

Oxidative allene amination for the synthesis of nitrogen-containing heterocycles

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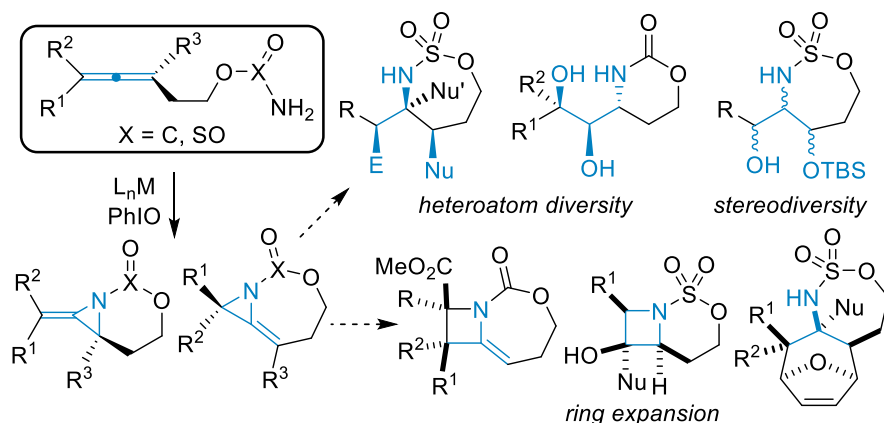
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Abstract

The prevalence of stereochemically complex amines in natural products, pharmaceuticals and other bioactive compounds, coupled with the challenges inherent in their preparation, has inspired work to develop new and versatile methodologies for the synthesis of amine-containing stereotriads ('triads'). The key step is a highly chemo-, regio-, and stereo-selective transition-metal catalyzed nitrene transfer reaction that transforms one of the cumulated double bonds of an allene precursor into a bicyclic methyleneaziridine intermediate. This account summarizes our strategies for elaboration of such intermediates into stereochemically rich, densely functionalized amine triads, nitrogen heterocycles, aminated carbocycles and other useful synthetic building blocks.



Keywords: Allene, nitrene transfer, amine, axial chirality, methyleneaziridine, azetidine

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1. Introduction

Stereochemically complex, densely functionalized amine-containing stereotriads ('triads') are a recurring theme in a host of natural products, bioactive molecules and pharmaceuticals.¹⁻¹² However, the preparation of amines containing three or more contiguous, heteroatom-bearing stereocenters can be challenging using conventional oxidations of functionalized alkenes, including dihydroxylation and aminohydroxylation,¹³⁻¹⁸ diamination,¹⁹⁻²⁴ asymmetric aziridination/ring-opening,²⁵⁻³⁴ or other difunctionalizations,^{35,36} as issues with control over the regio- and/or stereoselectivity often arise. An attractive alternative strategy involves transforming each of the unsaturated carbons of a chiral allene to a new sp^3 stereocenter, where the resultant triads map onto diverse amine motifs found in an array of biologically significant molecules (selected examples, Figure 1).

Despite the potential of allenes as convenient three-carbon synthons for the preparation of saturated stereotriads, they have been traditionally underutilized in this context.³⁷⁻⁴⁴ However, we felt that their ready accessibility from well-established reactions, the rapid increase in recent methods for their enantioselective syntheses, and their unique axial chirality, make them ideally suited for this purpose. Our group has been engaged in efforts to rapidly elaborate chiral allenes into densely functionalized and stereochemically complex amine triads via oxidative allene amination strategies. In this review, we describe a suite of methods to introduce heteroatoms into allenes through a highly chemo-, regio-, and stereo-selective allene aziridination reaction. Key features of our chemistry include versatility in the position of the C-N bond in the resulting triad, flexibility in the identity of the remaining two carbon-heteroatom bonds, stereochemical diversity, and effective transfer of axial-to-point chirality to furnish enantioenriched amines.

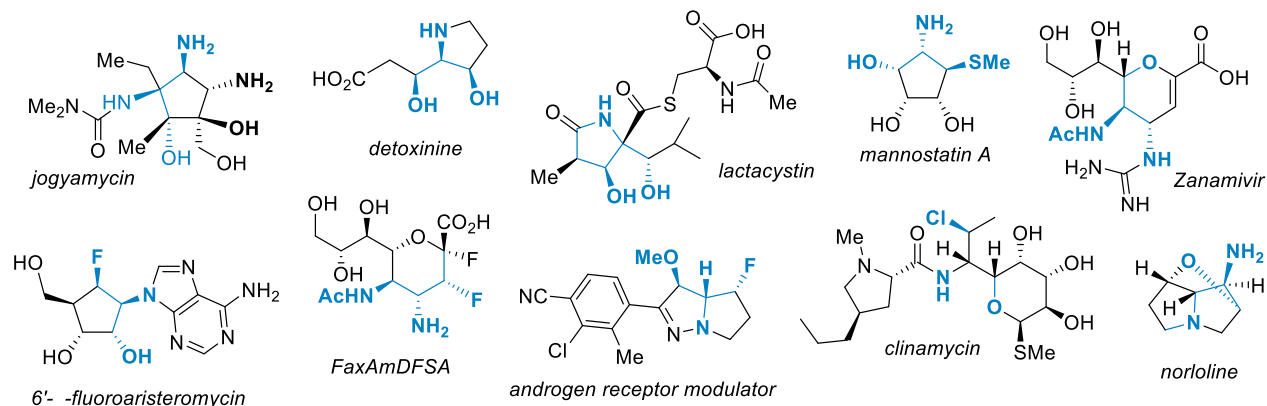
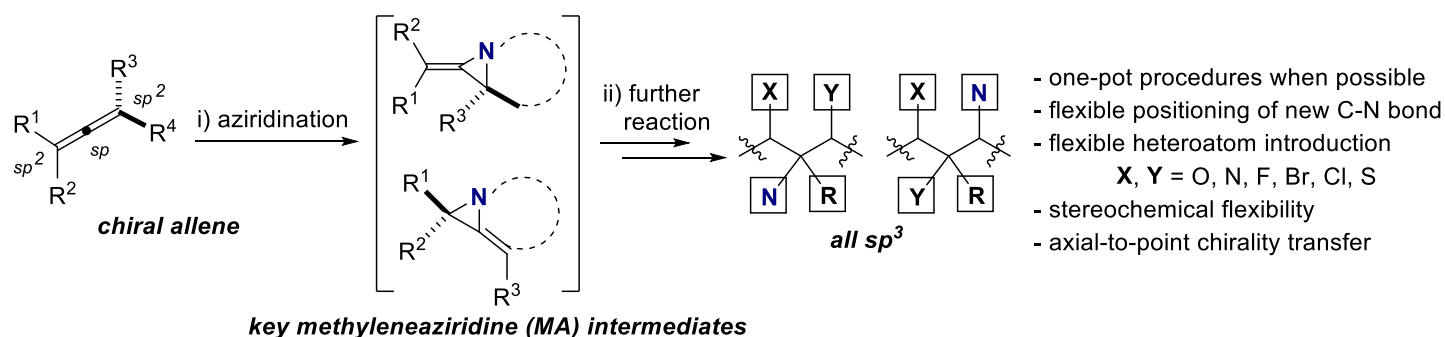


Figure 1. Selected bioactive molecules containing amine 'triads'.

1.1 Key features of chiral allenes enabling stereoselective syntheses of amine triads

Chiral allenes contain unique structural features poised to enable the tunable introduction of three new heteroatoms at each site of unsaturation (Scheme 1). For example, many allenes display axial chirality that is readily transferred to point chirality in the products with high fidelity.⁴⁵⁻⁵⁰ Allenes are more stereochemically flexible than their alkene counterparts, as a single allene can be selectively transformed into multiple stereoisomeric products. Finally, allenes offer the potential for the controlled introduction of an array of heteroatoms into the triad in a versatile manner.



Scheme 1. Goals for transition metal-catalyzed oxidative allene amination.

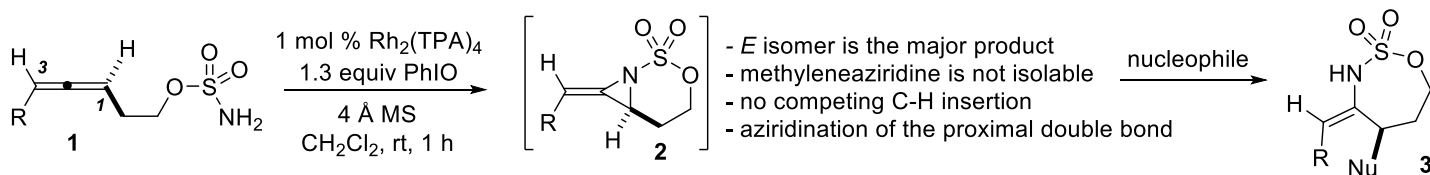
The key to harnessing the power of the allene synthon to deliver amine triads hinges on exploiting a chemo-, regio-, and stereoselective aziridination that generates reactive, strained methyleneaziridine (MA) intermediates (Scheme 1). Depending on the regioselectivity, two MA intermediates are possible, both of which display remarkable versatility in subsequent transformations to deliver acyclic and heterocyclic amines. In this review, we discuss several strategies to transform allenes to amine triad building blocks through the intermediacy of MAs, as well as applications of this chemistry to the preparation of bioactive molecules and the exploration of novel amine chemical space.

2. Methods for Transition Metal-catalyzed Allene Aziridination

2.1 Exocyclic bicyclic methyleneaziridines (MA) from sulfamate nitrene precursors

The first challenge in developing oxidative allene amination methodologies was to identify robust methods to achieve chemo-, regio- and stereoselective allene aziridination. Based on literature precedent and our initial

investigations, controlling the regioselectivity of intermolecular allene aziridination was difficult and often led to unstable products.⁵¹⁻⁵³ In contrast, intramolecular aziridination of homoallenic sulfamates of the form **1** (Scheme 2) using a dinuclear Rh(II) catalyst, such as Rh₂(TPA)₄ (TPA = triphenylacetate), yielded exocyclic methyleneaziridines of the form **2** with excellent chemo-, regio-, and stereoselectivity.⁵⁴⁻⁵⁶ While the labile **2** could be observed by NMR, it was readily opened in the presence of water or silica gel. Therefore, the aziridination was followed by immediate ring-opening to afford the enesulfamate **3** in good yield and excellent stereoselectivity in favor of the *E* isomer.⁵⁴

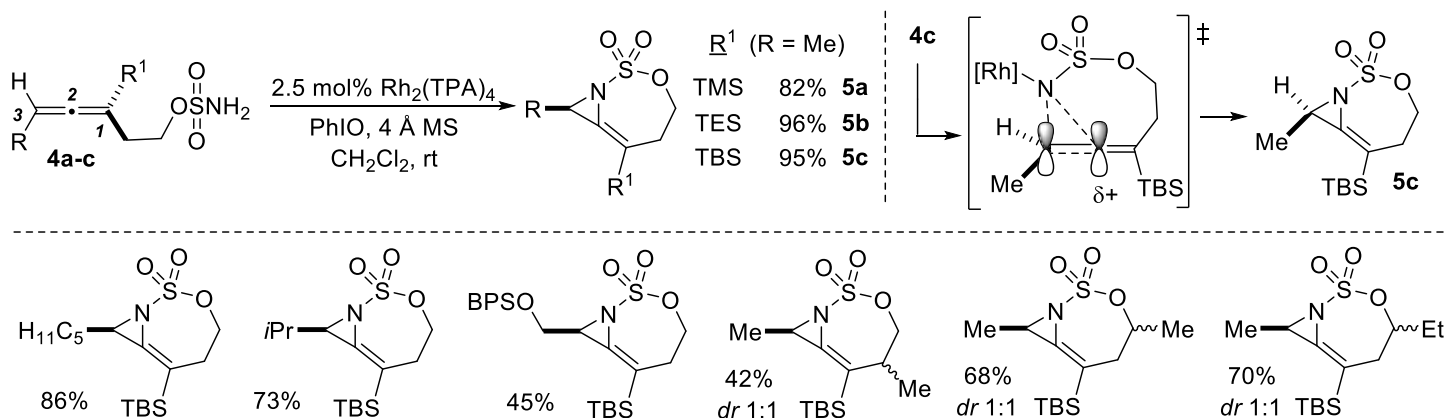


Scheme 2. Rh(II)-catalyzed aziridination of homoallenic sulfamates to bicyclic methyleneaziridines.

