Invited paper

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Recent advances in the chemistry of bicyclo- and 1-azabicyclo[1.1.0]butanes

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Abstract: Bicyclo[1.1.0]- and 1-azabicyclo[1.1.0]butanes are structurally unique compounds that exhibit diverse chemistry. Bicyclo[1.1.0]butane is a four-membered carbocycle with a bridging C(1)-C(3) bond and 1-azabicyclo[1.1.0]butane is an analog of bicyclo[1.1.0]butane featuring a nitrogen atom at one bridgehead. These structures are highly strained, allowing them to participate in a range of strain-releasing reactions which typically cleave the central, strained bond to deliver cyclobutanes or azetidines. However, despite these molecules being discovered in the 1950s and 1960s, and possessing a myriad of alluring chemical features, the chemistry and applications of bicyclo[1.1.0]- and 1-azabicyclo[1.1.0]butanes remain underexplored. In the past 5 years, there has been a resurgent interest in their chemistry driven by the pharmaceutical industry's increasing desire for new methods to access cyclobutanes and azetidines. This short review intends to provide a timely summary of the most recent developments in the chemistry of bicyclo[1.1.0]- and 1-azabicyclo[1.1.0]butane to highlight the diverse chemistry they can access, their value as synthetic precursors to cyclobutanes and azetidines, and to identify areas for future research.

Keywords: 1-azabicyclo[1.1.0]butane; 2019 IUPAC-Solvay Award; azetidines; bicyclo[1.1.0]butane; carbopalladation; cyclobutanes; C–C bond reactivity; nucleophilic addition; organic synthesis; ring-opening reactions.

Introduction

Cyclobutanes and azetidines are becoming increasingly prominent structures in medicinal chemistry programs owing to their structural novelty and favorable electronic, steric and conformational features. Due to the small ring system rigidifying their carbon skeletons, cyclobutanes and azetidines adopt well-defined three-dimensional orientations, which enables substituents to be presented along precise vectors and gifting chemists a greater control over the three-dimensional shape of the molecule. In efforts to '*escape flatland*' [1, 2], medicinal chemists have become increasingly interested in investigating more three-dimensional, C(sp^3)-rich molecules, which have been mooted to enjoy increased clinical success relative to their 'flatter' counterparts due to increased solubility and reduced melting points, promiscuity and Cyp450 inhibition. For these reasons, medicinal chemists have begun investigating using cyclobutanes, azetidines and other small strained rings in place of flat aromatic structures in their discovery programs. Accordingly, there has also been interest in replacing flat, aromatic structures within pre-existing pharmaceuticals with saturated bioisosteres [3–5], including cyclobutanes and azetidines. Furthermore, because easily available 'chemical space' is poorly populated with cyclobutane and azetidine-containing structures, the investigation of such species potentially avoids patented synthetic methods or molecules.

Article note: A collection of peer-reviewed articles by the winners of the 2019 IUPAC-SOLVAY International Award for Young Chemists.

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However, because of the challenges associated with the synthesis of these four-membered rings, the methods to prepare cyclobutanes and azetidines bearing a variety of synthetically and pharmaceutically relevant functional groups are limited [6–13]. Therefore, to satisfy the desire for efficient methods to prepare these crucial motifs, chemists have recently begun turning to highly strained bi-cycles, such as bicyclo[1.1.0]butane and 1-azabicyclo[1.1.0]butane, to discover novel methods for their synthesis. These unusual structures rose to prominence shortly after their discovery in the 1950s and 1960s, with much of their basic chemistry being explored shortly after, but were only the subject of sporadic reports until a flurry of papers published within the past 5 years.

This review will address all reports from the past 5 years which present significant developments in the synthesis and applications of bicyclo[1.1.0]- and 1-azabicyclo[1.1.0]butanes.

Bicyclo[1.1.0]butane

Bicyclo[1.1.0]butane (**1**) is a four-membered carbocycle featuring a bridging C(1)-C(3) bond (Fig. 1) [14–16]. Unsurprisingly, the most captivating feature of bicyclo[1.1.0]butane has been its high strain energy, which is calculated to be 66.3 kcal/mol [17], making **1** the most strained fully saturated carbon-based bi-cycle in existence and ca. 12 kcal/mol more strained than the sum of its two cyclopropane constituents (27 kcal/mol each) [18]. The origin of this increased strain energy is suggested to arise from destabilizing 1,3-carbon-carbon interactions across the bicyclo[1.1.0]butane ring [19, 20] and/or the large angle deformations at the two terminal carbon atoms [21]. Because bicyclo[1.1.0]butanes are comprised of two cyclopropane rings, they are forced to adopt a highly puckered conformation, where the angle between the plane of the two cyclopropane rings is ca. 120° [22]. The two terminal carbon atoms possess an inverted geometry, where all four of its bonds fall within a single hemisphere. The electronic structure of the central C(1)–C(3) bond has been extensively studied. It has been calculated that this bent σ-bond is formed almost exclusively of two unhybridized *p*-orbitals that are bent towards each other at approximately 30° to the bond vector [23, 24]. This geometry results in significant orbital density protruding out from the *exo* face of the bicyclo[1.1.0]butane ring and it is along their axis which both nucleophiles and electrophiles can engage in reaction with bicyclo[1.1.0]butanes [25–30]. Given the high *p*-character of the C(1)-C(3) bond, the carbon atoms of bicyclo[1.1.0]butanes have an increased degree of *s*-character, resulting in the two methine C-H bonds being relatively strong and facile to deprotonate [31–36]. These unique properties endow the C(1)-C(3) bond with both *p*- and *s*-bond character, enabling it to access a wide range of different chemistries, including reaction with both electrophiles and nucleophiles, transition metals, and radicals [14, 15]. However, despite these interesting features and an ability to access a mechanistically diverse set of reaction pathways, the chemical potential of bicyclo[1.1.0]butanes, especially in recent years, has remained largely untapped.

Despite its unusual structure and high strain energy, bicyclo[1.1.0]butanes can often be easily prepared and isolated. Indeed, 2007 saw the report of the first-ever bicyclo[1.1.0]butane containing natural product [37], and its total synthesis was disclosed shortly after in 2011 [38]. The first reported synthesis of the general bicyclo[1.1.0]butyl scaffold was in 1959 by Wiberg and Cuila [39], with the preparation of ethyl bicyclo[1.1.0]

