New Strategies for the Synthesis of 1- and 2-Azetines and Their Applications as Value-Added Building Blocks

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Four-membered nitrogen-containing heterocycles are highly desirable functional groups with synthetic and biological applications. Unsaturated 4-membered N-heterocycles, 1- and 2-azetines, are historically underexplored, but have recently been gaining increased interest due to the development of new synthetic methods to access these compounds, and to their potential as reactive intermediates. This review covers new strategies for the synthesis of 1- and 2-azetines with a particular focus on advances made since 2018. Additionally, the use of these compounds as intermediates to access other heterocycles (3- to 6-membered) and complex products is comprehensively discussed.

Introduction

Four-membered nitrogen-containing heterocycles (Fig. 1A) have recently gained increased interest and popularity for their potential as underexplored biologically active compounds. While azetidines (1) represent fully saturated four-membered N-heterocycles, azetines (2, 3), also known as dihydroazetes, are their corresponding counterparts with one unit of unsaturation. Specifically, 1-azetines (2) contain an imine functional group with a double bond between the nitrogen atom and the neighbouring carbon atom. In comparison, 2-azetines (3) incorporate a carbon-carbon double bond in the heterocycle. Much of the focus in the area of synthesis and reactivity of four-membered N-heterocycles has been on azetidines (1), which offer a variety of advantages compared to larger ring heterocycles including three dimensionality, increased metabolic stability,1-3 and potential as bioisosteres for other N-heterocycles such as pyridines.4-6 Although access to azetidines and azetines has historically been challenging, interest in functionalized azetidines has rapidly heightened due to recent synthetic advances.1,2 While development of methods to access azetines has been more limited, the field has seen a recent rise in popularity with the development of five new synthetic methods since 2018.7-12 Azetidines and azetines share desirable physical properties including high ring-strain and the potential to serve as bioisosteres; however, these four-membered heterocycles have important differences in their inherent reactivity, making azetines highly desirable synthetic targets.

In comparison to azetidines (1), incorporating exclusively sp³-hybridized carbons, the azetine scaffold (2, 3) includes two sp²-hybridized centers, which are responsible for their distinct

Fig. 1. A. Structure of 4-membered N-heterocycles, azetidines and azetines. B. The biological relevance of 2-azetines is demonstrated by their prevalence in the DNA photodegradation process. C. Limited medicinal relevance has been demonstrated in studies of synthetic azetines (7) and through the isolation of metabolites from ClpP inhibition (8).

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reactivity. A key challenge in the development of efficient methods to synthesize azetines (2, 3) is their unsaturated nature, resulting in elevated strain compared to azetidines (1). Importantly, azetines (2, 3) are prone to undergo competing thermal fragmentation through electrocyclic ring-opening resulting in the formation of aza-dienes,13–17 which has hampered the development of general synthetic strategies for their construction. Compared to azetidines, 1-azetines (2) possess an imine functionality, which can engage in additional reactivity and modulates its basicity compared to azetidines’ inherently more basic amine functionality.18

Despite challenges in synthetic access, azetines have been shown to be biologically relevant, which holds great promise for future pharmaceutical and biological applications. The photodegradation of DNA is known to proceed through the formation of Dewar isomers (6), which form upon isomerization of (6-4)-pyrimidinone photoproducts (5) arising from UV-light-promoted cycloaddition and rearrangement of 4.19–22 Additionally, 2-azetine 8 has been found to be the product of the reaction between a recently discovered inhibitor for bacterial caseinolytic protease (ClpP) and a serine residue in the binding pocket. This product is formed when the inhibitor and the serine form a covalent bond, leading to the formation of the azetine 8 and inhibition of the ClpP enzyme.23 Furthermore, azetine-containing compounds hold potential as cancer therapeutics. Specifically, 1-azetine 7 was shown to induce apoptosis in and have high cytotoxicity against THP-1 (human monocytic leukemia) cells.18 Additionally, other azetines similar to 7 were shown to vary greatly in their activity, demonstrating the importance of being able to synthesize a wide range of substituted azetines for further testing.18 As such, the development of more general and efficient methods for the formation of 1- and 2-azetines is expected to lead to important future discoveries in the area of azetine biological activity.

Access to 1- and 2-azetines has historically been limited to three main approaches including [2+2]-cycloadditions (Fig. 2A), elimination reactions (Fig. 2B), and ring expansions (Fig 2C). General challenges that plague strategies to synthesize azetines include competing aza-diene formation via electrocyclic ring-opening, and facile imine hydrolysis in the case of 1-azetines (2). Consequently, established synthetic methods tend to be limited in terms of scope or generality.

Methods to access azetines through [2+2]-cycloadditions (Fig. 2A) fall into two categories, [2+2]-cycloadditions of imines (9) and alkynes (10) to access 2-azetines (11)24–26 and [2+2]-cycloadditions of nitriles (12) and alkenes (13) to access 1-azetines (14).27–29 Cycloadditions relying on imines (9) and alkynes (10) have been shown to proceed either under UV light irradiation24 or metal-mediated conditions.29 In comparison, cycloadditions between nitriles (12) and alkenes (13) have been promoted exclusively with UV light and are limited to aryl substituted nitrile groups.27–29

Access to azetines via elimination from an azetidine starting material or intermediate has also been demonstrated for both 1-azetines (2)15,30–37 and 2-azetines (3)38–44 (Fig. 2B). Access to 1-azetines (2) can be mediated by elimination of a leaving group on the azetidine nitrogen atom,15,30–32 or by alkylation of a carbonyl, thiocarbonyl, or imine in the azetidine’s 2-position, followed by tautomerization to the 1-azetine product.33–36 2-Azetines (3) are similarly accessible by elimination of a leaving group from an azetidine (16),38,43 which can occur in situ from

![Diagram](image-url)
an azetidine intermediate\textsuperscript{39–41} or by alpha-deprotonation of a 3-azetidinone followed by trapping with an electrophile.\textsuperscript{42,44}

