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Synthesis and applications of methyleneaziridines

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Methyleneaziridines (MAs) are a special subset of aziridines featuring an exocyclic C–C double bond on the three-membered ring. They have found great potential in organic synthesis. In this review, the structural characterization of MAs, synthetic methods, chemical transformations and mechanisms, especially the advances achieved over the past decade are comprehensively summarized.

1. Introduction

Aziridines are versatile building blocks in organic synthesis because their high strain energy associated with small rings provides a significant driving force for ring-opening functionalizations.[1] Besides, their derivatives featuring unsaturated C–C bonds attached to the ring, such as vinylaziridines and ethynylaziridines, have attracted considerable attention as well. Surprisingly, in contrast, methyleneaziridines (MAs) with an exocyclic C–C double bond are much less studied, possibly due to their facile degradation and lack of practical synthetic methods (Fig. 1).

One of the most fundamental features of MAs is the introduction of a trigonal sp^2-centre into the three – membered ring, which leads to a further increase in the angle strain energy. Computational studies have demonstrated that the strain energy of 2-methyleneaziridine is 12–13 kcal mol^{-1} (HF/6-31G*) higher than that of aziridine.[2] NMR data shows that the $^1J_{C,H}$ of 1-*tert*-butylmethyleneaziridine is 170 Hz,[3] a little higher than the corresponding coupling constants in methylenecyclopropane.[4] Additionally, the C=C stretching frequency in the IR spectra of MAs is raised to around 1770 cm^{-1}.[5]

Theoretical studies, together with a number of X-ray analyses,[6] indicate that the conjugation between the π-electrons of C=C and the lone-pair electrons of nitrogen atom is rather limited.[2] Even so, compared with simple aziridines,[7] this weak

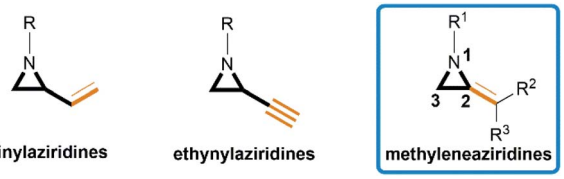

Fig. 1 Structures of vinylaziridines, ethynylaziridines and methyleneaziridines.

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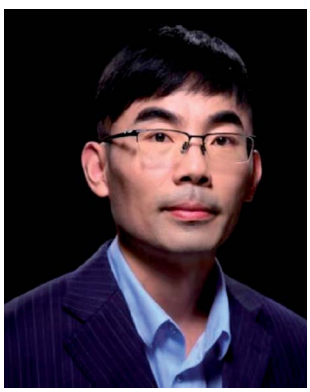

Feng Li obtained his M.S. degree in medicinal chemistry in 2007 from Nanchang University, China. He obtained his PhD degree in organic chemistry in 2012 from Fudan University, China. After postdoctoral studies (2012–2014) in Zhejiang University, he worked at Ocean University of China for 5 years, then joined Weifang University of Science and Technology in 2019. His current research focuses on medicinal chemistry, chiral chemistry and pharmaceutical process.

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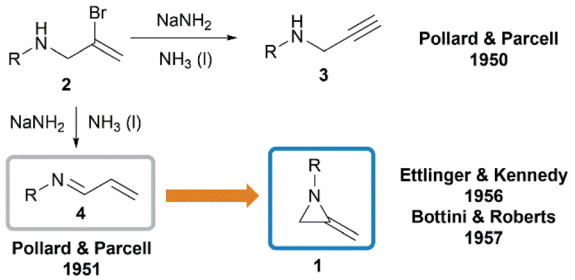
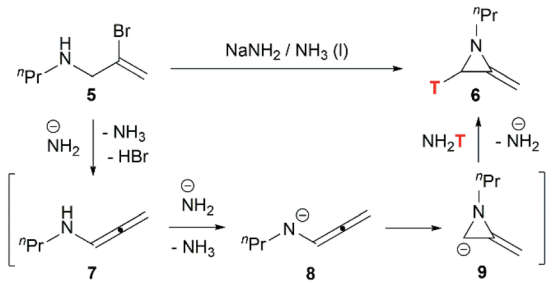
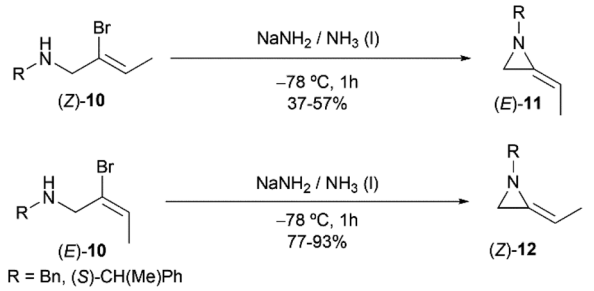


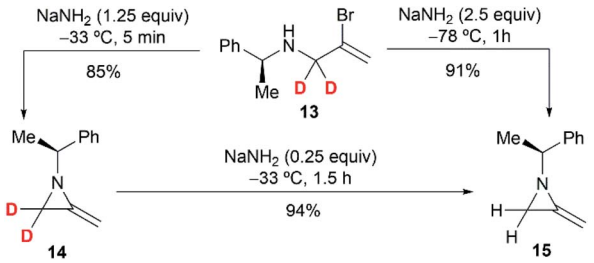
Scheme 1 Synthesis and structure of MAs.



Scheme 2 Proposed elimination–addition mechanism.



Scheme 3 Stereocontrolled ring-closing to 2-ethyleneaziridines with inversion at the vinylic carbon atom.



Scheme 4 Cyclization studies using deuterium labelled substrates.

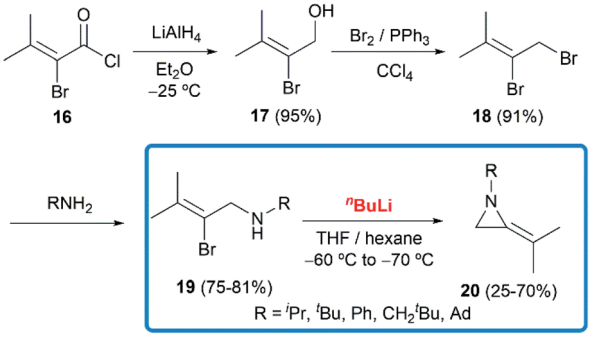
conjugated effect can still shorten the length of the N–C2 bond and cause the faster rate of inversion of the nitrogen, thus leading to the higher reactivity of MAs. Owing to these unique structural properties, the MAs have shown great potential in chemical transformations. In 2006, Shipman and co-workers published an account on their own contributions to the synthesis and reactivity of MAs.[8] Tehrani and Kimpe, in 2009, also summarized some representative works on this area.[9] Nevertheless, to facilitate the understanding of the principles of MAs and discover new reactions of MAs, it would be highly desirable to provide a comprehensive review of these compounds. Furthermore, given the increasing number of publications in this area over the past decade, there is also an urgent need to give an updated summary on recent advances. This review attempts to cover the literatures of MAs, comprehensively, including the synthesis of these heterocycles and their useful transformations, such as nucleophilic ring-opening reactions, multicomponent reactions, cycloadditions and transition-metal-catalyzed reactions. Additionally, the synthesis of bicyclic MAs and their typical reactions will also be discussed in detail in Section 4.

Yingying Zhao was born in Hebei Province, China, in 1990. She received her B.S. degree from Jiangsu University in 2013 and PhD degree from Dalian Institute of Chemical Physics, Chinese Academy of Sciences, in 2018, under the guidance of Prof. Boshun Wan. Then she began her career at Liaoning Normal University, where she works on the exploration of new catalytic cycloadditions for the synthesis of heterocycles.

2. Synthesis of monocyclic MAs

2.1. Base-induced cyclization and dehydrobromination reaction

In 1951, when Pollard and Parcell attempted to synthesize propargylamines **3** by reacting *N*-(2-bromoallyl)ethylamine **2** with sodium amide in liquid ammonia, MAs were first obtained accidentally.[10] The results were inconsistent with their previous work on the preparation of propargylamines from the corresponding tertiary amines.[11] However, at that time, Pollard and Parcell proposed *N*-allylidene-alkylamine **4** as the product (Scheme 1), based on the fact that the strong signal detected at



Scheme 5 ^{n}BuLi-induced cyclization to synthesize MAs.

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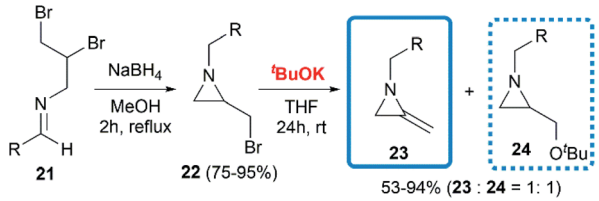
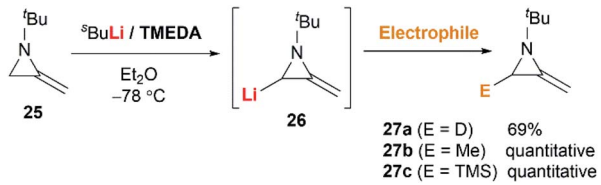
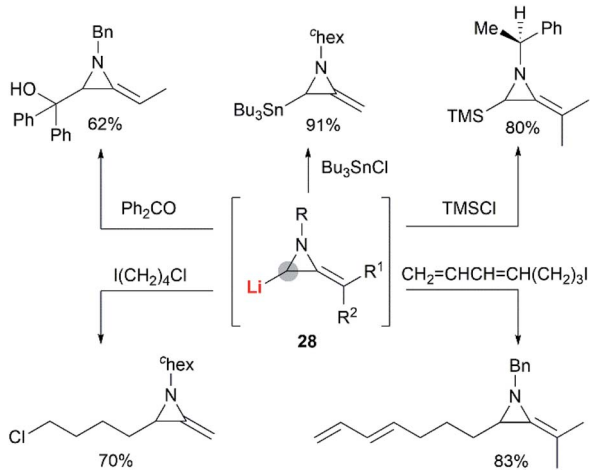


Scheme 6 ^{t}BuOK-induced dehydrohalogenation of aziridines.



Scheme 7 Functionalization of MAs by deprotonation–alkylation.



Scheme 8 Examples of C-3 functionalization using lithiated MAs.

1770 cm^{-1} in infrared spectrum and absence of the N–H or C=C stretching frequencies.

In 1956, Ettlinger and Kennedy noted that the stretching frequency of 1770 cm^{-1} was similar to exocyclic alkene bond in methylenecyclopropanes and reassigned the structures as methyleneaziridines **1** (Scheme 1),[12] which was later confirmed by Bottini and Roberts through NMR spectroscopy and chemical degradation studies.[5] It is noteworthy that, up till now, $NaNH_2$-promoted cyclization still remains the most general method for the synthesis of *N*-alkyl/benzyl substituted monocyclic MAs.[13]

Although this cyclization has been used for nearly 70 years, the mechanism is still controversial. Bottini and Olsen found that when the ring-closing reaction of **5** was performed in tritium-enriched ammonia, C-3 tritium-labelled product **6** was obtained exclusively. Besides, neither **5** nor **6** could undergo hydrogen–tritium exchange with the solvent under the reaction conditions. Therefore, it is suggested that the MAs are formed *via* an elimination–addition process (Scheme 2).[14]

However, this explanation was questioned by Shipman and co-workers. Because they observed that (*E*)- and (*Z*)-**10** yielded different regioselective products (Scheme 3),[15] while if following the elimination–addition mechanism, both substrates would yield the same allene intermediate and lead to the convergence of stereochemistry.