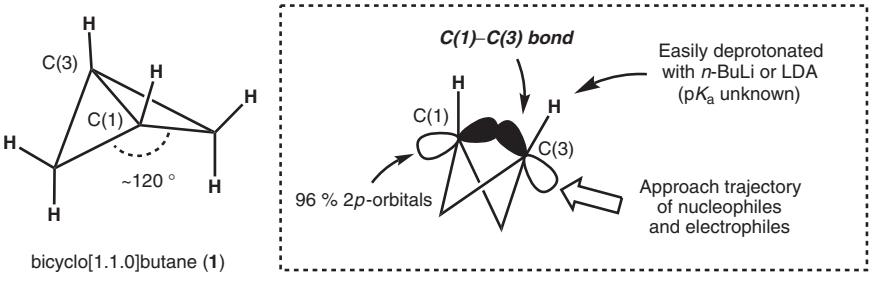
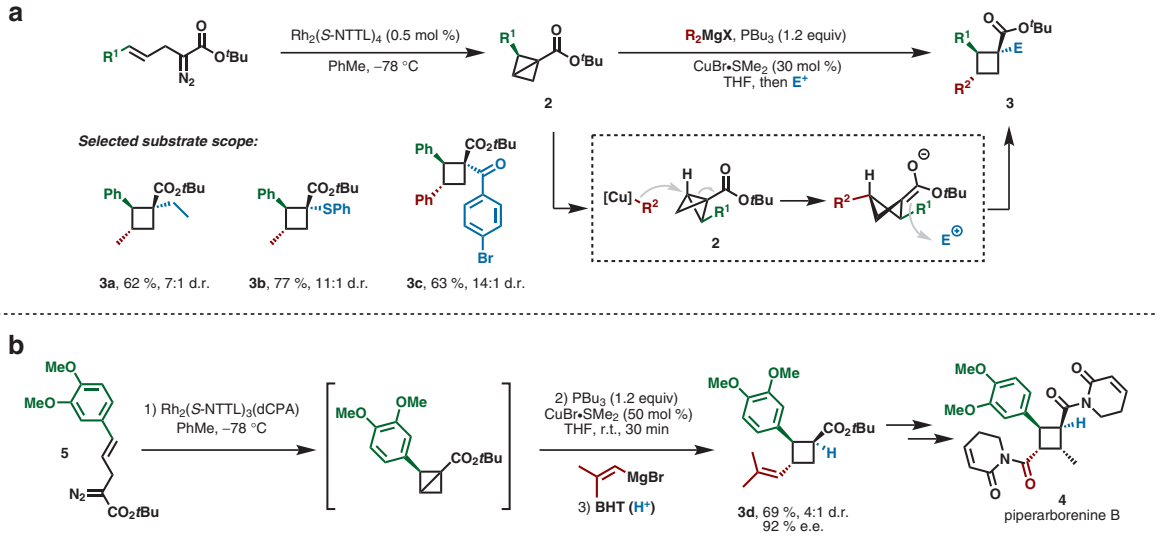


Fig. 1: The structure and bonding of bicyclo[1.1.0]butane (**1**).

butane-1-carboxylate. The parent structure, bicyclo[1.1.0]butane itself, was not prepared until 1963 [40–42]. Typical approaches to the preparation or incorporation of the bicyclo[1.1.0]butane group are the 3-*exo-tet* cyclization reaction of a cyclopropane or cyclobutane precursor, the addition of bicyclo[1.1.0]butyl lithium to an electrophile [43], or the cyclopropanation of an appropriate unsaturated functional group, such as the intramolecular cyclopropanation of olefins or the double cyclopropanation of an alkyne [14, 15]. Most recently, a range of chiral polysubstituted cyclobutanes have been prepared by an enzyme-catalyzed double cyclopropanation of alkynes [44].

Wipf and co-workers have been the most active in the field of bicyclo[1.1.0]butane research within the past 15 years and produced a handful of reports from 2003 to 2009 which further revealed the diverse reaction pathways accessible to bicyclo[1.1.0]butanes. These reports included the investigation of pericyclic reactions between amino bicyclo[1.1.0]butanes and pendent olefins [45–47], the rhodium(I)-catalyzed ligand-controlled isomerization of *N*-allyl bicyclo[1.1.0]butyl amines to give pyrrolidines and azepines [48], the platinum-catalyzed isomerization of *N*- and *O*-propargyl bicyclo[1.1.0]butyl amines and ethers [49, 50], and other miscellaneous transformations [51]. Since an engaging account of this work has recently been published [49], a summary of the works discussed in this account will not be included here.

In 2013, Fox and co-workers demonstrated the expedient synthesis of densely functionalized enantiomerically-enriched cyclobutanes via the homoconjugate addition of organocuprates to bicyclo[1.1.0]butyl carboxylates followed by trapping of the enolate with electrophiles (Scheme 1) [52]. It was discovered that enantiomerically-enriched *tert*-butyl bicyclo[1.1.0]butyl carboxylates **2** could be prepared via the enantioselective intramolecular cyclopropanation of (*E*)-2-diazo-5-arylpent-4-enoates using Rh_2(*S*-NTTL)$_4$ in toluene at –78 °C. After a solvent exchange to THF, **2** could be treated with an organomagnesium reagent, CuBr · SMe_2, and PBu_3 to achieve a homoconjugate addition reaction. This was followed by addition of an electrophile to trap the enolate and ultimately deliver 1,2,3-tris and 1,1,2,3-tetra substituted cyclobutanes **3** with high diastereoselectivity, whereby the organomagnesium reagent and the electrophile have effectively been added across the C-C σ-bond of the bicyclo[1.1.0]butyl unit (Scheme 1a). Whilst the addition of organocuprates to bicyclo[1.1.0]butyl sulfones had been previously shown by Gaoni [31, 53–55], Fox and co-workers demonstrated that this can be extended to bicyclo[1.1.0]butyl carboxylates (**2**) and that two new groups could be incorporated across the C-C σ-bond with high diastereoselectivity. In 2016, this method was applied to the first enantioselective synthesis of natural product piperarborenine B (**4**) (Scheme 1b): diazoester **5** was treated with 0.1 mol % Rh_2(*S*-NTTL)$_3$(dCPA) at –78 °C to form the corresponding *tert*-butyl bicyclo[1.1.0]butyl

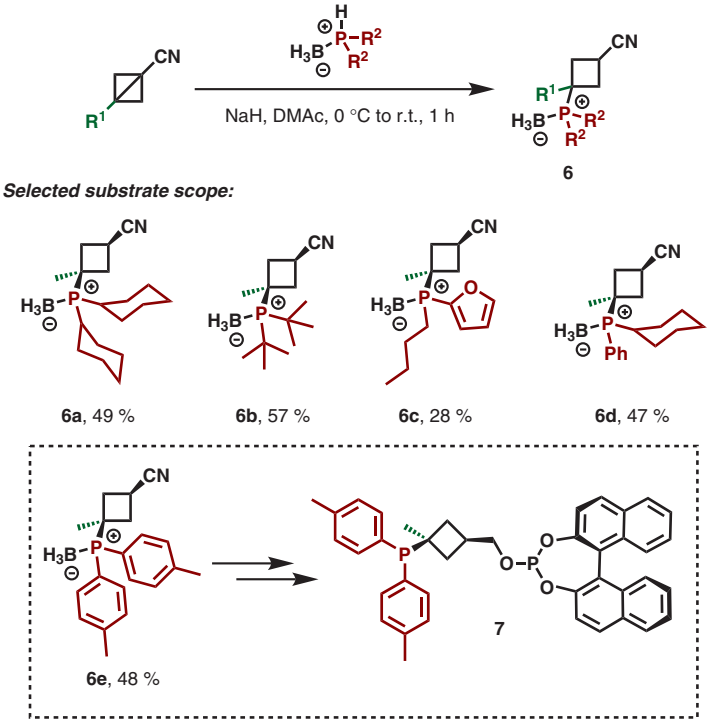


Scheme 1: Fox's addition of organocuprates and electrophiles across the C(1)-C(3) bond of bicyclo[1.1.0]butanes. (a) Reaction conditions and selected substrate scope. (b) Application of the method to the enantio- and diastereoselective synthesis of piperarborenine B (**4**).

