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1,2-Diazetidines – Structure, Synthesis, and Functionalization

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ABSTRACT

1,2-Diazetidines are saturated four-membered heterocycles featuring two adjacent nitrogen atoms. Despite their promising potential as rigid molecular scaffolds for drug discovery, their synthesis and reactivity remain largely unexplored. This review summarizes their three-dimensional structural features, which have been characterized using various spectroscopic and crystallographic methods. Current synthetic approaches of 1,2-diazetidines fall into three main categories: (i) [2 + 2] cycloadditions between azo compounds and electron-rich olefins, (ii) photochemical ring contraction of dihydropyridazines, and (iii) intramolecular ring closure of hydrazine derivatives, the latter enabling stereocontrol at the four-membered ring. Finally, the reactivity and functionalization of these cyclic hydrazines are discussed, including derivatization at both nitrogen atoms.

1 | Introduction

Four-membered heterocycles are prevalent in biologically active molecules [1]. These densely functionalized small rings possess well-defined vectors and offer a low molecular weight scaffold for medicinal chemistry. Among them, 1,2-diazetidines are saturated four-membered heterocycles containing two adjacent nitrogen atoms. Compared to other ring systems, they have received relatively little attention from the scientific community, likely because their synthesis has proven challenging and only a limited number of synthetic routes are available. Consequently, the chemistry and biological activity of 1,2-diazetidine derivatives remain largely unexplored. Nevertheless, facile modification at the two nitrogen atoms should enable considerable structural diversity within this heterocyclic class. Due to their structural similarity to β-lactams [2] and 1,2-diazetidin-3-ones [3], 1,2-diazetidines and their derivatives are highly attractive compounds for pharmaceutical applications.

Here, we review the structure and properties of 1,2-diazetidines and discuss strategies for their synthesis, mainly focusing on fully saturated rings. In addition, selected examples of further functionalization of these molecules are discussed. A general overview of four-membered heterocycles containing two nitrogen atoms has been discussed previously [4–8]. In particular, the review by Richter and Ulrich provides a comprehensive summary of the topic up to 1983 [8]. The synthesis and chemistry of 1,2-diazetin-3-ones [3] and dihydro-1,2-diazetes [9] have also been reviewed previously, and these compounds and their derivatives will not be covered in this account.

Abbreviations: Ac, acetyl; Ala, alanine; Ar, aryl; ATH, asymmetric transfer hydrogenation; BHA, *N,N'*-(2,3-dimethylbutane-2,3-diyl)bis(hydroxylamine); Bn, benzyl; Boc, *tert*-butyloxycarbonyl; CAN, ceric ammonium nitrate; Cbz, benzyloxycarbonyl; DABCO, 1,4-diazabicyclo[2.2.2]octane; DBA, dibenzylideneacetone; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCE, 1,2-dichloroethane; DEAD, diethyl azodicarboxylate; DIAD, diisopropyl azodicarboxylate; DIPEA, *N,N*-diisopropylethylamine, Hünig's base; DMAc, *N,N*-dimethylacetamide; DMAD, dimethyl azodicarboxylate; DMAP, 4-(dimethylamino)pyridine; DMEDA, *N,N'*-dimethylethylenediamine; DMF, *N,N*-dimethylformamide; ee, enantiomeric excess; Fmoc, fluorenylmethyloxycarbonyl; FVT, flash vacuum thermolysis; Gly, glycine; HATU, hexafluorophosphate azabenzotriazole tetramethyl uronium; HSAB, hard and soft acids and bases; im, imidazole; LiDBB, lithium 4,4′-di-*tert*-butylbiphenylide; mCPBA, 3-chlorobenzoic acid; MMTr, *p*-monomethoxytrityl; Ms, mesityl; MTAD, 4-methyl-1,2,4-triazoline-3,5-dione; NBD, norbornadiene; NHC, *N*-heterocyclic carbene; PTAD, 4-phenyl-1,2,4-triazoline-3,5-dione; pyr, pyridine; TBAF, tetrabutylammonium fluoride; TCNE, tetracyanoethylene; TCPE, tetracyclopropylethylene; TEBAC, benzyltriethylammonium chloride; TFA, trifluoroacetic acid; TIPS, triisopropylsilyl; Ts, tosyl.

2 | Structure of 1,2-Diazetidines

Structural studies of simple 1,2-diazetidines have been carried out using various spectroscopic analytical techniques. It is noteworthy that most of these investigations were conducted several decades ago, when available synthetic methodologies provided access only to the simplest diazetidine structures. Seminal structural analysis of the conformation of 1,2-dimethyl-1,2-diazetidine (**1**) using photoelectron spectroscopy was performed by Rademacher [10, 11]. Assuming that the interaction between the electron lone pairs in the two nonbonding molecular orbitals is primarily determined by the dihedral angle between them, Rademacher predicted a dihedral (torsional) angle of $\varphi = 145 \pm 10°$ between the nitrogen lone pairs by placing both methyl groups in *trans*-equatorial positions and measuring the orbital energy differences of the nitrogen lone pair electrons (Figure 1) [10]. Later, the same author reported a value of $\varphi = 154 \pm 10°$ for compound **1** [11]. For larger cyclic hydrazines, higher φ values were predicted, likely due to increased flexibility of these ring systems.

Oberhammer et al. combined electron diffraction, microwave spectroscopy, and normal coordinate analysis to examine the structure of compound **1** in the gas phase [12]. They concluded that the equilibrium conformation of this species retains C_2 symmetry and that the ring is significantly distorted from planarity (ring puckering angle $\phi = 24.3°$), with the methyl groups adopting *trans*-equatorial positions at a dihedral angle (φ) of $149.6 \pm 2°$, in close agreement with Rademacher's findings [10, 11]. For diazetidine **1**, a N–N bond length of 1.427(7) Å and an endocyclic C–N bond length of 1.481(8) Å were determined. A subsequent theoretical study confirmed these experimental values for the endocyclic N–N and C–N bond lengths in compound **1** [13].

Hall and Bigard applied variable-temperature ^{1}H NMR spectroscopy to analyze the structure of 1,2-dialkyl-1,2-diazetidines (**2**), including compound **1** [14]. Low temperature (< 0 °C) ^{1}H NMR spectra of **2** displayed an AA'BB' coupling pattern for the methylene protons. The geminal ring hydrogens were nonequivalent, as shown in the *trans* equatorial conformer *trans eq*-**2** ($H^1 = H^4$ and $H^2 = H^3$), indicating a highly puckered ring structure (Figure 2a). Upon warming, these signals coalesced as double inversion at nitrogen became rapid. The free energy of double bond nitrogen inversion for **1** was determined to be $\Delta G^* = 16.2$ kJ mol^{-1}. Increasing the size of the alkyl substituents on nitrogen from methyl to *tert*-butyl resulted in restricted rotation and slower inversion, accompanied by progressive flattening of the four-membered ring.

Landis et al. used photoelectron spectroscopy [15] and variable-temperature ^{13}C NMR spectroscopy [16] to investigate the structure of mono- and bicyclic diazetidines. Among other observations, they found that increasing the size of substituents on **2** (Me, *i*Pr) causes the two *trans*-oriented substituents to repel each other more strongly. Consequently, the two methyl groups adopt exclusively the *trans*-equatorial conformation, whereas for the sterically more demanding diisopropyl substituents, both *trans*-equatorial and *trans*-axial conformations are accessible.

FIGURE 1 | Dihedral angle φ between the nitrogen lone pairs in **1**.

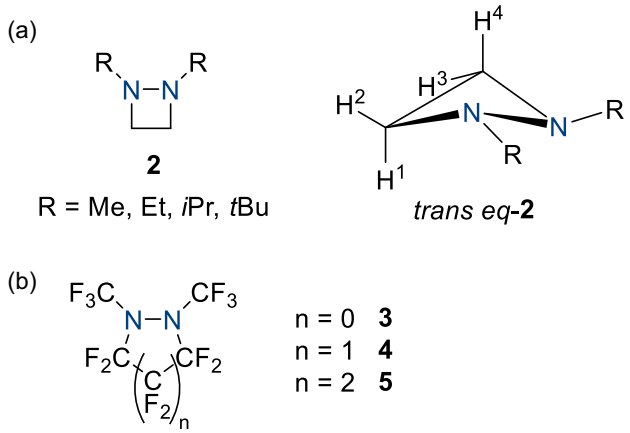


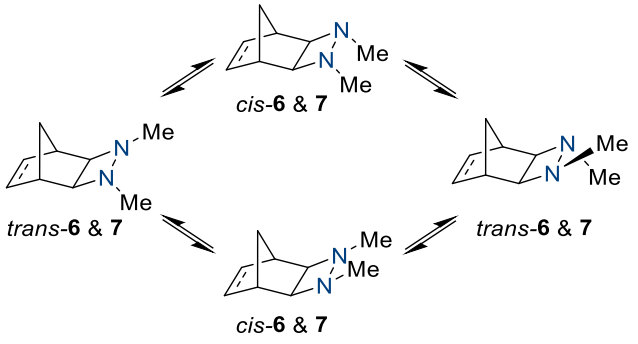
FIGURE 2 | (a) Conformation of 1,2-dialkyl-1,2-diazetidines (**2**) with puckered ring structure. (b) Perfluorinated cyclic hydrazines **3–5**.

Similarly, Ogden applied variable-temperature ^{19}F NMR spectroscopy to investigate nitrogen inversion in perfluoro-(1,2-dimethyl-1,2-diazetidine) (**3**) and its larger ring homologs **4** and **5** (Figure 2b) [17]. These perfluorinated cyclic hydrazines were prepared via photochemical decarboxylation (see Section 3.2) [18]. It was found that the activation energy for inversion is lowest for perfluorinated 1,2-diazetidine **3** and increases with expanding ring size. This trend was attributed to increasing steric hindrance to inversion of the bulky trifluoromethyl groups as the C–N–N bond angle decreases (**3** > **4** > **5**).

Nelsen et al. investigated the fused-ring systems 3,4-dimethyl-3,4-diazatricyclo [4.2.1.0.2.5]nonane (**6**) and 3,4-dimethyl-3,4-diazatricyclo [4.2.1.0.2.5]non-7-ene (**7**) (Scheme 1) [15]. In these systems, the four-membered ring is constrained to remain nearly planar, with the two methyl groups in *trans* position to minimize torsional effects. Nitrogen inversion occurs consecutively through two high-energy *cis* intermediates. Variable-temperature ^{1}H NMR measurements revealed nearly identical inversion rates for both compounds.

Gessner and Ball calculated the molecular and fundamental thermodynamic properties of unsubstituted *cis*- and *trans*–1,2-diazetidine [19]. For both conformers, puckering of the four-membered ring was predicted. Moreover, their calculations indicated that the presence of an N–N bond in 1,2-diazetidines destabilizes the molecule by ≈60 kJ mol^{-1} compared to replacement of the NH group with a methylene unit.

Based on these fundamental studies, Shipman and co-workers proposed that C3-substituted cyclic hydrazines **8** adopt favorably an



SCHEME 1 | Inversion of the methyl groups in **6** and **7**.

anti,anti-conformation, in which all three substituents are oriented *trans* to their neighbors to minimize repulsive interactions (Scheme 2) [20]. This proposal was supported by several solid-state structures of 1,2-diazetidines [20–25]. These structures revealed that the four-membered heterocycles are essentially planar, with both nitrogen substituents adopting an *anti*-configuration. Moreover, the nitrogen atoms exhibit pronounced pyramidal character, positioning their substituents on opposite sides of the ring to minimize the interaction between the two nitrogen lone pairs. This pronounced pyramidalization imparts unusually high sp^3 character at the two nitrogen centers. Consequently, the fluxional behavior of these pyramidal nitrogen atoms within the sp^3-rich heterocyclic framework enables 1,2-diazetidines to adopt a well-defined confirmation in which each substituent projects away from its neighbors, thereby minimizing repulsive interactions.

