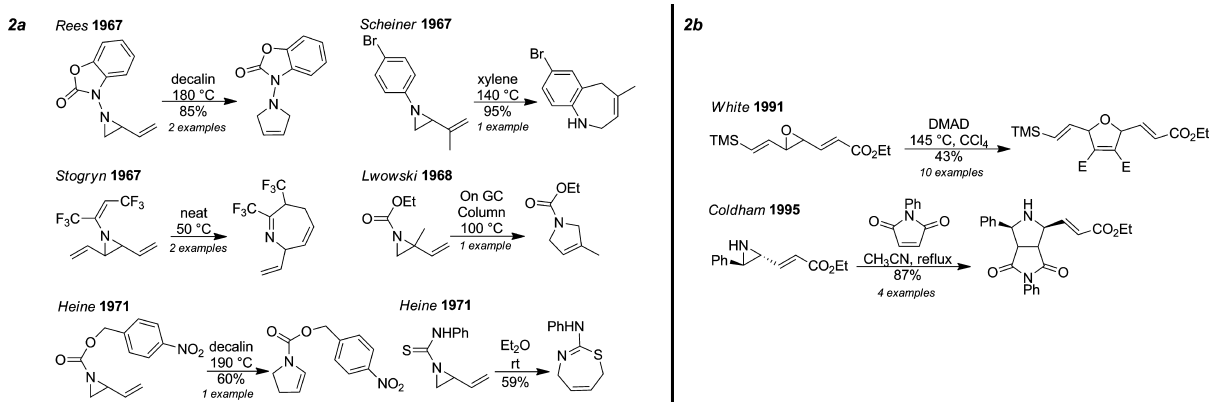
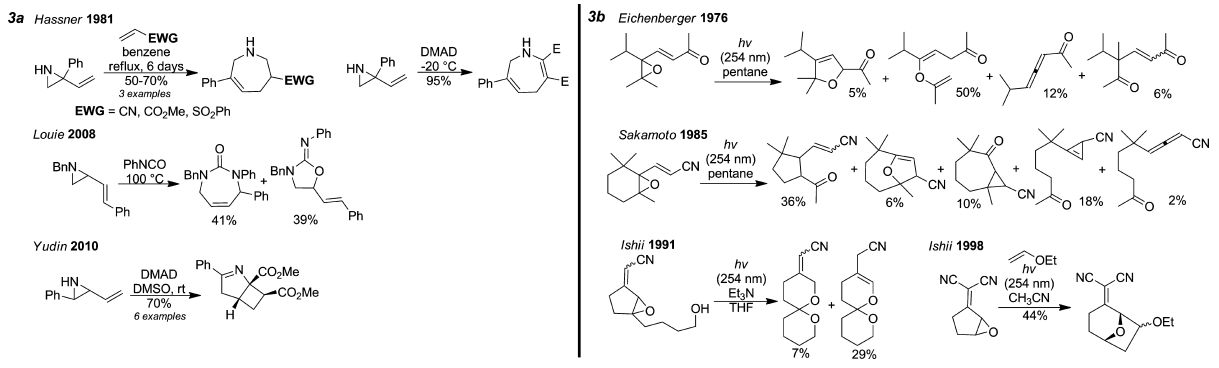
**Scheme 1. (a) Thermal Ring Expansions of *cis*-Divinyloxiranes, -aziridines, and -thiiranes. (b) Pyrolysis of Vinyloxiranes and *N*-Alkyl-Substituted Vinylaziridines**




**Scheme 2. (a) Thermal Ring Expansions of Vinylaziridines: Impact of Nitrogen Substituent. (b) Interrupted Oxonium and Ammonium Ylides**




**Scheme 3. (a) Alkylative Ring Expansions of Vinylaziridines. (b) Photochemically Mediated Ring-Opening of a Special Class of Vinyloxiranes**




Ylide intermediates involved in the ring expansions of *trans*-divinyloxiranes can be intercepted using suitable electrophiles (Scheme 2b). White[16] discovered that dimethyl acetylenedicarboxylate (DMAD) can serve this role, diverting the reaction pathway from yielding oxepines and 2,3-dihydrofuran to afford 2,5-divinyl-substituted 2,5-dihydrofuran products. Coldham[17] showed an analogous reaction wherein *N*-phenylmaleimide acts as the interrupting olefin component to cleanly deliver the desired *endo* cycloadduct.

