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Inter- and intramolecular reactions of epoxides and aziridines with π-nucleophiles

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Contents

1. Introduction

The synthesis and reactions of epoxides and aziridines has been regularly reviewed.[1–6] The most typical reaction of both heterocyclic systems is the ring-opening reaction in which a nucleophile opens the C–X bond of the heterocycle. There are of course a number of carbon nucleophiles that have been used in these ring-opening reactions, ranging from cyanide to Grignard reagents, organolithium reagents or organocuprates. An additional carbon nucleophile that has been used for ring-opening of aziridines and epoxides is the broad class of π-nucleophiles. π-Nucleophiles are neutral ambident nucleophiles, which add an additional level of reactivity, control, and convenience to the overall reaction. The reaction of epoxides and aziridines with π-nucleophiles, arenes, olefins, allylsilanes, is a valuable method for the synthesis of a variety of heteroatom containing molecules. The purpose of this

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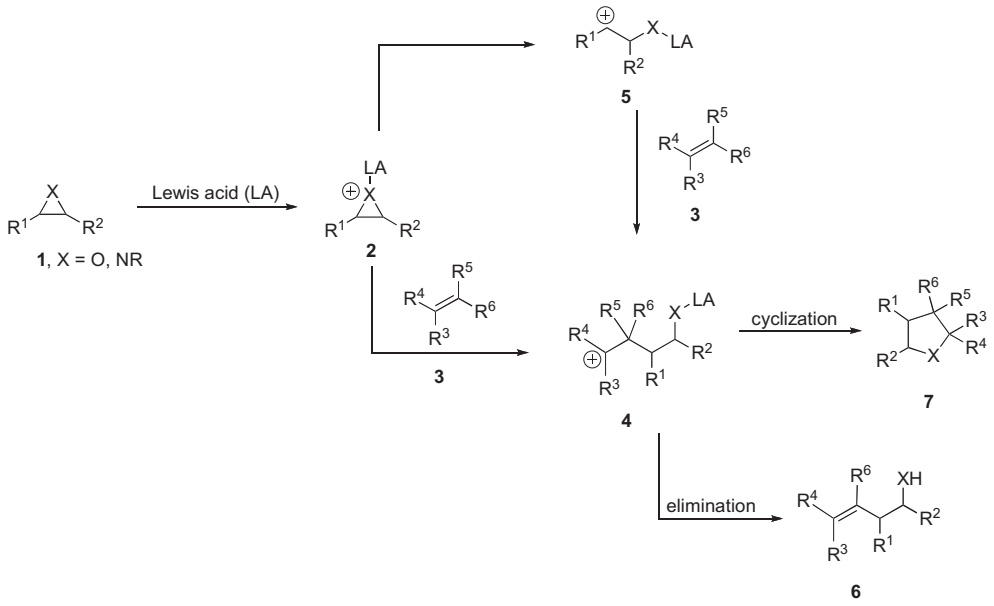
review is to bring together the various type of π-nucleophiles that have been used in the reaction with aziridines and epoxides. We will examine the chemo-, regio-, and stereoselectivity of their inter- and intramolecular reactions with aziridines and epoxides.

As outlined in Scheme 1, the reaction of a carbon–carbon π-bond with an epoxide or aziridine under Lewis acid catalyzed conditions will provide intermediate **4**. While only one possible regioisomeric product is shown here, three additional regioisomeric products can be formed (either carbon of the heterocycle can be attacked and either carbon of the π-nucleophile can form the new C–C bond). The control of which product is formed is a key aspect to the utility of this method. The initial adduct will then typically undergo one of two processes, cyclization leading to a larger heterocyclic ring, such as **7** or elimination (e.g., when R^5=H) leading to a homoallylic alcohol or amine **6**. Control over which of these two processes predominates is a key aspect to the utility of this reaction. We will discuss structural and reaction determinants that control the regiochemistry of the initial addition as well as the subsequent cyclization/elimination pathways.



Scheme 1.

Mechanistically, two general paths have been reported (Scheme 1). The reaction is initiated by coordination of the three-membered heterocycle **1** with an acid (usually a Lewis acid). The mechanistic pathway can diverge here depending upon the substitution on the heterocycle. The heterocycle **2** can directly react with the π-nucleophile to provide intermediate **4** via an S_N2 like reaction path. Alternatively, the heterocycle can open in an S_N1 like reaction path and then react with the π-nucleophile **3** to provide intermediate **4**. Substitution on the heterocycle will obviously have a large impact on the reaction pathway. Intermediate **4** will then undergo an elimination to provide olefin **6** or a cyclization to provide heterocycle **7**.

In addition to the general intermolecular pathway outlined in Scheme 1, the intramolecular reactions of π-nucleophiles with epoxides and aziridines present interesting problems in stereoelectronic control and useful methods for the synthesis of carbo- and heterocyclic ring systems. A useful method for both determining, which cyclization are allowed, as well as providing a descriptive name is the use of Baldwin's rules for ring closure. The most well-known of the Baldwin's rules are predicated on a freely rotatable nucleophile (e.g., alcohol, thiol etc.) attached to an sp^3 hybridized carbon.[7,8] This treatment does not take into account the lack of freedom to rotate of the nucleophile in the π-nucleophile addition to an epoxide or aziridine ring. A subsequent publication by Baldwin and Lusch proposed a new set of cyclization rules and nomenclature for the reactions of enolates with carbonyls.[9] As reported by Baldwin, direct comparisons to the original rules cannot be guaranteed. For example, a 6-(*enol-endo*)-*exo-trig* cyclization is favored where as the 5-(*enol-endo*)-*exo-trig* is disfavored. In the original rules both a 6- and 5-*exo-trig* cyclization are favored. We plan to use a variation of this nomenclature as outlined in Figure 1. Equation A shows an example of a n-(π-*exo*)-*exo*-aziridine/epoxide cyclization. This name indicates that the π-nucleophile is *exo* with respect to the newly formed ring while the three-membered ring (in typical Baldwin's rules fashion) is *exo*. Three other modes of ring closure are possible; a n-(π-*exo*)-*endo*-aziridine/epoxide

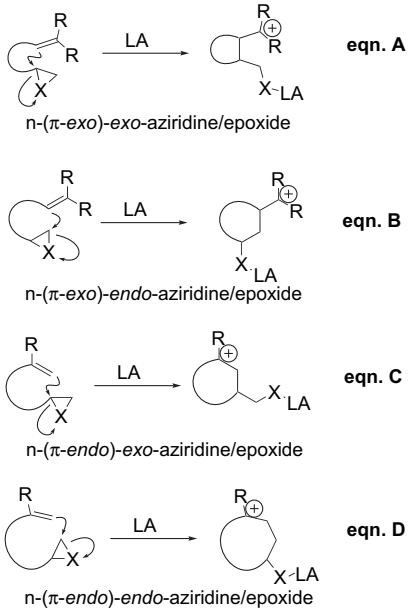


Figure 1.

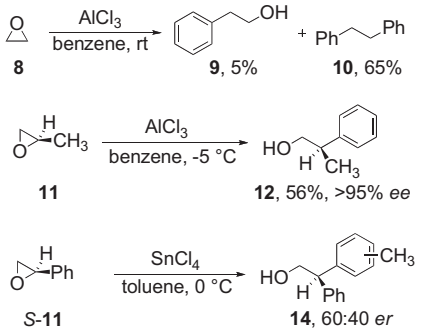
(Equation B), a n-(π-*endo*)-*exo*-aziridine/epoxide (Equation C), and a n-(π-*endo*)-*endo*-aziridine (Equation D).

2. Reactions of epoxides and aziridines with arenes

The reactions of epoxides and aziridines with arenes typically follow the elimination pathway (Scheme 1) that leads to products, such as **6**. A very limited number of examples undergo a subsequent cyclization (formation of **7**), which results in a loss of aromaticity.

2.1. Intermolecular reactions of arenes with epoxides

The first example of the reaction of an arene with an epoxide was reported in 1931. A reaction between benzene (and derivatives) with ethylene or propylene oxide provided a very low yield of the epoxide ring-opened product **9**, along with 65% of **10** (Scheme 2).[10] The major product **10** is formed from a second arylation of the product **9**.[11] Further studies provided similar products and yields.[12]

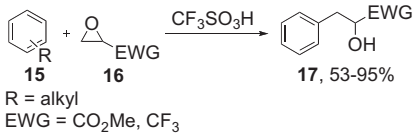


Scheme 2.

The reaction of (+)-propylene oxide with benzene provided **12** with high levels of inversion.[13–17] Mechanistically this reaction appears to proceed via an S_N2 type process. In contrast to this S_N2 process the reaction of styrene oxide with toluene provides the product **14** as a 60:40 mixture of enantiomers indicating a more S_N1 type mechanism.[18] As will be noted in later examples, this lack of enantioselectivity is often a consequence of reaction conditions.

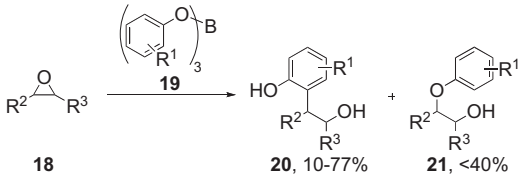
Competition experiments between benzene and toluene showed that the reaction with toluene is faster by a factor of ~3. The regioselectivity on the aromatic ring is poor with *ortho*-, *para*-, and *meta*-substituted products obtained in an approximately 1:1:1 ratio.[18–20] An enantioselective synthesis of the natural product galaxolide has been reported using the reaction of enantiopure propylene oxide and a substituted benzene ring as the key step.[21]

The reaction under superacidic conditions was used for the reaction with electron withdrawing substituted epoxides (Scheme 3).[22,23] These conditions are of special value for the reaction with glycidate (EWG=CO_2Me), as the carboxyl group renders this molecule unstable under the usual Friedel–Crafts conditions. As with other intermolecular reactions, substitution on the π-nucleophile generally provides a mixture of regioisomers.



Scheme 3.

A useful approach to control the regiochemistry of the intermolecular reaction has been the development of arylborates as the nucleophile. The Lewis acid thus contains the π-nucleophile and directs the attack from the position *ortho* to the borate (Scheme 4).[24–26] With only a single product **20**, this method is able to provide higher yields. The only problem is an O-alkylation side reaction, which cannot be completely suppressed.

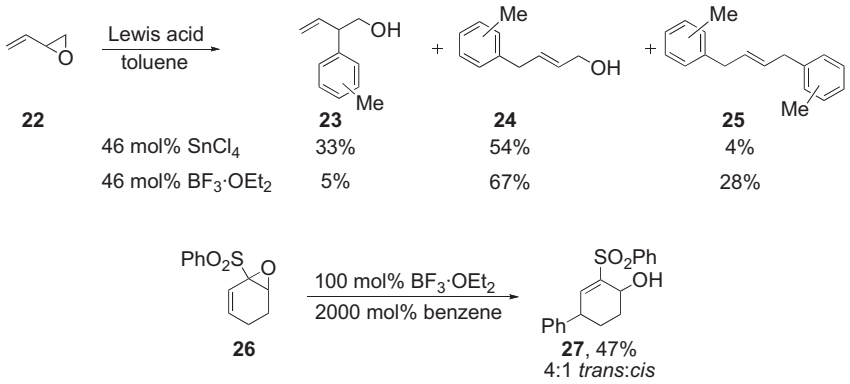


Scheme 4.

The reaction of vinylic epoxides with arenes has been reported only rarely. An initial report investigating the reaction of butadiene monoepoxide with toluene provided a mixture of both the S_N2' addition product **24** as well as the typical epoxide opening product **23**.[20] Regardless of the Lewis acid used, the S_N2' addition is the major product. None of the product resulting from nucleophilic attack at the less substituted end of the epoxide is observed. As one might expect, the inclusion of electron withdrawing substitution on the epoxide provides exclusively the conjugate addition product.[27] As shown in Scheme 5, treatment of epoxide **26** with a large excess of benzene provided the conjugate addition product in moderate yield as a 4:1 mixture of the *trans*/*cis* product **27**.

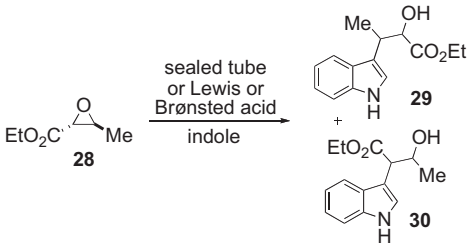
2.2. Intermolecular reactions of heteroaromatic rings with epoxides

Heteroaromatic (π-excessive) rings, such as indole, pyrrole, furan, and thiophene readily react with epoxides, often under milder



Scheme 5.

conditions than the corresponding benzene rings. Of these indole is probably the most widely studied. The first epoxide opening with a heteroaromatic compound was reported in 1963 and described the formation of α- and β-indolmycenic acid esters **29** and **30** (Scheme 6).[28] Several reaction conditions were examined for the reaction of indole with epoxide **28**. Initial reactions employing simply heat (sealed tube, 260 °C) provided a mixture of **29** and **30**. The use of Brønsted acids (phenol or TFA) allowed the reaction to proceed at only 140 °C but again provided a mixture of both products. Use of $SnCl_4$ at −10 °C provided the ethyl ester of α-indolmycenic acid **29** in 18% yield. These conditions were later used for the synthesis of enantioenriched (+)-α-indolmycin through the reaction of (−)-**28** and indole. The reported $[\alpha]_D^{25}$ of synthetic **29** was +7.8 (*c* 2.0 M in MeOH) while the $[\alpha]_D^{25}$ of the naturally derived material was −10 (*c* 2.0 M in MeOH) indicating a large degree of inversion of configuration.[29]



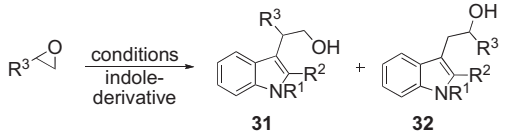
Scheme 6.

