Recent Advances in the Synthesis and Reactivity of Azetidines: Strain-Driven Character of the Four-Membered Heterocycle

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REVIEW

Recent Advances in the Synthesis and Reactivity of Azetidines: Strain-Driven Character of the Four-Membered Heterocycle

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Azetidines represent one of the most important four-membered heterocycles used in organic synthesis and medicinal chemistry. The reactivity of azetidines is driven by a considerable ring strain, while at the same the ring is significantly more stable than that of related aziridines, which translates into both facile handling and unique reactivity that can be triggered under appropriate reaction conditions. Recently, remarkable advances in the chemistry and reactivity of azetidines have been reported. In this review, we provide an overview of the synthesis, reactivity and application of azetidines that have been published in the last years with a focus on the most recent advances, trends and future directions. The review is organized by the methods of synthesis of azetidines and the reaction type used for functionalization of azetidines. Finally, recent examples of using azetidines as motifs in drug discovery, polymerization and chiral templates are discussed.

1. Introduction

Azetidine is a fascinating four-membered nitrogen-containing heterocycle that is an analogue of cyclobutane.[1–5] The majority of the properties of azetidines are driven by the ring strain of approx. 25.4 kcal/mol (Fig. 1).[3] The ring strain of azetidines lies between that of less stable and difficult to handle aziridines (27.7 kcal/mol) and unreactive pyrrolidines (5.4 kcal/mol), which provides a highly attractive entry to bond functionalization by σ-N–C bond cleavage. Furthermore, the unique four-membered ring scaffold of azetidines containing the embedded polar nitrogen-atom represents a privileged motif in medicinal chemistry and appears in bioactive molecules and natural products,[4,5] the most known examples of which are *azelnidipine*, an antihypertensive calcium channel blocker, *cobimetinib*, a mitogen-activated protein kinase inhibitor, or *ximelagatran*, an oral anticoagulant (Fig. 2), in addition to the structurally-related 2-azetidinones best represented by the critically important β-lactams that inherit the reactive properties of the strained four-membered azetidine ring.[6]

Thus, it is not surprising that since its first synthesis in 1888,[1] the chemistry of azetidines has attracted major attention in organic synthesis.[1–5] Although initially azetidines had been regarded as esoteric analogues of aziridines,[1,2] the considerable differences in ring-strain, geometry and reactivity as well as the discovery of azetidine-containing natural products, such as azetidine-2-carboxylic acid[4,5] have resulted in an increased interest in this unique four-membered heterocycle. Recently, many exciting advances in the synthesis, functionalization and application of azetidines have been reported. In particular, the synthesis of azetidines has attracted major interest both (1) as

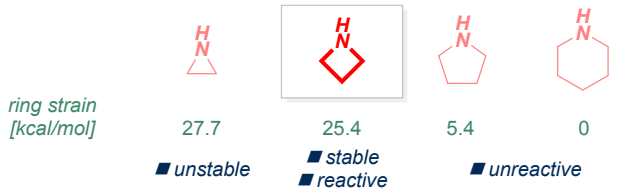

Figure 1 Ring strain [kcal/mol] of azetidines and related heterocycles.

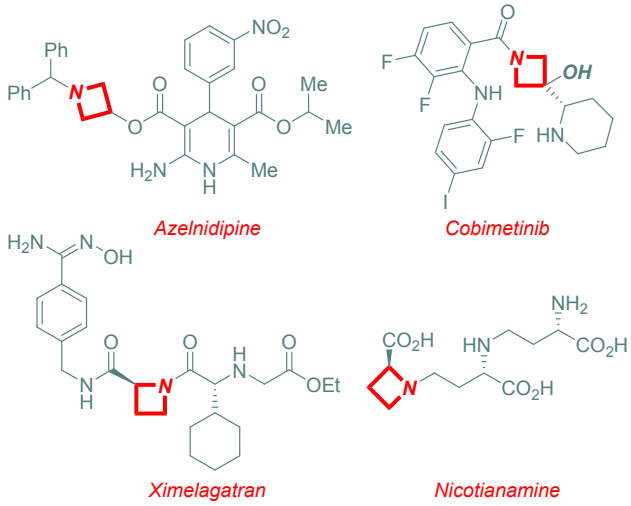

Figure 2 Pharmaceuticals and natural products with azetidine ring.

a novel, unexplored scaffold in organic synthesis, and (2) as a precursor for chemoselective, strain-driven σ N–C bond opening. Thus, the synthesis, functionalization and ring opening of azetidines has been widely studied, including enantioselective, metal-catalyzed, transition-metal-free and reductive methods. Furthermore, numerous applications of azetidines in medicinal chemistry, polymer synthesis and stereoselective synthesis have been reported. In this review article, we provide an overview of the synthesis, reactivity and

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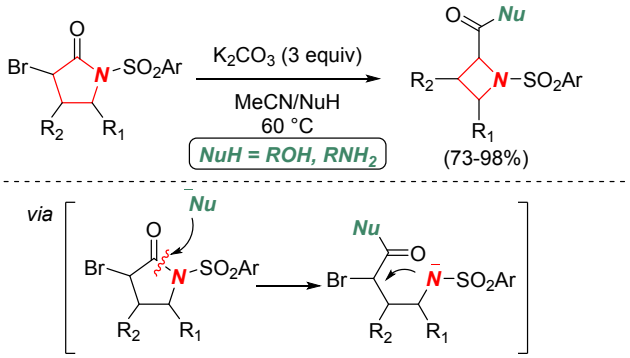


Scheme 1 Synthesis of α-carbonyl-azetidines by ring contraction of 2-pyrrolidinones by Blanc.

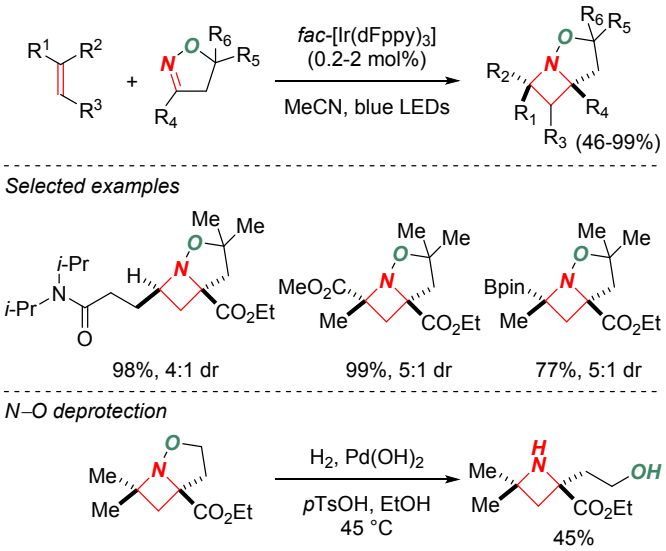
application of azetidines that have been published in the last years with a focus on the most recent advances, trends and future directions. The review is organized by the methods of synthesis of azetidines and the reaction type used for functionalization of azetidines. Finally, recent examples of using azetidines as motifs in drug discovery, polymerization and chiral templates are discussed.

We hope that this review will serve as a useful reference for the organic chemistry audience involved in the synthesis and application of azetidines as well as those interested in expanding their portfolio of nitrogen-containing motifs. Finally, it is our hope that the review will stimulate additional interest in applications of this important four-membered heterocycle by a range of interested chemists.

2. Synthesis

Several important advances have been reported in the synthesis of azetidines, including ring contraction, cycloaddition reactions, C–H activation, coupling with Grignard reagents and strain-release homologation.

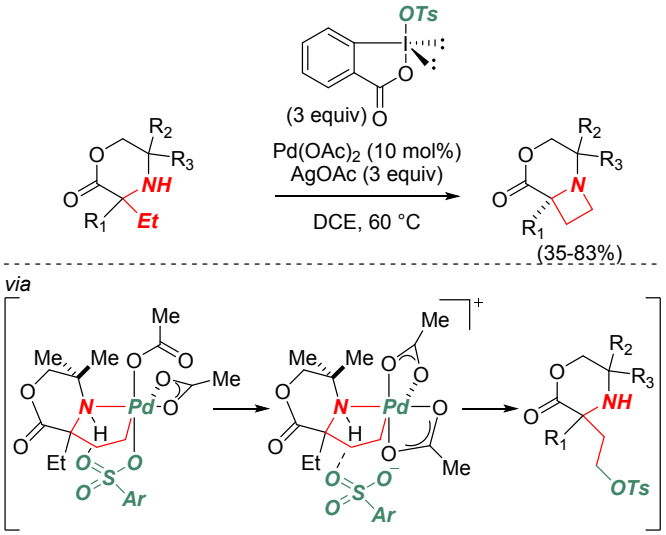
In 2014, the Blanc group reported the synthesis of *N*-sulfonylazetidines via ring contraction of α-bromo-*N*-sulfonylpyrrolidinones (Scheme 1).[7] The proposed mechanism involves nucleophilic addition to the N-activated amide carbonyl group by N–C(O) cleavage[8] to give an α-bromocarbonyl derivative featuring a γ-positioned amide anion. This intermediate undergoes an intermolecular cyclization via an S_N2 mechanism resulting in a formal ring contraction. The authors found that the use of 3 equiv of K_2CO_3 as a base at 60 ˚C for 3 hours in MeCN/MeOH solvent system (9:1 ratio) provided the best yield of the product *N*-sulfonylazetidine using methanol as nucleophile. It is important to note that the method is quite versatile as the starting material could be synthesized via a two-step sequence involving in situ enol ether formation and bromination with NBS, thus providing an efficient entry to α-acylated azetidines using various alcohols and amines as nucleophiles. Subsequently, the same group reported an expanded protocol[9] and an intriguing ring reverse expansion of 2-azetidinyl ynones to pyrrolin-4-ones (see section 3, Scheme 19).[10]



Scheme 2 Synthesis of azetidines by aza-Paterno-Büchi reaction of 2-isoxazoline-3-carboxylates by Schindler.