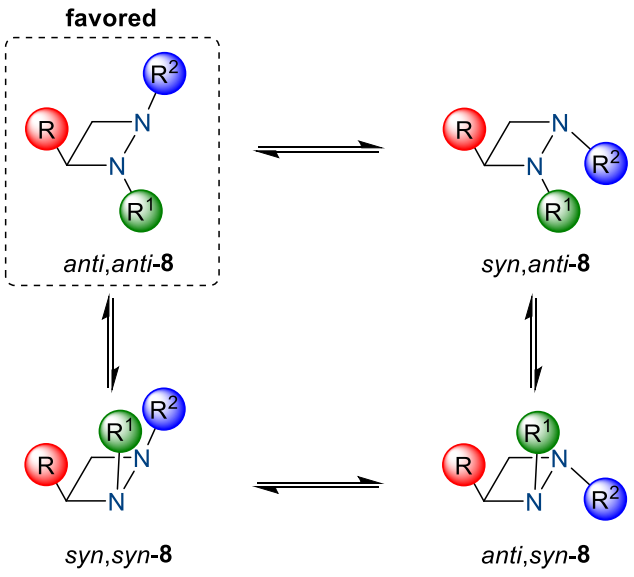
Raban et al. conducted dynamic ^{1}H NMR studies on 1,2-diazetidine **9** (Figure 3) [26]. They calculated that restricted rotation around the amide bonds was responsible for an energy barrier of $\Delta G_C^{\ddagger} = 56.9$ kJ mol^{-1} ($T_C = -27$ °C), as a result of steric interactions between the ring methoxy and *N*-carboxyethyl groups. No evidence for slow nitrogen inversion could be detected, which seems to occur rapidly in the four-membered ring.

While theoretically investigating the influence of azaproline derivatives on peptide conformation, Che and Marshall extended their study to the smaller four-membered ring homolog aza-azetidine acid (Figure 4) [27]. For the model system Ac-azAzc-NHMe (**10**), they found that the *trans*-amide conformer is more stable than the *cis*-amide conformer due to a strong intramolecular hydrogen bond (shown in red in Figure 4b). Accordingly, they calculated that the *trans*-amide conformer of **10** was stabilized by 1.69 kcal mol^{-1} relative to the *cis*-amide conformer.

Δ^3–1,2-Diazetine **11** formally satisfies Hückel's (4n + 2) rule for aromaticity (Figure 5). However, this heterocycle was found to be thermally unstable undergoing electrocyclic ring opening to 1,4-diazabutadiene with a half-life of 6.9 h at 20 °C [28]. Computational studies indicated that the ring of **11** distorts from planarity to minimize π-orbital overlap between the nitrogen lone pairs and the C = C double bond, resulting in very little aromatic stabilization.

3 | Synthetic Strategies for the Synthesis of 1,2-Diazetidines

Although 1,2-diazetidines and their derivatives have been known for a long time, practical and efficient synthetic routes have only



SCHEME 2 | Potential conformations of C3-substituted 1,2-diazetidine **8**.

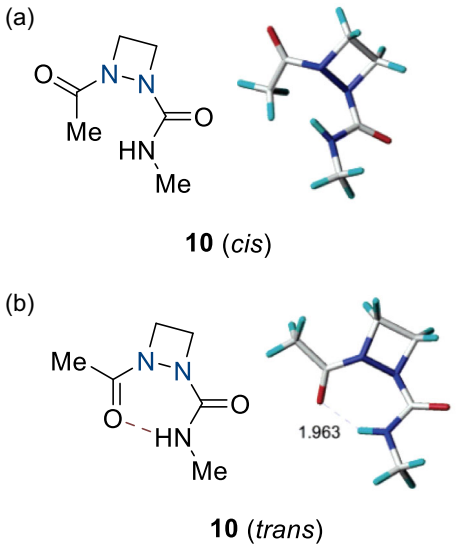


FIGURE 4 | Optimized structures of the (a) *cis*- and (b) *trans*-amide conformer of **10**. Adapted with permission from ref. [27]. Copyright 2004 American Chemical Society.

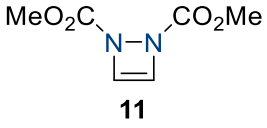


FIGURE 5 | Structure of 1,2-diazetine **11**.

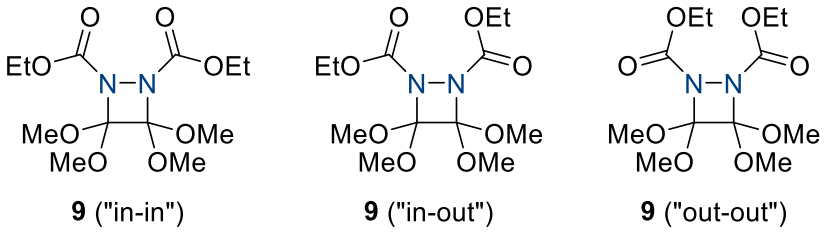


FIGURE 3 | Restricted rotation around the amide bonds in **9**.

been reported within the past two decades. In general, most reported synthetic strategies toward 1,2-diazetidines can be categorized into three main groups: (i) [2 + 2] cycloaddition reactions of azo compounds with electron-rich olefins, (ii) photochemical ring contraction of dihydropyridazine derivatives, and (iii) intramolecular ring-closure of suitable hydrazine derivatives (Scheme 3). Alternatively, 1,2-diazetidine derivatives can be obtained via direct double alkylation of substituted hydrazines with 1,2-dihaloalkanes. A few additional approaches, including [3 + 1] cycloadditions and syntheses involving N–N bond formation, have also been reported. These synthetic strategies will be discussed in detail in the following section.

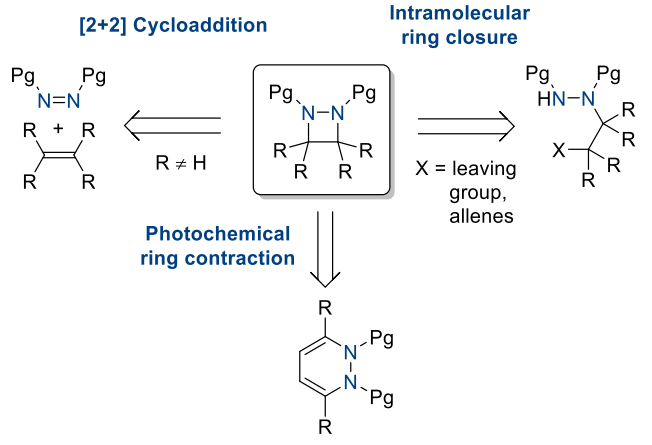
3.1 | Cycloadditions

3.1.1 | Thermal [2 + 2] Cycloadditions

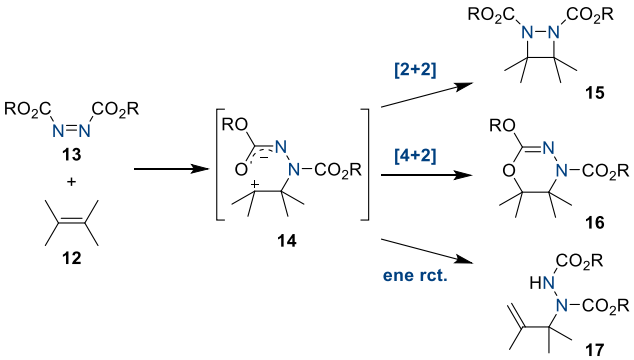
Numerous procedures have been reported that employ [2 + 2] cycloadditions of an alkene derivative with azo compounds. Early synthetic approaches to 1,2-diazetidines predominantly followed this pathway. These reactions require at least one of the two components to be activated, either by electron-donating or electron-withdrawing substituents. Typically, electron-donating groups are introduced adjacent to the C = C double bond (e.g., in enol ethers, enamines, ketene acetals, or ketene aminals), whereas electron-withdrawing groups are attached to the azo moiety.

Thermally induced cycloadditions involving alkenes **12** and azodicarbonyl compounds **13** that afford 1,2-diazetidines are believed to proceed via a dipolar (**14**) or diradical intermediate, since a concerted process would be forbidden by the Woodward–Hoffmann rules (Scheme 4) [29]. If the azodicarbonyl reagent acts as a heterodiene, a competing [4 + 2] cycloaddition can occur, leading to oxadiazine derivatives (**16**) rather than the desired [2 + 2] products (**15**) [30]. In addition, if a C–H bond is present at the β-carbon, an ene reaction may take place, yielding an insertion product (**17**) accompanied by a shift of the double bond [31–33].

The first synthesis of a 1,2-diazetidine was reported in 1948 in a patent by Cramer at DuPont [34]. Building on this seminal work, Kauer and Schneider at the same company synthesized dimethyl 3,3,4,4-tetrafluoro-1,2-diazetidine-1,2-dicarboxylate (**20**) by the thermal addition of tetrafluoroethylene (**19**) to dimethyl



SCHEME 3 | Strategies for the synthesis of 1,2-diazetidines.



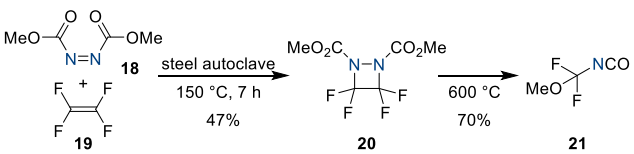
SCHEME 4 | Competing [2 + 2] and [4 + 2] cycloadditions and ene reaction in the conversion of an alkene (**12**) with an azodicarbonyl compound (**13**).

azodicarboxylate (DMAD, **18**), which was proposed to proceed via a stepwise mechanism (Scheme 5) [35]. Flash pyrolysis of **20** generated methoxydifluoromethyl isocyanate (**21**). Subsequently, researchers at DuPont further investigated the cycloadditions of highly fluorinated unsaturated compounds, obtaining [2 + 2] cycloaddition products from diethyl azodicarboxylate (DEAD) with 1,1,4,4-tetrafluorobutadiene [36] and 1,1-difluoroallene [37], respectively.

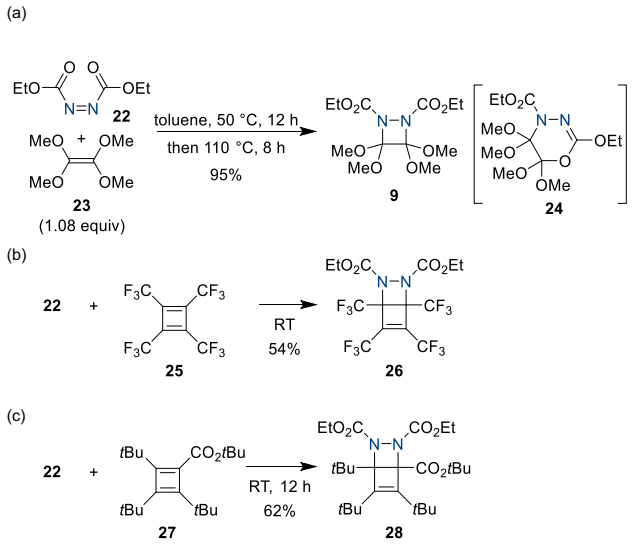
In 1964, Hoffmann and Häuser reported the thermal cycloaddition of tetramethoxyethylene (**23**) with DEAD (**22**) to give diazetidine **9** (Scheme 6a) [38]. The structure of the [2 + 2] cycloaddition product was supported by spectroscopic analysis by von Gustorf [29]. However, the authors later considered the possibility of the [4 + 2] by-product oxadiazine **24** forming via a competing reaction pathway [39]. Nonetheless, based on IR and ^{1}H NMR spectroscopy analysis, 1,2-diazetidine **9** was confirmed as the major reaction product.

To demonstrate that tetrakis(trifluoromethyl)cyclobutadiene (**25**) occurs as intermediate in the photolysis of hexakis(trifluoromethyl)benzvalene oxide, Kobayashi and co-workers trapped the intermediate with DEAD to obtain the [2 + 2] cycloaddition product **26** in 54% yield, corresponding to a diazadihydro-Dewar benzene derivative (Scheme 6b) [40]. Similarly, [2 + 2] cycloadditions between cyclobutadiene **27** and DEAD (Scheme 6c) or 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) were reported by Eisenbarth and Regitz [41].

Building on the work of von Gustorf [42], Firl and Sommer reported the cycloaddition of DMAD with vinyl amines, ethers and thioethers to give 1,2-diazetidine derivatives [43]. They found that more electron-rich alkenes react faster in these cycloaddition reactions. Subsequently, the same authors observed for some substrates a competing [4 + 2] cycloaddition, leading to mixtures of diazetidines (via [2 + 2]) and oxadiazines (via [4 + 2]



SCHEME 5 | Thermal [2 + 2] cycloaddition forming perfluorinated 1,2-diazetidine **20** and its flash pyrolysis.

