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Strained spiro heterocycles as potential bioisosteres: an update on the synthesis of heteroatom-containing spiro[2.3]hexanes and spiro[3.3]heptanes

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The interest of medicinal chemists in strained spiro heterocycles has continuously risen, given their potential as non-classical three-dimensional bioisosteres, as it has been shown that their inherent structural characteristics can impose beneficial physicochemical properties on lead compounds (*e.g.*, metabolic stability, lipophilicity). In particular, strained spiro heterocycles containing at least one four-membered ring are in demand, as the inclusion of a small ring results in a more rigid and denser molecular space, whereas the inclusion of a heteroatom allows for placement of an exit vector orthogonal to the neighbouring carbon-centered exit vectors. The continuous development of new strained spiro heterocycles, their site-specific functionalisation, and their application as bioisostere is thus imperative. This review provides an overview of progress since 2014 with a particular focus on heteroatom-containing spiro[2.3]hexanes and spiro[3.3]heptanes.

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1. Introduction

Since the introduction of scaffold hopping,[1] escape from flatland,[2,3] and conformational restriction concepts,[4] synthetic chemists have been on a quest to replace classic aromatic building blocks with novel three-dimensional and sp^3-rich alternatives in medicinal drug discovery programs (Fig. 1(A)). To this end, spirocyclic compounds have, over the last two decades, gained particular popularity in medicinal chemistry programs, as their potential for biological activity has been proven by numerous spirocycle-containing natural products so

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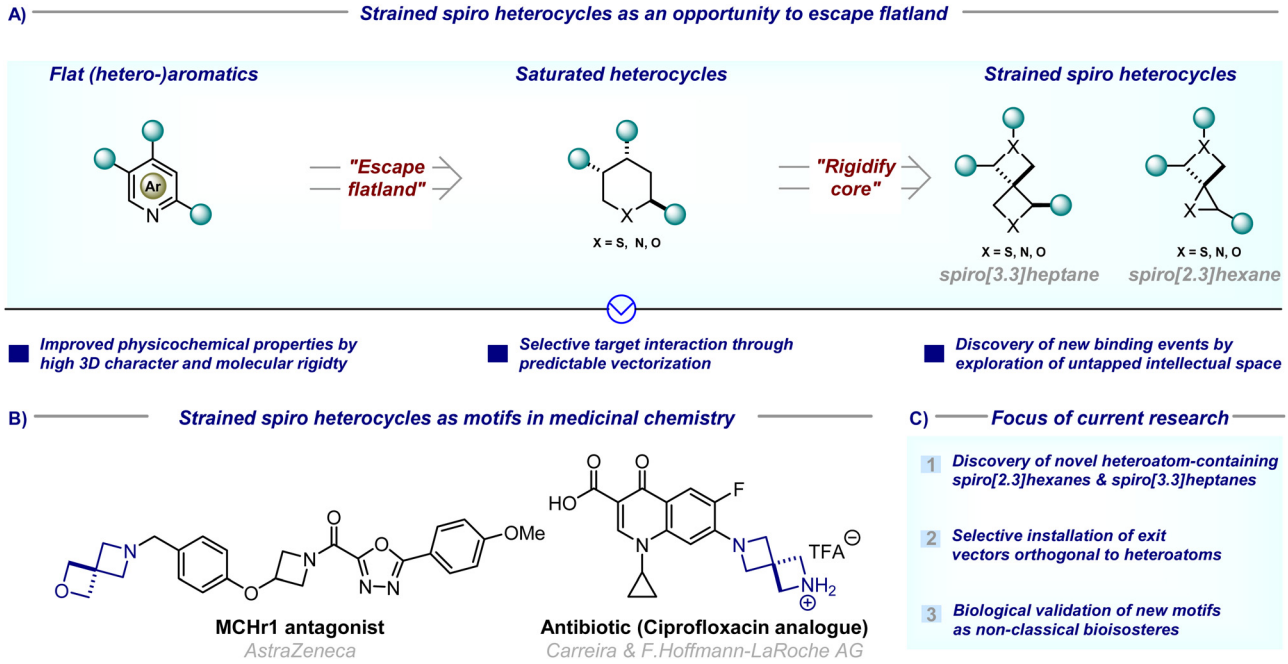

Fig. 1 (A) Strained spiro heterocycles as an opportunity to escape flatland; (B) strained spiro heterocycles as motifs in medicinal chemistry; (C) focus of current research.

their inclusion into lead compounds is imperative.[5,6] Their inherent structural characteristics (high sp^3-fraction, three-dimensionality, good balance between rigidity and flexibility) meet the requirements of modern drug design concepts.[7] In addition, their well-defined exit vectors allow the precise positioning of substituents in three-dimensional space (*cf.* two-dimensional space for flat moieties) which often leads to improved physicochemical properties of lead compounds, including reduced lipophilicity, improved metabolic stability, or enhanced target selectivity.[7]

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Within the broad area of spirocycles, those bearing a heteroatom and at least one four-membered ring are particularly attractive for medicinal discovery campaigns, as the inclusion of a small ring results in a more rigid and denser molecular space, whereas the inclusion of a heteroatom allows for relative facile functionalisation/placement of an exit vector orthogonal to the neighbouring carbon-centered exit vectors.[7] In addition, this novel chemical space is relatively underexplored, allowing the development of novel lead compounds without overlapping with existing patents, thus relieving the challenge of ever-narrowing intellectual property space in drug development.

Spiro[3.3]heptanes containing at least one ring heteroatom have received special attention due to their proven track record as non-classical bioisosteres of saturated heteroatom-containing six-membered rings (Fig. 1(B)). For example, piperidine, piperazine, and oxane are the respectively third, fourth, and seventh-most frequently used ring systems in small molecule drugs so suitable bioisosteric replacement is highly sought after.[8] Given promising initial results,[9–11] significant effort has been devoted to the discovery of new spirocycles, and their application as bioisosteres. In addition, methodologies that allow the installation of exit vectors at positions orthogonal to heteroatoms were particularly sought-after as these are synthetically more challenging compared to the installation of exit vectors off heteroatoms (Fig. 1(C)).

In contrast, heteroatom-containing spiro[2.3]hexanes – the lower homologues incorporating one three-membered ring – have hitherto received comparatively less attention. This is surprising given that they often exhibit similar physicochemical properties, and have the added advantage of populating different, less widely intellectually claimed chemical space.[12]

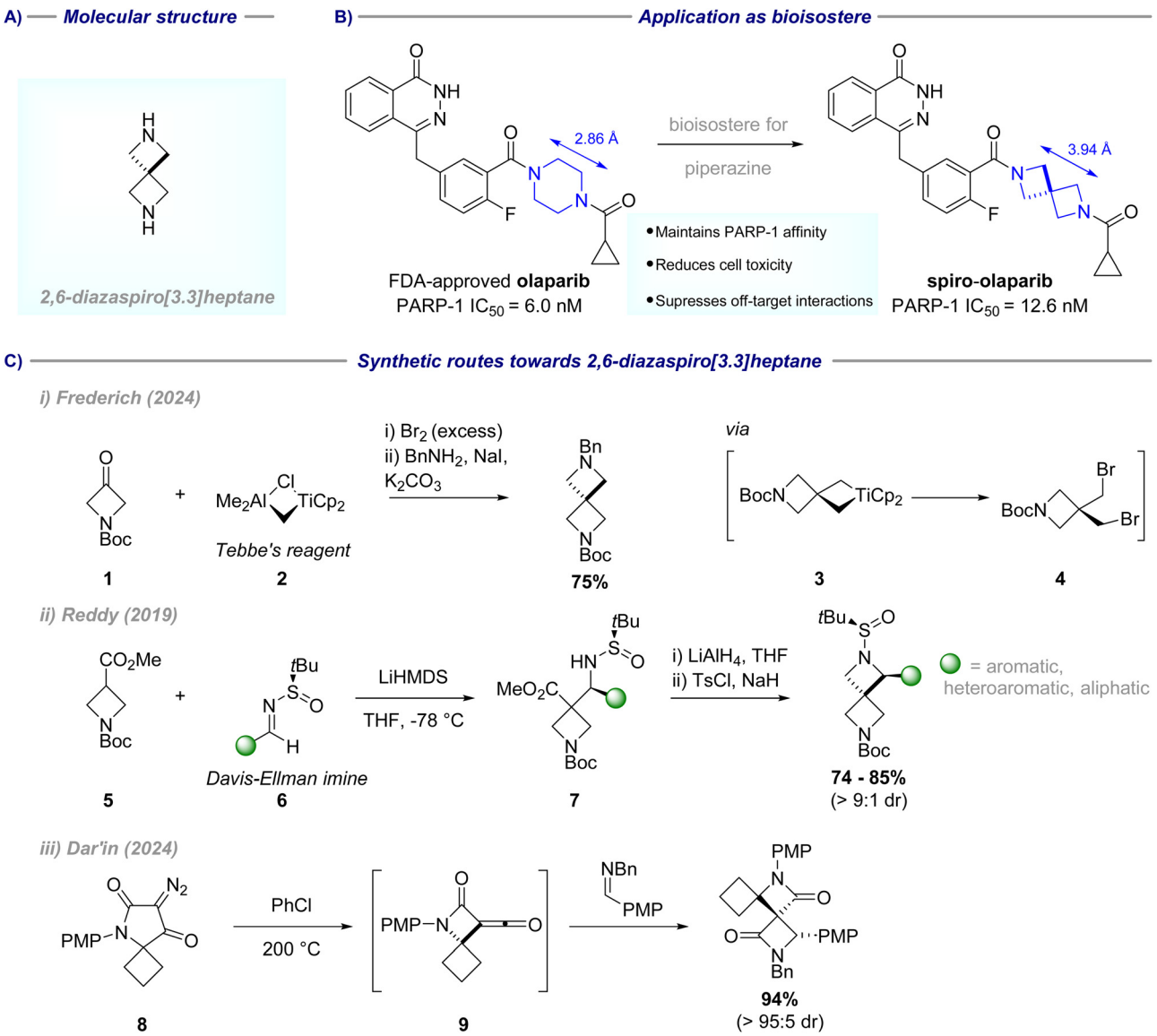
Particularly the incorporation of a cyclopropyl ring – the sixth most common ring in small molecule drugs[8] – can enhance biological target binding due to the decreased conformational flexibility, and increase three-dimensional vector space.[13] In addition, the high ring-strain-induced bond strength renders it stable to oxidative metabolism. The exploration of this chemical space as potential bioisosteres is hence imperative (Fig. 1(C)).