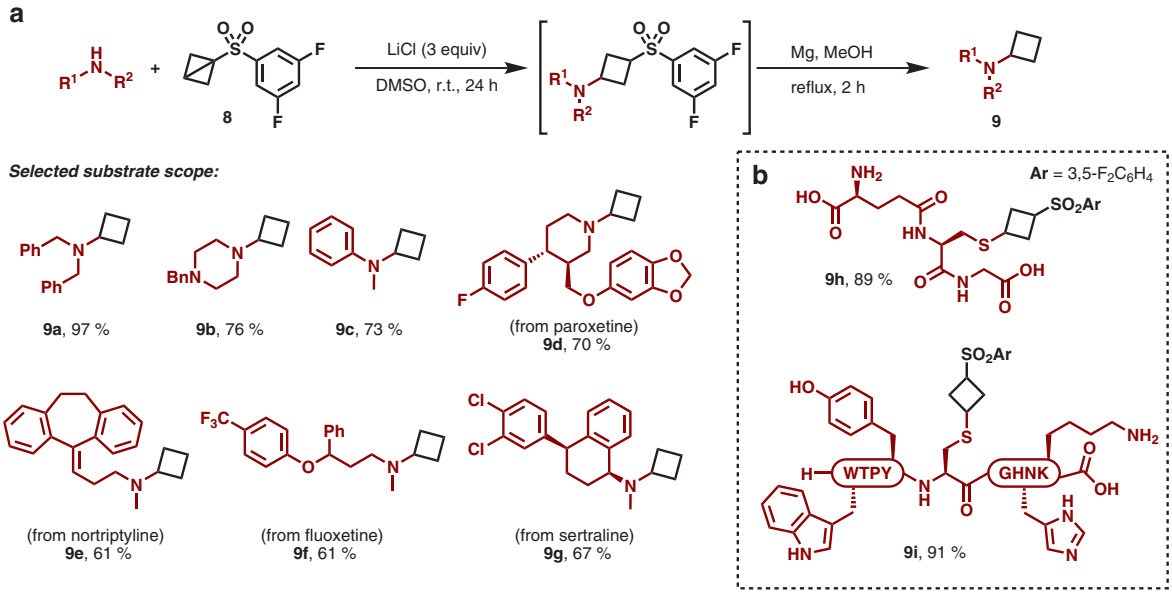
carboxylate intermediate *in situ*, this was then treated with $CuBr \cdot SMe_2$, PBu_3 and 2-methyl-1-propenylmagnesium bromide in THF followed by protonation of the enolate with BHT to deliver 1,2,3-trisubstituted cyclobutane **3d** in 69 % yield from **5** with 4:1 d.r. and 92 % ee [56]. From cyclobutane **3d**, six following steps delivered **4** in a total of 10 steps and 8 % overall yield from **5**. This efficient synthesis demonstrates that bicyclo[1.1.0]butanes are valuable intermediates for the preparation of cyclobutane-containing natural products [57].

In 2016, Busacca, Senanayake, and Wipf gave the first examples of P-centered nucleophiles reacting with bicyclo[1.1.0]butanes for the synthesis of cyclobutyl phosphines (Scheme 2) [58]. They found that the C(1)-C(3) bond of substituted 1-cyanobicyclo[1.1.0]butanes could react with phosphine boranes to deliver cyclobutyl phosphine boranes **6** in good yields and typically with an approximate 2:1 ratio of separable cis:trans products. The reaction was proven to be under thermodynamic control since the same ratio of cis/trans products is regenerated when either isomerically pure cyclobutane was subjected to the same reaction conditions. One cyclobutyl phosphine borane, **6e**, was transformed into a diphosphine **7**, which was shown to be a competent ligand for an enantioselective rhodium-catalyzed hydrogenation reaction, showing that these cyclobutyl phosphines have potential application in the design and preparation of novel phosphine ligands for asymmetric catalysis.

In 2016 and 2017, Baran greatly improved the addition of amine nucleophiles to bicyclo[1.1.0]butanes to form 3-amino cyclobutanes (Scheme 3) [59, 60]. Prior to these reports, Gaoni had shown that benzylamine could undergo nucleophilic addition to the 3-position of a range of substituted 1-(arylsulfonyl)bicyclo[1.1.0]butanes [61]. Whilst the yields were generally high, the method suffered from a series of drawbacks: solvent quantities of amine were used, high temperatures (140 °C) were required, and only benzylamine was shown to be successful. The addition of azide was also precedented [31, 62]. Baran's discovery was that an electronically-tuned 1-(arylsulfonyl)bicyclo[1.1.0] butane (**8**), could be used as an electrophile to efficiently 'cyclobutylate' amines (Scheme 3a). It was found that simply stirring the free amine, lithium chloride and **8** in DMSO at ambient temperature for 24 h delivered the functionalized amines **9** in generally excellent yields. In a testament to the mildness of these conditions, a small range of pharmaceutical compounds was also successfully



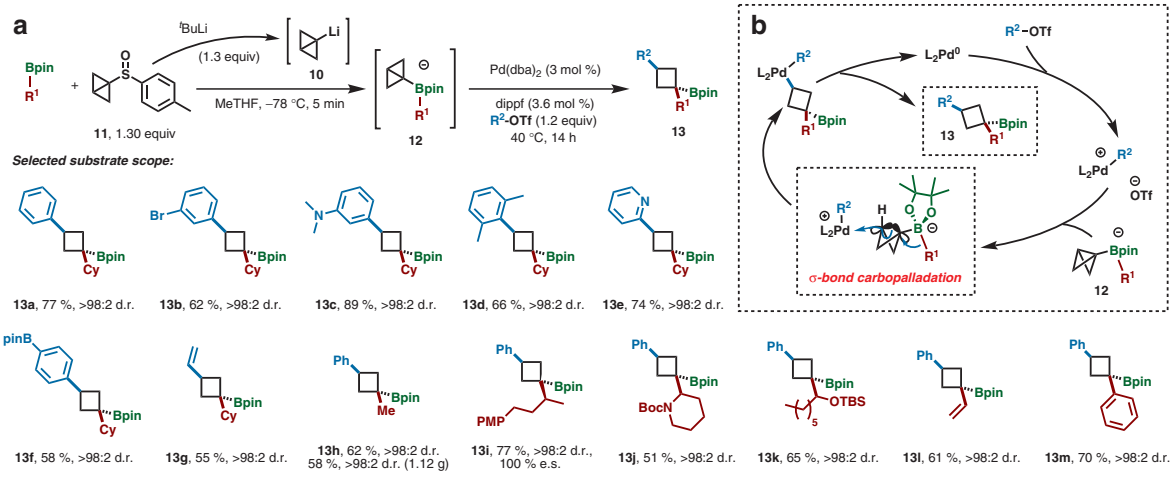
Scheme 2: Busacca, Senanayake, and Wipf's addition of phosphine boranes to 1-cyanobyclo[1.1.0]butanes to prepare cyclobutyl phosphine boranes.



Scheme 3: Baran's reaction of amines and thiols with bicyclo[1.1.0]butyl sulfones. (a) Reaction conditions and selected substrate scope. (b) The reaction of thiols embedded within complex molecules with bicyclo[1.1.0]butyl sulfones.

cyclobutylated. Impressively, **8** was also able to selectively react with the thiol of cysteine residues within glutathione and a complex polypeptide without any observed off-target reactivity, paving the way for 'strain-release' protein-labeling (Scheme 3b). Bicyclo[1.1.0]butyl sulfone **8** is a convenient to handle solid and is now commercially available [63], which should lead to its widespread adoption as a cyclobutylation reagent.