The reaction of indole and simple derivatives has been extensively studied with many examples of different reaction conditions being examined (Table 1).[30] As an example of the higher reactivity of indole simply mixing indole and styrene oxide provides **31** in 13% yield (entry 1). Mixing the two reactants under high pressure (10 kbar) provides a good yield of the ring-opened product (entry 2). The addition of 1 equiv of water to the reaction increases the yield further (entry 3). The introduction of electron donating substituents on the aromatic ring of styrene oxide again provides a substantial increasing yield presumably through activation of the epoxide toward ring-opening (entry 6). The introduction of a methyl group on the nitrogen of the indole ring substantially decreases its nucleophilicity and decreases the yield to 13% (entry 4). Similarly, the additional steric bulk introduced via a 2-methyl substituent leads to a moderate decrease in yield (entry 5). As an example of the decrease reactivity of alkyl epoxides, phenoxy glycidal requires an increase in temperature and time and still only provides the product in 16% yield (entry 7).[31]

In addition to the results outlined in Table 1, a host of Lewis acids including $InCl_3$,[32] $RuCl_3 \cdot H_2O$,[33] $Bi(OTf)_3$,[34] $LiClO_4$,[35–37] Cp_2ZrCl_2,[38] [bmim][OTf],[39] HBF_4/SiO_2,[40] CF_3CH_2OH,[41] urea-based catalyst,[42] a polymer supported In-cat.,[43] nanocrystalline TiO_2,[44] $SbCl_3$/Montmorilonite K-10[45] or sulfated zirconia[46] have been examined and provide good to excellent yields of the expected products as a single regioisomers. Aliphatic epoxides (e.g., phenyl glycidyl ether) have also been examined using these catalysts and as is the case for simple arenes, the site of ring-opening is the less hindered epoxide carbon to provide **29**.[31–34,36,37,46–48] While the regiochemistry can sometimes be variable the yields are typically good. For example, the reaction of indole with phenyl glycidyl ether under $InCl_3$ catalysis, provides product **32**/**31** in a ratio of 85:15 in 82% yield (entry 8).[32] The use of $RuCl_3$ under solvent free conditions provides a 52% yield of a single regioisomer.[33]

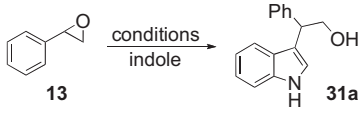
The ring-opening reactions of enantiopure epoxides typically provides products resulting from largely an S_N2 type attack (Table 2). As has been previously noted, high pressure catalyzed the ring-opening reaction providing the product **31** with 92% ee. SiO_2 also provided reasonable enantioselectivity leading to **31** with 88% ee. The ring-opening reaction catalyzed by $InBr_3$ provides an interesting example of how minor changes in reaction conditions can alter the enantioselectivity of a reaction. The use of 1 mol % of $InBr_3$ provides **31** with 99% ee, while increasing the amount of $InBr_3$ decreases the enantioselectivity.[49] The low catalyst load was necessary to suppress a partial S_N1 reaction, which negatively affected the ee-value. Other catalysts, which have been examined include Amberlyst-In[43] and trifluoroethanol.[41]

Table 1
Intermolecular reactions of indoles with epoxides



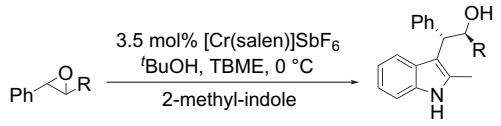
Entry	R^1	R^2	R^3	Conditions	Product	Yield (%)
1	H	H	Ph	CH_3CN, rt, 24 h	**31**	13
2	H	H	Ph	CH_3CN, 10 kbar, 42 °C, 24 h	**31**	58
3	H	H	Ph	CH_3CN, 10 kbar, 1 equiv H_2O, 42 °C, 24 h	**31**	66
4	Me	H	Ph	CH_3CN, 10 kbar, 42 °C, 24 h	**31**	13
5	H	Me	Ph	CH_3CN, 10 kbar, 42 °C, 24 h	**31**	44
6	H	H	4-(OMe)C_6H_4	CH_3CN, 10 kbar, 42 °C, 24 h	**31**	90
7[31]	H	H	$PhOCH_2$	CH_3CN, 10 kbar, 65 °C, 3 d	**32**	16
8[32]	H	H	$PhOCH_2$	10 mol % $InCl_3$, CH_2Cl_2, rt, 3.5 h	**32**:**31**, (85:15)	82
9[33]	H	H	$^nC_4H_9OCH_2$	5 mol % $RuCl_3 \cdot xH_2O$, TFA, neat, rt, 6 h	**32**	52

Table 2
Enantioselectivity in the reaction of indole with epoxides



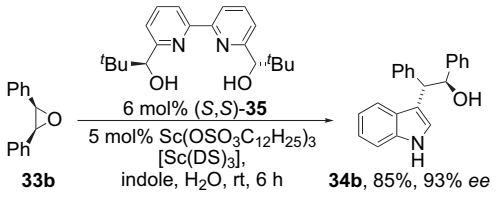
Entry	Conditions	Yield (%)	ee (%)
1[31]	CH_3CN, 10 kbar	56	92
2[31]	SiO_2	88	88
3[49]	CH_2Cl_2, 1 mol % $InBr_3$, rt, 12 h	70	99
4[43]	Wet Et_2O, 20 mol % Amberlyst-In, rt, 24 h	54	90
5[41]	CF_3CH_2OH, 80 °C, 4 h	67	>99

Several examples of kinetic resolution or enantioselective processes have been reported. As shown in Scheme 7, the reaction of 2-methyl indole with racemic styrene derivative with a Cr(salen) catalyst has been used in a kinetic resolution process (Scheme 7).[50] The reaction of styrene oxide (R=H) provided the ring-opened product with only 56% ee. The introduction of substitution on the terminus of the epoxide dramatically enhanced the enantioselectivity. Typical ee values were ~90% with all chemical yields >80%. This is a unique kinetic resolution process for epoxides.



Scheme 7.

The desymmetrization of *meso*-epoxides has been realized as shown in Scheme 8.[51,52] The ring-opening of stilbene oxide with indole was catalyzed by $Sc(DS)_3$ and the chiral ligand **35** in water (Scheme 8). Unfortunately, this is a rather limited reaction as even moderate derivatization of stilbene leads to lower enantioselectivity. For example, the reaction of the *p*-bromo derivative of **33b** proceeded in only 70% ee.



Scheme 8.

A number of natural products and compounds with interesting biological activity have been prepared via an epoxide opening with indole or an indole derivative (Fig. 2). In these cases the catalysts are typically classic Lewis acids. Diolmycin A1[53] and A2,[47,54] kurasoin B,[55–58] tryptophan analogs **38**,[59] (+)-milnamide A,[60] indoline spiroaminal framework **36** of neoxaline and oxaline,[61] and hymenialdisine analogs **37**.[62]

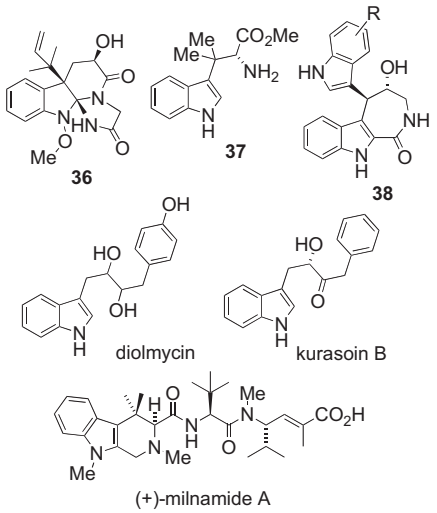
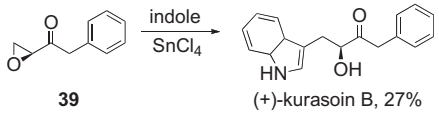


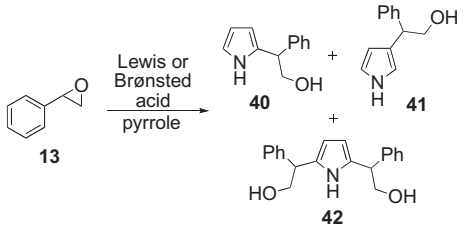
Figure 2.

As an example, the synthesis of the protein farnesyltransferase inhibitor (+)-kurasoin B was completed via the reaction of indole with enantiopure epoxide **39** (Scheme 9). The addition of excess indole (200 mol %) to **39** at 0 °C provided the natural product in 27% yield.



Scheme 9.

Pyrroles are less commonly used for epoxide openings. The reasons for this include the weak nucleophilicity of pyrrole compared with indole; the lability of the pyrrole ring, especially after the introduction of alkyl groups; as well as providing a mixture of 2-, 3-, and 2,5-substituted products. Due to their weak nucleophilicity, relatively reactive aryl substituted epoxides are the common reaction partners with pyrrole (Scheme 10). The first reaction of this kind was published in 1996 and employs high pressure and silica gel as reaction promoters.[31] Under these conditions, a mixture of all three products **40**–**42** was obtained. In order to form exclusively the product of the 3-alkylation, the introduction of additional methyl groups in 2,5-position of the pyrrole is necessary.[31,41]

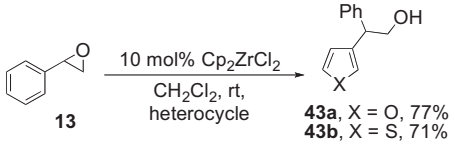


Scheme 10.

The utilization of different catalysts and solvent systems has a major influence on the outcome of the reaction. Successful transformations occurred under catalysis by a number of Lewis acids including $LiClO_4$,[35] $Bi(OTf)_3$,[34] HBF_4/SiO_2,[40] sulfated zirconia,[46] and $InBr_3$.[63] In addition ionic liquids ([bmim][OTf][39]) and the Brønsted acid trifluoroethanol[41] have also been used for this process. In general, the 2-substituted product **40** is the major product with varying amounts of **41** and **42** being formed. Two examples stand out of the reactions of pyrrole with styrene oxide. The first is the use of $SbCl_3$ on Montmorilonite K-10, which provides the 2-substituted product **40** in 88% yield with none of **41** being observed.[45] Most of the other methods provide a mixture of the 2- and 3-substituted products. A second method of interest is the use of Cp_2ZrCl_2 as a catalyst, which exclusively provides the 3-substituted product **41** in 84% yield.[38] This is in marked contrast to all of the other methods, which provide primarily the 2-substituted products.

Another method, which provides useful results is the catalyst $InBr_3$.[63] The reaction of pyrrole with styrene oxide provides **40** and **41** in good yields (75% and 15%). These yields and product ratios are typical of most other reaction conditions. The reaction with phenyl glycidyl ether derivatives and aliphatic epoxides gave good yields resulting from epoxide ring-opening at the less substituted carbon. As with styrene oxide, a mixture (7:1) of 2- to 3-substituted pyrrole products was obtained. An epoxide ring-opening with pyrrole has been used in the synthesis of an analog of **38** (Fig. 2).[62]

Furans and thiophenes are not as commonly used in epoxide ring-opening reactions as indoles or pyrroles. Nonetheless, these aromatic heterocycles do participate in the reaction with generally good yields. For example, styrene oxide readily reacts with either thiophene or furan upon catalysis with Cp_2ZrCl_2 to provide **43** in good yields (Scheme 11).[38,64]



Scheme 11.

The reactions of epoxides with other heterocycles, such as imidazole, pyrazole, and 7-azaindole all result in an N-alkylation product.[33]

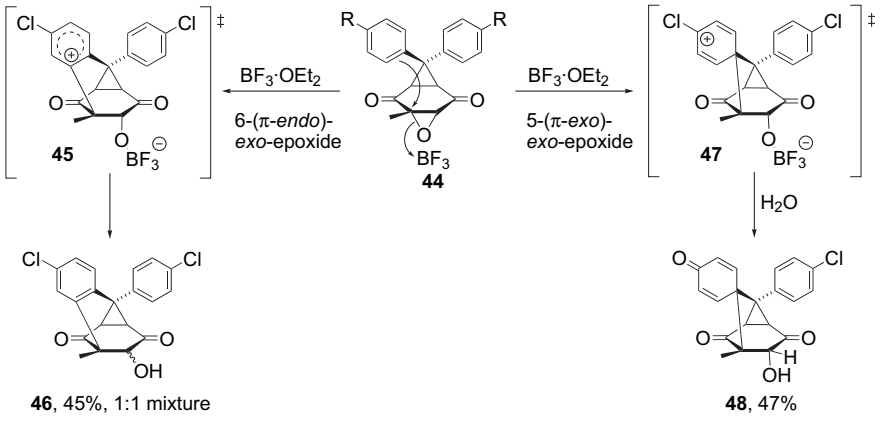
2.3. Intramolecular reactions of arenes with epoxides

A review of the intramolecular cyclization of arenes with epoxides has been published.[65] Intramolecular reactions between epoxides

and aromatic rings are generally limited to π-*endo* cyclizations as π-*exo* cyclizations either destroy the aromaticity or produce an aryl bridged ring system. Only one example for a 5-(π-*exo*)-*endo*-*epoxide* cyclization is known as shown in Scheme 12. The treatment of **44** with $BF_3 \cdot Et_2O$ leads to a transannular cyclization to form tricyclic diketo alcohols **46** and **48**.[66,67] When the substitution on the aromatic ring is H or Me, only the 6-(π-*endo*)-*exo*-epoxide cyclization occurs.[68] In addition, a related cyclization of an arene with an epoxide has been reported to initially proceed via a 5-(π-*exo*)-*endo*-epoxide cyclization which with rearranges to a product, which is formally the product of a 6-(π-*endo*)-*endo* cyclization.[69]

Several reports have shown that the reaction is stereospecific with complete inversion of configuration as would be expected in an S_N2 type reaction pathway (entries 4–6). In contrast, the *cis*-epoxide **49** (entry 7) provides similar yields of product but lower diastereoselectivity, indicating a significant level of the S_N1 type mechanism. Tertiary epoxides will also undergo the expected cyclization albeit in poor yield (entry 8).

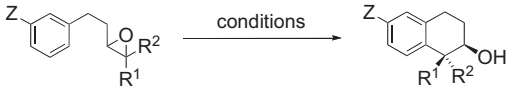
In addition to the catalysts noted in Table 3, Brønsted acids (HFIP, H_2SO_4)[77,78] have been successfully used. Other Lewis acids include $EtAlCl_2$,[79] $TiCl_4$,[79] $FeBr_3/Ag(OTf)_2$,[80] $AuCl_3/3Ag(OTf)_2$,[81,82] and $FeBr_3$.[81,82]



Scheme 12.

With a 2-atom link between an aromatic ring and an epoxide either a 5-(π-*endo*)-*exo*-epoxide cyclization or a 6-(π-*endo*)-*endo*-epoxide cyclization can take place. No examples of the 5-(π-*endo*)-*exo*-epoxide cyclization have been reported. All such systems provide only the product of a 6-(π-*endo*)-*endo*-epoxide cyclization. In 1964 the first intramolecular Friedel–Crafts reaction with epoxides observed occurred during the treatment of **49** with TFA (Table 3). The 6-(π-*endo*)-*endo* product **50** was isolated in only trace amounts (entry 1).[70]

Table 3
Intramolecular reactions of arenes with epoxides

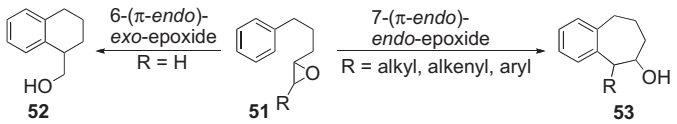


Entry	R^1	R^2	Z	Conditions	Yield (%)
1[70]	H	H	H	TFA	Trace
2[71]	H	H	H	H-mordenite	87
3[72]	H	H	OMe	$SnCl_4$	30[a]
4[73]	H	Me	H	$SnCl_4$	66
5[74]	H	Ph	H	$BF_3 \cdot OEt_2$	45
6[75]	H	$CHCH_2$	H	$BF_3 \cdot OEt_2$, TMS-N_3	52
7[73]	Me	H	H	$SnCl_4$	63
8[76]	Me	Me	H	$SnCl_4$	29

[a] A 71:29 mixture of the two possible regioisomeric products (*p*-OMe/*o*-OMe) was obtained.