Vinylaziridines provide additional ring-expansion opportunities. Hassner[18] established that *N*-H vinylaziridines react with enoates to facilitate in situ hetero-Michael additions followed by a ring expansion to azepines. Yudin[19] revisited this approach using a different N−H vinylaziridine substrate. Although the cascade proceeded as Hassner's, it further progressed to generate the cyclobutane-fused 1-pyrroline product shown (Scheme 3a). Louie[20] revealed that benzyl-protected vinylaziridines can be heated in the presence of isocyanates to form five- and seven-membered ring products.

## ■ PHOTOCHEMICAL (RADICAL) RING EXPANSIONS

There are very few reports of the ring expansions of vinyloxiranes, -thiiranes, and -aziridines involving radicals. Photochemical studies (Scheme 3b) have focused on a very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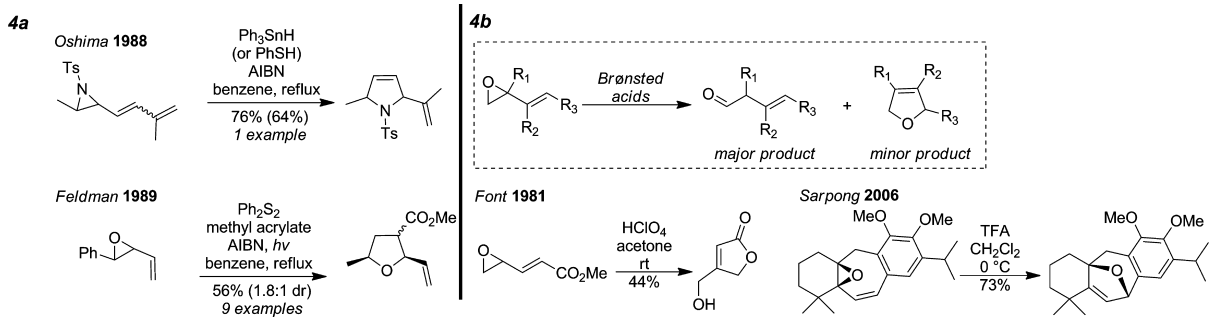
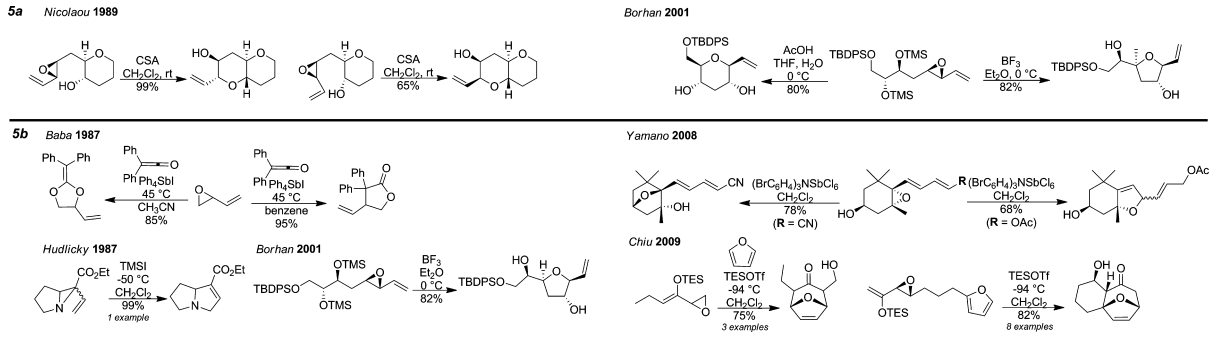
**Scheme 4. (a) Trialkyltin Radical Mediated Ring-Opening of Vinyloxiranes and -aziridines. (b) Vinyloxirane Ring Expansion Challenges and Special Cases**




