

Synthesis and strain-release reactions of 1-azabicyclo[1.1.0]butanes: an update

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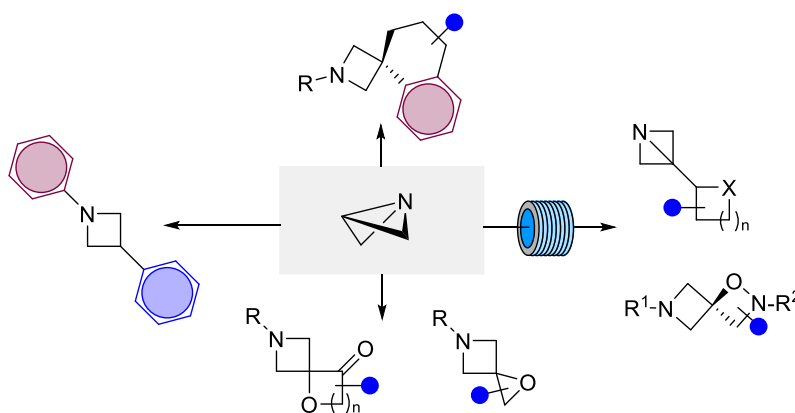
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Abstract

Azabicyclo[1.1.0]butanes (ABBs) are important synthetic tools for the preparation of functionalized azetidines. The transformations of azabicyclo[1.1.0]butanes generally involve the C3-N bond cleavage, which allows for the functionalization of the azacycles in the 1,3 positions. Recently, important advances in the field have led to the preparation of novel strained compounds from ABBs. Diverse spirocyclic and heterocyclic-substituted azetidines could be prepared, also harnessing enabling technologies. This review aims to discuss the most recent reports regarding the synthesis and transformations of ABBs as versatile synthons for the construction of pharmaceutically relevant heterocycles.



Keywords: Azabicyclo[1.1.0]butanes, azetidines, heterocycles, flow chemistry, spiro compounds

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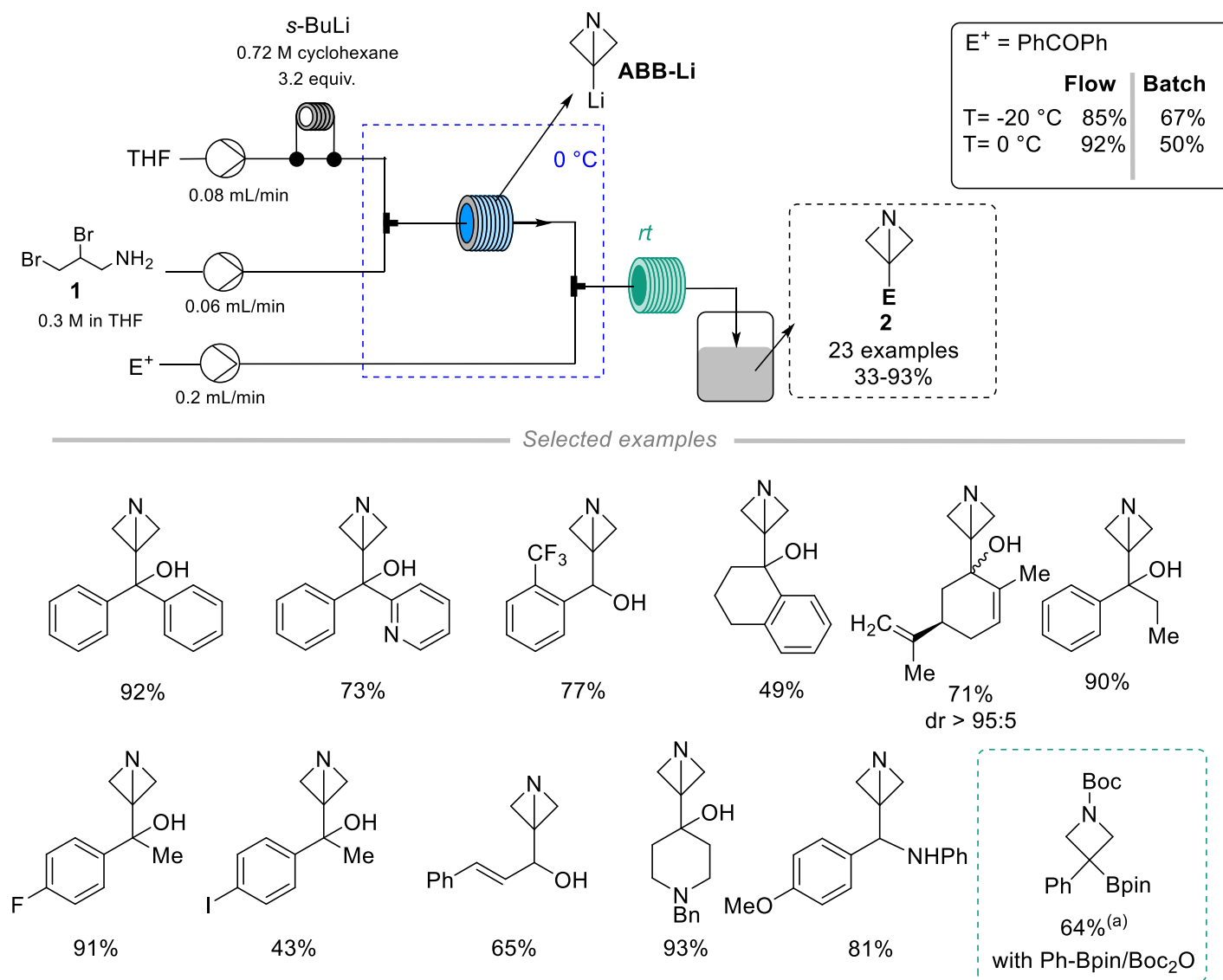
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1. Introduction

