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Recent strategies used in the synthesis of saturated four-membered heterocycles

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The importance and prevalance of O-, N-, and S-atom containing saturated four-membered ring motifs in biologically active molecules and potential therapeutics continues to drive efforts in their efficient synthetic preparation. In this review, general and recent strategies for the synthesis of these heterocycles are presented. Due to the limited potential bond disconnections, retrosynthetic strategies are broadly limited to cyclizations and cycloadditions. Nonetheless, diverse approaches for accessing cyclization precursors have been developed, ranging from nucleophilic substitution to C–H functionalization. Innovative methods for substrate activation have been developed for cycloadditions under photochemical and thermal conditions. Advances in accessing oxetanes, azetidines, and thietanes remain active areas of research with continued breakthroughs anticipated to enable future applications.

1. Introduction

Compounds containing 4-membered heterocycles bearing O-, N- or S-atoms – oxetanes, azetidines, and thietanes, respectively – are a growing interest area in recent years due to their structural properties and biological activities (Fig. 1).[1–5] Oxetanes have been identified as carbonyl bio-isosteres[6,7] and oxetane, azetidine, and thietane containing compounds have been used as therapeutic agents[8–14] and exploited to create unique 3-D structures of biopolymers.[15–17] Various methods for the synthesis of these heterocycles have been reported and reviewed.[18–23]

With conformational properties determined by the heteroatom identity, the strained cyclic structures of four-membered heterocycles have contributed to their observed biological activities. While thietane and oxetane rings are nearly planar, 19.6 and 24.7 kcal mol^{-1} ring strain, respectively,[24,25] azeti-

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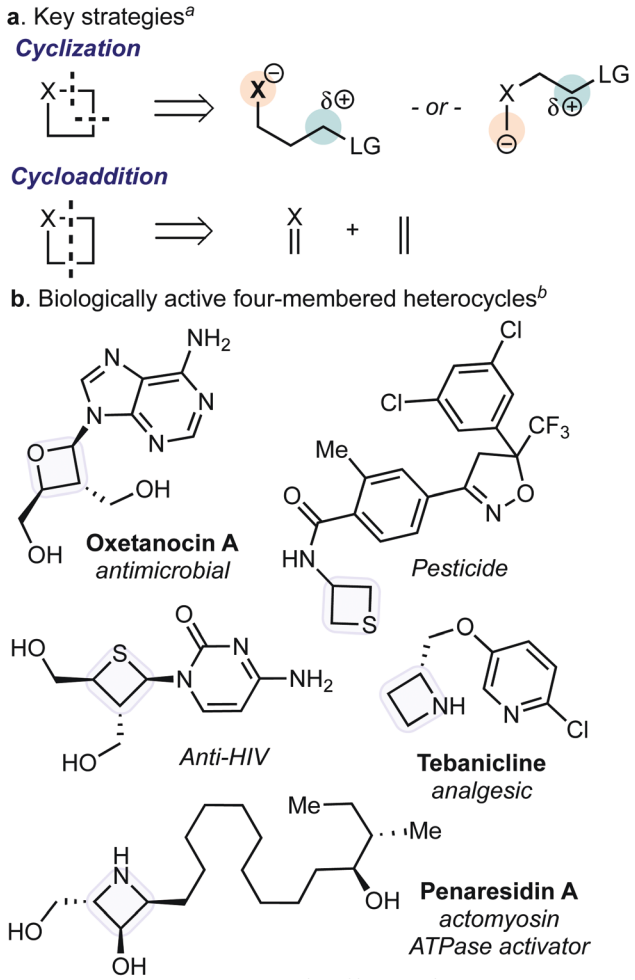

Fig. 1 Synthetic strategies to 4-membered heterocycles. [a] X = NR, O, S. LG = leaving group. [b] Ref. 3–5 and 13. Throughout sections 2 and 3 of this article, the atoms involved in the 4-membered ring formation are highlighted throughout the synthetic scheme with the nucleophilic component in orange and electrophilic component in teal.

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Valerie A. Schmidt received her Bachelor of Science degree from Towson University in 2007. She then went on to earn her Ph.D. in chemistry from the University of North Carolina Chapel Hill under the tutelage of Prof. Erik J. Alexanian. From there, she went to post doc with Prof. Paul J. Chirik at Princeton University. In 2016 she began an assistant professor position in the Department of Chemistry and Biochemistry at the University of California, San Diego. Her research focuses on the development of novel synthetic methodologies harnessing the reactivity profiles of organic and organometallic radical species.

dine, 25.2 kcal mol^{-1} ring strain, has a puckered conformation that undergoes inversion.[26] Their utility as synthetic intermediates[27,28] rather than final targets is also rooted in their ring strain as they commonly participate in a variety of ring expansions and contractions,[29] desymmetrizations,[30] and ring opening reactions.[21]

This review strives to discuss recently applied approaches for the preparation of oxetanes, azetidines, and thietanes focused around 4 key strategies in the synthesis of four-membered heterocycles: (1) cyclization through carbon–heteroatom bond formation, (2) cyclization through carbon–carbon bond formation, (3) ring expansion and contraction, and (4) cycloaddition. These methods bear distinct strategic considerations and offer various opportunities and limitations.

While cycloadditions are generally more amenable to convergent syntheses compared to cyclizations due to the possibility of intermolecular processes, the generality of activation approaches has proven traditionally limiting, although recent developments have greatly expanded possibilities.

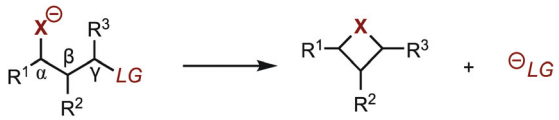
Cyclization approaches typically generate stoichiometric waste and may necessitate protecting group manipulations, leading to longer syntheses. Despite this, a variety of mild cyclization approaches have been developed that make this straightforward strategy broadly successful and commonly used. Due to widespread preparative methods of three- and five-membered heterocycles, ring expansion and contraction approaches from these more readily available precursors provide attractive routes to four-membered heterocycles.

The scope of coverage provided herein is largely from 2014 onward or since other excellent review articles;[1,20] earlier work has been included to provide context in some cases.[31] While notable advances have been made in the selective functionalization of 4-membered ring frameworks, these works will not be covered in this review.[32] The works covered herein are organized by similar mechanisms of ring formation or installation of functionality used to achieve cyclization, rather than by heterocycle. This serves to illustrate the similarities of bond construction approaches across oxetanes, azetidines, and thietanes.

2. Cyclization approaches

2.a. Cyclization *via* carbon–heteroatom bond formation

The synthesis of four-membered heterocycles *via* cyclization is typified by intramolecular nucleophilic substitution wherein a heteroatom nucleophile displaces a leaving group at an activated electrophilic γ-carbon under basic conditions (Scheme 1). This generally requires the installation of two



Scheme 1 General approach to C–X bond forming cyclizations.

heteroatom groups connected by three carbon atoms and often takes advantage of differences in heteroatom reactivity either through steric effects or inherent nucleophilicity.

For example, 3-amino propanol was used to prepare *N*-phosphoramidate protected azetidine in three synthetic steps (Fig. 2).[33] This approach achieved the requisite 1,3-positioning of the heteroatom nucleophile and the heteroatom-based leaving group by using 3-amino-1-propanol as a convenient, commercially available starting material. By leveraging the differences in relative nucleophilicity, the amino group was first converted to a phosphoramidate using diethyl phosphite. Subsequent *O*-mesylation and cyclization in the presence of potassium *tert*-butoxide afforded the *N*-protected azetidine. Acid hydrolysis gave azetidine as its hydrochloride salt, making this multi-step process both mild and a convenient way to store azetidine as its corresponding diethyl phosphoramidate.

Another approach to install leaving groups at the γ-position relative to a heteroatom nucleophile was through the nucleophilic reactivity of enolates. Bis-α-acylation of a bicyclic lactam followed by reduction and *O*-sulfonylation was used to access 1,3-bis-mesylates (Fig. 3a). Sodium sulphide double nucleophilic displacement was used to construct a thietane *en route* to the total synthesis of the thiolane-containing sesquiterpene alkaloid, (−)-thionuphlutine.[34] This double displacement strategy was also used in the synthesis of thietane and thiolane nucleoside analogs.[35] The reduction of β-chloronitriles, accessed through an organocatalyzed aldehyde α-chlorination–reduction–cyanide substitution–reduction sequence yielded γ-chloroamines. Cyclizations in the presence of potassium hydroxide yielded a variety of azetidines bearing aliphatic substituents in modest yields and good enantioselectivities (Fig. 3b).[36]

The preparation of enantiopure *N*-tosyl azetidines was previously achieved by making use of α-amino acids as chiral pool feedstocks.[37] Following reductive C1 homologation at the carboxylic acid using cyanide and selective reduction, *O*-tosylation, C–N bond forming cyclization was performed under basic conditions. Reductive aldol reactions have classically been used to create 1,3-diols, with opportunities for enantioinduction, and the analogous imino-aldol approach generates 1,3-amino alcohols. A 3-step strategy (1. Imino-aldol, 2. Reduction, 3. Cyclization) towards the preparation of substituted azetidines was first developed using *N*-tosylaldimines and enolate esters[38] and later, acetophenone derived enolates.[39] Non-racemic, substituted azetidines were analogously prepared using aryl (*S*)-(+)-*N*-sulfinimines (Fig. 4a).[40]

The *N*-sulfinyl-β-amino ester products were reduced using lithium aluminium hydride to access the 1,3-amino alcohols which subsequently underwent preferred *O*-tosylation. Cyclization in the presence of potassium hydroxide produced enantiopure 2-substituted-*N*-sulfinylazetidines in three steps. Aldehyde allylation and crotylation reactions have served as alternative approaches to aldol processes by accessing homoallylic alcohols, which yield 1,3-diol products upon oxidative alkene cleavage.[41] Transition-metal-catalysed C–C bond forming transfer hydrogenations allowed for enantioselective allylations, crotylations, and prenylations using alcohols as starting materials to produce similar products.[42] Iridium-catalysed *tert*-hydroxyl-prenylation of primary alcohols with isoprene oxide was used to synthesize chiral 1,3-diols.[43]