A variety of substitution patterns on **1** were tolerated, including 1,3-dialkyl-, 3-aryl-, and 1,1',3-trialkyl-substituted allenes. The nucleophile scope encompassed carboxylic acids, alcohols, thiols, halides and amines (Scheme 6, *vide infra*). The axial chirality of enantioenriched **1** was transferred to the enesulfamate products **3** with >95% fidelity.⁵⁴

2.2 Endocyclic methyleneaziridines (MA) from sulfamate nitrene precursors

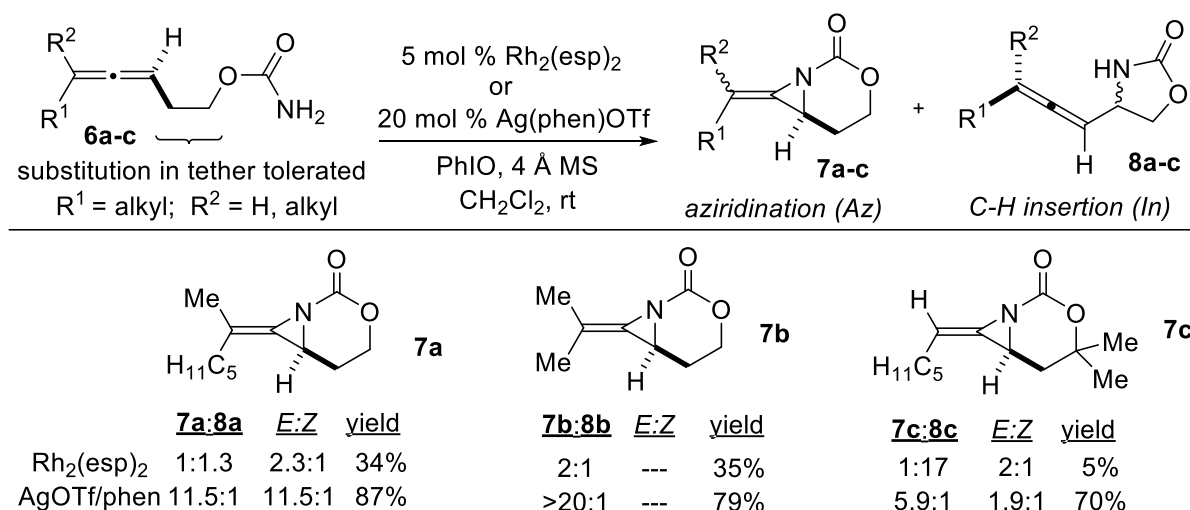
Reaction at the distal C2-C3 double bond of **4a-c** (Scheme 3) to generate endocyclic methyleneaziridines was achieved by installing a silyl group at C1 of the allene.⁵⁷ The electronic effect exerted by the trialkylsilyl group stabilizes the developing positive charge on the β carbon in the transition state through hyperconjugative interaction with the C-Si bond that is coplanar with the distal π orbitals, leading to **5c**. Monoalkyl substitution on C3 was well-tolerated in this chemistry, as was alkyl substitution in the tether between the allene and the sulfamate; however, 1,1',3,3'-tetrasubstituted allenes gave only elimination products. In contrast to the exocyclic MAs described in Section 2.1, endocyclic MAs were stable to column chromatography and could be readily isolated.



Scheme 3. Electronic control over the regioselectivity of allene aziridination at the C2-C3 bond.

2.3 Exocyclic methyleneaziridines (MA) from carbamate nitrene precursors

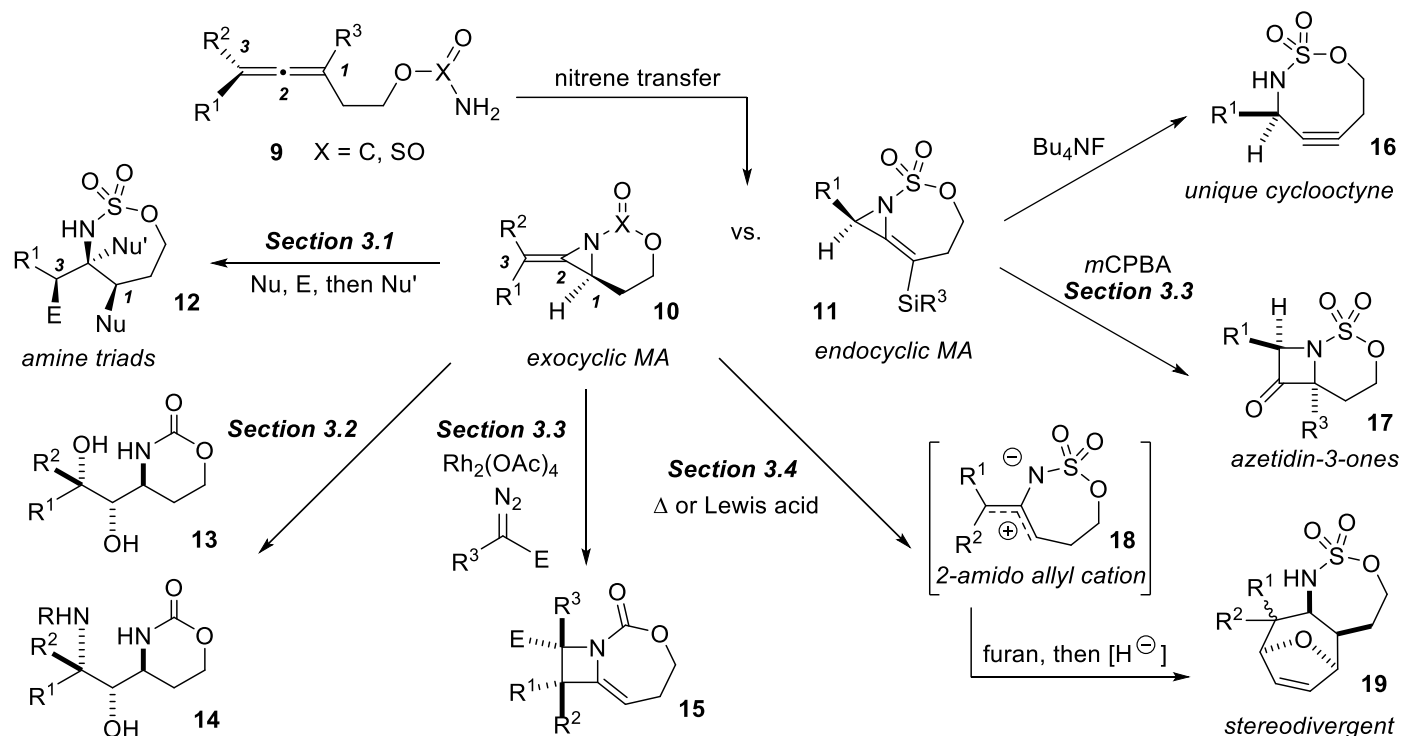
To expand the versatility of oxidative allene amination, homoallenic carbamates of the form **6** were explored in intramolecular allene aziridination (Scheme 4). In contrast to sulfamates, carbamates gave mixtures of *E:Z* isomers of **7**, as well as competing C-H bond amidation to **8**.^{58,59} The use of the Rh₂(esp)₂ catalyst (esp = $\alpha,\alpha,\alpha',\alpha'$ -tetramethyl-1,3-benzenedipropionic acid) and PhIO generally gave poor chemoselectivity for **7** over **8**. Fortunately, we found that AgOTf supported by bipyridine (bipy), 1,10-phenanthroline (phen), or dimethyl-bisoxazoline (tmbox) ligands resulted in excellent catalyst control over the chemoselectivity of the nitrene transfer event.⁶⁰⁻⁶² Approximately equimolar amounts of AgOTf and a phen ligand transformed allenes **6a-c** of diverse substitution patterns selectively into MAs **7a-c** with moderate-to-good *E:Z* ratios; the two isomers were easily separated by column chromatography. The carbamoyl-derived MAs were more robust than the analogous sulfamoyl-derived MAs and survived column chromatography with no competing ring-opening.



Scheme 4. Ag(I)-catalyzed aziridination of homoallenic carbamates.

3. Strategies for the Synthesis of Heterocycles from Oxidative Allene Amination

With methods in hand for chemo-, regio-, and stereo-selective syntheses of bicyclic MAs from allenes, chemistry to exploit their unusual features was explored. Scheme 5 presents a summary of the complex amine scaffolds accessible from **9** through the intermediacy of **10** and **11**. Approaches are divided into four main strategies; Section 3.1 addresses the ring-opening of sulfamoyl-derived aziridines **10** with an array of nucleophiles ultimately to furnish triads **12** with stereochemical flexibility at C1-C3. Section 3.2 describes reactions of carbamoyl-derived MAs **10** to furnish aminodiols and diaminoalcohols of the form **13-14**. Ring expansion strategies in Section 3.3 enable access to densely substituted azetidines **15** and **17**, heterocycles that are challenging to prepare with other synthetic methods. Finally, bicyclic MAs provide a convenient way to access 2-amidoallyl cation intermediates **18**, which are under-explored compared to their 2-oxallyl cations; this chemistry is discussed in Section 3.4.

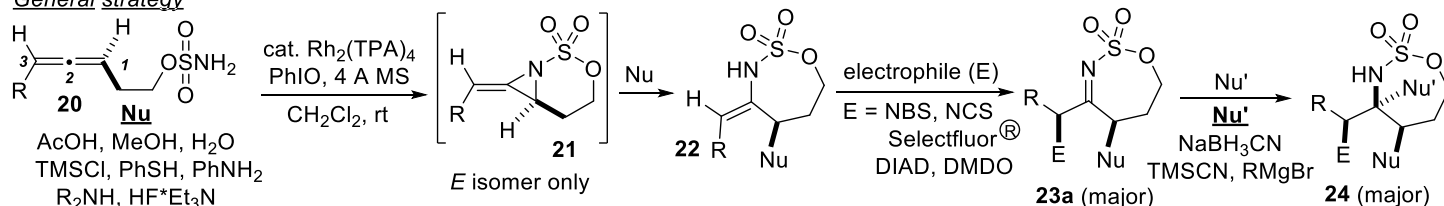
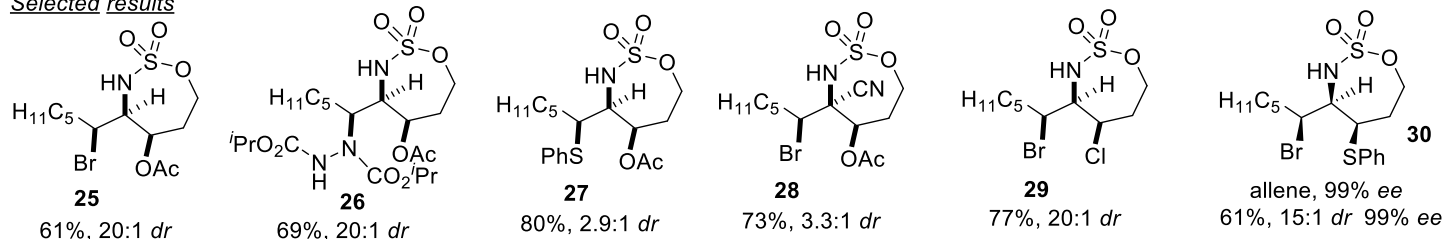
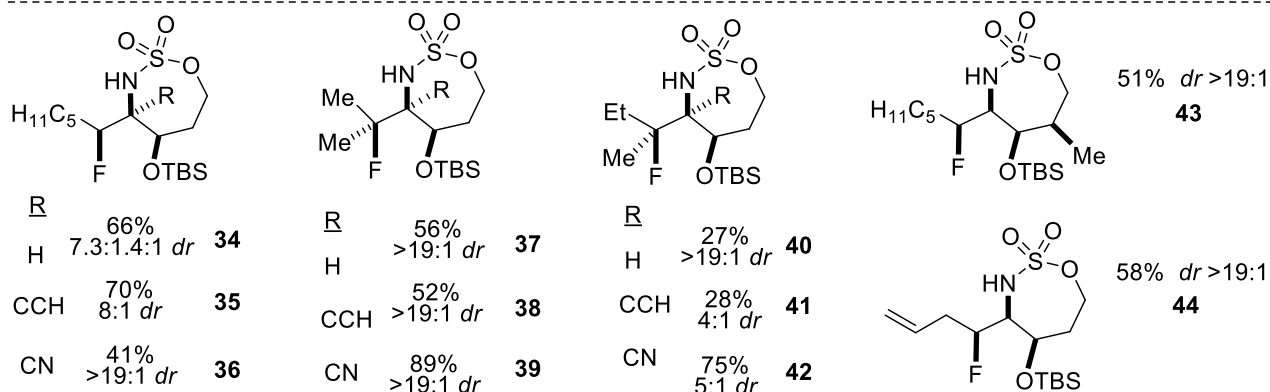
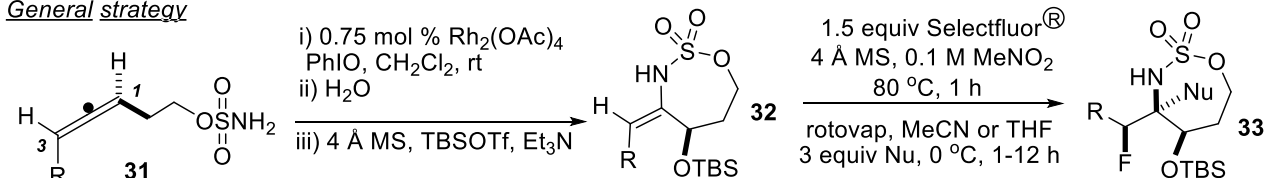


Scheme 5. Summary of oxidative allene amination methods.