To further investigate the mechanism, the Shipman group studied the ring-closing of deuterated 2-bromoallylamine **13** (Scheme 4). There is no significant deuterium loss in the product **14** (92% D) when treating **13** with $NaNH_2$ for five minutes at −33 °C, indicating that anion **9** could not be intermediate in this cyclization. Treatment of **13** with excess $NaNH_2$ (2.5 equiv.) for a longer time (1 h) yielded normal MA **15** wherein all the deuterium had been lost. Additionally, deuterated MA **14** (92% D) could be completely converted into non-deuterated **15** (2.5% D) under the cyclization conditions. These experimental results, along with the observed stereochemical inversion in the preparation of MAs (Scheme 3) support an 'SN_2-like' substitution mechanism with inversion by in-plane σ-attack from the backside of the C–Br bond.[16]

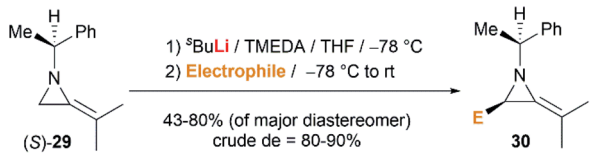
In 1981, Steinberg and co-workers reported the ^{n}BuLi-induced cyclization route to obtain MAs.[17] Treatment of **19** with ^{n}BuLi in THF and hexane at low temperatures gave the disubstituted MAs **20** with acceptable overall yields (16–49% over 4 steps) (Scheme 5).

De Kimpe and co-workers attempted to build the MA structures by a base-induced, exocyclic β-elimination reaction of 2-(bromomethyl) aziridines.[18] A series of substrates were synthesized in good yield, then treated with ^{t}BuOK in THF at room temperature. A 1,2-dehydrobromination reaction furnished the expected products **23** in moderate yield, however, the production of an equimolar amount of *tert*-butyl ether **24** seemed unavoidable (Scheme 6).

2.2. Functionalization of monocyclic MAs

MAs could be lithiated using *sec*-butyllithium and subsequently alkylated with a range of electrophiles. Quast and Vélez first demonstrated that 1-*tert*-butyl-2-methyleneaziridine **25** could be converted into **26**, quantitatively, by deprotonation with ^{s}BuLi in the presence of TMEDA.[19] This organolithium species further reacted with a limited range of electrophiles (MeOD, MeI or Me_3SiCl) to give MAs **27a–c** in good yield (Scheme 7).

The Shipman group successfully achieved deprotonation–alkylation sequences with MAs bearing different N-substituents and alkene substitution patterns. Many common electrophilic reagents such as MeOD, MeI, $PhCH_2Br$, CH_2=$CHCH_2Br$, PhCHO, Ph_2CO, Me_3SiCl and Bu_3SnCl could be used



Scheme 9 Asymmetric induction in the lithiation–alkylation of MAs.

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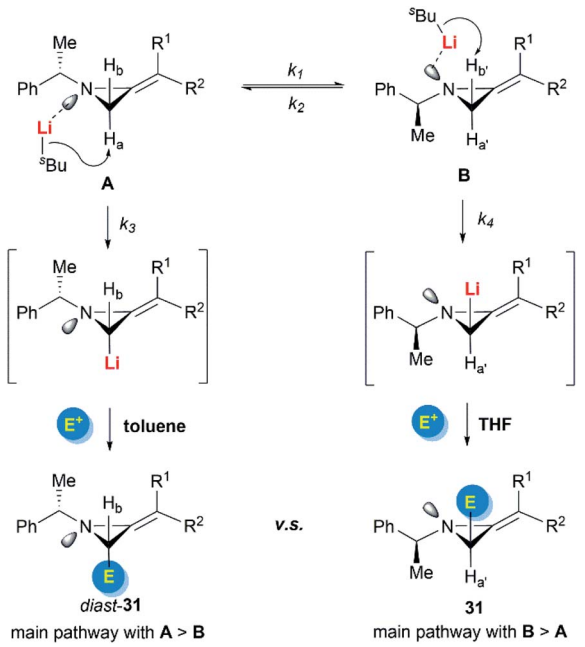
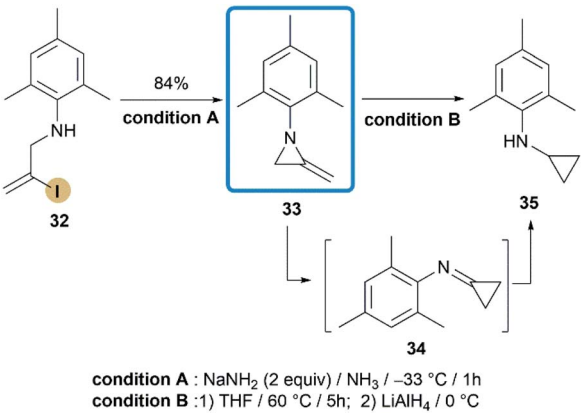


Scheme 10 Reactivity switch based on nitrogen stereodynamics.



Scheme 11 Synthesis and rearrangement of 1-mesityl-2-methyleneaziridine.

successfully (Scheme 8).[20] However, the reaction was limited to the formation of monosubstituted products at C-3.

Considering a new stereocenter generated in this process, Quast and Vélez had tried adding [(*S*,*S*)-(+)-bis(dimethylamino)-2,3-dimethoxybutane] as auxiliary chiral agent to control the stereochemistry of reactions as depicted in Scheme 7.[21] Unfortunately, very modest enantioselectivity (12.3% ee) was detected in the deprotonation–alkylation. Shipman *et al.* reasoned that the introduction of a chiral element into nitrogen atom of the aziridine might improve the enantioselectivity. Gratifyingly, high levels of asymmetric induction have been achieved when isopropylidineaziridine (*S*)-**29** was lithiated and alkylated by a range of electrophiles, including MeI, $PhCH_2Br$, $CH_2{=}CHCH_2Br$, Ph_2CO and Me_3SiCl (Scheme 9).[22]

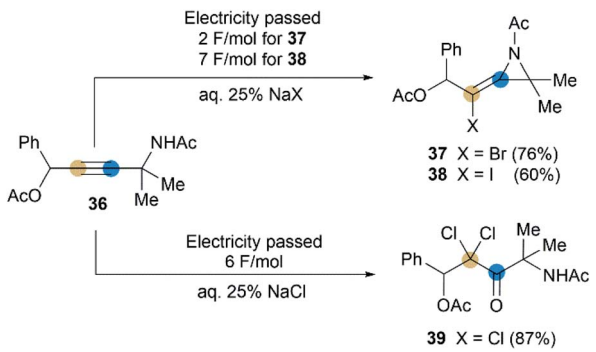
Shipman and Luisi *et al.* further investigated the stereoselectivity observed in the lithiation–alkylation of MAs.[23] Factors such as nitrogen inversion barrier, the stereochemistry at the nitrogen atom, the substitution pattern of the MAs, and the reaction conditions were all taken into consideration. As described in Scheme 10, they concluded that the interplay between nitrogen stereodynamics and complexation phenomena seems to be crucial in determining the stereochemical outcome of the lithiation/trapping sequence. The findings were rationalized by a synergistic use of NMR experiments, run on the lithiated intermediates, alongside computational data.

2.3. Synthesis of *N*-aryl and N-electron-withdrawing groups substituted monocyclic MAs

In contrast to the convenient synthesis of MAs bearing alkyl or benzyl groups on nitrogen, construction of aryl or electron-withdrawing groups substituted MAs on the N-atom remains a big challenge.

In 2015, Shipman and co-workers reported their effort on the synthesis of *N*-aryl MAs.[24] Based on the DFT calculations and competition experiments, a vinyl iodide **32** was designed and prepared for ring-closing reaction. Inspiringly, treatment of **32** with $NaNH_2$ successfully provided MAs **33** in a high state of purity after aqueous workup with 84% yield (Scheme 11). Although there was only one case in this research, the methodology did enable the synthesis of *N*-aryl MA derivatives, that cannot be achieved before.[25] Interestingly, MA **33** displayed low thermal stability and rapidly rearranged to cyclopropanimine **34** according to first-order kinetics ($t_{1/2}$ < 9 min at 88 °C). The similar behaviour has been noted previously for 1-methyl-2-methyleneaziridine but much higher temperature is required ($t_{1/2}$ = 9 min at 190 °C).[26]

Although rare examples have been reported, intramolecular cyclization of propargyl amides is no doubt a feasible method to synthesize MAs. In 1992, Torii *et al.* reported that an electrohalogenation of propargyl amides **36** could furnish the corresponding MAs **37** and **38** (Scheme 12),[27] which were highly functionalized, bearing halogen atom on exocyclic alkene and acetyl group on N-atom. This reaction was carried out by using CH_2Cl_2-aqueous 25% NaX (X = I or Br)-Pt system (buffered at pH = 7) under 20 mA cm^{-2}. However, the same electrolytic reaction with NaCl only produced dichloroketone **39** exclusively.



Scheme 12 Electrohalogenation of propargyl amides.

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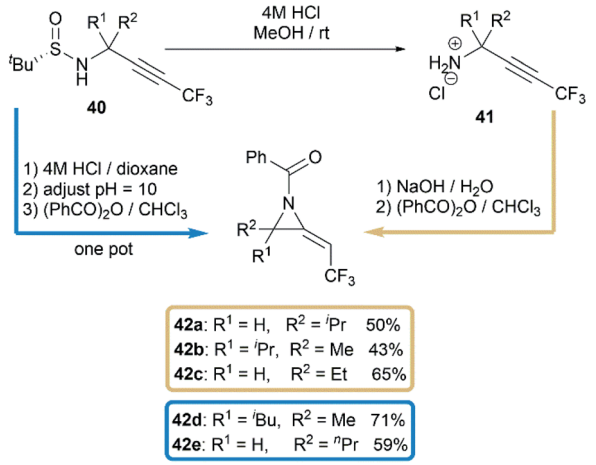
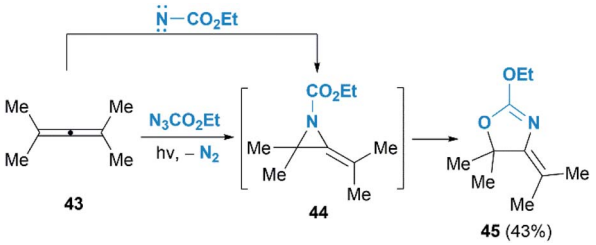
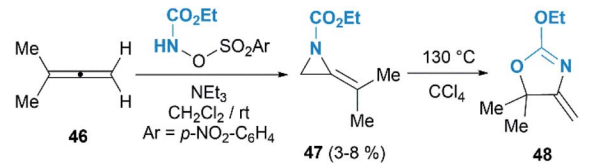


Scheme 13 Syntheses of *N*-benzoyl-2-trifluoroethylideneaziridines.



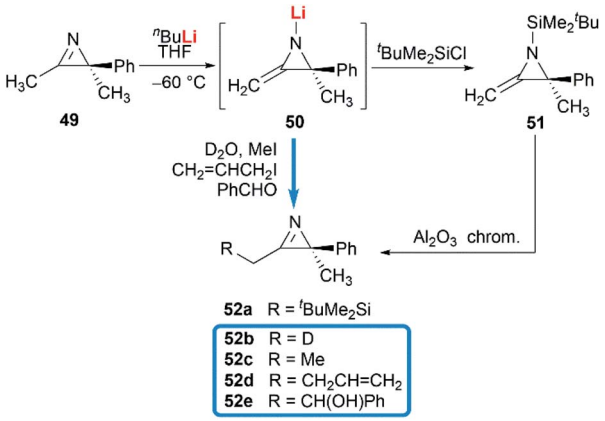
Scheme 14 Photolysis of ethyl azidoformate in the presence of dimethylallene.



Scheme 15 Synthesis of MAs by addition of nitrene with allene.

Another interesting research was reported by Qing and co-workers when they studied benzoylation reaction of trifluoromethylated propargylamine substrates **40**.[28] *N*-benzoyl-2-trifluoroethylideneaziridines **42a–e** were surprisingly obtained in moderate yields when using NaOH as base, as illustrated in Scheme 13. The relatively strong basicity of NaOH, considered as key factor, promoted the deprotonation of *N*-benzamide intermediates **41**, followed by an intramolecular addition of nitrogen anion to alkynyl group to deliver methyleneaziridines.

As we known, the allene cyclopropanation is the most common method to access methylenecyclopropanes.[29] In contrast, the corresponding aziridination of allenes to construct heteroatom analogues such as MAs have been underutilized. Pioneering research in this area was reported by Bleiholder and Schecter in the reaction of ethyl azidoformate and dimethylallene **43** (Scheme 14).[30] They postulated that an addition of singlet nitrenes, *in situ* generated from ethylazidoformates, to allenes under photolysis condition might deliver MAs. Unfortunately, instead of the MA products, an oxazoline **45** was obtained in 43% yield as the sole product. It is proposed that the oxazoline is produced *via* further rearrangement of MA **44**, but the mechanism involving a direct [3 + 2] cycloaddition of the allene with carbethoxynitrene, N_2 extrusion and rearrangement could not be ruled out.