Strained nitrogen-containing heterocycles are important scaffolds for the development of new small-molecule pharmaceuticals.¹ In particular, the use of azetidines in medicinal chemistry has grown over the recent years because of their improved pharmacokinetic properties compared with their cyclic homologs.^{2,3} The presence of the azetidine ring in biologically active molecules confers greater bioavailability and metabolic stability than non strained rings and can improve clinical success due to its 3D character.⁴ These advances have led to the development of several marketed drugs that contain an azetidine ring. In parallel with this innovation, organic chemists devoted their efforts to the development of efficient methods for the construction and functionalization of the azetidine ring.⁵⁻¹⁰ The strategies that allow for the preparation of azetidines generally involve cycloaddition, cyclization, ring-expansion, and ring-contraction transformations.¹¹ Aside from these general methods, the exploitation of azabicyclo[1.1.0]butanes (ABBs) represents an innovative approach and recently enabled the access to an unexplored chemical space. The reactivity of ABBs mostly relies on strain-release transformations involving the cleavage of the C3-N bond and the consequent functionalization on 1,3 positions. Considering the growing interest in the manipulation of azabicyclo[1.1.0]butanes for the synthesis of functionalized azetidines, we recently reviewed this chemistry offering a comprehensive picture of the methods published until 2020.¹² However, during the past two years, several relevant methods for the transformation of azabicyclo[1.1.0]butanes have been reported. This review covers the last recent advances in the synthesis of novel spirocyclic and bicyclic entities of ABBs, also exploiting the use of enabling technologies.

2. Telescoped Flow Synthesis and Trapping of (1-Azabicyclo[1.1.0]butan-3-yl)lithium

In 2021, Luisi, Kappe *et al.* reported a continuous and telescoped flow approach for the generation, lithiation, and functionalization of azabicyclo[1.1.0]butane from 2,3-dibromopropylamine.¹³ It is worth mentioning that the exploitation of the microfluidic technology required milder conditions compared with those needed in traditional batch reactors. The optimized flow method allows for the preparation of azabicyclo[1.1.0]butane and its lithiation at C3 within a few minutes at 0°C and employing 3 equivalents of *s*-BuLi, with better yields compared to the batch process (Scheme 1). **ABB-Li** was subsequently trapped in a multistep one-flow fashion with a selection of aldehydes and ketones furnishing unprecedented C3-functionalized-1-azabicyclobutanes **2**.

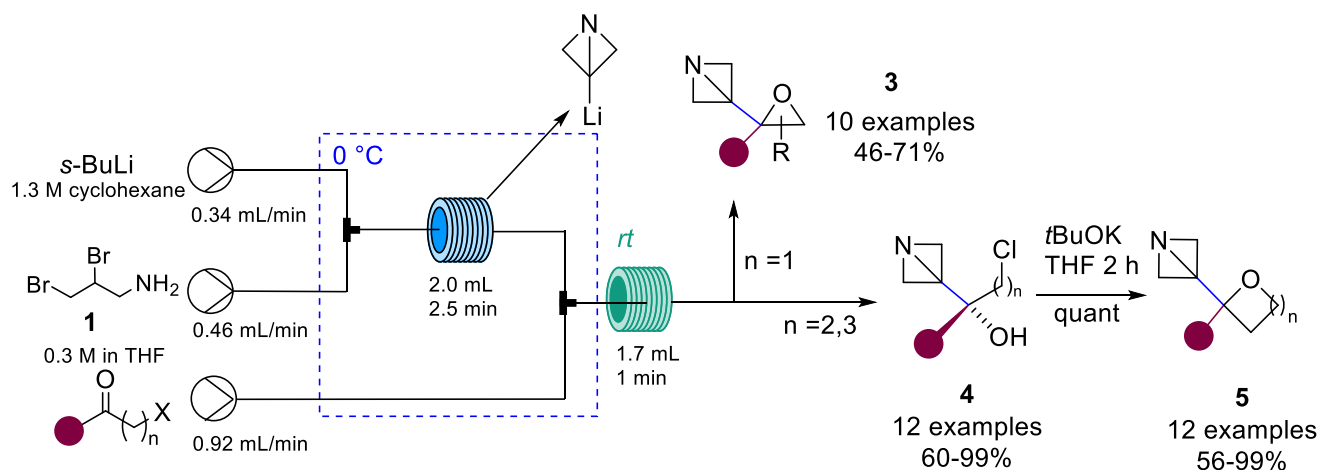


Scheme 1. Continuous flow preparation of 3-substituted ABBs. a) The resulting intermediate boronate complex was treated with AcOH, then with Boc₂O and Et₃N.