3.1 Tandem allene aziridination/nucleophilic ring-opening

Two major advantages of utilizing MAs as reactive intermediates are their strain (*ca.* 42 kcal/mol) and the ability to exquisitely control the regioselectivity of nucleophilic ring-opening. Sulfamoyl-containing MAs are not isolable, but their high reactivity enables a convenient one-pot process to convert allenes to triads bearing contiguous, stereodefined C(*sp*³)-X or C(*sp*³)-C bonds.⁵⁴ Selected scope for the four-step, one-pot process is shown in Scheme 6 and entails: 1) aziridination of **20**, 2) in situ ring-opening of **21**, 3) electrophilic substitution of the resulting enesulfamate **22** to furnish **23**, and 4) a final imine reduction to furnish **24**. The ring strain and leaving group ability of the sulfamoyl group in **21** enabled diverse nucleophiles, including alcohols, carboxylic acids, amines, thiols, halides and water, to open the aziridine at rt. The resulting enesulfamates **22** reacted with a variety of electrophiles to introduce halogen, oxygen, sulfur, and nitrogen groups at C3 of the original allene. Imine **23** could be reduced with hydride, cyanide, or Grignard nucleophiles to give triad **24**. The 1,2-*syn*:2,3-*syn* diastereomer was typically the major product, due to the conformations adopted by **22** and **23** to minimize A^{1,3}-strain. The heteroatoms flanking the C2 amine could be tuned to give a diverse array of triads in good *dr*, including **25-29**. Importantly, efficient axial-to-point chirality transfer from the allene precursor to the triad was noted for **30**.

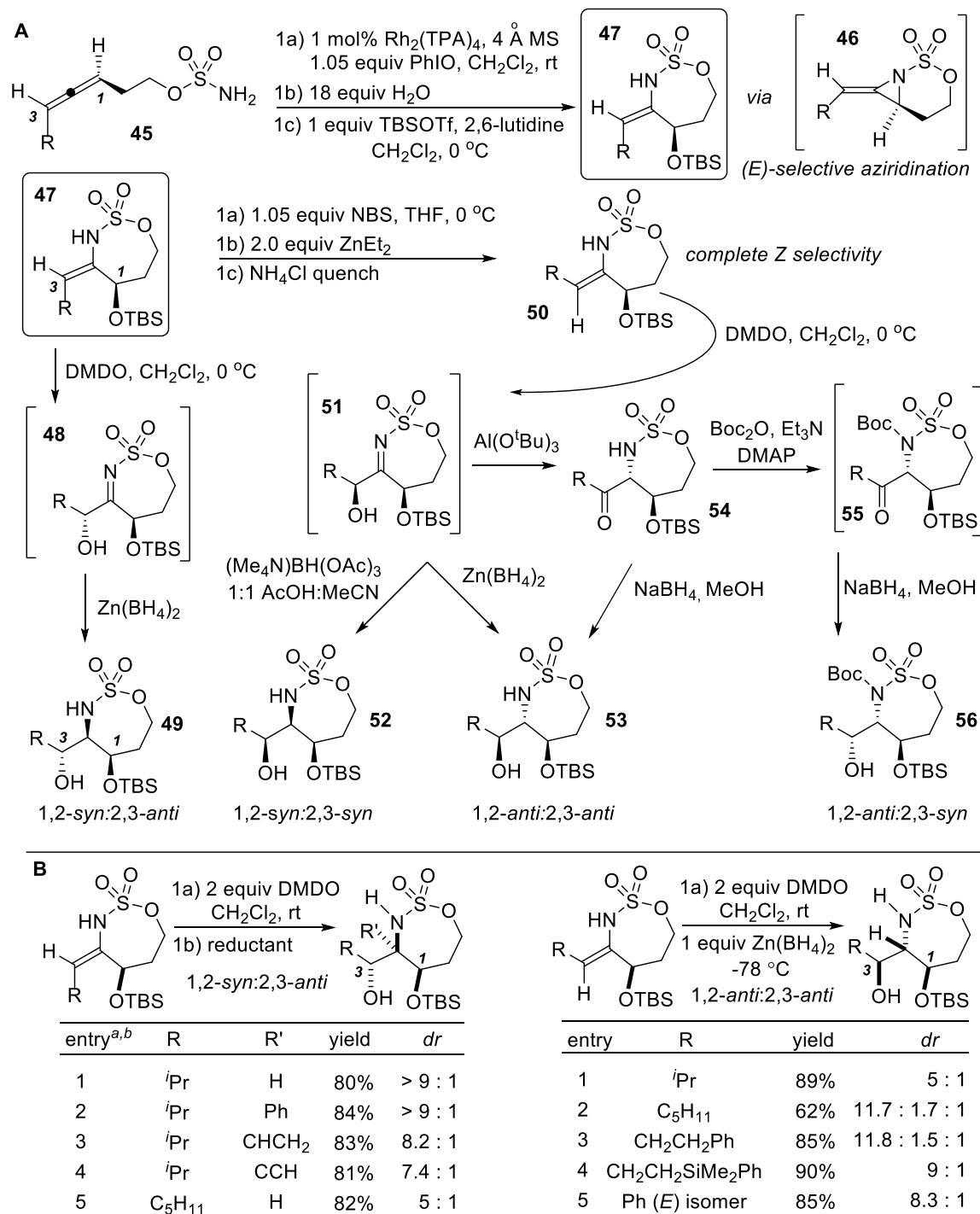
The presence of fluorine in drugs often leads to improved pharmacological properties; indeed, C(*sp*³)-F bonds are embedded in aminated triads that occur in anti-virals, neuraminidase inhibitors and modulators of androgen receptors (Figure 1, *vide infra*).⁶³⁻⁷⁰ Oxidative allene amination provides convenient access to fluorinated triads in good-to-excellent *dr* (Scheme 7)⁷¹ via reaction of **32** with Selectfluor^R,⁷² followed by reduction with hydride, Grignard or cyanide nucleophiles to furnish **34-44** in moderate-to-excellent *dr*. Our ability to install fluorine at quaternary carbons in **37-42** was particularly noteworthy, as this is challenging to achieve via fluoride ring-openings of typical epoxides or aziridines.

General strategySelected results**Scheme 6.** Selected scope of ring-opening of sulfamoyl-derived methyleneaziridines to aminated stereotriads.General strategy**Scheme 7.** Introduction of fluorine into all-*syn* amine stereotriads.

In addition to flexibility in the identity of the heteroatoms that can be introduced into amine triads, oxidative allene amination offers the potential for stereochemical versatility. For example, stereodivergent syntheses of O/N/O triads from single allene precursors has been achieved.⁷³ The general strategy is shown in Scheme 8A, where a single enantioenriched allene **45** can be converted to any one of the four possible diastereo- and enantioenriched amine triads **49**, **52**, **53**, and **56**.

The stereodivergent oxidative allene amination begins with a one-pot transformation of **45** to **47**, where a bulky OTBS group at C1 ensures good *dr* in the subsequent addition of **47** to dimethyldioxirane (DMDO) to give 1,3-*anti*-**48**, presumably via a concerted addition displaying an early transition state. The oxidation event can be telescoped with the reduction using $\text{Zn}(\text{BH}_4)_2$ to yield the 1,2-*syn*:2,3-*anti* triad **49**. Yields over the two steps are in the range of 80-84% (Scheme 8B, left) with moderate-to-good *dr*. Access to the remaining diastereomers requires isomerization of (*E*)-**47** to (*Z*)-**50**, which is achieved in near-stoichiometric yield using a one-pot addition/elimination sequence. Conversion of **50** to the 1,2-*anti*:2,3-*anti* triad **53** proceeds in a similar fashion

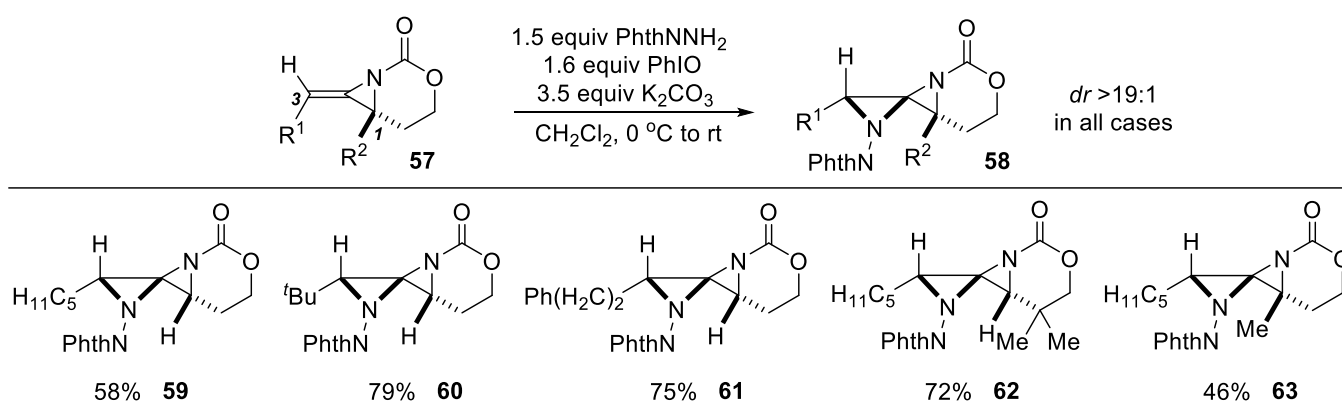
to that described for reaction of **47**. Selected scope is illustrated in Scheme 8B, right-hand table, furnishing 62–90% yields of the triads over the two steps with good *dr*. The reader is referred to the original reference for the scope of the remaining two triads **52** and **56**.⁷³



Scheme 8. Stereochemical diversity in oxidative allene amination.