Ring expansions of azirines (17),\textsuperscript{45–48} cyclopropanes (19),\textsuperscript{32,49,50} or aziridines (21) to form azetines capture the inherent reactivity of 3-membered rings to enable access to the strained azetine products (Fig. 2C). In the presence of a carbene, azirine 17 is converted to 1-azetine 18 through a formal [3+1]-cycloaddition.\textsuperscript{45–48} In an alternative approach, cyclopropyl azides (19) can be converted to 1-azetines (20) upon heating.\textsuperscript{32,49,50} Finally, a ring expansion of a diazo-aziridine (21), formed in situ from aziridination of an α,β-unsaturated diazo-compound, under copper-catalyzed conditions results in a variety of 2-azetines (3).\textsuperscript{51} Notably, [3+1]-cycloaddition reactions resulting in azetines are not limited to three-membered rings. It has been shown that [3+1]-cycloadditions between 5-membered oxazaphospholes and isocyanates can form 1-azetine products, yet these examples are limited.\textsuperscript{52,53}

Although access to and applications of azetine compounds has historically been more limited than those of their saturated azetidine counterparts, evolving synthetic methodology has enabled their further exploration as synthetic intermediates and valuable building blocks. This review aims to provide a comprehensive overview of new synthetic protocols giving rise to 1- and 2-azetines, and to highlight applications of these heterocycles as versatile synthetic intermediates. Specifically, strategies resulting in the formation of azetidines as well as 3-, 5-, 6-membered and larger heterocycles upon conversion of azetine intermediates have been developed and are discussed in this review together with their utilization in complex molecule synthesis. Previous reviews have focused on providing overviews of established methods to access 1- and 2-azetines.\textsuperscript{54–56} This comprehensive review will highlight advances made in the area of azetine synthesis since 2018.

**Synthetic advances since 2018**

Methods for the syntheses of 1- and 2-azetines have been the subject of previous reviews.\textsuperscript{54–56} Figure 3 provides an overview of new synthetic methods developed since 2018 that include advances in cycloaddition, ring-expansion, and elimination strategies.

In the area of [3+1]-cycloadditions, in 2019, Doyle and co-workers reported a new strategy for the enantioselective synthesis of 2-azetines (24) upon [3+1]-cycloadditions between imido-sulfur ylides (23) and enoldiazoacetates (22) under copper catalysis in the presence of a chiral sabox ligand. The methods achieved high enantiomeric excess of up to 95% (Fig. 3A).\textsuperscript{7,12} The reports also showed further utility of the azetine products, namely in accessing azetidines by reduction\textsuperscript{8} and amino acid derivatives upon ring-opening.\textsuperscript{9}

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**Fig. 3. Recent advances in synthetic methods to access azetines.** A. Copper-catalyzed enantioselective [3+1]-cycloaddition to access tetrasubstituted 2-azetines. B. Ring-expansion of aziridines via rhodium carbenoids to access 1-azetines. C. Lewis acid catalyzed [2+2]-cycloaddition to access 2-azetines. D. Flow synthesis of 2-substituted 2-azetines via formation of α-lithiated-2-azetines. E. Divergent synthesis of 1- and 2-azetines via a [2+2]-photocycloaddition.
In the area of ring-expansions, Novikov and co-workers’ 2019 report showcased the synthesis of substituted 3-(2′-pyridyl)-1-azetines (26) via ring-expansion of azirines (25) with rhodium carbenes (Fig. 3B). To accomplish the transformation it was necessary to incorporate a silyl protecting group on the pyridine nitrogen to limit side reactivity, which was installed and removed in a sequential one-pot reaction.
In 2021, Ito and co-workers reported a Lewis acid catalyzed stepwise [2+2]-cycloaddition to generate 2-azetines (29) from substituted iminopyruvates (27) and aryl alkynes (Fig. 3C). The authors proposed that intermediate 28, in which the titanium is chelated by the iminopyruvate, is crucial in preventing side reactivity between the ester and the electrophilic carbon of the alkyne.

Expanding on the area of eliminations to synthesize azetines, Luisi and co-workers’ 2021 report demonstrated a flow-synthesis protocol capable of facilitating an elimination and incorporating an electrophile to synthesize 2-azetines (32). Specifically, in the presence of LDA, the N-Boc-3-iodoazetidines (30) undergo an elimination to form a 2-azetine that is then further deprotonated to generate α-lithiated-2-azetines (31). Downstream in the flow reactor, this intermediate is reacted with an electrophile to yield 2-azetines (32) bearing additional substitution at the 2-position (Fig. 3D). The scope of electrophiles included aldehydes, ketones, imines, and silyl chlorides.

A divergent synthesis of 1- and 2-azetines enabled by visible-light-mediated triplet energy transfer (EnT) photocatalysis was reported by Schindler and co-workers in 2021 (Fig. 3E). This method utilized a [2+2]-photocycloaddition to access these products either directly (2-azetine 34) or from a cycloaddition-rearrangement sequence (1-azetine 35). Therein, 2-azetines formed upon initial [2+2]-cycloaddition between cyclic oximes (33) and aryl alkynes can undergo a consecutive sensitization and subsequent rearrangement to 1-azetines (35). In the absence of aryl substituents on the alkyne component, 2-azetine products (34) are isolable as the initial [2+2]-cycloaddition products between aliphatic alkynes and isoxazolines (33).

Azetines as intermediates

Synthesis of 4-membered heterocycles

1- and 2-azetines contain reactive π-bonds, due in part to the strained nature of the four-membered ring. The imine moiety in 1-azetines and the alkene subunit in 2-azetines promote imine or alkene addition reactions, which allows access to a wide range of substituted and/or polycyclic azetidines (Fig. 4). There are eight types of addition reactions, not including cycloadditions, that 1- and 2-azetines undergo to produce azetidines. These classes of addition reactions are radical addition to 2-azetines (Fig. 4A), acid-facilitated addition to both 1- and 2-azetines (Fig. 4B), metal-catalyzed addition to 2-azetines (Fig. 4C), β-lactam formation from 1-azetines (Fig. 4D), hydride reduction of 1-azetines (Fig. 4E), base-facilitated addition to 1- and 2-azetines (Fig. 4F), metal-catalyzed hydrogenation of 2-azetines (Fig. 4G), and N-methylation/sulfide formation of 1-azetines (Fig. 4H).