It should also be noted that important methods for the synthesis of 2-azetidinones have been published, such as Lee's Rh(I)-catalyzed oxygenative [2+2] cycloaddition of terminal alkynes and imines;[11] however, the preparation of lactam heterocycles is beyond the context of azetidine synthesis.

In 2020, Schindler's laboratory reported an intermolecular [2+2] photocycloaddition of 2-isoxazoline-3-carboxylates with alkenes to synthesize azetidines (Scheme 2).[12] In this impressive [2+2] cycloaddition reaction, visible light (blue light) is used to promote an aza-Paterno-Büchi reaction using 2-isoxazoline-3-carboxylates as key oxime precursors. The reaction relies on Ir(III) photocatalyst, *fac*-[Ir(dFppy)$_3$], to activate 2-isoxazoline-3-carboxylates via triplet energy transfer. Mechanistic studies suggested that the singlet excited state is not reactive towards this [2+2] cycloaddition. Alkenes used for this reaction can be activated or unactivated, including hydrogen, alkyl, carbonyl, or aromatic substituents.



Scheme 3 Synthesis of azetidines by intramolecular Pd(II)-catalyzed C(sp^3)–H amination by Gaunt.

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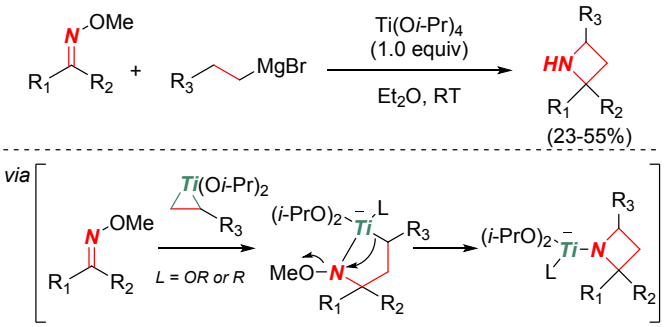
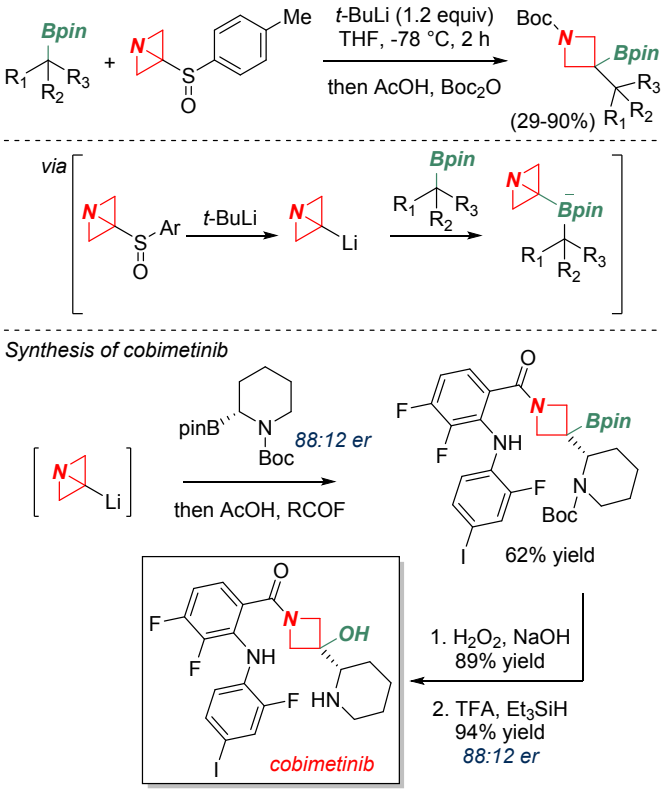


Scheme 4 Synthesis of spirocyclic *NH*-azetidines by intermolecular Kulinkovich-type coupling with oxime ethers by Kürti.

The method is particularly notable for its remarkably broad substrate scope and the potential to construct densely-functionalized azetidines that would be difficult to access by other methods. Importantly, facile N–O scission of isoxazoline[13] permits for deprotection of the azetidine ring nitrogen atom under mild and practical conditions.

In another important development, in 2018, Gaunt and co-workers reported a palladium(II)-catalyzed intramolecular γ-C(sp^3)–H amination for the synthesis of functionalized azetidines (Scheme 3).[14] The key step involves reductive elimination at alkyl–Pd(IV) promoted by the combination of benziodoxole tosylate as an oxidant and AgOAc as an additive. In this mechanism, dissociative ionization of OTs anion from the amino-alkyl-Pd(IV) generates an octahedral Pd(IV) species, which then undergoes displacement at the alkyl–Pd(IV) with tosylate, followed by intramolecular cyclization to form the azetidine ring. The method shows excellent functional group tolerance, while the cyclic six-membered template can be cleaved to reveal functionalized azetidines.

In 2019, Kürti and co-workers reported a Ti(IV)-mediated coupling to synthesize spirocyclic *NH*-azetidines from oxime ethers and alkyl Grignard reagents (Scheme 4).[15] The mechanism was proposed as a Kulinkovich-type pathway.



Scheme 5 Synthesis of azetidines by strain-release homologation of azabicyclo[1.1.0]butanes by Aggarwal.

Thus, two molecules of the Grignard reagent transmetalate with the Ti(IV) complex to give titanium dialkyl species. Next, β-hydride elimination affords titanacyclopropane Kulinkovich-type intermediate. This intermediate reacts with the oxime ether to give the five-membered cyclic complex, which is followed by a loss of the methoxide to form the four-membered azetidine ring coordinated to the titanium. Acidic quench completes the synthesis. The regioselectivity is explained by the insertion of the oxime ether into the weaker terminal carbon–titanium bond. The method provides a synthetically valuable entry to the spirocyclic azetidines using Grignard reagents as coupling partners. Furthermore, the method has been extended to terminal olefins by ligand exchange of the titanacyclopropane intermediate.[15]

In 2019, Aggarwal and co-workers reported an inventive method for the synthesis of azetidine boronic esters by the σ N–C bond cleavage of highly-strained azabicyclo[1.1.0]butanes (Scheme 5).[16] The study follows a related homologation of boronic esters by the σ C–C bond opening of bicyclo[1.1.0]butanes, highlighting the close similarity between cyclobutanes and azetidines.[17] The reaction mechanism relies on a 1,2-metalate rearrangement of the boronate complex generated in the addition of azabicyclo[1.1.0]butyl lithium to a boronic ester. The azabicyclo[1.1.0]butyl sulfoxide electrophile is synthesized in a sequence, including (1) synthesis of azabicyclo[1.1.0]butane, (2) lithiation to form azabicyclo[1.1.0]butyl lithium, (3) addition of methyl 4-methylbenzenesulfinate. This homologation proceeds using *t*-BuLi to generate azabicyclo[1.1.0]butyl lithium, which then

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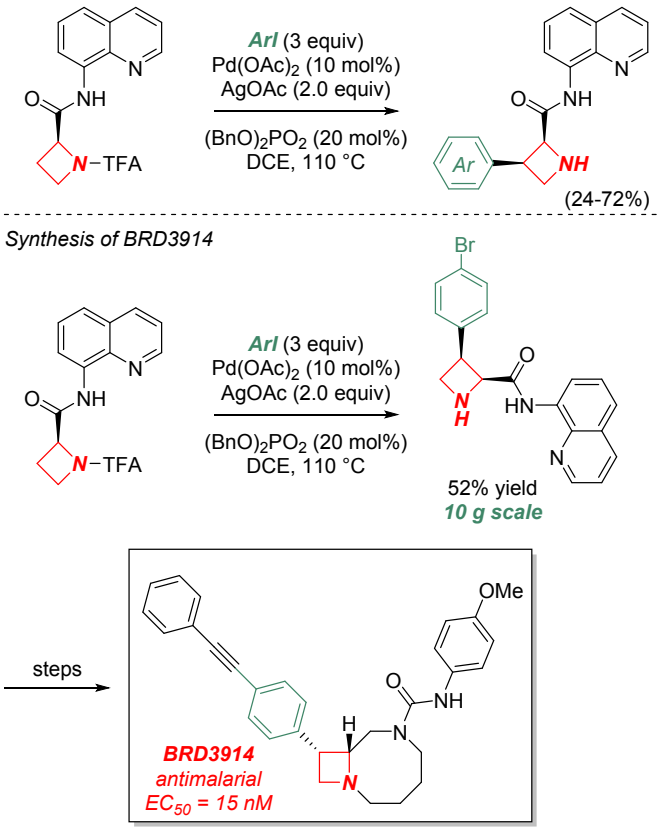
reacts with a borane substrate to generate the boronate complex. Finally, the reaction with two equivalents of AcOH to facilitate B–to–C migration creates a 3,3-di-substituted azetidine salt, which is isolated after Boc protection. Impressively, the scope of this reaction is highly tolerant to various alkyl, vinyl and aryl boronic esters, providing access to a wide range of functionalized azetidines. The authors highlighted the efficiency of this novel strain-release approach in the facile enantioselective synthesis of *cobimetinib*, a selective kinase inhibitor centred on the azetidine ring (see also Fig. 2).