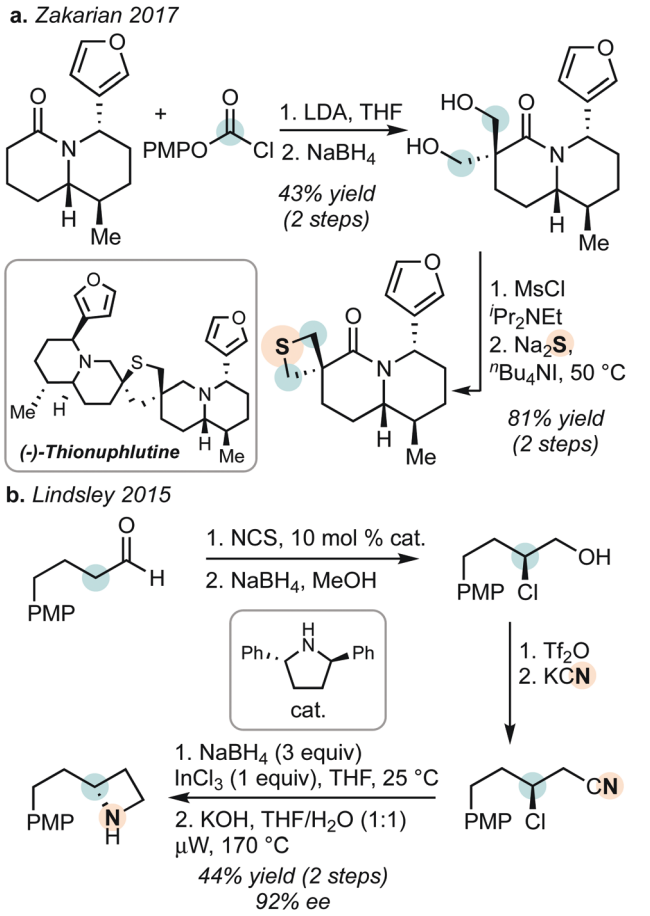


Fig. 3 Using α-carbonyl functionalization to generate cyclization electrophiles. PMP = *p*-methoxyphenyl, LDA = lithium diisopropylamide, NCS = *N*-chlorosuccinimide, Tf = trifluoromethylsulfonyl.

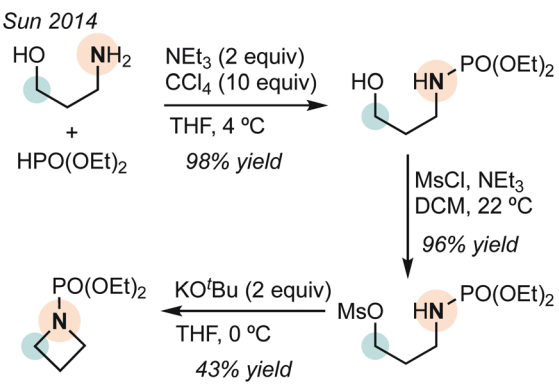


Fig. 2 Azetidine synthesis by selective *O*-mesylation. Ms = methanesulfonyl.

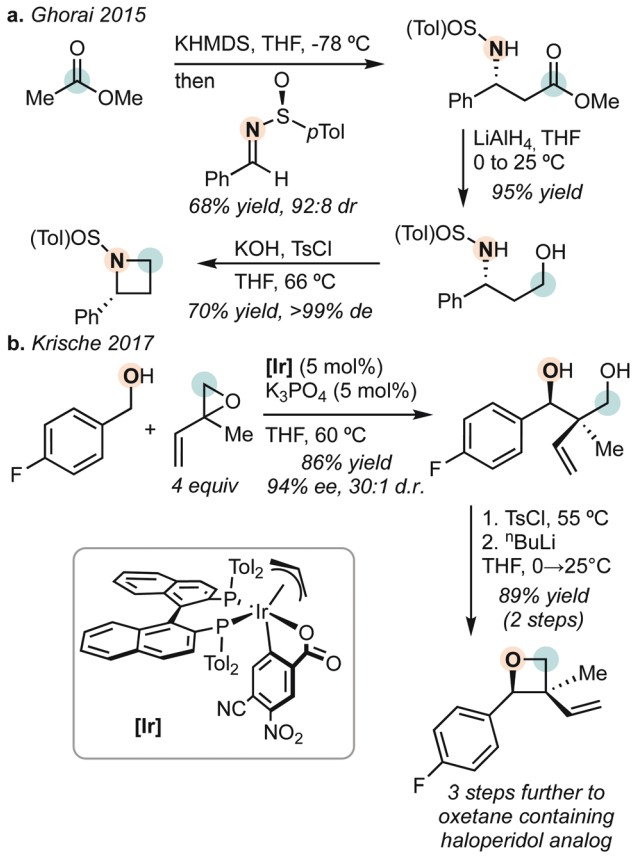


Fig. 4 Generation of 1,3-diheteroatoms by aldol-type reactions. Tol = *p*-tolyl, KHMDS = potassium bis(trimethylsilyl)amide, Ts = *p*-toluenesulfonyl.

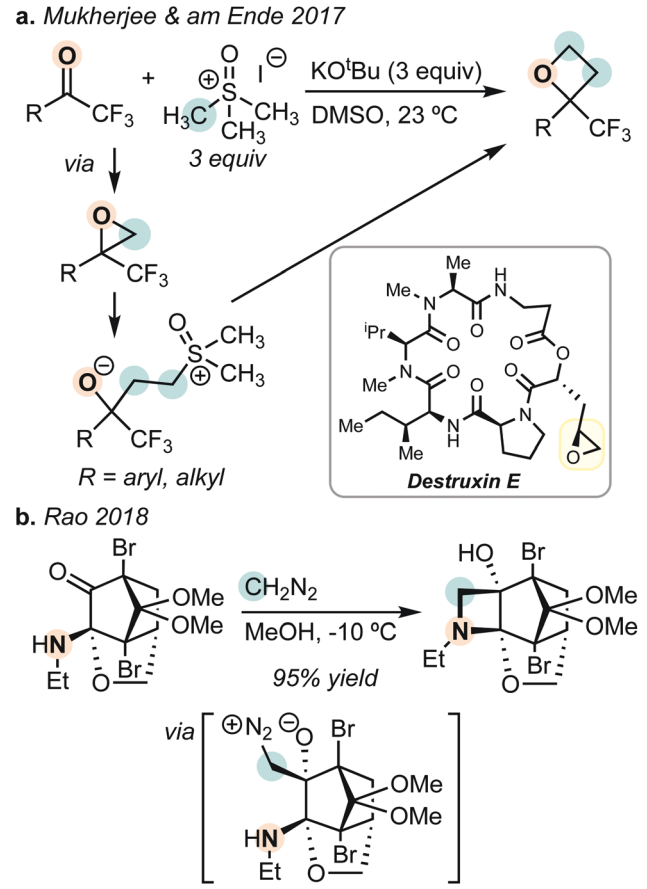


Fig. 5 Generation of cyclization electrophile by nucleophilic additions to ketones.

Activation of these 1,3-diols through mesylation or tosylation followed by cyclization using *n*-butyl lithium yielded oxetanes containing two chiral centers within the ring (Fig. 4b). Reactivity differences between the secondary and primary alcohols allowed for chemoselective *O*-sulfonylation and subsequent oxetane C–O bond formation. This strategy allowed for synthesis of oxetanes with an all-carbon quaternary center in the oxetane ring, the importance of which was highlighted through synthesis of an oxetane-containing analog of an antipsychotic drug, haloperidol. Azetidines containing two chiral centers were also accessed using this strategy through substitution of the primary sulfonate ester with a primary amine prior to ring closure.

The addition of C-based nucleophiles bearing α-leaving groups to ketones constructs a C–C bond that forms part of the 4-membered heterocycle while also creating the requisite 1,3-positioning of nucleophile and electrophile for cyclization. Using excess dimethyloxosulfonium methylide, trifluoromethyl ketones underwent two sequential insertion reactions, first to form a trifluoromethyl epoxide and then the corresponding oxetane (Fig. 5a).[44] A similar epoxidation–expansion strategy was used in the 2018 synthesis of an oxetane-containing analog of destruxin E.[45] Analogously, diazomethane addition to α-amino ketones generated both the C3–C4 bond of the resultant heterocycle and the needed γ-dinitrogen leaving group (Fig. 5b).[46] This strategy was used in the synthesis of tetracyclic ketals, leveraging the rigidity of this system to facilitate azetidine ring closure.

The reductive ring opening of β-lactones is another strategy for accessing 1,3-diols. Highly substituted spirocyclic oxetanes were accessed using this approach when the starting β-lactone was prepared *via* a Rh-catalyzed intramolecular C–H insertion (Fig. 6a).[47] Leveraging reactivity differences enabled selective *O*-tosylation of a primary alcohol in the presence of a sterically encumbered tertiary alcohol which was deprotonated, forming the corresponding alkoxide which cyclized to form the final C–O oxetane bond. In an analogous conceptual approach, a Ni-catalyzed organozinc aziridine ring opening was used towards the preparation of chiral azetidines (Fig. 6b).[48] This multi-step strategy began with L-homoserine lactone and through nucleophilic lactone opening, ultimately converted the alkoxy portion of the lactone into a phenyl thioether. Methylation of this thioether generated the leaving group used for azetidine ring closure.