**Scheme 5. (a) Ring Expansion via Intramolecular Acid Assisted Vinyloxirane Ring Opening. (b) Lewis Acid-Mediated Ring Expansions of Vinyloxiranes and -aziridines**[a]




[a]Key: TES = triethylsilyl; TBDPS = *tert*-butyldiphenylsilyl.

specific class of vinyloxirane substrates containing a tetrasubstituted oxirane and a conjugated olefin. Eichenberger[21] confirmed that such substrates could be ring expanded to afford 2,5-dihydrofuran products, albeit in very poor yield. Sakamoto[22] verified that conjugated nitriles behaved differently than the enones reported by Eichenberger. In that study, ring-expanded and ring-contracted compounds were formed, including both cyclopropane and cyclopropene products. Ishii used the conclusions gained from previous experiments to develop intra- and intermolecular methods for capturing reactive intermediates. It was determined that spiroketals[23] could be accessed using a substrate with an alcohol tether, while in another report the intermediate oxonium ylide could be captured with electron-rich olefins.[24]

Oshima[25] and Feldman[26] explored radical ring-expansion approaches wherein a trialkyltin or phenylthio radical adds in a reversible fashion to the olefin terminus of a vinyl oxirane or an aziridine (Scheme 4a). In the context of this mechanistic framework, Oshima proved that a diene-substituted sulfonylated aziridine could be converted to a 3-pyrroline. Feldman determined that the intermediate radical could be intercepted by acceptors, such as methyl acrylate, to form tetrahydrofuran products by using a substituted (1-aryl) class of vinyloxirane as substrates.

## BRONSTED ACID MEDIATED RING EXPANSIONS

In the majority of cases, when vinyloxiranes are treated with Brønsted acids, the intermediate allylic cation undergoes a hydride shift to form $\beta,\gamma$-unsaturated carbonyl products (Scheme 4b). For the group of compounds wherein a hydride shift pathway is not accessible, or is conformationally less attractive (endocyclic epoxides), 2,5-dihydrofurans are usually the major products. Sarpong and co-workers showcased this outcome in their total synthesis of salviasperanol.[27] Alternatively, as demonstrated by Font's[28] butenolide-forming reaction, the intermediate allyl cation can be captured by a neighboring nucleophile.

A significant Brønsted acid catalyzed ring expansion application involves alcohol tethered vinyl oxirane substrates (Scheme 5a). Nicolaou[29] showed that pyran-tethered vinyloxiranes favor 6-*endo* cyclization. The stereochemistry of the new 2,6-tetrahydropyran can be controlled by using either *cis*- or *trans*-vinyloxirane precursors. Later, Borhan[30] disclosed that acyclic vinyloxiranes containing trimethylsilyl-protected diols can be cyclized 6-*endo* by utilizing a Brønsted acid and 5-*exo* by employing a Lewis acid.