3. Functionalization

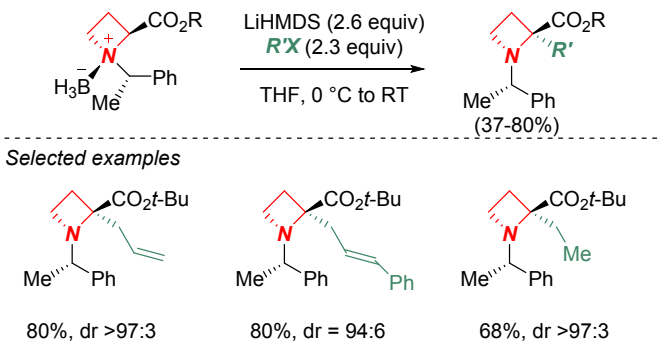
Another approach that has experienced rapid progress is direct functionalization to furnish more complex azetidine derivatives and related methods. Recent advances in this area include direct and stereoselective C(sp^3)–H functionalization, diastereoselective alkylation, chemoselective displacement, direct lithiation and acylation.

In 2017, the Schreiber group reported a novel method for C(sp^3)–H arylation of azetidines as part of their studies on the total synthesis of bicyclic azetidines with antimalarial activity (Scheme 6).[18] The reaction relies on 8-aminoquinoline as a directing group and N-TFA protection of the azetidine ring. The optimized conditions involve $Pd(OAc)_2$ (10 mol%), AgOAc (2 equiv) and $(BnO)_2PO_2H$ (20 mol%) in DCE at 110 °C. The role of phosphate is presumably to act as a phase-transfer catalyst. The arylation is *cis*-stereoselective, providing broad substrate scope including heterocyclic iodides. Importantly, the TFA protecting group can be removed in situ using NH_3 in MeOH, furnishing free *NH*-azetidines. The method was then exemplified in the synthesis of an antimalarial compound, featuring a bicyclic azetidine as a key motif. The C(sp^3)–H arylation methodology was later expanded to C3-arylation of pyroglutamic acid derivatives.[19] Furthermore, this class of bicyclic azetidines has been exploited in performance-diverse libraries[20] and identified as promising lead compounds for the treatment of cryptosporidiosis, highlighting a considerable potential of the less explored azetidine-containing bioactive motifs.[21]

In 2018, the Tayama laboratory reported borane-promoted diastereoselective α-alkylation of *N*-borane-azetidine-2-carboxylic acid ester complexes (Scheme 7).[22] This α-alkylation can be promoted by different bases, including LDA, LiTMP, LiHMDS, or KHMDS. Yields and diastereoselectivity are high using allyl, cinnamyl, methyl, ethyl and acyl electrophiles. The *N*-azetidinyl borane complex is formed by the reaction of azetidine with BH_3-SMe_2 as a single diastereoisomer in greater than 90% yield. The reaction is proposed to proceed via stabilization of the formed lithium enolate by another molecule of LiHMDS, wherein it coordinates to the borane and blocks the *Si* face of the azetidine. This method provides a valuable access to chiral building azetidine-building blocks by chirality transfer from 1-phenylethylamine.



Scheme 6 Cis-stereoselective C(sp^3)–H arylation of azetidines with aryl iodides by Schreiber.



Scheme 7 Diastereoselective α-alkylation of azetidine 2-carboxylic acid esters by Tayama.

In 2020, Wang and Duncton reported a single-step method for the synthesis of azetidine-3-amines by the selective displacement of the 3-OMs group with various amines (Scheme 8).[23] In this method, the starting material is either commercially-available or readily prepared from 1-benzyhydryl-3-azetidinol. This highly practical reaction is performed using 1.0 equiv of the amine and 1.0 equiv of *i*-Pr_2NEt in MeCN at 80 °C. Alternatively, 2.0 equiv of the amine could be used in the absence of *i*-Pr_2NEt. The method is broad in scope, including aromatic, aliphatic, heterocyclic, primary and secondary amines as well APIs, such as fluoxetine or sertraline, which allows for a rapid introduction of azetidine template into biologically-active amines.

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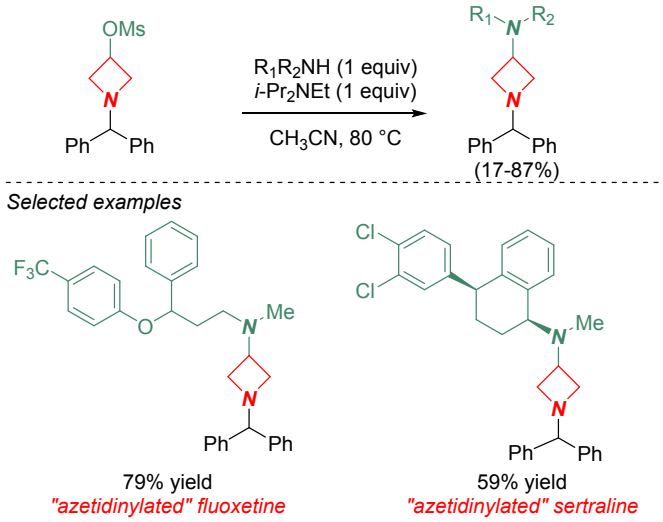
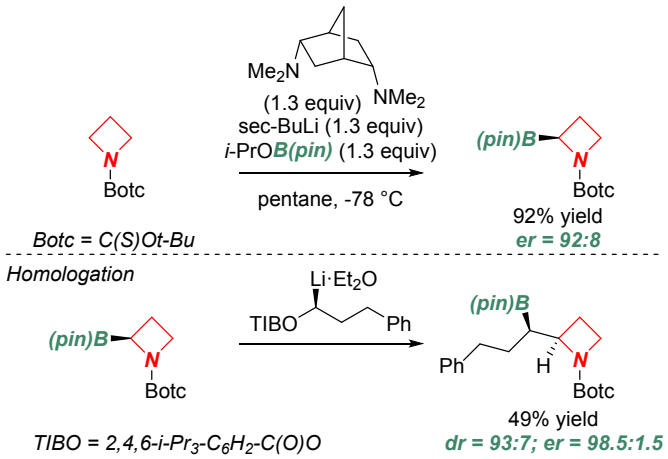


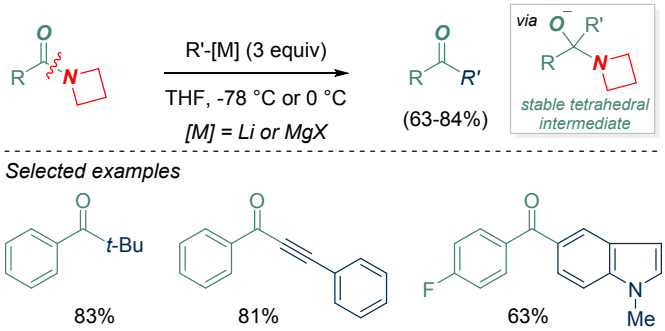
Scheme 8 Single-step synthesis of 3-azetidinyl amines by Duncton.



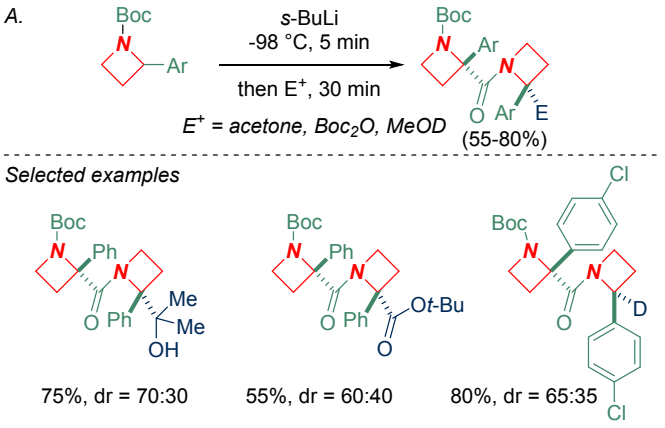
Scheme 9 Homologation of azetidin-2-yl boronic ester by Hodgson.

In 2019, the Hodgson group reported the synthesis and homologation of azetidin-2-yl boronic ester (Scheme 9).[24] To synthesize the target α-boryl azetidine, N-Botc (Botc = *tert*-butoxythiocarbonyl) azetidine was reacted with *sec*-BuLi in the presence of chiral DIANANE ligand and *i*-PrOB(pin) in pentane at -78 ˚C to afford the desired product in 92% yield with 92:8 er. Next, the reaction with triisopropylbenzoyloxy organolithium reagents afforded homologated boronic esters with excellent diastereoselectivity. Both diastereoisomers can be obtained with excellent er, depending on the matched/mismatched configuration of the α-boryl azetidine and organolithium. Mechanistic study on the configurational stability of α-lithiated N-Botc azetidines has been reported.[25] These studies add to the growing arsenal of reactions of metalated azetidines, which open new possibilities in azetidine functionalization.[26]

In 2016, our group reported the synthesis of ketones by the addition of organometallics to N-acyl-azetidines (Scheme 10).[27] In this reaction, N-acyl-azetidines form stable tetrahedral intermediates owing to the combined effect of half pyramidalization of the amide bond nitrogen atom (approx. 33°; Winkler-Dunitz χ_N pyramidalization)[28] and the large strain of the ring (ca. 25.4 kcal/mol), which collectively decrease the aptitude



Scheme 10 Synthesis of ketones from N-acyl-azetidines by stable tetrahedral intermediates by Szostak and co-workers.