Heteroatom nucleophilic conjugate addition to an α,β-unsaturated ketone was an alternate approach used to produce molecular fragments that contain two heteroatoms connected by three carbon-atoms. This was used in the prepa-

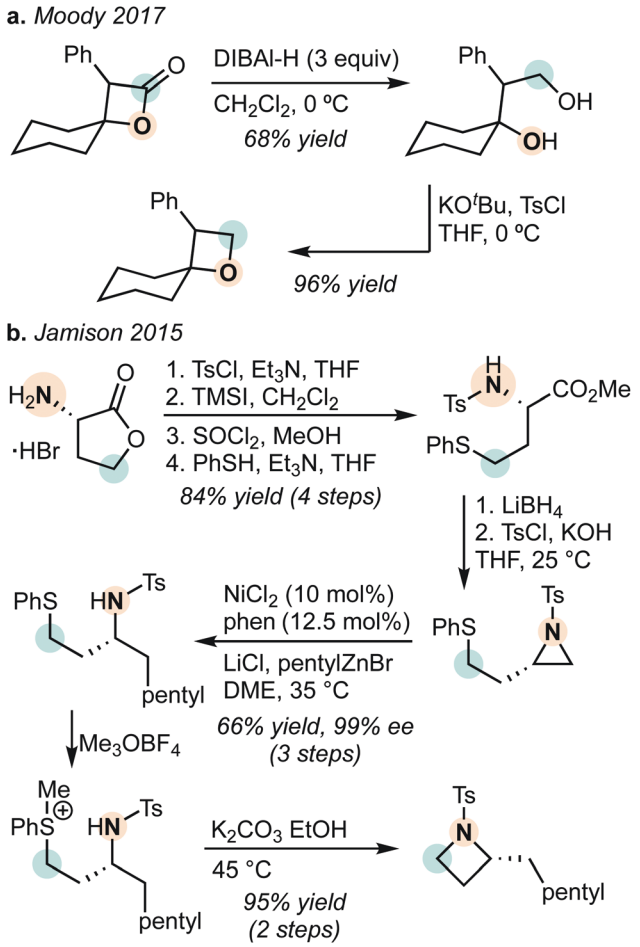


Fig. 6 Use of lactone opening to generate γ-nucleophiles. DIBAl-H = diisobutylaluminum hydride, phen = 1,10-phenanthroline, DME = 1,2-dimethoxyethane, TMS = trimethylsilyl.

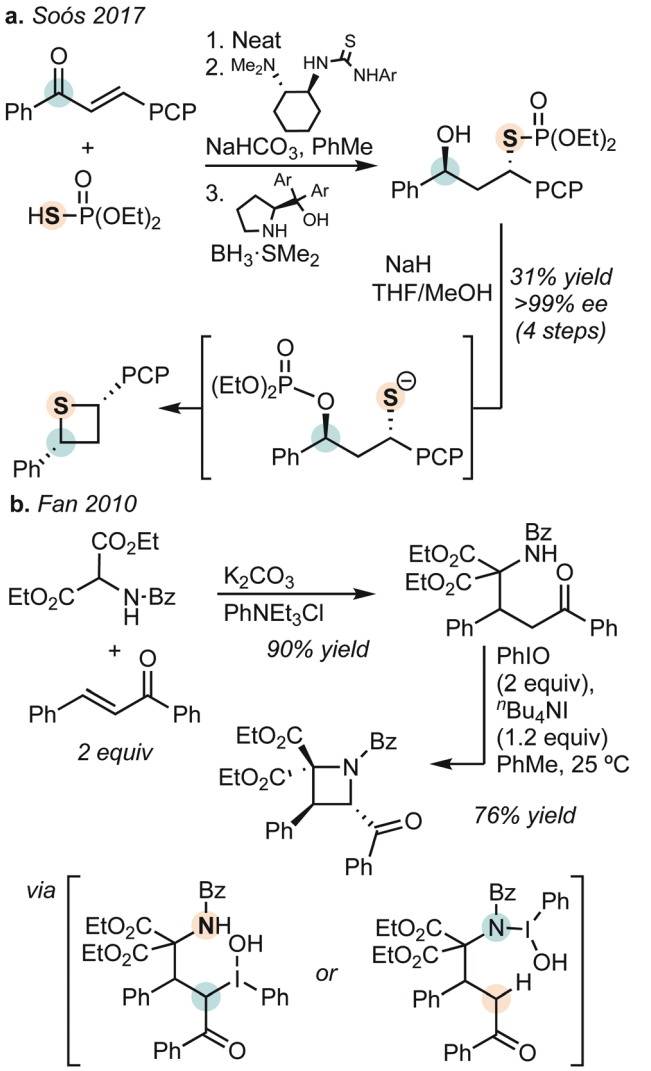


Fig. 7 Generation of γ-nucleophiles by conjugate additions. Ar = 3,5-bis-trifluoromethylphenyl, PCP = *p*-chlorophenyl, Bz = benzoyl.

ration of substituted thietanes. The rearrangement of β-hydroxy thiophosphates, accessed through conjugate addition to an α,β-unsaturated ketone followed by an asymmetric Corey–Bakshi–Shibata reduction, to phosphate esters was another means of converting alcohols into leaving groups (Fig. 7a).[49] This ester rearrangement, or thiophosphate hopping, is thermodynamically driven by P–O bond formation.[50] Deprotonation by sodium hydride triggered transesterification with the thiophosphate ester to produce a thiolate *in situ*. This thiolate then underwent thietane-forming cyclization with the liberation of diethylphosphate.

If carbon-based nucleophiles bearing α-heteroatoms are instead added to α,β-unsaturated ketones, the nucleophilic α-position of the resulting ketone can be used to cyclize. Aminomalonate addition to chalcones and subsequent treatment with hypervalent iodine(III)-oxide, formed *in situ* from tetrabutyl ammonium iodide and polymeric iodosobenzene, generated the necessary 1,3-positioning of the nucleophile and the iodine-based leaving group to form highly substituted azetidines (Fig. 7b).[51] The hypervalent iodine reagent was postulated to form two possible cyclization precursors. Iodination of the α-position of the chalcone would allow for the *N*-benzyl amino group to function as the nucleophile. Alternatively, iodination may occur at the amino group, and proton-transfer would allow enolization to render the chalcone α-position nucleophilic for ring closure.

Alkene functionalization was also used to install a γ-leaving group relative to a heteroatom-based nucleophile. Enantioenriched *cis*-2,3-disubstituted azetidines were accessed from protected chiral allylic amines *via* intermediate γ-iodoamines (Fig. 8a).[52] This was achieved through a stepwise, regioselective alkene hydrozirconation to form a terminal alkyl zirconium species that was converted to the corresponding iodide by molecular iodine. This alkene hydrofunctionalization occurred with high diastereoselectivity dictated by the preferred pseudoaxial conformation adopted during hydrozirconation through carbamate coordination. Base-promoted cyclization formed the 2,3-disubstituted azetidine. Treatment of homoallylic amines with phenyl selenium bromide and

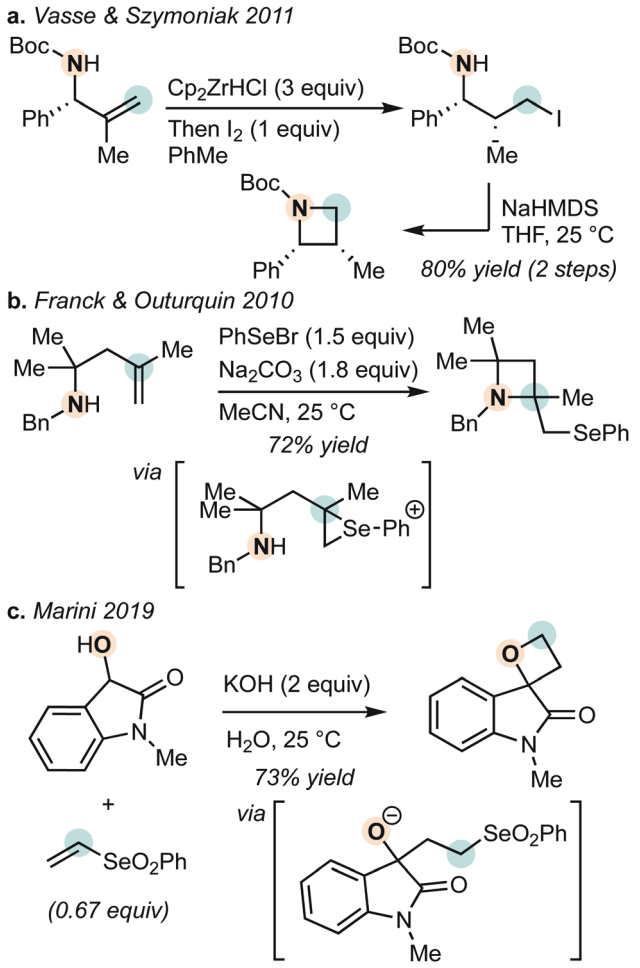


Fig. 8 Generation of γ-electrophiles by alkene functionalization.

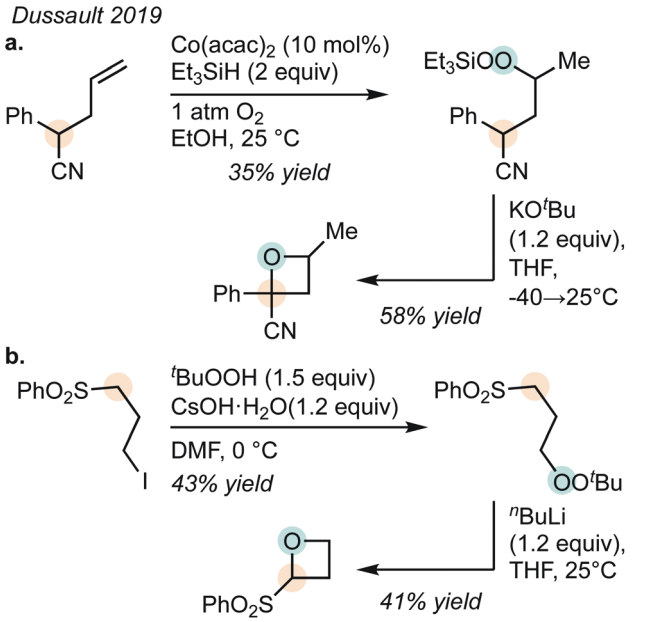


Fig. 9 Generation of oxetanes by nucleophilic O–O bond cleavage. acac = acetoacetonate.

sodium carbonate resulted in alkene selenization followed by cyclization to form azetidines (Fig. 8b).[53] Reaction efficiencies were increased with bulkier substituents at the positions adjacent to the amine. Alternative pyrrolidine-forming pathways outcompeted azetidine formation when a phenyl group was incorporated at the alkene terminus, indicating that electronic stabilization of the seleniranium intermediate dictated cyclization selectivity. An alkene addition–cyclization sequence between 3-hydroxy-2-oxindoles and vinyl phenyl selenone was developed for the synthesis of spirooxindole oxetanes (Fig. 8c).[54] Crossover experiments with phenyl vinyl selenone and phenyl vinyl sulfone as the Michael acceptor demonstrated the necessity of the selenone leaving group.