The Zard group has developed methods relying on xanthenes as radical precursors to facilitate addition across the olefinic π-bond of 2-azetines to access functionalized azetidines (Fig. 4A). Zard and co-workers initially disclosed two examples in which 37 (PG = Bz) in the presence of catalytic lauryl peroxide and mono-substituted xanthenes (36) afforded disubstituted azetidines (38) in up to 50% yield. For both substrates the trans isomer was preferred over the cis isomer, although both isomers were formed. Zard and colleagues furthered this work by employing similar reaction conditions with a Boc-protected 2-azetine (37) and xanthenes (36) to produce azetidines (38) regioselectively. In these examples the authors added 2,6-lutidine to their initially disclosed reaction conditions to suppress lauric acid-induced decomposition of the 2-azetene substrates (37). Incorporation of the xanthenate group into the final product was advantageous as it allowed conversion of the resultant azetidines (38) into complex pyroles, or could be reductively removed to afford monosubstituted azetidines bearing complex carbon skeletons including a steroid scaffold.

The π-systems of 1- and 2-azetines are labile under acidic conditions, and the propensity of the azetine π-system to react with acids can be harnessed to access functionalized azetidine scaffolds (Fig 4B). Wulfman and Steinheimer reported that the formation of 39 (Fig 4B), a 1-azetine, via thermolysis of a cyclic azide and upon purification on silica gel provided a mixture of azetidine 40 and its ring-opened isomer 41 in equilibrium. Presumably, the acidity of silica gel and nucleophilicity of water account for the formation of the observed products. Hodgson and co-workers also recognized the lability of azetines to mildly acidic conditions. Hodgson’s group observed an acid-driven isomerization from a 2-azetine (42, Fig. 4B) to form azetidine 43 when 42 was dissolved in deuterated chloroform, which is known to be slightly acidic. Although the acid-driven reactivity of 1- and 2-azetines has not been extensively explored, there is great potential for accessing functionalized azetidines using this class of reactivity.

Transition-metal-catalyzed additions across π-systems have been extensively explored and have similarly been employed to control the reactivity of 2-azetines (Fig. 4C). In this area, Zhang and co-workers developed a nickel-catalyzed arylfluoroalkylation across the alkenes of 2-azetines (44) that affords trans-disubstituted azetidines (45). This metal-catalyzed transformation of 2-azetines (44) proceeded with a diastereoselectivity greater than 20:1, and produced azetidines with ester or amide functionality for subsequent modifications such as amide couplings.

Functionalized β-lactams are a well-established motif that have demonstrated medicinal properties. 1-Azetines have been identified by researchers as precursors to functionalized β-lactam rings under a variety of reaction conditions (Fig 4D). The first example of a 1-azetine being converted to a β-lactam was disclosed by Atkinson and co-workers. The Atkinson group showed that two different 1-azetines (46, R=Cl or MeO, R=Ph, R=Cl, R=Me, R=H) were converted to the same N-hydro β-lactam (47) upon exposure to 10% hydrochloric acid.
Likewise, Aue and Thomas were able to synthesize a N-methyl β-lactam (47, R²=R³=Me, R⁴=R⁵=H) from a 1-azetine (46, R¹=OMe) via a thermally induced Chapman rearrangement. Ghosez and co-workers developed a general protocol that allows conversion of a 1-azetine (46, R¹=NMe₂, R²=R³=Me, R⁴=Ph, R⁵=H) to β-lactams with an N-electrophile bond (47) in the presence of an electrophile such as methyl iodide or acrylonitrile following basic hydrolysis. Pifferi and co-workers synthesized a series of 1-azetines (46, R¹=OEt, R²=alkyl or aryl, R³=alkyl or aryl, R⁴=R⁵=H) from β-lactams (47). The authors observed that anhydrous hydrochloric acid in ethereal solvents reverted 1-azetines (46) to the corresponding β-lactams (47) from which they were formed. The four protocols described (vide supra) allow access to highly functionalized β-lactams from 1-azetines and proceed through different mechanisms, which highlight the potential of 1-azetines as useful building blocks to access β-lactam rings.

Hydride-driven reduction of imines is a well-established class of reactivity that has also been demonstrated to readily convert 1-azetines to azetidines (Fig 4E).
Hydride reduction of a 1-azetine to form azetidine products was presented by Pifferi and co-workers, who employed LiAlH₄ to reduce three different 1-azetines (46, Fig 4E) to the corresponding azetidine (48) scaffolds.¹⁴ Interestingly, the R¹ substituent (R¹=O-OME) was cleaved in the course of this transformation and replaced with a hydrogen atom.¹⁴ Both Hassner and co-workers and Denis and colleagues also demonstrated that various 1-azetine (46) scaffolds could be reduced by LiAlH₄ in ethereal solvents.¹⁵,⁴⁹ Notably, Wulfman and Steinheimer were able to reduce a [4.2.0]-fused cyclic 1-azetine (46) with the less reactive NaBH₄ to afford the corresponding [4.2.0]-fused-cyclic azetidine (48).⁶⁰ Finally, Burger and co-workers disclosed an intriguing example of a LiAlH₄ reduction of 49 (Fig 4E) to 50, which left the exocyclic imine motif intact.⁶⁷ Hydride reduction of 1-azetines offers a viable strategy to access the valuable azetidine scaffolds in a straightforward manner.

1- and 2-azetines are also reactive under basic conditions, which often leads to rearrangements (Fig. 4F). De’l’Tossa and co-workers identified that highly fluorinated 2-azetines (51, Fig. 4F) undergo a rearrangement to afford a fluorinated azetidine product (52) with an exocyclic π-bond under basic conditions.⁶⁸ The importance of fluorinated compounds in medicinal chemistry is extensively documented,⁶⁹⁻⁷⁵ which highlights the potential applications of this base-driven rearrangement. In 1970, Bormann developed a method to couple 1-azetine 53 (Fig. 4F) to a β-lactam moiety giving adduct 54.⁷⁶ Under basic conditions, adduct 54 cyclized to produce [4.2.0]-cycloadduct 55, which contains an azetidine structural unit.⁷⁶ Similar to acid-driven reactivity of 1- and 2-azetines, basic reaction conditions of azetines have not been extensively explored. However, the research to date highlights the potential to generate useful 4-membered nitrogen-containing scaffolds using base-mediated reactions of azetines.