## LEWIS ACID MEDIATED RING EXPANSIONS

Lewis acids have been explored for ring expansions (Scheme 5b). Baba[31] reported examples of inserting a ketene into a vinyloxirane using the Lewis acid, $Ph_4SbI$. The reaction could be diverted to a different pathway simply by switching the solvent from benzene to acetonitrile. Hudlicky[32] employed trimethylsilyl iodide to form a 3-pyrroline while Borhan used boron trifluoride to access substituted tetrahydrofuran products. Yamano's recent total synthesis[33] disclosed that exposure of a class of divinyloxiranes to the Lewis acid, tris(4-bromophenyl)aminium hexachloroantimonate, enables the formation of the desired products through a different ring expansion pathway. Perhaps the most efficacious reactions in this category are inter- and intramolecular [4 + 3] cycloaddition reactions developed by Chiu.[34] An electron-rich vinyloxirane is reacted with triethylsilyl triflate and trapped by furan to generate oxatropane products in high yields. Chiu[35] has shown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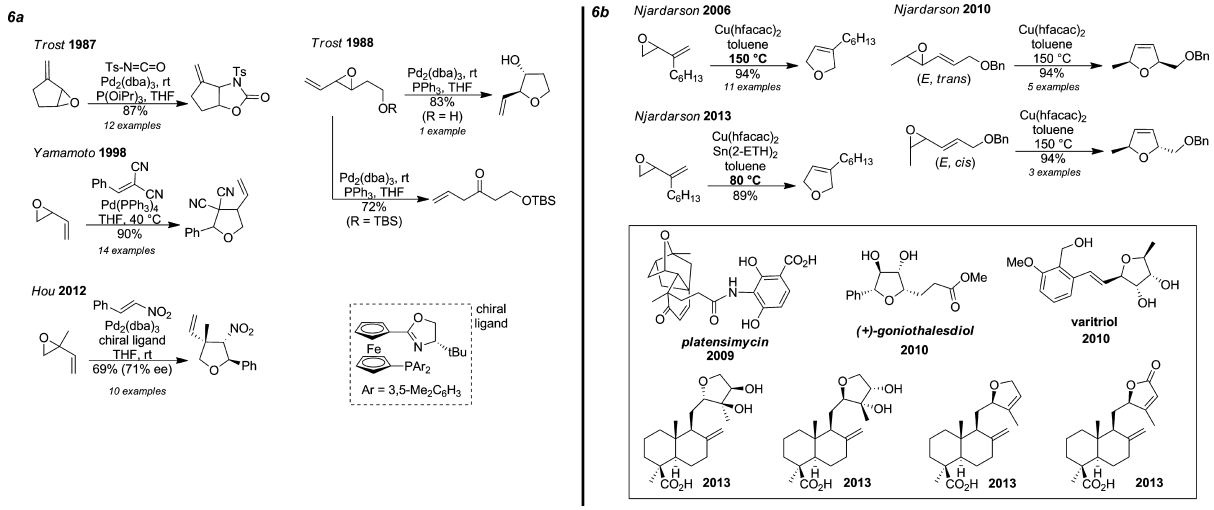
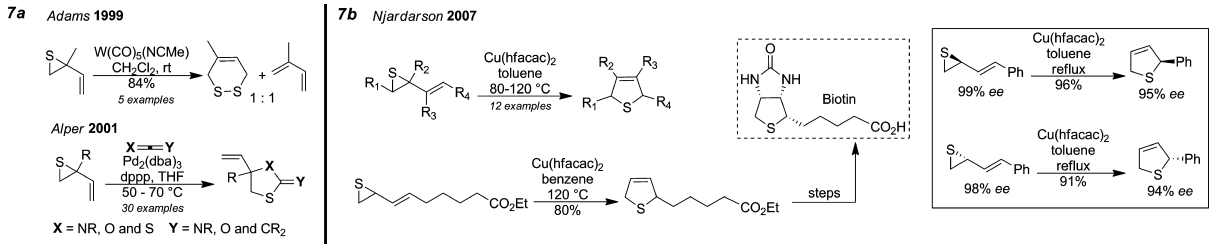
**Scheme 6. (a) Palladium-Catalyzed Vinyloxirane Ring Expansions. (b) Copper-Catalyzed Vinyloxirane Ring Expansions[a]**




[a]Key: dba = *trans*-dibenzylidineacetone; 2-ETH = 2-ethyl hexanoate; hfacac = hexafluoroacetylacetonate.