The use of C-centered nucleophiles in C–heteroatom bond forming cyclization is less common due to the difficulty of regioselective deprotonation with multiple protic groups present. Substituted alkyl peroxides serve as excellent O-atom electrophiles which tolerated the formation of C-nucleophiles through deprotonation. As a general strategy for the synthesis of cyclic ethers, sulfone- and nitrile-stabilized carbanions cyclized by cleaving the O–O bonds of tethered peroxides (Fig. 9).[55] Although this work mainly focused on tetrahydrofurans and oxanes, it presented a distinct etherification strategy applicable to the synthesis of oxetanes. Two approaches for alkyl peroxide formation were described. The first generated a triethyl silyl peroxide through an aerobic Co-catalyzed alkene hydrofunctionalization.[56] The second approach produced alkyl *tert*-butyl peroxides formed through iodide substitution.

Cyclization through carbon–heteroatom bond formation has proven useful in the synthesis of complex molecules that contain 4-membered heterocycles. In the total synthesis of (+)-dictyoxetane, Magauer and coworkers used selective monomesylation of a secondary allylic alcohol followed by sodium hydride promoted cyclization to construct the oxetane ring (Fig. 10a).[57] Aerobic photo-oxidation of a tertiary allylic alcohol intermediate was key to the installation of the sterically differentiated 1,3-diol. Carreira and coworkers used an oxidative C–O cyclization to install the necessary oxetane after constructing the carbon framework of (-)-mitrephorone A (Fig. 10b).[58] Fluoride-mediated silyl ether deprotection and subsequent addition of Koser's reagent activated C5 through the formation of an *O*-iodoenol which prompted the oxetane-forming cyclization. The 1,3-positioning for cyclization was accomplished through an intramolecular [4 + 2] diene-alkyne cycloaddition that not only formed the pentacyclic framework, but also established the correct orientation between the C9 siloxy group and C5, which was rendered electrophilic in the final step. A complementary oxidative cyclization approach was similarly used to forge the oxetane ring through the incorporation of the C9 alkoxy group *via* C–H oxidation.[59]

2.b. Cyclization *via* carbon–carbon bond formation

Cyclization through C–C bond formation can overcome many challenges associated with C–heteroatom cyclization in four-

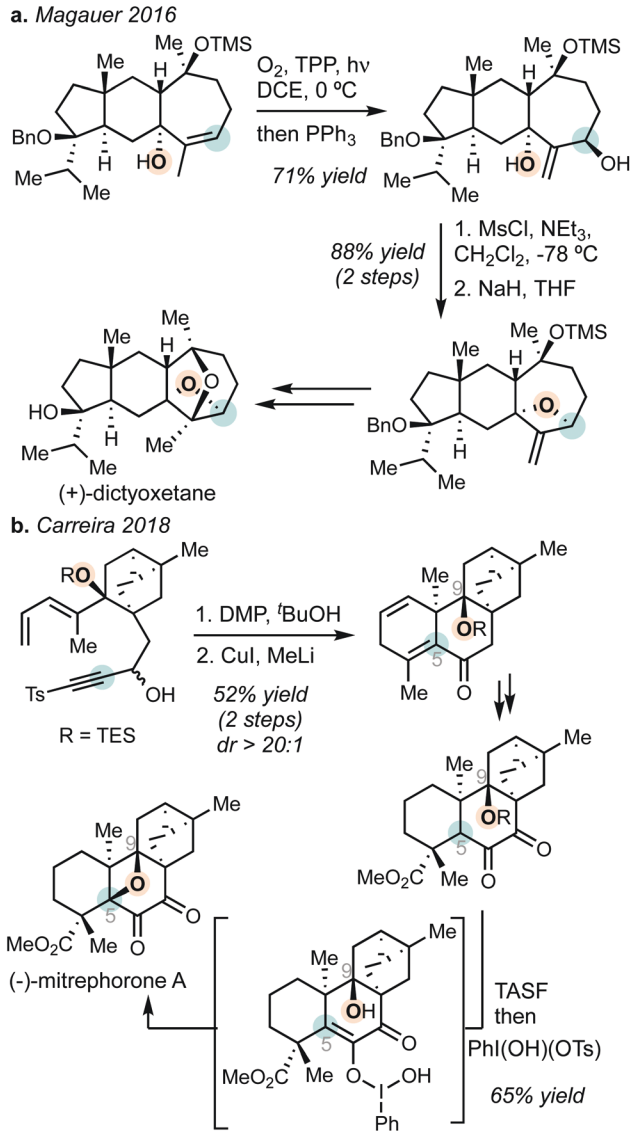
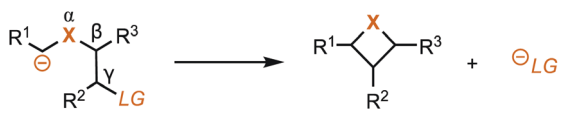


Fig. 10 Oxetane formation *via* C–O bond cyclizations in total synthesis. TPP = tetraphenyl porphyrin, TES = triethylsilyl, DMP = Dess-Martin periodinane, TASF = tris(dimethylamino)sulfonium difluoromethylsilicate.



Scheme 2 General approach to C–C bond forming cyclizations.

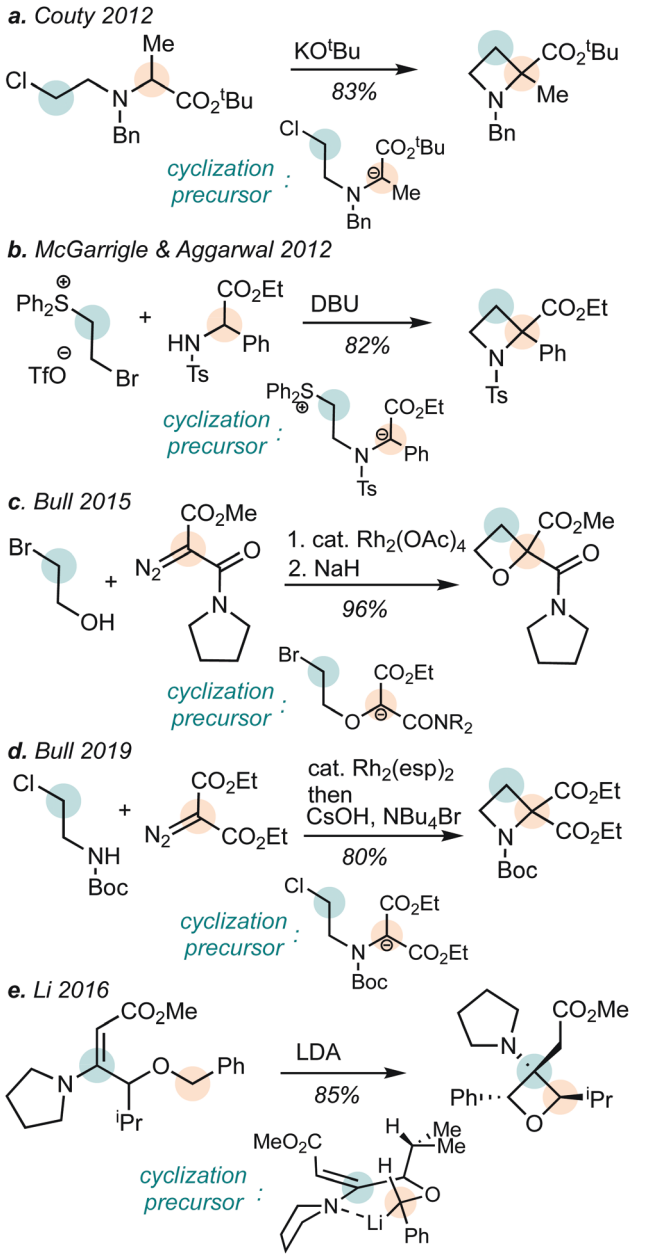


Fig. 11 Oxetane and azetidine synthesis *via* C–C bond forming cyclizations. DBU = 1,8-diazabicylco[5.4.0]undec-7-ene, esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid, Boc = *tert*-butoxycarbonyl.

membered ring synthesis (Scheme 2). Steric repulsion often limits the efficiency of synthesizing four-membered heterocycles bearing bulky substituents at C2 and C4 positions. Conversely, bond formation between C2 and C3 does not suffer this constraint. A common strategy for 4-membered ring synthesis *via* C–C bond formation is the *in situ* generation of enolates bearing δ-leaving groups *via* deprotonation (Fig. 11a–d).[60–63] This approach delivers 4-membered heterocycles with ester substituents at C2 giving access to azetidine-2-carboxylic acid derivatives which are of interest as four-membered analogues of α-amino acid, proline. Oxetane cyclization through C–C bond formation has also been achieved through an intramolecular conjugate addition (Fig. 11e).[64] Lithiation of an allylic or vinylogous ether generated stabilized benzylic carbanions which underwent addition to the tethered α,β-unsaturated ester. This 4-*exo*-trig cyclization between C2 and C3 contrasts unfavorable 4-*exo*-tet cyclizations and enables the synthesis of highly substituted oxetanes. However, this was sensitive to the Michael acceptor, as unhindered γ-positions

underwent competitive γ-lithiation, which triggered undesired [2,3]-Wittig rearrangement and lactonization.