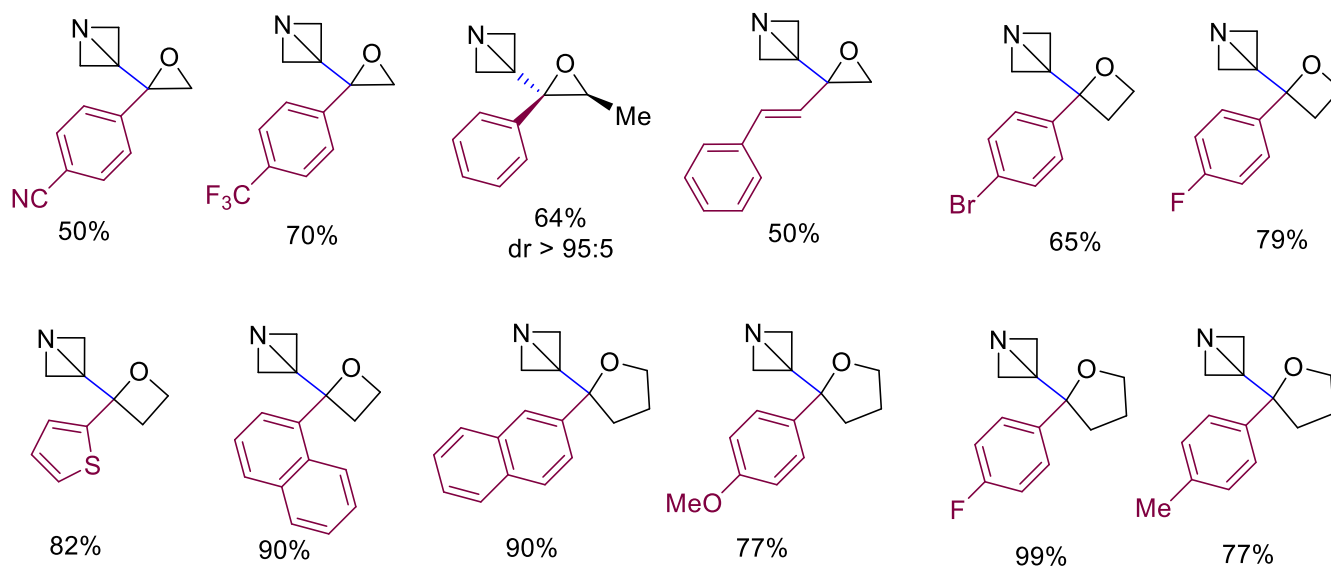
The transformation was found to be tolerant to several functionalities installed on the electrophiles including halogens (Cl, Br, I), a trifluoromethyl, benzyloxy, and methoxy group, and tertiary amines. It is worth noting that, when alkyl aryl ketones were employed, the transformation afforded smoothly the desired product and no enolization was observed. Moreover, the use of aryl aldehydes and ketones bearing a substituent in the *ortho* position was well tolerated, and the addition of **ABB-Li** to chiral optically active carvone led to the preparation of the corresponding product with a remarkable stereoselectivity (dr >95:5). As a further application, an imine and boronic esters could be efficiently trapped, proving that the flow method is not limited to the use of ketones and aldehydes as the electrophilic partners. In detail, when boronic esters were employed, the resulting boronate complexes were directly treated with AcOH and subsequently with Boc₂O and triethylamine, promoting the 1,2-metalate rearrangement and furnishing the corresponding functionalized azetidines. An additional advantage of the use of microfluidic reactors is that the reaction can be easily scaled up by an adjusted set-up and, for a model compound, the yield remained constant for 4 h in continuous flow mode, ensuring the scalability of the process.

In 2022, Luisi and coworkers further expanded the method and opened access to unexplored structural motifs bearing two different heterocycles with C2-C3 connectivity (Scheme 2).¹⁴ By utilizing a similar continuous flow approach, various electrophiles such as α -, β -, and γ -haloalkylketones could be involved in the reaction. Interestingly, the use of α -haloketones resulted in the isolation of epoxides **3** derived from an intramolecular displacement of the chlorine atom by the alkoxy group, which in turn is generated by the addition of the **ABB-Li** to the electrophile. The reaction proceeded stereoselectively when α -substituted- α -haloalkylketones were employed, affording the products in good yields and with excellent diastereomeric ratios (dr > 95:5). In these novel species, two different heterocycles, epoxide, and azabicyclo[1.1.0]butane, are linked through a C3(N_{het})-C2(O_{het}) connectivity.