3.2 Treatment of MA with electrophilic reagents

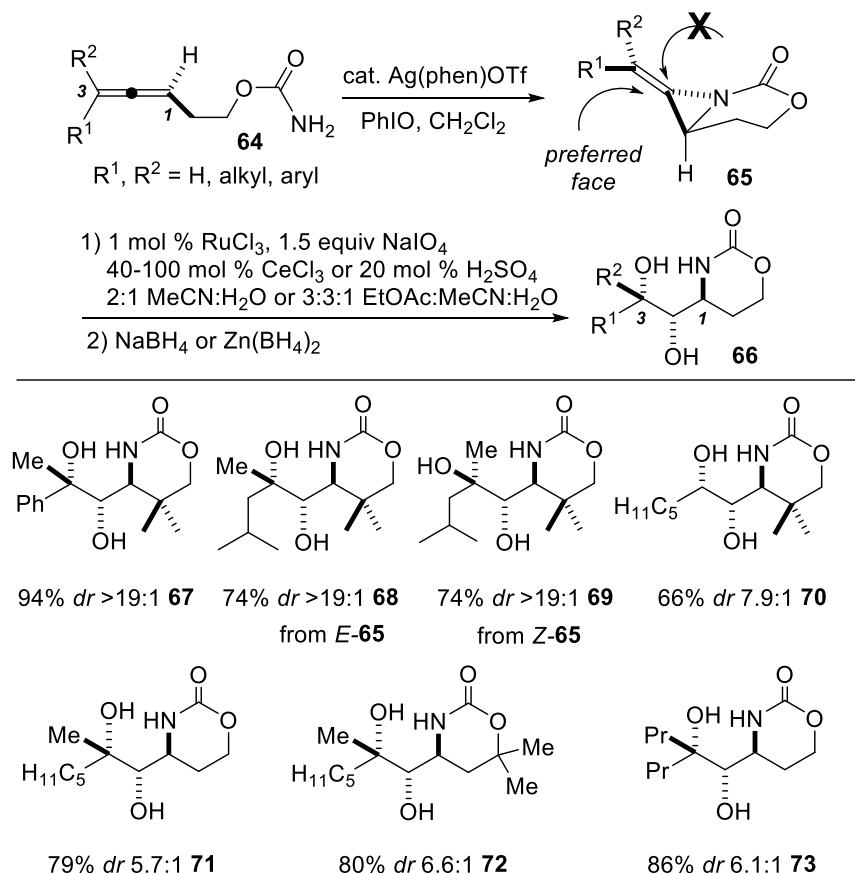
An alternative mode of reactivity of bicyclic MA intermediates involves functionalizing the exocyclic alkene prior to aziridine ring-opening. In this context, a carbamate nitrene precursor was necessary to ensure that the MA **57** was stable and isolable. The bicyclic ring renders electrophilic transformations of the alkene highly diastereoselective. For example, treatment of MAs of the form **57** (Scheme 9) with *N*-aminophthalimide (PhthNNH₂) in the presence of PhIO resulted in complete facial selectivity to give tricyclic 1,4-diazaspiro[2.2]pentanes **58** (DASPs) in >19:1 *dr*. Monoalkyl substitution⁵⁸ at C3 of the MA furnished **59-62** in good yields. The substitution pattern of the original allene, and hence the MA, could be varied to furnish DASPs **62-63** in good-to-moderate yields. One important feature of this 'intra/intermolecular' aziridination strategy is that the two rings of the DASP are electronically differentiated; the bicyclic aziridine contains an electron-withdrawing group, while the spiro ring bears an electron-donating group. Methods to selectively open either of these rings have been reported by our group; however, the difficulty of cleaving the N-N bond of the protecting group limits the utility of DASPs in this context.⁵⁸



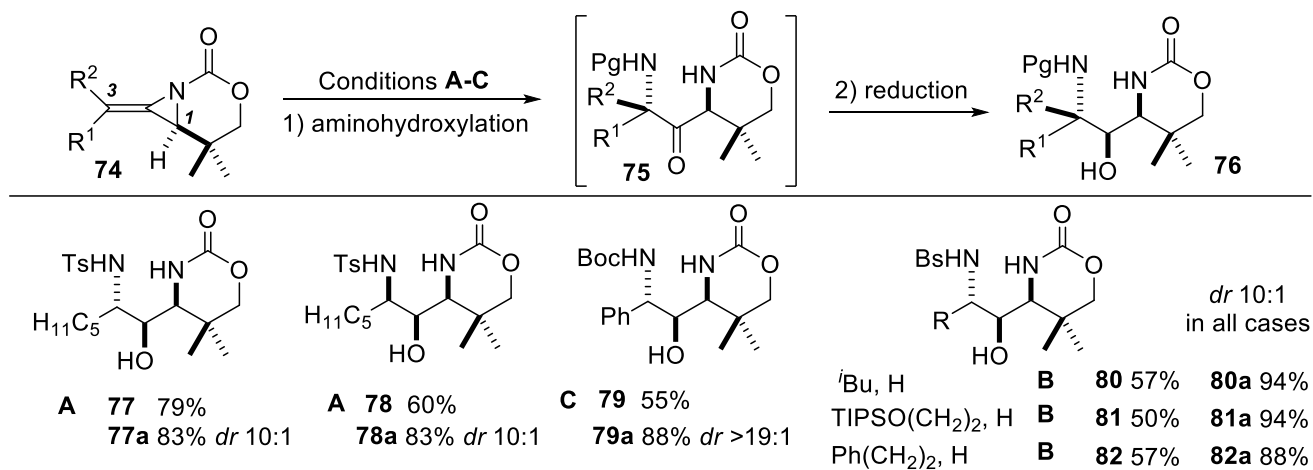
Scheme 9. Intermolecular aziridination of methyleneaziridines to 1,4-diazaspiro[2.2]pentanes.

An alternative strategy to functionalize **64** via **65** (Scheme 10) involves a RuCl₃-catalyzed dihydroxylation to yield 1-amino-2,3-diols of the form **66**.⁷⁴ The substitution pattern of **64** dictates the optimal conditions for the dihydroxylation, with 40 mol% CeCl₃ required for 1,3,3'-trisubstituted allenes and 100 mol% for 1,3-disubstituted precursors. Subsequent reduction with NaBH₄ furnished **67-70**. Removal of the *gem*-dimethyl group in the carbamate ring of **65** required a switch in additive from CeCl₃ to H₂SO₄ to prevent competitive aziridine ring-opening, as well as the use of Zn(BH₄)₂ as the reducing agent to give the 1,2-*anti*:2,3-*syn* aminodiol **71-73**.

Aminohydroxylation of carbamoyl-derived MA **74** furnished 1,3-diamino-2-ols **76** in good *dr*, provided a *gem*-dimethyl group was present in the precursor (Scheme 11).⁷⁵ The initial oxidation event gave direct access to the 1,3-diaminoketone products **77-82**, with the exocyclic nitrogen protected with an easily cleaved sulfonyl or Boc group. Selective reduction was achieved using NaBH₄ in either CH₂Cl₂ or a 1:1 mixture of CHCl₃:H₂O to give **77a-82a**. The process was general for a variety of alkyl- and aryl-substituted MAs derived from 1,3-disubstituted allenes, although the identity of the chloramine was crucial to obtain good yields. For example, sulfonamides (Conditions A-B) worked best for alkyl-substituted allenes, while BocNNaCl was a better nitrogen source when the allene was aryl-substituted. In contrast to the dihydroxylation of MAs, 1,3,3'-trisubstituted MAs were not tolerated and the *gem*-dimethyl group was critical for good *dr* in the reduction.



Scheme 10. Stereocontrolled dihydroxylation of MA to furnish 1-amino-2,3-diols.



A: Aminohydroxylation: 7.5 mol % $\text{K}_2\text{OsO}_2(\text{OH})_4$, Chloramine T, 33 °C. Reduction: NaBH_4 in CH_2Cl_2 , rt.

B: Aminohydroxylation: 10 mol % OsO₄, Chloramine B, 37 °C. Reduction: NaBH₄ in CH₂Cl₂.

C: Aminohydroxylation: 7.5 mol % OsO₄, BocNNaCl, 30 °C. Reduction: NaBH₄ in 1:1 CHCl₃:H₂O with sonication.

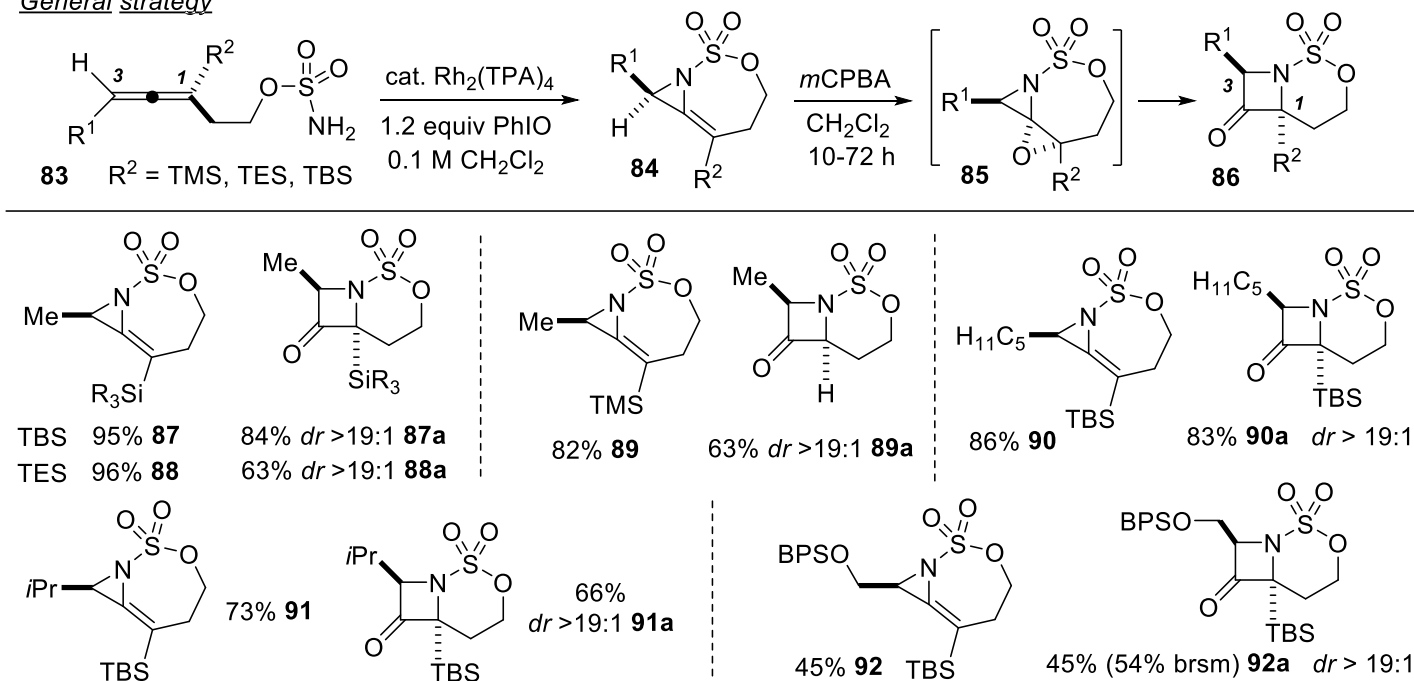
Scheme 11. Aminohydroxylation/reduction of MA to furnish 1,3-diamino-2-ols.

3.3 Ring-expansion strategies

Azetidines are four-membered saturated nitrogen heterocycles that are of interest for the rigidification of alkyl-substituted amines and for their potential as pharmaceutical candidates. The dearth of methods to prepare densely substituted azetidines with high levels of regio- and stereocontrol have stimulated interest in new synthetic approaches.⁷⁶⁻⁸³ Ring-expansion reactions of both sulfamoyl- and carbamoyl-derived MAs present a unique opportunity to provide stereocontrolled access to these heterocycles from allene precursors.

Endocyclic MAs are generated via aziridination of the distal allene double bond of a silylated allene **83** (Schemes 12 and 3, *vide supra*).⁵⁷ Following formation and purification of the column-stable MA **84**, oxidation of the double bond with *m*CPBA delivered the fused azetidin-3-one **86** in good yield and excellent *dr*.