Metal-catalyzed hydrogenation of olefins is a well-established transformation, and 2-azetines can be easily converted to the corresponding azetidine by this approach (Fig. 4G). The first example of a 2-azetine being converted to the corresponding azetidine was presented by Barluenga, López, and co-workers in 2012.⁵¹ The authors exposed N-tosyl 2-azetines (56, R¹=CO₂Et, R²=H or Me, R²=H, Fig. 4G) to hydrogen gas in the presence of palladium-on-carbon (Pd/C) to produce the desired cis-disubstituted azetidines (57).⁵¹ Both Hodgson and co-workers and Didier and colleagues utilized a similar strategy to hydrogenate various N-Boc-2-azetines (56) giving the respective mono- or disubstituted-azetidinone frameworks (57).⁴²,⁴⁴ Notably, Doyle and co-workers have synthesized chiral 2-azetines (56) bearing a stereocenter at the carbon substituted with R¹.⁷ The authors highlighted that Pd/C-catalyzed hydrogenation of chiral 2-azetines (56) allowed access to chiral azetidines (57), preserving the high enantiomeric excess observed in their initially synthesized 2-azetines (56).⁷ Similarly, Didier and co-workers expanded upon their earlier work with 2-azetines and employed a ruthenium catalyst and chiral ligand to convert achiral 2-azetines (58, Fig. 4G) to chiral azetidines (59) in high yields with enantiomeric ratios up to 95:5.⁴²,⁷⁷⁻⁷⁹ 2-Azetines bear a highly strained olefin, which makes them primed to be reduced under metal-catalyzed hydrogenation to the corresponding azetidine scaffolds. As demonstrated (vide supra), this allows facile access to a wide range of functionalized four-membered nitrogen heterocycles.

The cyclic imine contained within 1-azetines provide a unique reactivity profile, which is centered on the nucleophilicity of the imine nitrogen and the electrophilicity of the imine carbon. In 1981, de Boer and co-workers harnessed this reactivity to convert 60 to a highly functionalized azetidine (62, Fig. 4H).⁵⁰ The authors methylated the imine nitrogen of 60 using methyl fluorosulfonate to result in the resonance stabilized carbenium ion 61 that was subsequently trapped with sodium methanethiolate to give azetidine 62.⁵⁰ Azetidines have been identified as useful isosteres of other N-heterocycles,⁴⁻⁶ which makes accessing highly functionalized azetidines such as 62 of interest.

1- and 2-azetines contain n-systems that prime them to react via cycloadditions, which afford valuable fused-polycyclic azetidines. Specifically, azetines have been demonstrated to undergo four types of cycloaddition reactions. These classes of reactivity are [3+2]-cycloadditions (Fig. 5A), cycloadditions with ketenes and isocyanates (Fig. 5B), [4+2]-cycloadditions (Fig. 5C), and cycloadditions that lead to dimerization (Fig. 5D).

[3+2]-Cycloaddition reactions of 1- and 2-azetines are attractive because they rapidly build complexity and form fused heterocycles containing a four- and five-membered ring, both of which can be challenging to synthesize (Fig. 5A). 3+2]-Cycloadditions involving azetines were first disclosed by Smalley and Luheshi in 1990.⁸⁰,⁸¹ Upon reaction of 1-azetines (63) with nitrile oxides (Z=O), nitrile ylides (Z=CHAr), and nitrilimines (Z=NR) generated in situ from hydroximidoyl, imidoyl, or hydrazonoyl halides, highly functionalized bicyclic or tricyclic scaffolds were produced (64).⁸⁰,⁸¹ Polycyclic azetidines (64) resulting from nitrile oxides were synthesized in up to 95% yield, and azetidines formed from nitrile ylides were isolated in up to 68% yield.⁸¹ Similarly, fused azetidines (64) formed from nitrilimines were isolated with a maximum of 89% yield.⁸⁰ Hemming and co-workers expanded upon this methodology with the synthesis of bicyclic azetidines (64) from the [3+2]-cycloaddition of 1-azetines (63) and hydroximidoyl chlorides.⁸² This reaction proceeded through the in situ generation of nitrile oxides (Z=O) from hydroximidoyl chlorides to afford bicyclic-azetidine products (64) in up to 72% yield as single diastereomers.⁸² Azetidines 64 were further converted to functionalized oxadiazoles upon heating in toluene.⁸²

Cyclopropenones are also highly useful reagents for [3+2]-cycloadditions. Unlike other 1,3-dipoles that commonly contain at least one heteroatom, cyclopropenones provide a source of three contiguous carbon atoms (Fig. 5A). As such,
cyclopropenone reagents allow access to fused polycyclic structures (67) with a higher carbon content than nitrile oxides and similar 1,3-dipolar reagents. The first example of a cycloaddition between cyclopropenones and 1-azetines was disclosed by Heimgartner and co-workers in 1983. A series of 1-azetines (65, X=NR₂) were reacted with difunctionalized cyclopropenones to afford [3.2.0]-cycloadducts containing a fused azetidine ring (65). Smalley and co-workers extended...
these initial studies in 1992 with the synthesis of fused-bicyclic 
ofused-tricyclic azetidines (65) from highly functionalized 1- 
azetines (63, X=SMe) and diphenylcyclopropenone.84 In 2006, 
Hemming and co-workers also presented a single example of a 
1-azetine (63, X=SMe) reacting with diphenylcyclopropenone to 
afford a similar azetidine adduct (65) to the azetidines disclosed 
by Small and colleagues.84,85 Hemming and co-workers 
expanded upon their 2006 work in 2011 when they presented 
a [3+2]-cycloaddition reaction of 1-azetines (63, X=SMe) with 
difunctionalized cyclopropenones to access [3.2.0]-fused 
azetidines (65).86 These adducts were subsequently converted 
to highly functionalized pyridines, which are useful building 
blocks.86