Continuous flow preparation of C3-oxacyclic-ABBs

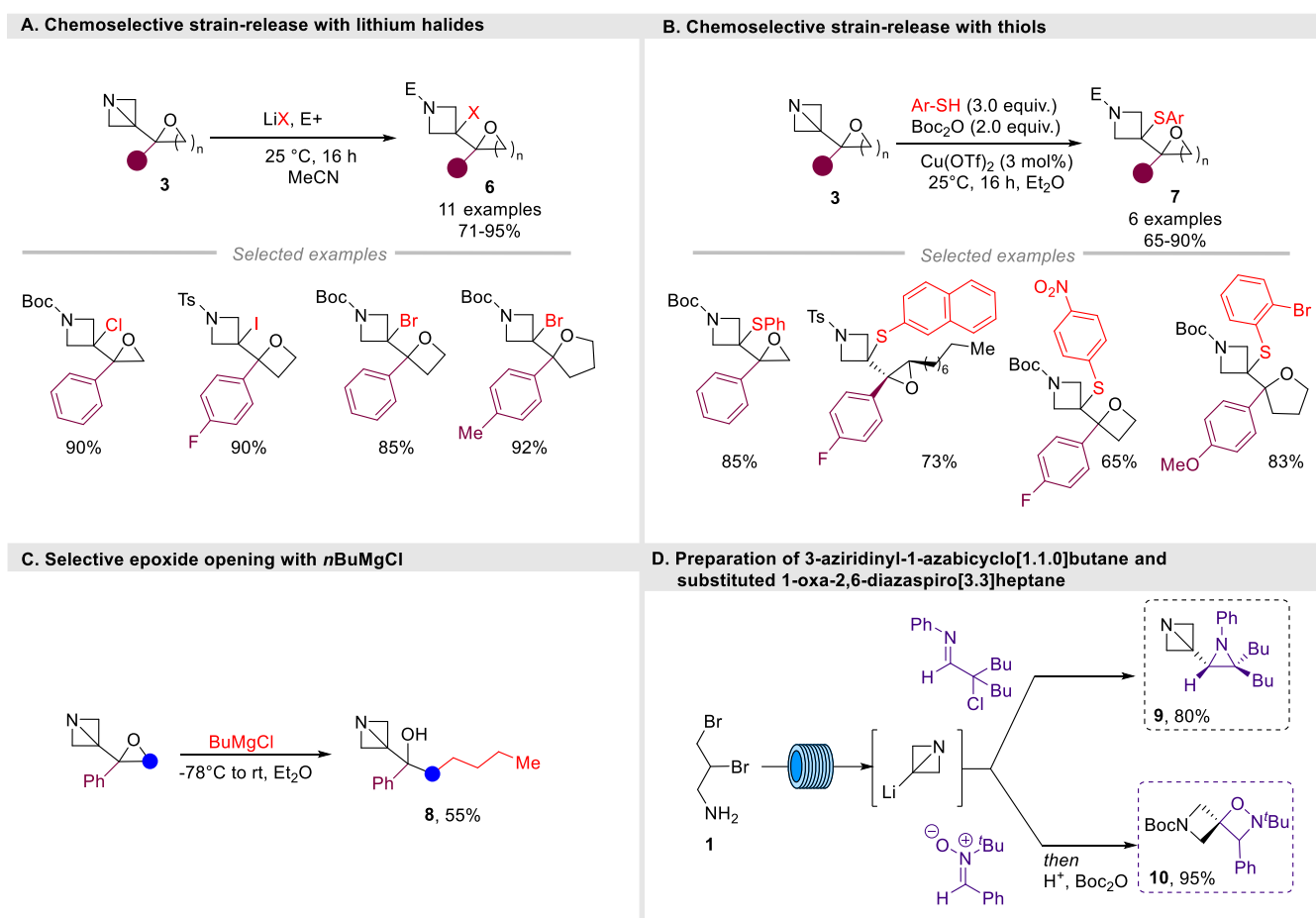


Selected examples



Scheme 2. Continuous flow synthesis of C3-oxacyclic ABBs.

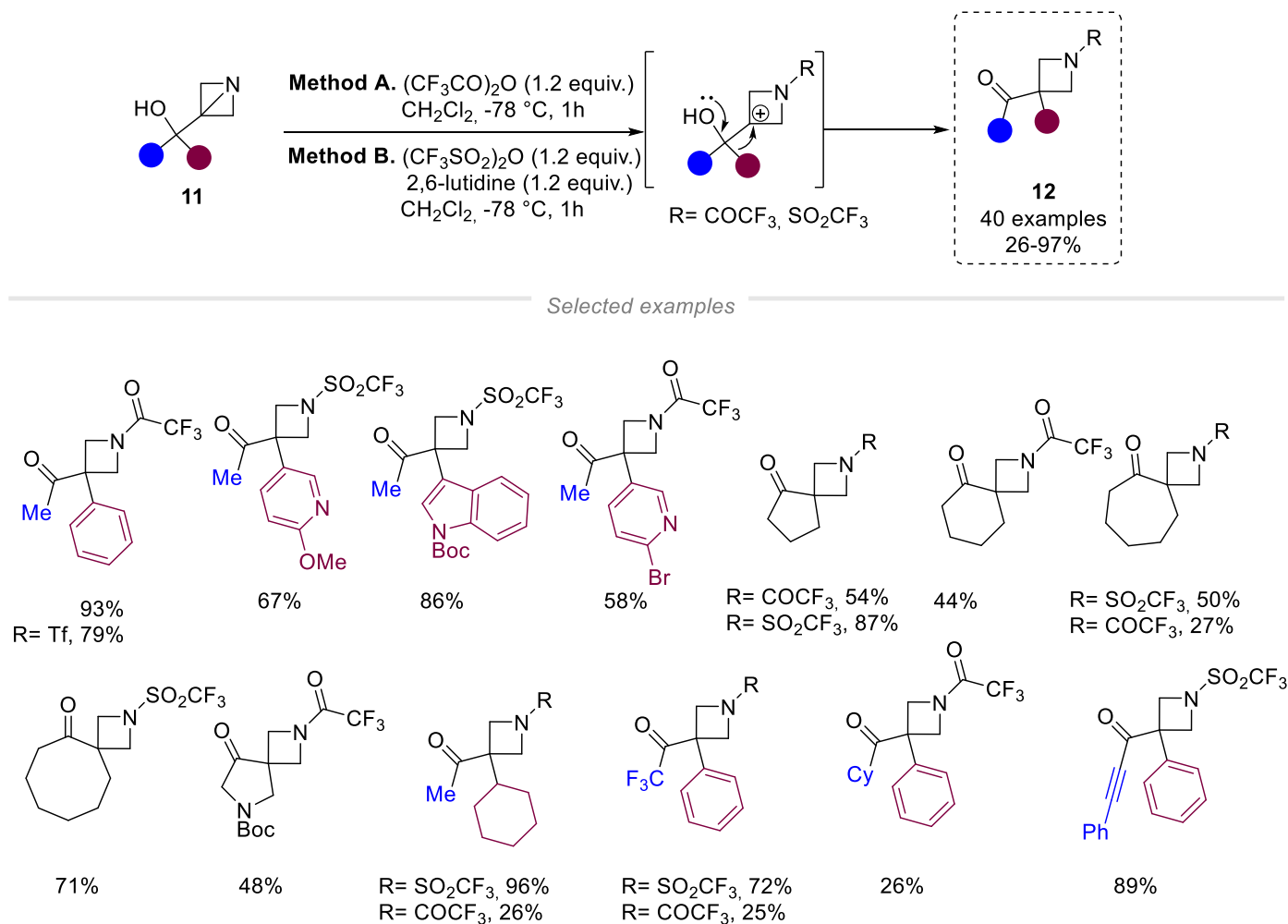
The use of β - and γ -haloalkylketones furnished isolable β - and γ -halohydrins **4**, which could be quantitatively converted into the corresponding oxetanes and tetrahydrofuran derivatives **5** by treatment with *t*BuOK. In general, the reaction is tolerant to the presence of diverse functionalities (CN, CF₃, F, Br, OMe) installed on the electrophiles. Moreover, chemoselective strain-release transformations of the products were explored. The treatment of these compounds with lithium halides in the presence of an electrophile allowed the selective cleavage of the C3-N bond of the ABB system and furnished the corresponding saturated azetidines **6** in good yields (Scheme 3, A). Similarly, the C3-N bond cleavage could be achieved with thiols upon copper catalysis leading to 3-thiolated azetidines **7** bearing the saturated oxygen heterocycle with C3-C2 connectivity (Scheme 3, B). The addition of BuMgCl proceeded differently and the nucleophile was added to the oxygenated ring, avoiding the transformation of the ABB system, furnishing azabicyclo[1.1.0]butyl carbinol **8** in 55% yield (Scheme 3, C). In addition, the treatment of **ABB-Li** with an α -chloroimine led to the preparation of an unprecedented 3-aziridinyl azabicyclo[1.1.0]butane **9**, while the addition of a nitron and the subsequent acidic treatment in the presence of Boc₂O promoted the strain release, allowing for the formation of the spirocyclic azetidine-oxazetidine **10** in excellent yield (Scheme 3, D).