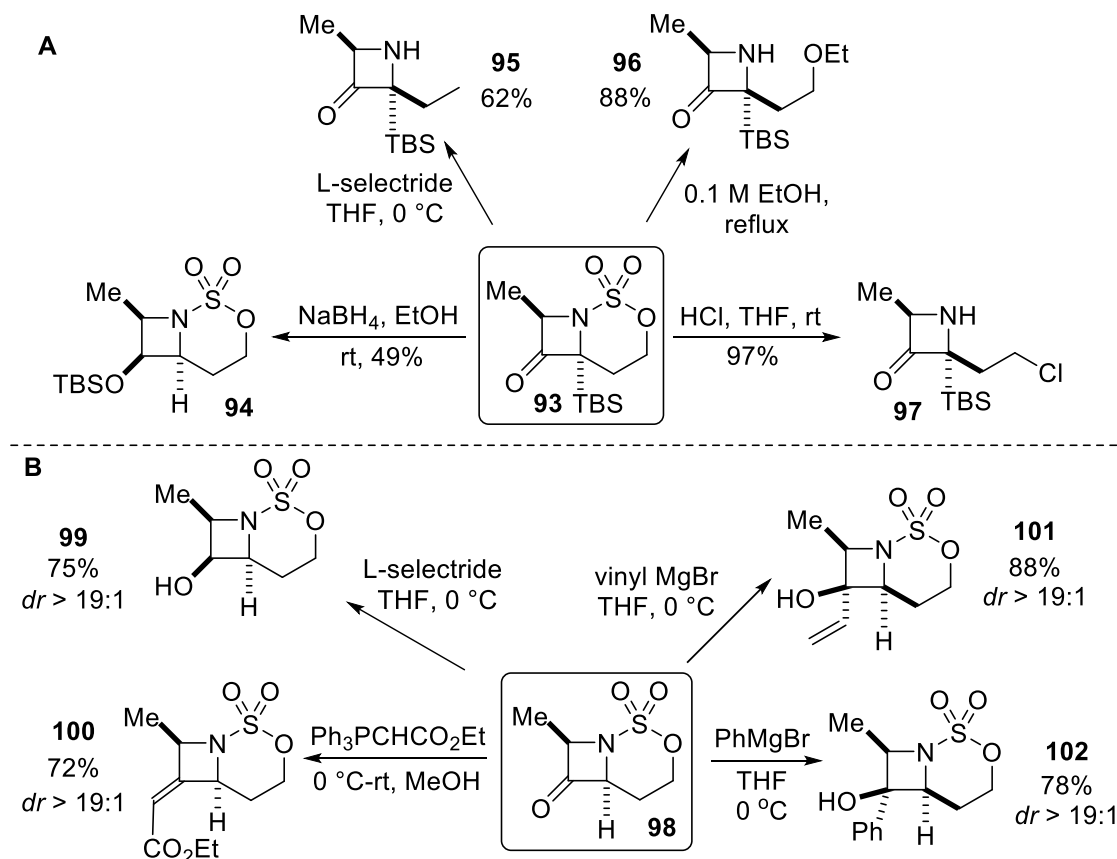
General strategy



Scheme 12. Selected substrate scope of the azetidin-3-one formation from endocyclic MA.

Formation of **86** was proposed to occur through rearrangement of a transient 1,4-oxaza-[2.2]spiropentane **85**, although this intermediate was not observed spectroscopically. In terms of the substrate scope, 1,1',3-trisubstituted allenes were well-tolerated to furnish heterocycles **87-92**. The size of the silyl group at R^2 (TBS vs. TES vs. TMS) did not affect the regioselectivity or the subsequent transformation of the endocyclic MA to the azetidinone, but could be engaged to control subsequent functionalizations of the heterocycle (Scheme 13). When diastereomeric mixtures of allenes were employed, two diastereomeric azetidinones were formed (not shown); these could be readily separated by column chromatography. In all cases, axial-to-point chirality transfer occurred with excellent fidelity to deliver enantioenriched products.

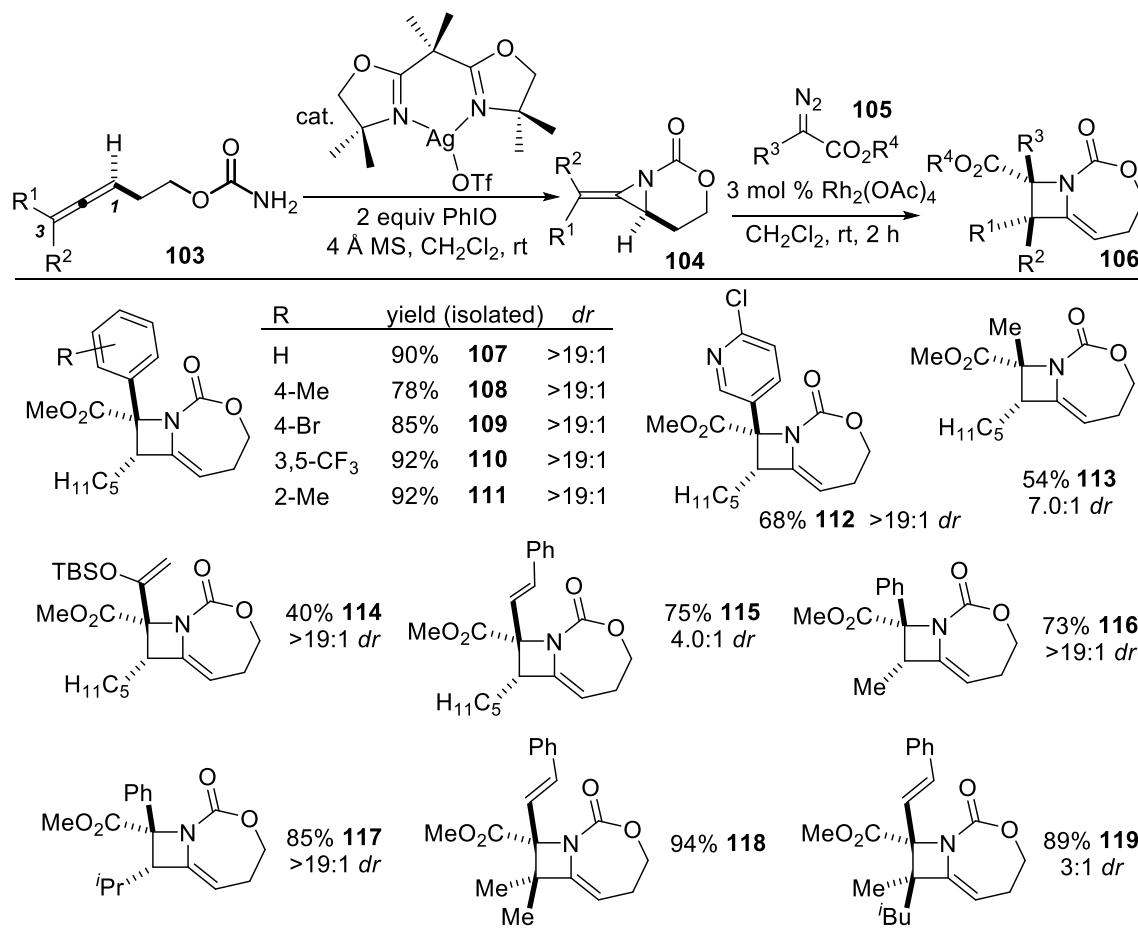
Further manipulations of azetidin-3-ones could be carried out by opening the sulfamate ring of the TBS-substituted **93** with nucleophiles to give **95-97** (Scheme 13A), where the bulky TBS group blocks the expected reaction at the carbonyl group. In contrast, the use of a TMS group on allenes of the form **83** leads to desilylation; treatment of the representative azetidin-3-one **98** gave reaction at the carbonyl group to deliver **99-102** (Scheme 13B).⁵⁷



Scheme 13. Further manipulations of azetidin-3-ones controlled by the identity of the silyl group.

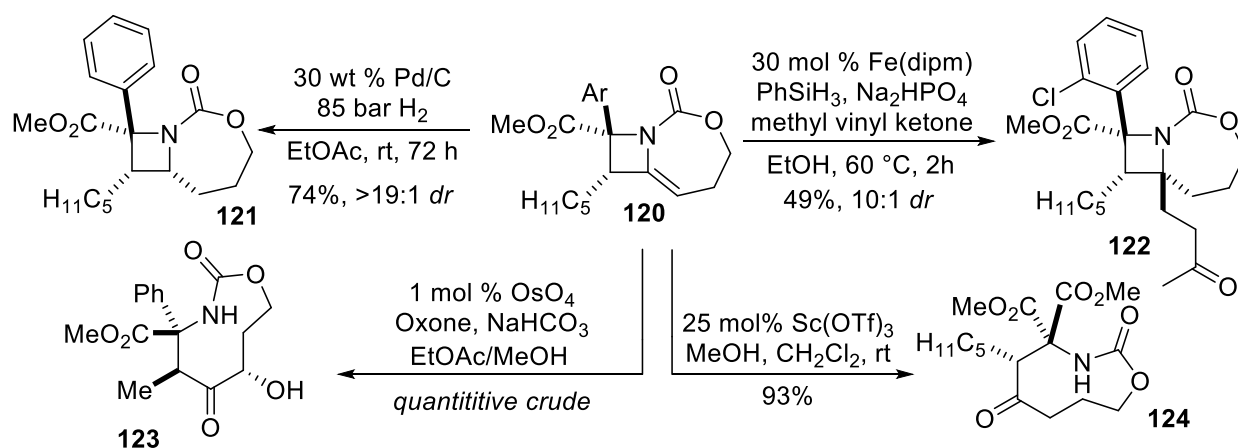
Silver-catalyzed aziridination of **103** gives excellent chemoselectivity for the carbamoyl-based MA **104** over competing C-H bond amidation (Scheme 14).^{60-62,84} Addition of a $\text{Rh}_2(\text{OAc})_4$ catalyst and a donor/acceptor carbene precursor **105** results in a stereoselective, one-carbon ring expansion to yield highly substituted methyleneazetidines of the form **106**. Phenyl diazoacetate, as well as electron-rich and electron-poor aryl diazoacetates, were successful in the reaction to furnish azetidines **107-111** in 78-92% yield and >19:1 *dr*.⁸⁴ Ortho substitution on the aryl ring of the carbene was tolerated, as were heterocycles represented by **112**. The aryl group of the donor/acceptor carbene precursor could be replaced with an alkyl or vinyl group, as in **113-114**; alternatively, a styrenyl-based carbene precursor cleanly gave azetidine **115**.

Alkyl-substituted *E*-MA isomers (>10:1 *E:Z*) were successful in the reaction, delivering **116-117** in good yields and excellent *dr*. While 1,3,3'-trisubstituted allene precursors gave bicyclic MAs that reacted slowly with bulky carbene partners, employing a less-hindered styrenyl diazo precursor gave fully substituted azetidine **118** in 94% yield. A highlight of the method was the conversion of a 4:1 mixture of *E/Z* isomers of a chiral MA to **119** in 3:1 *dr* and 89% yield. The diastereomers were easily separated to give the *syn*-Me/ CO_2Me isomer of **119** in 54% yield and 15:1 *dr*.



Standard conditions: Slow addition of the diazoester (1.3 equiv) to aziridine (1.0 equiv) over 2 h.

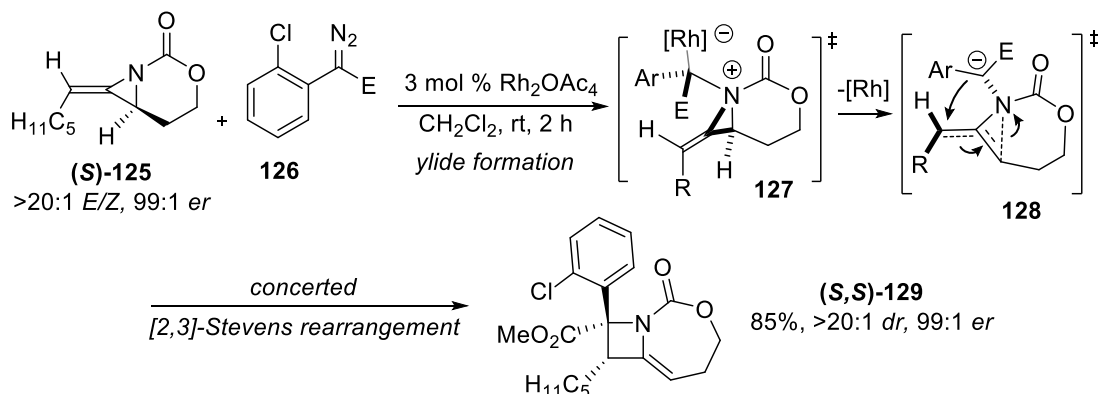
Scheme 14. Rh-catalyzed one-carbon ring expansions of carbamoyl-derived methyleneaziridines.



Scheme 15. Further transformations of bicyclic methyleneazetidines.

Methyleneazetidine **120** was further functionalized via hydrogenation to give azetidine **121** in high *dr* (Scheme 15). Baran's iron-catalyzed C-C coupling successfully delivered **122** in good *dr* to forge a second quaternary stereocenter on the azetidine.⁸⁵ Attempts to oxidatively cleave the alkene to give the β -lactam were unsuccessful, due to the tendency of the **120** to undergo ring-opening to furnish the interesting macrocycles **123-124** in good yield and *dr*.