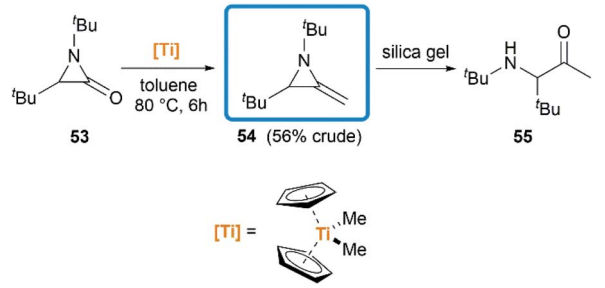


Scheme 16 *N*-Lithiation/silylation of 3-methyl-2*H*-azirine to synthesis of MAs.

The Gilbert group reinvestigated this work in the reaction of nosyloxycarbamate with allenes.[31] Intriguingly, trace amounts of MAs **47** could be isolated, as confirmed by MS and NMR analysis, when using *N*-(*p*-nitrobenzenesulfonoxy) urethane as a nitrene precursor (Scheme 15). Thermolysis of the MAs products gave oxazolines **48** indeed, demonstrating the competency of MAs as intermediates in the formation of oxazolines.

2.4. Conversion reactions *via* aziridine derivatives

Notably, some aziridine derivatives could be converted into MAs under suitable conditions. A meaningful attempt for building MAs structure *via* a *N*-lithiation/silylation of 3-methyl-2*H*-azirine **49** was reported by Belloir and co-workers.[32] Deprotonation of 2H-azirine with butyllithium gave rise to *N*-lithio-2-methyleneaziridine **50**, which could be trapped by *tert*-butylchlorodimethylsilane to provide *N*-silyl MA **51** (Scheme 16). Unfortunately, the alkylation of **50** with other electrophiles (MeI, allyl iodide, benzaldehyde, D_2O) all failed to give expected



Scheme 17 Synthesis of MAs by Cp_2TiMe_2 mediated methylenation of α-lactam.

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MAs but yielded C-alkylation products. In addition, all attempts on the purification of **51** by chromatography on aluminium oxide irreversibly transformed it into the C-silyl isomer **52a.**

Another conversion involving α-lactam, was reported by De Kimpe *et al.*[33] An olefination reaction of 1,3-di-*tert*-butyl-2-aziridinone **53** with dimethyltitanocene in toluene gave the MA in 56% crude yield (Scheme 17). Purification of product by column chromatography on neutral alumina or vacuum distillation (24–26 °C/1.3 mm Hg) was achievable. In contrast, the MA **54** was completely hydrolyzed to 3-(*tert*-butylamino)-4,4-dimethyl-2-pentanone **55** by chromatography on silica gel.

3. Reactions of monocyclic MAs

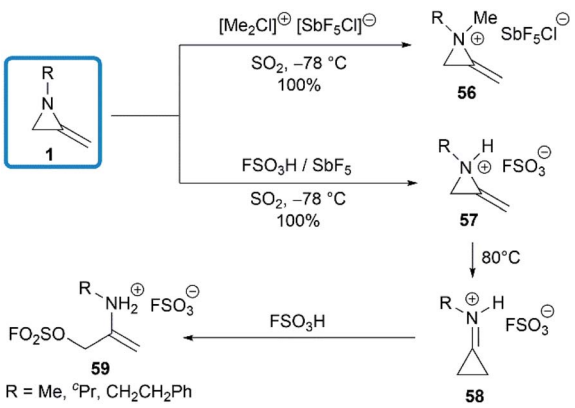
3.1. Protonations

The domino protonation and ring-opening reactions of MAs were investigated in details by Jongejan and co-workers.[34] Extraction of pentane solutions of **1** with FSO_3H/SbF_5 in sulphur dioxide at −78 °C gave the corresponding methyleneaziridinium ions **57** without any side products. Under similar conditions, the nitrogen atom of MA **1** could be methylated by $[(Me)_2Cl]^+[SbF_5Cl]^-$ to yield **56.** Both methyleneaziridinium salts **56** and **57** showed remarkable thermal stability below 60 °C, no decomposition of either cation being observed by ^1H NMR. Thermally induced isomerization and the following ring opening required higher temperature (Scheme 18).[13,35]

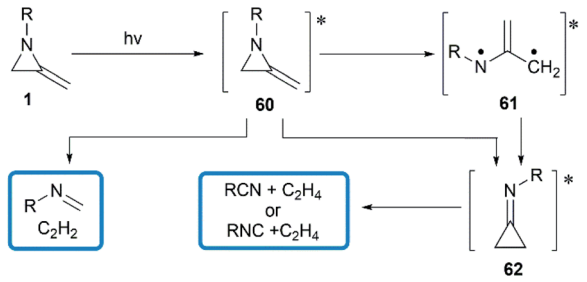
3.2. Decompositions and rearrangements

In 1964, Brinton reported the photolysis decomposition of MAs, giving the corresponding alkenes, nitriles and isonitriles as major products.[36] The author concluded that the rearrangement mechanism might either proceed by a direct concerted mechanism (**60** → **62**) or through a short-lived biradical **61** as illustrated in Scheme 19.

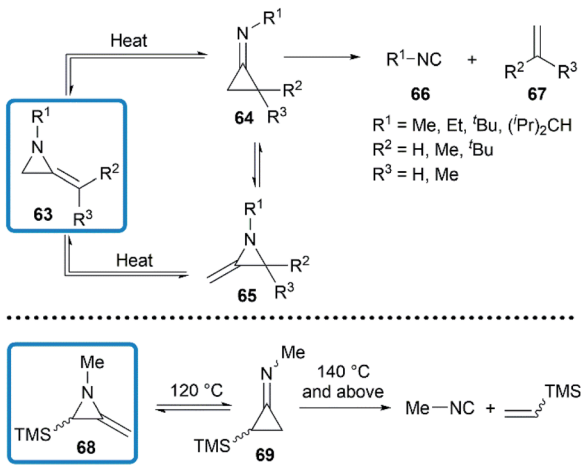
The valence isomerization of methyleneaziridine-cyclopropanimine was also observed under thermal conditions. Quast and Risler demonstrated that a series of MAs primarily rearranged to cyclopropanimine **64** and isomer **65** at 190 °C, which were rapidly converted into isonitriles **66** and



Scheme 18 Generation and isomerization of methyleneaziridinium cations.



Scheme 19 Photolysis decomposition of MAs.

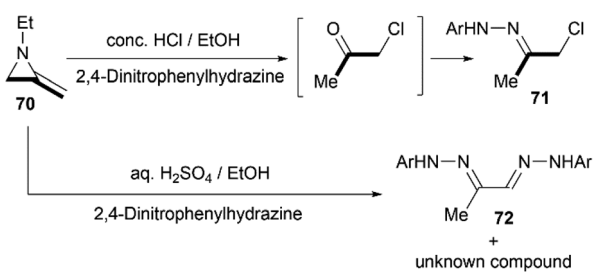


Scheme 20 Thermal isomerization and decomposition of MAs.

alkenes **67** in quantitative yield (Scheme 20).[26] Surprisingly, unlike the notorious instability of cyclopropanones,[37] cyclopropanimine **64** was relatively stable and readily accessible. The rearrangement of trimethylsilyl MA **68** was also observed at 120 °C, while decomposition did not occur only at 140 °C and above, although to a small extent (Scheme 20).[21]

3.3. Nucleophilic ring-opening reactions

Protonation of the nitrogen atom of MAs and subsequent nucleophilic attack to the aziridine ring lead to ring opening at the N–C3 bond. Bottini and Roberts have reported that a treatment of 1-ethyl-2-methyleneaziridine **70** with hydrochloric acid could provide chloroacetone, which was isolated as its 2,4-dinitrophenylhydrazone derivative **71.** However, the hydrolysis



Scheme 21 Brønsted acid-promoted hydrolysis reaction of MAs.

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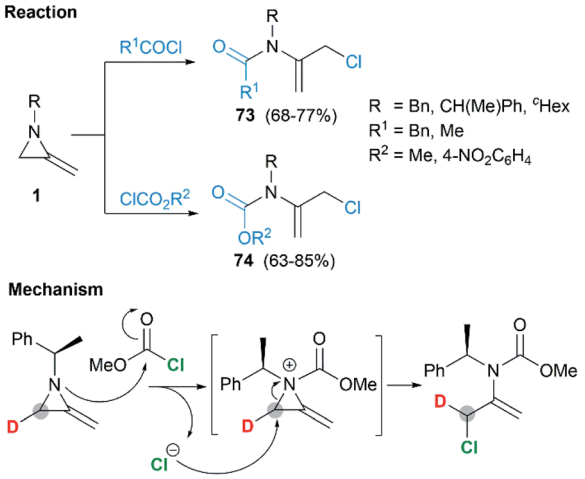
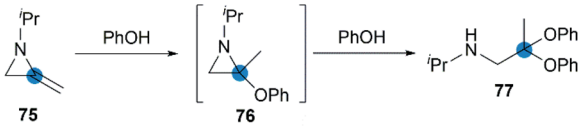


Scheme 22 Ring-opening and mechanism of MAs with acid chlorides and chloroformates.



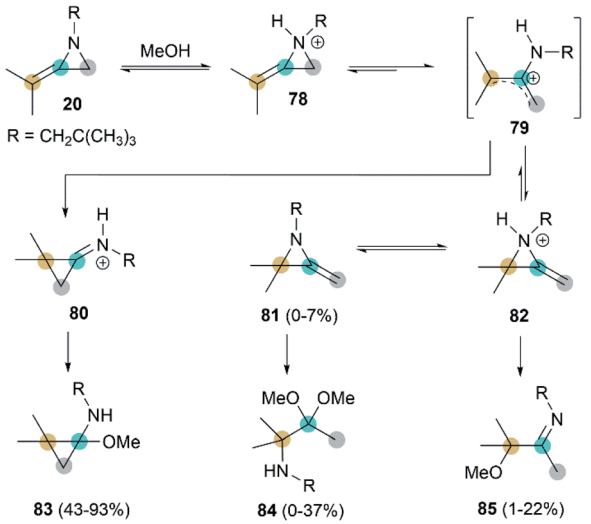
Scheme 23 Reaction of MA with phenol.

with aqueous sulfuric acid in the presence of 2,4-dinitrophenylhydrazine gave osazone **72** and an unknown compound (free of sulfur), as illustrated in Scheme 21.[5]

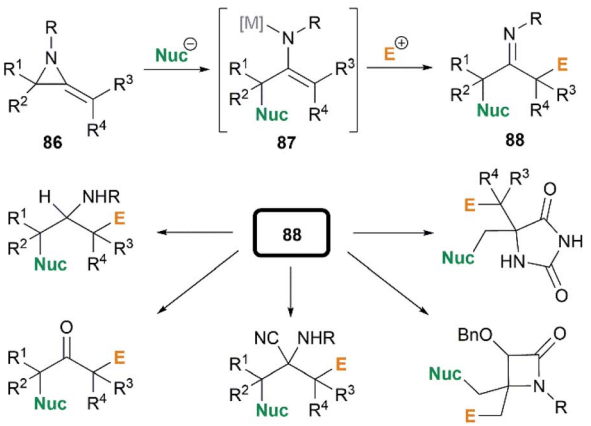
Shipman and co-workers demonstrated that MAs could react with acid chlorides and chloroformates, giving corresponding tertiary amide **73** and carbamates **74** respectively.[38] These reactions proceeded well with a series of *N*-alkyl/benzyl substrates. However, *N*-trityl MAs, owing to its steric hindrance, could not participate in the process. In addition, these reactions were proved to be less tolerant to more electron-rich acid chlorides such as benzoyl chloride and *p*-anisoyl chloride. Deuterium labelling studies confirmed that attack of the chloride anion occurred solely at C-3 of the methyleneaziridinium ion (Scheme 22).[39]

Crandall *et al.* reported that, *N*-isopropyl-2,2-diphenoxypropan-1-amine **77** was rapidly and smoothly obtained from the reaction of MA **75** with excess phenol at 25 °C.[40] This transformation probably proceeded *via* initial Markovnikov addition of the first equivalent of the phenol across the exocyclic double bond, followed by ring-opening of the aziridine intermediate by the second equivalent of phenol (Scheme 23).