Didier and co-workers were also able to leverage a [3+2]- 
cycloaddition strategy that used 2-azetines (66, Fig. 5A) and 
nitrile oxides in a telescoped sequence to access fused- 
isoaxazoline-azetidine scaffolds (67 and 68).78 2-Azetines and 
hydroxymidoyl chlorides were reacted under microwave 
irradiation to afford fused azetidines (67 and 68) in up to 83% 
yield over four or five steps. Interestingly, the 2-azetine 
precursors were generated by a three to four step telescoped 
sequence from a substituted-Boc-protected azetidine, and the 
nitrile oxides were generated in situ. Monosubstituted 2- 
azetines gave single products (67), but disubstituted 2-azetines 
gave a mixture of regioisomers (67 and 68) with a maximum 
regioselectivity of 16:1 (the identity of the major regioisomer is 
substrate dependent).78

Another useful class of reactivity to access fused-azetidine 
scaffolds from 1- and 2-azetines involves cycloaddition with 
ketenes and isocyanates (Fig. 5B). Both ketenes and 
isocyanates are highly reactive species, and cycloadditions 
involving these compounds with 1- and 2-azetines lead to fused 
[2.2.0]-bicyclic compounds (70) and [4.2.0]-bicyclic skeletons 
(72, 73) containing an azetidine. Correia and co-workers 
published the first example of a [2+2]-cycloaddition between 2- 
azetine 69 (Fig. 5B) and dichloroketene to afford a [2.2.0]-fused 
azetidine product (70).87 The initial adduct formed bears a 
ketene instead of the hydroxyl substituent in 70, but was 
deemed too unstable to be isolated and handled effectively. To 
overcome this instability, Correia and colleagues reduced this 
transient species with NaBH\(_4\), giving rise to azetidine alcohol 
70.87 The first example of a ketene reacting with a 1-azetine was 
disclosed in 1973 by Hassner and co-workers, who showed a 
single example of the reaction of a 1-azetine (46, R=SPh, 
R\(^2\)=R\(^2\)=Cl, R\(^3\)=Me, R\(^4\)=H, Fig. 5B) with diphenylketene to give 
cycloadduct 73 (X=O, Z=CPh\(_2\)).88 The reactivity of ketenes with 
1-azetines was expanded by Aue and Thomas in 1975 when they 
presented additional examples of a 1-azetine (46, 
R\(^1\)=OME, R\(^2\)=R\(^2\)=H or Me, R\(^2\)=R\(^2\)=Me) reacting with a ketene 
(R\(^2\)=CN, R\(^2\)=Bu) to afford cycloadducts 73 (X=O or C(CN)\(_2\)Bu, 
Z=O or C(CN)\(_2\)Bu).89 Aue and Thomas in the same year 
published a similar report that used 1-azetines (71, R\(^1\)=H or Me, R\(^2\)=H or 
Me, Fig. 5B) with tosylated isocyanates to form cycloadducts 
72.90 Ketenes and isocyanates are well established highly 
reactive species, and their application in reacting with 1- and 2- 
azetines allows access to complex polycyclic azetidines.

One of the most powerful classes of cycloaddition reactions 
are [4+2]-cycloadditions, and the olefinic \(\pi\)-bond in 2-azetines 
allows these strained heterocycles to participate in this class of 
reactivity (Fig. 5C). The first example of a [4+2]-cycloaddition 
involving 2-azetines was presented by Dave and co-workers, 
who presented a Diels-Alder reaction of an N-acetyl-2-azetine 
(75, Fig. 5C) dienophile with various dienes (74) to afford 
complex cycloadducts (76).91 This Diels-Alder reaction 
proceeded in a straightforward manner, only requiring heat, 
giving the endo products selectively in up to 94% yield.91 Didier 
and co-workers employed an alternate approach utilizing 
functionalized 2-azetines with a pendant vinyl group (78 or 80, 
Fig. 5C) as the diene with a succinic anhydride or succinimide 
dienophile (77).79 The [4+2]-cycloaddition proceeded with 
good yields and high diastereoselectivity, which favored an 
endo transition state, to give tricyclic azetidines (79 or 81).79 
Notably, the aforementioned two examples demonstrate that 
2-azetines can act as both the diene or dienophile component 
in a Diels-Alder cycloaddition reaction depending on the 
substitution of the 2-azetine.79,91 Stevenson and co-workers 
utilized a Y(OTf)\(_3\)-catalyzed [4+2]-cycloadduction between N- 
acetyl-2-azetine 75 (Fig. 5C) and various aromatic imines (82) 
to access azetidines fused to tetrahydroquinolines (83).92,93 These 
cycloadducts proved unstable upon standing overnight, so 
were trapped with aromatic amines to selectively break open 
the azetidine ring (98 and 99, Fig. 6C).92,93 These examples 
highlight the value of [4+2]-cycloaddition reactions resulting in 
the rapid formation of molecular complexity in the form of 
polycyclic azetidine scaffolds.

Olefins-containing compounds can often be induced to 
dimerize or polymerize under thermal or photochemical 
conditions. 2-Azetines consist of a cyclic enamine that enables 
a photochemical dimerization process (Fig. 5D). Dave and 
co-workers disclosed the [2+2]-cycloadduction of N-acetyl-2-azetine 
75 to an approximately 1:1 ratio of the two possible head- 
to-head dimers 84 and 85 in a 52% combined yield.94 This 
dimerization reaction was initiated by irradiation from a 500 
Watt high pressure mercury lamp, and no head-to-tail 
dimerized products were observed.94

**Synthesis of 3-, 5-, 6-membered and larger heterocycles**

In addition to being used as intermediates to access azetidines, 
azetines can also be used to form 3-, 5-, 6-membered and larger 
heterocycles. The ring-contraction of isolated azetines for the 
synthesis ofazine has rarely been reported in the literature. Only 
a single example was observed by Regitz and co-workers in 1988, 
who observed that upon heating or irradiation of a dihydrotriazole 
(86), azizine 87 formed (Fig. 6A).95 This was proposed to occur via 
a zwitterionic intermediate.