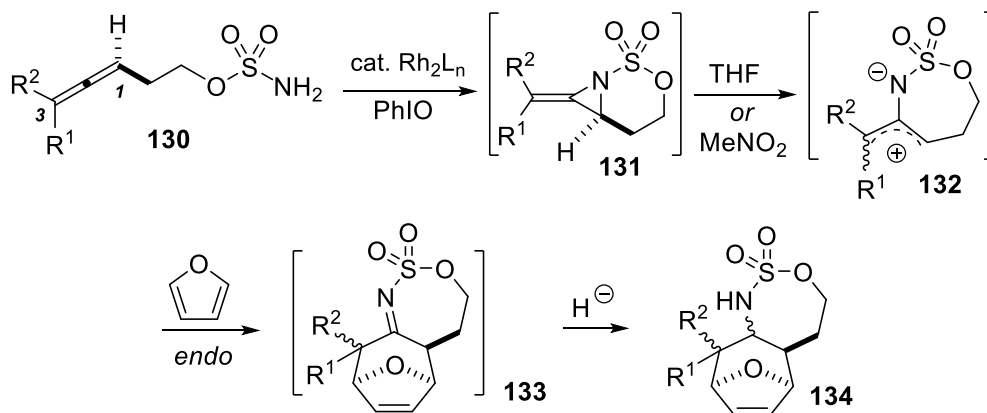
Mechanistic studies of this unusual Rh-catalyzed aziridine ring expansion showed that the chirality was transferred from the enantioenriched MA (*S*)-**125** to the azetidine (*S,S*)-**129** with excellent fidelity (Scheme 16).⁸⁴ Experimental and computational studies support the formation of an initial aziridinium ylide **127** *via* attack of the nitrogen on the Rh-bound carbene. Loss of Rh to **128**, followed by concerted [2,3]-Stevens rearrangement furnishes the azetidine product (*S,S*)-**129**.^{84,86}



Scheme 16. Mechanistic insight into Rh-catalyzed [3+1] ring expansions of Mas.

3.4 Formation and trapping of 2-amidoallyl cation intermediates

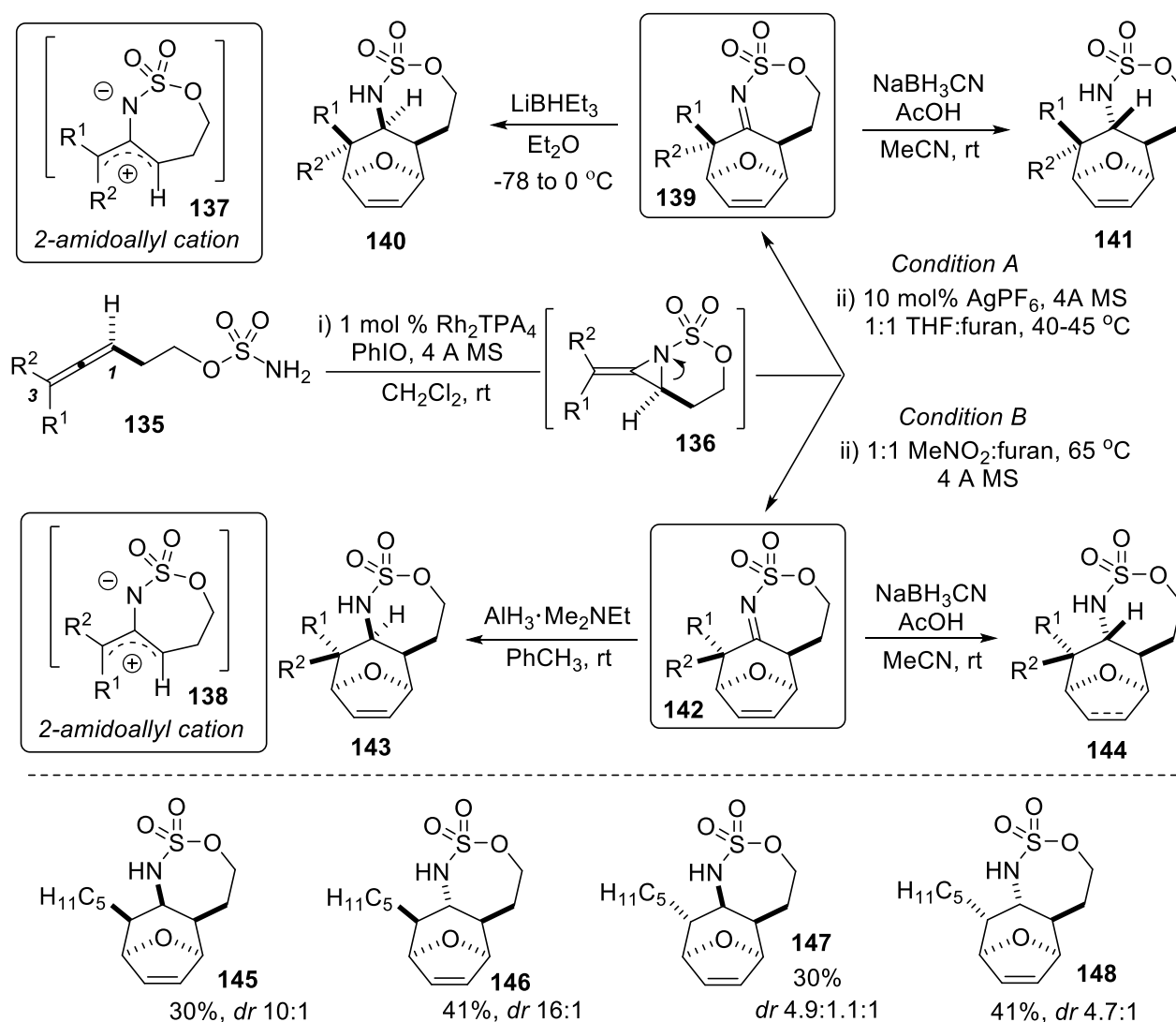
In contrast to the chemistry of 2-oxaallyl cations, their 2-azaallyl cation counterparts have received much less attention, due to the limited methods available to generate these reactive species cleanly.⁸⁷⁻⁹¹ Allene aziridination of **130** to **131** (Scheme 17) offers a stereodivergent approach to the synthesis of cycloheptenes of the form **134**. The general strategy involves the use of different reaction conditions to control the geometry of the 2-amidoallyl cation **132**.⁹² In this manner, the stereochemistry of the subsequent [4+3] cycloaddition with furan to furnish **133** could be altered in a tunable manner.⁹³ Likewise, reagent-controlled reduction in the transformation of **133** to **134** provides an opportunity to vary the relative stereochemistry between the amine at C2 and the stereochemistry at C1 and C3 of the original allene precursor. In this manner, stereodivergent syntheses of four different stereoisomers of **134** from a single allene might be accomplished.



Scheme 17. General strategy for stereodivergent transformations of allenes to carbocycles.

Stereodivergent [4+3] reactions were initiated by treating allene **135** with catalytic Rh₂TPA₄ to generate **136** *in situ*. Addition of a 1:1 mixture of furan/THF furnished the 1,3-*syn* heterocycle **139** through the intermediacy

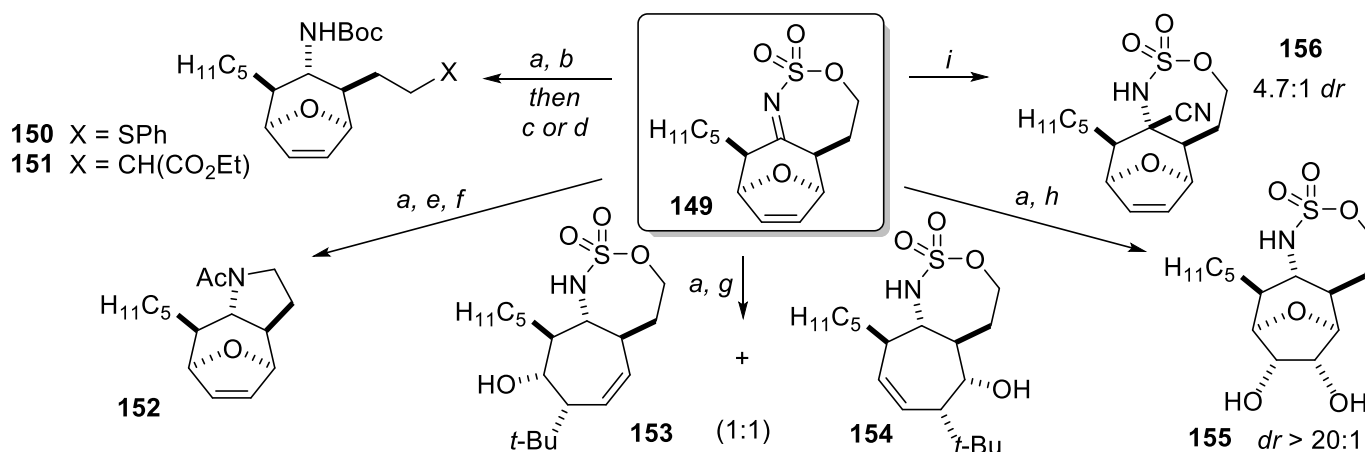
of **137**, whereas a 1:1 furan/MeNO₂ mixture delivered the 1,3-*anti* heterocycle **142** via **138**.⁹³ Further stereodivergence was accomplished in reagent-controlled reduction of the imines of **139** and **142**. Small hydrides, such as NaBH₃CN, favored approach of the nucleophile from the top face of **139** to furnish **141**, while reaction of **142** provided **144**. A bulky LiBHEt₃ reductant with **139** favored **140**, provided R² was H. Unfortunately, the use of LiBHEt₃ with **142** did not deliver **143** in good *dr*, and AlH₃Me₂NEt was required to yield the final diastereomer **143**, albeit with limited scope. The reaction sequence could be accomplished in one pot, with moderate yields over the three steps (Scheme 18, bottom for one example) and moderate-to-excellent *dr*. As expected, formation of the achiral 2-amidoallyl cation precluded effective transfer of axial-to-point chirality; however, an external asymmetric center was able to control the diastereoselectivity of the [4+3] reaction to yield product in 97% *ee* (not shown).⁹³



Scheme 18. Stereodivergent, [4+3] cycloadditions of furan with 2-amidoallyl cations from allenes.

Despite the moderate yields, this one-pot sequence significantly increases the structural complexity of a simple allene to give densely functionalized carbocycles. The products can be manipulated in a number of ways (Scheme 19), including ring-opening to yield **150-151**, ring contraction to deliver the pyrrolidine **152**, opening of

the oxygen bridge to furnish **153-154**, diastereoselective dihydroxylation to provide a fully substituted cycloheptane **155**, and addition of carbon nucleophiles to **149** to give **156**.



a: NaBH₃CN, AcOH, MeCN; 41%, 16:1 *dr* from allene. **b:** Boc₂O, DMAP, Et₃N, CH₂Cl₂, rt. **c:** PhSH, K₂CO₃, CH₃CN, rt; 75% from **149**. **d:** CH₂(CO₂Et)₂, Bu₄NBr, Cs₂CO₃, MeCN, rt; 58% from **149**. **e:** KO*t*-Bu, DMAP, CH₂Cl₂, 0 °C, then Ac₂O, rt; 96%. **f:** NaI, DMF, 60 °C, then NaH, 40-60 °C; 83%. **g:** *t*-BuLi, THF, -40 °C; 61%, 1:1 mix of regioisomers. **h:** 10 mol% OsO₄, NMO, acetone/H₂O, *t*-BuOH, rt; 65%, >20:1 *dr*. **i:** *n*-Bu₄NCN, MeCN, rt; 80% from allene.

Scheme 19. Synthetic utility of cycloheptene products.

4. Applications to the Synthesis of Complex Molecules

In addition to developing the utility of allenes for the synthesis of amine triads, we wanted to demonstrate how these methods might be utilized to synthesize complex molecules. Targets include novel aminosugars, unnatural and unique amino acids and aminocyclitol scaffolds.