This review thus provides an overview of major advances from the last decade (since 2014) in the synthesis of known heteroatom-containing spiro[2.3]hexanes and spiro[3.3]heptanes, and discusses new spirocycles which have been reported for the first time. Where possible, their use as bioisosteres is highlighted. Given the brevity of this highlight, reports on all-carbon spirocycles are not included, as the use of these motifs as non-classical benzene bioisosteres is discussed in depth elsewhere.[14–16]

2. Discussion

2.1. Spiro[3.3]heptanes

2.1.1. 2,6-Diazaspiro[3.3]heptane. 2,6-Diazaspiro[3.3]heptane (Scheme 1(A)) has found application as a bioisostere for piperazine in medicinal chemistry, and examples with notable benefits have been reported (Scheme 1(B)). For example, the replacement of the piperazine ring in Olaparib with its 2,6-diazaspiro[3.3]heptane surrogate significantly improved target selectivity and reduced off-mechanism cytotoxicity.[17] Given their unchallenged utility, the development of shorter and more effective routes to this motif is an ongoing research area. To this end, Frederich and co-workers report that *N*-Boc azetidinone **1** can be converted into the corresponding 2,6-diazaspiro[3.3]heptane in a scalable telescoped two-step approach (Scheme 1(C)-i).[18] Specifically, treatment of the ketone with an excess of Tebbe's reagent **2** formed a



Scheme 1 (A) Molecular structure of 2,6-diazaspiro[3.3]heptane; (B) application as piperazine bioisostere; (C) synthetic routes towards 2,6-diazaspiro[3.3]heptane.

titanacyclobutane intermediate **3** *via* sequential carbonyl methylenation and alkene cyclometallation. Quench of this intermediate with bromine afforded dihalide **4**, which could be converted to the corresponding azetidine with benzylamine under Finkelstein conditions in 75% yield over both steps on a gram-scale. Given the orthogonality of the protecting groups, selective N-deprotection and functionalisation are feasible.

Although this presents a viable route towards unsubstituted 2,6-diazaspiro[3.3]heptane, the use of Tebbe reagent precludes (asymmetric) functionalisation on the constructed azetidine ring in the same transformation. However, the asymmetric synthesis of substituted 2,6-diazaspiro[3.3]heptanes is desirable for introducing an exit vector orthogonal to the heteroatom substituent. With this objective in mind, Reddy and co-workers reported an asymmetric synthesis of 1-substituted 2,6-diazaspiro[3.3]heptanes in a three-step one-pot approach starting from methyl 1-Boc-azetidine-3-carboxylate **5** (Scheme 1(C)-ii).[19] Enolate formation by LiHMDS and addition to (hetero-) aromatic and aliphatic Davis–Ellman imines **6** afforded sulfinamide **7**. A subsequent reduction/protection/intramolecular substitution sequence afforded the desired spirocycles in up to 85% yield and generally good diastereoselectivity ($>9:1$ dr), even on a multigram scale.

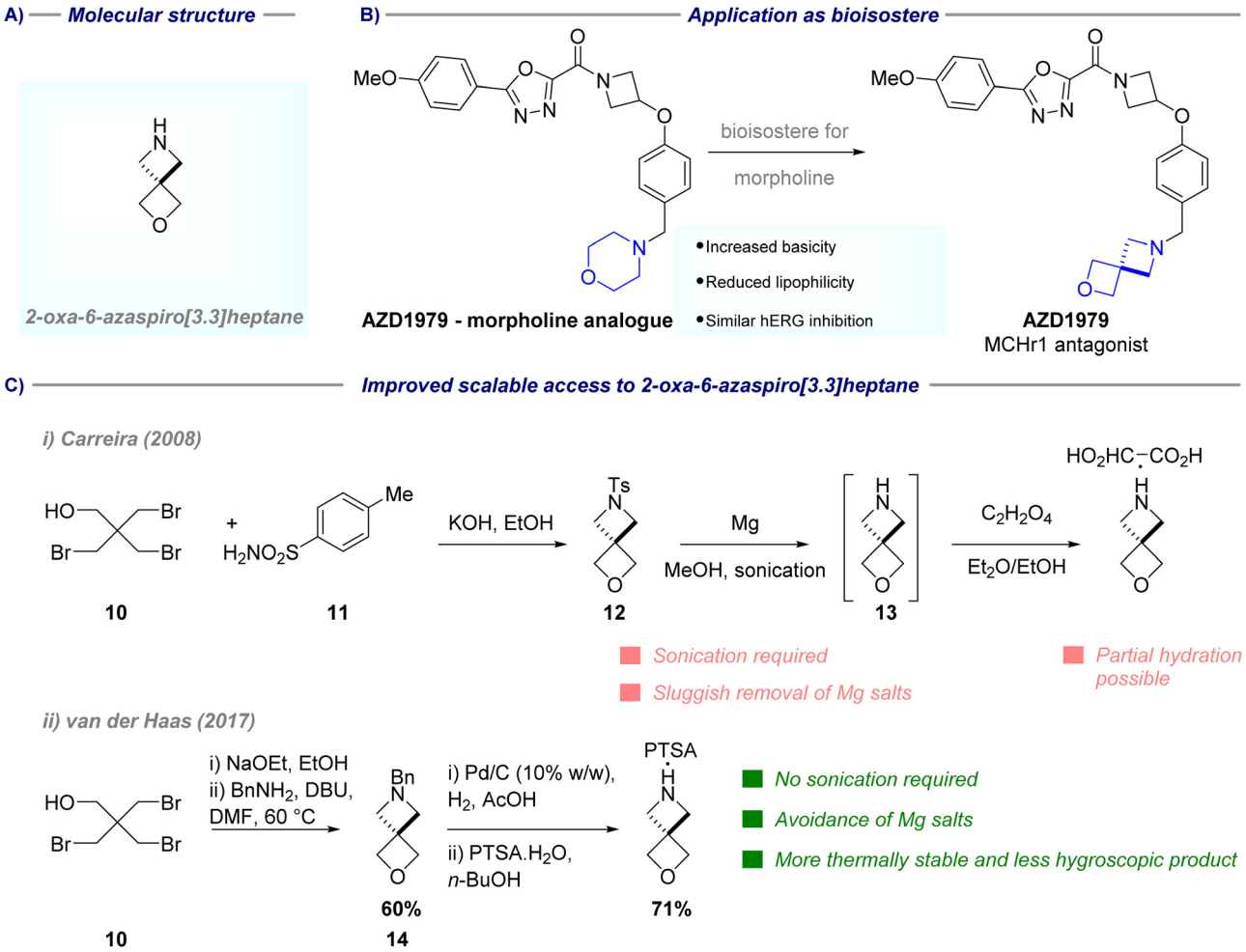
The configurational arrangement of the nitrogen atoms in 2,6-diazospiro[3.3]heptane allows an interesting spirocyclic bis-β-lactam to be conceived. Indeed, Dar'in and co-workers recently reported an attractive cascade to this new sub-class of 2,6-diazospiro[3.3]heptane (Scheme 1(C)-iii).[20] Starting from 3-diazotetramic acids **8**, a microwave-assisted Wolff rearrangement produces the ring-contracted ketene intermediate **9**, which undergoes a Staudinger-type [2+2]-cycloaddition with imines to the desired spirocycle. Notably, the cycloaddition step was found to be highly diastereoselective in most cases ($>95:5$ dr) for the *cis*-products, although the presence of an electron-withdrawing substituent in the imine structure can lead to a decrease in the diastereoselectivity. A series of potentially medicinally useful and synthetically interesting strained and highly substituted bis-spirocyclic motifs are thus accessible in up to 95% yield.

2.1.2. 2-Oxa-6-azaspiro[3.3]heptane. This heteroatom-containing spirocycle has since its introduction by Carreira and co-workers in 2008,[21] become a valuable surrogate for morpholine in several drug candidates and drug-like molecules (Scheme 2(A) and (B)). Most commonly, this spirocycle is prepared by cyclisation of tribromopentaerythritol **10** with *p*-toluenesulfonamide **11** to *N*-tosyl-protected analogue **12**, followed by *N*-tosyl deprotection with magnesium turnings under sonication (to **13**), and oxalate salt formation (Scheme 2(C)-i). Whereas viable on a laboratory scale, this route is faced with several challenges upon scale-up to an industrial scale, including the requirement for sonication, sluggish removal of the magnesium salts formed during *N*-tosyl deprotection, and the presence of partially hydrated oxalic acid in the product, which hampers an accurate determination of the actual content of 2-oxa-6-azaspiro[3.3]heptane oxalate. To address these concerns, scientists at Merachem and Bayer developed a modified route suitable for large-scale synthesis (Scheme 2(C)-ii).[22] Beginning from the same tribromide starting material **10**, the *N*-benzylated 2-oxa-6-spiro[3.3]heptane core **14** is prepared in a two-step telescoped approach by initial intramolecular substitution to form the oxetane, followed by intermolecular substitution with benzylamine and DBU. Debenzylation occurred smoothly using Pd/C (10%) and hydrogen gas (5 bar) to provide the desired spirocycle as its free base, which could be isolated as its PTSA salt. Notably, in contrast to the oxalate salt, this salt was found to be non-hygroscopic and thermally stable, while maintaining high efficiency in further synthetic transformations.

2.1.3. 2-Azaspiro[3.3]heptane. As early as 2010, Careirra and co-workers demonstrated the high potential of aza-spirocycles as medicinal building blocks (Scheme 3(A)).[23] In particular 2-azaspiro[3.3]heptane was introduced as a more water-soluble bioisostere for the piperidine core (Scheme 3(B)).[24] With a view on the substitution pattern present in FDA-approved drugs, 2-substituted piperidines are particularly prominent (*e.g.*, cobimetinib, thioridazine), so that an analogously substituted rigidified spiro-analogue would be a useful addition to the medicinal chemists' toolbox. Indeed, significant effort has been devoted in the last decade to accelerate access to this motif. For example, Mykhailiuk reported a thermal Staudinger [2+2]-cycloaddition between ketene **16**, prepared by chlorination/ketene-formation from cyclobutanecarboxylic acid **15**, and a TMS-imine **18**, prepared *in situ* by treatment of aldehydes **17** with $LiN(TMS)_2$ (Scheme 3(C)-i).[24] The obtained β-lactam **19** could be reduced to the azetidine with aluminium hydride providing the desired 1-substituted spirocycle in 62% overall yield on a 50 g scale. The reaction is tolerant of electronically deficient aromatic imines, heteroaromatic imines, and even aliphatic imines providing the desired spirocycles substituted with medicinally relevant motifs (*e.g.*, cyclopropyl groups, pyridine rings) in generally good yields (56–98% yield).