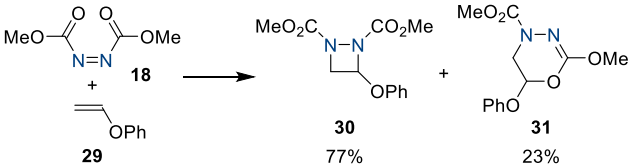


SCHEME 6 | [2 + 2] Cycloadditions involving DEAD (**22**) to 1,2-diazetidines **9** (a), **26** (b) and **28** (c).

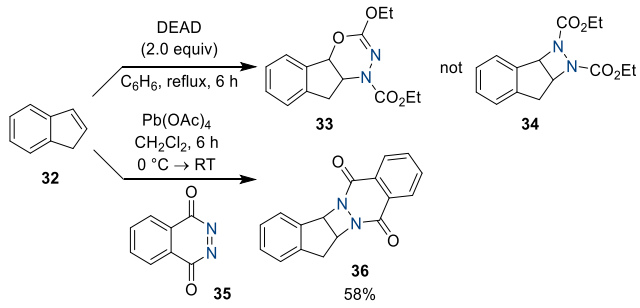
cycloaddition) [44–46]. In these cases, increasing the electron-donating character of the alkene favored formation of the diazetidine product. For example, the reaction of DMAD (**18**) with phenyl vinyl ether (**29**) gave a mixture of 1,2-diazetidine **30** and dihydrooxadiazine **31** in a 3:1 ratio, as determined by IR and NMR analysis (Scheme 7) [44]. Strong evidence for the stepwise formation of **30** came from studies of secondary α-deuterium isotope effects, which revealed an unsymmetrical transition state [47]. Taken together, these findings indicate that, depending on the electronic characteristics of the reacting species, these "cycloaddition" reactions lie on a continuum between a stepwise mechanism and a concerted transition state. Only when electron-rich alkenes are employed as substrates, 1,2-diazetidines can be formed via a formal [2 + 2] cycloaddition.

The reaction of either DMAD or DEAD with indene (**32**) gives an oxadiazine, as reported by von Gustorf [29, 30] and by Wenkert [48]. The same groups had previously assigned the annulated 1,2-diazetidine **34** as the product of this cycloaddition [42, 49]. However, detailed analysis of IR data and chemical degradation studies corrected the structure to that of the oxadiazine **33** instead (Scheme 8). Similarly, the formation of an oxadiazine from the reaction between DEAD and norbornadiene was supported by strong analytical evidence [50]. In contrast, the [2 + 2] cycloaddition of **32** with the sterically constrained phthalazine-1,4-dione (**35**) afforded the 1,2-diazetidine **36** (Scheme 8) [51]. A similar [2 + 2] cycloaddition was also observed in the reaction of phthalazine-1,4-dione with phenanthrene.

In another case, Marchetti and Tosi reported the reaction of cyclohexanone enamines **37** with dibenzoyldiimide (**38**) (Scheme 9a)



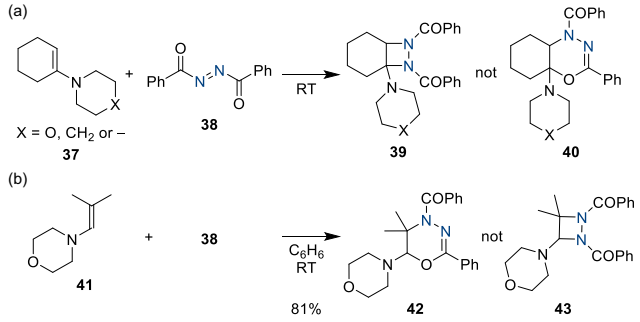
SCHEME 7 | [2 + 2] Cycloaddition of DMAD (**18**) with phenyl vinyl ether (**29**).



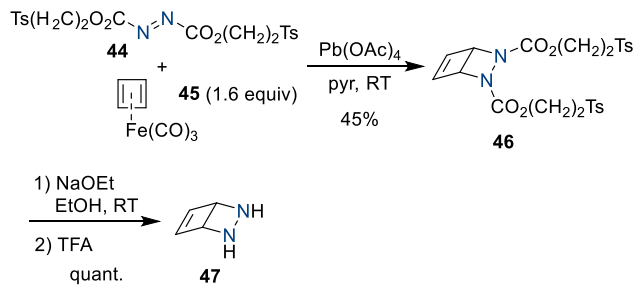
SCHEME 8 | Formation of oxadiazine **33** and diazetidine **36** from indene.

[52]. Based on ^{1}H NMR and infrared spectroscopic data, the products were initially assigned the 1,2-diazetidine structure **39** rather than the corresponding oxadiazine derivative **40**. However, neither specific reaction conditions nor yields were provided. This assignment was challenged by Firl and Sommer, who concluded the exclusive formation of oxadiazine **42** in the reaction of enamine **41** with **38** (Scheme 9b) [53]. Based on ^{1}H NMR, IR and UV spectroscopic data, as well as comparison with previous results [44], the formation of 1,2-diazetidine **43** was excluded.

Masamune et al. reported the synthesis of 2,3-diazabicyclo [2.2.0] hex-5-ene (**47**), a synthetic precursor to 2,3-diaza-Dewar benzene and cyclobutadiene (Scheme 10) [54]. Cyclobutadiene iron tricarbonyl (**45**) and 1,2-bis(β-tosylethoxycarbonyl)diazene (**44**) were converted in the presence of lead tetraacetate in pyridine to afford the bicyclic diazetidine **46** in 45% yield. Treatment of **46** with sodium or potassium ethoxide in ethanol, followed by neutralization with TFA, furnished **47** in quantitative yield, which was characterized by ^{1}H NMR spectroscopy. The same synthetic



SCHEME 9 | Cycloadditions of enamines **37** (a) and **41** (b) with dibenzoyldiimide **38**.



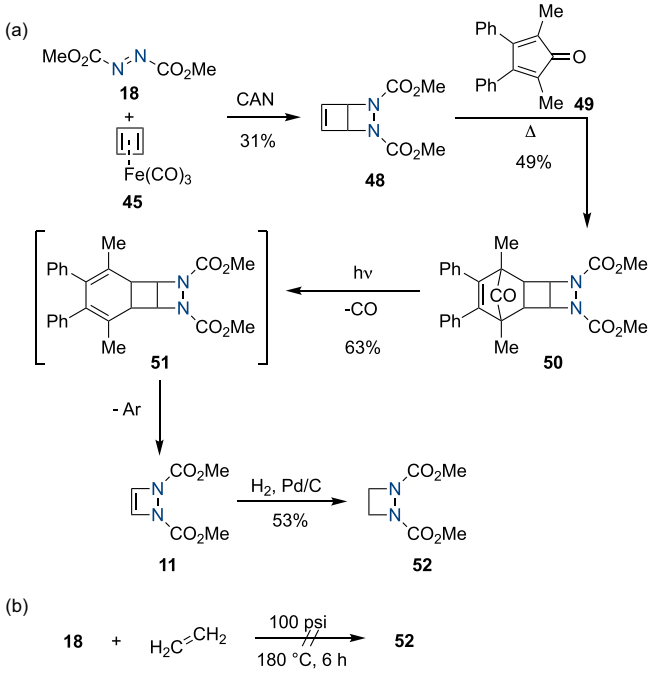
SCHEME 10 | Preparation of bicyclic diazetidine **47**.

strategy was later employed by Wildi and Carpenter, who used DEAD as the diazo compound in their synthesis of 2,3-diazabicyclo [2.2.0]hex-2-ene [55].

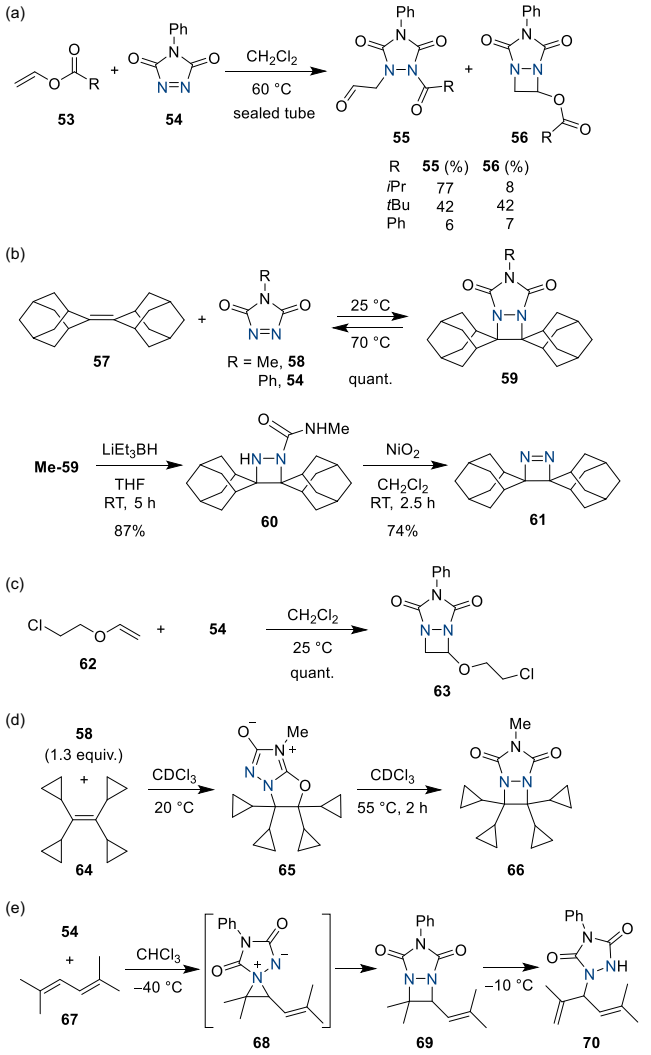
Adopting a similar strategy, Nunn and Warrener synthesized 1,2-diazetidine **52** via the unsaturated analog **11** (Scheme 11a) [56]. Oxidation of the cyclobutadiene iron tricarbonyl complex (**45**) with CAN generated cyclobutadiene in situ, which underwent cycloaddition with DMAD (**18**) to afford the bicyclic compound **48**. This intermediate was identical to the compound previously prepared by photocatalytic ring contraction (see Section 3.2) [57]. Diazabicyclohexene **48** underwent a thermal [4 + 2] cycloaddition with 2,5-dimethyl-3,4-diphenylcyclopenta-2,4-dienone (**49**) to give tricyclic compound **50**. Upon UV irradiation, elimination of carbon monoxide occurred to generate **51**, which underwent spontaneous 1,2-photoaromatization to furnish dimethyl Δ^3–1,2-diazetidine-1,2-dicarboxylate (**11**). Finally, catalytic hydrogenation over palladium on carbon afforded 1,2-diazetidine **52**.

As discussed previously, 1,2-diazetine **11** formally satisfies Hückel's aromaticity specification. However, **11** was found to be thermally unstable, and the absence of a ring current renders this heterocycle effectively non-aromatic [28]. It is worth noting that the synthesis of **52** had previously been reported via a thermal [2 + 2] cycloaddition of ethylene and DMAD (Scheme 11b) [58]. However, Nunn and Warrener [28], as well as others, were unable to reproduce this reaction, with no evidence of the 1,2-diazetidine product being formed.

The cycloaddition of both *N*-phenyltriazolidinone (PTAD, **54**) and *N*-methyltriazolidinone (MTAD, **58**) with a variety of alkenes has been reported. In this account, only a selection of these reactions will be discussed in detail. Butler and co-workers were the first to report on the stepwise cycloaddition of PTAD with vinyl esters **53** [59]. Depending on the substituent on the vinyl ester substrate, various ratios of triazolidinone **55** and bicyclic diazetidine **56** were obtained, along with polymeric material (Scheme 12a).



SCHEME 11 | (a) Reaction sequence to 1,2-diazetidine **52** and (b) unsuccessful synthesis of **52**.



SCHEME 12 | (a)-(e) Thermal [2 + 2] cycloadditions of triazolidiones **54** and **58** with alkenes.

Sterically more demanding substituents favored formation of the diazetidine product.

The thermal [2 + 2] cycloaddition between **54** or **58** and adamantylideneadamantane (**57**) to afford **59** has also been reported and mechanistically investigated (Scheme 12b) [60–62]. A crystal structure for **Me-59** unambiguously confirmed the diazetidine structure. However, upon heating, **59** underwent a cyclorevision to regenerate the starting materials. Further studies showed that **Me-59** and its norbornyl analog could be converted via a reduction/oxidation sequence into the corresponding diazetine **61** [63]. Moreover, **Me-59** was found to undergo ring expansion in the presence of triethyloxonium tetrafluoroborate to a pyrazolidine derivative.