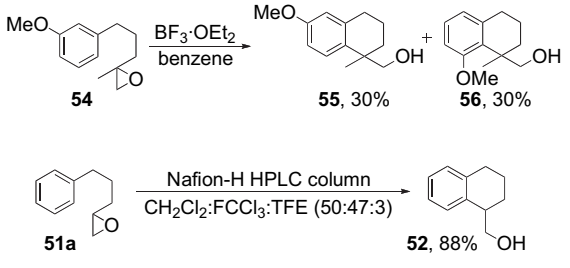
Since then a number of studies on epoxide substitution, arene substitution, and acid catalyst have been reported. Changing the acid from TFA to the zeolite H-mordenite dramatically improves the yields of the simple reaction substrate **50** (entry 2).[71] Substitution on the arene typically provides a regioisomeric mixture of products as observed in entry 3. In this case a 71:29 mixture of the *para* (**50**)/*ortho* products are obtained in moderate yield.[72]

With the introduction of one more carbon atom into the tether linking the arene with the epoxides, two cyclizations are possible, a 6-(π-*endo*)-*exo*-epoxide cyclization and a 7(-π-*endo*)-*endo*-epoxide cyclization (Scheme 13). Both ring closures are known, the 6-(π-*endo*)-*exo* attack occurs mainly on monosubstituted epoxides, whereas the 7-(π-*endo*)-*endo* attack takes place exclusively with 1,2-disubstituted epoxides.



Scheme 13.

The first 6-(π-*endo*)-*exo* cyclization was reported in 1972, when epoxide **54** was treated with $BF_3 \cdot OEt_2$ to give a 1:1 mixture of the two regioisomeric 6-(π-*endo*)-*exo*-epoxide products (Scheme 14).[83] An interesting example of the 6-(π-*endo*)-*exo*-epoxide cyclization is the on-column conversion of **51a** to **52**.[84,85] A Nafion-H HPLC column was prepared and **51a** was eluted with $CH_2Cl_2/FCCl_3$/TFE to provide **52** in 88% yield. Solvent mixtures lacking the TFE yielded

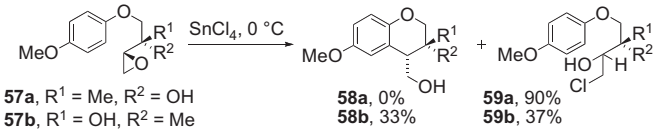


72,73,76

Scheme 14.

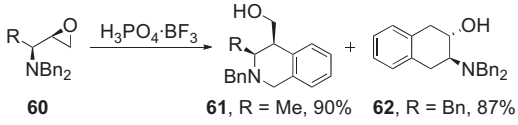
the product in only 69%. It is worth noting that the conversion of **51a** to **52** using $SnCl_4$ also provides a yield of 85%. [72,73,76]

An interesting example of a cyclization, which is controlled by conformation is shown in Scheme 15.[86] Treatment of diastereomeric hydroxy epoxides provides two different product mixtures depending upon the stereoisomer. Isomer **57a** provides exclusively the chlorohydrin **59a** in excellent yield. In contrast, **57b** provides a 1:1 mixture of the 6-(π-*endo*)-*exo*-epoxide cyclization product **58b** and the chlorohydrin **59b**. It is believed that the Sn-complex between the epoxide and alcohol of stereoisomer **57b** orients the epoxide for nucleophilic attack while the similar complex of isomer **57a** shifts the epoxide orientation such that overlap with the aromatic ring will not lead to ring-opening. A similar process has been observed in the intramolecular reaction of an epoxide with an allylsilane.[87]



Scheme 15.

An interesting example of selectivity has recently been reported in terms of the preference for a 6-(π-*endo*)-*exo*-epoxide relative to a 6-(π-*exo*)-*endo*-epoxide cyclization (Scheme 16).[88] Treatment of the *N*,*N*-dibenzyl aminoepoxide **60** with $H_3PO_4 \cdot BF_3$ provides the 6-(π-*endo*)-*exo*-epoxide product **61** in excellent yields. However when R=benzyl the 6-(π-*endo*)-*endo*-epoxide product **62** is the only product obtained.



Scheme 16.

A number of other examples for the 6-(π-*endo*)-*exo*-epoxide cyclization have been widely used for the synthesis of natural products and biologically active molecules. Examples (Fig. 3) include the synthesis of **63** and **64**,[89] (−)-pseudopertosin A,[90] 4-aminomethyl chroman **65**,[91] VLA-4 antagonist **66**,[92] diterpene **67**[93] and (−)-aphanorphine, and (+)-eptazocine.[94]

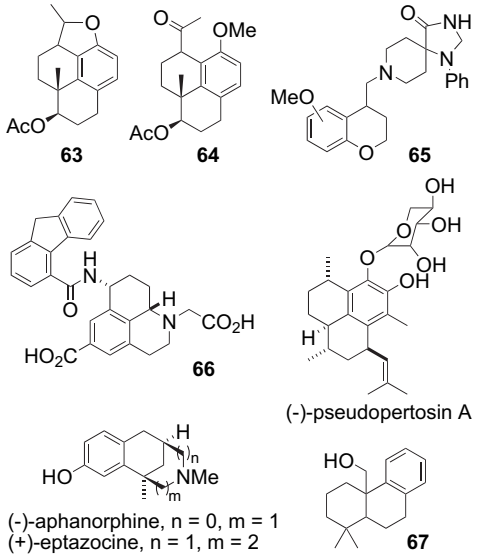
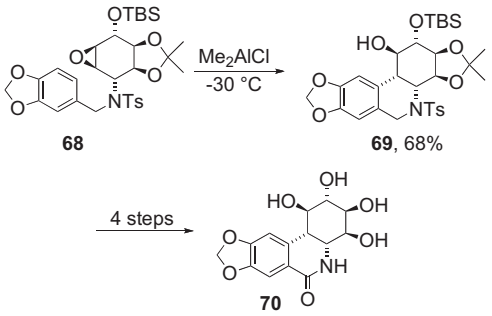


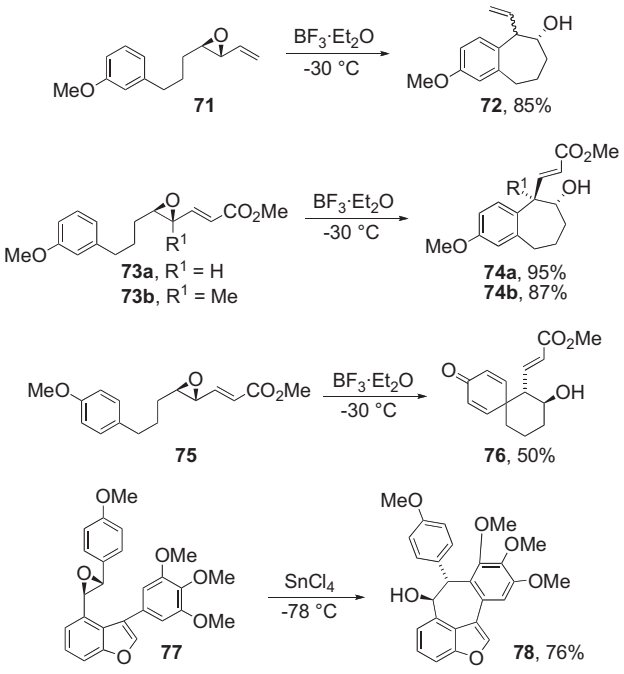
Figure 3.

This general strategy has been used several times for the synthesis of *Amaryllidaceae* alkaloids.[95–98] An interesting example is shown in Scheme 17. Treatment of epoxide **68** with Me_2AlCl provides the cyclized product **69** in 68% yield. This compound is converted to the *cis*-C10b epimer of 7-deoxypancratistatin **70**.[97]



Scheme 17.

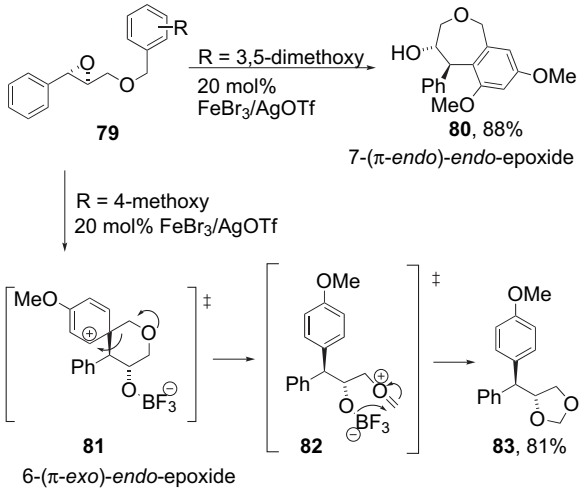
As mentioned previously, the 7-(π-*endo*)-*endo* attack only takes place if the corresponding epoxide is substituted on the terminal position as well. Substrates that undergo this type of cyclization usually bear olefinic or aromatic substituents on the terminal position of the epoxide (Scheme 18).[99] Substrate **71** readily undergoes cyclization to provide **72** as a mixture of diastereomers. This is attributed to a more S_N1 like reaction path due to the simple vinyl group on the epoxide. Changing the electronic nature of the double bond as in **73a** leads to an excellent yield of **74a** as a single diastereomer. Significantly, the fully substituted epoxide **73b** also undergoes the cyclization reaction to provide **74b** as a single diastereomer. Changing the position of the methoxy group on the aromatic in **75** leads to **76** via an *ipso* attack and a 6-(π-*exo*)-*endo*-epoxide cyclization.[100] A similar reaction with a substrate containing nitrogen in its carbon backbone is known to give the corresponding seven-membered product in good yields under



Scheme 18.

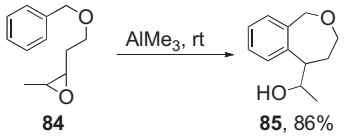
TMSOTf catalysis.[101] The highly substituted epoxide **77** undergoes the 7-(π-*endo*)-*endo*-epoxide cyclization to provide **78** in very good yield.[102] This molecule was a model system for the synthesis of maltibol A.

As noted in Scheme 18, substitution on the π-nucleophile can lead to alternate reaction products. Another example of this principle is outlined in Scheme 19.[73,80,103] The 3,5-dimethoxy derivative of **79** undergoes the expected 7-(π-*endo*)-*endo*-epoxide cyclization upon treatment with $FeBr_3$/AgOTf to provide **80** in excellent yield. A number of additional Lewis acids were examined, all of which provided similar yields. Like the 4-methoxy derivative **75** (Scheme 18), the 4-methoxy derivative of **79** does not provide the expected 7-(π-*endo*)-*endo*-epoxide cyclization, but rather underwent an initial 6-(π-*exo*)-*endo*-epoxide cyclization to yield intermediate **81**, which rearranged to acetal **83** in good yield. Unfortunately, no additional examples of this interesting cyclization were reported.



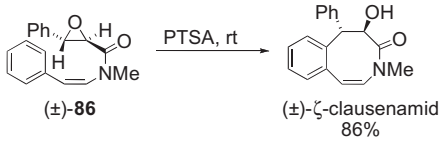
Scheme 19.

With a further extension of the carbon backbone, 7-(π-*endo*)-*exo*-epoxide, and 8-(π-*endo*)-*endo*-epoxide reactions become possible. The number of examples for these reactions is limited, but it appears that 8-(π-*endo*)-*exo*-epoxide cyclizations occur with aryl substituents on the epoxide and 7-(π-*endo*)-*exo*-epoxide cyclization occur when the epoxide has an aliphatic substituent. Only one example of a 7-(π-*endo*)-*exo*-epoxide cyclization has been reported to date. Treatment of epoxide **84** with $AlMe_3$ provided **85** in a surprisingly good yield of 86% (Scheme 20).[104]



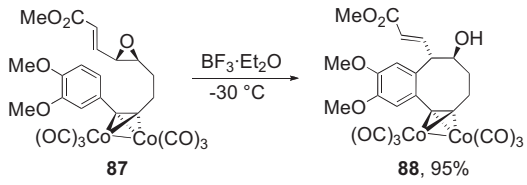
Scheme 20.

A limited number of examples of the 8-(π-*endo*)-*endo*-epoxide cyclization have been reported. Both of these examples utilized some type of conformational restriction on the tether linking the epoxide and arene to improve formation of this relatively unfavored ring closure. Epoxide **86** can undergo three different cyclizations. An 8-(π-*endo*)-*endo*-epoxide cyclization would occur in the reaction with the aromatic ring, a 6-(π-*endo*)-*endo*-epoxide cyclization, and a 5-(π-*exo*)-*endo*-epoxide cyclization would occur by reaction with the olefin. In an interesting example of selectivity, all three products can be selectively formed depending upon the reaction conditions. The 8-(π-*endo*)-*endo*-epoxide cyclization of (±)-**86** was catalyzed by PTSA in CH_3CN at room temperature. This provided a synthesis of ζ-clausenamid (Scheme 21).[105] The 5-(π-*exo*)-*endo*-epoxide cyclization product could be formed by reaction under aqueous conditions (acid or base) while the 6-(π-*endo*)-*endo*-epoxide cyclization product was formed by reaction with PTSA in refluxing CH_3CN.[106]



Scheme 21.

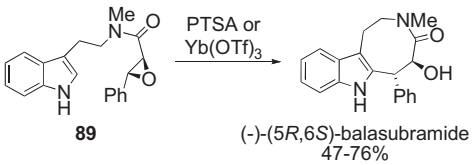
The reaction of the $Co_2(CO)_6$-complexed acetylene **87** was used in an 8-(π-*endo*)-*endo*-epoxide cyclization which provided **88**. This is attributed to the resonance effect of the vinyl group, which was able to stabilize the partial positive charge in the transition state (Scheme 22).[100] The introduction of an additional carbon atom in the backbone of **87**, did not provide any products from an attempted 9-(π-*endo*)-*endo*-epoxide cyclization.



Scheme 22.