Scheme 11 (a) Synthesis of azetidine-based peptidomimetics by Luisi and co-workers; (b) Functionalization of 2-oxazolinylazetidines by Luisi, Degennaro and co-workers.

to collapse after addition of magnesium or lithium organometallics. The scope of the method is broad and accommodates various alkyl, aryl, heteroaryl and alkynyl nucleophiles and azetidines. It is noteworthy that the addition is selective over less electrophilic Weinreb amides, which results in a new class of azetidinyl-based, bench-stable reagents for acyl transfer reactions.

It is also worth noting the recent excellent progress in the concept of "strain-driven" character of azetidines expanding the portfolio of this important heterocycle in lithiation of N-Boc-2-arylazetidines with the *ortho*-directing effect for regioselective functionalization and self-condensation, which allows access to azetidine-based peptidomimetics (Scheme

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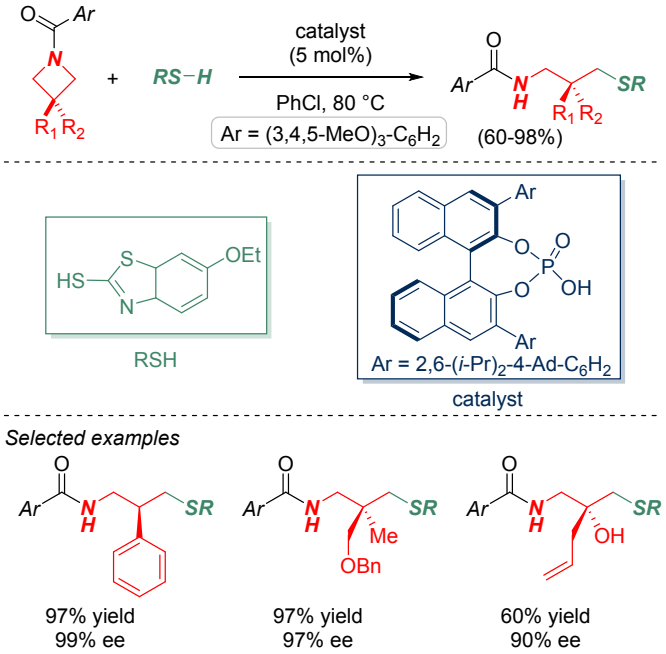
11A)[29] as well as a method for highly stereoselective addition of organolithium reagents to N-alkyl-oxazolinylazetidines followed by acidic hydrolysis of the resulting oxazolidine intermediates, which affords enantioenriched N-alkyl-2-acylazetidines without racemization (Scheme 11B).[30] These reactions advance the synthetic access to functionalized azetidines by utilizing this four-membered ring as a template building block.

4. Opening

Although ring opening of aziridines has been established as one of the most important reactions in organic synthesis,[31] a similar N–C σ bond cleave of less strained azetidines is dramatically behind their three-membered congeners.[1,2] Recent studies demonstrate several highly promising avenues to develop a broad arsenal of N–C bond cleavage reactions of azetidines, including enantioselective desymmetrization, regioselective opening with carbon and fluorine nucleophiles, ring expansion reactions and reductive σ N–C bond cleavage.

In 2015, the Sun group reported an enantioselective desymmetrization of azetidines using thiols as nucleophiles and a BINOL-type chiral phosphoric acid as a catalyst (Scheme 12).[32] Azetidine ring is activated towards the opening by acylation with 3,4,5-trimethoxybenzoyl group. The catalyst is used at only 5 mol% loading. Although thiols are limited to 2-mercaptobenzothiazole derivatives, the method affords the desymmetrized ring opening products with excellent ee of >90%. The substrate scope of azetidines is also very broad and includes alkyl, aryl, ethers, amines or thioethers. Another advantage is rapid deprotection of the benzothiazole unit to give more synthetically useful thioesters by alkoxide substitution. Mechanistically, the authors proposed that the reaction proceeds by O–to–N switchable activation of the azetidine ring by the chiral phosphoric acid under the Curtin-Hammett principle. It is further interesting to note that the bulky phosphoric acid catalyst featuring a distant adamantly group, namely 2,6-(*i*-Pr)$_2$-4-(Ad)-C$_6$H$_2$, introduced by List in 2008[33] proved superior in this transformation. This efficient method was later expanded to the catalytic enantioselective desymmetrization of azetidinium ions with thiols using SPINOL-type chiral phosphoric acid catalyst.[34]



Scheme 12 Catalytic enantioselective desymmetrization of azetidines with thiols by Sun.

In 2018, the May group outlined an intriguing method for regioselective, transition-metal-free opening of azetidines with organotrifluoroborates under exceptionally mild conditions (Scheme 13).[35] The reaction works efficiently for 2-aryl-substituted N-tosyl-azetidines and a variety of organotrifluoroborates, including vinyl, alkynyl and aryl. This process is triggered by a combination of $LiClO_4$ (0.5 equiv) and $(n\text{-Bu})_4NHSO_4$ (0.5 equiv), which are proposed to generate $LiHSO_4$ in situ. Azetidine is activated towards the opening by N-H and O–Li coordination to give a carbocationic intermediate that is intercepted by the organotrifluoroborate nucleophile. The reaction highlights the capacity of azetidine α N–C bond opening under mild, transition-metal-free conditions to forge new C–C bonds on a pendant γ-substituted amine chain.

In this context, Ghorai and co-workers reported the Lewis acid-promoted ring opening of azetidines with aromatic nucleophiles by a Friedel-Crafts mechanism (Scheme 14).[36] The method accomplishes N–C azetidine cleavage under practical reaction conditions that closely match those observed for the less strained aziridines.

Fluorine imparts unique properties on synthetic molecules.[37] In 2019, the Jiang group reported a novel method for the synthesis of γ-fluorinated amines by the regioselective ring opening of azetidines using the Olah reagent, pyridine-HF (Scheme 15).[38] The reaction proceeds under very mild conditions and tolerates 2-aryl and 2-*tert*-Bu substitution of the azetidine ring. The reaction is proposed to proceed via acid-promoted N-activation of the nitrogen atom of the azetidine ring to give a carbocation. It is worth noting that the same reaction conditions are applicable to both aziridines and azetidines, again indicating the high propensity of the σ N–C cleavage in appropriately activated azetidines.

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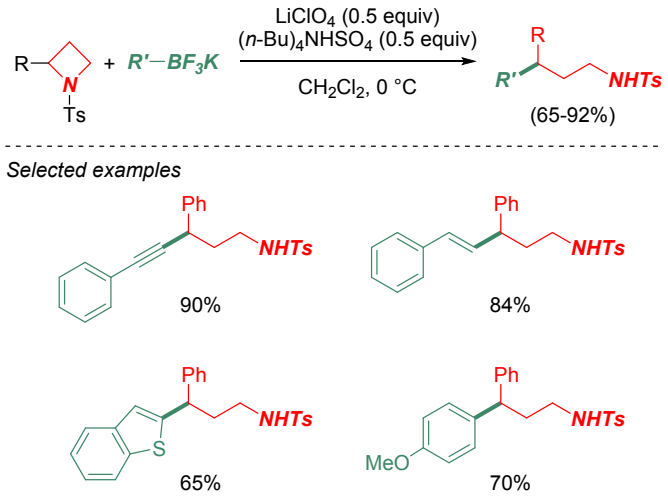
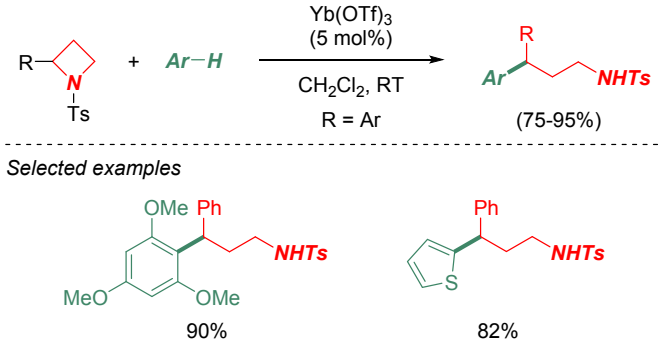
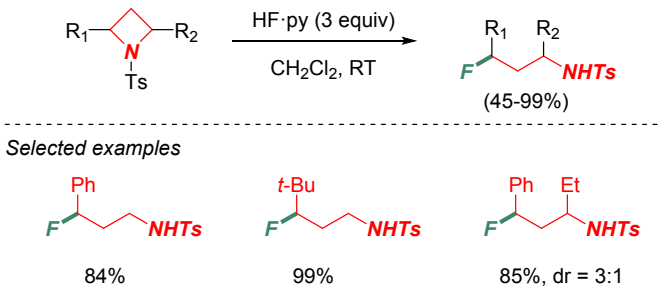


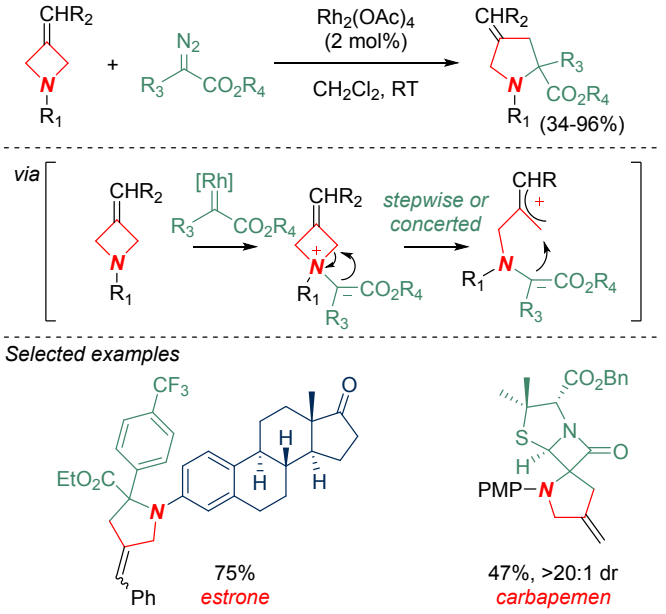
Scheme 13 Chemoselective ring opening of azetidines with organotrifluoroborates by May.