Interestingly, when heating MA **20** and methanol in the presence of benzene, adduct **83** was isolated as the major product.[41] This addition begins with rapid N-protonation with methanol, followed by a slow ring opening of **78** to afford the neopentylamino allyl cation **79**. Subsequent ring-closure delivers iminium ion **80**, which can be easily captured by methanol to generated product **83**. The minor ring-opening products methoxyimine **84** and aminoacetal **85** were formed probably *via* the protonated isomeric MA **82** (Scheme 24).



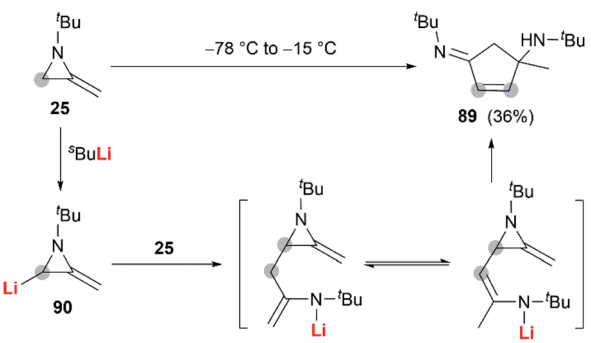
Scheme 24 Rearrangements of MA in methanol.



Scheme 25 Multi-component reactions of MAs.

3.4. Carbon-based nucleophilic ring-opening process and multicomponent reactions (MCR)

In the presence of an organometallic promoter, the ring-opening of MAs **86** with carbon-based nucleophile would produce a metalloenamine **87**, which might further undergo C-



Scheme 26 Dimerization reaction of MAs.

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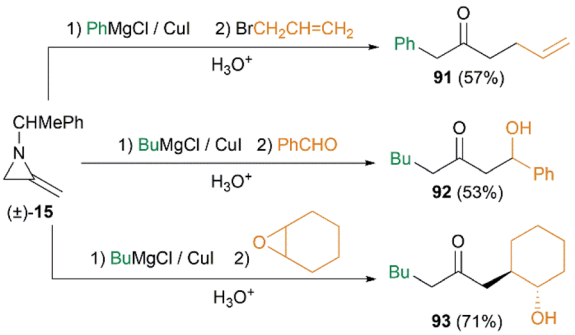
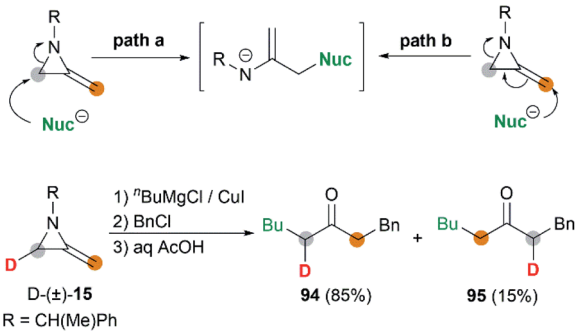


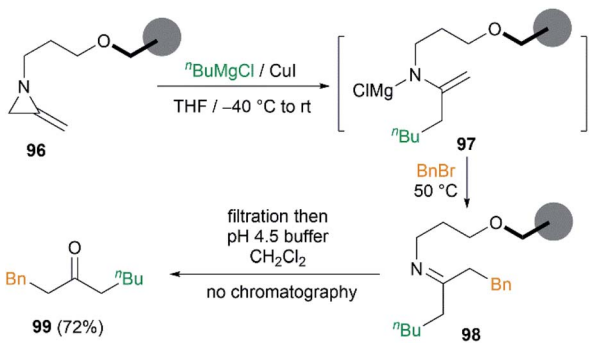
Scheme 27 Examples of ketone-forming reaction.



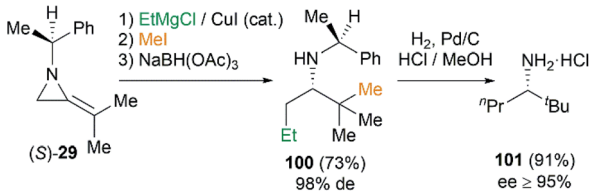
Scheme 28 Possible machanisms and duterium-labelled study for MAs ring-opening.

alkylation with an electrophile to yield ketimine **88** (Scheme 25). Obviously, the structure of the nucleophile, electrophile or the MAs could be changed to prepare a wide range of different ketimines, which displayed diverse chemical reactivities in organic synthesis, as shown in Scheme 25.

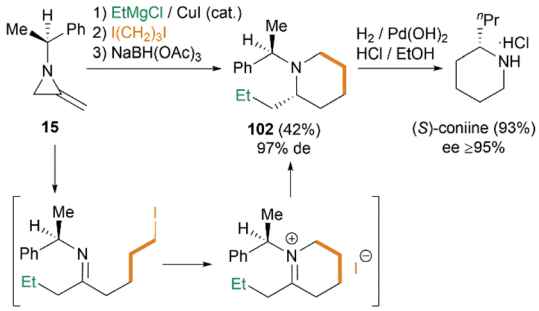
In 1974, Quast and Vélez reported a dimerization reaction of *tert*-butyl-2-methyleneaziridine **25** (Scheme 26).[20] A solution of 2-lithiated MA **90**, prepared by the treatment of **25** with butyllithium/TMEDA in ether, was quenched by H_2O to give a pale-yellow crystal, which was sensitive to air and moisture. Elemental analysis and mass spectrum confirmed the product structure as a dimer **89**. The mechanism involves nucleophilic attack of **25** with lithiated MA **90**, ring-opening and intramolecular cyclization.



Scheme 29 Solid-phase ketone-forming reaction.



Scheme 30 Synthesis of homochiral amines using MCR.

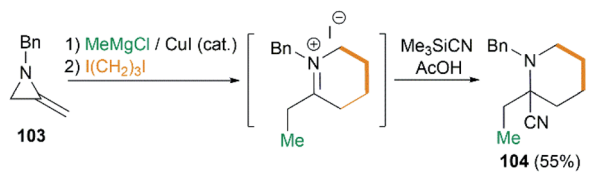


Scheme 31 Asymmetric synthesis of (*S*)-coniine using MCR.

MAs could also be conveniently ring-opened to the metalloenamines using Grignard reagents in the presence of CuI. Subsequent addition of an electrophile facilitates further C-alkylation to yield the ketimines which were then hydrolyzed to ketones. The Shipman group has reported that a range of ketones including **91–93** could be produced using this multicomponent reaction (MCR) (Scheme 27).[42] To further elucidate the reaction mechanism, when C-3 deuterated MA **15** was subjected to standard conditions using BuMgCl and BnCl, an inseparable mixture of deuterated ketones **94** and **95** was furnished in a ratio of 85 : 15 (Scheme 28). It is clear that ring opening of MA by Grignard reagents occurs predominantly by attack at C-3 of the aziridine ring as illustrated in Scheme 28 (path a), and the path b is also involved as a minor reaction pathway.

In order to remove excess reagents and simplify the purification of reaction, attachment of the MAs to solid-support *via* the nitrogen atom was carried out by Shipman *et al.*[43] It was demonstrated that merrifield resin bound MA **96** could be converted into 1-phenyloctan-3-one **99** under optimized conditions in 72% yield (Scheme 29). Although the yield was not better than that obtained in solution, the purification protocol was greatly simplified and no chromatography was required.

This MCR is also proved to be a useful tool to synthesize amines by way of reduction of the intermediate ketimine



Scheme 32 Synthesis of cyclic α-amino nitrile.

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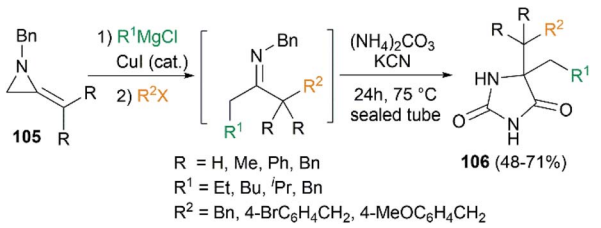
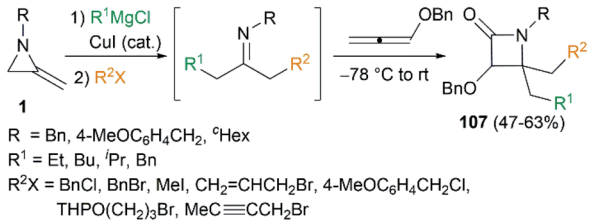


Scheme 33 Synthesis of 5,5′-disubstituted hydantoins *via* MCR of MAs.



Scheme 34 Synthesis of α-lactams *via* MCR of MAs.

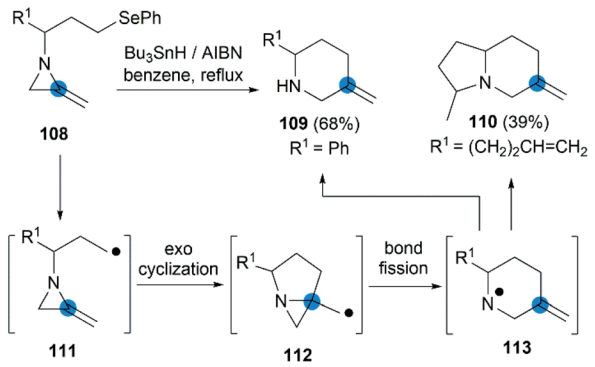
(Scheme 30). The stereochemistry of reaction could be well controlled by the substituents on the nitrogen atom of MAs. Isopropylidineaziridine (*S*)-**29** produced homochiral amines **100** in 73% yield and 98% de. Further transformation into amine **101** (≥95% ee) proceeds smoothly by hydrogenation in presence of palladium on carbon.[44]

Interestingly, using difunctionalized electrophiles, the scope of the MCR could be extended to the synthesis of 2-substituted piperidines.[45] Shipman group reported a concise asymmetric synthesis of the hemlock alkaloid, (*S*)-coniine,[46] as shown in Scheme 31. Treatment of **15** with EtMgCl, then 1,3-diiodopropane, and finally sodium triacetoxyborohydride gave piperidine **102** in 42% yield as essentially a single diastereomer after chromatography. Hydrogenolysis of **102** furnished (*S*)-coniine hydrochloride (≥95% ee) in 93% yield.

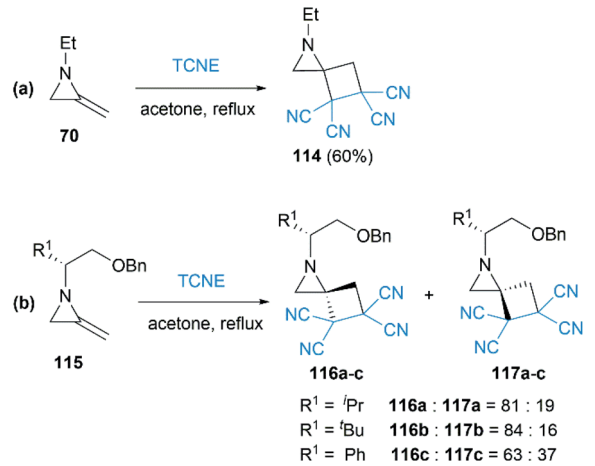
By combination of the MCR strategy with the Strecker reaction, a complicated four-component reaction could be achieved. Treatment of **103** with MeMgCl, 1,3-diiodopropane, then HCN (generated from Me_3SiCN and AcOH) provided piperidine **104** in 55% yield (Scheme 32).[47] This process is efficient in the production of the total number of new bonds (three C–C bonds and one C–N bond). It's also noteworthy that, the resulting imine in the MCR, without isolation, could be further treated with ammonium carbonate and potassium cyanide to give 5,5′-disubstituted hydantoins **106** *via* a Bucherer–Bergs protocol (Scheme 33),[48] or reacted with (benzyloxy)ketene leading to α-lactams **107** *via* a Staudinger [2 + 2] cycloaddition (Scheme 34).[49]

3.5. Radical cascades

The strain energy of the MAs ring provides a suitable driving force for radical cascades. Shipman *et al.* first found that the alkyl radical **111**, generated from a suitable precursor such as **108**, could undergo 5-exo-trig cyclization to form aziridinylcarbinyl radical **112**, which was transformed to aminyl radical **113** *via* N–C2 bond cleavage then provided piperidine derivatives in moderate yield (Scheme 35).[50] Using this radical cascade methodology, they also achieved a tandem radical process to form indolizidine **110** in 39% yield (dr = 4 : 1).[51]



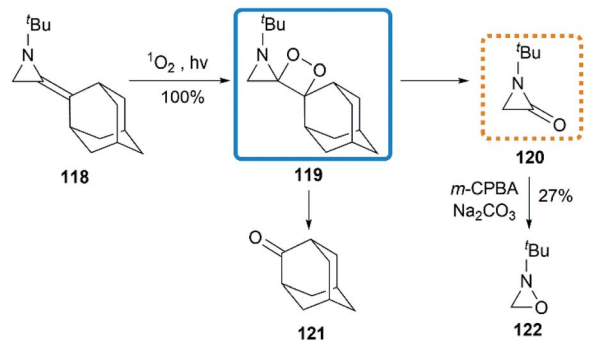
Scheme 35 Intramolecular radical rearrangement reactions of MAs.