In contrast to the previously discussed works which use bicyclo[1.1.0]butane as an electrophile, Aggarwal recently investigated the nucleophilic reactivity of bicyclo[1.1.0]butane, reporting the first examples of bicyclo[1.1.0]butyl boronate complexes and their reaction with palladium(II)-aryl complexes to form cyclobutanes via a unique carbopalladation of the central C-C σ-bond of the bicyclo[1.1.0]butyl unit (Scheme 4) [64]. It was discovered that pinacol boronic esters could be reacted with bicyclo[1.1.0]butyl lithium **10**, generated *in situ* from sulfoxide **11** by treatment with *tert*-butyl lithium in 2-methyl tetrahydrofuran at –78 °C,

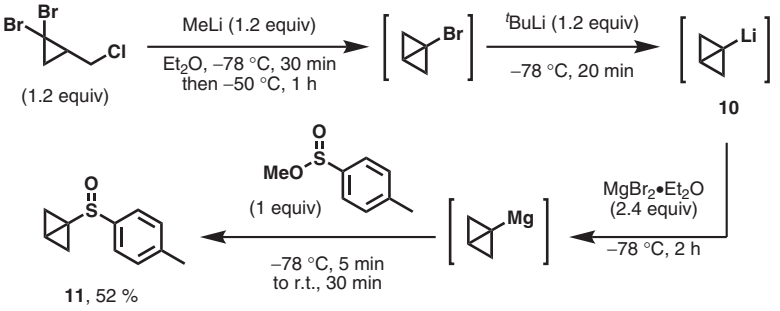


Scheme 4: Aggarwal's reaction of bicyclo[1.1.0]butyl boronate complexes with palladium(II)-aryl complexes. (a) Reaction conditions and selected substrate scope. (b) Proposed catalytic cycle and C-C σ-bond carbopalladation process. Enantiospecificity (e.s.) = [e.e. of product/e.e. of starting material] × 100 %.

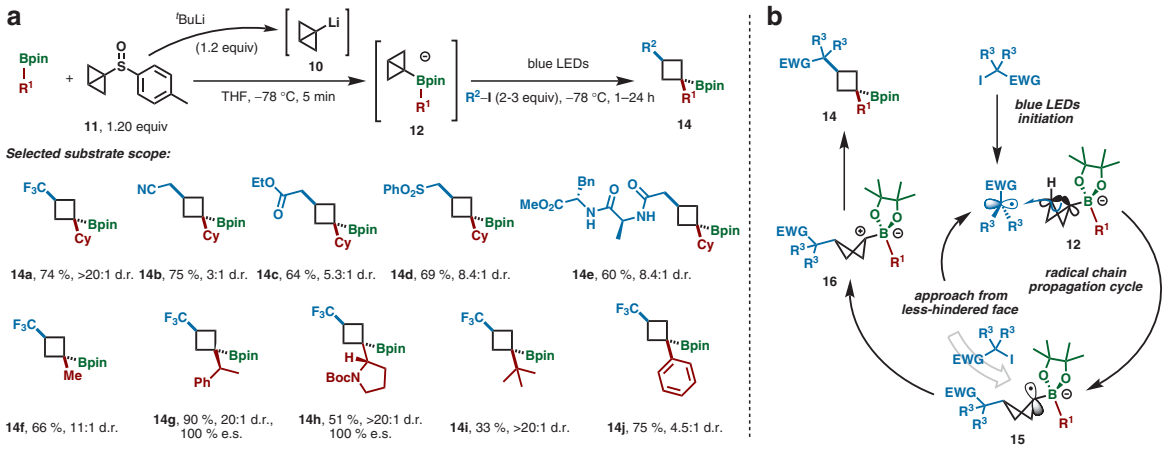
to quantitatively form the corresponding bicyclo[1.1.0]butyl boronate complexes (**12**). These could then be treated with bis(dibenzylideneacetone) palladium(0) ($Pd(dba)_2$), 1,1′-bis(diisopropylphosphino)ferrocene (dippf) and an aryl/vinyl triflate for 14 h at 40 °C to form 1,1,3-trisubstituted cyclobutanes (**13**). These conditions were applied to a wide range of boronic esters and aryl/vinyl triflates in generally good to excellent yields. In all examples, the cyclobutane products **13** were formed with perfect diastereoselectivity, with a *syn* relationship between the migrating substituent, R^1, and the incorporated aryl/vinyl group, R^2 (Scheme 4a). The reaction outcome was rationalized by the following mechanism (Scheme 4b): the cationic palladium(II) species, formed by oxidative addition of palladium(0) and the triflate, approaches the β-carbon of the bicyclo[1.1.0]butyl unit of **12** and induces a 1,2-metalate rearrangement, whereby substituent R^1 migrates onto the α-carbon to form a new C-C bond, the central C-C σ-bond of the bicyclo[1.1.0]butyl unit is cleaved, and a new C-Pd bond forms at the β-carbon. Due to the anti-periplanar requirement of the migrating and leaving groups for 1,2-migration, and because the bicyclo[1.1.0]butyl unit projects significant orbital density on its *exo* face, which can interact with the electrophilic palladium(II) complex, the new C-R^1 and C-Pd bonds form on the same face of **13**. Because the reaction is so highly diastereoselective, these steps are likely to be simultaneous. This overall process is the first report of a carbopalladation of a C-C σ-bond, where a carbon-based substituent, the migrating R^1 group, and a palladium complex are added across a C-C σ-bond. Finally, reductive elimination liberates the arylated cyclobutane product **13**.

Another noteworthy development in this report was the invention of a stable, solid precursor to bicyclo[1.1.0]butyl lithium **10**. Previously, **10** had only been prepared *in situ* from a dibromocyclopropane precursor [43]. In this report, **10** was generated from sulfoxide **11**. Bicyclo[1.1.0]butyl sulfoxide **11** was prepared by the treatment of 1,1-dibromo-2-(chloromethyl)cyclopropane with methyl lithium to form bicyclo[1.1.0]butyl bromide, which was then treated with *tert*-butyl lithium to give bicyclo[1.1.0]butyl lithium **10** (Scheme 5). This was next transmetalated using magnesium bromide ethyl etherate and then trapped with a sulfinate ester to finally give **11** in 52 % yield on gram-scale. After isolation as a conveniently handled solid, **11** could be treated with *tert*-butyl lithium to reveal **10** quantitatively and cleanly in under 5 min, avoiding 2 h of reaction time and the addition of two different organolithium reagents, significantly expediting development of the described method and investigation of the substrate scope.