**Scheme 7. (a) Palladium- and Molybdenum-Catalyzed Vinylthiirane Ring Expansions. (b) Copper-Catalyzed Vinylthiirane Ring Expansion[a]**




[a]Key: dppp = 1,3-bis(diphenylphosphino)propane.

that chiral vinyloxiranes can be transformed into chiral oxatropanes using similar reaction conditions.

## METAL-CATALYZED RING EXPANSIONS

Palladium is commonly explored for metal-catalyzed expansions (Scheme 6a). Trost has utilized vinyl oxiranes as reaction partners; therefore, the reactions of vinyloxiranes using palladium catalysis have also been investigated. It was shown that isocyanates readily insert into vinyloxiranes with the guidance of palladium to form 2-oxazilidone products.[36] In another report,[37] a vinyloxirane tethered to a free alcohol could be cyclized to a tetrahydrofuran, while the same substrate underwent a hydride shift using a protected alcohol as the starting material. Yamamoto[38] revealed that tetrahydrofurans could be accessed by inserting conjugated vinyl nitriles intermolecularly into oxiranes. Hou[39] elaborated on this catalytic insertion approach to an asymmetrical variant by using nitrovinyl insertion partners.

Our group[40,41] unveiled the first broadly applicable catalytic ring expansion of vinyloxiranes to 2,5-dihydrofuran using a cheap and stable copper(II) catalyst, $Cu(hfacac)_2$ (Scheme 6b). The scope for this new chemistry is expedient, as the reactions could be run in the absence of solvent. The main drawback was the use of elevated temperature (150 °C). Later, we favorably uncovered that this reaction was stereoselective.[42] In addition to greatly expanding the blueprint of opportunities for the reaction, this pioneering development also provided a key mechanistic insight. Detailed investigations involving a vital collaboration with the Cheong group determined that $Cu(hfacac)_2$ is a *pre*catalyst, which is transformed into a copper(I) catalyst that is responsible for the chemistry.[43] We confirmed that by adding robust and cheap single electron additives, specifically, ($Sn(2\text{-ethyl hexanoate})_2$ = $Sn(2\text{-ETH})_2$), the reaction can be performed at significantly lower temperatures (80 °C for a typical substrate). This innovative catalytic method was applied to the concise total syntheses of platensimycin,[44] varitriol,[45] goniothalesdiol, and a family of labdane[46] diterpenoids.

Vinylthiiranes are the most challenging of the three strained heterocycles to ring expand due to the ease of desulfurization. Adams and Alper individually reported two distinct metal-catalyzed ring expansions (Scheme 7a). Adams[47] found that the tungsten catalyst, $W(CO)_5(NCMe)$, could convert vinylthiiranes into an equimolar mixture of a dihydrodithiin and a conjugated diene. The catalyst initially coordinates to the sulfur atom of a vinylthiirane, which is then attacked by another vinylthiirane, followed by disulfide formation and accompanying desulfurization.[48] Alper[49] demonstrated that heterocumulenes could be inserted into thiiranes by means of a palladium catalyst. Yields of this regioselective reaction are high, and variable heterocumulenes are competent reaction partners.