Scheme 36 [2 + 2] Cycloaddition reactions and diastereoselective control strategy.

3.6. Cycloadditions

As early as 1967, Cookson and co-workers had shown that the exocyclic double bond of MAs underwent intermolecular [2 + 2]



Scheme 37 Photooxygenation of MAs.

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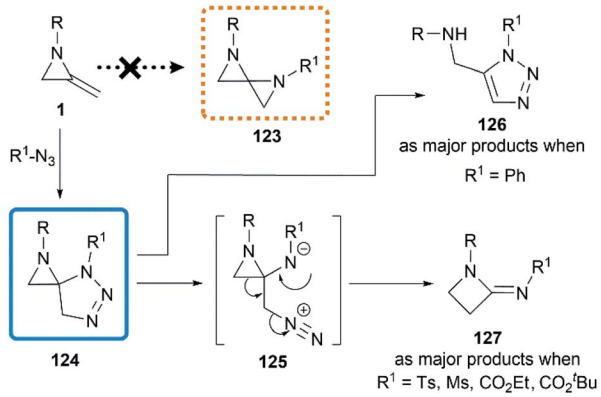
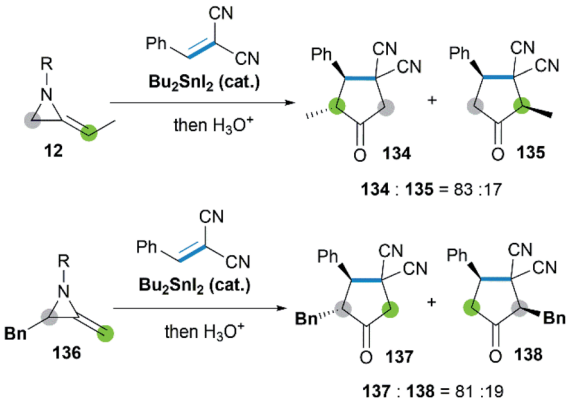


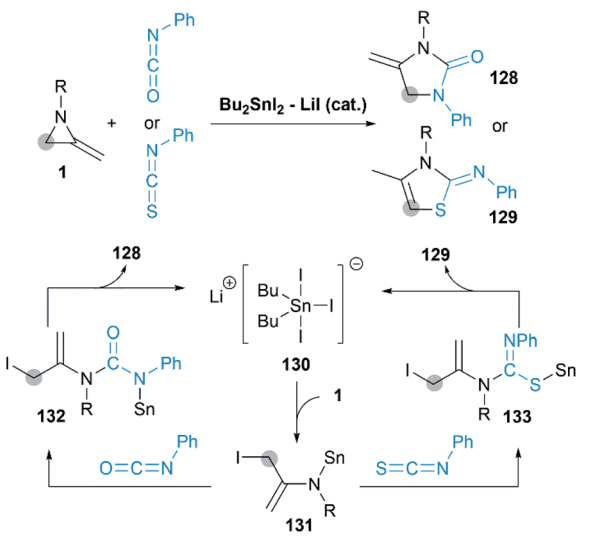
Scheme 38 Reaction of MAs with azides.



Scheme 40 Cycloaddition of MAs with 1,1-dicyanoalkenes.

cycloaddition reactions[52] with electron deficient alkenes.[53] Treatment of 1-ethyl-2-methyleneaziridine **70** with tetracyanoethylene (TCNE) in refluxing acetone resulted in the formation of the corresponding spiroadduct **114** in 60% yield (Scheme 36(a)). Shipman and co-workers employed unique MAs that bearing a chiral motif on the nitrogen atom in this [2 + 2] process.[54] The nature of the substituent on the stereocenter exerted an influence on the diastereoselectivity. Increasing the size of the R^1 substituent appeared to improve the diastereoselectivity, although low selectivity was observed when R^1 = Ph as shown in Scheme 36(b).

Ando *et al.* reported that the photooxygenation of 1-*tert*-butyl-2-adamantylideneaziridine **118** resulted in its oxidative cleavage (Scheme 37).[55] A typical [2 + 2] cycloaddition reaction firstly gave dioxetane **119**, which was found to be stable below −74 °C and characterized by low temperature NMR. However, the only isolable product in this reaction was adamantanone **121**, generated from the rapid decomposition of cycloaddition product **119**. While another fragment in this decomposition was α-lactam **120**, which was confirmed by the formation of oxaziridine **122** upon *in situ* oxidation with *m*-CPBA.



Scheme 39 [3 + 2] Cycloaddition of MAs with isocyanates/isothiocyanates.

Initial attempts at the [3 + 2] cycloadditon[56] were reported by Crandall and co-workers in 1975.[40] They expected that a conversion to 1,4-diazospiropentanes **123** might be achieved by treatment of MAs with organic azides following by release of nitrogen (Scheme 38). However, the reaction of 1-isopropyl-2-methyleneaziridine with phenyl azide at 90 °C for 5 days generated a mixture of starting material **1**, triazole **126** and β-lactamimide **127** in a ratio of 9 : 59 : 32. The triazole **126** probably arose from isomerization of the initial [3 + 2] product **124**, driven by relief of ring-strain, and the minor product **127** presumably generated from the rearrangement of **124** *via* intermediate betaine **125**. Notably, the β-lactamimide derivatives became major products when sulfonyl azides or alkyl azidoformates were used, such as *p*-toluenesulfonyl azide (up to 89% yield), methanesulfonyl azide (up to 82% yield),[18] ethyl azidoformate (60%) and *tert*-butyl azidoformate (sole product, yield was not mentioned).

In 2013, Shibata group reported a novel [3 + 2] cycloaddition of MAs with isocyanates/isothiocyanate catalyzed by Bu_2SnI_2/LiI to obtain 4-methylene-2-imidazolidinones.[57] As shown in Scheme 39, a pentacoordinate tin $Li^+[SnBu_2I_3]^-$ **130** is considered as the active catalytic species in this transformation. Sn–I first attacks at the C-3 position of MA to deliver enamine **131**, which is captured by the highly electrophilic carbon of isocyanate to give ureidostannane **132**. The following intramolecular N-alkylation affords adducts in moderate to good yields.

Sn-catalyzed cycloaddition of MAs with activated alkenes such as 1,1-dicyanoalkenes was also proved feasible, giving cyclopentanimines or corresponding cyclopentanone products.[58] It's worth noting that both the S_{N^2} attack of Sn–I bond toward C-3 on aziridine ring and C=C bond of MAs were observed (Scheme 40), resulting in the different regioselectivity of reactions.

Shipman group focused on the Lewis acids promoted cycloadditions of MAs. In 2004, they reported an efficient approach to access seven membered polycyclic systems *via* the Lewis acids promoted [4 + 3] cycloadditions[59,60] of MAs.[61] Treatment of precursor **139** with $BF_3 \cdot Et_2O$ or $Sc(OTf)_3$ provided tricyclic imine in moderate to good yield, or tricyclic ketone after acidic work-up. As shown in Scheme 41, the aziridine **139**

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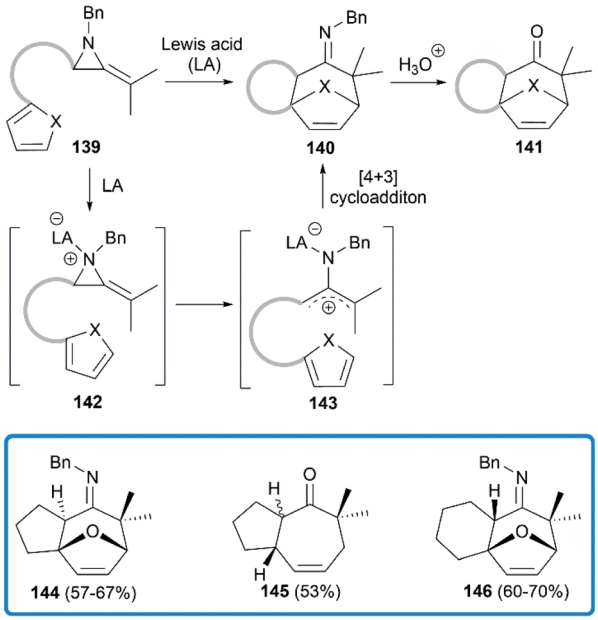
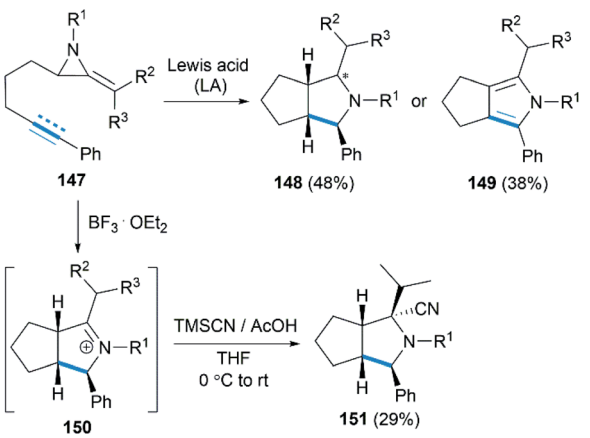


Scheme 41 Lewis acids promoted [4 + 3] cycloadditions of MAs.

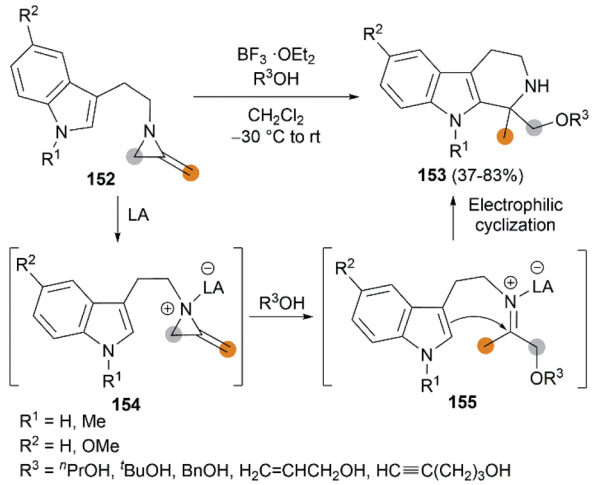
is first activated by Lewis acid to generate the intermediate aziridinium ion **142**, followed by the formation of 2-aminoallyl cation **143** *via* C–C bond cleavage. Further intramolecular 1,3-dipolar cycloaddition reaction with the appended 1,3-diene would lead to tricyclic cycloheptenone imine **140**.

Encouraged by their study on Lewis acid promoted [4 + 3] cycloaddition, Shipman and co-workers reported that intramolecular [3 + 2] cycloadditions of MAs with alkene and alkyne acceptors produced cis-octahydrocyclopenta[*c*]pyrroles **148** and 2,4,5,6-tetrahydrocyclopenta[*c*]pyrroles **149**, respectively (Scheme 42).[62] In addition, the intermediate iminium ions, such as **150**, could also be captured by cyanide to generate heterocycles **151** containing fully substituted stereocentres.