Following this, Hall and Jones described the cycloaddition of 2-chloroethyl vinyl ether (**62**) with **54**, affording diazetidine **63** in quantitative yield (Scheme 12c) [64]. However, when either ethyl or phenyl vinyl ether was reacted with PTAD under identical reaction conditions, only polymeric products were obtained.

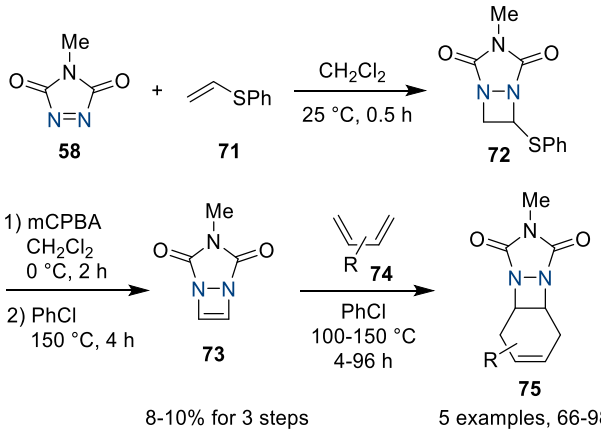
Moreover, Kim and O'Shea reported the reaction of tetracyclopropylethylene (TCPE, **64**) with **58** (Scheme 12d) [65]. At 20 °C, a mesoionic compound **65** was initially formed. Upon heating to

55 °C, this compound underwent rearrangement to 1,2-diazetidine **66**, accompanied by trace amounts of the corresponding ene product. The rearrangement of **65** involves cleavage of the C−O bond to generate an open intermediate, followed by a 180° rotation around the C−N bond and subsequent ring closure to yield **66**. The authors proposed that, due to the sterically demanding nature of TCPE, relatively high temperatures are required to facilitate the molecular motions necessary for adopting geometries leading to diazetidine formation.

Orfanopoulos et al. investigated the reaction mechanism of the addition of PTAD to conjugated diene **67** (Scheme 12e) [66]. At −40 °C, they observed a labile 1,2-diazetidine (**69**) as the sole reaction product. However, upon warming the sample to room temperature, the diazetidine completely rearranged to the ene product **70**, along with other unidentified side products. Mechanistically, the formation of an aziridinium imide intermediate (**68**) was proposed, which subsequently rearranges to the 1,2-diazetidine. In a related study, Jensen and Foote reported a diazetidine intermediate in the cycloaddition between PTAD and both (*Z*,*Z*)−2,4-hexadiene and 2,5-dimethyl-2,4-hexadiene [67]. In these cases, the diazetidine product was identified as an intermediate formed through a non-concerted [2 + 2] cycloaddition in a Diels−Alder reaction.

Additionally, [2 + 2] cycloadditions of triazolidinones **54** and **58** with acenaphthylene [68], divinyl ether [69], indene [61], isopyrazoles [70], substituted norbornenes [71], spirocyclic cycloheptatrienes [72], tetramethoxyallene [73], vinyl cyclopropane [74], and vinyl ethers [29] to form 1,2-diazetidines have also been reported.

Breton et al. reported the synthesis of the thermally stable bicyclic diazetine **73**, obtained via [2 + 2] cycloaddition between MTAD and phenyl vinyl sulfide (**71**) to **72**, followed by oxidation and subsequent elimination (Scheme 13) [75]. The overall yield for this three-step transformation was low as polymerization competed with the cycloaddition step. Compound **73** was then employed as a dienophile in Diels−Alder reactions with a variety of dienes (**74**), including 1,3-cyclopentadiene, 1,3-cyclohexadiene, anthracene, 2,3-dimethyl-1,3-butadiene and 2,4-hexadiene, providing the *endo* products **75** with high selectivity. The urazole rings of the products were hydrolyzed under basic conditions to afford the corresponding hydrazines, which were subsequently oxidized in situ with $CuCl_2$ to give the corresponding Δ^1−1,2-diazetines.



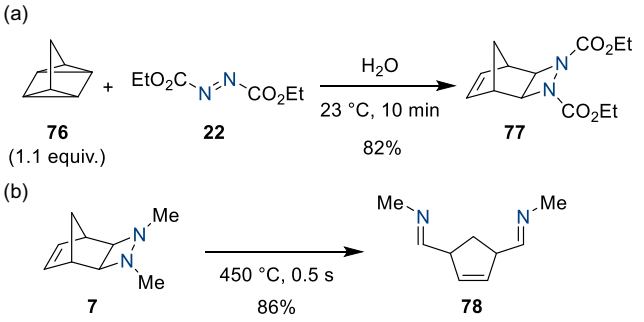
SCHEME 13 | Synthesis of diazetine **73** and its participation in Diels−Alder reactions.

Following this, Breton and Martin investigated the potential aromatic character of diazetine **73** [76]. However, no evidence of aromatic stabilization was found, as the compound readily underwent dibromination and acted as a dienophile in Diels−Alder cycloadditions.

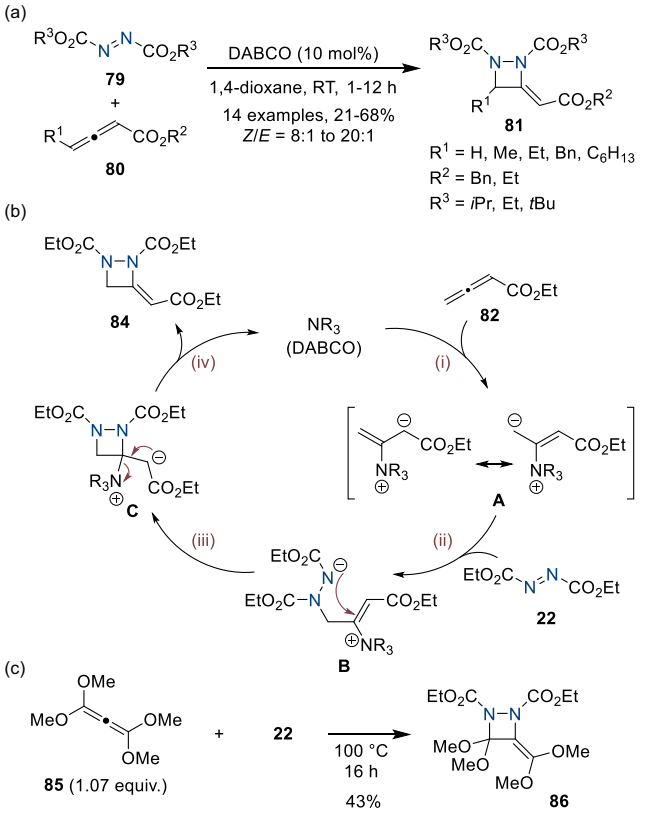
Initially described by Lemal and co-workers in the late 1960s [77], Sharpless later reported the formal [2σ + 2σ + 2π] cycloaddition of quadricyclane (**76**) with DEAD, affording tricyclic 1,2-diazetine **77** (Scheme 14a) [78]. Typical reaction conditions involved heating the substrates in toluene or benzene at 80 °C for 24 h or longer. In contrast, when the reaction mixture was vigorously stirred as a suspension "on water", the heterogeneous reaction was completed within minutes at room temperature. Subsequently, DFT calculations of the cycloaddition between quadricyclane and DMAD revealed a mechanistic shift in the presence of water, from a two-stage to a two-step pathway, accompanied by a decrease in activation energy from 23.2 kcal mol^{-1} to 14.6 kcal mol^{-1} [79]. Furthermore, several groups studied the reaction mechanism, kinetics, and potential explanations for this remarkable rate acceleration [80–82]. More recently, the same transformation was examined in aqueous microdroplets (≈5 μm in diameter) generated by electrospray ionization [83]. In comparison to Sharpless' "on-water" effect, an additional two orders of magnitude increase in reaction rate was observed for the "on-droplet" reactions.

Building on Lemal's synthesis of **77** [77] and earlier work by the group [15], Landis and co-workers prepared compound **7**, which was subjected to flash vacuum thermolysis (FVT) at 450 °C for ≈0.5 s of contact time [84]. Diimine **78** was obtained in high yield through a selective cycloreversion of the 1,2-diazetidine (Scheme 14b). A two-step process involving initial rupture of the N−N bond was proposed as the plausible reaction mechanism.

Xu et al. reported a divergent DABCO-catalyzed [2 + 2] annulation of allenoates **80** with azodicarboxylates **79** as a route to 3-alkylidene-1,2-diazetidines **81**, which were obtained with high *Z*-selectivity (Scheme 15a) [85]. Li et al. studied the mechanism of this DABCO-catalyzed annulation using DFT calculations [86]. The *Z*-isomer was predicted to be the major product, in good agreement with experimental observations. The proposed reaction mechanism involves four steps (Scheme 15b): (i) nucleophilic attack of DABCO on allenoate **82** to form a zwitterionic intermediate **A**, (ii) γ-addition of the zwitterionic intermediate to azodicarboxylate **22** forming intermediate **B**, (iii) an intramolecular 4-*exo*-*trig* cyclization to intermediate **C**, and (iv) release of



SCHEME 14 | (a) "On water" cycloaddition of quadricyclane (**76**) with DEAD (**22**) to diazetidine **77**. (b) Thermally induced cycloreversion of **7** to diimine **78**.

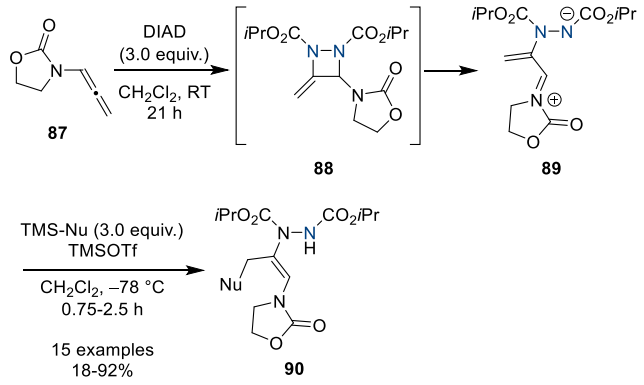


SCHEME 15 | (a) DABCO-catalyzed [2 + 2] annulation for the formation of **81**. (b) Proposed four-step mechanism for the DABCO-catalyzed [2 + 2] annulation. (c) [2 + 2] Cycloaddition to product **86**.

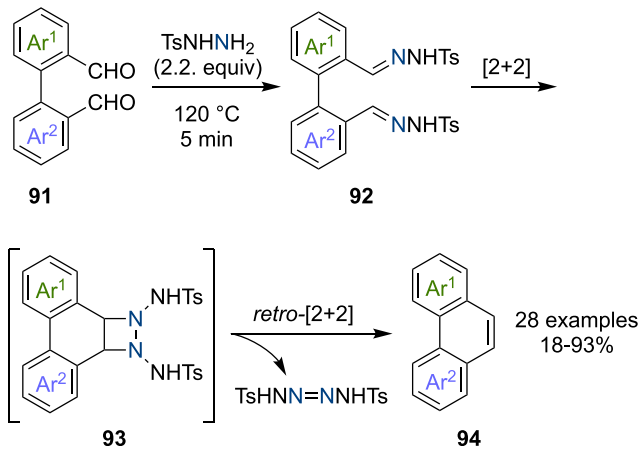
the DABCO catalyst to afford the final 1,2-diazetidine **84**. The authors also examined the experimentally observed shift to pyrazoline and pyrazole products when DABCO was replaced with triphenylphosphine [87]. In contrast, Wang and co-workers reported a DMAP-catalyzed reaction between allenoates and *N*-acyldiazenes to produce six-membered oxadiazine derivatives via a [2 + 4] cycloaddition mechanism [88]. Related to this, Hoffmann and Schäfer reported the thermal [2 + 2] cycloaddition of DEAD (**22**) with tetramethoxyallene (**85**) yielding diazetidine **86** in 43% yield (Scheme 15c) [73].

Okitsu et al. reported the use of 1,2-diazetidines as formal 1,4-dipole precursors [89]. Upon [2 + 2] cycloaddition, allenamide **87** was converted with diisopropyl azodicarboxylate (DIAD) to form an intermediate 1,2-diazetidine **88**, which underwent heterocyclic cleavage of the C–N ring bond to the zwitterionic species **89**, representing a new type of 1,4-dipole (Scheme 16). As the diazetidine intermediate was highly sensitive to moisture, the authors developed a sequential one-pot procedure to trap the 1,4-dipole intermediate with various nucleophiles, including silyl enol ethers, allylsilanes, and allenylsilanes, thereby generating a range of derivatives **90**.