2.c. Other cyclizations

Cyclizations mediated by transition metals have emerged for the preparation of four-membered heterocycles. These transformations are mechanistically diverse, ranging from the generation of organometallic C-based nucleophiles to C–H activation and oxidative cyclization.

Intramolecular, pyridyl-directed Pd-mediated C–H amination was used to synthesize azetidines (Fig. 12).[65] This strategy enabled cyclization without the installation of a leaving group. These processes proceeded *via* formation of a Pd(II)-substrate chelate that underwent C–H palladation to form a 5-membered palladacycle. Subsequent hypervalent iodine-mediated oxidation produced the corresponding Pd(IV)-palladacycle, which underwent reductive elimination to form the azetidine C–N bond. Indolines and pyrrolidines were analogously synthesized as reductive elimination from a 6-membered palladacycle was similarly favourable.

Metallocarbenes were used to synthesize oxetan-3-ones from propargyl alcohols and Au-catalysis (Fig. 13).[66] Gold phosphine triflimide-mediated alkyne oxidation with pyridine *N*-oxides formed α-oxo-γ-hydroxy-1-gold-carbenes that upon O–H bond insertion formed oxetane rings. This strategy allowed alkynes to be used as synthetic equivalents to α-diazoketones and was used in the library synthesis of spirocyclic oxetan-3-ols targeted for drug discovery.[67] A similar transformation was developed for the synthesis of azetidine-3-ones from *N*-propargylsulfonamides.[68]

Metallocarbene species were also used to generate organometallic nucleophiles to form azetines in the presence of a heteroatom-based electrophiles (Fig. 14).[69] The azetines were readily hydrogenated to azetidines in a subsequent step. The mechanistic proposal for 4-membered ring formation invoked the generation of Cu–carbene complexes from *Z*-enoldiazoacetates. These complexes underwent conjugate addition with *N*-arylsulfimines and cyclization occurs *via* C2 nucleophilic attack at nitrogen to release diphenyl sulfide. This reaction tolerated a broad scope of substituted enoldiazoacetates, generating a variety of trisubstituted, azetidines.

3. Ring expansions and contractions

Four-membered heterocycles can be accessed from cyclic starting materials through ring expansion or, less commonly, contraction (Scheme 3). A variety of transformations have been developed in this area that allow for the synthesis of highly substituted azetidines and thietanes. A ring expansion or contraction approach allows for select atoms to be added or

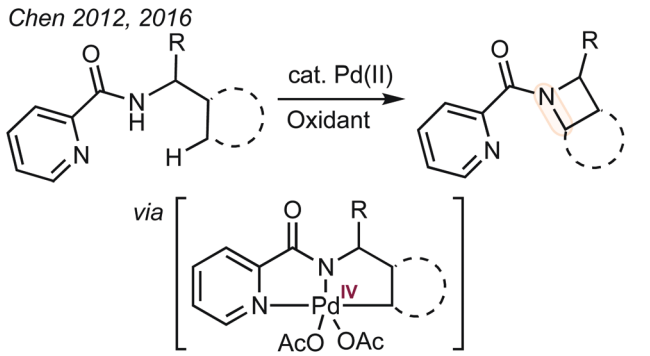


Fig. 12 Azetidine formation through C–N bond forming reductive elimination.

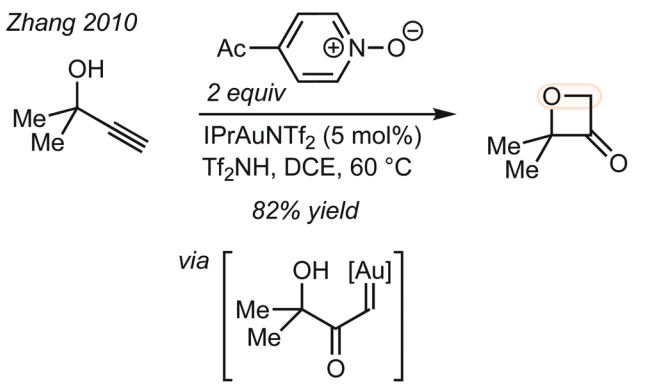


Fig. 13 Oxetane cyclization through O–H insertion. iPr = 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidine.

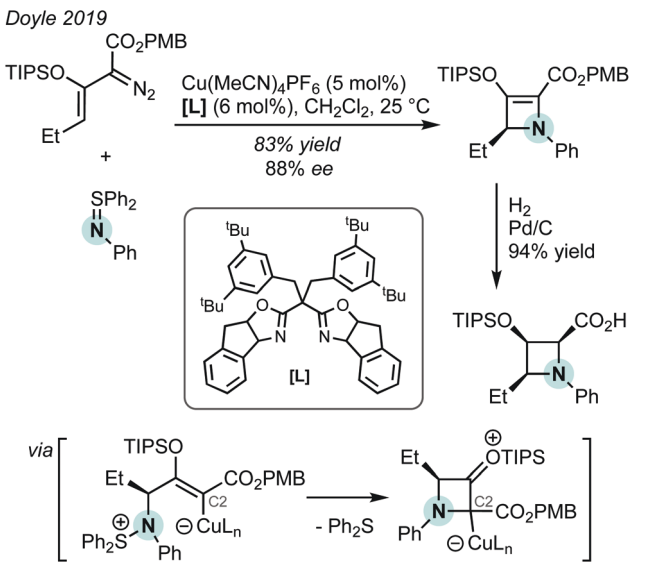
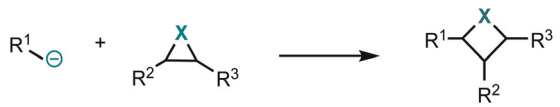


Fig. 14 Azetidine synthesis *via* Cu-catalyzed conjugate addition. TIPS = triisopropylsilyl, PMB = *p*-methoxybenzyl.



Scheme 3 General approach ring expansions.

removed from an existing cyclic precursor in a convergent manner.

3.a. Ring expansions

The ring strain and polarized bonds of thiiranes and aziridines lends them to consideration of thietane and azetidine preparation through a one-carbon homologation. This overall strategy requires the use of a one-carbon source that contains an adjacent leaving group so that the required 1,3-positioning of nucleophile and electrophile is formed. The expansion of thiiranes using dimethyloxosulfonium methylide was used to prepare thietanes (Fig. 15a). Nucleophilic attack of the thiirane produced a γ-dimethylsulfoxonium thiolate, which cyclized to form the 4-membered ring.[70] The DMSO additive was proposed to coordinate to the thiirane sulfur atom, activating the thiirane electrophile, although the use of excess DMSO decreased the nucleophilicity of the methylide partner suggesting a balance between the two competing factors.

α-Diazoesters are commonly used metallocarbene precursors and can serve as one-carbon sources for ring homologation. Fused bicyclic azetidines were prepared *via* a [3 + 1] aziridine expansion strategy using α-diazoesters and Rh_2OAc_4 (Fig. 15b).[71] This approach allowed the α-diazoester to serve as a one-carbon source to expand aziridines and produce highly substituted bicyclic methylene azetidines with moderate to high diastereoselectivity. This transformation was proposed to proceed *via* aziridinium ylide formation from N-based aziridine attack to the *in situ* formed Rh-bound carbene. A subsequent ring-opening and ring-closing cascade progressed through a proposed non-racemizing C-bound Rh-enolate to forge the azetidine C2–C3 bond. Alternatively, a variety of 2-acyl thietanes were synthesized through Rh-catalyzed ring expansion of thiiranes (Fig. 15c).[72] Sulfonium acylmethylides were used to generate analogous electrophilic Rh–carbenes *in situ*, which underwent nucleophilic attack by the thiirane. Nucleophilic ring opening of the activated thiirane by dimethyl sulfide produced a Rh-enolate with a dimethyl alkyl sulfonium leaving group located at the δ-position. Subsequent C2–C3 thietane bond formation turned over the catalyst. A thioether leaving group was shown to be necessary for promoting this reaction, as 2-diazoacetophenone used in place of the sulfonium acylmethylide did not yield any thietane until a thioether additive was introduced.

Cyclopropanes have been expanded to azetidines through a N-atom insertion process (Fig. 16a). This [3 + 1] annulation used a relay catalysis approach where an initial Lewis acid-mediated cyclopropyl ring opening preferentially forged a C–N bond at the benzylic position and subsequent (hypo)iodite-mediated oxidative α-amination led to azetidine ring for-

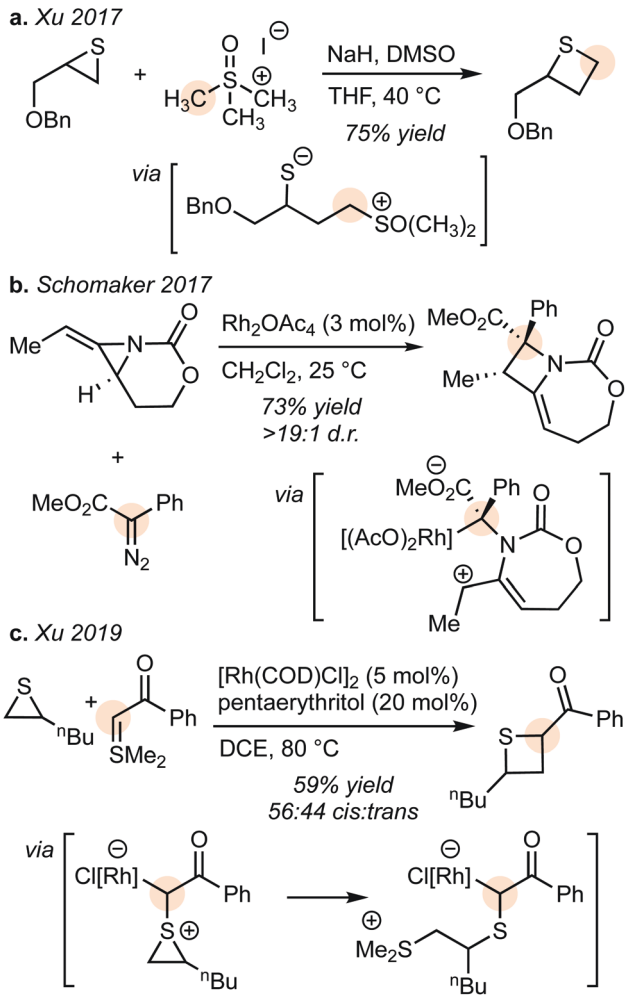


Fig. 15 Ring expansions *via* nucleophilic C1 insertions. COD = 1,5-cyclooctadiene.