2.4. Intramolecular reactions of heteroaromatic rings with epoxides

As with benzene rings, heteroaromatic rings also undergo intramolecular cyclizations with epoxides. The same limitations on this general reaction also apply to heteroaromatics in that the π-*endo* type of cyclization is the primary mode of reaction reported. In addition there are far fewer examples of these intramolecular cyclization reactions with heteroaromatics. The intramolecular reactions of indoles with epoxides have only been applied to the synthesis of the natural product balasubramide (Scheme 23).[105,107,108] This 8-(π-*endo*)-*endo*-epoxide cyclization takes place with either Lewis or Brønsted acid catalysis and results in the product in good yields with high enantioselectivities. As is common for cyclization reactions leading to larger ring sizes, the epoxide is substituted on the terminus with an aromatic ring.

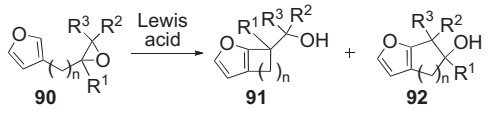


Scheme 23.

Two comprehensive reports on intramolecular cyclizations of furan and pyrrole with an epoxide were communicated in 1983. Studies aimed at determining optimal Lewis acids for the formation of a number of ring sizes were carried out. As shown in Table 4,[109] the first and only example of a 5-(π-*endo*)-*exo*-epoxide cyclization with an aromatic ring was reported using ZnI_2 as the catalyst (entry 1). While there have been other attempts to carry out a 5-(π-*endo*)-cyclization with an aromatic ring, none have provided the cyclized

product. In general only epoxide opening products are isolated. Other attempts to prepare the 5-(π-*endo*)-cyclizations using this system were unsuccessful, again providing products as the result of epoxide hydrolysis/elimination. The formation of six-membered rings via both 6-(π-*endo*)-*endo*-epoxide (entry 2) and 6-(π-*endo*)-*exo*-epoxide (entry 3) were successful using $Ti(O^iPr)_3Cl$. Both 7-(π-*endo*)-*endo*-epoxide (entry 4) and 7-(π-*endo*)-*exo*-epoxide (entry 5) cyclizations were also quite successful providing the cyclized products in 88% and 36% yields, respectively. This cyclization is likely made possible by the charge stabilization associated with the tertiary carbocation.

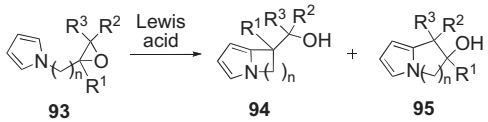
Table 4
Intramolecular reactions of furan with epoxides



Entry	R^1	R^2	R^3	*n*	Lewis acid	Product, yield (%)
1	H	H	H	2	ZnI_2	**91**, 25
2	H	Me	Me	2	$Ti(O^iPr)_3Cl$	**92**, 78
3	Me	H	H	3	$Ti(O^iPr)_3Cl$	**91**, 89
4	H	Me	Me	3	ZnI_2	**92**, 88
5	Me	H	H	4	$Ti(O^iPr)_3Cl$	**91**, 36

A similar set of investigations were made for pyrrole (Table 5).[110] When *n*=2 and R^1–R^3=H, only the *endo*-epoxide product **95** is formed (entry 1). The introduction of a methyl group at R^1 was made to attempt to stabilize positive charge and leads to an *exo*-epoxide ring-opening product. This strategy was unsuccessful and the *endo*-epoxide opening product **95** was still the only product obtained (entry 2). In an effort to sterically block the *endo*-epoxide ring-opening, methyl groups at R^2 and R^3 were introduced, which again still provided only the *endo*-epoxide ring-opening product **95** (entry 3). Clearly the formation of the six-membered ring is highly favored over the five-membered ring formation. Lengthening the tether between the pyrrole and epoxide while introducing a methyl group at R^1 now provides the epoxide-*exo* cyclization product (entry 4). Increasing the tether length allows for either a 6-(π-*endo*)-*exo*-epoxide, or a 7-(π-*endo*)-*endo*-epoxide cyclization to take place. The choice of Lewis acid can be used to control product distribution. The use of $Ti(O^iPr)_3Cl$ provides only the 6-(π-*endo*)-*exo*-epoxide cyclization product (entry 5) while $EtAlCl_2$ provides a 1:1.3 mixture of the 6-(π-*endo*)-*exo*-epoxide product (**94**) to 7-(π-*endo*)-*endo*-epoxide cyclization product (**95**).

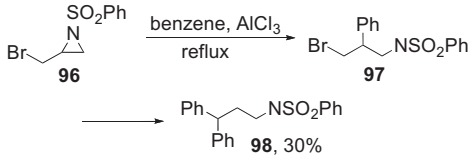
Table 5
Intramolecular reactions of pyrrole with epoxides



Entry	R^1	R^2	R^3	*n*	Lewis acid	Product, yield (%)
1	H	H	H	2	$BF_3{\cdot}Et_2O$, 1eq NEt_3	**95**, 70
2	Me	H	H	2	ZnI_2	**95**, 67
3	H	Me	Me	2	$BF_3{\cdot}Et_2O$, 1eq NEt_3	**95**, 91
4	Me	H	H	3	$EtAlCl_2$	**94**, 81
5	H	H	H	3	$Ti(O^iPr)_3Cl$	**94**, 64
6	H	H	H	3	$EtAlCl_2$	**94**, **37**; 95, 48
7	H	H	H	4	$Ti(O^iPr)_3Cl$	**94**, 85

2.5. Intermolecular reactions of arenes with aziridines

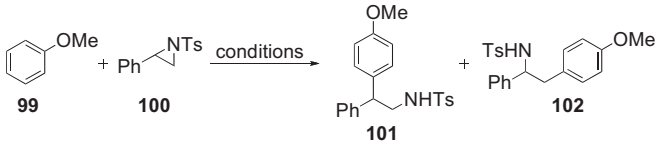
The first mechanistic studies of intermolecular Friedel–Crafts reactions were done in 1954 for the reaction of simple tosyl-protected aziridines with benzene, and were later further improved (Scheme 24).[111–113] As a result of these investigations, an S_N1 like transition state under Lewis acid catalysis was proposed. A number of side products are known (from amine elimination or rearrangement to oxazolines), which give further evidence for this mechanism.[114–116]



Scheme 24.

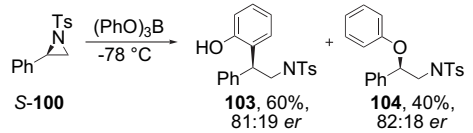
The reaction of phenyl aziridine **100** with electron rich arenes is a well-known reaction (Table 6).[117–120] A variety of Lewis acids is known to catalyze the reaction and provide **101** as the major product. A limitation of this reaction is that aliphatic aziridines are not sufficiently reactive and only electron rich arenes are sufficiently nucleophilic.

Table 6

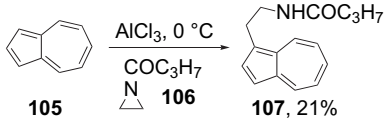


Entry	Conditions	Product, yield (%)
1[114]	10 mol % $In(OTf)_3$	**101**/**102** (95:5), 87
2[115]	2 mol % $AgPF_6$, 200 mol % 99	**101**, 80
3[116]	1 mol % AuCl, 3 mol % AgOTf	**101**, 80
4[117]	5 mol % $FeCl_3$	**101**, 77

A new and very interesting method, which was already studied for Friedel–Crafts reactions with epoxides, is the activation of the aziridine by an arylborate, which also contains the π-nucleophile (Scheme 25).[121,122] A mixture of O- and C-alkylation is observed, but the product is formed with retention of configuration.



Scheme 25.

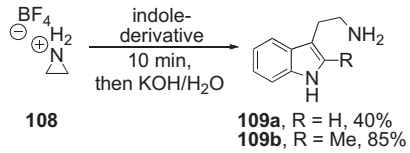


Scheme 26.

The aromatic ring azulene has been shown to undergo a reaction with 1-butanoylaziridine (**106**) upon $AlCl_3$-catalysis (Scheme 26).[123]

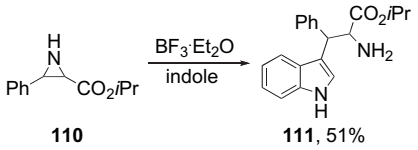
2.6. Intermolecular reactions of heteroaromatic rings with aziridines

The first known aziridine opening with indoles was accomplished in 1967 and describes the synthesis of tryptamine and 2-methyltryptamine from the reaction of indole with ethylene imine **108** (Scheme 27).[124] This reaction was a major breakthrough compared with the previous multistep methods required to make these compounds.



Scheme 27.

A similar reaction between indole and aziridine **110** was used to prepare the isopropyl ester of β-phenyltryptophan (Scheme 28).[125] This is a very unique ring-opening reaction of an aziridine in that no activating group is present on the aziridine ring nitrogen. This is a testament to the nucleophilicity of the indole ring and the reactivity of the aziridine **110**.

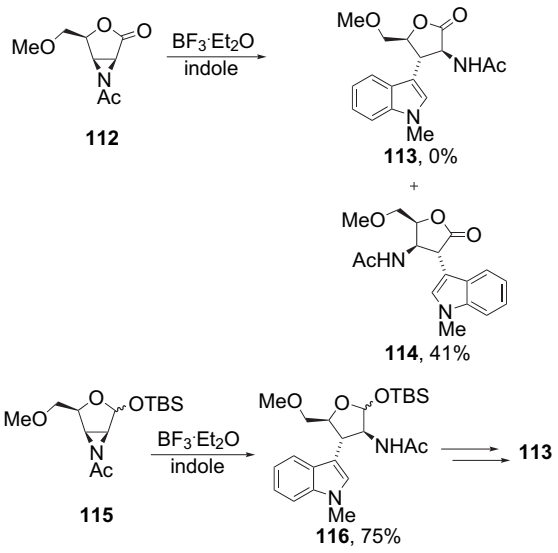


Scheme 28.

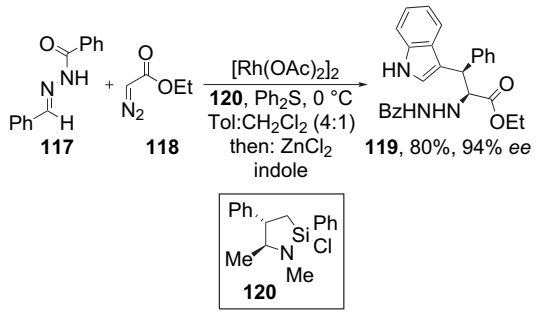
The main application of this method is indeed to obtain tryptophan analogs, such as **111**, which could then be utilized in the synthesis of small active peptides. In some cases, the product of attack on the aziridine carbon next to the ester group was observed, but only as a side product. With the right choice of Lewis acid, this side reaction can be suppressed almost completely. The nitrogen of the aziridines can be unprotected, or activated with acyl (e.g., acetate, Cbz), arylsulfonyl or aryl groups. The catalysts of choice are typically Lewis acids, such as $BF_3 \cdot OEt_2$,[126–128] $Zn(OTf)_2$,[129–131] $Sc(OTf)_3$,[132] $Sc(ClO_4)_3$,[133] and $InCl_3$.[134] Among the substitution possible for the indole, even derivatives with glycosyl moieties in 2-position are known to undergo aziridine openings to form glycosyl amino acids. This type of reaction is known to be catalyzed by $Sc(ClO_4)_3$.[135–137]

An interesting tryptophan analog has been prepared from aziridine-2-lactones such as **112** (Scheme 29).[138,139] Unlike non-fused-ring aziridines, **112** provides only **114** from attack on the carbon bearing the carboxyl group. The use of the lactol derivative **115** provides the product **116**, which can then be converted to the desired **113**.

An interesting approach to tryptophan analogs uses a one-pot aziridination/aziridine ring-opening method (Scheme 30).[140] The reaction of diazoester **118** with hydrazone **117** provides the expected aziridine in excellent enantioselectivity using rhodium acetate and the chiral catalyst **120**. The addition of indole and a Lewis acid provides the ring-opened product **119** in excellent yield and enantioselectivity.

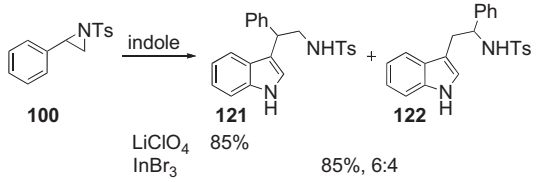


Scheme 29.



Scheme 30.

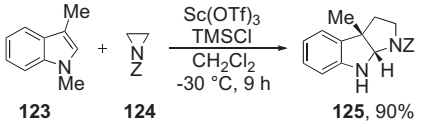
As with the reaction of tosyl protected, aryl substituted aziridines with simple arenes, reaction of these aziridines with indoles occurred at the more substituted position (Scheme 31).[35] The use of $InCl_3$ instead of $LiClO_4$ provided a 6:4 mixture of both the regioisomers **121** and **122**.[141] Fused-ring aliphatic aziridines, derived from cyclohexene and cyclopentene will also provide the ring-opened products upon reaction with indole under $LiClO_4$ catalysis.[141]



Scheme 31.

An interesting reaction has been shown to occur with 3-methylindole. With the methyl group at the normal site of nucleophilic attack, a rearomatization is not possible and therefore another ring closure to obtain **125** was observed (Scheme 32).[142] This reaction was applied during the synthesis of physostigime. This type of cyclization is quite rare in the cyclizations of arenes with aziridines or

epoxides in that an annulation reaction has taken place to provide a bicyclic product. Most of these types of cyclizations proceed through the elimination pathway (Scheme 1) in order to rearomatize the nucleophilic arene.



Scheme 32.

In addition to the already mentioned applications, the aziridine ring-opening with indole is found in a number of total syntheses including the GnRH antagonist **126**,[143] AJ-9677,[144] a β-carboline-1-one mimic of pancrastatin **127**,[145,48] a hymenialdisine analogs **128**,[146] and the BCRP inhibitor Kol43 (Fig. 4).[147]

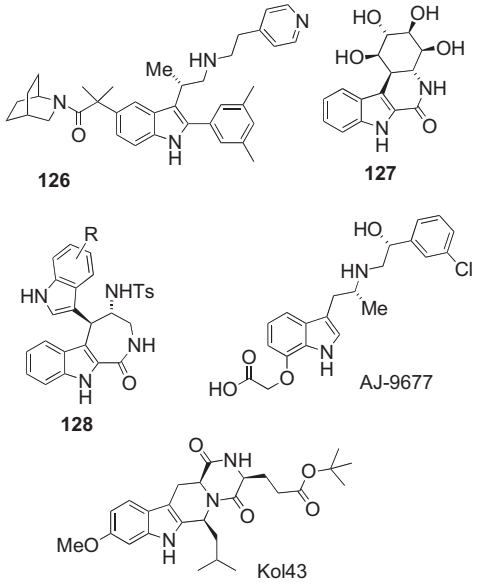
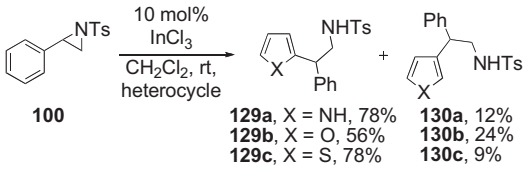


Figure 4.