Scheme 3. Chemoselective transformations of C3-heterocyclic-ABB, and synthesis of 3-aziridinyl-ABB and 1-oxa-2,6-diazaspiro[3.3]heptane.

3. Strain-Release Spirocyclization of 1-Azabicyclo[1.1.0]butanes

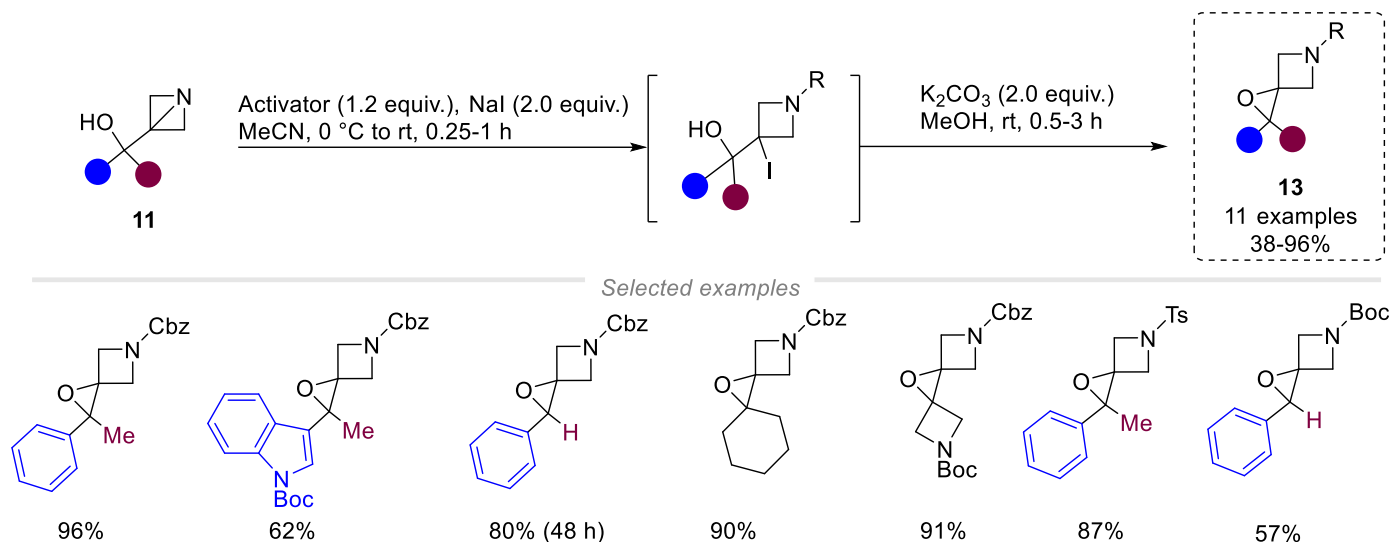
In 2021, Aggarwal and co-workers developed a pioneering work investigating various strain-release spirocyclization reactions of azabicyclo[1.1.0]butanes. Initially, the authors reported the preparation of semipinacol and spiroepoxy azetidines by strain-release of azabicyclo[1.1.0]butyl carbinols **11** (Scheme 4).¹⁵ At first, the simple treatment of azabicyclo[1.1.0]butyl carbinols with trifluoroacetic or triflic anhydride promoted the semipinacol rearrangement which led to keto 1,3,3-substituted azetidines **12**. The protocol utilizing triflic anhydride (Method B) requires the use of 2,6-lutidine for the effective migration of the allylic or aryl group. Outstandingly, the reaction scope is wide, and an interesting class of spirocyclic azetidines bearing a 5- to 8-membered (hetero)cycle could be easily prepared from the corresponding ABB-carbinols **11** (Scheme 4).