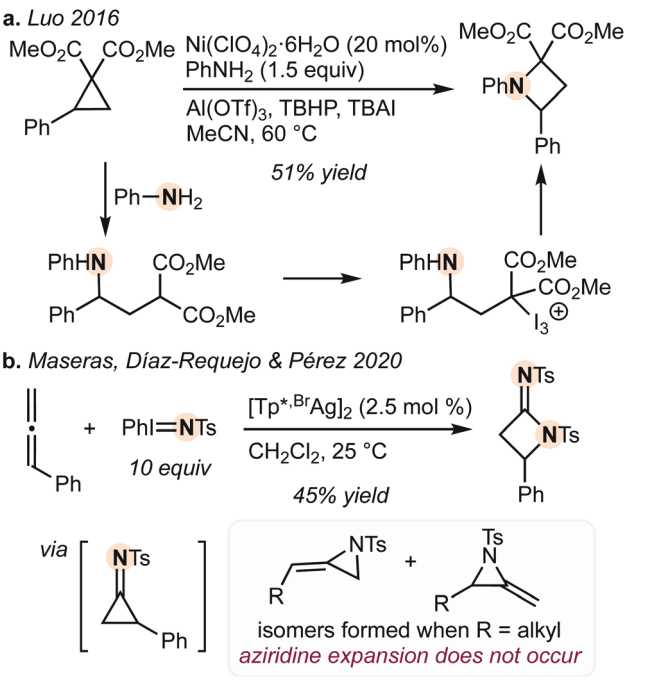


Fig. 16 Ring expansions *via* N-atom insertions. TBHP = *tert*-butyl hydroperoxide, TBAI = tetrabutylammonium iodide, $Tp^{*,Br}$ = hydrotris (3,5-dimethyl-4-bromopyrazolyl)borate.

mation.[73] Nickel(II) perchlorate and aluminum(III) triflate were used in combination as Lewis acids for this transformation. Although either one alone was demonstrated to promote azetidine formation, reaction efficiencies were generally improved when both were used. Notably, some cyclopropane 1,1-diesters containing electron-rich aryl substituents underwent spontaneous Lewis acid-mediated azetidine expansion to the corresponding tetrahydroquinolines.

Hydrotris(pyrazolyl)borate silver dimer was used to generate an *in situ* Ag-nitrene species that selectively performed nitrene transfer to aryl substituted allenes to form unstable cyclopropylimine intermediates.[74] Subsequent silver-mediated nitrene insertion afforded the observed azetidine products (Fig. 16b). The selectivity for the formation of aryl substituted cyclopropylimine intermediates is proposed to arise from a kinetically favored pathway over methylene aziridine formation, which is favored when alkyl substituted allenes are used.

Another ring expansion strategy used for azetidine synthesis involved the strain release of an azabicyclo[1.1.0]butane framework. Sodium borohydride reduction of *N*-alkylidene-(2,3-dibromo-2-methylpropyl) amines or *N*-(2,3-dibromo-2-methylpropylidene) benzylamines triggered a series of cyclizations that due to the 2-methyl substituent, passed through a bicyclic aziridinium intermediate that opened to the corresponding azetidine upon nucleophilic attack by methanol (Fig. 17a).[75] Prepared from 2,3-dibromopropyl amine and lithiated bases, azabicyclo[1.1.0]butyl lithium and a variety of alkyl boronic esters were also used to form azabicyclo[1.1.0]butyl picanolatoborates (Fig. 17b).[76] In the presence of acetic acid, a 1,2-metallate rearrangement accessed azetidine products.

Toleration of a wide variety of pinacol boronic ester coupling partners facilitated the use of this approach in the synthesis of cobimetinib, an MEK inhibitor used in the treatment of melanoma. Taken together, the methods presented in Fig. 17 offer two complementary strategies for the preparation of azetidines wherein the resultant C3 position is poised to serve as a nucleophile (part b) or as the site for nucleophilic displacement (part a).

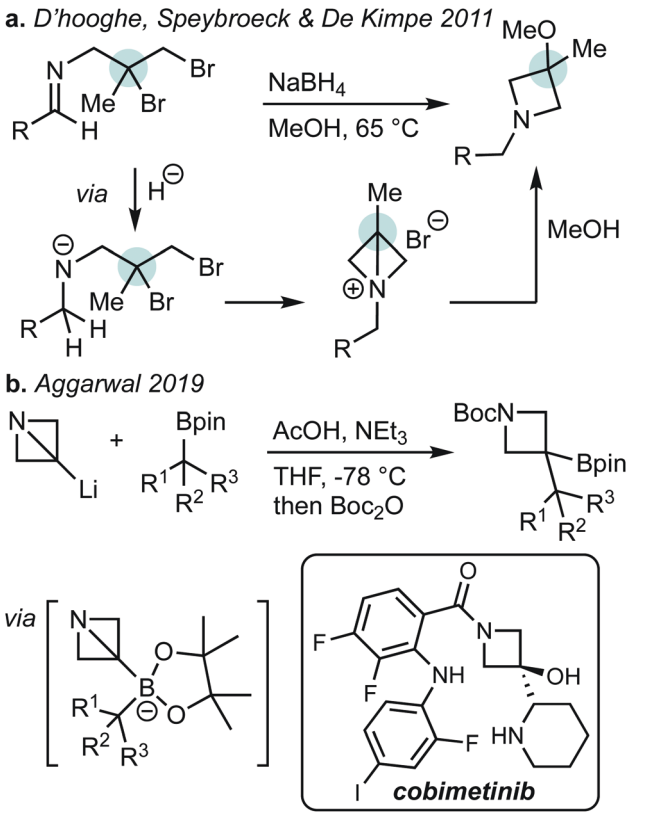


Fig. 17 Azetidine synthesis through ring strain release. pin = pinacolato.

3.b. Ring contractions

Azetidines bearing esters or amides at the 2-position were prepared *via* the ring contraction of α-bromo-*N*-sulfonylpyrrolidinones using alcohol or amine nucleophiles (Fig. 18a).[77] An initial nucleophilic acyl substitution cleaved the pyrrolidinone amide bond to produce the pendant sulfonamide nucleophile, which then preferentially displaced the α-bromo group to form the azetidine. This strategy benefits from the ease of access to substituted pyrrolidinones. In the total synthesis of (±)-gelsemoxonine, Carreira and coworkers used an isooxazoline ring contraction strategy to access the fused azetidine ring (Fig. 18b).[78] Treatment of the isooxazoline spirocycle containing precursor with trifluoroacetic acid induced a cyclopropyl expansion to an azetidine hemiaminal ether. This spirocyclic intermediate then eliminated ethylene to form the corres-

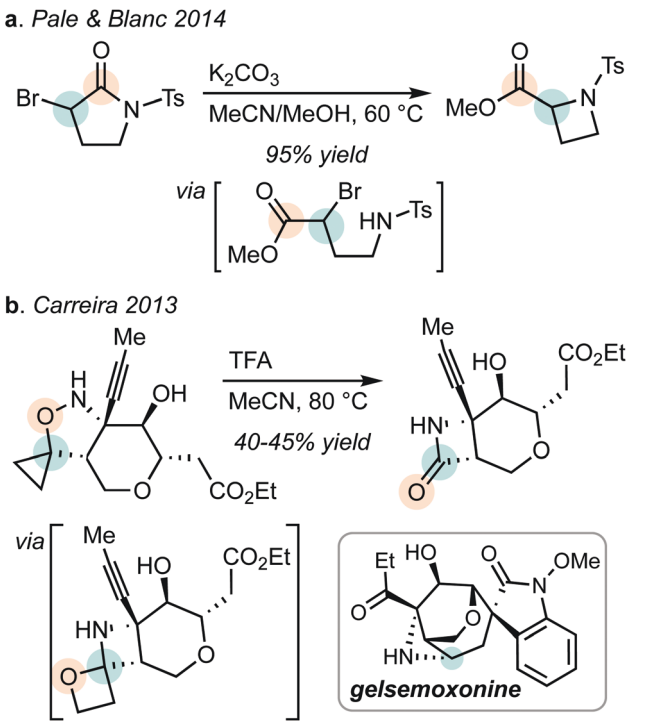


Fig. 18 Azetidine synthesis through ring contraction. TFA = trifluoroacetic acid.

ponding β-lactam. Elaboration of this β-lactam was key to accessing the tricyclic core of gelsemoxonine.

4. Cycloadditions

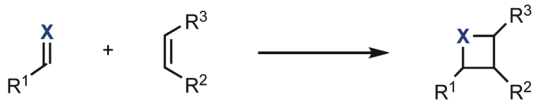
Cycloadditions are an important, mechanistically diverse class of reactions for the synthesis of a variety of functionalized heterocycles. Photochemically allowed [2 + 2] cycloadditions are common for the synthesis of four-membered heterocycles for which new synthetic methods continue to emerge including customized reagents that undergo direct excitation, photosensitization, and transition metal coordination approaches. Formal [2 + 2] cycloadditions under thermal conditions have emerged, and Lewis base-catalyzed [2 + 2] annulations have been extensively developed (Scheme 4).