Building on this work, an asymmetric variant was reported by Reddy and co-workers (Scheme 3(C)-ii).[25] To this end, ethyl cyclobutanecarboxylate **20** was deprotonated with LiHMDS, and the produced anion was quenched with a Davis–Ellman's imine **6**. Subsequent ester reduction, *N*-tosyl protection, and intramolecular substitution afford the spirocyclic azetidine with high diastereoselectivity ($>98:2$ dr) and yield, independent of the electronic nature of the aromatic substituent. Further analogues can be prepared from known 2-azaspiro[3.3]heptane-1-carboxylic acid,[26] by a Minisci-type photoredox-mediated α-heteroarylation of *N*-Boc protected 2-azaspiro[3.3]heptane,[27] or a nickel-catalyzed regio- and enantioselective *syn*-hydrometalative 4-*exo*-trig cyclization of alkynones.[28]

Elaboration on the 2-azaspiro[3.3]heptane scaffold in the last decade focused on the modular diversification of the 5- and 6-position (Scheme 3(C)-iii).[29,30] To this end, three conceptually related approaches were reported by Brown[31] and Tortosa,[32,33] leveraging the functionalisation of the alkene moiety in a cyclobutene precursor **21**. This allowed for the stereoselective diboration, Cu-/Pd-*co*-catalysed arylboration, or Cu-catalysed regioselective monoborylation. Notably, the newly installed

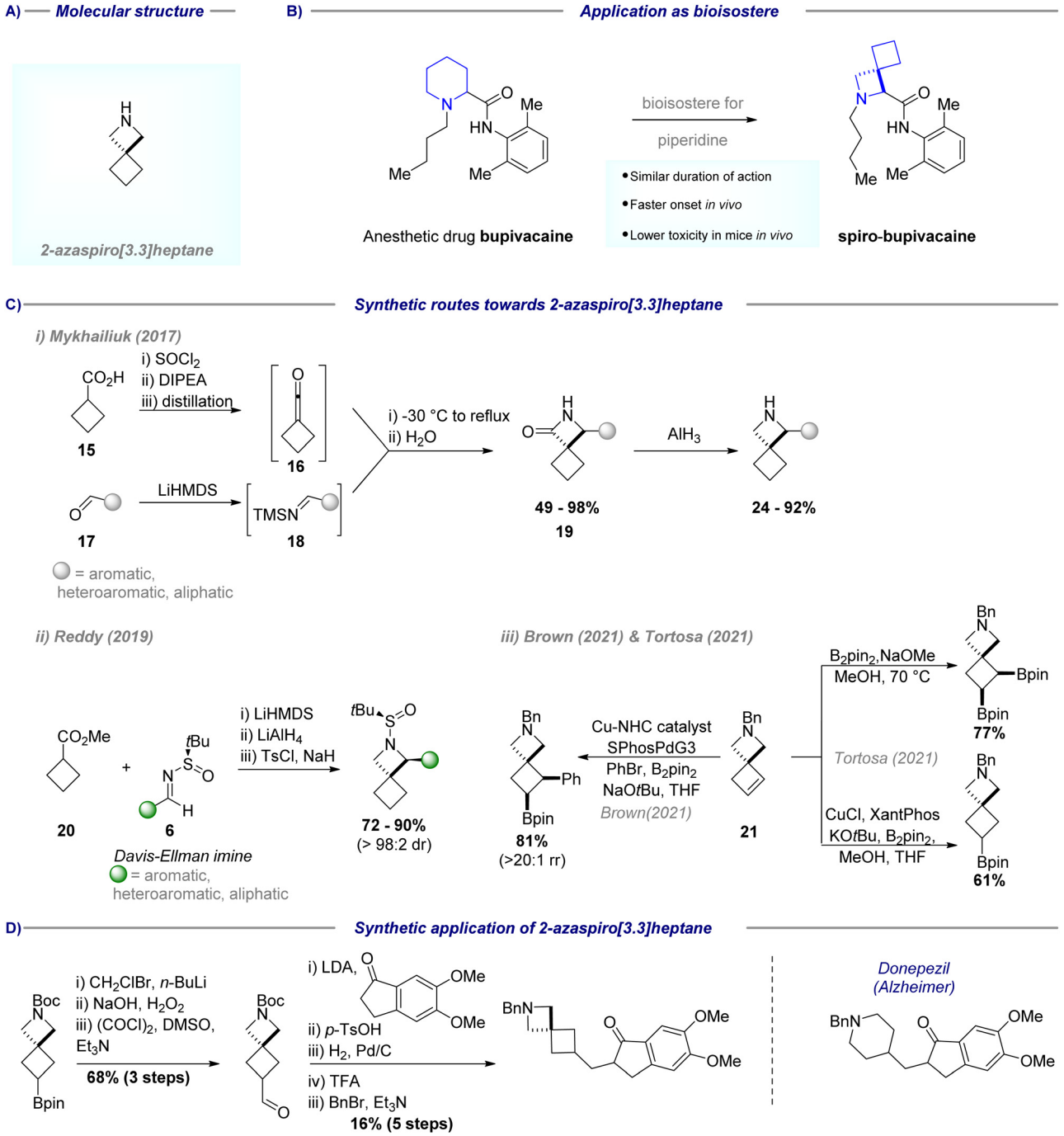


Scheme 2 (A) Molecular structure of 2-oxa-6-azaspiro[3.3]heptane; (B) application as morpholine bioisostere; (C) scalable route towards 2-oxa-6-azaspiro[3.3]heptane.

BPin-motifs served as valuable synthetic handles for further structural diversification, including Suzuki–Miyaura cross-coupling, oxidation, amination, or allyl-group installation. For example, Matteson homologation of the Bpin-group, followed by double oxidation afforded the formylated 2-azaspiro[3.3]-heptane derivative (Scheme 3(D)). A further five-step sequence consisting of Aldol reaction, dehydration, hydrogenation, and N-protecting group interconversion afforded the homospiro-derivative of FDA-approved Alzheimer drug Donepezil; showcasing the synthetic utility of this motif for bioisostere incorporation.

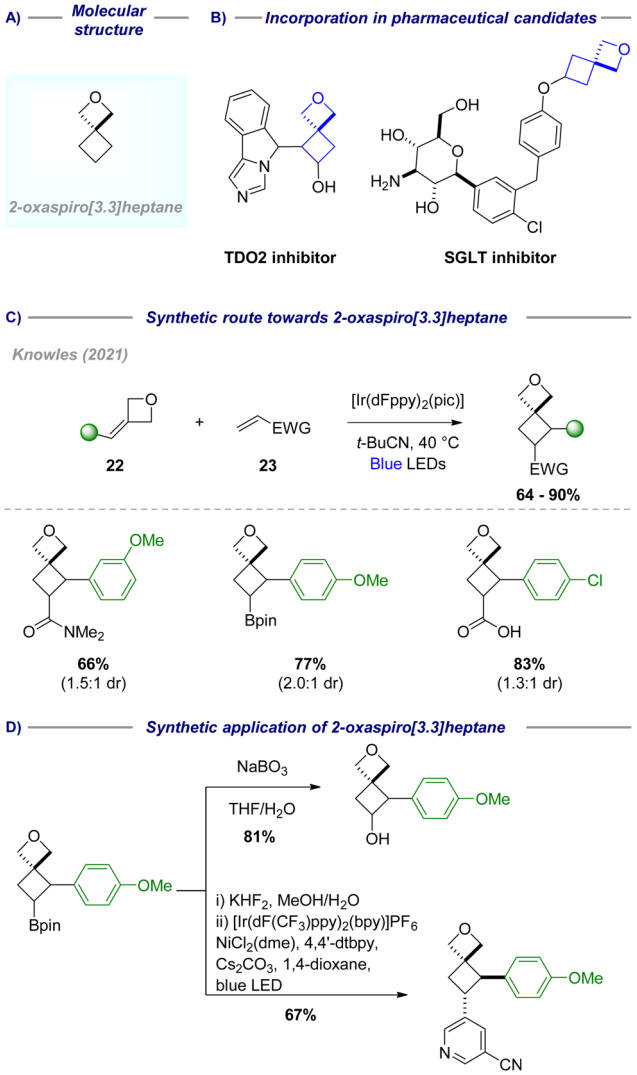
2.1.4. 2-Oxaspiro[3.3]heptane. In 2-oxaspiro[3.3]heptanes the medicinally relevant oxetane core is incorporated into a spirocyclic scaffold, which has also shown unique therapeutic value in a series of drug candidates (Scheme 4(A) and (B)).[34,35] Nonetheless, the currently available medicinal chemistry routes which are reliant on 3,3-bis(bromomethyl)oxetane or 2-oxaspiro[3.3]heptan-6-one as key building blocks, limit the incorporation of substituents around the spirocyclic motif. Leveraging an intermolecular cross-selective [2+2]-cycloaddition between exocyclic arylidene oxetane **22** and electron-deficient alkenes **23** promoted by visible-light triplet photosensitization, this shortcoming was addressed by Knowles and co-workers (Scheme 4(C)).[36] With respect to alkene moiety, vinyl-bearing ketones, esters, amides, Weinreb amides, sulfones, and even unprotected carboxylic acids and Bpin are tolerated. Similarly, electron-rich and electron-poor aromatic and heteroaromatic rings are suitable substituents on the arylidene oxetane to provide the desired bis-substituted spirocycles in typically good yields (64–90% yield), but with only modest diastereoselectivity (*ca.* 1.4 : 1 dr). Particularly the borylated derivatives provided a versatile platform for further synthetic derivatisation (Scheme 4(D)). For example, oxidation of the Bpin-substitutent with sodium perborate affords the cyclobutanol motif, present in TDO2 inhibitor shown in Scheme 4(B) in 81% yield. Alternatively, the Bpin-analogue can be converted into the corresponding BF_3K-salt by treatment with potassium hydrogen difluoride, which can be cross-coupled under nickel-/photoredox catalysis conditions to a pydridyl bromide to afford a drug-resembling derivative. Notably, the 2-oxaspiro[3.3]-heptane is tolerant to these conditions.