Scheme 4. Strain-release semipinacol rearrangement of azabicyclo[1.1.0]butyl carbinols.

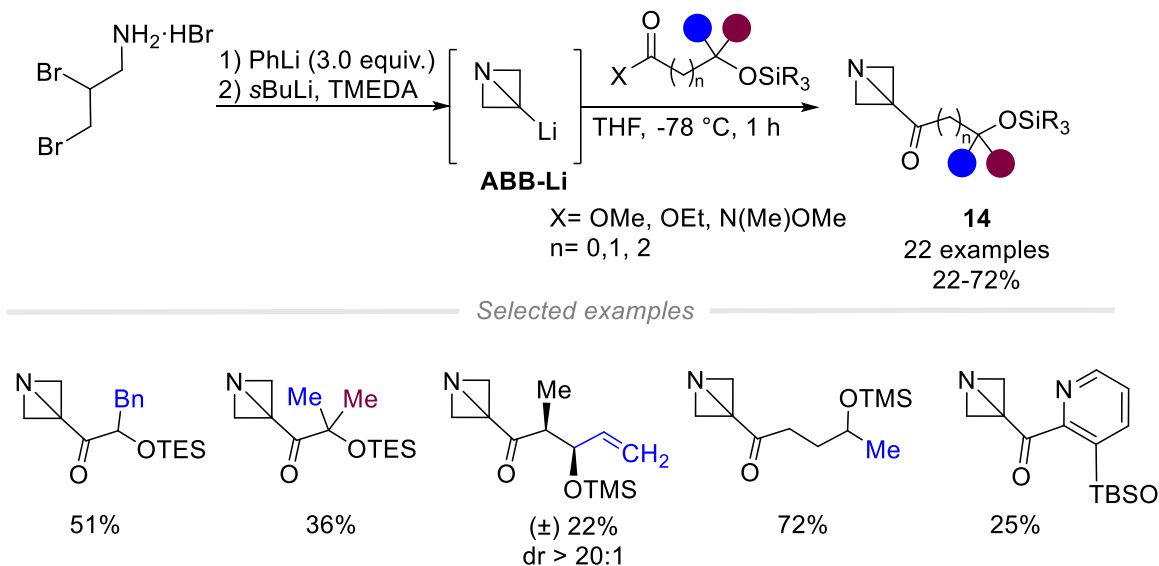
In this regard, the reaction yield and selectivity were found to be strongly influenced by the nature of the electrophile used for the nitrogen functionalization. In most of the cases, the treatment with triflic anhydride resulted in better yields. It is worth noting that the migration of aryl groups is favored when compared to alkyl groups, and the reaction generally proceeded with excellent selectivity, in particular when trifluoroacetic anhydride was used. In addition, the observed relative migratory aptitude in the semipinacol rearrangement was aryl > alkenyl > more substituted alkyl > less substituted alkyl, hydrogen. However, the reaction with triflic

anhydride is fast, and a loss of selectivity was observed in some cases. Alternatively, the reaction of azabicyclo[1.1.0]cyclobutyl carbinols with an electrophile and sodium iodide, and the subsequent addition of potassium carbonate, furnished spiro-epoxy azetidines **13** in good to excellent yields (Scheme 5). The reaction proceeds *via* the generation of an α -iodohydrin that undergoes a base-promoted intramolecular cyclization. It is worth mentioning that the cyclization rate drops severely with less substituted carbinols.