Song et al. described a strategy for the synthesis of polycyclic aromatic compounds via intramolecular [2 + 2] and *retro*-[2 + 2] cycloadditions proceeding through 1,2-diazetidine intermediates under microwave heating [90]. Based on a procedure developed by Jung [91], biaryl dicarbonyls **91** were reacted with *p*-tolylsulfonylhydrazine to form bis-*N*-tosylhydrazones **92** in a condensation reaction (Scheme 17). These substrates underwent an intramolecular [2 + 2] cycloaddition to afford the intermediate



SCHEME 16 | 1,2-Diazetidine **88** as formal 1,4-dipole precursor.

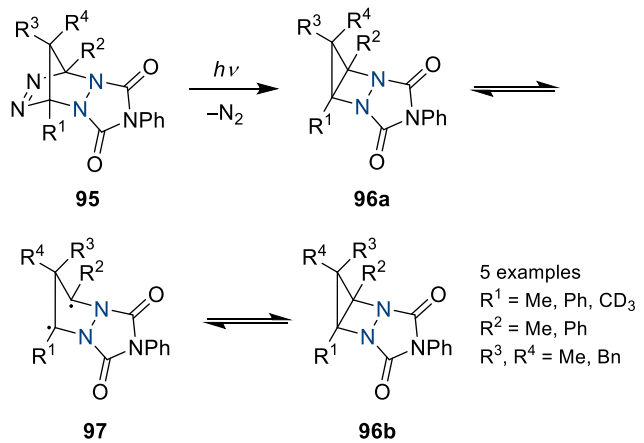


SCHEME 17 | Synthesis of polyaromatic compounds **94** via intramolecular [2 + 2] and *retro*- [2 + 2] cycloadditions.

1,2-diazetidines **93**, which subsequently underwent a stepwise *retro*- [2 + 2] cycloaddition to yield **94**. The byproduct, 1,4-ditosyltetraaz-2-ene, was unstable under the reaction conditions and decomposed under the liberation of nitrogen gas.

3.1.2 | Photochemically Mediated [2 + 2] Cycloadditions

Arnold and co-workers investigated the photolysis of azo compound **95** (Scheme 18) [70]. Loss of molecular nitrogen produced



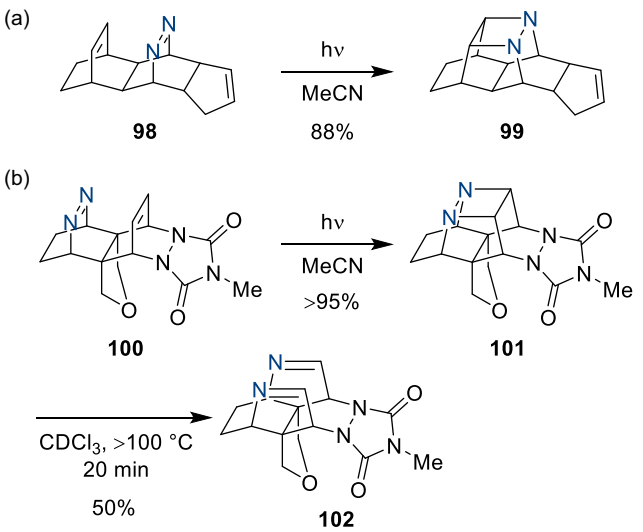
SCHEME 18 | Photolysis of cycloadduct **95** to tricyclic **96a** and its thermal isomerization.

the 1,5,7-triazatricyclo [3.1.0.0]octane derivative **96a** with good conversion, containing a notably weak central C−C bond connecting the cyclopropane and the diazetidine moieties. Consequently, **96a** readily isomerizes to **96b** via the 1,3-diradical intermediate **97**. In addition to this photochemical pathway, **97**, whose diradical character was confirmed by low-temperature ESR spectroscopy, could also be accessed through thermolysis of **95**.

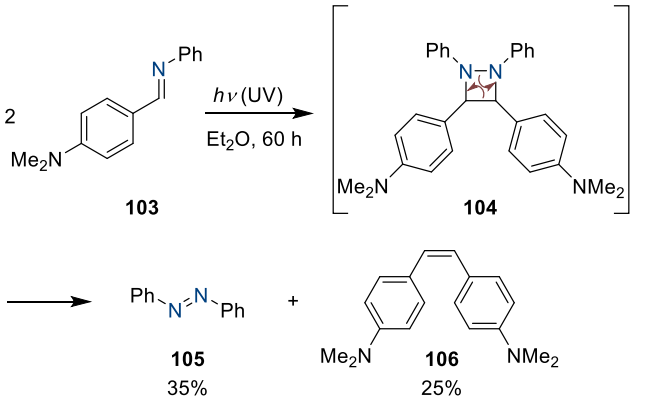
Berning and Hünig reported a photochemical [2 + 2] cycloaddition between parallel, non-activated C = C, and N = N double bonds of substrate **98**, yielding caged compound **99** upon UV irradiation (Scheme 19a) [92]. In a related study, Prinzbach and co-workers investigated the [2 + 2] photocycloaddition of various diazene systems as part of a broader mechanistic analysis. They successfully isolated 1,2-diazetidine **101** with full conversion of starting material **100** to the caged product. Although stable under ambient conditions, compound **101** decomposed above 100 °C via a [2 + 2] cycloreversion to afford diamine **102** in ca. 50% yield, which rapidly polymerized under the reaction conditions (Scheme 19b) [93].

Searles Jr. and Clasen investigated the photodimerization of *N*-*p*-dimethylaminobenzylideneaniline (**103**) [94]. Upon UV irradiation of imine **103**, the authors isolated *trans*-azobenzene (**105**) and 4,4′-bis(dimethylamino)stilbene (**106**) as the reaction products (Scheme 20). To rationalize the outcome, the formation of a transient 1,2-diazetidine intermediate **104** was proposed via dimerization of the imine. Although such an intermediate was not directly observed, its cycloreversion would account for the experimentally obtained products.

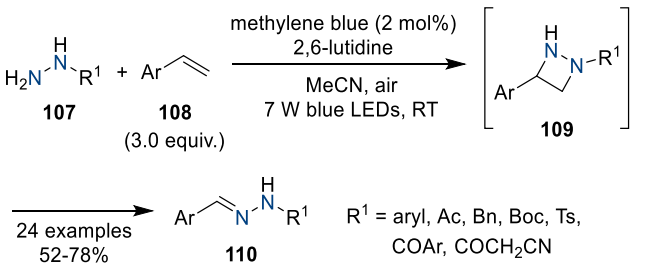
Ding et al. reported the formation of a diazetidine intermediate **109** during the conversion of hydrazines **107** and styrenes **108** into hydrazones **110** (Scheme 21) [95]. This metal-free transformation was mediated by visible light and required molecular oxygen from air as the oxidant. 1,2-Diazetidine intermediates **109** could be isolated and were proposed to originate from a [2 + 2] annulation between **107** and a diazene species generated in situ via single-electron oxidation of hydrazines **107**. When **109** were subjected to the reaction conditions, the 1,2-diazetidines further transformed into the corresponding hydrazones **110**, supporting the proposed mechanism that proceeds through the four-membered diazetidine intermediate.



SCHEME 19 | [2 + 2] Photocycloadditions to caged 1,2-diazetidines **99** (a) and **101** (b).



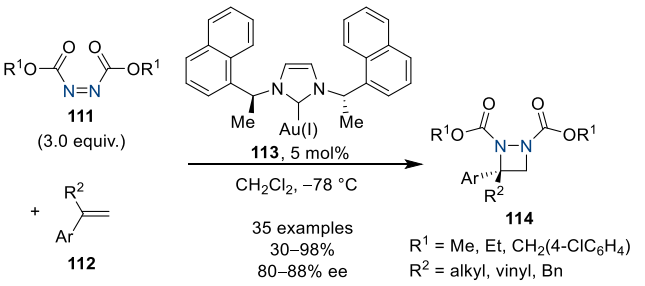
SCHEME 20 | Proposed 1,2-diazetidine intermediate **104** from the photodimerization of imine **103**.



SCHEME 21 | Reaction of hydrazines **107** and styrenes **108** to hydrazones **110** via 1,2-diazetidine intermediates **109**.

3.1.3 | Transition Metal-Catalyzed [2 + 2] Cycloadditions

Recently, Cai and co-workers reported an Au(I)/NHC-catalyzed asymmetric aza-electrophilic addition between unactivated 1,1-disubstituted styrenes **112** and dialkyl azodicarboxylates **111** [96]. In the absence of competing nucleophilic sites, a [2 + 2] cycloaddition between the styrene derivative and azodicarboxylate was observed, affording a range of highly enantiomerically enriched C3-disubstituted 1,2-diazetidines **114** via a carbocation intermediate (Scheme 22). Subsequent hydrogenation of **114** over palladium on carbon cleaved the benzylic C−N bond, resulting in ring opening of the four-membered heterocycle.



SCHEME 22 | Au(I)-catalyzed asymmetric aza-electrophilic [2 + 2] cycloaddition to 1,2-diazetidines **114**.

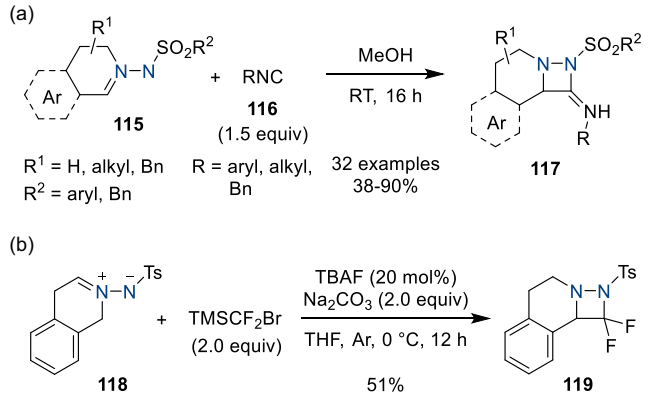
3.1.4 | [3 + 1] Cycloadditions

Examples for the synthesis of 1,2-diazetidine derivatives based on [3 + 1] cycloadditions are relatively sparse. Building upon seminal work by Deyrup [97], Cao et al. synthesized strained 1,2-diazetidines **117** via a [3 + 1] cycloaddition of *C*,*N*-cyclic azomethine imines **115** with isocyanides **116** (Scheme 23a) [98]. Further functionalization of **117** was achieved through either cleavage of the sulfonyl group or the N–N bond.

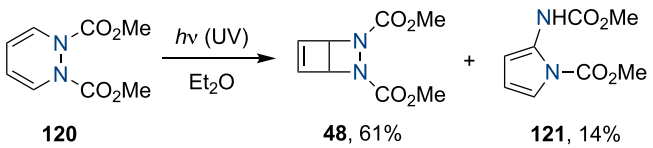
Similarly, Mao et al. described a TBAF-mediated [3 + 1] cycloaddition of *C*,*N*-cyclic azomethine imines (e.g., **118**) with difluorocarbenes to afford *gem*-difluorinated 1,2-diazetidine analogs (Scheme 23b) [99]. In this reaction, the difluorocarbene species was generated via TBAF-mediated dissociation of $TMSCF_2Br$. The corresponding 1,2-diazetidine products were obtained in moderate to good yields. For substrate **119**, the 1,2-diazetidine structure was confirmed by single-crystal X-ray analysis. Several of the cycloaddition products exhibited promising antiproliferative activity against various cancer cell lines.

3.2 | Photochemical Ring Contractions

Several 1,2-diazetidine derivatives have been synthesized from five- and six-membered heterocycles through either ring contraction or elimination of one or more atoms from the ring framework (e.g., nitrogen or carbon monoxide). Photochemically induced ring contraction to afford 1,2-diazetidines has been reported in several cases. Dimethyl 1,2-dihydropyridazine-1,2-dicarboxylate (**120**) underwent an intramolecular [2 + 2] cycloaddition to yield bicyclic diazetidine **48** in 61% yield upon irradiation with a high-pressure mercury lamp, accompanied by pyrrole side product **121** (Scheme 24) [57]. The corresponding diethyl ester derivative of **48** was employed as a cyclobutadiene precursor, and its ability to inactivate cytochrome P-450 through covalent modification of the porphyrin ring has been demonstrated [100].