2.1.5. 1-Oxaspiro[3.3]heptane. Compared to their constitutional isomer, 1-oxaspiro[3.3]heptane, in which the oxygen atom neighbours the spirocyclic center (Scheme 5(A)), is

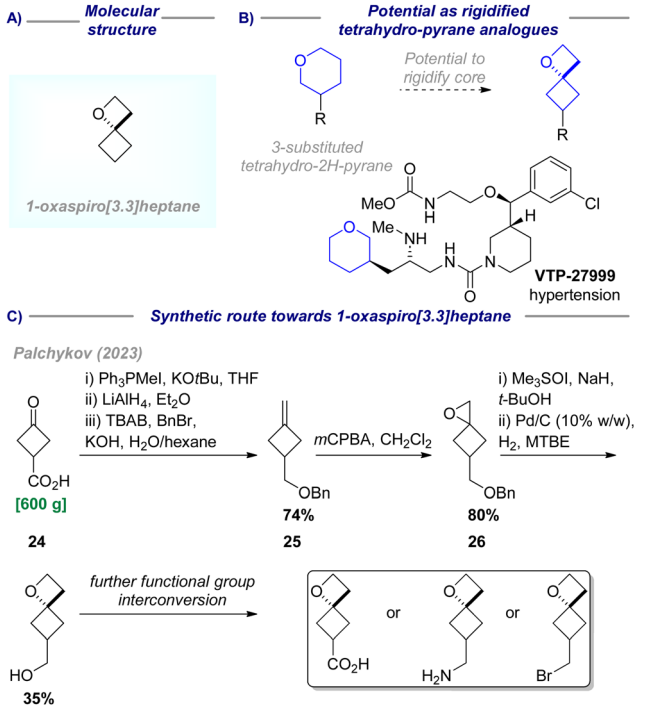


Scheme 3 (A) Molecular structure of 2-azaspiro[3.3]heptane; (B) application as piperidine bioisostere; (C) synthetic routes towards 2-azaspiro[3.3]heptane; (D) synthetic application of 2-azaspiro[3.3]heptane.

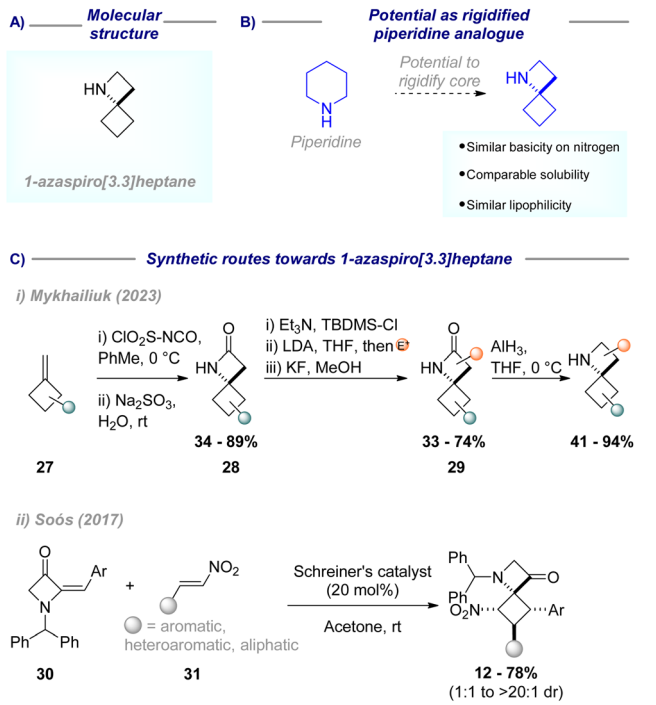
relatively underexplored in the academic literature – both in terms of medicinal exploration, and availability of synthetic methodology. This is surprising, given its incorporation of a medicinally relevant oxetane moiety, and its potential bioisosterism with 3-substituted tetrahydro-2*H*-pyranes, which are incorporated in some bioactive lead compounds (*e.g.*, VTP-27999 as renin inhibitor) (Scheme 5(B)).[37] A scalable, linear six-step route provides access to a 6-methyloxy-substituted 1-oxaspiro[3.3]heptane, which is a platform for the installation of further functionality (Scheme 5(C)).[38] Starting from 3-oxocyclobutane-1-carboxylic acid **24** (>600 g), Wittig olefination, reduction, and benzyl protection provided the exocyclic alkene **25** in 74% yield over three steps. Epoxidation of the alkene with *m*-CPBA provides epoxide **26**, followed by a Corey–Chaikovsky epoxide expansion and benzyl-deprotection to complete the assembly of the desired spirocycle. Although all synthetic steps are robust and scalable, the ring expansion required a reaction duration of six days, somewhat limiting its



Scheme 4 (A) Molecular structure of 2-oxaspiro[3.3]heptane; (B) incorporation in pharmaceutical candidates; (C) synthetic routes towards 2-oxaspiro[3.3]heptane; (D) synthetic application of 2-oxaspiro[3.3]heptanes.



Scheme 5 (A) Molecular structure of 1-oxaspiro[3.3]heptane; (B) potential as tetrahydro-2*H*-pyrane analogue; (C) synthetic route towards 1-oxaspiro[3.3]heptane.



Scheme 6 (A) Molecular structure of 1-azaspiro[3.3]heptane; (B) potential as piperidine analogue; (C) synthetic routes towards 1-azaspiro[3.3]heptane.

practicality. It is interesting to note, that the pendant methanol-moiety could be converted into other medicinally relevant functional groups, including carboxylic acids or amines. A slightly modified route enables access to the cyclobutanol analogue.

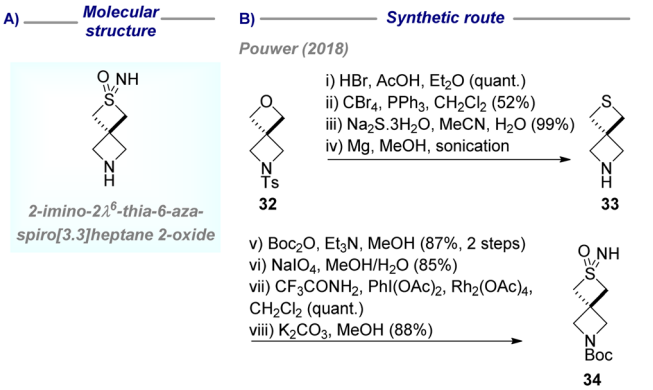
2.1.6. 1-Azaspiro[3.3]heptane. 1-Azaspiro[3.3]heptanes are the aza-analogues of 1-oxaspiro[3.3]heptanes (Scheme 6(A)) and can be considered a new-generation bioisostere of piperidine. Indeed, it has been biologically evaluated and showed similar basicity on the nitrogen atom, similar solubility, and lipophilicity compared to its 2-azaspiro[3.3]heptane isomer, which is a well-studied bioisostere for the piperidine ring (Scheme 6(B)).[39] From a synthetic standpoint, two conceptually distinct routes can be imagined – starting from the cyclobutyl fragment and constructing the azetidine ring or starting from the azetidine ring and constructing the cyclobutyl fragment. Both routes have been investigated in recent years. With regards to the first route, Mykhailiuk and co-workers reported a scalable three-step synthesis commencing from cyclobutanone (Scheme 6(C)-i).[39]

Wittig olefination gave the exocyclic alkene **27**, which smoothly reacted with the Graf isocyanate, ClO_2S–NCO, to afford the spirocyclic lactam **28.** Reduction with aluminium hydride provided the 1-azaspiro[3.3]heptane on a >50 g scale. The sequence is tolerant to a series of aromatic, aliphatic, spirocyclic, and heteroatom-bearing substituents on the cyclobutyl ring. Additional derivatisation to α-substituted lactam **29** on the azetidine ring can be achieved by treatment of the lactam intermediate **28** with LDA, and quenching of the resultant anion with electrophiles, prior to reduction to the azetidine ring.

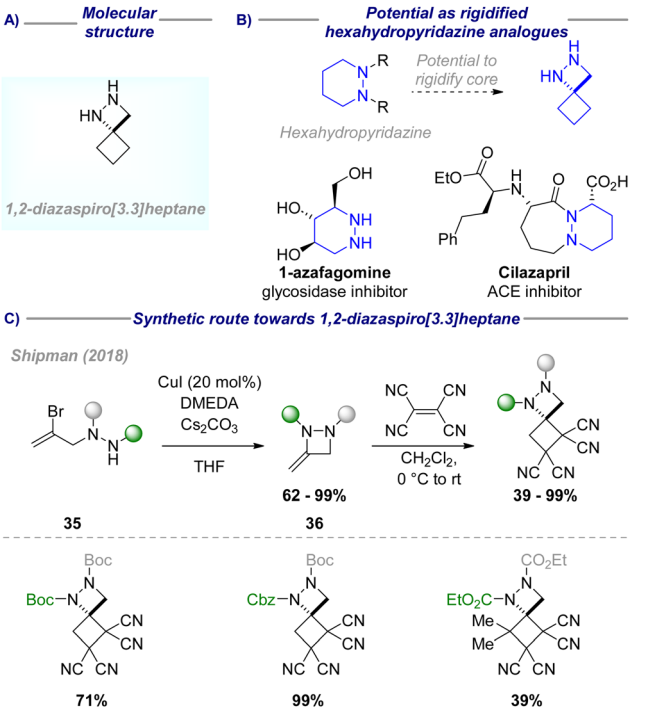
Also, the latter concept commencing from the intact azetidine ring to construct the cyclobutyl moiety has been reported (Scheme 6(C)-ii).[40] In this case, thermal [2+2]-cycloaddition between nitroalkenes **31** and olefin **30**, prepared by a straightforward three-step aldol condensation protocol from azetidinone, provided the desired spirocycles promoted by Schreiner's thiourea catalyst. Good diastereoselectivity is commonly observed for these highly substituted spiro-compounds, and nitro-alkenes substituted with aliphatic, as well as (hetero-) aromatic substituents are suitable reaction partners. Lower yields tend to be observed when the exocyclic alkene is deactivated by substitution with electron-deficient aromatic rings.

2.1.7. Sulfoximine-substituted spiro[3.3]heptanes. Sulfoximines are a relatively recent addition to the common building blocks in medicinal chemistry. With several sulfoximine-containing drug candidates entering clinical trials, the interest in this functional group climbed sharply. This ultimately culminated in the development of the sulfoximine-containing spiro[3.3]heptane **34** as a novel spiro heterocycle for medicinal exploration (Scheme 7(A)).[41] The synthetic route leverages well-established and scalable chemistry, commencing from *N*-tosyl-protected 2-oxa-6-spiro[3.3]heptane **32** (Scheme 7(B)). A four-step route consisting of oxetane opening/bromination/thietane formation and tosyl-group deprotection provides 2-thia-6-azaspiro[3.3]heptane **33**. Further *N*-Boc protection and sulfide oxidation to the sulfoximine provided spirocycle **34**. The free sulfoximine NH provides a useful diversity handle for *e.g.*, Chan–Lam coupling, amidation, sulfonylation, or urea formation.