4.a. [2 + 2] Photocycloadditions

Photocycloadditions are a broad class of methods for the synthesis of four-membered heterocycles. The classical oxetane forming [2 + 2] photocycloaddition is the Paternò–Büchi reaction, wherein an aldehyde or ketone and olefin are irradiated with ultraviolet light to yield the corresponding oxetane. The excited state, accessed through a carbonyl n–π* transition reacts with the alkene to form the 4-membered ring.[79–82] Variants that would similarly form azetidines have been significantly more limited though renewed interest has promoted the development of alternative approaches.[83]

The direct irradiation of cyclopentenones and alkenes with 300 nm light was used to synthesize tricyclic oxetanes (Fig. 19a).[84] This reaction proceeded by an initial intermolecular [2 + 2] cycloaddition to form a fused cyclobutane followed by Norrish type-I cleavage and subsequent γ-hydrogen atom transfer. The resultant cyclobutenyl aldehyde then underwent intramolecular Paternò-Büchi cycloaddition to produce a tricyclic oxetane. Support for this order of events was gained through the trapping of the intermediate aldehyde and characterization of cyclobutene acetal intermediates. Hydrolysis and subjection of the aldehyde to irradiation furnished the same tetracyclic oxetane.

Oxetanes have also been formed through visible light irradiation of benzophenone and unsaturated fatty acids (Fig. 19b).[85] The authors proposed that the addition of a Brønsted acid to the reaction mixture formed an alkene–proton–ketone complex which was observed by mass spectrometry, and served as the photoactive species leading to oxetane formation. While not regioselective, this allowed the position of unsaturation in the lipid starting material to be identified through tandem mass spectrometry. The use of



Scheme 4 General approach for [2 + 2] cycloadditions.

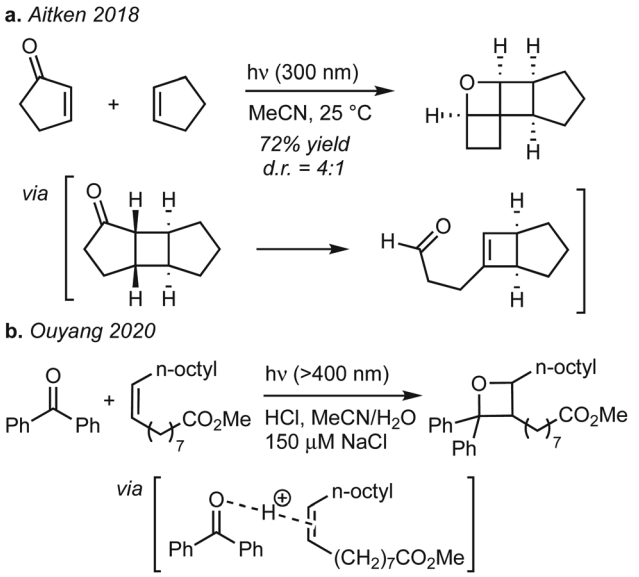


Fig. 19 Oxetane forming [2 + 2] photocycloadditions *via* direct irradiation.

anthraquinone in place of benzophenone allowed for the structural elucidation of lipids from human serum samples.[86]

Irradiation of *N*-sulfonyl aryl imines and styrenes with 365 nm light was also used to synthesize azetidines through [2 + 2] photocycloaddition (Fig. 20a).[87] Photochemical *E*/*Z* isomerization of the imine starting material is a potential relaxation pathway from the excited state that may decrease productive cycloaddition. However, the azetidine stereochemistry retained the stereochemistry of the alkene starting material, making a concerted, singlet pathway enabled by π-stacking pre-organization, the mechanism most consistent with the experimental data.

Hydrogen-bonding to a photosensitizer has been used as a pre-organization strategy for the visible light-mediated preparation of azetidines (Fig. 20b).[88] Triplet energy transfer from a chiral thioxanthone photosensitizer to quinoxalinones led to photoexcited imines which were subsequently trapped by vinyl arenes resulting in the formation of fused, multicyclic azetidines.

A xanthone photosensitized approach to [2 + 2] photocycloadditions was used for the synthesis of oxetanes and azetidines. Cyclic enamides, when tethered to either aldehydes,[89] oxime ethers, or hydrazones,[90] were excited through triplet energy transfer from photoexcited xanthone (Fig. 20c). The π–π* enamide triplet excited state added to the C=O or C=N double bond, leading to C2–C3 bond formation in the product and subsequent ring closure formed the heterocycles. This contrasts the Paternò–Büchi reaction mechanism, as the C=C double bond, rather than the carbonyl component, was photoexcited.

Iridium photocatalysts have also been used as photosensitizers in the synthesis of azetidines and oxetanes (Fig. 21). In an intramolecular example, mechanistic studies indicated that

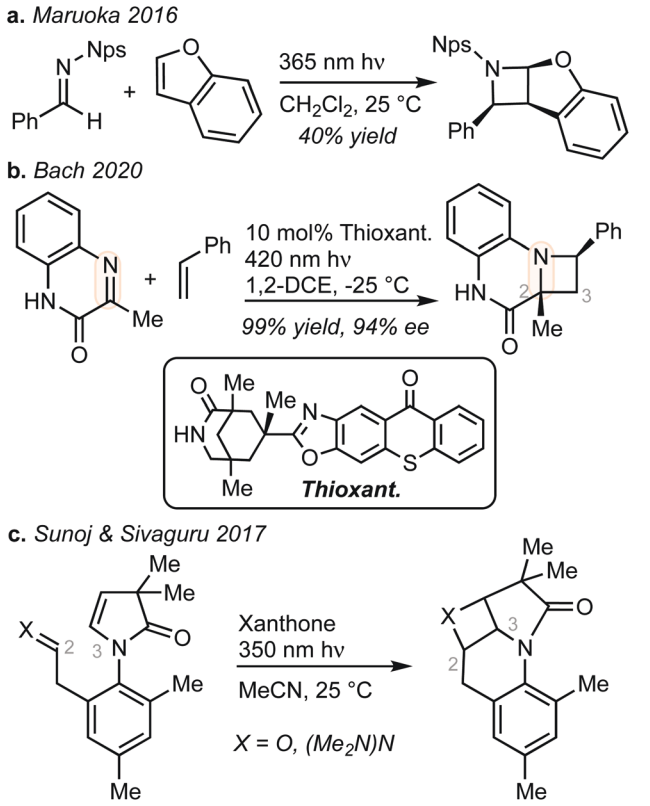


Fig. 20 Azetidine forming [2 + 2] photocycloadditions using substrate pre-organization approaches. Nps = naphthalene-2-sulfonyl, 1,2-DCE = 1,2-dichloroethane.

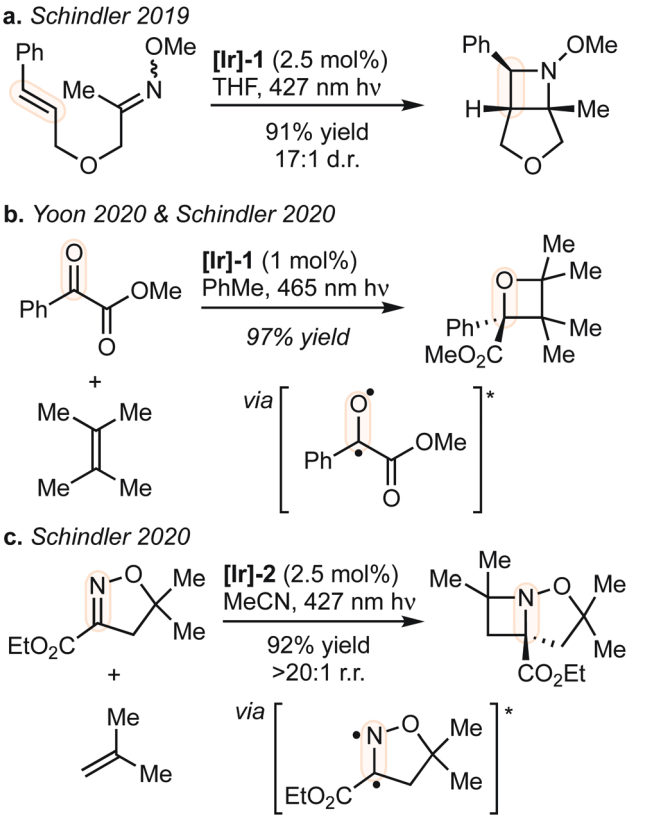


Fig. 21 [2 + 2] cycloadditions using Ir-based photosensitization of C=C, C=O, and C=N bonds. **[Ir]-1** = Ir[dF(CF$_3$)ppy]$_2$(dtbpy), **[Ir]-2** = fac-Ir(dFppy)$_3$.

azetidine formation was the result of triplet sensitization of the tethered aryl alkene C=C double bonds by the triplet excited state of **[Ir]-1** due to well-matched first triplet-excited state energies (Fig. 21a).[91] This strategy was extended to dienes, which allowed for the synthesis of vinyl-substituted azetidines. The same Ir-photocatalyst was simultaneously reported by two separate groups to achieve triplet energy transfer to the oxo C=O double bond of aryl α-keto esters and subsequently trapped by substituted alkenes to synthesize oxetanes using visible light (Fig. 21b).[92,93] Notably, divergent allylic functionalization was obtained when reactions were carried out using photoredox conditions which included Lewis acid activation of the benzoylformate esters and facilitated electron transfer rather than energy transfer. A similar Ir-photocatalyst, **[Ir]-2** with the same E_T (60.1 kcal mol^{-1}) as **[Ir]-1**, was optimally used to selectively excite the C=N bonds of cyclic glyoxylate oximes *via* triplet energy transfer (Fig. 21c).[94] This approach allowed for a large, diverse range of alkenes to be efficiently captured providing significant access to many novel azetidine containing fused heterocycles.

Alkene activation for [2 + 2] photocycloadditions was also achieved using a transition metal coordination, charge transfer approach (Fig. 22).[95] A Cu(I) center, supported by a hydrotris (pyrazolyl)borate chelate was used to coordinatively capture norbornene, forming the active chromophore in solution.