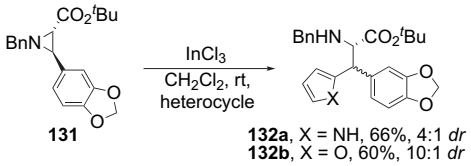
Pyrroles, furans, and thiophenes have primarily been used in reactions with aromatic substituted aziridines (e.g., **100**) with a tosyl group on the nitrogen of the aziridine (Scheme 33).[141] In the case of pyrrole even aliphatic aziridines can be used. As with other reactions of phenylaziridines, nucleophilic attack takes places at the benzylic position.



Scheme 33.

The reaction of pyrrole was also found to be catalyzed by $LiClO_4$[35] and $InBr_3$[63] to provide the ring-opened product in good yield and good regioselectivities. Furan was also observed to undergo nucleophilic attack on aziridines upon catalysis with $AuCl_3$/AgOTf[119] and $FeCl_3$.[120] $AgPF_5$ was found to catalyze the reaction of both furans and thiophenes with aziridines.[118]

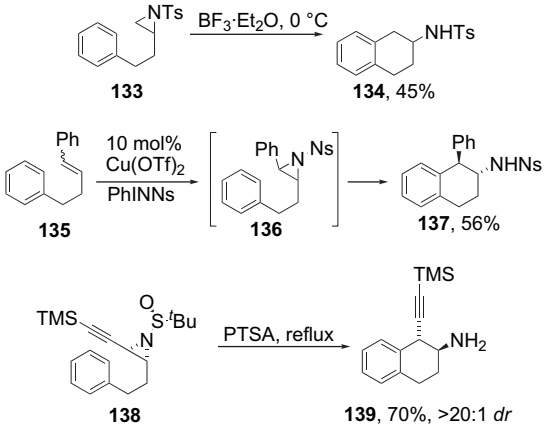
Both, pyrrole and furan can also be utilized in the ring-opening reaction with aziridine **131** (Scheme 34).[134] $InCl_3$ is used to catalyze the stereoselective ring-opening providing a diastereomeric ratio of up to 10:1. As with other aryl substituted aziridines, the reaction largely proceeds with inversion of configuration but a small amount of the S_N1 type mechanism allows for the loss of selectivity.



Scheme 34.

2.7. Intramolecular reactions of arenes with aziridines

For the intramolecular Friedel–Crafts reaction of aromatic π-nucleophiles with aziridines, only the formation of six-membered rings has been reported to date. The first report of a 6-(π-*endo*)-*endo*-aziridine cyclization was made by our group in 2004. The reaction of aziridine **133** with an excess of $BF_3 \cdot OEt_2$ provided cyclization product **134** in 45% yield (Scheme 35). As with related epoxide cyclizations, none of the 5-(π-*endo*)-*exo*-aziridine product was observed.



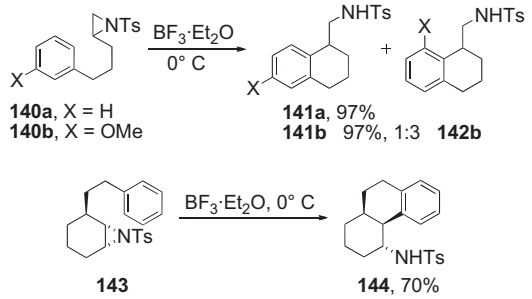
Scheme 35.

An interesting example of a 6-(π-*endo*)-*endo*-aziridine cyclization has been reported in which the aziridine is not isolated but prepared in situ. Treatment of 500 mol% of alkene **135** with 100 mol% of PhINNs under $Cu(OTf)_2$ catalysis provides aziridine **136**, which immediately cyclizes to provide substituted tetrahydronaphthalene product **137** in 56% overall yield (based on PhINNs).[148,149]

Aziridine substituted derivatives also undergo a 6-(π-*endo*)-*endo*-aziridine cyclization. An *N*-sulfinyl aziridine **138** with acetylenic substitution on the aziridine ring underwent cyclization with a Brønsted acid to provide **139** in 70% yield.[150] An acetylenic α-amino alcohol resulting from opening the aziridine ring with water was also obtained in 21% yield. This reaction is unique in that a protic acid was used for the cyclization, which then deprotects the *N*-sulfinyl aziridine during the reaction.

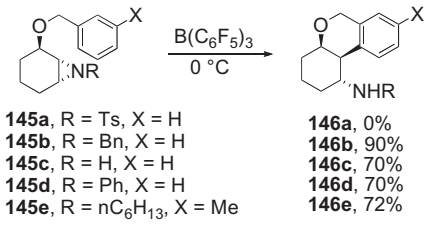
An interesting example of a 6-(π-*endo*)-*endo*-aziridine cyclization uses H_2SO_4 as the catalyst to provide the expected product, which under the reaction conditions undergoes an elimination of the toluenesulfonamide to provide a substituted naphthalene derivative.[151]

The first example of a 6-(π-*endo*)-*exo*-aziridine reaction was published in 2004 by our group (Scheme 36).[152] Treatment of **140** with an excess of $BF_3{\cdot}OEt_2$ provides **141** in excellent yield in only a few minutes. It is worth noting that the corresponding 6-(π-*endo*)-*endo*-aziridine cyclization (Scheme 35) takes several hours to go to completion. This is unlike the corresponding epoxide cyclizations in which the *endo*-epoxide cyclization appears to be more facile than the *exo*-epoxide cyclization. More recently a tricyclic system was prepared through the cyclization of aziridine **143**.[153]



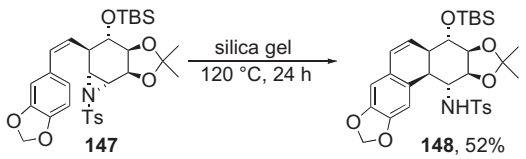
Scheme 36.

Changing one of the carbons linking the aziridine to the aromatic ring yields a profound change in reactivity of this system (Scheme 37).[153] Upon changing a methylene in the linking chain to an oxygen, the cyclization of the *N*-tosyl aziridine fails. It was proposed that the ether oxygen preferentially coordinates with Lewis acid, thus stopping the reaction. Changing the substitution on the aziridine nitrogen from the tosyl group to an alkyl, aryl or hydrogen allows the reaction to proceed providing the cyclized product in excellent yields. This reaction is unique in that it is one of only a few examples in which the aziridine ring is not activated with a sulfonyl group prior to reaction with a π-nucleophile.



Scheme 37.

A 6-(π-*endo*)-*exo*-aziridine cyclization was also used for the total synthesis of 7-deoxypancratistatin-1-carboxaldehyde. In this synthesis the complex fused-ring aziridine is linked via an alkene to a substituted arene. An unusual aspect of this cyclization is the use of neat silica gel as a catalyst (Scheme 38).[154]



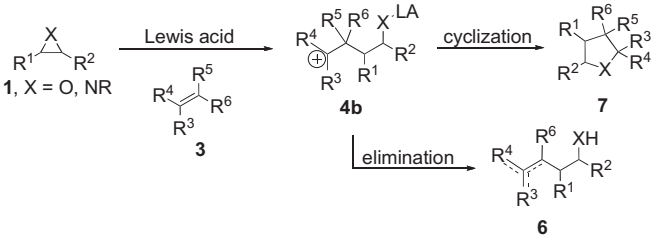
Scheme 38.

2.8. Intramolecular reactions of heteroaromatic with aziridines

To the best of our knowledge there have been no reports of an intramolecular reaction between an aziridine and a heteroaromatic ring.

3. Reactions of epoxides and aziridines with alkenes

One of the useful advantages of the reactions of epoxides and aziridines with alkenes, relative to aromatic rings, is the ability to make use of the cyclization pathway as noted in Scheme 39. When the π-nucleophile is an aromatic ring the elimination pathway leading to **6** is almost exclusively followed in order to rearomatize the aromatic π-nucleophile. When the π-nucleophile is an alkene, no such requirement is found. Intermediate **4b** can thus cyclize to provide a five-membered heterocycle **7** or eliminate (R^5 in this case) to provide an olefin. A key challenge in using olefins as the π-nucleophile is controlling, which carbon of the alkene is the nucleophilic carbon. An additional challenge is controlling the direction of elimination when elimination is desired.



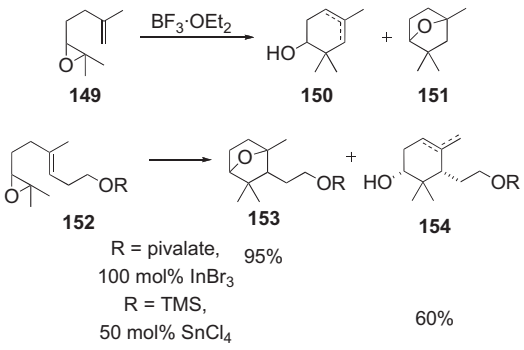
Scheme 39.

3.1. Intermolecular reactions of olefins with epoxides

To the best of our knowledge there have been no reports of an intermolecular reaction between an epoxide and an alkene π-nucleophile.

3.2. Intramolecular reactions of olefins with epoxides

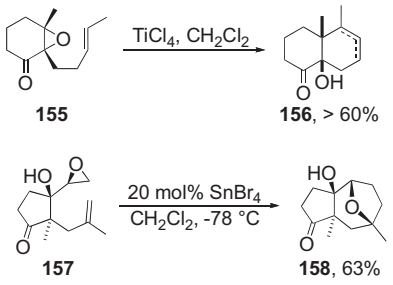
The first reaction between a double bond and an epoxide was observed in 1962 for the cyclization of geraniolene monoepoxide (**149**) upon treatment with $BF_3{\cdot}Et_2O$ (Scheme 40).[155,156] This reaction provided a mixture of products **150** and **151**. More recent work on this simple reaction has examined a variety of Lewis acids for optimization of the product formation. The optimal method using $Yb(OTf)_3$ gave a mixture of olefin isomers (1:1 to 4:1) along with a small amount of oxabicycle **153** and approximately 30% of a variety of Meinwald rearrangement products. Simply changing substitution



Scheme 40.

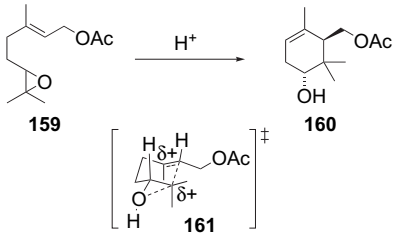
on the π-nucleophile (**152**) provided the oxabicycle **153** in 95% yield with less than 5% of the olefinic products being observed.[157] Changing the Lewis acid to $SnCl_4$ provided the olefinic compound **154** as an 85:15 mixture of *endo*/*exo* olefin regioisomers.[158]

More complex epoxide–alkenes can also undergo the cyclization. Reaction of epoxy ketone **155** with $TiCl_4$ provided the product of a 6-(π-*endo*)-*endo*-epoxide cyclization **156** in greater than 60% yield (Scheme 41).[159,160] The reaction may not be general as minor modifications to this substrate (e.g., a dimethyl olefin) lead to completely different reaction pathways.[161] A 7-(π-*endo*)-*endo*-epoxide cyclization can also be carried out. The reaction of **157** with $SnBr_4$ provides a modest yield of the oxabicyclo system **158**, via a second cyclization of the ring-opened product, in 63% yield.[162,163]



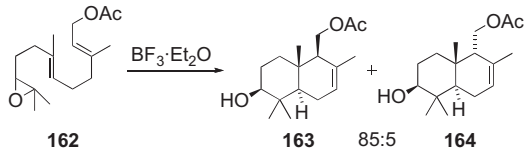
Scheme 41.

Recently, an investigation of intramolecular kinetic β-isotope effects for the reaction of 6,7-epoxy geraniol was published in the context of conformations studies about acid-catalyzed cyclization of terpenes.[164] The isotope and computational studies showed that a chair-like transition state was favored (Scheme 42). In addition the isotope studies ruled out a stepwise mechanism with formation of a tertiary acyclic carbocation intermediate.



Scheme 42.

The early reaction was followed by a cyclization of the epoxide derived from farnesyl acetate (Scheme 43).[165] As with all polyene cyclizations, the carbocation derived from the initial epoxide–olefin cyclization reacts with the allylic acetate to form the bicyclic system. As with many of these early reactions, the yields are poor. Regarding the yield the authors simply state 'after extensive chromatographic purification a modest yield' of **163** and **164** was obtained in a ratio of 85:15.

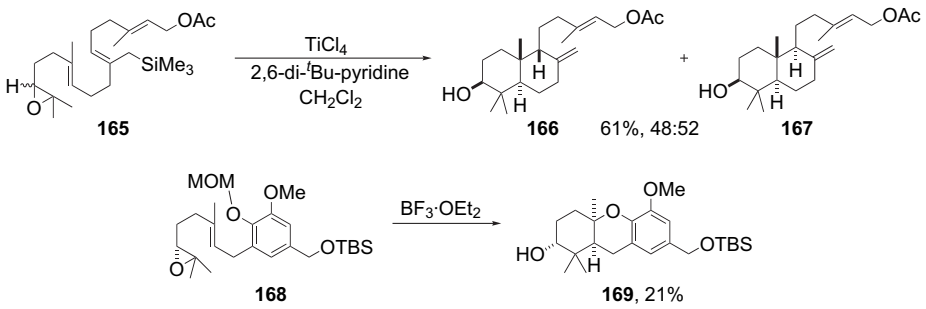


Scheme 43.