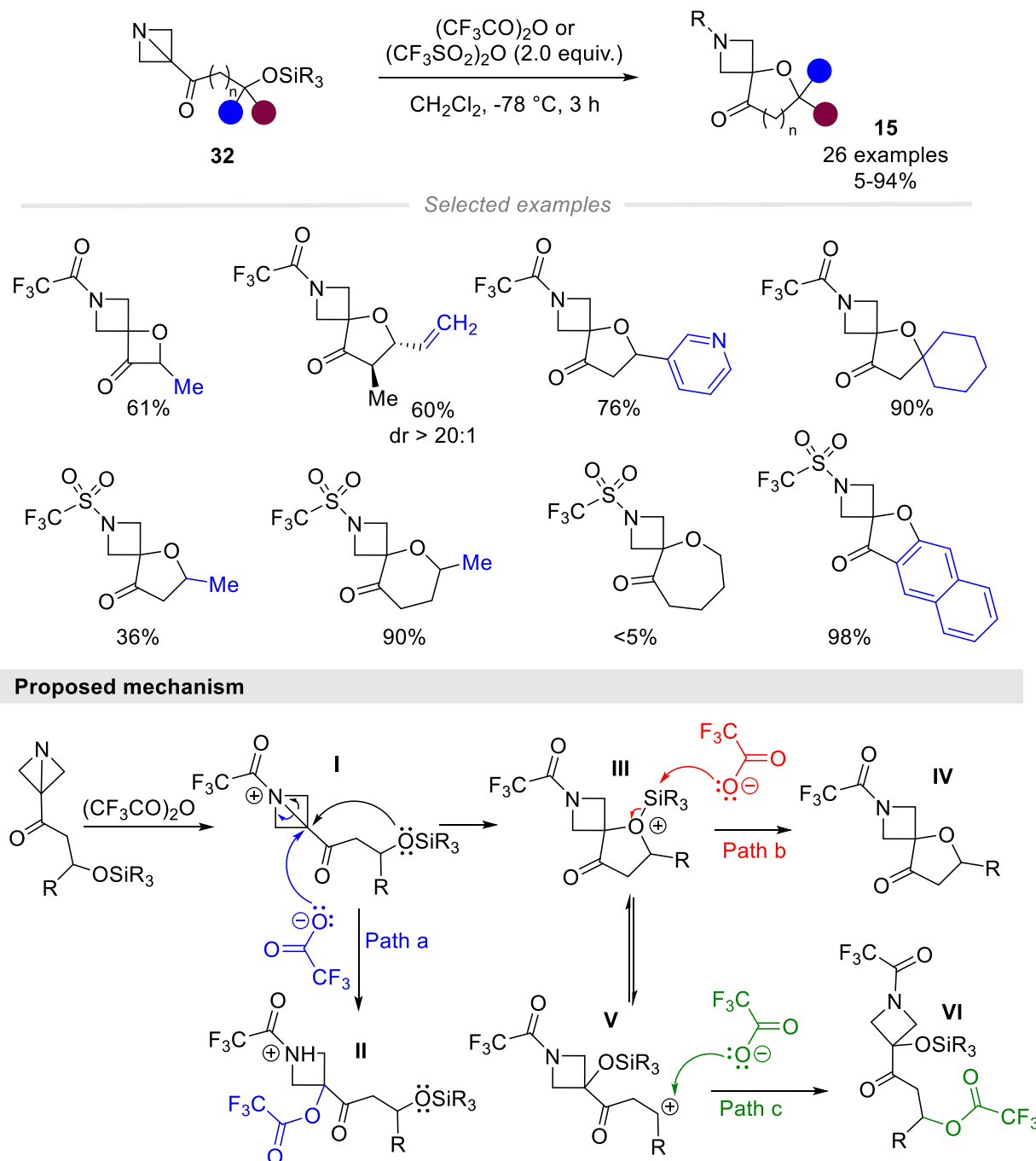
Scheme 5. Strain-release spirocyclization of azabicyclo[1.1.0]butyl carbinols.

In 2021, Aggarwal *et al.* also reported the spirocyclization of azabicyclo[1.1.0]butyl ketones.¹⁶ Freshly prepared **ABB-Li** was treated with esters or Weinreb amides bearing a silyl protected hydroxy group in α -, β -, γ - or δ - position, furnishing stable azabicyclo[1.1.0]butyl ketones **14** (Scheme 6). Interestingly, these compounds could be engaged in an intramolecular cyclization/desilylation reaction upon treatment with an electrophile. While Lewis acids such as boron trifluoride failed in promoting the cyclization, the use of triflic and trifluoroacetic anhydrides successfully furnished the spirocyclic products in good yields.



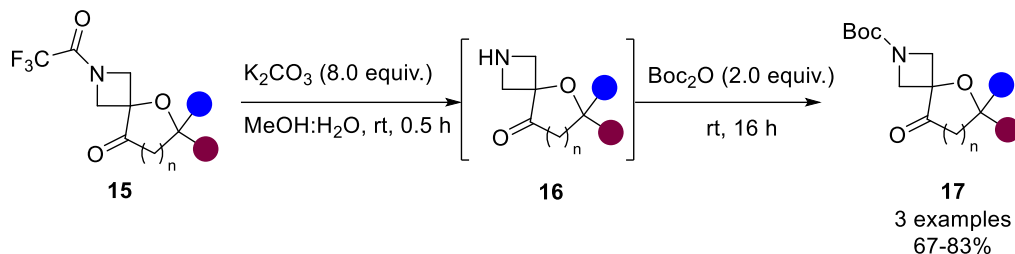
Scheme 6. Synthesis of azabicyclo[1.1.0]butyl ketones.

The method allowed for the preparation of a selection of oxa-azaspiro[3.3]heptane, oxa-azaspiro[3.4]octanes, and larger ring analogues **15** (Scheme 7). The synthesis of a selection of aromatic fused spirocyclic compounds was likewise accomplished and a gram scale-up was achieved for a selected oxa-azaspiro[3.3]heptane without any substantial loss of yield. A reaction mechanism was proposed based on the isolation of different by-products. The desired products could arise from the trifluoroacetate-mediated desilylation of a transient spirocyclic oxonium ion **III** (Scheme 7). Alternatively, the generated cationic ABB **I** can be directly attacked by trifluoroacetate leading to subproduct **II**. In addition, the isomerization of the oxonium ion to the carbocation **V** and the subsequent attack of trifluoroacetate generated the subproduct **VI** (Scheme 7).