2.1.8. 1,2-Diazaspiro[3.3]heptanes. Hexahydropyridazine, a six-membered aliphatic heterocycle containing two adjacent nitrogen atoms, is a privileged motif in medicinal chemistry, with several molecules including actinoramide A, cilazapril, and 1-azafagomine exhibiting prominent bioactivity (Scheme 8(B)). Given the promising results obtained by bioisosteric replacement of unstrained aliphatic (hetero-)cycles with their rigidified spirocyclic analogues, the development of a spirocyclic analogue of hexahydropyridazine appears intuitive. 1,2-Diazaspiro[3.3]heptanes (Scheme 8(A)), available from 3-alkylidene-1,2-diazetidines **36**, were suggested as potential rigidified hexahydropyridazine analogues by Shipman and co-workers (Scheme 8(C)).[42] Synthesis of the alkene-bearing 3-alkylidene-1,2-diazetidines **36** is achieved by a copper-catalysed cyclisation of 2-bromo-2-propenyl hydrazines **35** in the presence of *N*,*N*′-dimethylethylenediamine (DMEDA) and



Scheme 7 (A) Molecular structure; (B) synthetic route.

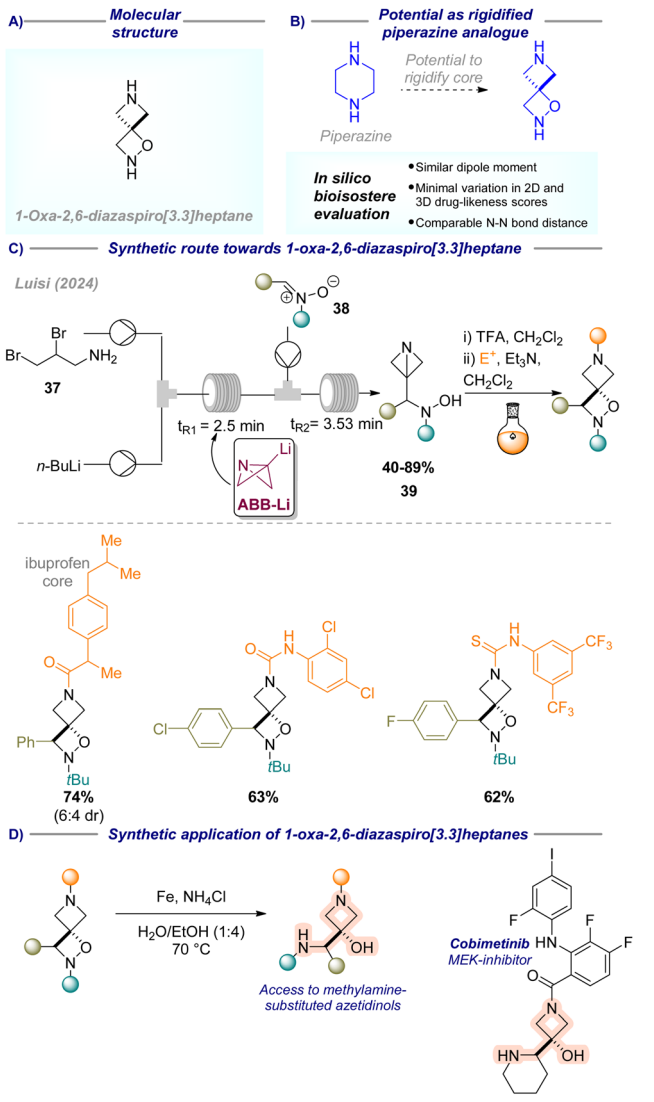


Scheme 8 (A) Molecular structure of 1,2-diazaspiro[3.3]heptane; (B) potential application as rigidified hexahydropyridazine analogue; (C) synthetic route towards 1,2-diazaspiro[3.3]heptane.

caesium carbonate. Notably, this route allows for an orthogonal protecting group strategy on the nitrogen atoms (*e.g.*, Boc and Cbz) for selective deprotection/functionalisation. Subsequent [2+2]-cycloaddition with tetracyanoethylene as the reaction partner under mild conditions affords the desired spirocycles in up to 99% yield, although reaction efficiency is reduced with increasing steric bulk from the N-protecting group and substituents on the exocyclic double bond.

2.1.9. 1-Oxa-2,6-diazaspiro[3.3]heptane. All hitherto presented spiro heterocycles contain a maximum of two heteroatoms in the spirocyclic scaffold. The introduction of a third heteroatom could, however, further (positively) affect desirable physicochemical properties, or open up additional explorable

intellectual property space. To this end, we have recently reported 1-oxa-2,6-diazaspiro[3.3]heptane as a novel potential spirocyclic bioisostere (Scheme 9(A)).[43,44] *In silico* investigations suggested potential bioisosterism for piperazine based on several medicinally relevant descriptors, including dipole moment, N–N bond distance, and 2D-and 3D drug-likeness scores (Scheme 9(B)). Leveraging the advantages of flash chemistry to tame unstable metalated intermediates,[45,46] the spirocycle was assembled by flow-assisted preparation of lithiated ABB (**ABB-Li**) from amine **37** and subsequent addition to aryl nitrones **38** to provide ABB-substituted hydroxylamine intermediates **39** (Scheme 9(C)). Subsequent acid-mediated activation of the ABB bridge-head bond initiates intramolecular spirocyclisation and opportunity for N-functionalisation, thus providing overall three points of derivatisation. A range of electrophiles, including isocyanates, isothiocyanates, or acid chlorides of non-steroidal anti-inflammatory drugs proved suitable for this transformation. In addition to its potential application as a piperazine bioisostere, we demonstrated the core's utility as a valuable synthetic intermediate to access other medicinally relevant motifs (Scheme 9(D)). To this end, the nitrogen–oxygen bond can be cleaved mildly with iron and ammonium chloride in ethanol to afford methylamine-substituted azetidinols – a motif present in *e.g.*, MEK-inhibitor Combimetinib.



Scheme 9 (A) Molecular structure of 1-oxa-2,6-diazaspiro[3.3]heptane; (B) potential application as rigidified piperazine analogue; (C) synthetic route towards 1-oxa-2,6-diazaspiro[3.3]heptane; (D) synthetic application of 1-oxa-2,6-diazaspiro[3.3]heptane.

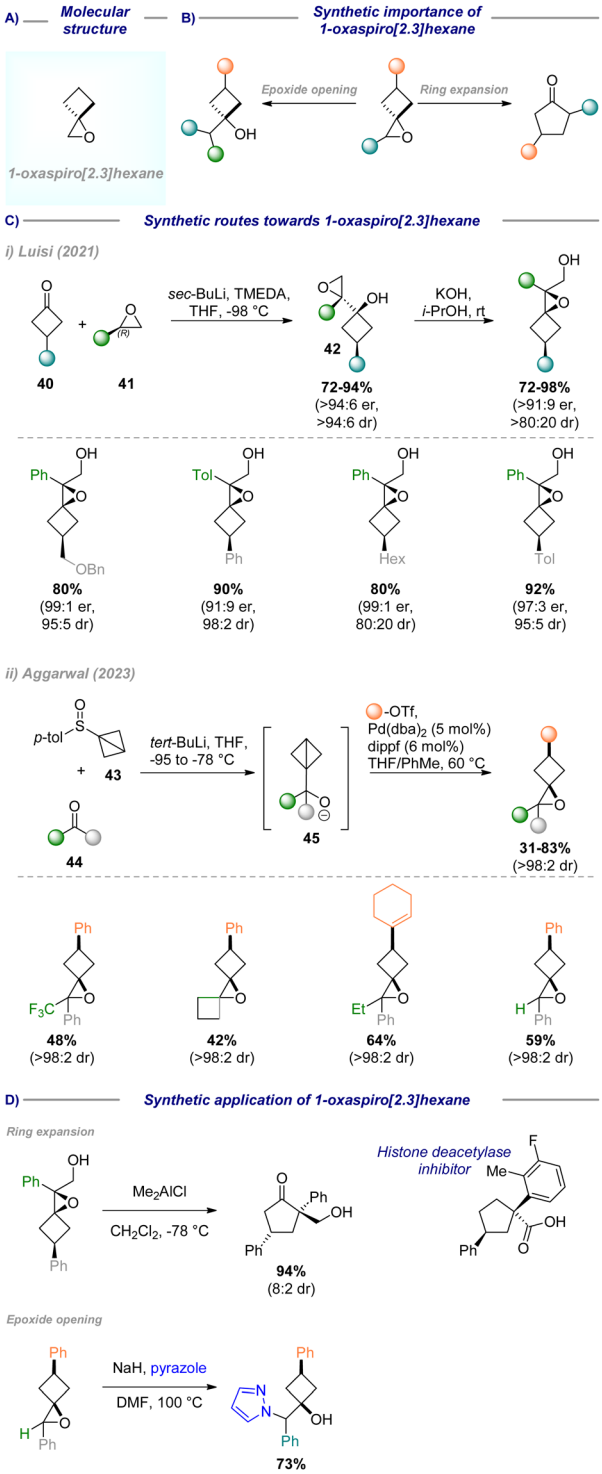
2.2. Spiro[2.3]hexanes

2.2.1. 1-Oxaspiro[2.3]hexanes. 1-Oxaspiro[2.3]hexanes (Scheme 10(A)) are useful intermediates in synthetic organic chemistry for further derivatization into biologically useful and interesting scaffolds (Scheme 10(B)). They are commonly obtained from cyclobutanones by reaction with a carbenoid, or in a two-step olefination/epoxidation sequence. Although convenient, such procedures often lack the flexibility in modularity for the introduction of substituents on the rings or the availability of enantioselective variants. Both issues have in the last decade been addressed.