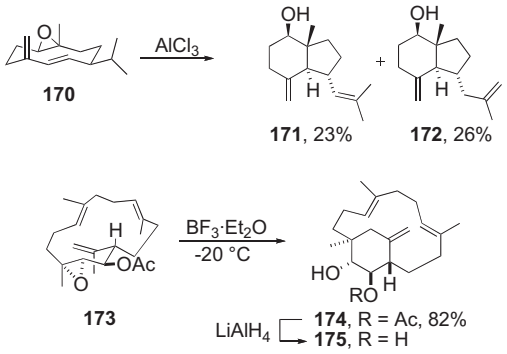
Following these early investigations, a large number of different polyene epoxide cyclizations have been reported. The majority of these reports deal with the synthesis of sterols, terpenes, and related core structures. Several review articles have been published and discuss patterns of polyene cyclization,[166,167] *O*-direction[168] and enzymatic mechanisms.[169,170] Typically, this type of reaction is catalyzed by Lewis acids[171–173] or enzymes,[174,175] but examples of Brønsted acids[176] and solid supported catalysts[177,178] are known as well. For example, the solid phase catalyst, zeolite NaY, is reported to only catalyze a monocyclization and therefore polyenes will only form one new ring in the product.[179]

Polyene cyclizations are not always terminated by simple double bonds. Allylsilanes (Scheme 43),[180] aromatic,[173] heteroaromatic rings,[181] alkynes,[182] and alkynylsilanes[183] have all been used as the terminator for these types of cyclizations. Two interesting examples are shown in Scheme 44. In the first example a typical epoxide polyene is substituted by an allylsilane **165**.[180] Treatment of this epoxide with $TiCl_4$ and a mild base provides a good yield of the bicyclic ring system **166**/**167** as a 1:1 mixture of diastereomers. The allylsilane moiety ensures the placement of the exocyclic olefin for further synthetic transformations. In the second example, the initial carbocation is trapped by an oxygen nucleophile.[184] Treatment of epoxide **168** with $BF_3 \cdot OEt_2$ provides a modest yield of the tricycle product **169**. It is interesting to note that choice of Lewis acid is critical in this reaction as $In(OTf)_3$ provides only products of epoxide rearrangement.

Transannular cyclizations have been investigated to some extent. An interesting example is the reaction of epoxigermacrene under treatment with acetic acid, basic alumina or $AlCl_3$. As is common in these types of reactions, the products and product distribution are critically dependent upon reaction conditions (Scheme 45).[185,186] Treatment of **170** with $AlCl_3$ provides a modest yield of the isomeric 6-(π-*exo*)-*endo*-epoxide cyclization products **171** and **172**. Treatment of **170** with either a Brønsted acid (AcOH) or basic alumina provided a wide variety of bicyclo[4.4.0]decanes and bicyclo [5.3.0]decanes in very poor yields. Further examples of this type of reaction describe the utilization of $SnCl_4$ as Lewis acid[187,73] and an approach to the synthesis of verticillene.[188] The cyclization of **173** upon treatment with $BF_3 \cdot Et_2O$ provided the bicycle **174** in excellent



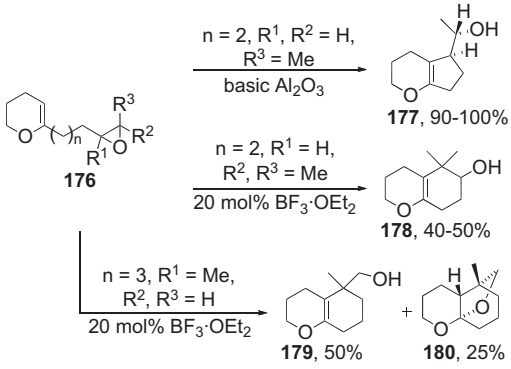
Scheme 44.



Scheme 45.

yield via a 6-(π-*endo*)-*endo*-epoxide cyclization. This molecule was used in the synthesis of (±)-secotrinerviten-2b,3a-diol (**175**).[189]

Investigations aimed at determining the ring size where first carried out in 1978, when enolether epoxides where cyclized upon treatment with Lewis acids (Scheme 46).[190] Both 5-(π-*endo*)-*exo*-epoxide and 6-(-π-*endo*)-*endo*-epoxide provide the expected products **177** and **178**, respectively. Attempts at carrying out a 5-(π-*endo*)-*endo*-epoxide cyclization were unsuccessful. In one of the few examples of an epoxide reaction proceeding through the cyclization pathway (e.g., **7**, Scheme 39) 25% of the tricyclic acetal **180** was obtained along with 50% of **179** from the elimination pathway.

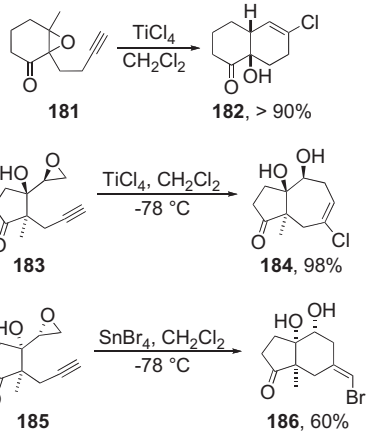


Scheme 46.

In addition to enolethers acting as nucleophile, enamides have also been reported to be an effective π-nucleophile in reactions with epoxides. A 6-(π-*endo*)-*endo*-epoxide cyclization has been reported as an approach for the synthesis of homoclausenamides.[191]

Alkynes somewhat surprisingly participate quite well in epoxide–π-nucleophile cyclizations. The first example of this reaction was reported in 1978 (Scheme 47).[192,160] Treatment of keto-epoxide **181** with $TiCl_4$ provided an excellent yield of the vinylhalide **182**. The hydroxy epoxides **183** and **185** have also been used in similar reactions providing **184** and **186**, respectively.[162,163] Coordination of the $SnBr_4$ to both the alcohol and epoxide is important for the reaction to generate product **186** via a 6-(π-*exo*)-*endo*-epoxide cyclization. The epimeric hydroxyepoxide provides only a 20% yield of the same product.

A competition study with arenes and olefins has been carried out. Substrates with both groups were treated with $BF_3 \cdot Et_2O$ to give the corresponding products and some generalization can be determined (Table 7).[193,194] Four different systems were prepared and studied, all with the π-nucleophile *endo* and the epoxide with both *endo* and *exo* possibilities. When both the olefin nucleophile and arene nucleophile can cyclize by an *endo*-epoxide route, the arene is the preferred nucleophile providing **188** as the major



Scheme 47.

product (entry 1). When the reaction can occur via either an *endo*-epoxide or *exo*-epoxide route, the *exo*-epoxide route is favored regardless of the nucleophile (entries 2 and 3). In entry 2, cyclization with the olefin π-nucleophile leads to **190** via the *exo*-epoxide cyclization. In entry 3, the arene π-nucleophile provides the only route to an *exo*-epoxide cyclization. If only an *exo*-epoxide route is available, the olefin is the preferred nucleophile (entry 4). It is important to note that these results can only be generalized to terminal olefins.

Table 7

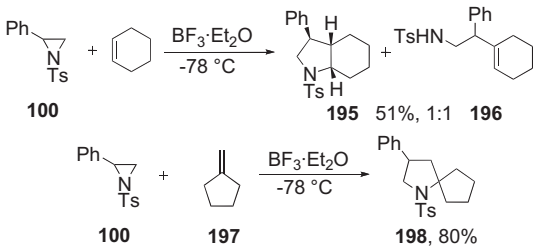
Entry	Epoxide	Major product
1	**187**	**188**
2	**189**	**190**
3	**191**	**192**
5	**193**	**194**

Further investigations with derivatives of **187** and **191**, which contain an additional methyl substitution in 2-position of the olefin, showed that the attack of the aromatic is still favored, but in addition a side product of the olefin attack is observed.[195] For derivatives of **189** and **193**, with *para*-methoxy substitution on the aromatic ring, products of the aromatic attack are now observed to be the preferred product, but a number of side products including derivatives of **190** and **194** were isolated as well.[196]

3.3. Intermolecular reactions of olefins with aziridines

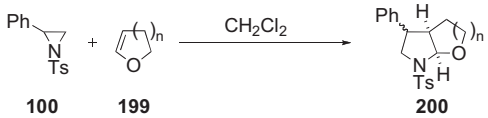
Unlike epoxides, a few examples of the intermolecular reaction of an aziridine with an alkene are known. Although like the

intermolecular reaction of aziridines with arenes only aryl substituted aziridines participate in this reaction. The first example of this intermolecular reaction showed that a variety of substituted alkenes would react with phenyl aziridine to provide the ring-opened products.[197] For example, the reaction of **100** with cyclohexene provided a 1:1 mixture of **195** and **196** in 51% yield (Scheme 48). Presumably the lack of stabilization of the intermediate carbocation formed after the initial ring-opening leads to the mixture of olefin and bicyclic product. The use of an exocyclic olefin provided the spirocyclic product **198** as the sole product in good yield. The more stable tertiary carbocation is now more likely to undergo cyclization.



Scheme 48.

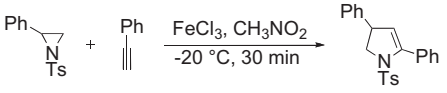
Both dihydropyran and dihydrofuran are known to undergo this type of reaction to form exclusively the fused pyrrolidine derivatives **200** (Scheme 49).[198–200] As with the previous example of using a more highly substituted olefin to stabilize the intermediate carbocation and thus favor cyclization, the enolether again generates a more stabilized intermediate oxonium ion to favor cyclization.



n = 2, $BF_3{\cdot}OEt_2$, 80%, 1:1 *endo*:*exo*
n = 2, $Sc(OTf)_3$, 78%, 1:1 *endo*:*exo*
n = 1, $Sc(OTf)_3$, 72%, 1:1 *endo*:*exo*

Scheme 49.

Similar to olefins, alkynes are also known to react with aziridines to form 2-pyrroline derivatives. As shown in Scheme 50, the reaction of phenyl aziridine with phenylacetylene provides a good yield of the pyrroline **202**.[201] Silver catalysts ($AgSbF_6$) have also been used to catalyze this cyclization.[202,203]

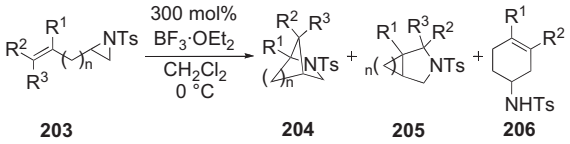


Scheme 50.

3.4. Intramolecular reactions of olefins with aziridines

Intramolecular reactions between alkenes and aziridines are scarce. This is unfortunate in that this reaction has the capability to generate a variety of structures. We reported on the first intramolecular reaction between an alkene and an aziridine in 2004. A limited study provided some insight into the preferred ring sizes that can be formed (Table 8). When n=1, a relatively facile cyclization takes place to provide the azabicyclo[2.1.1]hexane ring system (**204**, entry 1). The ability to prepare such a strained ring system is unusual. The position of the substitution on the alkene leads to the 4-(π-*endo*)-*exo*-aziridine cyclization. Adding an

Table 8

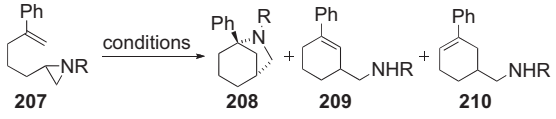


Entry	R^1	R^2	R^3	n	Product, yield (%)
1	Me	H	H	1	**204**, 71
2	Me	H	H	2	**206**, 41
3	Me	H	H	3	**204**, 71
4	Ph	H	H	3	**204**, 63
5	Me	Me	H	3	**204**, 75
6	H	Me	Me	3	**205**, 41
7	H	Me	Me	4	**205**, 75

additional methylene on the tether between the alkene and aziridine provides an option for a 5-(π-*endo*)-*exo*-aziridine or a 6-(π-*endo*)-*endo*-aziridine cyclization. As has been shown in several examples already, the 5-(π-*endo*)-*exo*-aziridine cyclization is highly disfavored and thus only the 6-(π-*endo*)-*endo*-aziridine cyclization occurs to yield **206** in 41% yield. As expected, the 6-(π-*endo*)-*exo*-aziridine cyclization occurs readily to provide **204** when n=3 and R^1=Me or Ph (entries 3 and 4). Moving the cation stabilizing groups to the terminus of the alkene changes the orientation of the cyclization. Thus when n=3 or 4 and R^2=R^3=Me, a 5- or 6-(π-*exo*)-*exo*-aziridine cyclization takes place leading to **205** (entries 6 and 7). It is worth noting that with the exception of entry 2, all of the ring-opening reactions in this report lead to the cyclized product **204** or **205**. The elimination pathway (e.g., **6**, Scheme 39) is not followed.

A study on the effect of the nitrogen substitution has also been reported as outlined in Table 9. Many reactions of aziridines with π-nucleophiles are conducted with *N*-tosyl aziridines. It is well known that removal of the *N*-tosyl protecting group can be problematic.[204] Four different substitutions on the aziridine nitrogen were examined, N–H, N–Ts, N–Ns (nosyl), and *N*-Dpp (diphenylphosphinyl) in order to identify a substituent on the aziridine that would provide bicyclic product and a more readily removed N activating group. Interestingly, both $B(C_6F_5)_3$ and TFA provided a good yield of the elimination product **209b** (entries 2 and 3). The nosyl group on the nitrogen provided an excellent yield of the bicyclic product upon treatment of **207c** with $B(C_6F_5)_3$ (entry 4). A variety of acids were examined with the Dpp group. The optimum acid was a catalytic amount of TFA, which provided **209d** in good yield (entry 5). Under certain conditions, **210** can be observed as side product.

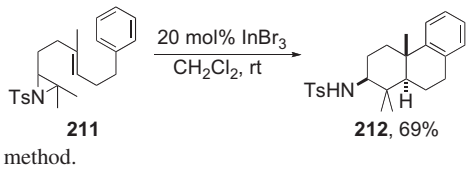
Table 9



Entry	Substrate	Conditions	Products
1	R=Ts	100 mol % $BF_3{\cdot}Et_2O$	**208a**, 73%
2	R=H	100 mol % TFA	**209b**, 65%
3	R=H	100 mol % $B(C_6F_5)_3$	**209b**, 73%
4	R=Ns	100 mol % $B(C_6F_5)_3$	**208c**, 95%
5	R=Dpp	15 mol % TFA	**209d**, 64%

While a large number of polyene cyclizations with epoxides have been reported, a similar reaction with aziridines has been rarely studied. Recently the intramolecular cyclization of aziridine

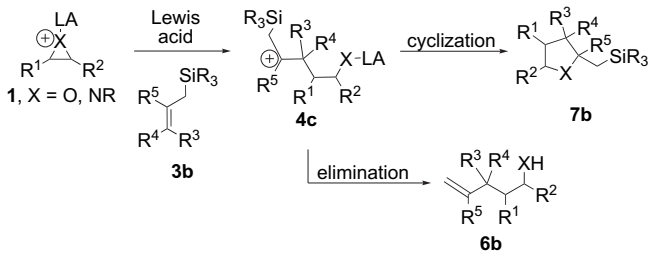
211 has been reported (Scheme 51).[205] The treatment of **211** with $InBr_3$ provides a good yield of the tricyclic product as a single stereoisomer. More complex tetracyclic ring systems have also been prepared using the same general method.



Scheme 51.