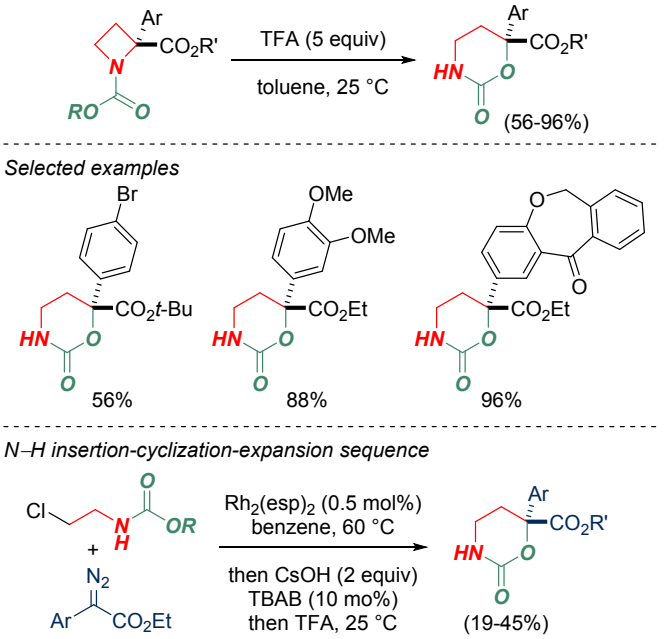
Scheme 14 Regioselective ring opening of azetidines with arenes by Ghorai.



Scheme 15 Regioselective ring opening of azetidines with HF by Jiang.



Scheme 16 Ring expansion of 3-methyleneazetidines to 4-methyleneprolines by N–C bond cleavage by Lu.



Scheme 17 Regioselective ring expansion of azetidines to 1,3-oxazinan-2-ones by N–C bond cleavage by Bull.

In 2019, Lu and co-workers reported an impressive method for the ring expansion of 3-methyleneazetidines with diazo compounds in the presence of $Rh_2(OAc)_2$ as a catalyst (Scheme 16).[39] This formal [4+1] cycloaddition represents another attractive mode of the ring opening of azetidines, wherein the azetidine nitrogen atom is activated by the nucleophilic addition to Rh-carbene, followed by concerted 1,2-migration or stepwise N–C ring opening/closure via a zwitterionic intermediate. The scope of the reaction is very broad, encompassing various diazo compounds, while the azetidine is activated by an easily removable N-PMP group (PMP = *p*-methoxyphenyl), benzyl or N-aromatic substituents. The authors demonstrated the utility of the method in the gram scale synthesis at 0.10 mol% catalyst loading and late-stage functionalization of complex molecules, such as estrone or carbapenem, showcasing the mild conditions of this ring expansion.

In 2019, the Bull group outlined acid-promoted ring expansion of 2,2-disubstituted azetidines to 6,6-disubstituted 1,3-oxazinan-2-ones (Scheme 17).[40] The proposed mechanism involves activation of the azetidine ring by N-protonation, followed by N–C cleavage to give a carbocation intermediate, which is then intercepted by the carbamate oxygen. The reaction occurs very rapidly (around 1 hour) with good yields (up to 96%) at room temperature. The group nicely

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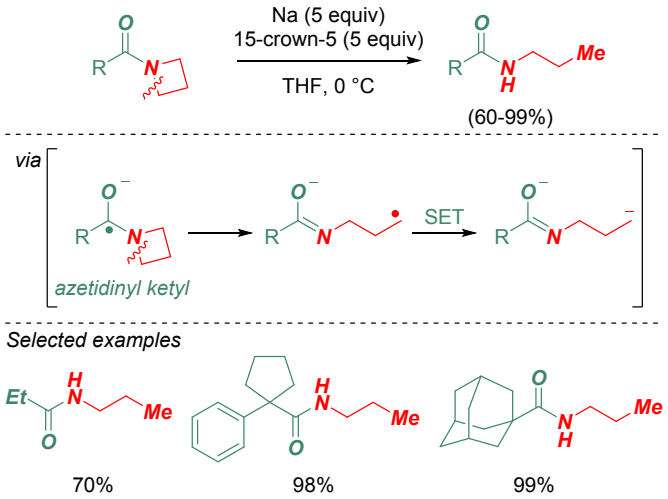
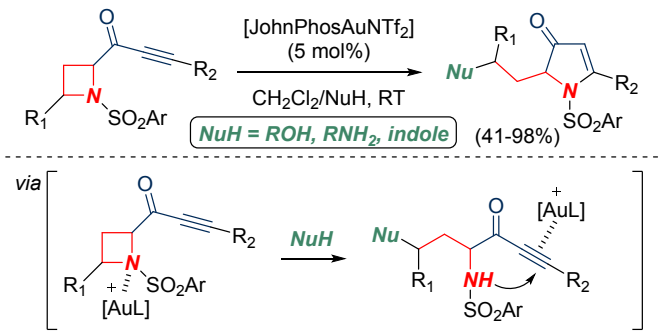


Scheme 18 Reductive single-electron-transfer σ N–C ring opening of azetidines using Na/15-crown-5 by An.



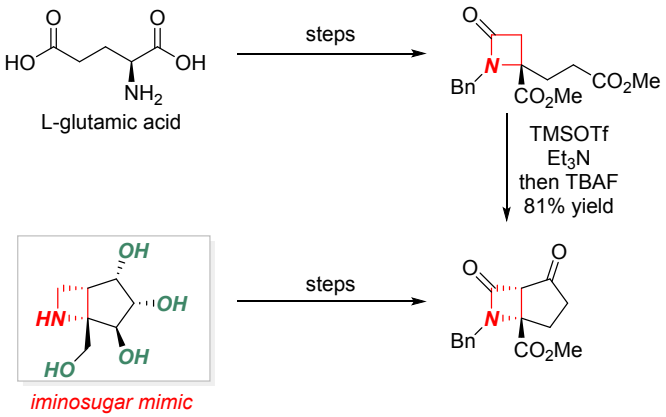
Scheme 19 Ring expansion of 2-azetidinyl ynones to pyrrolin-4-ones by Blanc.

demonstrated that the acid-mediated ring expansion can be combined with their previous two-step method for azetidine synthesis by Rh-catalyzed N–H insertion of diazo compounds and base-mediated cyclization.[41] Thus, the overall protocol superbly demonstrates the utility of azetidines by a rapid assembly–ring opening to access 1,3-oxazinan-2-ones that represent a privileged motif in medicinal chemistry. The same group reported protocols for azetidine elaboration by Friedel-Crafts-type arylation of azetidine-3-ols[42] (cf. Scheme 8).

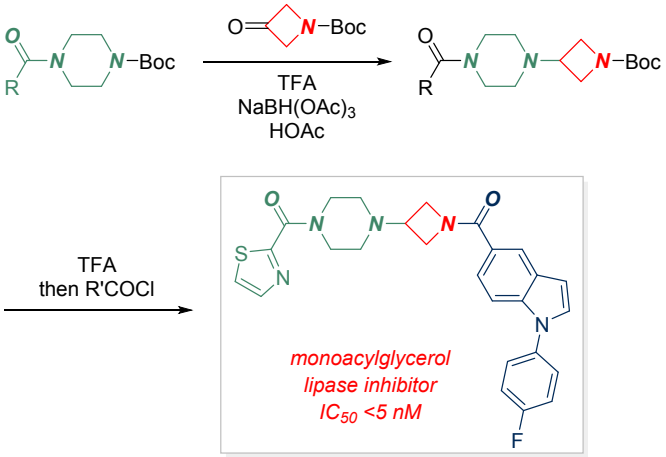
Finally, an impressive method for the reductive ring opening of azetidines was reported by the An group (Scheme 18).[43] This reaction is promoted by a combination of Na dispersion and 15-crown-5 under exceedingly mild conditions. The authors proposed that the reaction proceeds through an outer-sphere electron transfer mechanism, wherein SET to the amide bond carbonyl to give amide ketyl radical is followed by a radical σ N–C bond scission to furnish the N-propyl amide product after another SET and protonation. The scope of the method includes a range of alkyl, benzyl and aryl N-azetidinyl amides. Interestingly, the reaction is fully selective for the N–C bond cleavage of the four-membered ring (cf. pyrrolidines or N,N-dialkyl amides). The method is particularly important as it demonstrates a novel mechanistic platform for the azetidinyl bond cleavage that in principle can be applied to a broad range of electron-transfer processes[44,45] and azetidine precursors.