With regards to enantioselective synthesis, Secci and Luisi reported a sequential nucleophilic addition/Payne rearrangement between cyclobutanones **40** and chiral oxiranes **41**, leveraging the predictable face-stereoselectivity upon the addition of sterically demanding nucleophiles to C3-substituted cyclobutanones (Scheme 10(C)-i).[47] Readily available chiral oxiranes **41** were selectively α-lithiated at the more stable benzylic position using *sec*-BuLi and TMEDA at −98 °C, and subsequently added to C3-substituted cyclobutanones **40** to afford enantioenriched cyclobutanol intermediates **42** (er > 98 : 2) in good to excellent yields (72–94%). A subsequent base-initiated stereospecific Payne rearrangement afforded the desired 1-oxaspiro[2.3]hexanes in up to 98% yield without depreciation of the enantiomeric ratio. A chiral phosphoric-acid catalysed enantioselective rearrangement on alkenylcyclobutanols involving the opening of a bromonium ion was reported by Merino.[48]

The oxirane motif can also be obtained by strain-release of the "spring-loaded" bridge-head bond on bicyclo[1.1.0]butanes (Scheme 10(C)-ii).[49] The required carbinol **45** can be obtained by lithiation of bicyclo[1.1.0]butyl sulfoxide **43** with *tert*-BuLi at −95 °C, followed by addition to ketones or aldehydes **44**. In the same pot, a palladium-catalysed cross-coupling with aryl triflates activates the bridge-head bond for strain-release driven opening by the carbinol **45**, concomitantly forming the oxirane, as well as the new carbon–carbon bond in a *syn*-periplanar arrangement. A wide range of aliphatic and aromatic ketones and aldehydes, as well as aryl-triflates can undergo the desired reaction two-step approach. Although the yield is dependent on the steric and electronic properties of the carbonyl and aryl triflate starting materials (31–87%), excellent diastereoselectivity (typically > 98 : 2 dr) is observed in all cases.

The inherent ring strain of 1-oxaspiro[2.3]hexanes can be exploited for further synthetic derivatisation (Scheme 10(D)). Luisi and co-workers showed that a Lewis acid-mediated ring expansion of their 1-oxaspiro[2.3]hexanes readily affords

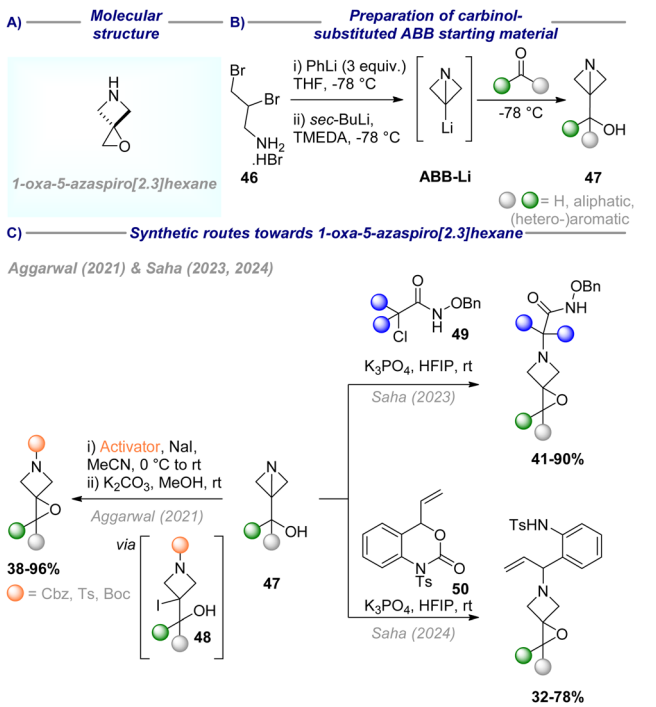


Scheme 10 (A) Molecular structure of 1-oxaspiro[2.3]hexane; (B) synthetic application of 1-oxaspiro[2.3]hexane; (C) synthetic route towards 1-oxaspiro[2.3]hexane; (D) synthetic application of 1-oxaspiro[2.3]hexane.

cyclopentanones in excellent yield and good diastereomeric ratio. The thus obtained substitution pattern resembles closely a known histone deacetylase inhibitor. In contrast, Aggarwal and co-workers exploited the ring-strain of the tri-substituted epoxide towards ring-opening functionalisation (*e.g.*, pyrazole) to afford cyclobutanols with a substitution pattern that would be challenging to obtain from the classic approach of nucleophilic addition to cyclobutanones.

2.2.2. 1-Oxa-5-azaspiro[2.3]hexanes. 1-Oxa-5-azaspiro[2.3]-hexanes (Scheme 11(A)) are the azetidine analogues of 1-oxaspiro[2.3]hexanes which have, given the medicinal community's growing interest in the azetidine ring, received attention from synthetic chemists to enable their efficient construction. Analogous to the assembly of 1-oxaspiro[2.3]hexanes by strain-release driven epoxidation of bicyclo[1.1.0]butanes, their aza-analogues can be obtained by epoxide formation onto the bridge-head bond of azabicyclo[1.1.0]butyl (ABB) fragments. First reported by Aggarwal in 2021, the required carbinol precursors **47** can be obtained by the addition of **ABB-Li**, prepared *in situ* by sequential reaction of amine salt **46** with phenyllithium and *sec*-butyllithium, to aldehydes and ketones (Scheme 11(B)).[50] Although such carbinols are set up to undergo semi-pinacol rearrangements, tuning of the reaction conditions enables selective formation of the desired 1-oxa-5-azaspiro[2.3]hexanes in a two-step approach (Scheme 11(C)). First, the addition of Cbz-Cl (or Boc_2O or TsCl) as an electrophilic activator and sodium iodide promotes the formation of iodohydrin **48** by nucleophilic addition of iodide to the bridge-head bond. Subsequent carbinol deprotonation triggered intramolecular substitution to afford the desired 1-oxa-5-azaspiro[2.3]hexanes in a telescoped one-pot approach within three hours and generally good yields.

Inspired by this reactivity, Saha sought to further extend the diversity-oriented nature of this approach, by introduction of



Scheme 11 (A) Molecular structure of 1-oxa-5-azaspiro[2.3]hexane; (B) preparation of carbinol-substituted ABB starting material; (C) synthetic routes towards 1-oxa-5-azaspiro[2.3]hexane.

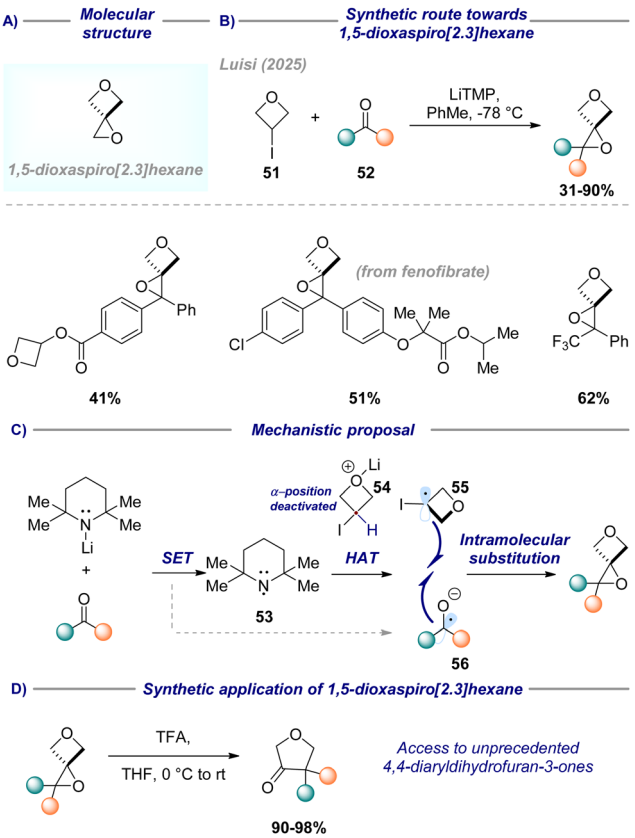
N-functionalisation beyond classical protecting groups (Scheme 11(C)). Thus, building on this approach, they found that the spiroepoxidation/N-functionalisation sequence could be triggered effectively by (aza)oxyallyl cations, generated *in situ* from α-halohydroxamate **49**.[51] Notably, and in contrast to Aggarwal's report, this eliminates the requirement for prior activation of the ABB-core by the formation of an iodohydrin. Various sterically challenging (aza)oxyallyl cations successfully triggered the formation of the desired epoxide in 41–90% yield.

In a further extension of this work, the same authors discovered that also aza-*ortho*-quinone methide, *in situ* generated from vinyl benzoxazinanone **50** by HFIP and K_3PO_4, could serve as an efficient N-activator for the desired sequence.[52] This enables the introduction of an alkene moiety, suitable for further synthetic derivatisation.

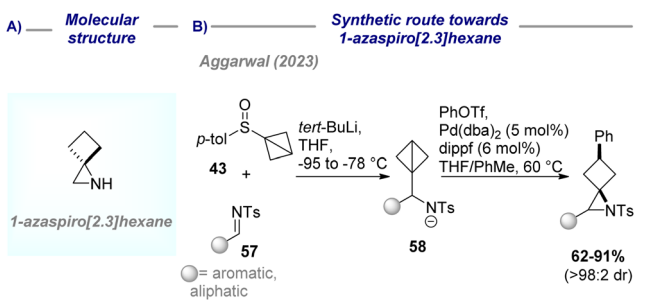
2.2.3. 1,5-Dioxaspiro[2.3]hexanes. Most recently, based on our experience with oxetane functionalisation,[53] we reported the oxetane analogue of 1-oxaspiro[2.3]hexanes (Scheme 12(A)).[54] Access to this motif was enabled by a mechanistically interesting and intriguing regioselective C–H functionalisation of 3-iodooxetane by *in situ* generation of a frustrated radical pair (Scheme 12(B) and (C)). Specifically, treatment of a mixture of 3-iodooxetane **51** and non-enolisable ketones **52** (*e.g.*, benzophenone or trifluoroacetophenone derivatives) with lithium tetramethylpiperidide initiates a single-electron transfer from the amide to the ketone generating an N-centered radical **53** and a ketyl radical anion **56** – reminiscent of a frustrated radical pair. The N-centred radical **53** subsequently acts as a potent hydrogen atom abstractor to selectively abstract the β-hydrogen from 3-iodooxetane **51** (generating radical **55**), initiating an exergonic radical–radical coupling reaction with the ketyl radical anion **56**. This process enables the formation of the desired bond between the oxetane core and benzophenone derivatives, ultimately yielding the novel 1,5-dioxaspiro[2.3]hexane core. The intriguing selectivity for the abstraction of the β-hydrogen from 3-iodooxetane was justified by deactivation of the α-hydrogen by complexation of the ring-oxygen with lithium cations (**54**). A range of non-enolisable ketones afforded the desired epoxides in up to 91% yield, including fenofibrate, a drug for the treatment of abnormal blood lipid levels. With regards to the core's synthetic utility, we demonstrated its stability towards a range of medicinally relevant reaction conditions (*e.g.*, sulfide oxidations, Buchwald–Hartwig conditions, epoxidations). Interestingly, upon treatment with trifluoromethanesulfonic acid, ring expansion to 4,4-diarlydihydrofuranon-3-ones was affected in up to 98% yield; motifs which are otherwise challenging to access.