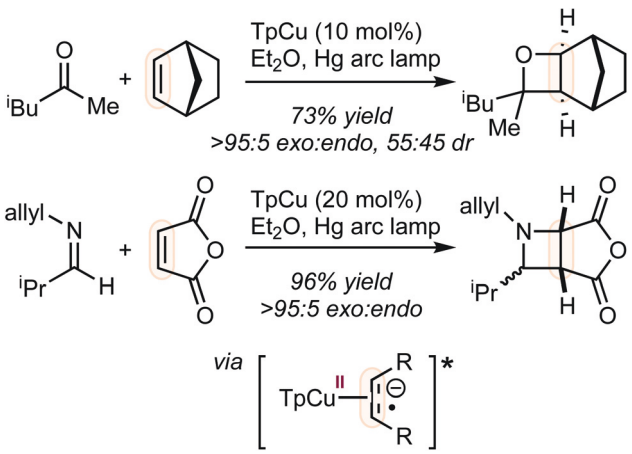


Fig. 22 [2 + 2] photocycloadditions *via* MLCT C=C bond activation.

Spectroscopic studies were consistent with a Cu(I)-alkene metal to ligand charge transfer (MLCT) which led to alkyl substituted ketone capture to form a variety of 2,2,3,4-tetrasubstituted oxetanes, including oxetane spirocycles. The analogous use of imines produced azetidines with a wider range of cyclic strained alkene partners including maleic anhydride and maleimide.[96]

4.b. Thermal [2 + 2] cycloadditions

Lewis base-catalyzed [2 + 2] cycloadditions between allenoates and unsaturated electrophiles were used to prepare 2-alkylidene substituted oxetanes,[97–102] azetidines,[103,104] and thietanes[105] (Fig. 23). These processes share a common mechanistic pathway of nucleophilic attack of the Lewis-base catalyst at the β-position of the allenoate rendering the γ-position nucleophilic. Intermolecular addition to the electrophilic C=X partner, ring closure, and elimination delivered the 4-membered heterocycle product and released the organocatalyst.

Alternatively, Au(I)-mediated activation of propargyl ethers in the presence of imines has been used to access benzylidene azetidines (Fig. 24).[106] Alkyne activation *via* coordination induced the formation of an electron-rich allene *via* the elimination of acetone allowing a thermal [2 + 2] cycloaddition to occur between the allene and imine.

Titanium-mediated synthesis of spirocyclic N–H azetidines from oxime ethers and alkyl Grignard reagents was recently reported (Fig. 25).[107] While the oxime ether partner was unsuccessfully engaged when large, sterically hindered group were present, the Grignard reagent tolerated a variety of aliphatic chain lengths and electronically diverse aryl groups. This reaction proceeded through a Kulinkovich-type mechanism to form the key bisalkoxy-Ti(II)-olefin intermediate. Oxidative cyclization between the olefin and oxime double bonds formed a five-membered titanacycle. Concomitant bond migration and methoxide elimination forged the necessary C–N azetidine bond. The use of terminal olefins as coupling partners in place of Grignards also resulted in the formation of azetidine products. This provided evidence for the formation of a Ti(II)-alkene intermediate, which was formed through alkyl magnesium-mediated reduction of the Ti(IV) precursor followed by alkene coordination.

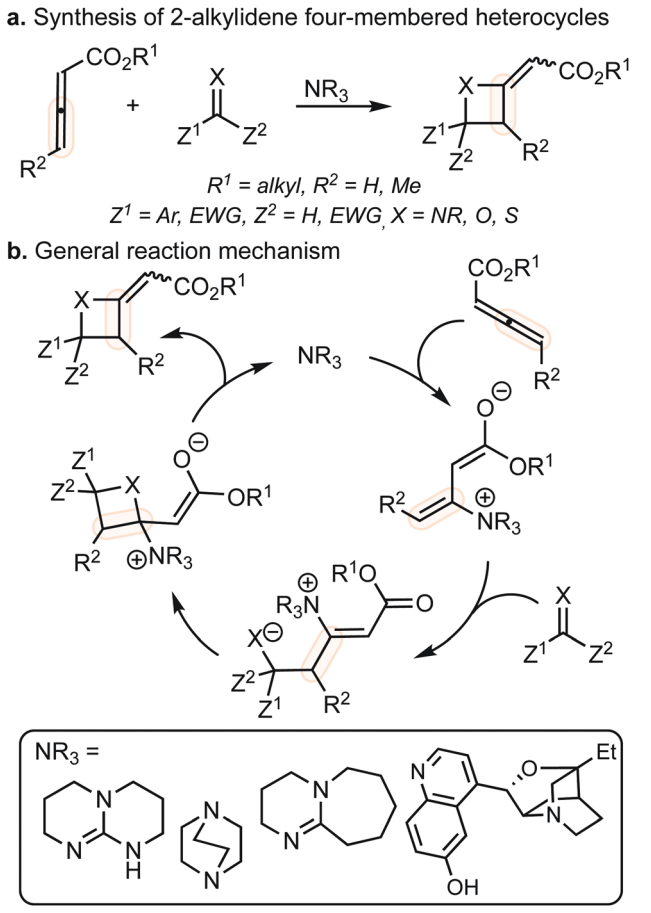


Fig. 23 Four-membered heterocycle formation *via* Lewis base-catalyzed [2 + 2] cycloadditions.

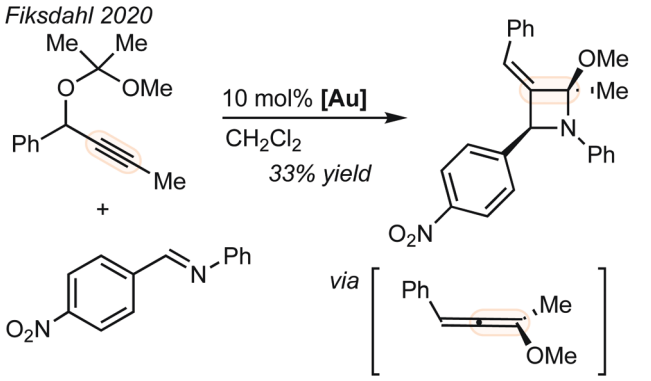


Fig. 24 Azetidine formation *via* Lewis acid-catalyzed [2 + 2] cycloaddition. **[Au]** = [(2-biphenyl)(^{t}Bu)$_2$]PAu(MeCN)SbF$_6$.

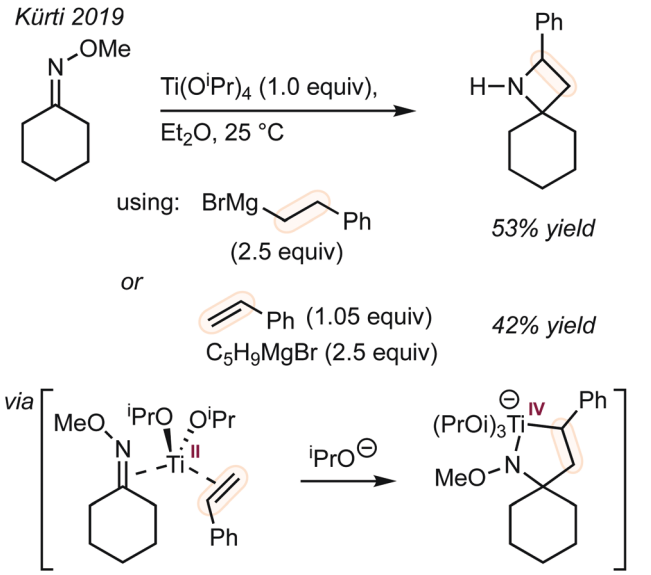


Fig. 25 Azetidine formation *via* Ti-mediated oxidative cyclization.

5. Summary and outlook

Azetidines, oxetanes, and thietanes have valuable structural properties which enable their use in synthetic chemistry and

result in unique biological activities. Cyclization is a key strategy for the synthesis of these four-membered heterocycles. Intramolecular substitution reactions between a heteroatom nucleophile and a γ-positioned leaving group are the most commonly used strategy. Annulations using carbon-based nucleophiles have allowed cyclization to proceed even with significant steric encumbrance. Oxidative cyclizations that build on C–H bond activation methods have emerged and have applications in total synthesis. While these cyclizations typically require stoichiometric amounts of strong bases or other harsh conditions that are scope limiting, these approaches continue to be the most broadly applied.

Ring expansion or contraction methodologies similarly access cyclization precursors by ring opening reactions of three- or five-membered rings, respectively. Notably, insertion reactions of three-membered rings allowed for the consideration of intermolecular processes to synthesize four-membered heterocycles, which makes target heterocycles accessible *via* convergent syntheses. Cyclization strategies using transition metals range from C–H activation, carbene insertion, and installation of heteroatoms.

Photocycloadditions have long existed as prototypical reactions to prepare 4-membered rings although the requirement of powerful, high-energy light sources and limited substrate viability has hindered the application of this approach. The use of transition metal catalysts has aided recent advances and expanded the scope of accessible 4-membered heterocycles. Despite the advances made in this area to access oxetanes and azetidines, thietane production *via* [2 + 2] photocylcoadditions are notably absent likely due to the distinct and non-analogous structural and photochemical properties of thioketones as compared to ketones and imines. Intermolecular Lewis base-catalyzed formal [2 + 2] cycloadditions are complementary methods for synthesizing 2-alkylidene oxetanes, azetidines, and thietanes.

Continued advances in the synthesis and applications of four-membered heterocycles are likely to drive innovation in both biology and synthetic chemistry. Cyclization approaches are anticipated to continue to benefit from developments that install a variety of leaving groups with γ-selective C–H activation as a particularly attractive strategy with potential to render the functionalization, and thus subsequent cyclization, enantioselective. These advances would significantly impact the synthetic accessibility of four-membered heterocycles containing stereocenters from simple precursors. Advances in late transition metal-mediated atom insertions to 3-membered rings also offer opportunities for stereoselective ring expansions using chiral ligand scaffolds.

Recent developments in the design and application of photosensitizers, especially those featuring transition metal ions, have likely only revealed the eve of further activation strategies using light to promote four-membered heterocycle synthesis. Particular promise in this area includes new bond activation approaches driven by mechanistic insights as well as the ability to achieve enantioselective heterocycle construction.

Author contributions

Conceptualization: SKC and VAS; writing – original draft: KPM, SKC, and VAS; writing – review & editing: KPM and VAS.

Conflicts of interest

There are no conflicts to declare.

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