4. Reactions of epoxides and aziridines with allylsilanes and −stannanes

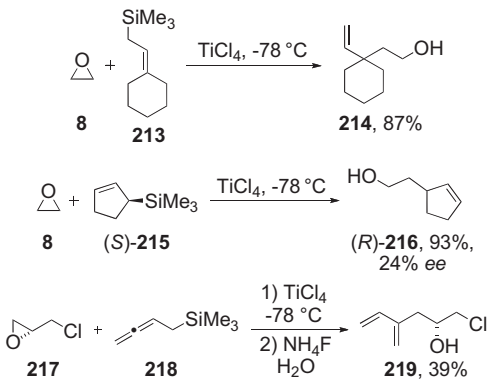
Allylsilanes are of special interest concerning epoxide and aziridine opening because of their capability to stabilize β-carbocations.[206] This provides several advantages relative to simple alkenes in this reaction system. First, the ability to stabilize a positive charge provides high-levels of control in terms of which carbon of the π-nucleophile is the nucleophilic carbon. Second, the allylsilane can also control the direction of elimination such that only one elimination product is formed (Scheme 52). Third, the stabilization of the intermediate carbocation can also help in promoting cyclization to provide products, such as **7b**. A final advantage is that the cyclization process can provide access to silicon-substituted products, **7b**, which are then available for further reactions.[207]



Scheme 52.

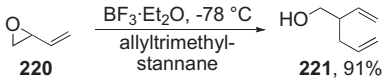
4.1. Intermolecular reactions of allylsilanes with epoxides

The utilization of allylsilanes for the ring-opening reactions of epoxides was first reported in 1979, when Fleming and Paterson investigated $TiCl_4$ as a mediator for the reaction of allylsilane **213** with oxirane (Scheme 53).[208] In 1983 it was reported that cyclic allylsilanes, such as **215** can also be used in this reaction.[209] This reaction provided **216** with only 24% ee suggesting that the approach of the epoxide to the allylsilane is not stereoselective. Allenylsilanes (**218**) can also be used to provide diene **219** as the product.[210] This diene was subsequently used for the synthesis of (*S*)-(−)-ipsenol.



Scheme 53.

Allylstannanes can also be used in this general reaction. Butadiene monoepoxide reacts at the internal carbon of the epoxide as opposed to either the terminal carbon of the epoxide or an S_N2' type addition at the double bond (Scheme 54).[211]



Scheme 54.

Since then a number of new examples for reactions of both, allylsilanes and −stannanes, with different epoxides have been established[212] and used in the synthesis of (+)-isolaurepinnacin[213] and altohyrtin C (Fig. 5).[214,215]

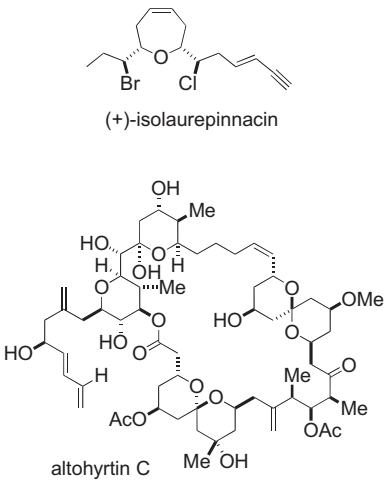
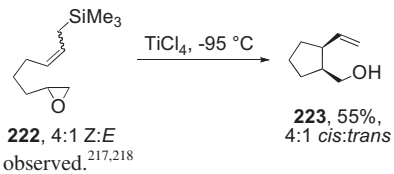


Figure 5.

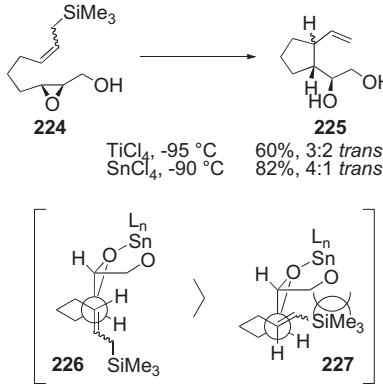
4.2. Intramolecular reactions of allylsilanes with epoxides

As previously discussed, the product of an intramolecular epoxide opening depends upon the substitution pattern, steric, and electronic effects, and the choice of Lewis acid. The first intramolecular reaction between an allylsilane and an epoxide involved the cyclization of the simple epoxyallylsilane **222** (Scheme 55).[216] Treatment of **222** with $TiCl_4$ at −95 °C provided cyclopentane **223** in 55% yield as a 4:1 mixture of cis and trans isomers. This reaction is an example of a 5-(π-*exo*)-*exo*-epoxide cyclization. The attempt to carry the reaction out after introduction of oxygen within the tether linking the epoxide and allylsilane, did not lead to formation of the expected tetrahydrofuran, but only desilylation was observed.[217,218]



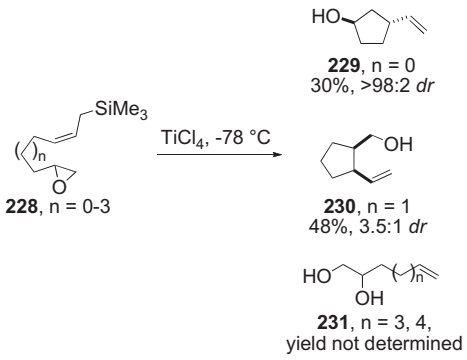
Scheme 55.

The reaction of an alcohol substituted epoxide using $TiCl_4$ provided a 3:2 mixture of the *trans*/*cis* mixture **225**. In order to improve the stereoselectivity of this reaction the Lewis acid was changed to $SnCl_4$, to form a chelate complex with substrate **224** (Scheme 56).[219,220] The complex **226** (leading to the trans-fused isomer) in which the epoxide/alcohol/Sn complex is *anti* to the allylsilane was proposed as the key intermediate as compared to the energetically less favored *gauche* complex **227**. Under these conditions it was possible to increase the selectivity to *cis*/*trans* (1:4). This is the opposite relative stereochemistry to that observed in the simple system (**222**, Scheme 55) in which the cis-isomer predominates.



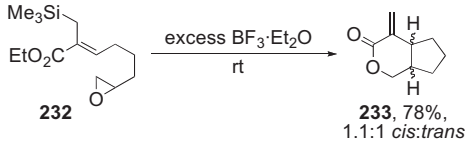
Scheme 56.

In addition to the substitution and the Lewis acid, the length of the carbon backbone is an important factor for the reaction process. As shown in Scheme 57, when n=0, only the 5-(π-*exo*)-*endo*-epoxide **229** is formed. The 4-(π-*exo*)-*exo*-epoxide is not formed.[217] When n=1, the possibility exists for both the 5-(π-*exo*)-*exo*-epoxide and the 6-(π-*exo*)-*endo*-epoxide cyclizations to occur, however both this study and earlier work[216,219,220] shows that only the 5-(π-*exo*)-*exo*-epoxide cyclization occurs. It is interesting to note that the diastereoselectivity of the *exo*-epoxide cyclization (**230**) is only about 4:1 while the *endo*-epoxide cyclization (**229**) is >98:2. When n=2 or 3 only the desilylated product **231** is formed.



Scheme 57.

Another interesting example showing the tolerance of the reaction to substitution on the allylsilane is the tandem reaction of epoxy-allylsilane **232** to form lactone **233** in 78% yield (Scheme 58) as a 1:1 mixture of isomers.[221] While the major isomer is the product of a 5-(π-*exo*)-*exo*-epoxide cyclization, a small amount (6%) of the 6-(π-*exo*)-*endo*-epoxide cyclization product was formed.

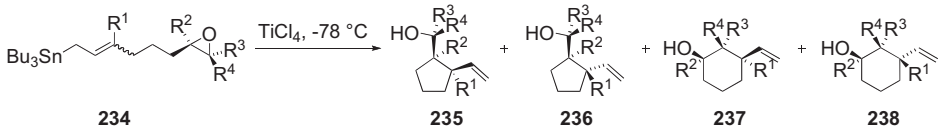


Scheme 58.

As has already been reported, the 5-(π-*exo*)-*exo*-epoxide is an allowed cyclization with an allylsilane. Allylstannanes can also participate in this general reaction (Table 10). Allylstannanes **234a**–**c** provide exclusively the 5-(π-*exo*)-*exo*-epoxide cyclization products (entries 1–3).[222–224] In these examples, the substitution on either side of the epoxide can be considered to be electronically equal. Introduction of additional substitution on the terminal carbon of the epoxide can change the stereoelectronic preference previously observed. Thus the reaction of **234d** (entry 3) and **234e** (entry 4), which might more readily stabilize an incipient carbocation, lead to the almost exclusive formation of the 6-(π-*exo*)-*endo*-epoxide product. As observed previously, this *endo*-epoxide ring closure provides substantially better diastereoselectivity than the *exo*-epoxide cyclization (30 to 40:1 relative to 2.8 to 2.7:1). Further experiments have shown that reactions, which are carried out under BuLi-promotion to form the corresponding allyl-lithium-species of **234**, tend to give very different regioselectivity.

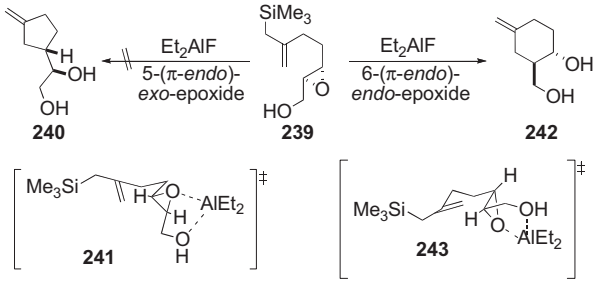
In the previous examples of allylsilane/epoxide cyclizations, the allylsilane was connected to the epoxide via the 3- or terminal carbon of the allylsilane moiety. This type of connectivity forces a π-*exo* type of cyclization. Changing this connectivity from the 3-carbon of the allylsilane to the 2-carbon of the allylsilane should force a π-*endo* type of cyclization. Epoxyallylsilane **239** can lead to either a 5-(π-*endo*)-*exo*-epoxide cyclization (**240**) or a 6-(π-*endo*)-*endo*-epoxide (**242**) cyclization. The reaction of epoxyallylsilane **239** with Et_2AlF, a mild and chelating Lewis acid, led exclusively to cyclohexanol **242** in 75% yield (Scheme 59) via a 6-(π-*endo*)-*endo*-epoxide cyclization.[87] None of the *exo*-epoxide **240** was formed in this reaction. Molecular modeling showed good overlap between

Table 10



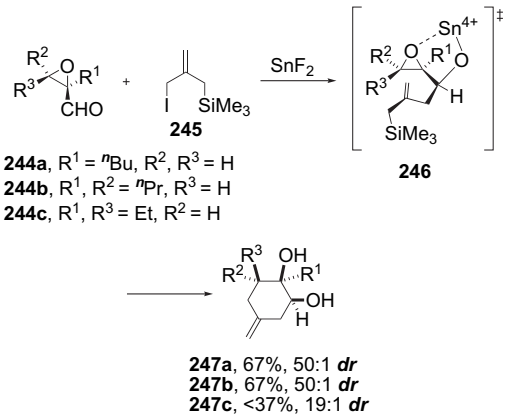
Entry	R^1	R^2	R^3	R^4	Product, yield (%)
1	H	H	H	H	**235**, 74; **236**, 26
2	^{i}Pr	Me	H	H	**235**, 69; **236**, 26
3	H	H	H	Et	**235**, 69; **236**, 26
4	H	H	Me	Me	**236**, 2; **237**, 88
5	H	H	Ph	H	**236**, 3; **237**, 97

the π-orbital of the allylsilane and the C–O-orbital of the distal epoxicarbon in **243**. On the other hand the overlap between of the π-orbital of the allylsilane with the proximal C–O-orbital in **241** was very poor. The authors hypothesized that the *endo*-epoxide cyclization might be due to the chelating effect of the Lewis acid. However, the substitution of the terminal alcohol with a tosylate still led to the 6-*endo* attack. Variation in this general connectivity in which the tether is substituted with a phenylsulfone can also provide the 6-(π-*endo*)-*endo*-epoxide cyclization. A side reaction on a similar substrate, which led to a ketone in comparable yield took place as hydride migration.[225] With variation of the reaction conditions, other pathways, such as protodesilylation and fluorination were observed as well.[226]



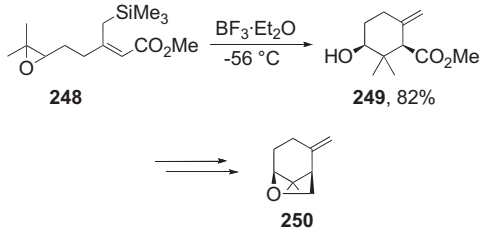
Scheme 59.

Similar regioselectivity was observed when the in situ generated epoxyallylsilane **246** underwent cyclization under tin-catalysis (Scheme 60).[227] This reaction led to good yields and good diastereoselectivities provided sufficient steric hindrance at the R^1-residue in **244**.



Scheme 60.

The 6-(π-*endo*)-*endo*-epoxide cyclization has advantages over the *exo*-epoxide cyclization in terms of improved levels of diastereoselectivity. Consequently, it has been used in natural product syntheses. This reaction provided an easy entrance to the synthesis of the (±)-karahana ether **250** (Scheme 61). Cyclization of **248** leads to an excellent yield of **249** as a single diastereomer.



Scheme 61.

Typical examples (Fig. 6) of the 6-(π-*endo*)-*endo*-epoxide cyclization lead to derivatives of the geranyl skeleton (**251**),[228,229] which also found application during the synthesis of taxol (ring C)[230–233] and *seco*-taxane **253**.[234] Steroid **252** is a good example for a cyclization different from the usual geranyl skeleton.[235]

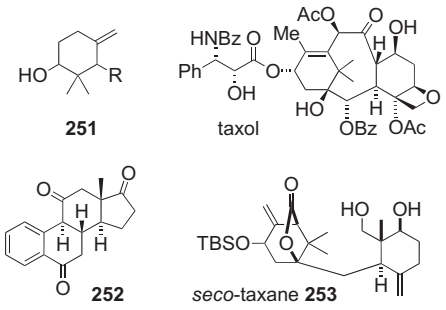
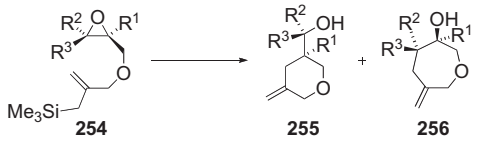


Figure 6.

A study on the stereoelectronic factors governing product distribution when both an *exo*-epoxide and an *endo*-epoxide cyclization possible have been reported.[236] As shown in Table 11, a 6-(π-*endo*)-*exo*-epoxide or a 7-(π-*endo*)-*endo*-epoxide cyclization is possible, which would lead to six- or seven-membered ring systems **255** or **256**. When R^1 was substituted and a non-chelating Lewis acid was used to catalyze the reaction the major product was **255**, the result of a 6-(π-*endo*)-*exo*-epoxide cyclization (entry 1). Presumably the improved stabilization of the incipient positive charge at the carbon bearing R^1 drove the reaction in this direction. Moving the substitution around the epoxide to R^2 or R^3, providing equivalent substitution on either side of the epoxide provided a 1:1 mixture of **255** to **256** (entries 2 and 3). Enhancing the charge stabilization at this terminal position by phenyl (entry 4) or dimethyl substitution (entry 5) changed to product ratio to favor the 7-(π-*endo*)-*endo*-epoxide cyclization. Regardless of the epoxide substitution, the corresponding allylstannanes provided a 1:1 mixture of **255** and **256**.