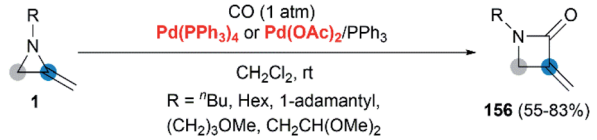
The Lewis acid activation strategy was also used in the synthesis of substituted tetrahydro-*β*-carbolines. In this process, 2-methyleneaziridines **152**, bearing an indole nucleus tethered to the aziridine nitrogen, is activated by $BF_3{\cdot}OEt_2$, followed by



Scheme 42 Lewis acids promoted [3 + 2] cycloadditions of MAs.



Scheme 43 Synthesis of 1,1-disubstituted tetrahydro-*β*-carbolines from MAs.



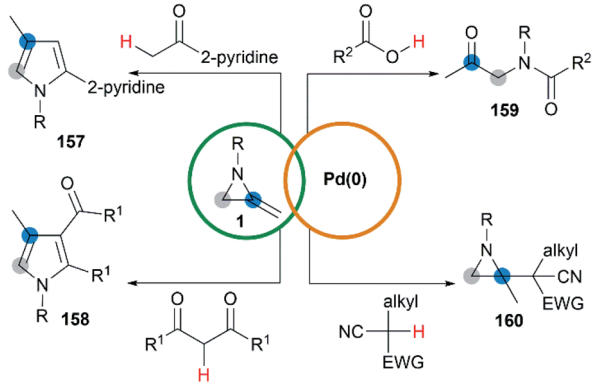
Scheme 44 Palladium-catalyzed ring expansion reaction of MAs.

a nucleophilic attack of alcohol to generate an iminium ion intermediate **155**. An eventual Pictet–Spengler cyclization furnishes products in moderate to good yields (Scheme 43).[63]

3.7. Transition metal catalyzed reaction

Transition metal catalyzed cycloaddition of MAs was first reported by the Alper group in 1987. Under palladium-catalyzed conditions, ring expansion reactions of these strained heterocycles with carbon monoxide furnished corresponding 3-methyleneazetidin-2-ones **156** in moderate yield, *via* N–C2 bond cleavage (Scheme 44).[64]

Yamamoto and co-workers found that the hydrocarbonation/hydrocarboxylation reaction of MAs with a range of pronucleophiles proceeded smoothly under palladium-catalyzed



Scheme 45 Pd(0)-catalyzed hydrocarbonation reaction of MAs.

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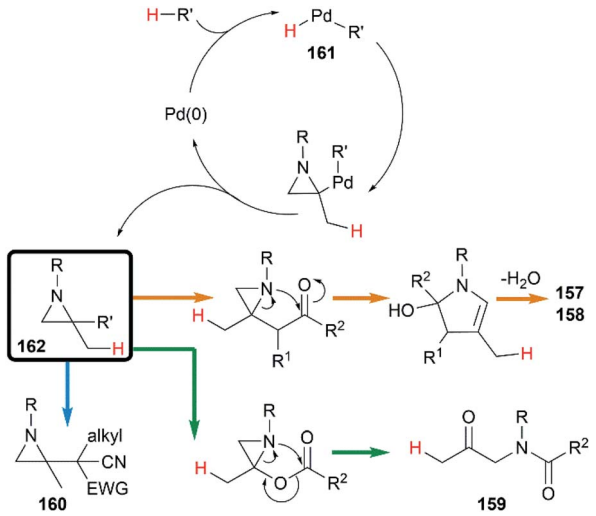
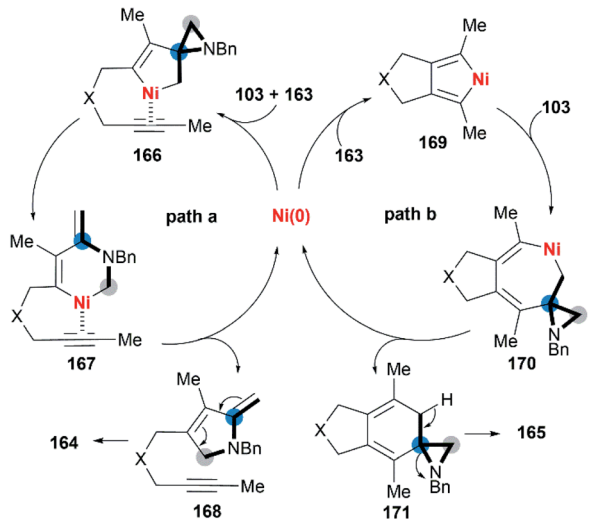


Scheme 46 Plausible mechanism of Pd(0)-catalyzed hydrocarbonation reaction of MAs.

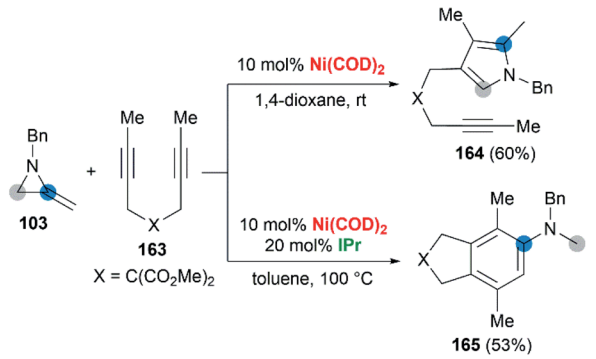


Scheme 48 Plausible reaction mechanism of Ni(0)-catalyzed cycloaddition reactions.

conditions (Scheme 45).[65] A ring expansion reaction of MAs took place and gave the corresponding pyrroles derivatives **157**,[65c] when acetylpyridine, 2,6-diacetylpyridine or acetylpyrazine were introduced into the reaction. Similar strategy could also be extended to 1,3-diketones, giving tetrasubstituted pyrroles **158** in good yields.[65a] However, the reaction outcomes were quite different when carboxylic acids or malononitrile derivatives were used as pronucleophiles. The former gave α-amidoketones **159** and the latter gave functionalized aziridines **160** without any ring-opening products.[65b,65d,65e]

A hydropalladation mechanism was proposed to explain the Pd-catalyzed procedure. Initially, the oxidative addition of Pd(0) with a C–H or O–H bond of pronucleophiles leads to the palladium-hydride species **161**. Then a hydropalladation of the exocyclic double bond and reductive elimination provide functionalized aziridines **162** and Pd(0) species. The structural diversities of final products depend on the different thermal rearrangement of disubstituted aziridines **162** as illustrated in Scheme 46.

Wan and co-workers first reported the transition-metal-catalyzed cycloaddition reaction[66] *via* C–C bond cleavage[67] of MAs (Scheme 47).[68] They developed a pyrrole synthesis by combining MAs **103** with diynes **163** in the presence of $Ni(COD)_2$.[69] Interestingly, the use of $Ni(COD)_2$/IPr containing a N-heterocyclic carbene (NHC) ligand furnished a fused aniline **165** as the major product. A plausible reaction mechanism is depicted in Scheme 48. In path a (Scheme 48), an oxidative cyclization of MA, alkyne and Ni(0) forms nickelacyclopentene **166**, followed by preferential β-carbon elimination (rather than β-nitrogen elimination) to afford **167**. Finally, reductive elimination and isomerization provide the products. The spectator alkyne motif in the substrate proves to be essential for the efficiency of the process, likely because its coordination with the nickel center can stabilize the intermediate. In addition, the free alkyne unit of products is advantageous for further derivatization.[70] In path b (Scheme 48), alternatively, the catalytic cycle starts with the oxidative cyclization of the diyne **163** on the nickel center to form the nickelacyclopentadiene complex **169**. Coordination of the vinyl moiety of MA **103** and insertion into the Ni(II)–C bond gives intermediate **170**. Then, reductive elimination of **170** affords the [2 + 2 + 2] cycloadduct **171**, which isomerizes to product **165** *via* C–C bond cleavage.



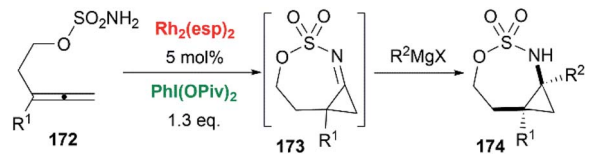
Scheme 47 Ni(0)-catalyzed cycloaddition reactions of MAs with alkyne *via* C–C bond cleavage.

4. Bicyclic MAs

4.1. Synthesis of bicyclic MAs

As we have discussed in Section 2, intermolecular aziridination of allenes with nitrenes was reported to build MAs structure. But the low yield limited the application of this reaction.[71]

Allenes aziridination was refocused since the popularization of sulfamate-based nitrene precursors by the Du Bois group in



Scheme 49 Aminocyclopropane formation from allenes.

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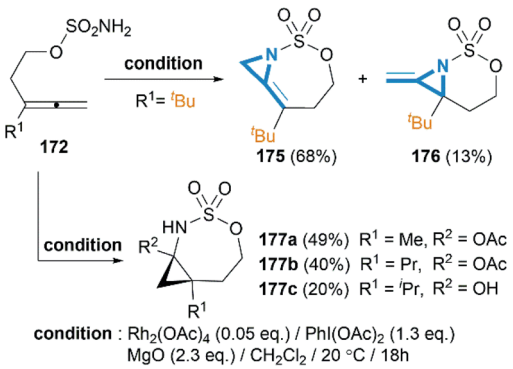
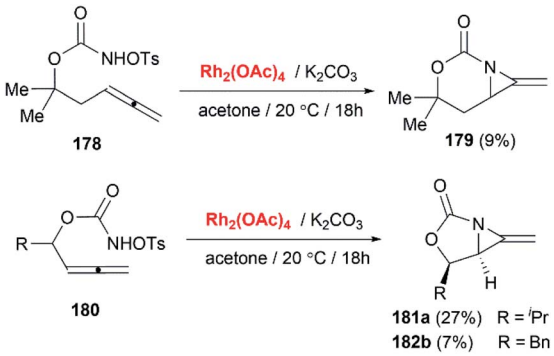


Scheme 50 Cyclizations of homoallenic sulfamates.



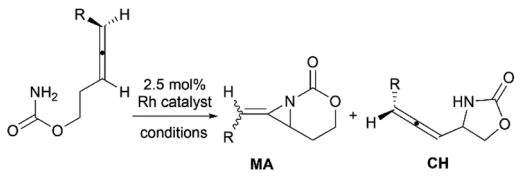
Scheme 51 Rh(II)-catalyzed aziridinations of allenyl carbamate derivatives.

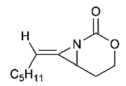
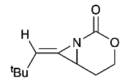
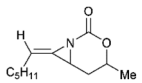
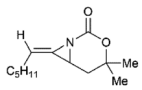
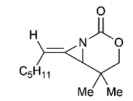
the early 2000s.[72] The first application of intramolecular Rh-catalyzed allene aziridination was reported by the Blakey group in 2009.[73] In the presence of $Rh_2(esp)_2$ and $PhI(OPiv)_2$, 1,1-disubstituted allene sulfamates yielded iminocyclopropanes **174**, however, Blakey and co-workers did not observe bicyclic MAs formation during the course of their reactions (Scheme 49).