Conversely, the ring-expansion of isolated azetines has 
been more widely studied, mostly to result in 5- and 6-
membered heterocycles. In 1973, Aue’s group reported one of the first examples of a 5-membered heterocycle that was derived directly from an isolated azetine.\(^9^6\) The initial report described that oxidation of tetra-substituted azetine \(88\) \((R^1=R^2=Me)\) provided an oxazoline \(89\) in 56% yield (Fig. 6B). A subsequent report discussed the effect of \(R^1\) and \(R^2\) substitution on azetine \(88\) on ring-expansion.\(^9^7\) Oxidation of tri-substituted \(88\) \((R^1=Me, R^2=H)\) resulted in a product mixture of \(89\) and a nitroso ester \(112\), Fig. 7B) that is proposed to form via a bicyclic oxazirane intermediate \(111\), Fig. 7B). The authors proposed that \(89\) forms via a Baeyer-Villiger oxidation and is favored when \(R^2≠H\) or \(R^3≠H\) due to the increased migratory aptitude of alkyl substituents.

Smalley and co-workers reported that 2-ethoxy- and 2-ethylthio-1-azetines \(90\) and arynitrilimines underwent a 1,3-dipolar cycloaddition to afford 1,2,4-triazoles \(91\), rather than the expected fused bicyclic triazole that would arise from a direct \([3+2]\)-cycloaddition (Fig. 6B).\(^8^0\) The absence of -XEt \((X=O, S)\) in \(91\) suggests that after the cycloaddition, -XEt is expelled to result in a resonance-stabilized triazolium intermediate. This intermediate can undergo ring-opening and subsequent aromatization to the observed product \(91\). Nitrilimines incorporating a nitrophenyl substituent resulted in only the non-rearranged bicyclic triazole, likely due to the decreased stability of the proposed triazolium intermediate.

Azetines have also been used to access various pyrrole scaffolds. In 1997, Regitz and co-workers reported that azetine \(92\) underwent thermolysis in toluene to the 2\(H\)-pyrrole \(93\) (Fig. 6B).\(^9^8\) Zard’s group reported a two-step approach towards 4-(aminomethyl)pyrroles \(95\), which occurs via an isolable azetidine intermediate \(38\), Fig. 4A) that is observed from the radical addition of 2-azetine \(44\) (Fig. 6B) to xanthates \(94\).\(^5^8,^5^9\) Upon addition of excess ammonia or amine to the azetidine intermediate \(38\), Fig. 4A), the xanthate group on \(38\) undergoes
aminoysis, which induces fragmentation of the azetidine ring and allows for condensation of the amine to furnish products. Both 2,4-disubstituted and 2,3,4-trisubstituted pyrroles were obtained in moderate to high yields, 64-95% (from the isolated azetidine intermediate 38, Fig. 4A) and 58-68% (from the xanthate 94 and 2-azetine 44, Fig. 6B), respectively.

Recently, Schindler and co-workers reported a one-pot photochemical method enabled by triplet energy transfer to access highly-functionalized tetrahydrofurans 97 (Fig. 6B).\textsuperscript{11} Irradiation of 2-isoxazolines (33) and aryl alkynes (96) in a mixture of acetonitrile and 0.1 M HCl furnished tetrahydrofuran products 97 in up to 69% yield. Product 97 forms from in situ hydrolysis of an azetine intermediate (35) that forms via an initial [2+2]-cycloaddition and subsequent rearrangement. Both terminal alkynes (R=H) and internal alkynes (R=CO₂Me, Me) were tolerated. For terminal alkynes, both electron-donating and electron-withdrawing groups were also compatible with the reaction conditions. However, substrates in which R² and R³ were larger led to lower reactivity.

In an extension of an azza Diels-Alder reaction developed using 2-azetines, Stevenson and co-workers demonstrated a one-pot method to access tetrahydroquinolines from N-acetyl-2-azetine 75 and N-aryl imines (82) in the presence of yttrium(III) triflate as a Lewis acid catalyst. Following the azza Diels-Alder cyclization to generate intermediate tetrahydroquinolines bearing fused azetidines (83, Fig. 5C), the aniline is able to facilitate ring-opening of the azetidines to ultimately generate substituted tetrahydroquinolines with a large preference for the less sterically congested diastereomer (98, 99, Fig. 6C).\textsuperscript{92}

Stevenson and co-workers, while screening conditions to convert their tetrahydroquinolines (98, 99), found that upon heating the substituted tetrahydroquinolines (98) in the presence of yttrium(III) triflate, they were able to form quinolines in good yield. The authors subsequently showed that quinolines (101) could be formed from the corresponding N-acetyl-2-azetine (75) and N-aryl imines (82) in a sequential one-pot reaction sequence.\textsuperscript{93}

Yan and co-workers showed that similar quinolines (101) could be formed from N-aryl-nitrones (100, X=O) and N-Boc-2-azetines (37) under catalytic silver(I) triflate. In this case, the reaction was proposed to proceed through a 3+2-cycloaddition to form an intermediate isoxazolidine before subsequent rearrangements.\textsuperscript{99}

In addition to N-containing 6-membered heterocycles, O-containing oxazines can be obtained. As demonstrated by Barluenga and co-workers, 1,3-oxazines (103) were formed through the reaction of stable 2-azetine chromium carbenes (102) and alkynes. The proposed mechanism begins with the insertion of the alkyne into the carbene-metal bond, followed by CO insertion to ultimately form a metal-ketene intermediate. Upon an intramolecular nucleophilic attack of the ketene motif by the 2-azetine, a spirocyclic 1-azetinium intermediate is formed. This 1-azetinium intermediate can then undergo a ring-expansion and rearrange to form the product 1,3-oxazine (103).

The synthesis of sulfur-containing heterocycles was demonstrated by Ito and Hara in 2021. Their method shows the formation of 6-membered cyclic sulfonamide 105 upon treating N-mesyalted 2-azetine 104 with three equivalents of potassium tert-butoxide.\textsuperscript{9} The authors hypothesized that the reaction proceeded via a [2,3]-rearrangement following deprotonation of the mesyl group.

The formation of larger polycyclic ring systems was shown by Hemming and co-workers in their 2006 report. Therein, the authors demonstrated the formation of azabicyclo[4.2.1]nonene products (107, Fig. 6D) from 1-azetines (106) with cyclopropenones. These reactions were proposed to proceed through a Michael-type addition of the 1-azetine (106) into the cyclopropenone, and subsequent ring expansion of the cyclopropenone followed by an azza-Cope [3,3]-rearrangement.\textsuperscript{85}

**Synthesis of complex molecules enabled by azetines**

Historically, the use of azetines to synthesize more complex molecules has favored addition and cycloaddition methods, as discussed above. However, the use of these compounds to access other complex molecules shows the potential for the use of azetines to access a diverse range of new products (Fig. 7).