We also discovered a vinylthiirane ring-expansion reaction that provides direct access to 2,5-dihydrothiophenes (Scheme 7b).[50] The same catalyst, $Cu(hfacac)_2$, proved to be optimal for the ring expansion of vinyl oxiranes, with less thermal assistance. The catalytic method has wide scope and was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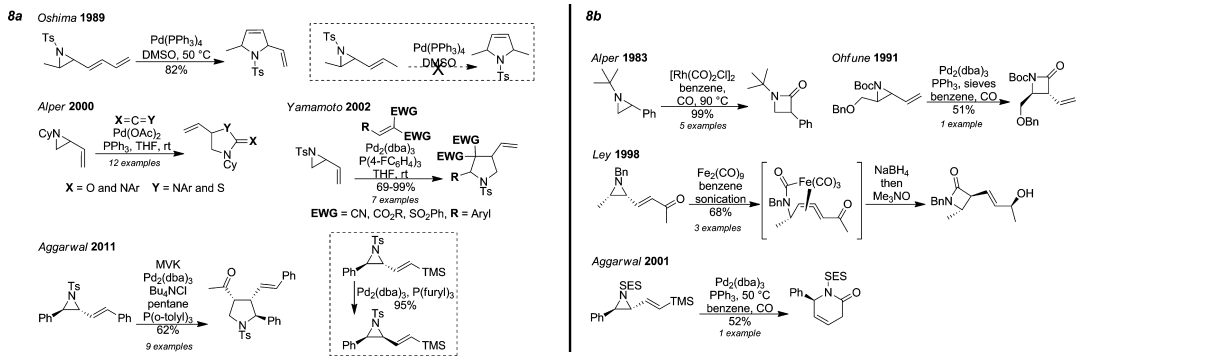
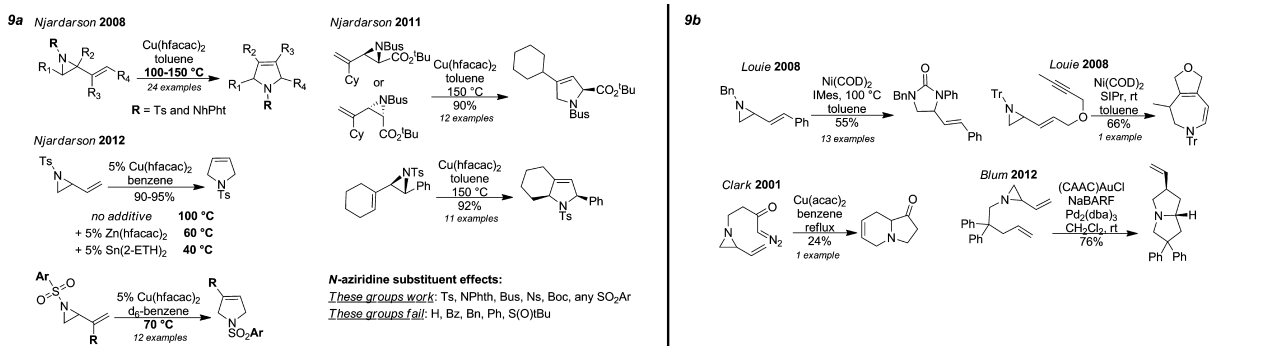
**Scheme 8. (a) Palladium-Catalyzed Vinylaziridine Ring Expansions; (b) Metal-Catalyzed Carbonylative Ring Expansions of Vinylaziridines[a]**




[a]Key: MVK = methyl vinyl ketone; SES = 2-trimethylsilylethanesulfonyl.

**Scheme 9. (a) Copper-Catalyzed Vinylaziridine Ring Expansion. (b) Metal-Catalyzed Vinylaziridine Ring Expansions[a]**




[a]Key: BARF = tetrakis(pentafluorophenyl)borate; CAAC = cyclic(alkyl)(amino)carbene; COD = 1,5-cyclooctadiene; CSA = camphorsulfonic acid; IMes = 1,3-dimesitylimidazol-2-ylidene; SIPr = *N*,*N*′-bis(2,6-diisopropylphenyl)dihydroimidazol-2-ylidene.

showcased in applications to the formal syntheses of both biotin and Plavix. Moreover, we were excited to determine that similar to its strained oxygen relative, vinyl thiiranes also ring expand stereoselectively.

Vinylaziridines have been ring expanded using a range of palladium-catalyzed reactions (Scheme 8a). Oshima[51] showed that diene-substituted aziridines could be converted to 3-pyrroline products using a Pd(0) catalyst. The *N*-tosyl group and the diene moiety were essential to the success of this rearrangement, as the nondienic vinylaziridines produced a complex mixture of products. Alper[52] found that certain *N*-alkyl-substituted vinylaziridines react with heterocumulenes to form vinyl-substituted heterocyclic products. Yamamoto[53] enacted an alternative insertion strategy, wherein electron-poor olefins served as the insertion partners and the nitrogen aziridine was protected as a sulfonamide. Aggarwal[54] pursued an approach using enones and 1,4-substituted vinylaziridines. One of the intermediates formed using this process was advanced in a few steps to kainic acid. Notably, the sulfonamide-protected *trans*-vinylaziridine will isomerize to the more stable *cis*-vinylaziridine without an insertion partner present.