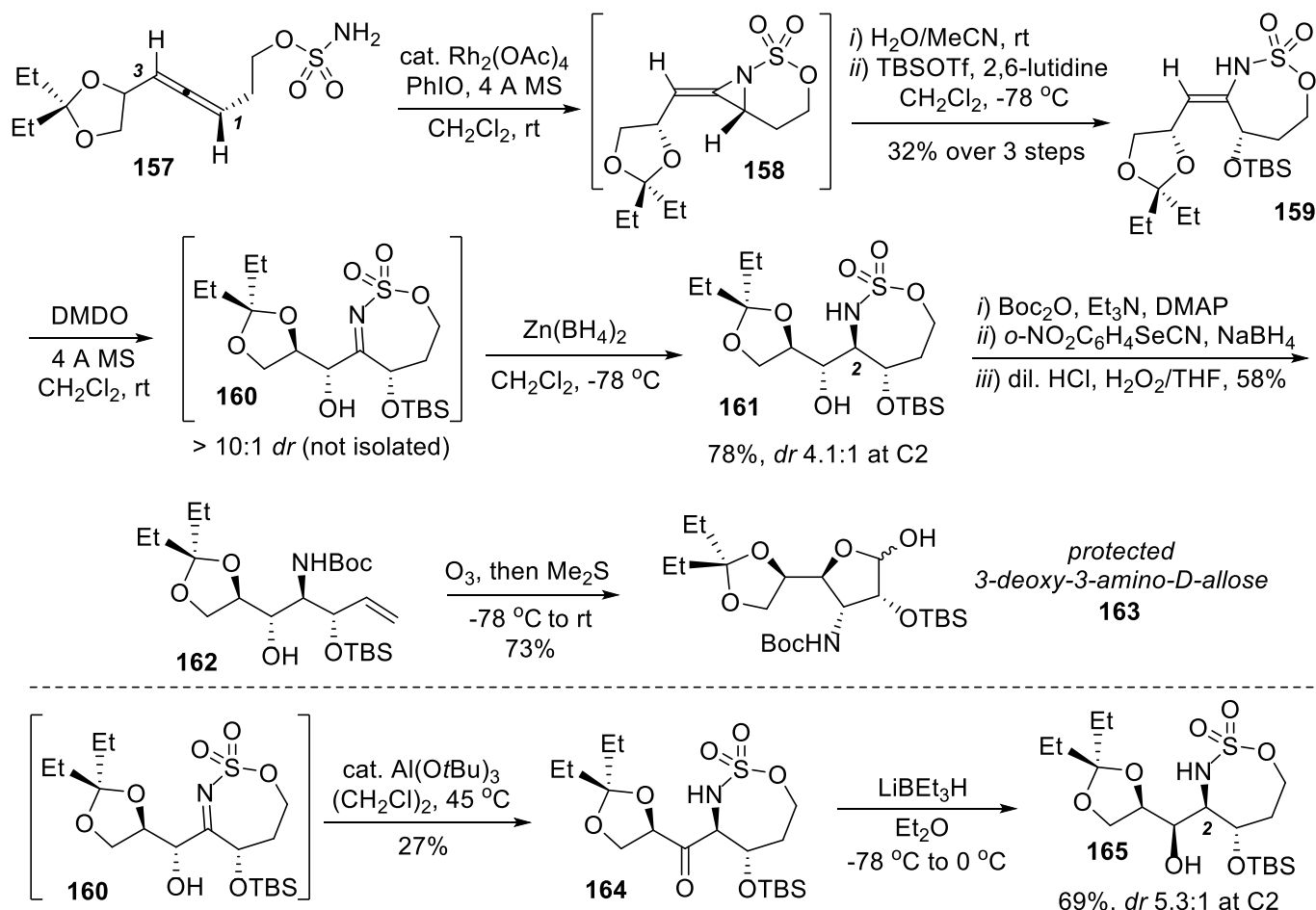
4.1 Synthesis of aminosugars

Aminosugars are present in a host of bioactive compounds, including mono- and polysaccharides, glycolipids, nucleotides, anthracycline antitumor agents, and antibiotics.⁹⁴⁻⁹⁸ While aminosugars, such as neuraminic acid and glucosamine, are commonly found in nature, there continues to be a need for versatile strategies to prepare 'designer' aminosugars with specific properties for incorporation into glycoconjugates. The ability to flexibly install three contiguous heteroatom-bearing stereocenters at each unsaturated carbon of an allene, coupled with control over relative stereochemistry and effective axial-to-point chirality transfer, has the potential to deliver useful building blocks for aminosugar libraries.

An example of the strategy employed for aminosugar synthesis from allenes is outlined in Scheme 20.⁹⁹ Enantioenriched allene **157** was easily prepared from D-mannitol; a one-pot aziridination to **158**, followed by water ring-opening and alcohol protection furnishes the enesulfamate **159**. Treatment of **159** with DMDO and a reductant yielded the 2-amino-1,3-diol motif **161** as a 4.1:1 mixture of easily separable diastereomers. A one-pot removal of the sulfamoyl group and cleavage of the resulting olefin *via* ozonolysis gave a protected derivative of 3-deoxy-3-amino-D-allose **163**.

While stereochemical flexibility in this chemistry (Scheme 8) was not thoroughly explored, Amadori-type rearrangement of α -hydroxyimine **160** to the α -aminoketone **164** (Scheme 20, bottom), followed by reduction

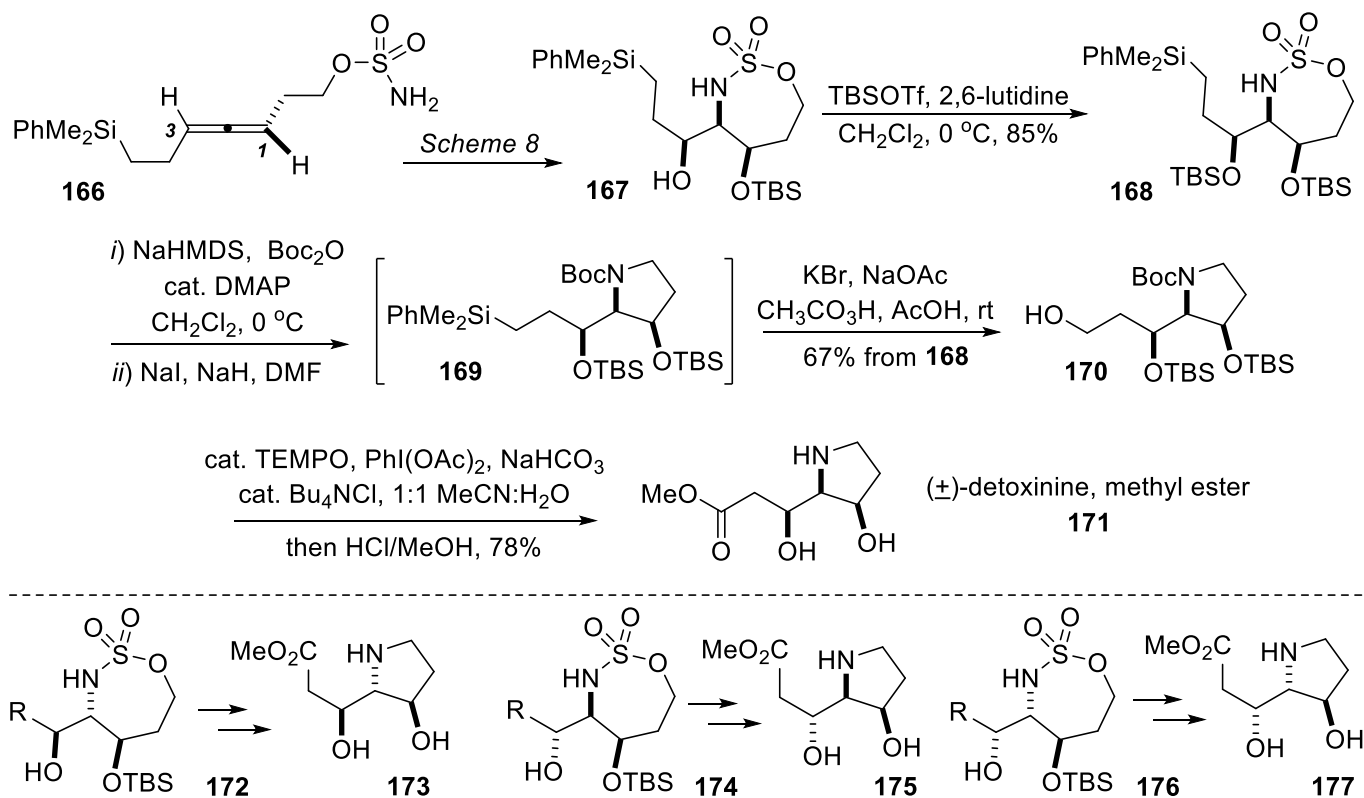
with LiEt_3H , gave **165** as the major stereoisomer, which maps onto 3-amino-3-deoxy-D-glucose.⁹⁹ We envisage this strategy could also be engaged to introduce a number of other heteroatoms into amine triads to furnish novel aminosugars.



Scheme 20. Synthesis of aminosugar building blocks via oxidative allene aziridination.

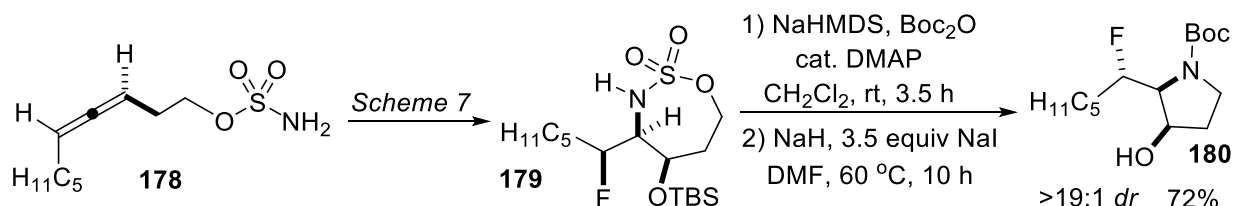
4.2 Synthesis of unusual and unnatural amino acids, and fluorinated pyrrolidines

4.2.1. Total synthesis of (±)-detoxinine, its methyl ester, and stereoisomers. Detoxinine is an unusual bis-hydroxylated γ -amino acid comprising the core of the detoxifying agent detoxin, a pyrrolidine that is co-administered with blasticidin S for treating rice blast disease.¹⁰⁰⁻¹⁰² The stereochemical flexibility of oxidative allene amination, as described in Scheme 8, enables a single homoallenic sulfamate **166** to be transformed to all four possible diastereomers of the methyl ester of detoxinine. A representative O/N/O triad **167** (Scheme 21) was prepared from **166** and transformed into methyl detoxinine. Protection of the free secondary alcohol of the all-*syn* stereotriad **167** gave **168** in 85% yield. A Boc group was installed on the amine, followed by a NaI -mediated ring contraction to give intermediate **169**, which was immediately subjected to Tamao-Fleming oxidation to furnish **170** in 67% yield from **168**. A two-step oxidation sequence, followed by an acidic workup, delivered the product (±)-detoxinine methyl ester **171**.¹⁰⁰ The same sequence of reactions could be applied to the three remaining diastereomers of **166** (**172**, **174** and **176**, Scheme 21, bottom) to give diastereomeric analogues of detoxinine, **173**, **175** and **177**.



Scheme 21. Total synthesis of (±)-detoxinine methyl ester and stereoisomers.