While imine hydrolysis of 1-azetines can be detrimental to their stability, this reaction can also be employed to form value-added products. The first known report of 1-azetine hydrolysis was described by Pifferi and co-workers in 1967 (Fig. 7A), who observed that dilute HCl facilitated hydrolysis of azetines 108 to afford ethyl α,α-disubstituted β-aminopropionate hydrochlorides 109 (Fig. 7A).\textsuperscript{4} Additionally, when R²=R³=Ph, 3,3-diphenylazetidin-2-one was formed as a minor by-product.

In addition to hydrolysis, the imine moiety of 1-azetines has also been documented to be sensitive to oxidation (Fig. 7B). Aue’s group reported that upon exposure to mCPBA, 2-methoxy-4,4-dimethylazetine (110) oxidized to form the non-isolable 1-aza-5-oxabicyclo[2.1.0]pentane 111 that further oxidized to afford the acyclic nitroso ester 112 (Fig. 7B).\textsuperscript{96}

In contrast to the formation of a reactive cyclic intermediate such as 111 (Fig. 7B) from a 1-azetine, Müller and co-workers diversified an acyclic nitrile ylide intermediate (114) that originated from 1-azetine 113 (Fig. 7C) to form a variety of products (115-117).\textsuperscript{100} Irradiation of 1-azetines (113) in benzene with UV light resulted in the reversible [3+1]-cycloelimination of isocyanide to afford nitrile ylides 114. The nitrile ylides (114) were trapped by alcohols, dimethyl acetylenedicarboxylate, or dimethyl maleate or fumarate to provide benzimidic ester (115), 2H-pyrole (116), or 1-pyrrrole (117) products respectively. The use of acyclic esters as the dipolarophile resulted in a mixture of regioisomers. Importantly, the diversity of both cyclic and acyclic products shows that azetines can be utilized to form desirable products...
that are not heterocycles, examples of which are much more
limited than methods resulting in new heterocyclic products.

There are only two known examples of azetines being used as precursors in natural product synthesis. In 1991, Jung and co-worker reported a three-step synthesis of (±)-6-coniceine, a 1-azabicyclo[4.3.0]nonane, derived from a 1-acetyl-2-azetine. Initial electrocyclic ring-opening of the 1-acetyl-2-azetine allowed for an intramolecular Diels-Alder reaction with a terminal olefin moiety on the acyl-chain. Subsequent hydrogenation afforded (±)-6-coniceine. In 2000, Stevenson and co-worker reported a concise, four-step synthesis of the biologically active alkaloid Luotonin A (122), in which N-acetyl-2-azetine (75) was used as an initial precursor (Fig. 7D). An initial Diels-Alder reaction of 75 and 118, followed by an elimination, aromatization reaction under acidic conditions, afforded the 2,3-disubstituted quinoline 119 in 78% yield. The authors attempted to oxidize 119 with DDQ, but instead recovered 119 in 80% yield. Alternatively, cyclization of 119 using NaN3 provided lactam 120 in 99% yield. Final addition of 2-sulfinylaminobenzoyl chloride (121) under basic conditions afforded Luotonin A (122).

More recently, Doyle and co-workers described the synthesis of amino acid derivative (125) using chiral donor-acceptor azetines (Fig. 7E). Upon treatment with a nucleophile, 2-azetine-2-carboxylates 123 underwent strain-induced ring-opening via 3-azetidinone carbonyl azetidinone carboxylate intermediates (124, Fig. 7E). Amine nucleophiles with electron-withdrawing substituents on the N-aryl group provided moderate to high yields and high enantiopurities (63-96% yield, up to >99% ee), while electron-donating substituents resulted in diminished enantiopurity (e.g. 126). Other nucleophiles such as alcohols, hydrazines, hydroxylamine, and ammonia were also compatible (e.g. 127-128) in good yields and enantiopurities. Mechanistic studies suggested that two equivalents of the nucleophile are required, with the first equivalent desilylating the TIPS group and the second equivalent adding into the carbonyl of 124. In contrast to the β-amino acid derivatives obtained via hydrolysis of 1-azetines (Fig. 7A), this method allows for modular access to chiral, highly functionalized α-amino acid derivatives from chiral 2-azetines.

Azetines as proposed intermediates

Many discussions of azetines in early literature propose them as non-isolable intermediates towards various complex structures. A common reaction pathway for azetines is electrocyclic ring-opening to the corresponding azabutadiene, as shown by the reversible reaction between 2-azabutadiene 134 and 1-azetine 135 (Fig. 8B). In 1972, Cantrell reported that benzonitrile (129) underwent a photochemical [2+2]-cycloaddition with excess 2,3-dimethyl-2-butene or 1,1-dimethoxy-2,2-dimethylethylene (130) to afford 132 in 71% and 45% yield, respectively (Fig. 8A). This was postulated to occur via a [2+2]-cycloaddition of 129 in the singlet excited state to form the 1-azetine intermediate (131), which subsequently underwent electrocyclic ring-opening. While 131 was not detected or isolated in the initial report, its isolation was later reported. The electrocyclic ring-opening of 1-azetines was also proposed as a reversible process in the pyrolysis of 2H-azirines 133 by Bergman and co-workers in 1974 (Fig. 8B). The authors proposed that 133 undergoes two sequential hydrogen atom transfers to first form a carbene intermediate and then 134, which is in equilibrium with 135.

1-Azetines have been invoked as intermediates in the photochemical reactions of thiadiazolium compounds. Kato and co-workers observed that thiadiazoliums 138 underwent desulfurization using UV light and tributylphosphine (Fig. 8C). They postulated that 138 initially isomerizes to a bicyclic intermediate and subsequently desulfurizes to form an azetone (X = O) or imino 2-azetine (X = N) (139) intermediate, which then undergoes ring-opening to the corresponding ketone or ketenimine, respectively. While the ring-closed products (140) were observed when X=O, acyclic enamino-nitriles (141) were observed when X=NH2.