Finally, it is worth noting that the Blanc group reported Au(I)-catalyzed ring expansion of 2-azetidinyl ynones to pyrrolin-4-ones (Scheme 19).[10] The method utilizes 2-acyl azetidines synthesized by the same group via ring contraction of α-halo pyrrolidinones (cf. Scheme 1)[7] and involves sequential σ-activation of the azetidine nitrogen and π-activation of the ynone by the cationic Au(I)-phosphine catalyst.

5. Applications



Scheme 20 Synthesis of bicyclic polyhydroxylated azetidine iminosugar mimics by Compain.



Scheme 21 Synthesis of azetidine–piperazine diamides as selective monoacylglycerol lipase inhibitors by Zhu and co-workers.

Azetidines represent an immensely attractive scaffold for chemical applications.[1,2] In this section, we outline recent advances in application of azetidines with a focus on medicinal chemistry, polymer synthesis and enantioselective catalysis.

In 2018, Compain and co-workers reported the synthesis of novel iminosugar mimics based on a polyhydroxylated bicyclic azetidine scaffold (Scheme 20).[46] This synthetic approach uses L-glutamic acid as a chiral starting template to prepare ß-lactam,[47] followed by a cationic Dieckmann cyclization to form a bicyclic intermediate and dehydrogenation, reduction, oxidation sequence to afford the bicyclic polyhydroxylated azetidine. The key step involves a cationic Dieckmann cyclization, which was performed using TMSOTf/Et_3N

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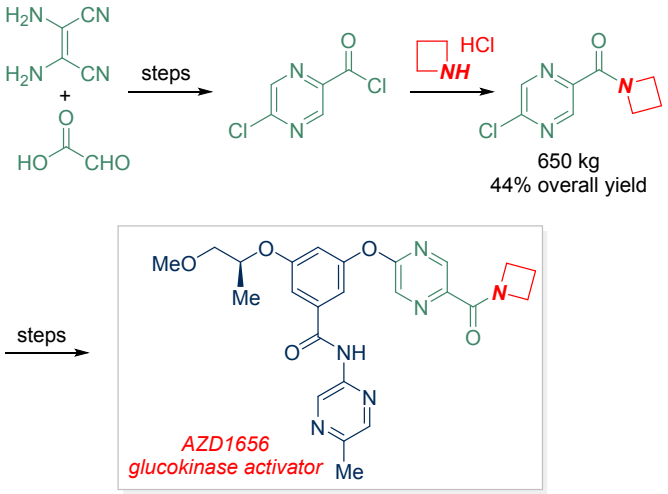
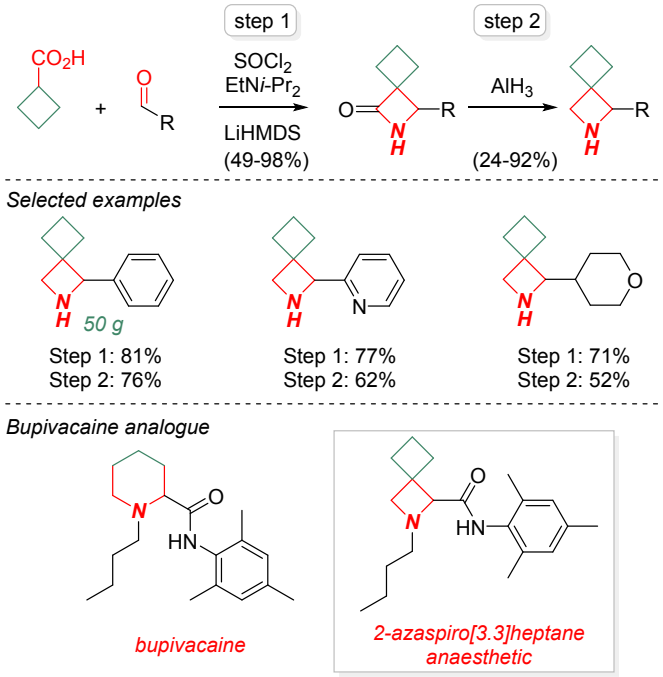
combination and TBAF-mediated desilylation. To reduce the ß-lactam, the nitrogen was first benzylated, followed by a reaction with AlH_2Cl. Finally, the azetidine ring nitrogen was debenzylated with the use of Pearlman's catalyst. Preliminary studies indicated inhibitory activity of this azetidine mimic against *Saccharomyces cerevisiae* α-glucosidase.

In 2020, Zhu and co-workers at Janssen reported the synthesis of azetidine–piperazine diamides with potent activity as reversible inhibitors of monoacylglycerol lipase (Scheme 21).[48] Monoacylglycerol lipase (MAGL) represents a drug target for a variety of diseases including many cancers. This approach



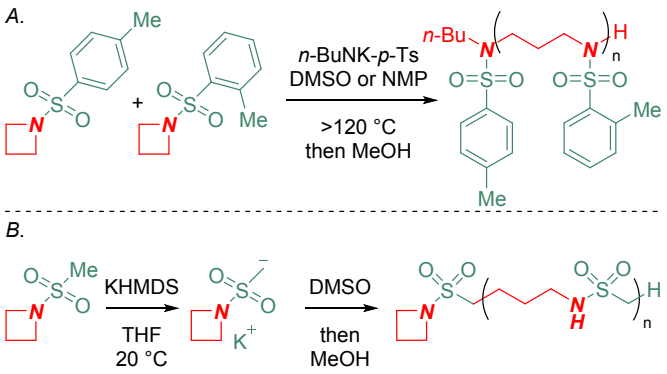
Scheme 22 Synthesis of the key azetidinyl-amide fragment of glucokinase inhibitor AZD1656 by Steven and co-workers.



Scheme 23 Synthesis of 2-azaspiro[3.3]heptanes as restricted analogues of 2-substitued piperidines by Mykhailiuk.

relies on reductive amination between *N*-Boc-3-azetidinone and *N*-acyl-piperazines. Removal of the Boc protecting group and reaction with acid chlorides permits to rapidly synthesize a library of azetidine–piperazine diamides for biological activity screening. A variety of amide groups were examined, and the most active compound showed highly promising selectivity for monoacylglycerol lipase and oral efficacy in animal studies.

In process chemistry, Steven and co-workers at AstraZeneca reported an impressive 650-kg scale synthesis of a key azetidin-1-yl-(5-chloropyrazin-2-yl)methanone unit of AZD1656, a glucokinase inhibitor for diabetes 2 treatment (Scheme 22).[49] The group developed a procedure using slow addition of K_2CO_3 to azetidine hydrochloride in toluene to free-base the azetidine nucleophile, followed by a slow addition of aroyl chloride. This



Scheme 24 (a) Anionic-ring-opening-copolymerization of N-sulfonyl azetidines; (b) Anionic-ring-opening-polymerization of N-sulfonyl-azetidine at room temperature by Rupar.

method prevented facile ring opening of the azetidinyl amide and permitted to access 647 kg of the target amide in a single manufacturing route.

In 2017, Mykhailiuk and co-workers developed a practical synthesis of 2-substituted azaspiro[3.3]heptanes as conformationally-restricted analogues of 2-substituted piperidines, a motif that is found in many bioactive molecules (Scheme 23).[50] The synthesis of the spirocyclic amine relies on a thermal Staudinger [2+2] cycloaddition between cyclobutylidenemethanone and TMS-imines. The azetidine is obtained by AlH_3-mediated reduction. Impressively, the method can be scaled up to 50 g in a single run to provide rapid access to various azaspiro[3.3]heptanes bearing up to 3 points of diversity. The method is very broad in scope, including alkyl or aromatic groups at the 2-position of the azetidine ring, while 2-carboxylic acid group is accessed by the oxidative cleavage of 2-furyl-subsitutent. The authors showcased a significant pharmaceutical potential of the azaspiro[3.3]heptane scaffold by preparing a conformationally-restricted analogue of *bupivacaine*, a pyridine-containing local anaesthetic. The azaspiro[3.3]heptane analogue showed highly promising activity in biological assays, including similar duration and faster onset of action than *bupivacaine*. Subsequently, the same group reported a related protocol for the synthesis of azetidines bearing 5-7-membered spirocyclic rings.[51]

Significant progress in showcasing azetidine ring opening in polymer synthesis has been reported by the Rupar group. In 2018, they reported the anionic ring-opening-copolymerization of *N*-ortho-tosyl and *N*-para-tosyl azetidines, giving a statistical co-polymer (Scheme 24A).[52] Later they investigated the effect

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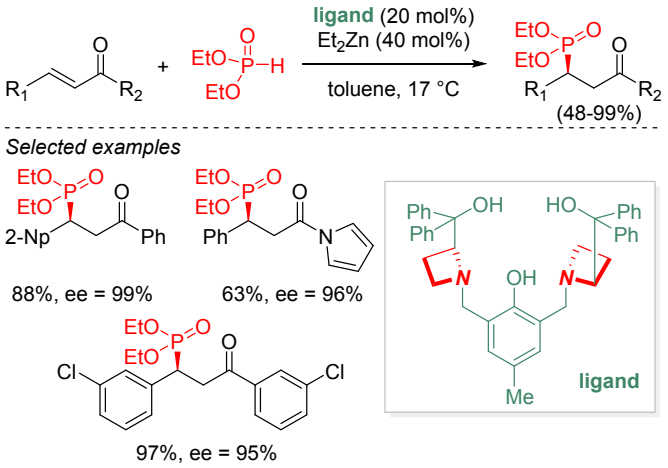
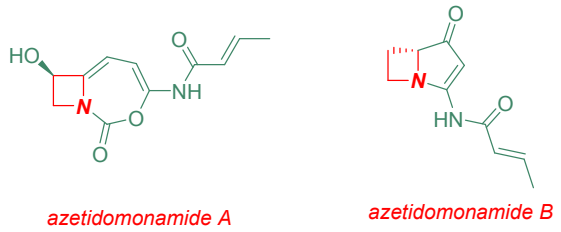
of different alkyl sulfonyl group activating the azetidine ring towards opening in anionic ring-opening polymerization.[53] A recent study focused on polymerization of *N*-sulfonylazetidine via deprotonation of the methanesulfonyl group to create a carbanion under very mild room temperature conditions (Scheme 24B).[54] The polymerization occurs using KHMDS as a base. Intriguingly, the formation of the anion activates the monomer to initiate the polymerization. This is contrasted with the previous conditions for polymerization of *N*-sulfonylazetidine that required temperatures higher than 100 °C. The propagation step involves the nucleophilic attack at the



Scheme 25 Phospha-Michael addition of phosphites catalyzed by a binuclear zinc-chiral azetidine catalyst by Wang.