This initial work was shortly followed by a demonstration that the central C-C σ-bond of bicyclo[1.1.0]butyl boronate complexes can also react with electrophilic radicals (Scheme 6) [65]. Specifically, Aggarwal showed that bicyclo[1.1.0]butyl boronate complexes (**12**) could be treated with electrophilic radicals, generated by the irradiation of electron-deficient alkyl iodides with visible light, in THF at –78 °C for 1 h to form the corresponding 1,1,3-trisubstituted cyclobutanes **14** in generally good to excellent yields and good diastereoselectivities across a range of different boronic esters and alkyl iodides bearing α-electron-withdrawing functional groups (Scheme 6a). In an analogous manner to the previous report, it was proposed that the electrophilic radical reacts at the β-carbon of the bicyclo[1.1.0]butyl unit of **12** with simultaneous cleavage of the central C-C σ-bond to give intermediate **15**. Here, however, to induce 1,2-metalate rearrangement, single electron transfer from a second molecule of the alkyl iodide is required to furnish an intermediate zwitterionic boronate complex **16** which rapidly undergoes 1,2-metalate rearrangement. The diastereoselectivity was



Scheme 5: Synthesis of bicyclo[1.1.0]butyl sulfoxide **11**.



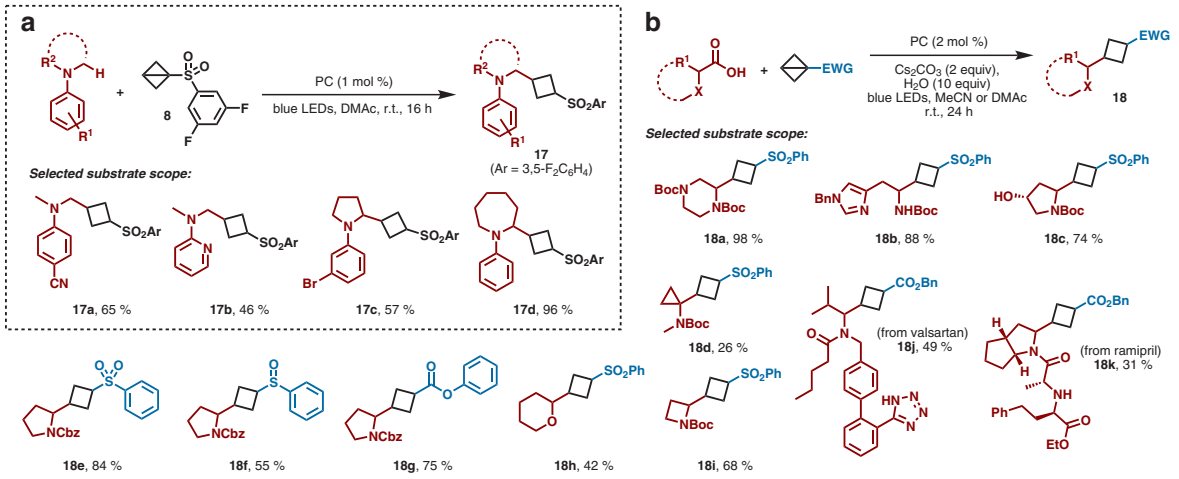
Scheme 6: Aggarwal's addition of electrophilic radicals to bicyclo[1.1.0]butyl boronate complexes. (a) Reaction conditions and selected substrate scope. (b) Proposed reaction mechanism. Enantiospecificity (e.s.) = [e.e. of product/e.e. of starting material] × 100 %.

proposed to arise from the alkyl iodide approaching and accepting an electron from the less hindered face of intermediate **15**, resulting in **16** which undergoes 1,2-metalate rearrangement before the C-B bond has time to rotate (Scheme 6b).

The use of bicyclo[1.1.0]butyl boronate complexes (**12**) as common reaction intermediates provide an entirely new concept for the preparation of diversely substituted cyclobutanes from simple starting materials. Given that it has now been demonstrated that cationic palladium(II)-aryl complexes and electrophilic radicals can react with bicyclo[1.1.0]butyl boronate complexes, it will be prudent to further explore the electrophile scope to expand the range of functionalized cyclobutanes accessible using the same intermediates. Furthermore, now that bicyclo[1.1.0]butyl lithium (**10**) is now more easily accessible on a day-to-day basis, via the bicyclo[1.1.0]butyl sulfoxide **11**, it will greatly enable the development of new methods requiring **10** as a key reaction component or to prepare bicyclo[1.1.0]butane-containing substrates which would otherwise be inaccessible or tedious to prepare.

In a similar fashion, there have been two further reports of the addition of alkyl radicals to bicyclo[1.1.0]butanes, a reaction class which had been the subject of a few previous reports [38, 54, 66–68]. Firstly, Jui reported the addition of α-aminoalkyl radicals to bicyclo[1.1.0]butyl sulfones (Scheme 7a) [69]. Aniline derivatives were treated with an iridium photocatalyst under blue LED irradiation to deliver α-aminoalkyl radicals, which subsequently reacted with bicyclo[1.1.0]butyl sulfone **8** to ultimately form the corresponding cyclobutylated product **17** in what is the first reported C-H cyclobutylation reaction. Similarly, Ernouf and Cintrat disclosed the addition of alkyl radicals to bicyclo[1.1.0]butanes bearing electron-withdrawing groups in the C(1) position to give cyclobutanes (Scheme 7b) [70]. Here, carboxylic acids were treated with cesium carbonate in the presence of an iridium photocatalyst to induce radical decarboxylation and form the corresponding alkyl radical, which subsequently reacted with a bicyclo[1.1.0]butyl reagent to form cyclobutanes **18**. Overall, this process could be considered the first decarboxylative cyclobutylation reaction. The scope of the carboxylic acid portion was shown to be broad, including several α-amino and α-oxy carboxylic acids and a handful of peptides and drug molecules. A small selection of electron-withdrawing group bearing bicyclo[1.1.0]butanes was successfully reacted, including sulfones, carboxylates, and a sulfoxide [64]. In both reports, the 1,3-disubstituted cyclobutane products were obtained as mixtures of the *cis*/*trans* stereoisomers, as would be expected for reactions that are proposed to proceed via radical intermediates.

Finally, and in contrast to all the previously discussed works, in 2019 reports from Ma *et al.* [71] and Mykhailiuk *et al.* [72] detailed the synthesis of difluorinated bicyclo[1.1.1]pentanes by the reaction of substituted bicyclo[1.1.0]butanes with difluorocarbene. Prior to this work, a small number of 3-arylbicyclo[1.1.0]butane-1-carboxylates had been reacted with dichloro- and dibromocarbene to generate the corresponding

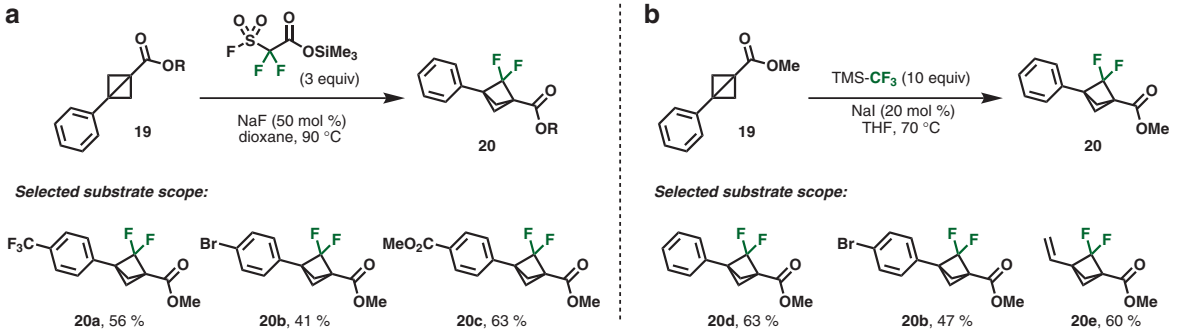


Scheme 7: The addition of radicals to bicyclo[1.1.0]butanes to make cyclobutanes. (a) Jui's addition of α-aminoalkyl radicals to bicyclo[1.1.0]butyl sulfones. (b) Ernouf and Cintrat's decarboxylative radical addition to electron-withdrawing group-bearing bicyclo[1.1.0]butanes. PC = photocatalyst = $Ir[dF(CF_3)ppy]_2(dtbbpy) \cdot PF_6$.