Alper determined that heterocumulenes could be inserted into the heterocycles under discussion, which is why it is appropriate that he would attempt direct carbonylations. This report indicated that styrenylaziridine substituted with large *N*-alkyl groups could be catalytically ring expanded to $\beta$-lactams using a rhodium catalyst (Scheme 8b).[55] Ohfune[56] described the catalytic carbonylation of a Boc-protected vinylaziridine. Carbonylation proceeded exclusively at the allylic C−N bond without any scrambling or involvement of the allylic olefin. Somfai[57] later confirmed this observation. Although not catalytic, Ley[58] divulged an iron-mediated carbonylation of alkyl-protected vinylaziridines. As opposed to originating from carbon monoxide gas, the CO equivalent used for this transformation originates from the iron complex itself ($Fe_2(CO)_9$). Aggarwal showed that the olefin of a SES-protected 1,4-substituted vinylaziridine could facilitate a catalytic carbonylation reaction that affords a six-membered lactam, which is particularly interesting when compared to the work of Ohfune.[59]

Our vinyloxirane and -thiirane studies were extended to vinylaziridines (Scheme 9a). We disclosed that a range of sulfonamide- and phthalimide-protected vinylaziridines could be ring expanded in high yields using catalytic $Cu(hfacac)_2$.[60] Unlike Oshima's palladium-catalyzed ring expansions, which are limited to diene-substituted aziridines, we demonstrated that our method is forgiving of substitution patterns and the electronics of the olefin. The vinylaziridine ring expansion is stereospecific,[61] and many other aziridine *N*-R groups are compatible. We also revealed that the chiral aziridine starting materials could be assembled on scale using either Ellman- or Aggarwal-type chiral auxiliaries. Mechanistic studies concluded that several key factors impact the rate of this catalytic reaction.[62] The reaction is significantly accelerated by using an electron-poor sulfonamide (nosyl instead of tosyl) and modestly accelerated when electron-rich olefins are employed, compared to electron-poor olefins. Moreover, a $M(hfacac)_2$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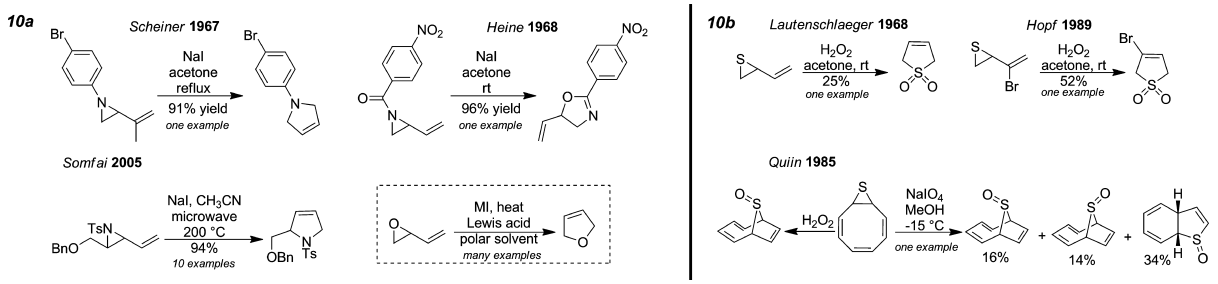
**Scheme 10. (a) Iodide-Mediated Vinyloxirane- and -aziridine-Mediated Ring Expansions. (b) Oxidative Ring Expansions of Vinylthiiranes**




additive can accelerate the reaction, with $Zn(hfacac)_2$ providing optimal results. This suggests that the reaction was proceeding through an in situ formed copper(I) species and confirmed following the observance of rate acceleration and disappearance of an induction period in our kinetic curves upon the addition of single electron-reducing agents. The proposed copper(I)-(hfacac) that was independently synthesized (or purchased) also produced the same outcomes. These mechanistic revelations resulted in the use of milder reaction conditions (lower temperature), and the cheap single electron additive enabled this transformation to be performed on larger scales.