2.2.4. 1-Azaspiro[2.3]hexanes. Spiro[2.3]hexanes are however not limited to including oxiranes as the three-membered ring, but progress has also been made with a view to incorporate aziridines and cyclopropanes efficiently as three-membered rings. With regards to aziridines, Aggarwal reported a method to access 1-azaspiro[2.3]hexanes (Scheme 13(A)) by extension of his work on 1-oxaspiro[2.3]hexanes.[49] Specifically, BCB-substituted amines **58**, generated by the addition of BCB-Li to imines **57**, could undergo the palladium-catalysed cross-coupling with phenyl triflate with concomitant strain-release driven opening of the bridge-head bond by the amine, concomitantly forming the aziridine, as well as the new carbon–carbon bond (Scheme 13(B)). *N*-Tosyl protected imines generated from aliphatic and (hetero-)aromatic aldehydes underwent the desired reaction in 62–91% yield, and excellent diastereoselectivity in all cases (>98 : 2 dr).

2.2.5. 5-Azaspiro[2.3]hexanes. Cyclopropane-containing spiro[2.3]hexanes have, based on the number of publications discussing this motif, received most attention over the last decade. This is unsurprising given that cyclopropanes are the sixth most common ring found in medicines.[8] In particular, a wide range of methodologies for the synthesis of functionalised



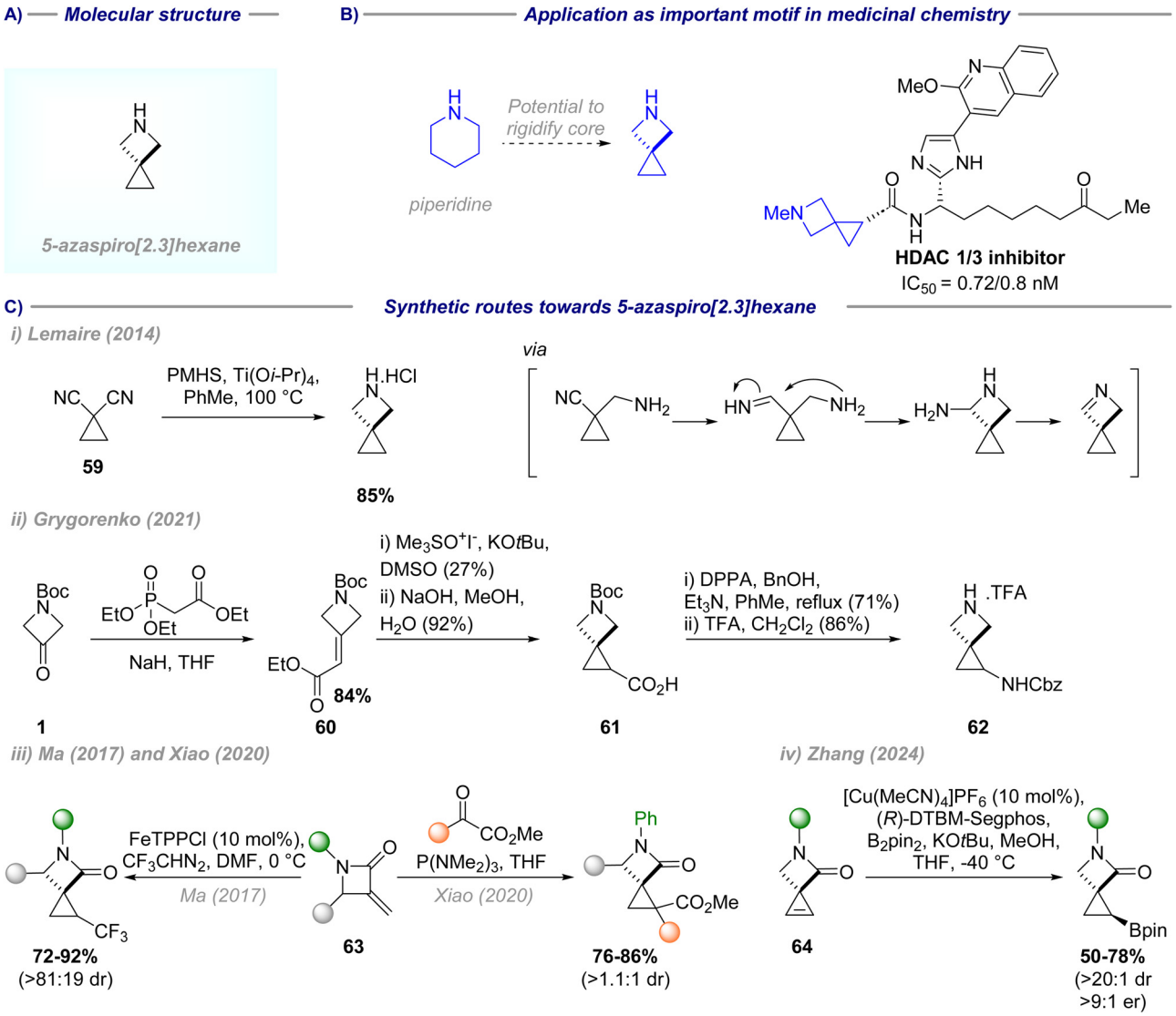
Scheme 12 (A) Molecular structure of 1,5-dioxaspiro[2.3]hexane; (B) synthetic route towards 1,5-dioxaspiro[2.3]hexane; (C) mechanistic proposal; (D) synthetic application of 1,5-dioxaspiro[2.3]hexanes.



Scheme 13 (A) Molecular structure of 1-azaspiro[2.3]hexane; (B) synthetic route towards 1-azaspiro[2.3]hexane.

derivatives of the azetidine-containing 5-azaspiro[2.3]hexane (Scheme 14(A)) have been reported – a motif which has been suggested a potential alternative piperidine bioisostere and already found application in medicinal chemistry (Scheme 14(B)). Its synthesis often relies on the introduction of the cyclopropane moiety leveraging carbene addition onto an exocyclic double bond. Other mechanistically distinct methods have however been reported.[55] For example, Lemaire and co-workers reported a synthesis of 5-azaspiro[2.3]hexane by selective reduction of cyclopropyl-bearing dinitrile **59** (Scheme 14(C)-i). Treatment of this dinitrile with a polymethylhydrosiloxane-Ti(OiPr)$_4$ reducing system afforded the desired spirocycle in 70% after work-up.[56] Notably, the developed reaction conditions also aimed to address common selectivity issues known for related transformations and the corresponding diamines or amino-nitriles were found only in reduced quantities.

Given the demand for motifs containing exit vectors orthogonal to the heteroatom, the synthesis of conformationally frozen *N*-Boc protected amino acid **61** was reported by Grygorenko and co-workers, and further derivatised to the monoprotected diamine analogues – promising leads in the design of new saturated ring bioisosteres and peptidomimetics (Scheme 14(C)-ii).[57] Beginning from commercially available *N*-Boc-protected azetidinone **1** the acid-bearing cyclopropyl moiety in spirocycle **61** was introduced by a three-step sequence consisting of Horner–Wadsworth–Emmons olefination (forming ester **60**), followed by a low-yielding Corey–Chaikovsky cyclopropanation, and hydrolysis. Albeit low-yielding, the method was found to be scalable, affording the 5-azaspiro[2.3]hexane **61** on a 10 g scale. The amino acid **61** could be converted into the monoprotected diamine **62** by a modified Curtius rearrangement and acid-catalysed Boc-deprotection. In a related work, di Fabio and co-workers reported the synthesis of conformationally frozen analogues of L-glutamic acid.[58]



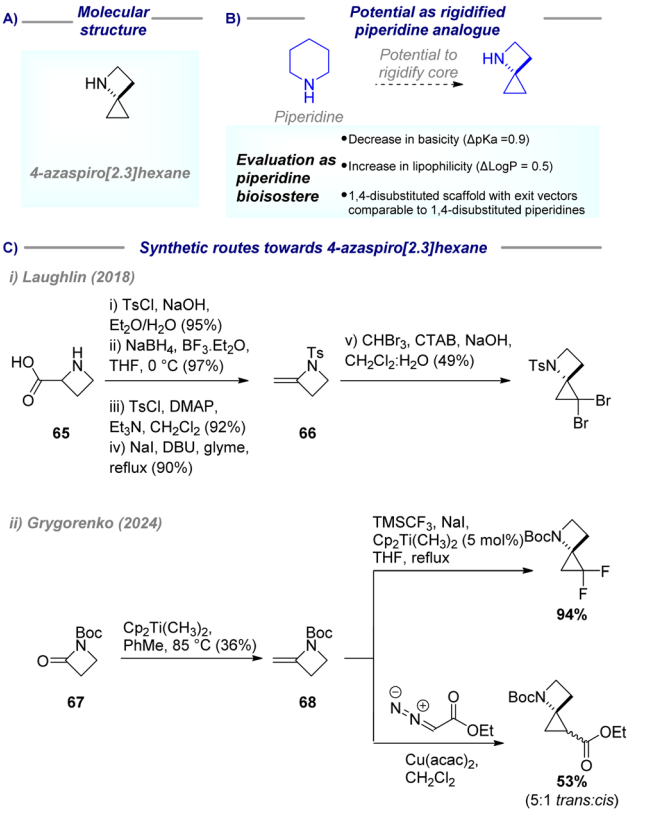
Scheme 14 (A) Molecular structure of 5-azaspiro[2.3]hexane; (B) potential as bioisostere and medicinal importance; (C) synthetic routes towards 5-azaspiro[2.3]hexanes.

Given the importance of the β-lactam scaffold as a privileged structure in drug discovery, also spirocyclic β-lactams have received great interest in the medicinal chemistry community. Thus, also the synthesis of β-lactam-containing 5-azaspiro[2.3]-hexanes has received particular attention in the last decade (Scheme 14(C)-iii). To this end, Ma reported that the desired spirocyclic β-lactam could be obtained by carbene addition onto 3-methylene-1,4-diphenylazetidin-2-one **63**.[59] Specifically, this [2+1]-cycloaddition between azetidine-2-one and unstable 2,2,2-trifluorodiazoethane in DMF catalysed by FeTPPCl (TPP = 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine), which promoted the reaction in up to 89% yield and *ca.* 8 : 2 dr.