Soon after the publication by Blakey, the Robertson group reported similar work in their experiments with homoallenic sulfamates.[74] Interestingly, they found that a more hindered-^{t}Bu substrate gave the novel bicyclic MAs as a 5 : 1 mixture of regioisomers (Scheme 50). Although yields were modest, this work represented the first synthesis of carbamoyl MAs since the work of Gilbert and co-workers in 1975 (Scheme 15).[31] Almost at the same time, Robertson group discovered that the corresponding carbamates could also be used as nitrene precursors for allene aziridination. Under the conditions of Rh catalysis, tosyloxycarbamates gave bicyclic MA products in low but reproducible yields (Scheme 51).[75]

Schomaker and co-workers documented their research on Rh-catalyzed allene aziridination in further detail.[76] For the purposes of isolating the target MAs, they found that carbamates provided the best balance between the reactivity of the nitrene precursor and the stability of the product. Rh_2esp_2 (esp = *R*,*R*,*R*$_0$,*R*$_0$-tetramethyl-1,3-benzenedipropionate) and $Rh_2(TPA)_4$ (TPA = triphenyl acetate) were proved to be more effective catalysts, giving complete conversion of the carbamate

Table 1 Chemoselectivity in carbamoyl allene aziridination



Entry	Desired product	Conditions	MA : CH % : %	*E* : *Z*
1		$Rh_2(TPA)_4$, PhIO, 4 Å MS	80 : 15	4 : 1
2		$Rh_2(TPA)_4$, PhIO, 4 Å MS	45 : 23	*E* only
3		$Rh_2(TPA)_4$, PhIO, 4 Å MS	48 : 31	1.5 : 1
4		$Rh_2(esp)_2$, $PhI(OPiv)_2$, MgO	10 : 72	2.8 : 1
5		$Rh_2(esp)_2$, $PhI(OPiv)_2$, MgO	94 (MA only)	3 : 1

in most cases (Table 1). The use of PhIO in the presence of 4 Å molecular sieves minimized the MAs ring-opening and gave 94% yield of the desired MA (Table 1, entry 5). Unfortunately, the chemoselectivity of this aziridination depends heavily on the structural features of the allene substrates.

Competing C–H insertion was exacerbated when allene was trisubstituted or branching in the link between the allene and the N atom.[77] To overcome the disadvantage, Schomaker *et al.* investigated other transition metal catalysts for the aziridination of homoallenic carbamates. Catalysts formed *in situ* from silver triflate and bipyridyl-type ligands were found to be well-suited to this reaction (Table 2).[78] These Ag(I)-based catalysts promote aziridination with superior chemoselectivity over conventional Rh-based catalysts, and greatly increase the yield of bicyclic MAs and the substrate scope of this reaction.

4.2. Reactions of bicyclic MAs

Along with the successful synthesis of bicyclic MAs, research on the chemical transformation of these structurally fascinating molecules was quickly followed. Robertson *et al.* first investigated the nucleophilic ring-opening reaction of [5.3]-bicyclic MAs with organolithium and Grignard reagents.[75] The only identified product was the S_NV (nucleophilic vinylic substitution) product, with the cleavage of Csp^2–N bond (Scheme 52, (**a**)). The Schomaker group focused more on the reactivity of the [6.3]-bicyclic MAs. In contrast to [5.3]-bicyclic analogues, the [6.3]-bicyclic MAs were smoothly ring-opened by a series of

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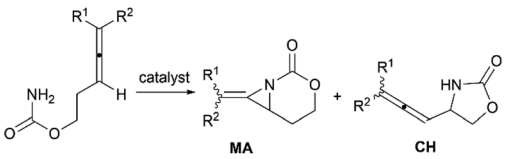
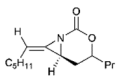
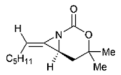
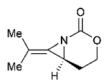
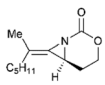
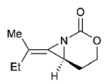
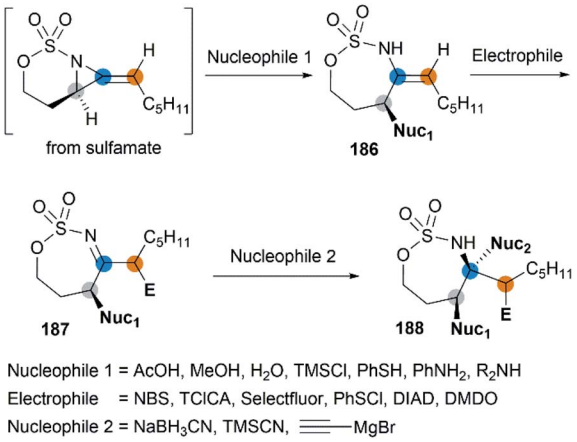
Table 2 Silver *vs.* Rhodium catalysis in the amination of homoallenic carbamates



Entry	Desired product	Catalyst	MA : CH	*E* : Z	Yield (%)
1		$Rh_2(esp)_2$	1 : 1	—	34
		AgOTf/phen	9 : 1	4.8 : 1	80
2		$Rh_2(esp)_2$	1 : 1.7	2 : 1	5
		AgOTf/phen	5.9 : 1	1.9 : 1	70
3		$Rh_2(esp)_2$	2 : 1	—	35
		AgOTf/phen	>20 : 1	—	79
4		$Rh_2(esp)_2$	1 : 1.3	2.3 : 1	34
		AgOTf/phen	11.5 : 1	2.6 : 1	87
5		$Rh_2(esp)_2$	1.1 : 1	—	32
		AgOTf/phen	19 : 1	2.3 : 1	70

nucleophiles, with the Csp^3-N bond cleaved in preference to the Csp^2-N bond (Scheme 52, (**b**)).[76]

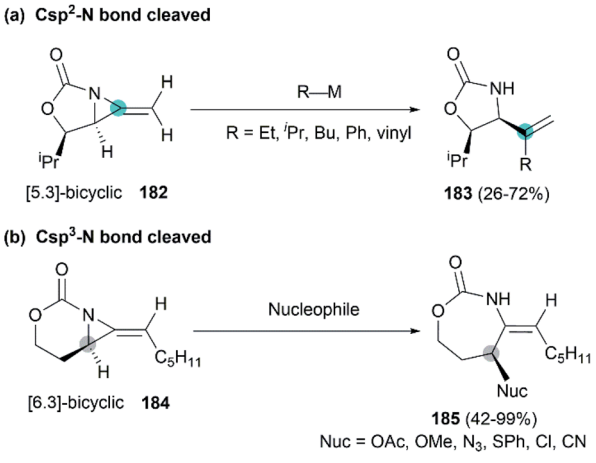
Notably, the resulting ring-opening enecarbamates of [6.3]-bicyclic MAs could serve as building blocks for the synthesis of stereotriad products. Schomaker group developed a strategy to form "all-heteroatom stereotriads" motifs of three contiguous centers containing stereodefined heteroatom substituents.[79] (1) Firstly, a series of nucleophiles were proved capable of ring-opening the bicyclic MA in mild conditions. (2) Then, the resulting enesulfamates reacted with a variety of heteroatom-based electrophiles to introduce halogen, oxygen, sulphur, and nitrogen groups at each of the three original allene carbons. (3) Finally, the resulting imines could be trapped with another nucleophile to give stereotriads as shown in Scheme 53.



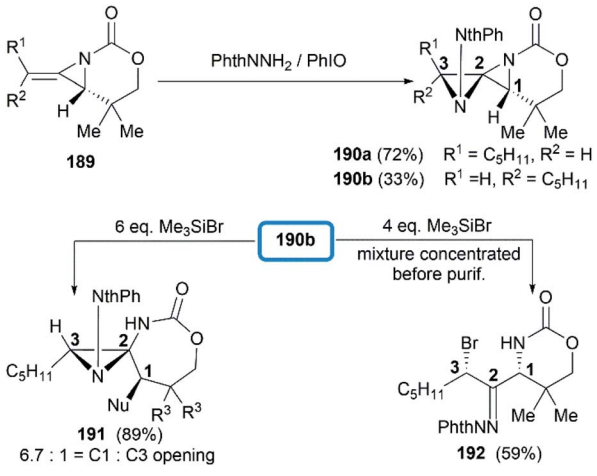
Scheme 53 Conversion of bicyclic MAs to "all-heteroatom stereotriads".

Direct functionalization of the exocyclic olefin of the bicyclic MAs was also proved as an efficient route to stereotriad products. Treatment of bicyclic MAs **189** with *N*-aminophthalimide in the presence of PhIO gave diazaspiro[2.2]pentane (DASP)[80] products **190** with complete facial selectivity (Scheme 54).[81]

It's worth noting that the ability to electronically differentiate between the two aziridine rings of the DASPs enabled regioselective ring opening at the terminal carbon of either aziridine depending on the reaction conditions. Mostly, the addition of nucleophiles to the DASP typically favored ring-opening at C1 position to give *N*,*N*-aminal products **194** (Scheme 55). In certain cases, however, manipulation of the reaction conditions could induce C3 ring-opening to yield α,α'-disubstituted hydrazones (Scheme 54, **192**).



Scheme 52 Cleavage of Csp^3–N bond and Csp^2–N bond of bicyclic MAs.



Scheme 54 Formation of DASP products and ring opening at C1 and C3.

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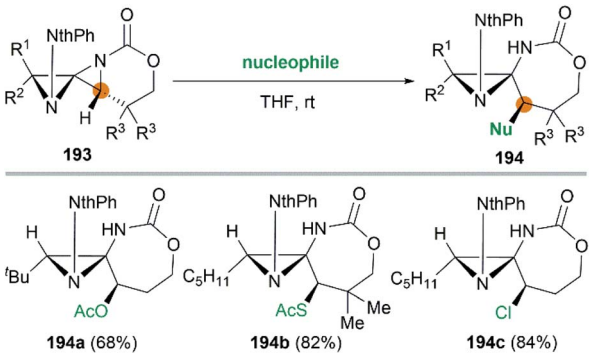
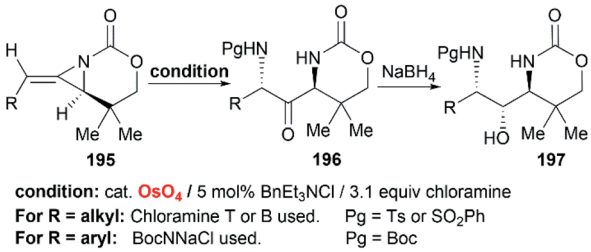


Scheme 55 Synthesis of *N,N*-aminals *via* ring opening at C1 of a DASP.

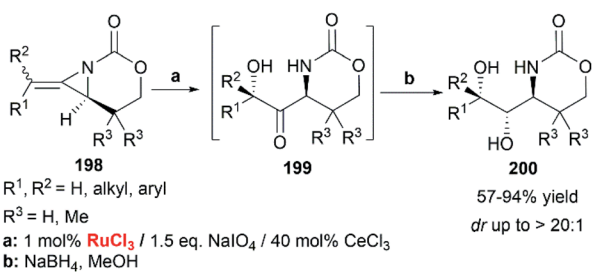


Scheme 56 Aminohydroxylation/reduction of bicyclic MAs.

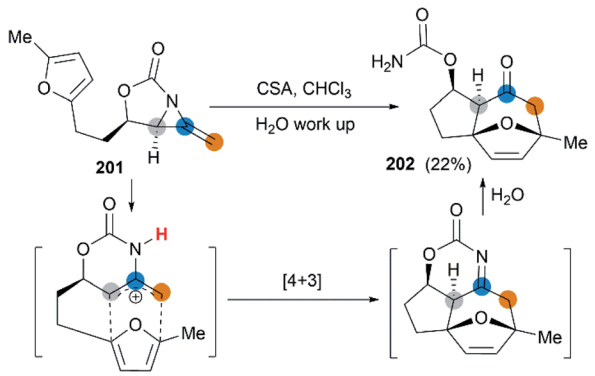
Schomaker *et al.* also reported the synthesis of 1,3-diaminoketone **197** through Os-catalyzed aminohydroxylation/reduction of bicyclic MAs (Scheme 56).[82] This process is general for a variety of alkyl and arylsubstituted MAs with excellent regioselectivity and good yield, which are presumably attributed to the presence of chloramine.