There is a renewed curiosity with nickel and gold catalysis using strained motifs. Louie imparted many nickel-based contributions, including inter- or intramolecular insertions into *N*-alkylvinylaziridine substrates (Scheme 9b). It was demonstrated that phenyl isocyanate[63] could be inserted using nickel catalysts in the presence of *N*-heterocyclic carbene ligands and that vinylaziridine-tethered alkynes[64] could be used to capture and cyclize the intermediate nickel metallocycle. Clark[65] reported that a copper-tethered carbene could be converted into a spiroaziridine intermediate that undergoes a [2,3]-sigmatropic rearrangement to form a fused product. Blum[66] used *N*-tethered vinylaziridines as substrates for ring expansion that could be trapped with unactivated olefins by utilizing a dual gold–palladium catalyst mixture.

## NUCLEOPHILE-ASSISTED ($S_N2'$) RING EXPANSIONS

An early strategy for ring expanding vinyloxiranes and -aziridines employed iodide (Scheme 19). This process relies on a reversible $S_N2'$-like process, wherein any intermediate *Z*-olefin product cyclizes to form a 2,5-dihydropyrrolidine or -dihydrofuran, while the *E*-olefin product reverts back to the starting material. The starting materials could be converted to the five-membered ring products in good yields by continuously running the reaction. Such reactions are sensitive to steric constraints and rarely succeed when the olefin terminus is substituted. Scheiner[13] converted *N*-aryl-substituted vinylaziridines to 3-pyrrolines, as opposed to the ring-expansion products from the Claisen rearrangement, using this approach (Scheme 10a). Heine[12] determined that the aziridine protecting group can interfere with this reaction when acylated vinylaziridines were treated with sodium iodide and formed a heterocycle originating from the attack of the acyl group onto the allylic iodide intermediate. Somfai[67] revisited this method for *N*-sulfonylated substrates using microwave heating. Vinyloxiranes have also been investigated. Studies by commodity chemical companies toward an alternate approach to make tetrahydrofuran exposed that it was essential to employ an iodide source with a large counterion and that an accompanying Lewis acid was imperative for achieving high yields.

## OXIDATIVE RING EXPANSIONS

Oxidations of vinylthiiranes have produced unique results. Lautenschlaeger[68] detected that a peroxide oxidation of vinylthiirane afforded 2,5-dihydrothiophene 1,1-dioxide in 25% yield (Scheme 10b). Hopf[69] confirmed this observation for 3-bromovinylthiirane. Quin[70] reported that cyclooctatetraene mono-episulfide provided different oxidized ring-expansion products when treated with hydrogen peroxide or sodium periodate.

In this paper, we surveyed the vibrant field of ring expansions of strained vinylic heterocycles. The presented approaches have found ubiquitous use in both the synthesis of natural products and in the development of methodologies. Ring-expansion reactions of strained substrates offer opportunities for the expansion of synthetic utility, including additional asymmetric and catalytic variants and further practicality enhancement of existing methods. Based on the groundwork laid within this area of research, we look forward to the contributions that will be disclosed.

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### Notes

The authors declare no competing financial interest.

### Biographies

Professor Njardarson received his Ph.D. at Yale University in 2001 with Professor John L. Wood. Following postdoctoral training with Professor Samuel J. Danishefsky at The Memorial Sloan-Kettering Cancer Center he started his independent career in 2004 at Cornell


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## ■ ACKNOWLEDGMENTS

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