Scheme 26 Azetidine-containing alkaloids from Pseudomonas aeruginosa PAO1 isolated by Li and co-workers.

C2 position of an unactivated monomer in DMSO or HMPA as solvent. The capacity to involve N-activated azetidines as monomers in polymerization is highly valuable owing to the utility of polyamines(amides) and strain-controlled activation of the azetidine ring towards opening.

The Wang group developed azetidine-derived binuclear zinc catalysts for enantioselective catalysis.[55] In one of the recent studies they reported asymmetric Michael addition of phosphites catalyzed by azetidine-containing binuclear zinc catalyst (Scheme 25).[56] The main advantage of the azetidine ring is in providing rigidity of the scaffold, which in turn leads to enhanced control of the catalytic pocket and increased enantioselectivity. The reaction is proposed to proceed via deprotonation of the phosphite by the catalyst to give zinc phosphonate intermediate. Coordination of the carbonyl group of the Michael acceptor is followed by the conjugate addition and proton exchange with a phosphite molecule. Several other protocols were reported by the same group.[57] The use of azetidines as scaffold-controlling feature represents a highly promising approach in enantioselective catalysis.

Finally, it is worthwhile to mention that the Li group identified azetidine-containing alkaloids from *Pseudomonas aeruginosa* PAO1 (Scheme 26).[58] Using isotope labelling experiments, the authors elucidated that biosynthetically the azetidine ring originates from azetidine 2-carboxylic acid. The physiological function of these azetidomonamides in the host adaptation has been proposed. The discovery of the azetidine-containing alkaloids presents a new view on the role of azetidine ring in environmental bacteria.

6. Conclusions

In conclusion, as demonstrated in this review, recently major advances in the chemistry of azetidines have been reported. This is highlighted by the establishment of new innovative methods for the synthesis of azetidines, including different reaction pathways and disconnections as well as by the growing arsenal of functionalization reactions of azetidines both with the retention of the ring and selective N–C bond cleavage.

The development of new methods provides a platform for acceleration of the use of azetidines (1) as a strain-driven precursors for the synthesis of extremely valuable homologated amines, and (2) as a valuable target compounds that have found numerous applications in medicinal chemistry. Among the most important developments in the last years are: (1) invention of new [2+2] cycloaddition reactions for azetidine synthesis; (2) applications of metalated azetidines; (3) practical C(sp^3)–H functionalization; (4) facile opening with carbon nucleophiles; (5) application of azetidines in polymer synthesis.

While the progress in the last years has been remarkable, there is still a number of challenges that needs to be addressed, including: (1) development of metal-catalyzed selective σ N–C bond functionalization; (2) development of enantioselective protocols involving azetidines; and (3) development of reductive processes for opening of azetidines. As the syntheses of azetidines become more practical, we anticipate that the unique, strain-driven reactivity of this ring system will find increasing applications in organic synthesis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 For early studies on azetidines, see: (*a*) S. Gabriel and J. Weiner, *Ber.*, 1888, **21**, 2669; (*b*) C. F. Gibbs and C. S. Marvel, *J. Am. Chem. Soc.*, 1934, **56**, 725; (*c*) J. B. Lambert, W. L. Oliver Jr. and B. S. Packard, *J. Am. Chem. Soc.*, 1971, **93**, 933.