Table 11

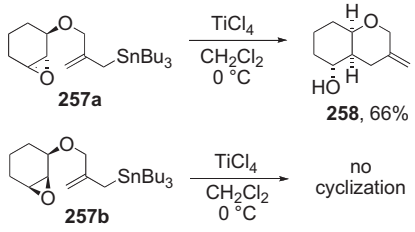


Entry	Substitution	Lewis acid	Ratio **255**/**256**, yield (%)
1	R^1=Me, R^2, R^3=H	$BF_3{\cdot}OEt_2$	7:1, 63
2	R^1=H, R^2=*n*Pr, R^3=H	$BF_3{\cdot}OEt_2$	1:1.2, 77
3	R^1=H, R^2=*n*Pr, R^3=*n*Pr	$BF_3{\cdot}OEt_2$	1:1.2, 78
4	R^1=H, R^2=Ph, R^3=H	$BF_3{\cdot}OEt_2$	1:9, 82
5	R^1=H, R^2, R^3=Me	$BF_3{\cdot}OEt_2$	1:7, 73
6	R^1=Me, R^2, R^3=H	$TiCl_4$	0:1, 75
7	R^1=H, R^2=*n*Pr, R^3=H	$TiCl_4$	0:1, 95
8	R^1=H, R^2=Ph, R^3=H	$TiCl_4$	0:1, 83

Changing the Lewis acid to a chelating Lewis acid ($TiCl_4$) leads to an intermediate structure involving a chelate between the epoxide, ether oxygen, and the titanium, this was hypothesized to disfavor any conformation leading to the 6-(π-*endo*)-*exo*-epoxide cyclization. Such a Lewis acid would then override the electronic factors

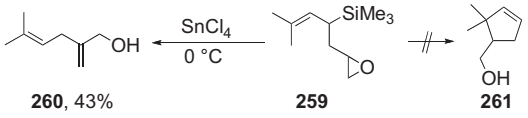
associated with epoxide substitution and provide the 7-(π-*endo*)-*endo*-epoxide cyclization product. This proved to be the case as all examples provided only **256**, the 7-(π-*endo*)-*endo*-epoxide cyclization product. Even examples where **255** was the major product with $BF_3{\cdot}OEt_2$ provided only **256** (entry 6).

The increased strain associated with the fused ring epoxide **257a** made the formation of the seven-membered ring impossible, even under chelating conditions that had previously generated only the seven-membered product (Table 11). The S_N2-character of the ring-opening was again indicated by the lack of reactivity of epoxide **257b** (Scheme 62).[236]



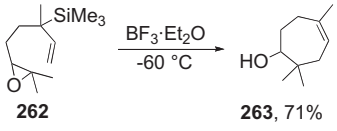
Scheme 62.

Not all allylsilane connectivity variations provide the expected cyclization product. For example, upon treatment of epoxy-allylsilane **259** with $SnCl_4$ the expected 5-(π-*endo*)-*exo*-epoxide cyclization leading to **261** does not occur. Rather, a rearrangement leads to allylic alcohol **260** in 43% yield (Scheme 63).[237]



Scheme 63.

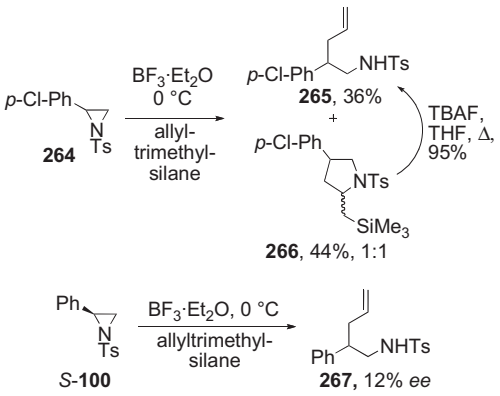
While this type of allylsilane connectivity to the epoxide does not provide product via a 5-(π-*endo*)-*exo*-epoxide cyclization other ring sizes can make this a viable substrate. For example, the reaction of epoxy-allylsilane **262** leads to a good yield of the seven-membered product karahanaenol, **263** (Scheme 64).[238]



Scheme 64.

4.3. Intermolecular reactions of allylsilanes with aziridines

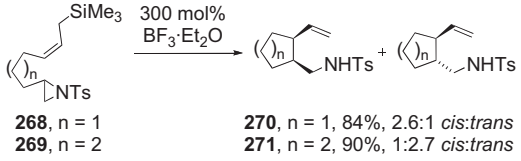
The first intermolecular aziridine opening with an allylsilane was accomplished in 1996 by Mann et al. and described the reaction of tosylaziridine **264** with allyltrimethylsilane to form γ-amino olefin **265** in 36% yield (Scheme 65).[239] A second compound, the pyrrolidine **266** was obtained in 44% yield. It was possible to transform the cyclic product into the amine with almost quantitative yield after treatment with $^nBu_4NF$. This reaction was carried out on a number of allylsilanes, from linear, over branched to cyclic ones. Similar results were obtained during the synthesis of (±)-phenylkainic acid for the reaction of protected phenylaziridines with (cyclopent-2-enyl)-trimethylsilane.[240] Significantly the reaction of homochiral aziridine **100** with allyltrimethylsilane provided the product **267** with only 12% ee.[198] This provides clear evidence of the carbocationic mechanistic pathway.



Scheme 65.

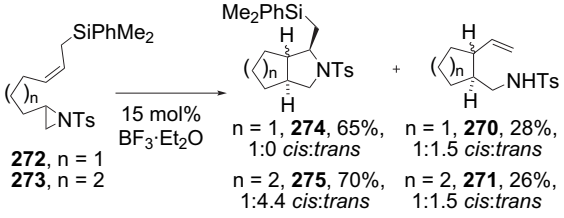
4.4. Intramolecular reactions of allylsilanes with aziridines

Our group reported the first intramolecular reaction of an allylsilane with an aziridine. Initial observations showed that the reaction of allylsilanes **268** and **269** (SiR_3=$SiMe_3$) with excess of $BF_3{\cdot}Et_2O$ led to products derived from a 5-(π-*exo*)-*exo*-aziridine or 6-(π-*exo*)-*exo*-aziridine cyclization (Scheme 66).[241] The cyclizations are reported to proceed through a chair-like cyclization conformation, which leads to the *trans* or the *cis* products of **270** and **271** as the major products in a roughly 3:1 ratio. It is worth noting that this product ratio is similar to that seen in the cyclization reactions of epoxyallylsilanes (Scheme 57).[217] This reaction found its application in the total synthesis of (−)-yohimbane.[242]



Scheme 66.

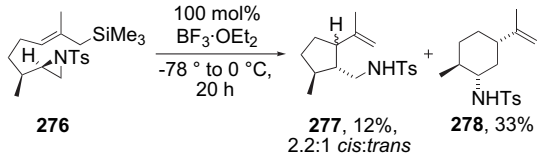
If the aziridine allylsilanes **272** and **273** (SiR_3=$SiPhMe_2$) are treated with only 15 mol% of the Lewis acid, a different major product was observed, the bicyclic pyrrolidines **274** and **275** (Scheme 67).[243] The more rigid five-membered ring **274** leads to the exclusive formation of the *cis*-fused product, while both diastereomers of the elimination product **270** are obtained in a ratio of 1:1.5. Similar results were observed for allylsilane **273**, but due to the more flexible backbone of the carbon chain, both isomers of **275** are obtained. This process provides a nice example of the utility of the allylsilane as the π-nucleophile, in that the β-silyl cation can be



Scheme 67.

trapped by the sulfonamide leading to a silyl substituted heterocycle. The silyl group was subsequently oxidized to generate bicyclic proline analogs.

A more substituted aziridine allylsilane **276** has also been prepared and cyclized (Scheme 68).[244] This type of substrate was expected to react via a 5-(π-*exo*)-*exo*-aziridine cyclization to provide **277**. However, **277** was the minor product with the major product being **278** resulting from a 6-(π-*exo*)-*endo*-aziridine cyclization. It is surprising that such a minor change in substitution to the reaction substrate provides such a shift in the reaction pathway. As has been noted previously, the *endo*-aziridine cyclization proceeded with much better diastereoselectivity, providing **278** as the sole product, while **277** (the *exo*-aziridine cyclization product) was obtained as a mixture of stereoisomers.



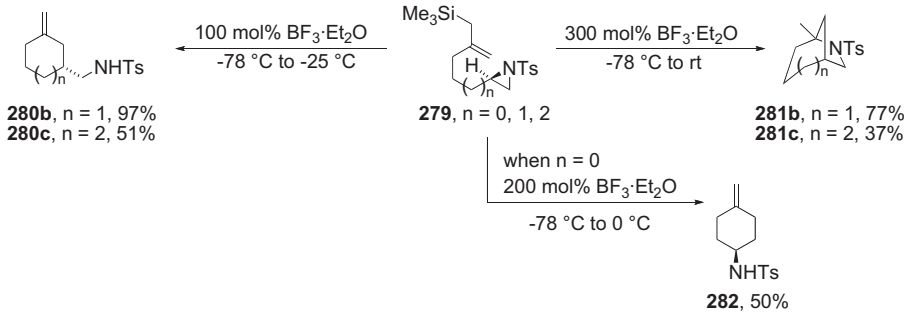
Scheme 68.

An alternate connectivity of the allylsilane can provide cyclization products as well. The 6-(π-*endo*)-*exo*-aziridine cyclization of **279** provides either **280** or **281** in excellent yields (Scheme 69). The bicyclic product **281** is presumably formed via an acid-catalyzed amidation of **280**. The formation of the seven-membered ring is also possible albeit with higher temperatures and more Lewis acid.[245]

The reaction of **279a** (n=0) provided none of the product derived from a 5-(π-*endo*)-*exo*-aziridine cyclization (e.g., **280**). Only **282**, the product of a 6-(π-*endo*)-*endo*-aziridine cyclization was obtained in a moderate yield of 50%. This inability to carry out a 5-(π-*endo*)-*exo*-aziridine cyclization has also been observed in cyclization reactions of epoxides.[225,227,230,246]

Table 12 presents a listing of all of the intramolecular cyclizations discussed in this review. It is not a fully comprehensive listing of all known cyclizations but does list the types of cyclizations that are known. Unlike the original Baldwin's rules, it is difficult to clearly identify cyclizations that are allowed and those that are disallowed. It is important to note that allowed cyclizations are π-nucleophile dependent. For example, there are a large number of 6-(π-*exo*) cyclizations with both epoxides and aziridines (*exo* and *endo*), however this cyclization is quite rare when the π-nucleophile is an aromatic ring.

While assigning an allowed or disallowed tag to a reaction is difficult due to the paucity of examples, it is fairly obvious from a cursory examination of the table that some cyclizations, notably the 6-(π-*endo*)-*exo*-heterocycle and the 6-(π-*endo*)-*endo*-heterocycle are allowed and very well represented. Almost every combination of π-nucleophile and heterocycle can be found in these two



Scheme 69.

Table 12
Summary of known intramolecular cyclizations of π-nucleophiles with epoxides/aziridines

Ring Size	π-Orientation	Heterocycle orientation	Arene epoxide	Indole epoxide	Furan epoxide	Pyrrole epoxide	Arene aziridine	Alkene epoxide	Alkyne epoxide	Alkene aziridine	Allylsilane epoxide,	Allylstannane epoxide,	Allylsilane aziridine
4	π-*exo*	*exo*											
4	π-*exo*	*endo*											
4	π-*endo*	*exo*								T8[a]			
4	π-*endo*	*endo*											
5	π-*exo*	*exo*	S12[b]							T8	S55–58	T10	S66–68
5	π-*exo*	*endo*									S57		
5	π-*endo*	*exo*			T4			S46		S46			
5	π-*endo*	*endo*											
6	π-*exo*	*exo*								T8			S66–67
6	π-*exo*	*endo*	S18–19					S45	S47			T10	S68
6	π-*endo*	*exo*	S12–17, F3[c]		T4	T5	S36–38	S46		T8, T9, S51	T11	S62	S69
6	π-*endo*	*endo*	T3, S16		T4	T5	S35	S40–46	S47	T8	S59–61, F6		S69
7	π-*exo*	*exo*											
7	π-*exo*	*endo*											
7	π-*endo*	*exo*	S20		T4	T5							S69
7	π-*endo*	*endo*	S13,18–19		T4	T5		S41	S47		T11, S64		
8	π-*exo*	*exo*											
8	π-*exo*	*endo*											
8	π-*endo*	*exo*	S21–22										
8	π-*endo*	*endo*		S23									

[a] T8 for example, refers to Table 8.
[b] S12 refers to Scheme 12.
[c] F3 refers to Figure 3.

classes. Somewhat surprisingly the 7-(π-*endo*)-*endo*-heterocycle is almost equally well represented.

As some classes are well represented, others are very poorly represented. For example, π-*exo* cyclizations (with a few exceptions) are poorly represented with only a select few examples in the formation of five- and six-membered rings. In addition the formation of five-membered rings via this general process is rarely seen even though a number of researchers have tried to carry out cyclizations to form this ring size. This is one of the few reactions that one might classify as a disallowed transformation. Not surprisingly both small (four-membered) and large (eight-membered) ring formation reactions have only a few examples.

The reactions between aziridines or epoxides and π-nucleophiles have provided a versatile set of chemical reactions that can be used both inter- and intramolecularly. While the reaction between aziridines/epoxides and π-nucleophiles has been used in a variety of synthetic efforts, there are still areas where no examples are known. For example, intermolecular reactions between epoxides and alkenes, as well as intramolecular reactions between heteroaromatic rings and aziridines. Similarly other types of π-nucleophiles such as alkynes and allenes have been rarely examined. The future of π-nucleophile—aziridine/epoxide reactions looks very interesting with a host of new reactions and applications to be discovered.

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Biographical sketch

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Susann Krake was born in Leipzig, Germany. She received her BS in 2005 and her MS in organic chemistry in 2008 under the supervision of Prof. Dr. Christoph Schneider from Universität Leipzig. During her Masters, she joined Ohio University for one semester as an exchange student. In 2008, she returned to Ohio University and joined the group of Professor Stephen C. Bergmeier as a Ph.D. candidate. Her current research involves the intramolecular Friedel–Crafts reaction of aziridines.