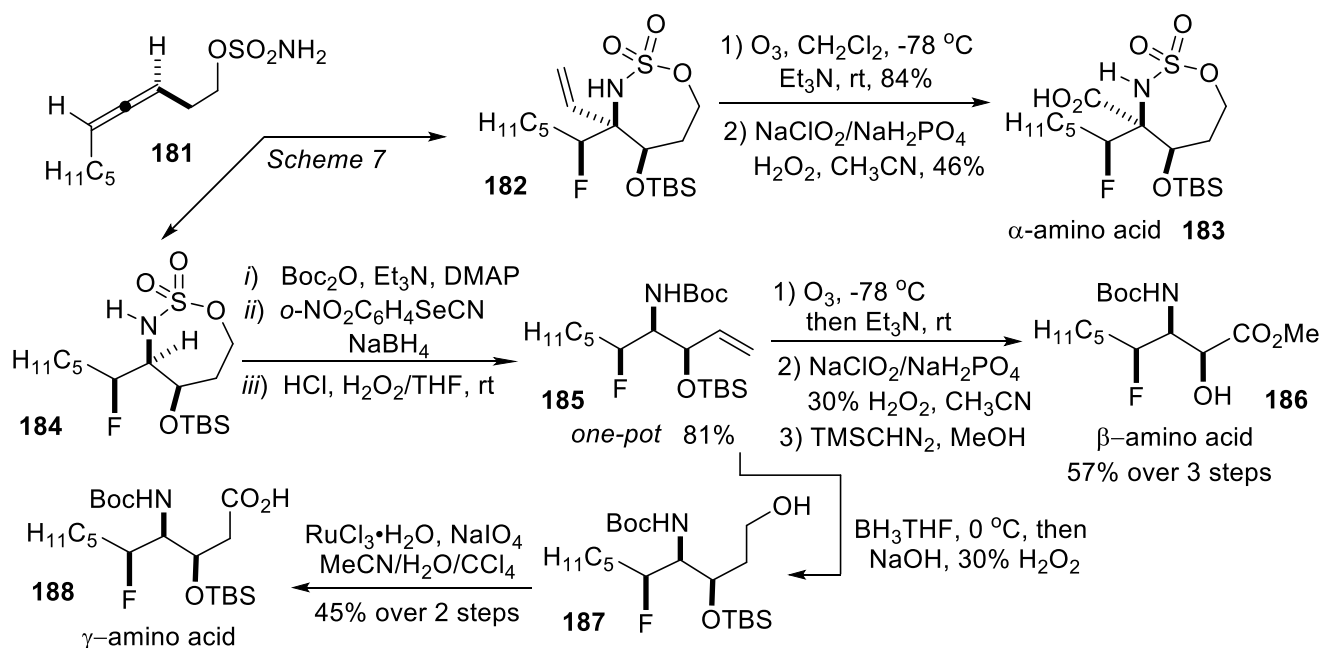
4.2.2. Fluorinated pyrrolidines and unnatural amino acids. Our ability to introduce fluorine into amine triads (Scheme 7, *vide supra*) was applied to the synthesis of fluorinated pyrrolidines found in powerful glucosidase inhibitors, including 2,5-dideoxy-2,5-imino-D-mannitol (DMDP)¹⁰³⁻¹⁰⁶ and inhibitors of purine nucleoside phosphorylase (PNP) (Scheme 22).¹⁰⁷⁻¹⁰⁹ Oxidative allene amination of **178** gave the triad **179** in moderate *dr* (Scheme 7, *vide supra*). The nitrogen was protected with a Boc group and the crude material subjected to a NaI-mediated ring contraction and purification to deliver the pyrrolidine product **180** in good yield and a *dr* >19:1.



Scheme 22. Synthesis of a fluorinated pyrrolidine scaffold through ring contraction.

Unnatural, fluorinated amino acids play key roles in directing protein-protein interactions, are frequently used in the design of hyperstable protein folds,¹¹⁰⁻¹¹⁴ and exhibit antitumor and antimicrobial activities.¹¹⁵⁻¹¹⁸ The fluorinated amine triads **182** and **184** obtained from the allene precursor **181** through the chemistry described in Scheme 7 are readily transformed in a few steps to α-, β- and γ-amino acids (Scheme 23). Ozonolysis of **182**, followed by Pinnick oxidation, yields the α-amino acid **183** in good yield. Triad **184** served as the substrate for the synthesis of β- and γ-amino acids. For example, the preparation of the protected β-amino acid **186** proceeded through an initial one-pot, three-step elimination of the sulfamate group of **184** to yield **185**.

Ozonolysis, Pinnick oxidation and esterification furnished **186**. The protected γ -amino acid **188** was obtained through the same intermediate **185** via a sequence involving hydroboration and RuCl₃-catalyzed oxidation of the alcohol to the carboxylic acid. The ability to transfer axial-to-point chirality from **181** to the amino acid products **183**, **186**, and **188** enables access to either enantiomer of these scaffolds.



Scheme 23. Transformations of fluorinated amine triads to unnatural amino acids.

4.3 Synthesis of the core of jogyamycin

The aminocyclopentitol core of jogyamycin. The natural product jogyamycin was isolated in 2012 from a culture broth of *Streptomyces* sp. a-WM-JG-16.2 (Figure 2).¹⁵² The molecule is a complex aminocyclopentitol, where each of the carbons in the core cyclopentane ring is functionalized with a stereodefined hydroxyl or amino group. Jogyamycin is a member of a small class of other natural products that display similar substitution patterns, including pactamycin, de-6-MSA-pactamycin and TM-026.¹²⁰⁻¹²⁶ Jogyamycin exhibits potent antiprotozoal activity against organisms that cause malaria and African sleeping sickness, while pactamycin and its analogs have been reported to display anticancer, antiviral and antimicrobial activities, in addition to antiprotozoal activities.¹¹⁹ A co-crystal structure of pactamycin bound to a *Thermus thermophilus* 70S ribosome indicate that the binding site is the 30S subunit; the molecule is believed to function as a universal inhibitor of translocation in a highly conserved region of the ribosome.¹²⁷⁻¹³⁰ Despite the similar binding sites for aminocyclitols in bacterial and mammalian cells, subtle structural changes in the aminocyclitol core can alter the activity of these natural products for reasons that are not yet well-understood.^{121,122}

The three contiguous quaternary stereogenic carbons of jogyamycin, as well as the dense functionalization around the ring that includes sensitive urea and aniline moieties, have inspired a number of strategies to achieve a total synthesis of this molecule.¹³¹⁻¹⁴² However, these efforts have either been unsuccessful or do not allow for deep-seated changes to the core of the molecule, rendering any future explorations of structure-activity relationships challenging.

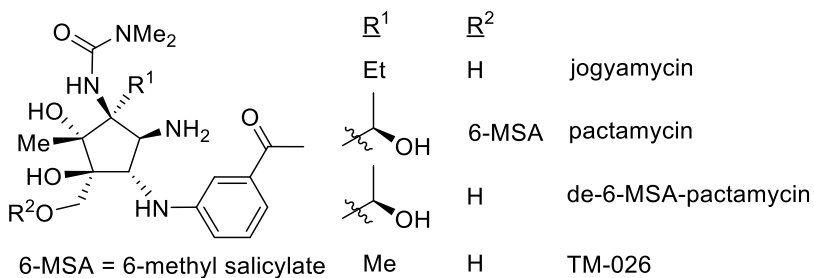
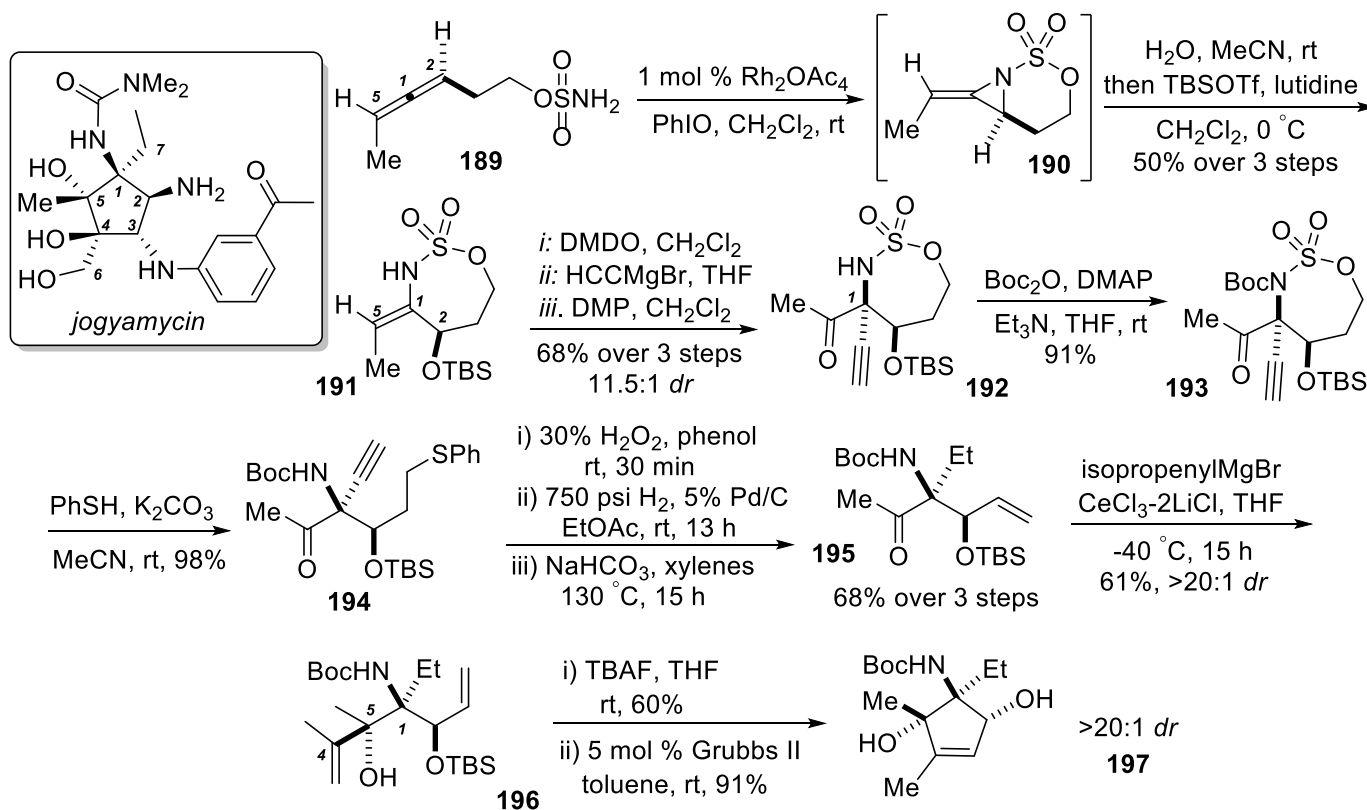


Figure 2. Aminocyclopentitol-containing bioactive natural products.

In order to investigate the impact of targeted changes to the core of jogyamycin on biological activity, we have applied oxidative allene amination to the synthesis of analogues of this natural product (Scheme 24).¹⁴³ A three-step, one-pot conversion of allene **189** to **191** was followed by another three-step, one-pot sequence to transform the enesulfamate **191** to the triad **192** in a *dr* of 11.5:1, which increased to >20:1 after purification. N-Boc protection of **192** furnished **193**; ring-opening of the sulfamate with a thiophenol nucleophile to **194** was followed by a one-pot, three-step sequence to install the alkene of **195** in a yield of 68% over the three steps. Chelation-controlled addition of isopropenylMgBr to **195** gave the amine triad **196** in >20:1 *dr*.



Scheme 24. Synthesis of the core of jogyamycin via oxidative allene amination.

Removal of the TBS protecting group from the secondary alcohol of **196** was required for successful ring-closing metathesis using Grubbs II catalyst to deliver cyclopentene **197** in 91% yield and >20:1 *dr*. In addition to accessing the core of jogyamycin, this approach offers flexibility in terms of the introduction of other heteroatoms into the cyclopentane core.

5. Concluding Remarks

Transition metal-catalyzed allene amination methods complement those of conventional alkene oxidation for the synthesis of complex amine-containing stereotriads. A chemo-, regio-, and stereo-selective allene aziridination reaction furnishes key bicyclic methyleneaziridines (MA) that can be manipulated in diverse ways. Ring-opening of the sp^3 aziridine carbon of the MA initiates a one-pot sequence to deliver C-X¹/C-N/C-X² triads, where the identities of the two flanking heteroatoms can be readily varied. This strategy was applied to the syntheses of aminosugars, detoxinine and its stereoisomers, fluorinated pyrrolidines, unnatural α -, β - and γ -aminoacids, and the core of a bioactive aminocyclopentitol, jogyamycin. The axial chirality of the allene offers the ability to achieve stereodivergence in the resulting triad products, as also enables axial-to-point chirality transfer in many cases.

In contrast to the direct nucleophilic ring-opening of MAs, diastereoselective dihydroxylations and aminohydroxylations on the exocyclic double bond of MAs furnished aminodiol and diaminoalcohols. Ring expansion of MAs to heterocycles, including azetidin-3-ones, methyleneazetidines, and unique sulfamoyl-containing cyclooctynes were reported. Finally, treatment of MAs with heat or Lewis acid generates 2-amidoallyl cations that could be trapped with furan in a stereodivergent manner to deliver aminated cycloheptene scaffolds were described.

Remaining synthetic challenges include the development of selective, intermolecular allene aminations, transition metal-catalyzed strategies to convert racemic allenes to enantioenriched triads, and converting each unsaturated carbon of the allene to a new sp^3 C-C bond.

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Jennifer M. Schomaker received her Ph.D. degree in 2006 from Michigan State University, working under the supervision of Prof. Babak Borhan. After completing an NIH postdoctoral fellowship at UC-Berkeley under Prof. Robert Bergman and F. Dean Toste, she began her independent career at the University of Wisconsin-Madison

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