When $RuCl_3/NaIO_4$ system was chosen as the terminal oxidant, employing $CeCl_3$ as an additive, bicyclic MAs cleanly provided the ketone **199** as a single diastereomer. Immediate reduction with $NaBH_4$ yielded the 1-amino-2,3-diol **200** in > 20 : 1 dr (Scheme 57).[83]

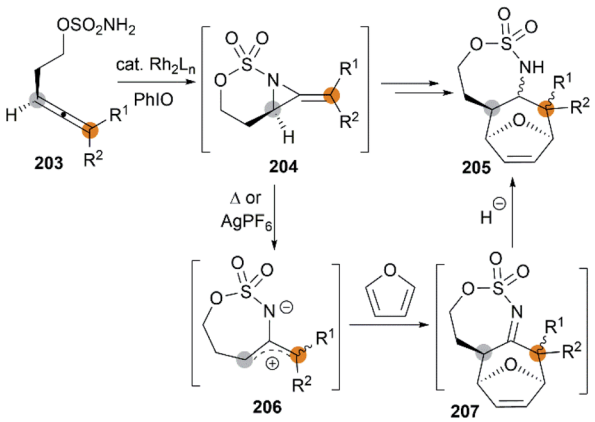
First attempt at cycloaddition reaction of bicyclic MAs was carried out by the Robertson *et al.*[75] Treatment of a furan-tethered [5.3]-bicyclic MA **201** with camphorsulfonic acid in chloroform gave an intramolecular [4 + 3] cycloaddition product in 22% yield (Scheme 58). In this case, the reaction characteristic of bicyclic MAs was analogous to monocyclic MAs, as reported by Shipman.[61]



Scheme 57 Stereocontrolled oxidation of MAs.

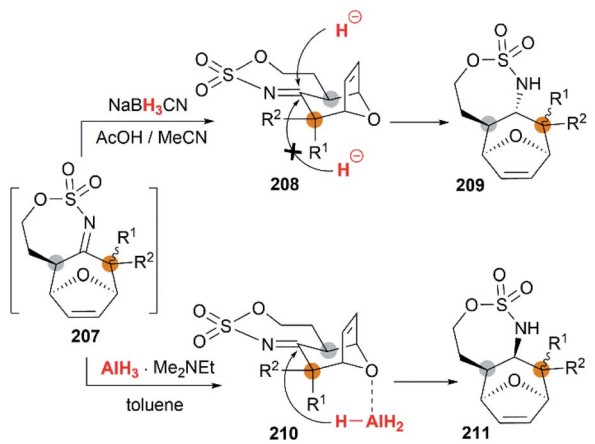


Scheme 58 Intramolecular [4 + 3] cycloaddition of a bicyclic MA.



Scheme 59 Intermolecular [4 + 3] cycloaddition of bicyclic MA intermediates.

The examples of intermolecular [4 + 3] reactions were reported by the Schomaker group.[84] Based on their previous research on bicyclic MAs, a tandem allene aziridination/[4 + 3]/reduction sequence was skillfully designed and successfully utilized to convert homoallenic sulfamates into densely functionalized aminated cycloheptenes. As shown in Scheme 59,



Scheme 60 Stereodivergent syntheses of stereoisomers.

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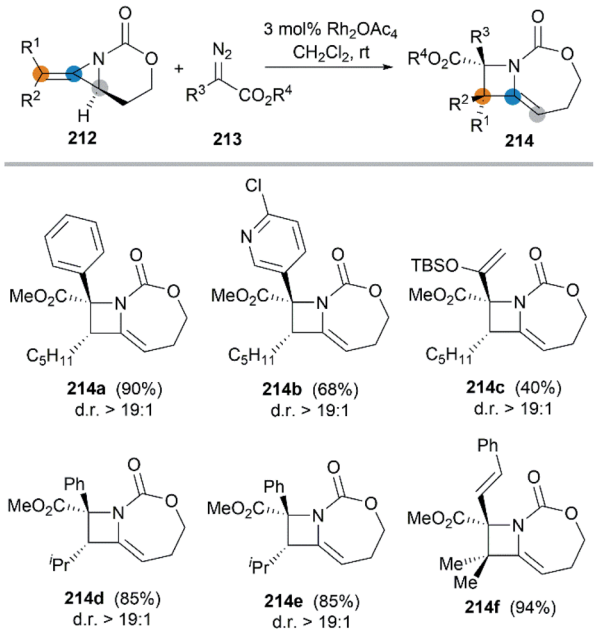
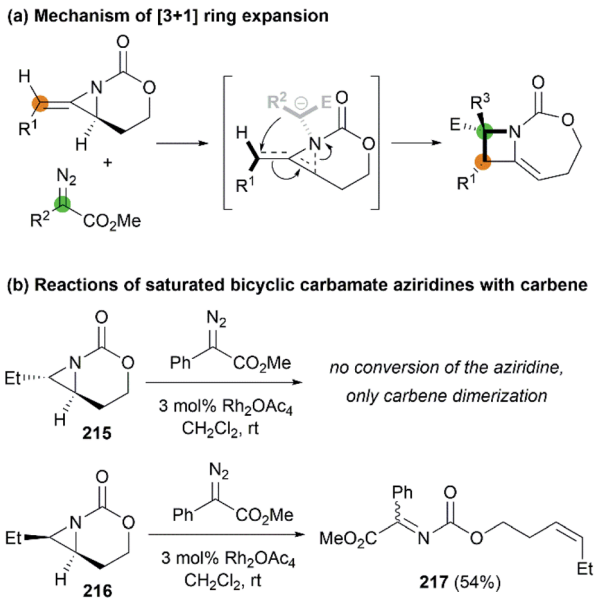
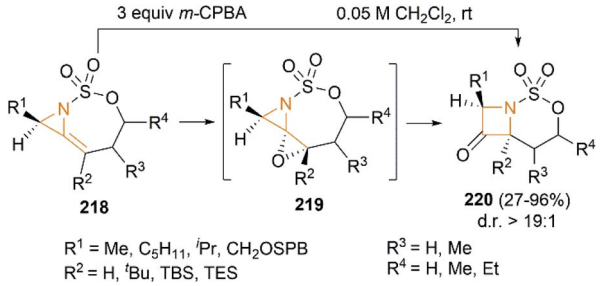


Scheme 61 Stereoselcetive [3 + 1] ring expansion of bicyclic MAs.

this strategy features (1) one-pot allene aziridination/ring opening of **204** giving 2-amidoallyl cations **206**. (2) Intermolecular [4 + 3] cycloaddition with furan, where the reaction conditions control the relative stereochemistry at C1 (or C3), and (3) reagent-dependent reduction of the imine **207** provides stereodivergent syntheses of stereoisomers (Scheme 60, **209** and **211**). Additionally, the functionality of the products enables access to a series of densely functionalized building blocks in few steps.



Scheme 62 Proposed mechanism and stereochemistry of [3 + 1] ring expansion.

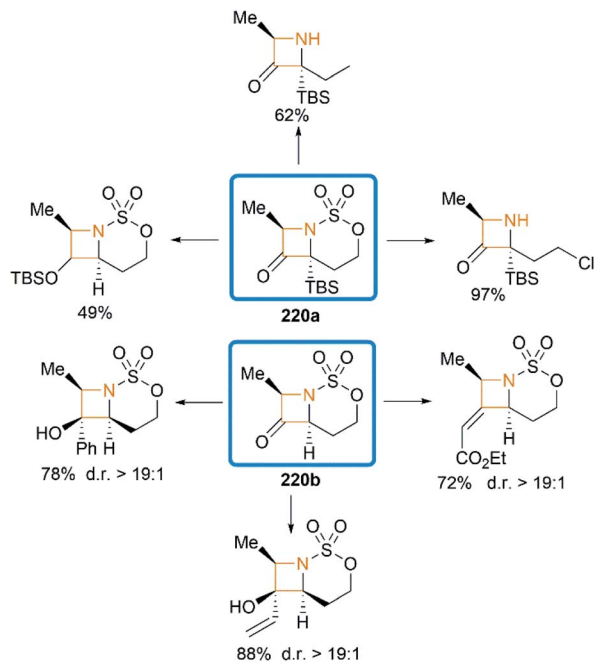


Scheme 63 Rearrangement of endocyclic bicyclic MAs to fused azetidin-3-ones.

In 2017, the Schomaker group reported an impressive [3 + 1] ring expansion of bicyclic MAs, in combination with Rh-supported carbenes, to deliver tri- and tetra-substituted methylene azetidines.[85] The unique strain and structure of the bicyclic MAs promoted this ring-opening/ring-closing cascade to yield highly substituted products with excellent regio- and stereoselectivity (Scheme 61, **214a–f**).

Later, Fernández, Schomaker and co-workers investigated the ring expansion mechanism and confirmed that such reaction proceeds through an aziridinium ylide, which undergoes a concerted, near-barrierless [2,3]-Stevens rearrangement to deliver substituted azetidines (Scheme 62, (**a**)). The olefin of the MA plays a key role in the success of this chemistry, channeling the aziridinium ylide toward ring expansion processes. In contrast, saturated bicyclic carbamate aziridines could not provide azetidine products (Scheme 62, (**b**)).[86]

We have so far discussed many conversions involving exocyclic bicyclic MAs. Further studies by Schomaker and co-workers demonstrated that endocyclic bicyclic MAs could also serve as



Scheme 64 Examples of transformation of azetidin-3-ones.

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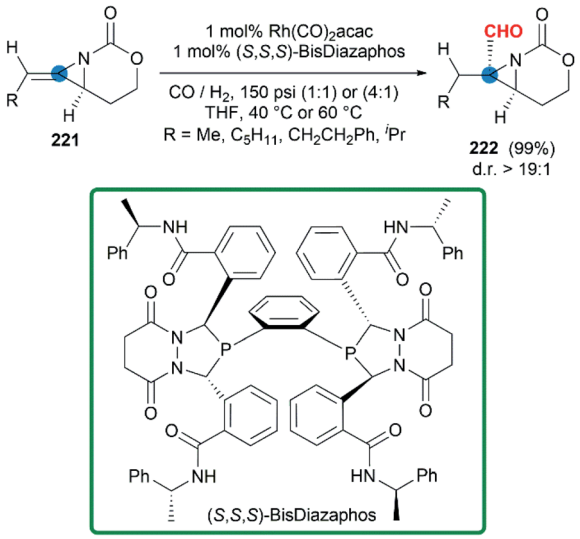

Scheme 65 Hydroformylation of bicyclic MAs.

a useful scaffold for the construction of heterocycles. In 2015, they reported a regioselective aziridination of silyl-substituted homoallenic sulfamates for the synthesis of endocyclic bicyclic MAs **218**, which could react with *m*-CPBA to yield azetidin-3-ones **220** (Scheme 63).[87] An initial epoxidation of endocyclic bicyclic MAs **218** affords reactive oxazaspiropentanes **219**, which rearrange to products in excellent d. r. Another key feature is the flexibility of subsequent transformations which could yield many densely functionalized azetidines (Scheme 64).

In some cases, bicyclic MAs prefer to show the chemical properties of olefins. More recently, a series of chiral bicyclic MAs were tested in hydroformylation.[88] In the presence of $Rh(CO)_2(acac)$ and chiral phosphine ligands, the hydroformylation afforded formyl functionalized aziridines in good yield (Scheme 65). Impressively, chiral trisubstituted bicyclic MAs were transformed to products with >99% regioselectivity and >19 : 1 diastereoselectivity at rates >50 catalyst turnovers per hour.

5. Conclusion

Monocyclic MAs have been synthesized for nearly seventy years. The combination of strained aziridine ring and exocyclic alkene group provides monocyclic MAs diverse reactivity toward a number of useful transformations, including ring-opening reactions, multicomponent reactions, cycloadditions, radical cascades and transition-metal-catalyzed reactions.

However, the methodologies for the synthesis of monocyclic MAs are not well-developed. A major limitation is lack of efficient chemistry to introduce diverse nitrogen substituents, such as aryl groups and electronic-withdrawing groups into its structure.

In the past decade, interest in these attractive scaffolds has led to the development of methods for the synthesis of bicyclic MAs. In addition to the chemical reactivities based on the monocyclic MAs, including nucleophilic ring-opening reactions and Lewis acid catalyzed [4 + 3] reactions, bicyclic MAs could also undergo unique chemical transformations such as diverse oxidation reactions, Rh-catalyzed ring expansion and hydroformylation of exocyclic alkene. Importantly, all of these reactions successfully construct densely functionalized products with structural and stereochemical complexity.

Given the wide occurrence of nitrogen-containing compounds and heterocycles in nature and drugs, we believe that MAs will increasingly attract the interest of synthetic community. Developing new efficient methods for synthesis of MAs with different types of substituents, along with revealing their unknown reactivities, will further expand their synthetic utility. We look forward to the contributions that will be uncovered in the near future.

Conflicts of interest

There are no conflicts to declare.

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