2,2-dihalobicyclo[1.1.1]pentanes [73–78]. Under Ma's conditions, 3-arylbicyclo[1.1.0]butane-1-carboxylates (**19**) were treated with three equivalents of trimethylsilyl 2-fluorosulfonyl-2,2-difluoroacetate (TFDA) and sodium fluoride in dioxane at 90 °C to form difluorinated bicyclo[1.1.1]pentanes **20** (Scheme 8a). Likewise, under Mykhailiuk's conditions, **19** was treated with superstoichiometric quantities of trifluoromethyltrimethylsilane ($TMSCF_3$) and 20 mol % of sodium iodide in THF at 70 °C to reach **20** (Scheme 8b). In both cases, yields of **20** were generally modest, with Mykhailiuk's method delivering overall slightly more favorable yields. The requirement of aryl substitution on **19** indicates that the reaction mechanism probably proceeds via an intermediate carbocation or carbon-centered radical at C(3), though the exact mechanism was not determined. These works confirm that bicyclo[1.1.0]butanes can be applied to the synthesis of other valuable motifs, not just cyclobutanes, and provides a hint that the addition of other carbenes to the C(1)-C(3) bond of bicyclo[1.1.0]butanes could provide a broad spectrum of laterally substituted bicyclo[1.1.1]pentanes.

1-Azabicyclo[1.1.0]butane

1-Azabicyclo[1.1.0]butane (**21**) is a nitrogen-containing analog of bicyclo[1.1.0]butane, featuring a nitrogen atom at one of the bridgehead positions, which shares a range of similar structural features and reactivity with its parent **1** (Fig. 2) [79]. The preparation and isolation of 3-phenyl-1-azabicyclo[1.1.0]butane, the first-



Scheme 8: Preparation of 2,2-difluorobicyclo[1.1.1]pentanes by the reaction of bicyclo[1.1.0] butanes with difluorocarbene as reported by Ma (a) and Mykhailiuk (b).

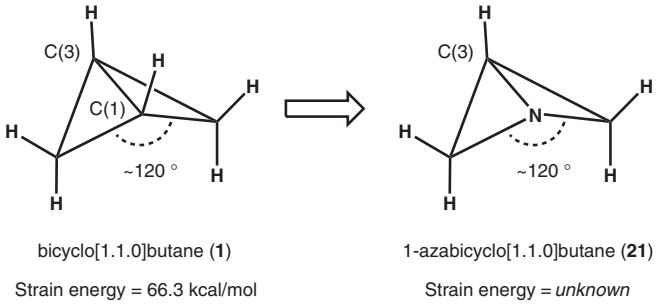


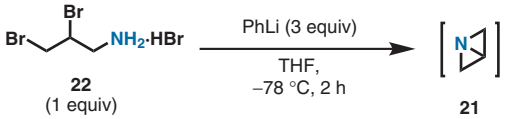
Fig. 2: The structure of 1-azabicyclo[1.1.0]butane (**21**).

ever reported 1-azabicyclo[1.1.0]butane, was conducted in 1967 by Hortmann and Robertson [80], and unsubstituted 1-azabicyclo[1.1.0]butane **21** was first synthesized by Funke in 1969 [81, 82]. A crystal structure later obtained in 1993 of 2,2,3-triphenyl-1-azabicyclo[1.1.0]butane revealed **21**'s strong resemblance to **1** [83], with bond lengths, bond angles, the dihedral angle between the plane of the two three-membered rings, and the N-C(3)-CR angle all being comparable to those found in bicyclo[1.1.0]butanes [14, 15]. Furthermore, molecular orbital analysis would also predict a similar bonding scenario, wherein the central bridging C-N bond is almost entirely comprised of unhybridized *p*-orbitals and the remaining C-N bonds have greatly elevated *s*-character [79]. As a result, the C(3)-H bond is predicted to parallel that of the strong and relatively acidic terminal acetylene C-H bond. However, the physical properties of 1-azabicyclo[1.1.0]butane have not been extensively studied so many of its features, such as its strain energy and the pK_a of the C(3)-H bond, remain to be determined.

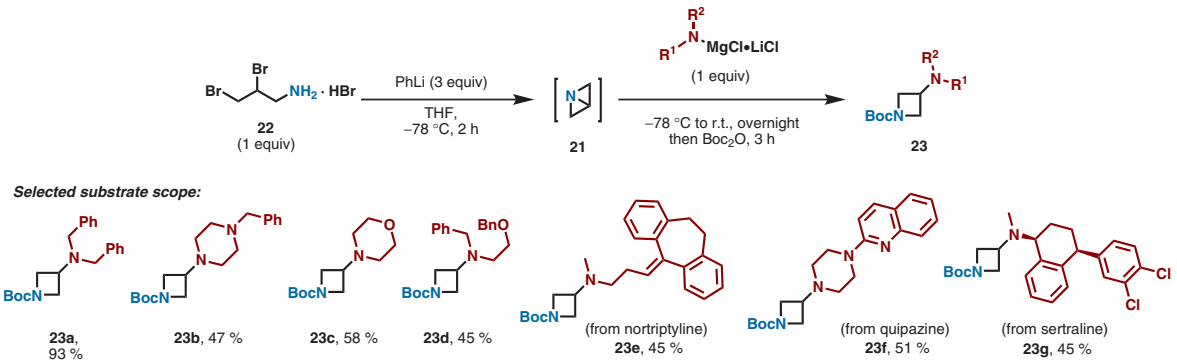
Unsurprisingly, these characteristics have led to the chemistry of 1-azabicyclo[1.1.0]butanes being dominated by its (presumed) high strain energy and the strongly nucleophilic nitrogen atom. This has resulted in numerous examples of the synthesis of 3-substituted azetidines from 1-azabicyclo[1.1.0]butanes, where typically the nitrogen atom initially reacts with an electrophile to extrude a leaving group which subsequently acts as a nucleophile to open the cationic intermediate to give the 3-substituted azetidine products [79].

Presumably because of its unusual structure and absence from natural products and pharmaceuticals, the preparative routes to 1-azabicyclo[1.1.0]butanes are currently limited to the cyclopropanation of azirines [80, 84–87], the intramolecular cyclization of allylnitrenes [88, 89], the photolytic expulsion of CO_2 from bicyclic carbamates [90, 91], and the intramolecular cyclization of 3-halo azetidines [84, 92], 3-carboxyl *N*-chloroazetidines [93], and acyclic dibromoamines [81, 82, 94, 95], with the last being the most direct and displaying the broadest scope, and indeed the only one used by the publications discussed below [96, 97]. In all examples, **21** was prepared *in situ* by the treatment of 2,3-dibromopropan-1-amine hydrobromide (**22**) with three equivalents of phenyl lithium in THF at –78 °C for 2 h (Scheme 9).