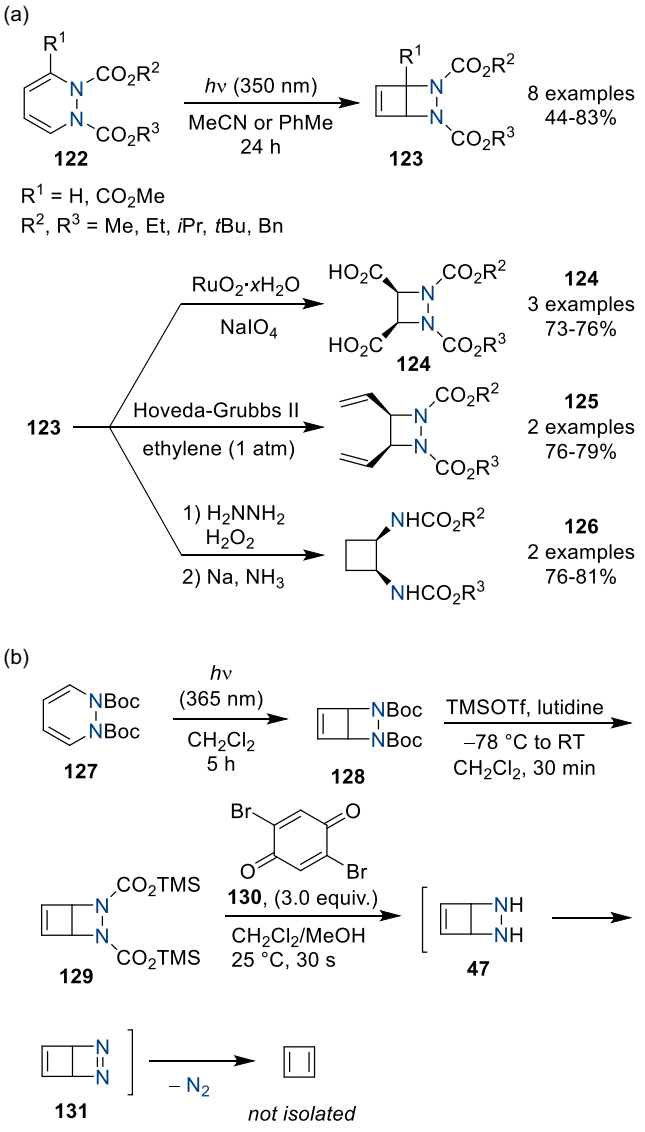
SCHEME 23 | (a) [3 + 1] Cycloaddition toward annulated 1,2-diazetidines **117**. (b) Preparation of *gem*-difluoro 1,2-diazetidine **119** via a [3 + 1] cycloaddition.



SCHEME 24 | Photochemical ring contraction of **120**.

This ring contraction of 1,2-dihydropyridazines **122** via 4-π-photocyclization was further investigated by Britten et al. [101]. The bicyclic 1,2-diazetidines **123** proved to be versatile synthetic intermediates, which could be selectively transformed into a variety of derivatives (Scheme 25a). For example, selective cleavage of the C = C double bond was achieved either via oxidative cleavage to **124** or ring-opening metathesis to **125**, while selective N–N bond cleavage yielded 1,2-diamines **126**.

Recently, MacMillan and co-workers applied this photochemical strategy to access cyclobutadiene in a highly efficient sequence for the synthesis of cubanes as benzene bioisosteres [102]. Starting from 1,2-dihydropyridazine **127**, light-mediated endocyclic 4-π-cyclization generated diazetidine **128**. After activation of the protection groups on the diazetidine, **129** was oxidized to diazine **131** by 2,5-dibromoquinone (**130**) (Scheme 25b). Subsequent nitrogen extrusion generated cyclobutadiene in situ, which immediately reacted with **130** in a [2 + 2] cycloaddition. Moreover, Burns and co-workers applied this approach for the



SCHEME 25 | (a) 4-π-Photocyclization of 1,2-dihydropyridazines **122** and further transformation of bicyclic diazetidines **123**. (b) Synthetic sequence towards the in situ generation of cyclobutadiene from 1,2-dihydropyridazine **127**.

synthesis of **123** (R^1 = H, R^2, R^3 = Et) on a multigram scale for the metal-free in situ generation of cyclobutadiene, which was subsequently employed in [4 + 2] cycloadditions with electron-deficient alkenes [103].

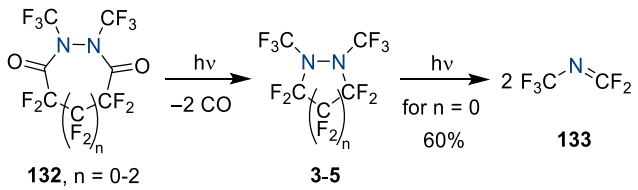
Ogden reported a decarboxylative photochemical ring contraction of perfluorinated hydrazides **132** for the synthesis of cyclic hydrazines **3**-**5** (Scheme 26) [18]. While the perfluorinated pyrazolidine **4** and pyridazine **5** were obtained in excellent yields upon UV irradiation (85–95%), the perfluorinated diazetidine **3** proved to be photochemically unstable and underwent further ring cleavage to generate perfluoro-2-azapropene (**133**).

3.3 | Intramolecular Ring Closure of Hydrazine Derivatives

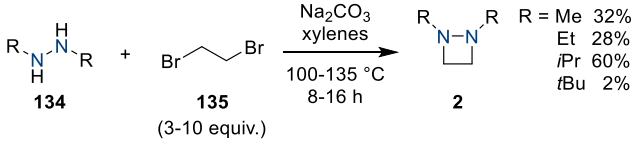
Besides [2 + 2] cycloaddition reactions and photochemical ring contractions, the intramolecular ring closure, either via nucleophilic substitution or transition metal catalysis, represents a third important pathway for the synthesis of 1,2-diazetidines.

3.3.1 | Nucleophilic Substitution of Hydrazine Derivatives

In 1964, FMC Corporation patented a route to simple 1,2-diazetidines via two successive alkylations of a dialkylhydrazine [104]. These compounds were initially developed as rocket fuels or additives for similar applications, owing in part to the high energy associated with the strained four-membered ring. Based on this methodology, Hall and Bigard prepared a series of simple 1,2-dialkyl-1,2-diazetidines **2** (Scheme 27) [14]. The reaction involved the addition of an excess of 1,2-dibromoethane (**135**, 3–10 equiv.) over an extended period to a dilute solution of the dialkylhydrazine **134**. Even under these optimized conditions, isolated yields were only moderate to poor. Despite this, the authors found the resulting 1,2-diazetidines **2** to be highly stable. For example, 1,2-dialkyl-1,2-diazetidines were recovered unchanged after treatment with sodium amide at room temperature for 2 weeks. Neither *n*-butyllithium, concentrated hydrochloric acid, nor 98% sulfuric acid affected 1,2-diisopropyl-1,2-diazetidine under ambient conditions. Catalytic hydrogenation at 50 psi using platinum on carbon failed to cleave the N–N bond.



SCHEME 26 | Photochemical ring contraction of perfluorinated hydrazides **132**.

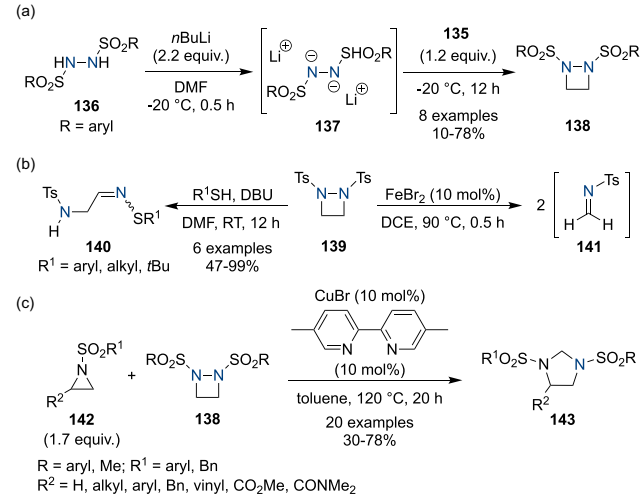


SCHEME 27 | Synthesis of 1,2-dialkyl-1,2-diazetidines **2**.

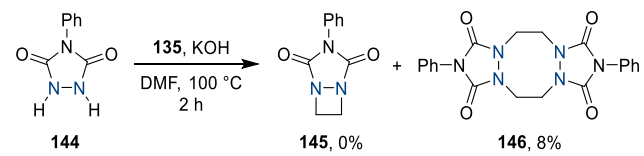
Similarly, Cui et al. reported the direct synthesis of carbon-unsubstituted 1,2-disulfonyl-1,2-diazetidines **138** via an intermolecular dialkylation of 1,2-disulfonylhydrazines **136** with 1,2-dibromoethane (**135**) (Scheme 28a) [105]. The vicinal dilithiation protocol proved effective for a variety of disulfonylhydrazine substrates. Using thiols as nucleophiles, selective N–N bond cleavage was achieved, affording *N*-sulfenylimine derivatives **140** with high selectivity for the *E* isomer (Scheme 28b). Subsequently, the same group demonstrated that 1,2-ditosyl-1,2-diazetidine (**139**) undergoes an Fe(II)-catalyzed [2 + 2] cycloreversion to release labile *N*-tosylformaldimidine **141**, which served as a reactive precursor for catalytic [2 + 2 + 2] cycloadditions in the synthesis of 2,4-disubstituted piperidine derivatives [106].

In a related study, Murakami and co-workers described a copper-catalyzed synthesis of various imidazolidines **143** through heterocyclic recombination between aziridines **142** and 1,2-diazetidines **138** (Scheme 28c) [107]. Mechanistic investigations indicated that the diazetidine is initially converted to an imine intermediate in the presence of the copper catalyst. The in situ formed imine subsequently reacts with the aziridine to yield five-membered imidazolidines **143**.

It is noteworthy that the intermolecular nucleophilic substitution of 1,2-dibromoethane with a hydrazine derivative does not always yield the desired 1,2-diazetidine. When Breton and Martin attempted the synthesis of **145** following a patented procedure, they isolated only the dimeric species **146** in low yield (Scheme 29) [108]. Due to the high symmetry of both **145** and **146**, the two compounds could not be distinguished by NMR spectroscopy. However, a high melting point (>250 °C) and, ultimately, X-ray crystallographic analysis confirmed the formation of the dimeric



SCHEME 28 | (a) Synthesis of sulfonyl-protected 1,2-diazetidines **138** and (b,c) their use as imine precursor.

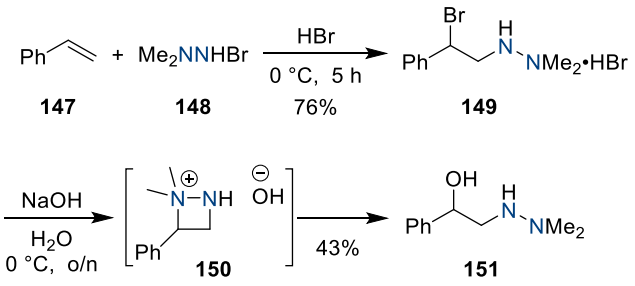


SCHEME 29 | Reaction of *N*-phenylurazole (**144**) with 1,2-dibromoethane (**135**).

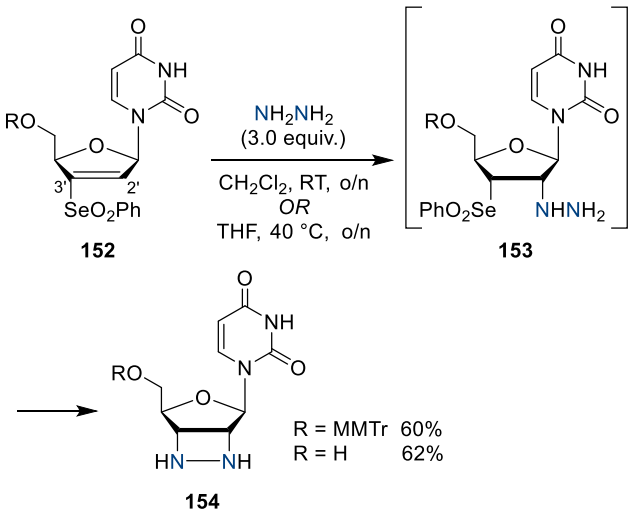
product **146**. The authors succeeded in synthesizing **145** only after modifying their strategy, which involved first preparing the four-membered 1,2-diazetidine by applying a strategy reported by Shipman [25], followed by formation of the urazole ring.