Although synthetically viable, the requirement of a relatively high catalyst loading (10 mol%), and a four-fold excess of unstable 2,2,2-trifluorodiazoethane posing a safety risk, mandate the necessity for more scalable, safer and environmentally friendlier procedures for the synthesis of β-lactam-containing 5-azaspiro[2.3]hexanes. Addressing these concerns, Xiao reported a metal-free synthesis of the desired β-lactam-containing spirocycles from the same azetidine-2-one starting material **63** and ketoesters catalysed by tris(dimethylamino)-phosphine at room temperature (Scheme 14(C)-iii).[60] These mild conditions enabled the synthesis of various ester-substituted cyclopropyl-containing spirocycles in 76–86% yield and some preference for the *trans*-diastereomer. Distinct from a classic carbene addition, the mechanism involves the initial formation of the Kukhtin–Ramirez intermediate, formed by oxophilic addition of tris(dimethylamino)phosphine to the ketoesters. This enolate undergoes Michael addition to the α-methylene-β-lactam, followed by 3-*exo*-tet ring-closure to afford preferably the *trans*-spirocyclopropyl β-lactam product to minimize steric hindrance.

Bearing in mind the importance of chirality in drug design, an enantioselective variant for the synthesis of β-lactam-containing 5-azaspiro[2.3]hexanes was recently reported by Zhang (Scheme 14-iv).[61] In contrast to previously discussed methods, the key step did not involve the (enantioselective) construction of the cyclopropyl ring, but instead a desymmetrization of highly strained spirocyclopropenes **64**. These can be prepared by the addition of dibromocarbene to an α-methylene-β-lactam, followed by an elimination/debromination sequence.[62] The enantioselective hydroboration was then achieved by treatment with a copper catalyst (10 mol%), and (*R*)-DTBM-Segphos, a bulky organophosphorus ligand, affording the β-lactam-containing 5-azaspiro[2.3]hexanes in moderate to good yields (50–78%) and high diastereoselectivity (>20 : 1 dr) and good enantioselectivity (>90 : 10 er). Importantly, installation of the BPin-handle allowed for further enantiospecific transformation suitable for late-stage structural diversification, accessing for example the corresponding hydroxy-, allyl-, or phenyl group.

2.2.6. 4-Azaspiro[2.3]hexanes. Most recently, 4-azaspiro[2.3]-hexane, the constitutional isomer of 5-azaspiro[2.3]hexane, has gained traction as a promising, and hitherto overlooked, piperidine bioisostere (Scheme 15(A)). Initial physiochemical profiling by Grygorenko and co-workers showed that the replacement of piperidine with the 4-azaspiro[2.3]hexane motif could decrease

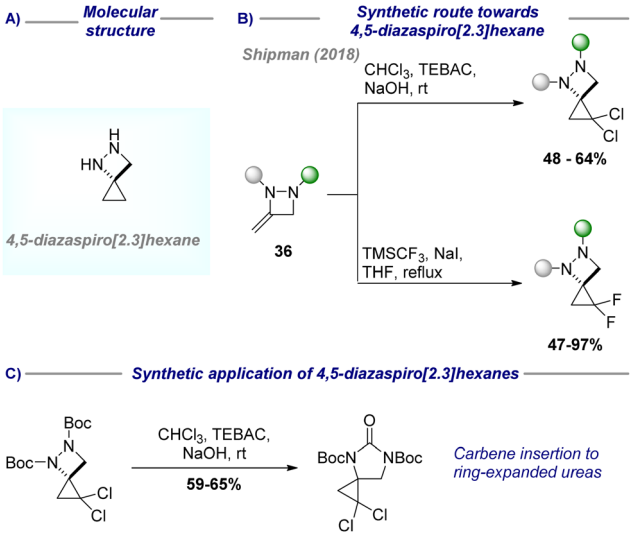


Scheme 15 (A) Molecular structure of 4-azaspiro[2.3]hexane; (B) potential application as rigidified piperidine analogue; (C) synthetic routes towards 4-azaspiro[2.3]hexane.

the parent compound's basicity, and increase lipophilicity (Scheme 15(B)).[63] In addition, exit vector analysis showed that 1,4-disubstituted 4-azaspiro[2.3]hexane scaffold is structurally similar to *trans*-1,4-disubstituted cyclohexanes and 1,4-disubstituted piperidines. The demand for efficient routes to this motif is thus imperative. One sequence to this spirocycle was reported by Laughlin in 2017 (Scheme 15(C)-i).[64] In their developed five-step route, commercially available 2-azetidinecarboxylic acid **65** was *N*-tosyl protected in 95% yield before the carboxylic acid was reduced to the primary alcohol with sodium borohydride. Subsequent *O*-tosylation, followed by base-induced elimination afforded the key enamine **66** on a multigram scale. Last, dibromocarbene insertion by action of bromoform and sodium hydroxide, afforded the dibromo-4-azaspiro[2.3]hexane in 49% yield. Reduction with lithium aluminium hydride afforded the mono-brominated analogue.

Building on this work, Grygorenko and co-workers showed that from the related *N*-Boc protected enamine **67**, difluorinated and ester-substituted cyclopropanes are accessible on a decagram scale by treatment with Ruppert–Prakash reagent ($TMSCF_3$)/Petasis reagent or ethyl diazoacetate/$Cu(acac)_2$, respectively (Scheme 15(C)-ii).[63] Notably, the ethyl ester moiety serves as a handle for the installation of other functional groups, *e.g.*, a free amine group.

2.2.7. 4,5-Diazaspiro[2.3]hexanes. The connectivity in 4,5-diazaspiro[2.3]hexane (Scheme 16(A)) at first appears unusual,



Scheme 16 (A) Molecular structure of 4,5-diazaspiro[2.3]hexane; (B) synthetic route towards 4,5-diazaspiro[2.3]hexane; (C) synthetic application of 4,5-diazaspiro[2.3]hexanes.

yet a straightforward protocol has been reported by Shipman and co-workers (Scheme 16(B)).[42] Analogous to their reported synthesis of 1,2-diazaspiro[3.3]heptanes, their synthesis relies on alkene-bearing 3-alkylidene-1,2-diazetidines **36** as the starting material. Subsequent carbene insertion into the exocyclic alkene by the Ruppert–Prakash reagent $TMSCF_3$ and NaI, or chloroform and under phase transfer conditions, provided the bis-fluorinated or bis-chlorinated cyclopropanes, respectively. Generally, higher yields were observed for the bis-fluorinated products. Interestingly, upon subjection of the cyclopropanes to identical carbene insertion conditions, a hitherto unprecedented ring-expansion to cyclic ureas was observed in good yields; further expanding the access to novel chemical space (Scheme 16(C)).

2.3. Further expected developments and future outlook

Spiro-heterocycles as three-dimensional scaffolds have shown promising results in scaffold-hopping and replacement of flat or non-strained cycles in drug design, due to their well-defined exit vectors, strain-induced reduced entropy and tuneable geometric properties. A number of recently FDA-approved drugs already incorporate well-studied (larger) strained spiro-heterocycles (*e.g.*, revumenib approved by FDA in 2024 as menin-KMT2A PPI inhibitor). Given the promising initial results of recently introduced spiro[2.3]hexane and spiro[3.3]-heptane analogues discussed in this highlight, and their prevalence in the patent literature, we expect further developments in this area to transfer these preliminary results into clinical trials and approved drugs.

To maximise the utility of heteroatom-containing spiro[2.3]-hexanes and spiro[3.3]heptanes in drug discovery, we foresee that several developments are necessary in this field. First, to navigate the crowded intellectual property space, the development of novel spiro[2.3]hexane and spiro[3.3]heptane motifs is imperative. We expect that a particular focus will be placed on motifs incorporating more than two heteroatoms as these are currently relatively underexplored, and provide an opportunity to modulate the geometric constraints, modify exit vector placement, and functionalise with further groups (*e.g.*, on nitrogen). Furthermore, we anticipate that spiro[2.3]hexane and spiro[3.3]heptane analogues with a further reduction in the degree of freedom (*e.g.*, incorporation of unsaturation) will be investigated as these not only further reduce entropy but provide a platform for functionalisation that are precluded for fully saturated analogues. In addition, the development of further enantioselective protocols will be beneficial for drug discovery programs.

From a practical perspective, we anticipate further progress in improving scalability and convergence of protocols to sustain the large quantities required for pre-clinical and clinical trials. We expect that the use of enabling technologies (*e.g.*, flow technology) will support the requirement for more scalable protocols. This will go hand-in-hand with increased commercialisation of such scaffolds for late-stage functionalisation which should catalyse their exploitation and incorporation in compound libraries and drug development campaigns.

Last, the current lack of confidence in which strained spiro heterocycle is suitable for the replacement of classic heterocycles in typical MedChem libraries could hinder its utilization in drug discovery programs. Whereas some bioisosteric replacement is well-established (*e.g.*, oxetane as a bioisostere for dimethyl- or carbonyl-groups), the knowledge base of physicochemical properties of known and novel spiro[2.3]hexanes and spiro[3.3]heptanes needs to be expanded. This would provide a high-confidence guide, which classic two-dimensional or non-strained three-dimensional heterocycle they could replace in initial lead compounds and accelerate their inclusion in building compound libraries around lead compounds. We expect that *in silico*-driven clustering approaches could proof useful in accelerating these investigations to compare the molecular properties (*e.g.*, physico-chemical properties, drug-likeness, shape-related indexes *etc.*) of novel motifs with those of classic heterocycles in typical MedChem libraries.

3. Conclusions

In the last decade, significant progress has been made to tackle the challenges laid out. Several new spiro[2.3]hexane (*e.g.*, 4,5-diazaspiro[2.3]hexane) and spiro[3.3]heptane (*e.g.*, 1-oxa-2,6-diazaspiro[3.3]heptane) motifs were synthesised for the first time. In addition, their applicability as non-classical bioisosteres for saturated heterocycles was investigated, with several cores showing promising initial results for further utilisation (*e.g.*, 4-azaspiro[2.3]hexane as a piperidine bioisostere). Last, significant effort has been devoted to enabling the introduction of orthogonal exit vectors with respect to the heteroatom at various carbon centres along the spiro[2.3]hexane or spiro[3.3]heptane core, which should facilitate selective target interaction for medicinal application by targeted substituent

positioning in three-dimensional space. We have also laid out our expected developments for the near future to aid the utility of these scaffolds in drug discovery.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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