In 2016, Baran greatly improved the addition of amine nucleophiles to 1-azabicyclo[1.1.0]butane to form 3-amino azetidines **23** (Scheme 10) [59, 60]. Previously, it had been shown by Sano and Nagao that dibenzylamine and a handful of anilines could undergo addition to **21** in modest yields, however the procedure required two equivalents of $Mg(ClO_4)_2$ for efficient reaction [98, 99]. Furthermore, the addition of morpholine and anilines to the 3-position of substituted 1-azabicyclo[1.1.0]butanes had also been achieved by activation of 1-azabicyclo[1.1.0]butane using dicyanofumarates [100, 101]. The addition of nitro and azide nucleophiles to 1-azabicyclo[1.1.0]butanes had also been described [94, 102–104]. Baran's discovery was



Scheme 9: Preparation of 1-azabicyclo[1.1.0]butane from 2,3-dibromopropan-1-amine hydrobromide **22**.

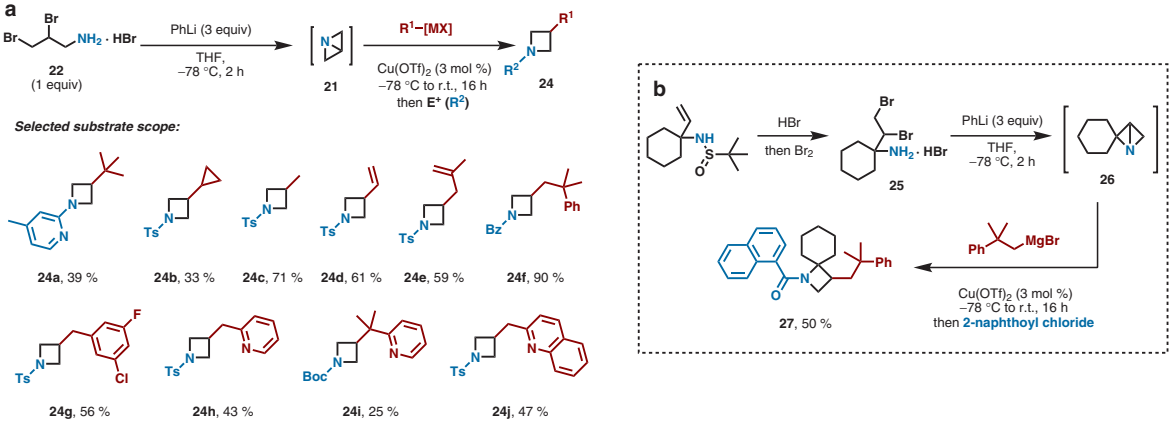


Scheme 10: Baran's 'azetidinylation' of amines by the reaction of *Turbo*-Hauser amides with 1-azabicyclo[1.1.0]butane.

that *Turbo*-Hauser amides, generated by the deprotonation of amines with isopropylmagnesium chloride lithium chloride, efficiently underwent addition to the 3-position of **21** overnight at ambient temperature to give azetidines **23**. This procedure was used for the 'azetidinylation' of a range of amines, including a handful of pharmaceutical compounds, in generally good yields. Given that azetidines are typically introduced into pharmaceuticals via a preformed azetidine building block, this approach potentially enables the late-stage introduction of the azetidine unit onto complex precursors. As a result of this work, **22** is now commercially available [105].

In a similar vein to Baran's work, in 2019 Gianatassio reported the addition of organometal reagents to **21** to yield functionalized azetidines **24** (Scheme 11) [106]. Prior to this work, the addition of carbon-centered nucleophiles to **21** was unprecedented. Presumably inspired by the efficient addition of organocuprates to bicyclo[1.1.0]butanes [31, 52–56], the key discovery here was that a catalytic amount of copper(II) triflate enables the addition of organomagnesium and zinc reagents to the 3-position of **21**. A variety of alkyl and vinyl organometal reagents, in the presence of 3 mol % of copper(II) triflate, added to the 3-position of 1-azabicyclo[1.1.0]butane to yield azetidines, which could subsequently be reacted at the nitrogen atom with a range of different electrophiles to deliver the corresponding bis-functionalized azetidines **24** in mostly good to excellent yields (Scheme 11a).

Another noteworthy addition reported here was the preparation of the first spirocyclic 1-azabicyclo[1.1.0]butyl reagent (Scheme 11b). Dibromoamine **25** was prepared from cyclohexanone by first forming the *N*-sulfinyl imine by condensation with *tert*-butyl sulfonamide, then treating this with vinylmagnesium chloride [107], removing the sulfinyl group using hydrobromic acid and finally dibromination of the olefin



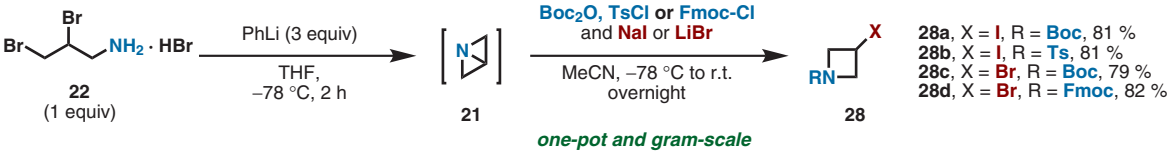
Scheme 11: Gianatassio's alkylation of 1-azabicyclo[1.1.0]butane using organometal reagents. (a) Reaction conditions and selected substrate scope. (b) Synthesis and application of a novel spirocyclic 1-azabicyclo[1.1.0]butane.

using bromine. This precursor could then be treated with phenyl lithium in THF at –78 °C to generate spirocyclic 1-azabicyclo[1.1.0]butane **26** *in situ*, which was then reacted with an organomagnesium reagent in the presence of copper(II) triflate and then 2-naphthoyl chloride to yield spirocyclic azetidine **27** in good yield. Given the importance of nitrogen-containing spirocycles in medicinal chemistry [108], this unique spirocyclic 1-azabicyclo[1.1.0]butane will likely inspire the synthesis of new 1-azabicyclo[1.1.0]butyl reagents for the preparation of novel spirocyclic azetidines.