Moore et al. reported the reaction of 1,1-dimethyldiazenium bromide (**148**) with conjugated alkenes [109]. For example, reaction of **148** with styrene (**147**) afforded 1,1-dimethyl-2-(2-bromo-2-phenylethyl)hydrazinium bromide (**149**), which gave intermediate diazetidinium hydroxide **150** after treatment with aqueous sodium hydroxide (Scheme 30). However, when **150** was exposed to the basic solution for an extended period, hydrolysis occurred, leading to the ring-opened product **151**.

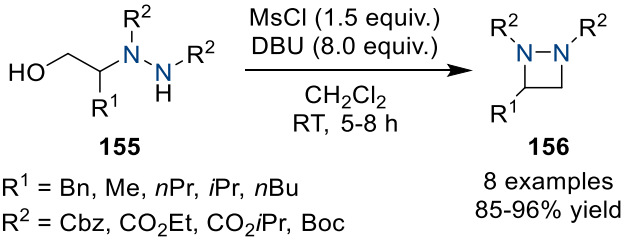
In their studies on nucleoside functionalization, Chattopadhyaya et al. developed a strategy for the synthesis of 2′, 3′-dideoxy-2′, 3′-α-fused-heterocyclic uridines [110]. The 3′-selenonyl group in **152**, being conjugated to the 2′, 3′-double bond, acts as a strong electron-withdrawing substituent that activates the double bond toward conjugate (Michael-type) addition of nucleophiles at the C-2′ position (Scheme 31). The resulting intermediate, 2′-substituted-3′-selenonyl nucleoside **153**, then undergoes intramolecular nucleophilic attack by the 2′-substituent to afford 2′, 3′-α-fused cyclic nucleoside **154**. In practice, 2′, 3′-ene-3′-selenone **152** behaves as a synthetic equivalent of a dication and reacts with dinucleophiles such as hydrazine to yield diazetidine **154**, a uridine derivative.



SCHEME 30 | Intramolecular ring closure of **149** to diazetidinium **150** under basic conditions.



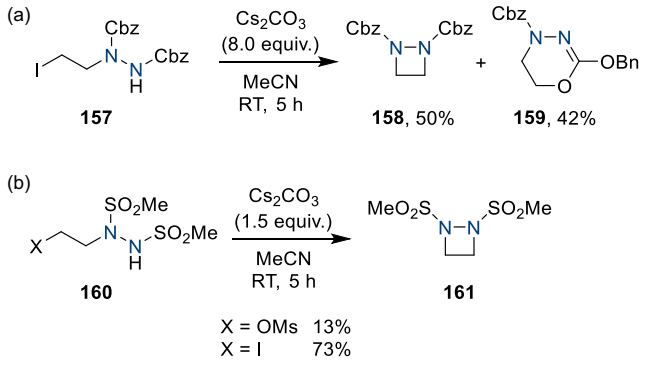
SCHEME 31 | Addition of hydrazine to phenylselenone **152**.



SCHEME 32 | Synthesis of diazetidine **156** via intramolecular ring closure of **155**.

Miao et al. reported the cyclization of hydroxyethylhydrazine derivatives **155** to afford C3-substituted 1,2-diazetidines **156** (Scheme 32) [111]. The substrates **155** were prepared via a proline-catalyzed addition of an azodicarboxylate to aldehydes followed by reduction. Subsequent treatment of these alcohols with methanesulfonyl chloride and DBU promoted intramolecular ring closure through nitrogen, yielding **156** in excellent yields. For one example (R^1 = Bn, R^2 = Cbz), the optical purity of **156** is reported to be 98% ee. However, no detailed experimental data or structural characterization were provided for this transformation, despite the method being patented in the same year [112].

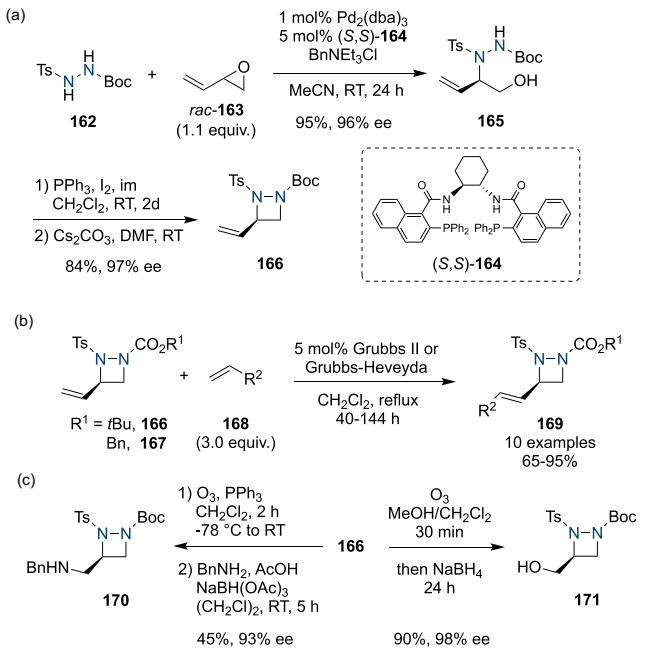
Building upon this report, Shipman et al. further investigated the nucleophilic ring closure of hydrazine derivatives [21]. When an alkyl iodide **157** was employed, formation of both 1,2-diazetidine **158** and oxadiazine **159** was observed (Scheme 33a). In this context, the ambidentate carbamate nucleophile could promote cyclization through either the nitrogen or oxygen atom. Moreover, the reaction outcome was found to be sensitive to the nature of the leaving group, consistent with the Hard and Soft Acids and Bases (HSAB) principle. When the cyclization precursor contained a "hard" leaving group (e.g., methanesulfonate), the oxadiazine was the exclusive product (cyclization via oxygen). In contrast, employing a "soft" leaving group such as iodide favored formation of the four-membered diazetidine (cyclization via nitrogen). Changing the protecting groups on the hydrazine precursor **160** from carbamates to sulfonamides resulted in selective formation of **161**, as cyclization could only proceed through the nitrogen atom (Scheme 33b). In this case, the yield was significantly improved by using iodide as a "soft" leaving group. These findings critically challenged Ma's earlier report, which described the selective formation of 1,2-diazetines without consideration of a competing oxadiazine pathway [111].



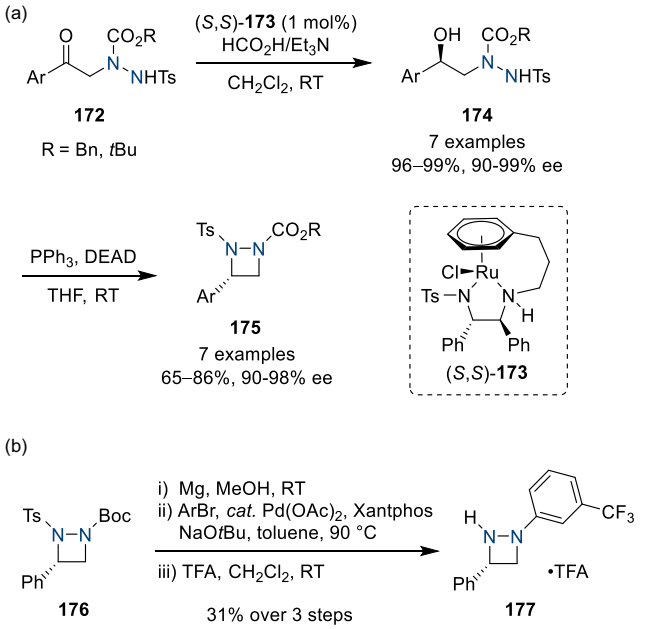
SCHEME 33 | Nucleophilic ring closure to 1,2-diazetidines **158** (a) and **161** (b) using the HSAB principle.

Shipman and co-workers developed a palladium-catalyzed asymmetric allylic amination of *rac*-vinyl epoxide (**163**) with unsymmetrically protected 1,2-hydrazines (e.g., **162**) to access differentially protected 3-vinyl-1,2-diazetidines [23]. High regio- and enantioselectivity was achieved in the allylic amination, affording **165** via kinetic resolution using the (*S*,*S*)-Trost ligand ((*S*,*S*)-**164**) (Scheme 34a). Conversion of alcohol **165** to the corresponding iodide, followed by an intramolecular cyclization, furnished 1,2-diazetidine **166** without any loss of optical purity. Further transformations of the alkene moiety were demonstrated, including hydrogenation of the double bond and subsequent N–N bond cleavage under hydrogenation conditions using a Raney nickel catalyst. Cross-metathesis employing either Grubbs II or Grubbs–Hoveyda catalyst converted 3-vinyl-1,2-diazetidines **166** and **167** into **169** (Scheme 34b), while reductive amination and ozonolysis transformed **166** into amine **170** and alcohol **171**, respectively (Scheme 34c). All these transformations proceeded without significant erosion of enantiopurity.

Dean et al. reported a strategy for the synthesis of sp^3-rich, nonplanar cyclic hydrazine-based scaffolds that exploits the fluxional behavior of pyramidal nitrogen atoms in heterocyclic frameworks [20]. This procedure was applied to the enantiocontrolled synthesis of 3-aryl 1,2-diazetidines and larger cyclic hydrazines. Starting from orthogonally protected hydrazines **172**, asymmetric transfer hydrogenation (ATH) using tethered Ru-catalyst (*S*,*S*)-**173** afforded enantiomerically enriched alcohols **174** (Scheme 35a). These benzylic alcohols were further transformed into four- to seven-membered cyclic hydrazines, for example, **175**, via Mitsunobu cyclization. Finally, 1,2-diazetidines **175** could be elaborated by iterative C–N functionalization at both nitrogen atoms, as demonstrated for the conversion of orthogonally protected 1,2-diazetidine **176** to **177** (Scheme 35b). NMR and crystallographic studies of **175** confirmed the *trans*, *trans* relative



SCHEME 34 | (a) Palladium-catalyzed asymmetric allylic amination to afford optically active 3-vinyl-1,2-diazetidines **166** after cyclization. (b,c) Further functionalization of orthogonally protected 1,2-diazetidines **166** and **167**.

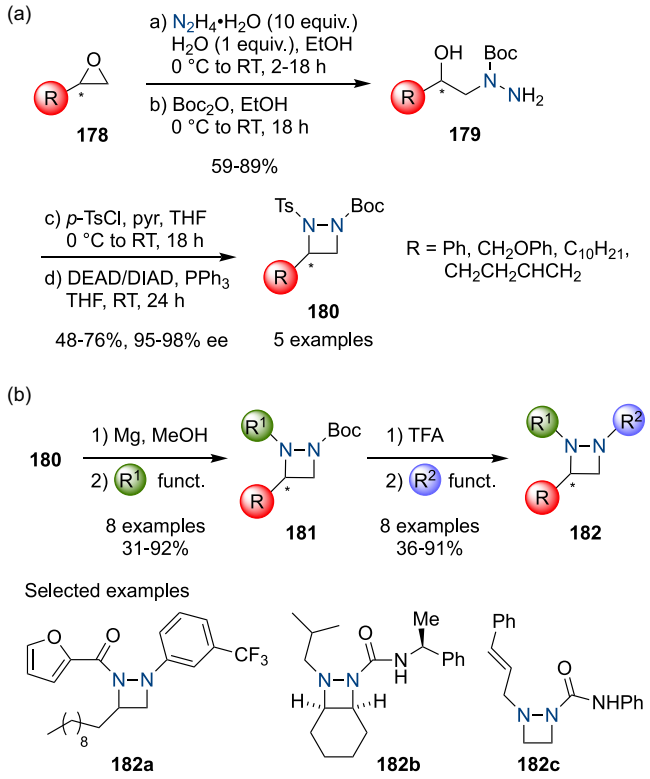


SCHEME 35 | (a) Synthesis of orthogonally protected 1,2-diazetidines **175** via ATH and Mitsunobu cyclization and (b) functionalization of **176** to **177**.

configuration of the C- and N-substituents, with the nitrogen atoms exhibiting significant sp^3-character (Scheme 2). Furthermore, the prepared compound library displayed excellent shape diversity and three-dimensionality, as determined computationally by analysis of the principal moments of inertia.