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2 For reviews and perspectives on azetidines, see: (*a*) N. H. Cromwell and B. Phillips, *Chem. Rev.*, 1979, **79**, 331; (*b*) Y. Dejaegher, N. M. Kuz'menok, A. M. Zvonok and N. De Kimpe, *Chem. Rev.*, 2002, **102**, 29; (*c*) A. Brandi, S. Cicchi and F. M. Cordero, *Chem. Rev.*, 2008, **108**, 3988; (*d*) F. Couty and G. Evano, *Synlett*, 2009, 3053; (*e*) V. Mehra, I. Lumb, A. Anand and V. Kumar, *RSC Adv.*, 2017, **7**, 45763; (*f*) T. W. Reidl and L. L. Anderson, *Asian J. Org. Chem.*, 2019, 931; (*g*) For a recent review on 1-azabicyclo[1.1.0]butanes, see: M. Andresini, L. Degennaro and R. Luisi, *Org. Biomol. Chem.*, 2020, **18**, 5798.
3 For ring strain of azetidines, see: T. Dudev and C. Lim, *J. Am. Chem. Soc.*, 1998, **120**, 4450.
4 For selected studies on azetidines in drug discovery, see: (*a*) Y. Yagil, M. Miyamoto, L. Frasier, K. Oizumi, H. Koike, *Am. J. Hypertens.*, 1994, **7**, 637; (*b*) B. I. Ericksson, S. Carlsson, M. Halvarsson, B. Risberg and C. Mattsson, *Thromb. Haemost.*, 1997, **78**, 1404; (*c*) K. D. Rice, N. Aay, N. K. Anand, C. M. Blazey, O. J. Bowles, J. Bussenius, S. Costanzo, J. K. Curtis, S. C. Defina, L. Dubenko, S. Engst, A. A. Joshi, A. R. Kennedy, A. I. Kim, E. S. Koltun, J. C. Lougheed, J. C. L. Manalo, J. F. Martini, J. M. Nuss, C. J. Peto, T. H. Tsang, P. Yu and S. Johnston, *ACS Med. Chem. Lett.*, 2012, **3**, 416; (*d*) C. R. Butler, E. M. Beck, A. Harris, Z. Huang, L. A. McAllister, C. W. am Ende, K. Fennell, T. L. Foley, K. Fonseca, S. J. Hawrylik, D. S. Johnson, J. D. Knafels, S. Mente, G. S. Noell, J. Pandit, T. B. Phillips, J. R. Piro, B. N. Rogers, T. A. Samad, J. Wang, S. Wan, and M. A. Brodney, *J. Med. Chem.*, 2017, **60**, 9860; (*e*) O. Robles, J. J. Jackson, L. Marshall, O. Talay, D. Chian, G. Cutler, R. Diokno, D. X. Hu, S. Jacobson, E. Karbarz, P. D. Kassner, J. M. Ketcham, J. McKinnell, C. Meleza, M. K. Reilly, E. Riegler, H. P. Shunatona, A. Wadsworth, A. Younai, D. G. Brockstedt, D. J. Wustrow and M. Zibinsky, *J. Med. Chem.*, 2020, **63**, 8584.
5 For selected studies on azetidine-containing natural products, see: (*a*) L. Fowden, *Nature*, 1955, **176**, 347; (*b*) T. Takemoto, K. Nomoto, S. Fushiya, R. Ouchi, G. Kusano, H. Hikino, S. Takagi, Y. Matsuura and M. Kakudo, *Proc. Jpn. Acad. B*, 1978, **54**, 469; (*c*) K. Higuchi, K. Suzuki, H. Nakanishi, H. Yamaguchi, N. K. Nishizawa and S. Mori, *Plant Physiol.* 1999, **119**, 471; (*d*) C. Y. Lai, I. W. Lo, R. T. Hewage, Y. C. Chen, C. T. Chen, C. F. Lee, S. Lin, M. C. Tang and H. C. Lin, *Angew. Chem. Int. Ed.*, 2017, **56**, 9478; (*e*) F. Yan, D. Auerbach, Y. Chai, L. Keller, Q. Tu, S. Huettel, A. Glemser, H. A. Grab, T. Bach, Y. Zhang and R. Mueller, *Angew. Chem. Int. Ed.*, 2018, **57**, 8754.
6 G. I. Georg, *The Organic Chemistry of β-Lactams*, Wiley-VCH, 1993.
7 N. Kern, N.; A.-S. Felten, J.-M. Weibel, P. Pale and A. Blanc, *Org. Lett.*, 2014, **16**, 6104.
8 For a review on amide bond activation, see: G. Li, S. Ma and M. Szostak, *Trends Chem.*, 2020, **2**, 914.
9 S. Miaskiewicz, J.-M. Weibel, P. Pale and A. Blanc, *Org. Lett.*, 2016, **18**, 844.
10 F. Sirindil, S. Miaskiewicz, N. Kern, A. Lalaut, A.-S. Felten, J.-M. Weibel, P. Pale and A. Blanc. *Tetrahedron*, 2017, **73**, 5096.
11 I. Kim, S. W. Roh, D. G. Lee and C. Lee, *Org. Lett.*, 2014, **16**, 2482.
12 M.-R. Becker, E. R. Wearing, E. R. and C. S. Schindler, *Nat. Chem.*, 2020, **12**, 898.
13 For a review on reactivity of isoxazoles, see: F. Hu and M. Szostak, *Adv. Synth. Catal.*, 2015, **357**, 2583.
14 M. Nappi, C. He, W. G. Whitehurst, B. G. N. Chappell and M. J. Gaunt, *Angew. Chem. Int. Ed.*, **2018**, *57*, 3178.
15 N. E. Behnke, K. Lovato, M. Yousufuddin and L. Kürti, *Angew. Chem. Int. Ed.*, 2019, **58**, 14219.
16 A. Fawcett, A. Murtaza, C. H. U. Gregson and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2019, **141**, 4573.
17 A. Fawcett, T. Biberger and V. K. Aggarwal, *Nat. Chem.*, 2019, **11**, 117.
18 M. Maetani, J. Zoller, B. Melillo, O. Verho, N. Kato, J. Pu, E. Coer and S. L. Schreiber, *J. Am. Chem. Soc.*, 2017, **139**, 11300.
19 O. Verho, M. Maetani, B. Melillo, J. Zoller and S. L. Schreiber, *Org. Lett.*, 2017, **19**, 4424.
20 B. Melillo, J. Zoller, B. K. Hua, O. Verho, J. C. Borghs, S. D. Nelson, Jr., M. Maetani, M. J. Wawer, P. A. Clemons and S. L. Schreiber. *J. Am. Chem. Soc.*, 2018, **140**, 11784.
21 S. Vinayak, R. S. Jumani, P. Miller, M. M. Hasan, B. I. McLeod, J. Tandel, E. E. Stebbins, J. E. Teixeira, J. Borrel, A. Gonse, M. Zhang, X. Yu, A. Wernimont, C. Walpole, S. Eckley, M. S. Love, C. W. McNamara, M. Sharma, A. Sharma, C. A. Scherer, N. Kato, S. L. Schreiber, B. Melillo, B. Striepen, C. D. Huston and E. Comer. *Sci. Transl. Med.*, 2020, **12**, eaba8412.
22 E. Tayama, R. Nishio and Y. Kobayashi, *Org. Biomol. Chem.*, 2018, **10**, 14122.
23 B. J. Wang and M. A. J. Duncton, *J. Org. Chem.*, 2020, **8**, 13317.
24 P. K. Delany and D. M. Hodgson, *Org. Lett.*, 2019, **21**, 9981.
25 P. K. Delany, C. L. Mortimer and D. M. Hodgson, *Chem. Commun.*, 2020, **56**, 12174.
26 For an excellent review on metallated azetidines, see: (*a*) D. Antermite, L. Degennaro and R. Luisi, *Org. Biomol. Chem.*, 2017, **15**, 34; For the first example, see: D. M. Hodgson and J. Kloesges, *Angew. Chem. Int. Ed.*, 2010, **49**, 2900.
27 C. Liu, M. Achtenhagen and M. Szostak, *Org. Lett.*, 2016, **18**, 2375.
28 For a review on amide bond distortion, see: C. Liu and M. Szostak, *Chem. Eur. J.*, 2017, **23**, 7157.
29 G. Parisi, E. Capitanelli, A. Pierro, G. Romanazzi, G. J. Clarkson, L. Degennaro and R. Luisi, *Chem. Commun.*, 2015, **51**, 15588.
30 P. Musci, M. Colella, F. Fanelli, A. Altomare, L. Pisano, C. Carlucci, R. Luisi and L. Degennaro, *Front. Chem.*, 2019, **7**, 614.
31 A. K. Yudin, *Aziridines and Epoxides in Organic Synthesis*, Wiley-VCH, 2006.
32 Z. Wang, F. K. Sheong, H. H. Y. Sung, I. D. Williams, Z. Lin and J. Sun, *J. Am. Chem. Soc.*, 2015, **137**, 5895.
33 zX. Cheng, S. Vellalath, R. Goddard and B. List, *J. Am. Chem. Soc.*, 2008, **130**, 15786.
34 D. Qian, M. Chen, A. C. Bissember and J. Sun, *Angew. Chem. Int. Ed.*, 2018, **57**, 3763.
35 T. N. Nguyen and J. A. May, *Org. Lett.*, 2018, **20**, 3618.
36 G. Goswami, N. Chauhan, A. Mal, S. Das, M. Das and M. K. Ghorai, *ACS Omega*, 2018, **3**, 17562.
37 M. G. Campbell and T. Ritter, *Chem. Rev.*, 2015, **115**, 612.
38 L. Zhu, J. Xiong, J. An, N. Chen, J. Xue and X. Jiang, *Org. Biomol. Chem.*, 2019, **17**, 3797.
39 W. Cai, J. Wu, H. Zhang, H. B. Jalani, G. Li and H. Lu, *J. Org. Chem.*, 2019, **84**, 10877.
40 A. J. Boddy, C. J. Cordier, K. Goldberg, A. Madin, A. C. Spivey and J. A. Bull, *Org. Lett.*, 2019, **21**, 1818.
41 A. J. Boddy, D. P. Affron, C. J. Cordier, E. L. Rivers, A. C. Spivey and J. A. Bull, *Angew. Chem. Int. Ed.*, 2019, **58**, 1458.
42 (*a*) C. Denis, M. A. J. Dubois, A. S. Voisin-Chiret, R. Bureau, C. Choi, J. J. Mousseau and J. A. Bull, *Org. Lett.*, 2019, **21**, 300; (*b*) M. A. J. Dubois, A. Lazaridou, C. Choi, J. J. Mousseau and J. A. Bull, *J. Org. Chem.*, 2019, **84**, 5943; (*c*) M. A. J. Dubois, M. A. Smith, A. J. P. White, A. L. W. Jie, J. J. Mousseau, C. Choi and J. A. Bull, *Org. Lett.*, 2020, **22**, 5279.
43 H. Li, Z. Lai, A. Adijiang, H. Zhao and J. An, *Molecules*, 2019, **24**, 459.
44 For other examples of Na/15-crown-5 system, see: (*a*) P. Lei, Y. Ding, X. Zhang, A. Adijiang, H. Li, Y. Ling and J. An, *Org. Lett.*, 2018, **20**, 3439; (*b*) Y. Ding, S. Luo, L. Ma and J. An, *J. Org. Chem.*, 2019, **84**, 15827.
45 For a non-selective reductive cleavage of azetidines, see: M. Szostak, M. Spain and D. J. Procter, *Angew. Chem. Int. Ed.*, 2013, **52**, 7237.
46 M. Malinowski, R. Hensienne, N. Kern, D. Tardieu, A.

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Bodlenner, D. Hazelard and P. Compain, *Org. Biomol. Chem.*, 2018, **16**, 4688.
47 P. A. Nocquet, D. Hazelard and P. Compain, *Tetrahedron*, 2012, **68**, 4117.
48 B. Zhu, P. J. Connolly, Y. M. Zhang, M. E. McDonnell, H. Bian, S. C. Lin, L. Liu, S. P. Zhang, K. M. Chevalier, M. R. Brandt, C. M. Milligan, C. M. Flores and M. J. Macielag, *Bioorg. Med. Chem. Lett.*, 2020, **30**, 127243.
49 D. R. J. Hose, P. Hopes, A. Steven and C. Herber, *Org. Process Res. Dev.*, 2018, **22**, 241.
50 A. A. Kirichok, I. Shton, M. Kliachyna, I. Pishel and P. K. *Angew. Chem. Int. Ed*., 2017, **56**, 8865.
51 A. A. Kirichok, I. O. Shton, I. M. Pishel, S. A. Zozulya, P. O. Borysko, V. Kubyshkin, O. A. Zaporozhets, A. A. Tolmachev and P. K. Mykhailiuk, *Chem. Eur. J.*, 2018, **24**, 5444.
52 L. Reisman, E. A. Rowe, E. M. Jackson, C. Thomas, T. Simone and Paul A. Rupar, *J. Am. Chem. Soc.*, 2018, **140**, 15626.
53 E. A. Rowe, L. Reisman, J. A. Jefcoat and P. A. Rupar, *Macromolecules*, 2019, **52**, 8032.
54 L. Reisman, E. A. Rowe, J. A. Jefcoat and P. A. Rupar, *ACS Macro Lett.*, 2020, **9**, 334.
55 Y. Z. Hua, X. W. Han, X. C. Yang, X. Song, M. C. Wang and J. B. Chang, *J. Org. Chem.*, 2014, **79**, 11690.
56 S. Liu, N. Shao, F. Z. Li, X. C. Yang and M. C. Wang, *Org. Biomol. Chem.*, 2017, **15**, 9465.
57 S. Liu, Z. H. Xu, X. Wang, H. R. Zhu and M. C. Wang, *J. Org. Chem.*, 2019, **84**, 13881.
58 Z. Hong, A. Bolard, C. Giraud, S. Prévost, G. Genta-Jouve, C. Deregnaucourt, S. Häussler, K. Jeannot and Y. Li, *Angew. Chem. Int. Ed.*, 2019, **58**, 3178.

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