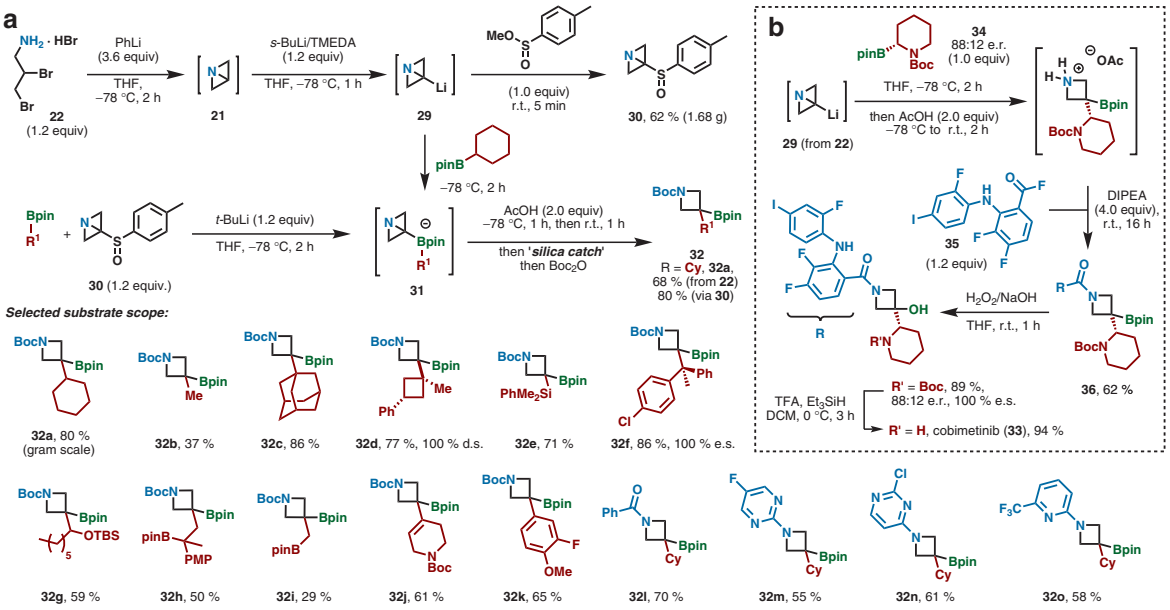
In 2018, Lopchuk and co-workers demonstrated the ability of **21** to greatly streamline the preparation of highly valuable 3-halo (**28**) and 3-carboxyl azetidine building blocks (Scheme 12), which are very commonly used to prepare medicinal agents [109]. It was shown that **21** could be treated with a sodium halide salt and either di-*tert*-butyl dicarbonate (Boc_2O) or *p*-toluenesulfonyl chloride (TsCl) to form the corresponding 3-halogenated azetidines **28** in excellent yields. Much like most of the previous work into the use of 1-azabicyclo[1.1.0]butanes to prepare 3-substituted azetidines, this reaction presumably proceeds via initial reaction of **21** with Boc_2O or TsCl to generate an intermediate cation, followed by nucleophilic attack of a halide anion onto 3-position of the 1-azabicyclo[1.1.0]butyl unit to open the ring and deliver the 3-halo azetidine. To transform **28** into the 3-carboxylazetidines, a cyano group was introduced by substitution of the halide using sodium cyanide which was then hydrolyzed to give the corresponding carboxylic acid. Previously, these azetidine building blocks had been prepared via lengthy sequences [110, 111]. Now, via the intermediacy of 1-azabicyclo[1.1.0]butane, they are available in just a single step from commercially available amine salt **22**, which significantly undercuts the previously reported routes on step count and overall time burden, and greatly improves the overall yields too.

Most recently, in early 2019, Aggarwal reported the first examples of 1-azabicyclo[1.1.0]butyl boronate complexes, formed using novel anion (1-azabicyclo[1.1.0]butan-3-yl)lithium **29**, and their subsequent reactions to form substituted azetidines (Scheme 13) [112]. It was found that boronic esters reacted with **29**, generated *in situ* by the treatment of 3-(p-tolylsulfinyl)-1-azabicyclo[1.1.0]butane (**30**) with *tert*-butyl lithium in THF at –78 °C or by the formation of 1-azabicyclo[1.1.0]butane *in situ* and then deprotonating it with *sec*-butyl lithium for 1 h at –78 °C, to quantitatively form the corresponding 1-azabicyclo[1.1.0]butyl boronate complexes (**31**) over 2 h. Acetic acid was found to be a general promotor of 1,2-metalate rearrangement, to ring-open the 1-azabicyclo[1.1.0]butyl unit and deliver the azetidinium acetates, which were conveniently 'caught' on the top of a silica gel plug, allowing all other contaminants to be eluted through the plug, then collected and reacted with di-*tert*-butyl dicarbonate to ultimately form *N*-*tert*-butyloxycarbonyl borylated azetidines **32** (Scheme 13a). This simple and general procedure resulted in the preparation of over 25 borylated azetidines from a broad range of alkyl, aryl and vinyl boronic esters in good to excellent yield. Bis(boronic esters) could also be regioselectively reacted to give azetidine-bearing 1,2- and 1,3-bis(boronic esters) [113, 114]. Intermediate acetic acid salts could also be reacted with a range of other electrophiles, including benzoyl halides and halogenated (hetero)arenes. Finally, this method was applied to the synthesis of Genentech's melanoma drug, cobimetinib (**33**) (Scheme 13b): [115] using 2-piperidinyl boronic ester **34** and reacting the intermediate acetic acid salt with benzoyl fluoride **35**, borylated azetidine **36** was prepared in 62 % yield from **22**. The final boronic ester oxidation and Boc removal steps resulted in **33** in just three steps and 52 % overall yield from **22**, which compares very favorably to the routes used for its preparation during development [116].

The major development given in this report is the discovery that (1-azabicyclo[1.1.0]butan-3-yl)lithium **29** can be formed in high yield by the deprotonation of **21** with *sec*-butyl lithium (Scheme 13a). This reactivity



Scheme 12: Lopchuk's synthesis of 3-halo azetidines using 1-azabicyclo[1.1.0]butane.



Scheme 13: Aggarwal's preparation of 1-azabicyclo[1.1.0]butyl boronate complexes and their application to the synthesis of azetidines. (a) Reaction conditions and selected substrate scope. (b) Application of this method to the synthesis of cobimetinib. Enantiospecificity (e.s.) = (e.e. of product/e.e. of starting material) × 100 %. Diastereospecificity (d.s.) = (d.e. of product/d.e. of starting material) × 100 %.

represents an umpolung approach as it completely reverses the typical electrophilic behavior of **21** by yielding **29** which is patently nucleophilic at the 3-position. The isolation of 3-(p-tolylsulfinyl)-1-azabicyclo[1.1.0]butane (**30**) as a convenient, solid precursor to **29** is important because it should facilitate its day-to-day use in the development of new methods requiring **29** as a key reaction component or to prepare 1-azabicyclo[1.1.0]butane-containing substrates which would be otherwise inaccessible using previously reported chemistry.

Conclusions

Recent interest in the preparation of cyclobutanes and azetidines for application in pharmaceutical synthesis has led to increased interest in the chemistry of bicyclo[1.1.0]- and 1-azabicyclo[1.1.0]butanes. In the past few years, a great number of exciting developments have been realized in these fields which cement the importance of these units in synthetic chemistry as precursors to functionalized cyclobutanes and azetidines, yet it is clear from this brief survey of recent developments that there are many areas of underexplored reactivity. For example, the reaction of the 1-azabicyclo[1.1.0]butane unit with transition metals and radicals is entirely unexplored, and the intramolecular reaction of functional groups with bicyclo[1.1.0]- and 1-azabicyclo[1.1.0]butane, and in general the use of bicyclo[1.1.0]butanes in catalysis, is underexplored. Studies such as these will be expedited by the recent development of convenient sources of nucleophilic bicyclo[1.1.0]butane and 1-azabicyclo[1.1.0]butane, and the commercialization of the 1-azabicyclo[1.1.0]butane precursor. These new reagents, coupled with the potential for bicyclo[1.1.0]butane and 1-azabicyclo[1.1.0]butane to be deprotonated and functionalized [31–36, 112], hint at a much broader range of bicyclo[1.1.0]- and 1-azabicyclo[1.1.0]butane-containing structures whose chemistry has yet to be evaluated.

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