In an effort to synthesize C3-functionalized 1,2-diazetidines covering a broader range of C3 substituents (H, alkyl, and aryl), Shipman and co-workers developed a four-step procedure starting from homochiral epoxides **178** [25]. Stereocontrolled ring-opening of **178** with hydrazine hydrate at the unsubstituted carbon, followed by selective protection of the secondary nitrogen, afforded hydrazine **179** (Scheme 36a). Subsequent sulfonylation of the primary amine and azodicarboxylate-mediated Mitsunobu cyclization yielded orthogonally protected, enantiomerically pure (95–98% ee) 1,2-diazetidines **180** bearing a variety of C3 substituents. Alternatively, unsubstituted 1,2-diazetidines could be synthesized from differentially N-protected 2-hydroxyethylhydrazine by Mitsunobu ring closure. The best results for regioselective functionalization at the two nitrogen atoms were obtained using Boc- and Ts-protected 1,2-diazetidines **180**. Iterative C–N functionalization at the two nitrogen atoms, employing a range of transformations including reductive amination, reaction with isocyanates, acylation, Buchwald–Hartwig coupling, and HATU-mediated peptide coupling, provided a small 1,2-diazetidine-based chemical library (Scheme 36b). Crystallographic data confirmed that 1,2-diazetidines **182** exhibit pronounced sp^3 character, with the nitrogen substituents adopting an *anti*-configuration.

This synthetic strategy was further applied to the stereoselective preparation of both enantiomers of the unnatural amino acid 1,2-diazetidine-3-carboxylic acid, which serves as a proline surrogate by mimicking its structural constraints [113]. Starting from compound **183**, synthesized from homochiral glycidol and following the four-step reaction sequence outlined in Scheme 36a [25], removal of the TIPS protecting group and Ru-catalyzed oxidation were followed by HATU-mediated coupling of the resulting

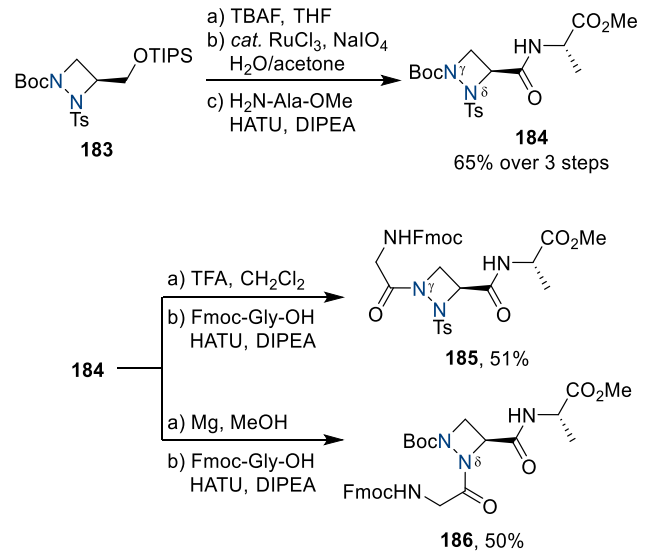


SCHEME 36 | (a) Synthesis of C3-functionalized 1,2-diazetidines **180** from enantiomerically enriched epoxides. (b) Iterative functionalization of **180**.

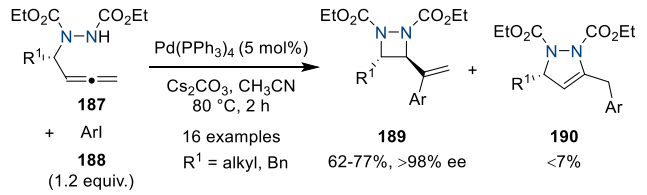
carboxylic acid with the methyl ester of alanine to afford compound **184** (Scheme 37). The use of orthogonal protecting groups on N^{γ} and N^{δ} enabled selective functionalization of either nitrogen, allowing incorporation into pseudotripeptides **185** and **186**.

3.3.2 | Transition Metal-Catalyzed Cyclizations

Cheng and Ma reported a regio- and diastereoselective palladium-catalyzed cyclization of aryl iodides **188** with 2,3-allenyl



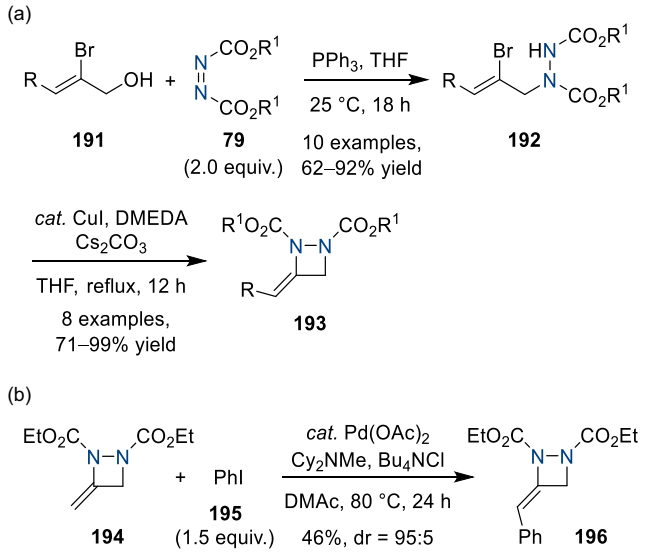
SCHEME 37 | Conversion of 1,2-diazetidine **183** into an unnatural amino acid precursor and incorporation into pseudotripeptides **185** and **186**.



SCHEME 38 | Palladium-catalyzed synthesis of 1,2-diazetidines **189** from allenoates **187** and aryl iodides **188**.

hydrazines **187** to afford *trans*–1,2-diazetidines **189** (Scheme 38) [114]. The *trans* configuration of **189** was confirmed by ^{1}H NMR analysis of the two methine protons, which exhibited a coupling constant of 5.2 Hz. When enantiomerically enriched substrates were subjected to the reaction conditions, compound **189** was obtained with excellent stereocontrol. Electron-deficient aryl iodides provided high yields for the 1,2-diazetidine products, whereas electron-rich aryl iodides led exclusively to the formation of the five-membered dihydropyrazole **190**.

Shipman and co-workers reported the synthesis of 3-methylene-1,2-diazetidines **193** from 2-haloally alcohols **191** and azodicarboxylates **79** in a two-step sequence involving reductive coupling followed by copper-catalyzed 4-*exo*-*trig* cyclization of hydrazines **192** (Scheme 39a) [22]. This ring closure tolerated variation in both the nature of the nitrogen substituents and the substitution pattern of the alkene double bond. 1,2-Diazetidine **194**, bearing an exocyclic double bond, was further functionalized via Heck coupling with iodobenzene (**195**), showing excellent diastereoselectivity in favor of the *E* isomer **196** (Scheme 39b). The high stereoselectivity was rationalized by considering the preferred conformation of the organopalladium intermediate prior to *syn* β-hydride elimination. The exocyclic C = C double bond in **193** could be selectively reduced by hydrogenation over palladium on carbon. In addition, cleavage of the N–N bond using lithium 4,4′-di-*tert*-butylbiphenylide (LiDBB) afforded the corresponding 1,2-diamines.



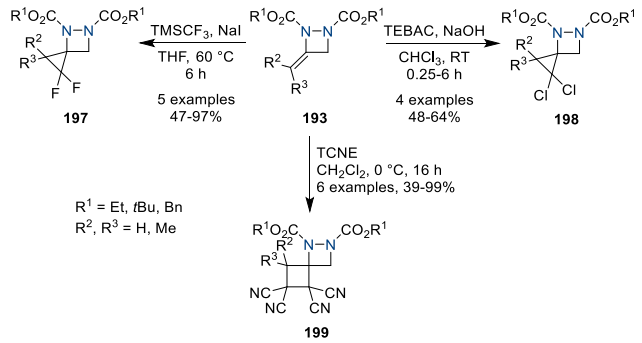
SCHEME 39 | (a) Copper-catalyzed synthesis of 1,2-diazetidines **193**. (b) Palladium-catalyzed Heck coupling of **194**.

Building on the availability of 3-methylene-1,2-diazetidines **193**, Iacobini et al. developed a highly chemo- and enantioselective hydrogenation of the exocyclic double bond using rhodium catalysis [115]. Asymmetric hydrogenation with a rhodium–Mandyphos complex under 50 atm of hydrogen proceeded in excellent yield, affording the corresponding saturated products with up to 89% ee. Notable, no N–N bond cleavage was observed under these conditions. For trisubstituted alkene derivatives, higher levels of optical purity were achieved using Josiphos ligands. In contrast, hydrogenation in the presence of a Raney nickel catalyst resulted in ring opening of substrates **193** to the corresponding diamine derivatives [23].

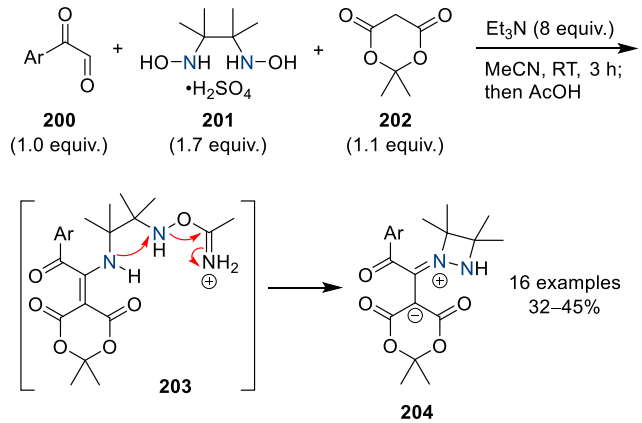
3-Methylene-1,2-diazetidines **193** also served as versatile precursors for the synthesis of spirocyclic 4,5-diazaspiro [2.3]hexanes through dihalocarbene addition across the exocyclic double bond (Scheme 40) [24]. Reaction with difluorocarbene, generated in situ from $TMSCF_3$ and sodium iodide, or with dichlorocarbene, formed by base-induced α-elimination of chloroform, afforded several fluorinated (**197**) and chlorinated (**198**) spirocyclic derivatives. Similarly, reaction of **193** and tetracyanoethylene (TCNE) produced the corresponding [2 + 2] cycloadducts **199**.

3.4 | Synthesis of 1,2-Diazetidines via N–N Bond Formation

Only a few examples for the synthesis of 1,2-diazetidines involving direct N–N bond formation have been reported. Recently,



SCHEME 40 | Cycloadditions of **193** to form spirocyclic products **197**-**9**.



SCHEME 41 | Synthesis of zwitterionic 1,2-diazetidines **204** via the postulated intermediate **203**.

Komogortsev and co-workers described the preparation of 1,2-diazetidines **204** through a multicomponent condensation of *N*,*N*′-(2,3-dimethylbutane-2,3-diyl)bis(hydroxylamine) (**201**), various arylglyoxals **200**, and Meldrum's acid (**202**) (Scheme 41) [116]. The reaction furnished **204** as a zwitterionic species, as confirmed by single-crystal X-ray diffraction analysis. The use of acetonitrile as solvent proved crucial for the success of the transformation. It was proposed that acetonitrile reacts with one of the hydroxylamine moieties, making it electrophilic and susceptible to nucleophilic attack by the second nitrogen atom, thereby generating a new N–N bond in intermediate **203** and closing the four-membered 1,2-diazetidine ring. Although the reported yields were moderate and the substrate scope was limited to variations in the aryl group of the glyoxal component, the proposed mechanism represents a unique pathway among the known methods for 1,2-diazetidine formation.

4 | Summary and Outlook

Although notable progress has been made in the synthesis of functionalized 1,2-diazetidines over the last two decades, this intriguing class of four-membered nitrogen heterocycles remains relatively unexplored. Among the reported synthetic routes, intramolecular nucleophilic ring closure has proven the most productive, offering access to a range of substituted 1,2-diazetidines. Nevertheless, challenges persist, particularly regarding control over cyclization selectivity and overall efficiency, which currently limit broader synthetic and practical applications.

Recent advances in transition metal catalysis, photochemistry, and asymmetric synthesis suggest that these barriers can be progressively overcome. The development of more selective and higher-yielding strategies will likely expand the accessible chemical space of 1,2-diazetidines, enabling their incorporation into increasingly complex molecular frameworks. Beyond synthetic innovation, further exploration of their unique structural properties could uncover valuable opportunities in medicinal chemistry and materials science. With ongoing methodological progress and growing interest in saturated three-dimensional scaffolds, the chemistry of 1,2-diazetidines offers significant opportunities for expansion in the future.

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Conflicts of Interest

The author declares no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Biographies

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