Additionally, azetine intermediates have been proposed to result upon elimination reactions of intermediate azetidines. Faure and co-workers discussed that elimination of HBr from 142 resulted in 144, rather than the expected 2-azetine product (Fig. 8D). Instead, the 2-azetine is proposed to form transiently as intermediate 143, which then reacts with atmospheric oxygen to form an oxetane species that undergoes ring-opening to 144. A polymer byproduct arising from 144 was also observed, demonstrating the reactivity of this intermediate.

2-Azetines are commonly invoked as intermediates in the reaction of alkyne derivatives with aldimines. Murai and co-workers disclosed the formation of 148 from the silylolate 145 and aldmine 146 under acidic conditions (Fig. 8E). This reaction proceeds through a 2-azetine intermediate 147 that forms via a [2+2]-cycloaddition. Similarly, in 1996, Kobayashi and co-workers observed the formation of 152 from alkynyl sulfides 149 and imines 150 (Fig. 8F). An initial [2+2]-cycloaddition between 149 and 150, catalyzed by Lewis acids including Sc(OTf)3, Yb(OTf)3, or BF3·OEt2 (10-100 mol %), resulted in the formation of the non-isolable intermediate 151. This intermediate (151) subsequently fragmented via cycloreversion to 152. Substituted alkynyl sulfides (149, R1 = Me, Bu) gave moderate to high yields (40-100%), while terminal alkynyl sulfides (149) yielded only 8% in a single example. An intramolecular example provided a cyclohexene thioimidate product in 46% yield. Analogous methods for the synthesis of α,β-unsaturated selenylimidates and α,β-unsaturated amidines have also since been reported.

In contrast to the formation of acyclic products as mentioned above (Fig. 8A-F), azetines have also been proposed as intermediates in the synthesis of aziridines from azetidines (Fig. 8G). De Kimppe and co-workers observed that in the presence of NaOMe, 3,3-dichloroazetidines (153) form aziridines (155) in refluxing methanol (Fig. 8G). Elimination
of HCl from 153 results in the formation of 154, after which addition of methanol allows for a bicyclic aziridinium intermediate to form that ring-contracts to 155 in high yields of up to 94%. The authors also reported that treatment of 153 with NaH in DMSO and subsequent hydrolysis afforded 2-acylaziridines in modest yields (46-59%). In a later report, the authors disclosed that under similar basic conditions, 2,4-diaryl-3,3-dichloroazetidines afforded benzimidoyl-substituted alkynes.\textsuperscript{111} This is proposed to proceed through elimination of HCl to a 3-chloro-2-azetine intermediate, which undergoes electrocyclic ring-opening. The acyclic intermediate then undergoes elimination of HCl to furnish the alkyne products.

The reversibility of the electrocyclic ring-opening of azetines has also been exploited for the synthesis of pyridine derivatives. Xi and co-workers reported the formation of 2,4,6-trisubstituted pyridines (158) from 2,4,6,8-tetrasubstituted 1,5-diazacyclooctatetraenes (156, Fig. 8H). This is proposed to proceed through electrocyclic ring-closing of 156 to 157 that then coordinates to TiCl\(_4\) through the azetine nitrogen atom to induce a retro-[2+2]-cycloaddition to 158.\textsuperscript{112} Similar scaffolds of 1H-triazepines were also previously reported by Regitz and co-workers to undergo ring-closing to 1H-pyrazoles via a bicyclic 1-azetine intermediate.\textsuperscript{58}

The mechanism for the reaction between alkyne derivatives and aldimines (Fig. 8E-F) can generally be rationalized by a concerted [2+2]-cycloaddition. In contrast, Zhao, Huang, and co-workers disclosed a method for the synthesis of 1-azadienes (162) through a stepwise [2+2]-cycloaddition between allenyl imides 159 and aldimines 160 (Fig. 8I).\textsuperscript{113} Mediated by a nickel-based Lewis acid, 159 and 160 underwent a stepwise [2+2]-cycloaddition and two sequential proton shifts to afford a 2-azetine intermediate (161). 2-Azetine 161 subsequently undergoes a conrotatory electrocyclic ring-opening to the trans product 162. Computational studies suggested that the presence of the 2-oxazolidinone group in 159 allows for the Lewis acid to bridge the oxygen atoms of the two carbonyls and facilitate proton transfer to 161.

Finally, Park and co-workers described a photochemical method for the synthesis of pyrrolizidinones (166) from imino-alkynes (163) using photocatalyst 164 and blue LEDs (Fig. 8J).\textsuperscript{114} Based on computational studies, it is suggested that the imino-alkyne 163 undergoes an intramolecular [2+2]-cycloaddition to 165, which then undergoes ring-opening and a second oxidation to rearrange to 166.

Conclusions

In summary, this review provides an overview of new methods to access 1- and 2-azetines and the importance of these compounds in respect to both their biological relevance and their utility as reactive intermediates, which allows access to a diverse array of value-added products. While methods to synthesize azetines have historically been limited, recent years have seen the development of innovative new approaches that overcome the challenges of azetine synthesis to access a range of both 1- and 2-azetine products. It is expected that this recent interest will promote further exploration of the properties and uses of these interesting heterocycles for biological and synthetic applications, which will in turn encourage the development of further synthetic approaches. In this area, the development of methods to synthesize azetines using simple or commercially available starting materials and reagents remains a challenge in the development of general methods to access these compounds easily.

The comprehensive review of developed synthetic methods to convert 1- and 2-azetines to a variety of complex products, including 3- to 6-membered heterocycles, demonstrates the versatility of these functional groups to enable the synthesis of diverse products. However, to our knowledge, azetines have only been used as intermediates in two total syntheses, demonstrating this as an area of future growth and application of these compounds.

With the potential for development in both the area of synthesis and applications of 1- and 2-azetines, along with the largely unexplored potential biological activity of these compounds, we consider the field of azetine synthesis and applications to be rich with future opportunities that will surely see many exciting developments in the near future.

Author Contributions

M.R.G., E.C.M., C.H.N., and E.R.W. contributed equally. E.R.W. and C.S.S. conceptualized the initial structure and topics for this review. All authors contributed to all further research, drafts, and the writing and editing of the final manuscript.

Conflicts of interest

There are no conflicts to declare.

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Notes and references