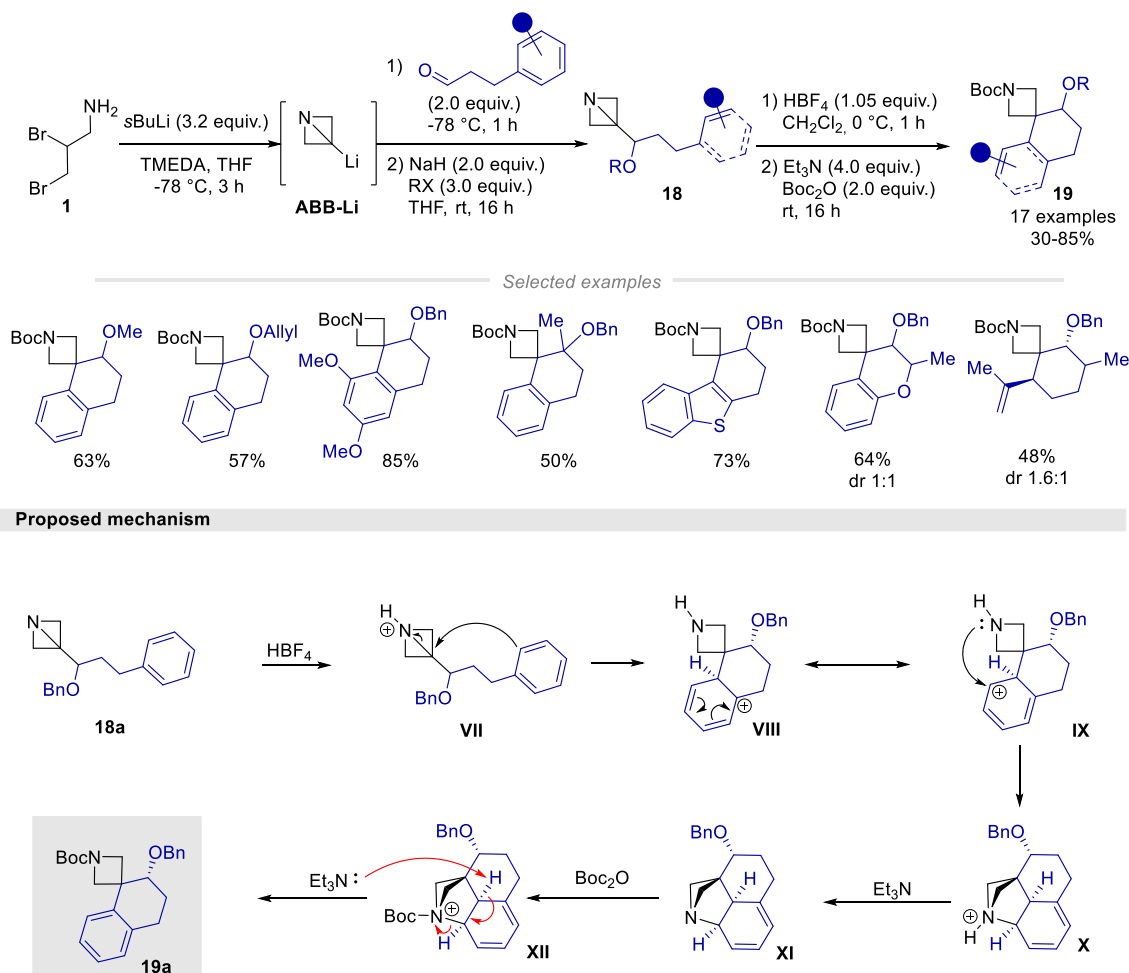
Scheme 7. Strain-release spirocyclization of azabicyclo[1.1.0]butyl ketones.

However, spirocyclic azetidines **15** could be obtained with good selectivity upon the optimized conditions. The authors additionally described the nitrogen deprotection from the trifluoroacetyl group that was achieved upon treatment with a large excess of potassium carbonate (8.0 equiv) in MeOH:H₂O and at room temperature (Scheme 8). The resulting NH-spiroazetidines **16** were directly reacted with Boc₂O *en route* to Boc-protected spirocyclic azetidines **17** in good yields (Scheme 8).



Scheme 8. Hydrolysis of trifluoroacetyl-protected azetidine spirocycles and Boc functionalization.

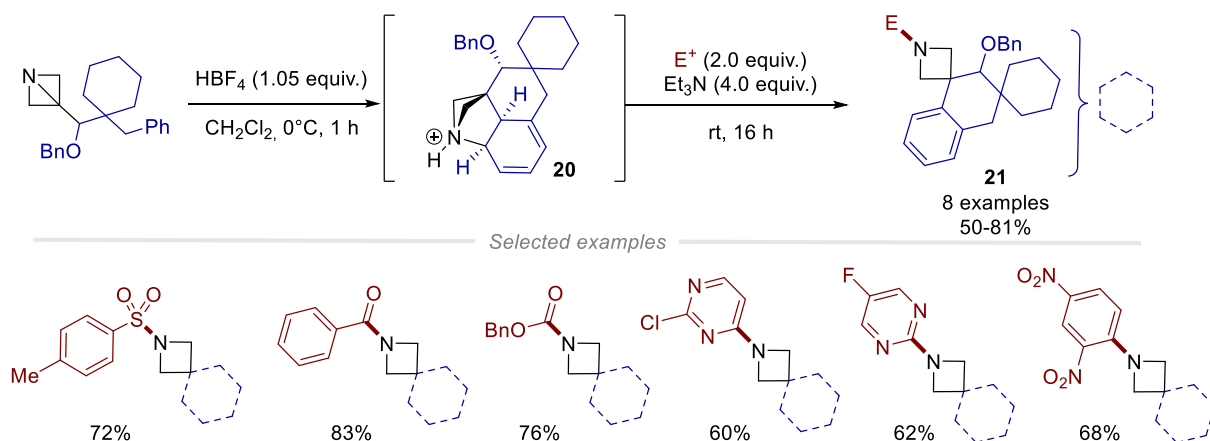
Subsequently, in 2021, the Aggarwal's group reported a novel strain-release-driven Friedel-Crafts spirocyclization of ABBs.¹⁷ In this approach, a library of azabicyclo[1.1.0]butyl carbinols was synthesized from **ABB-Li** by treatment with a selection of β -aryl aldehydes (Scheme 9).



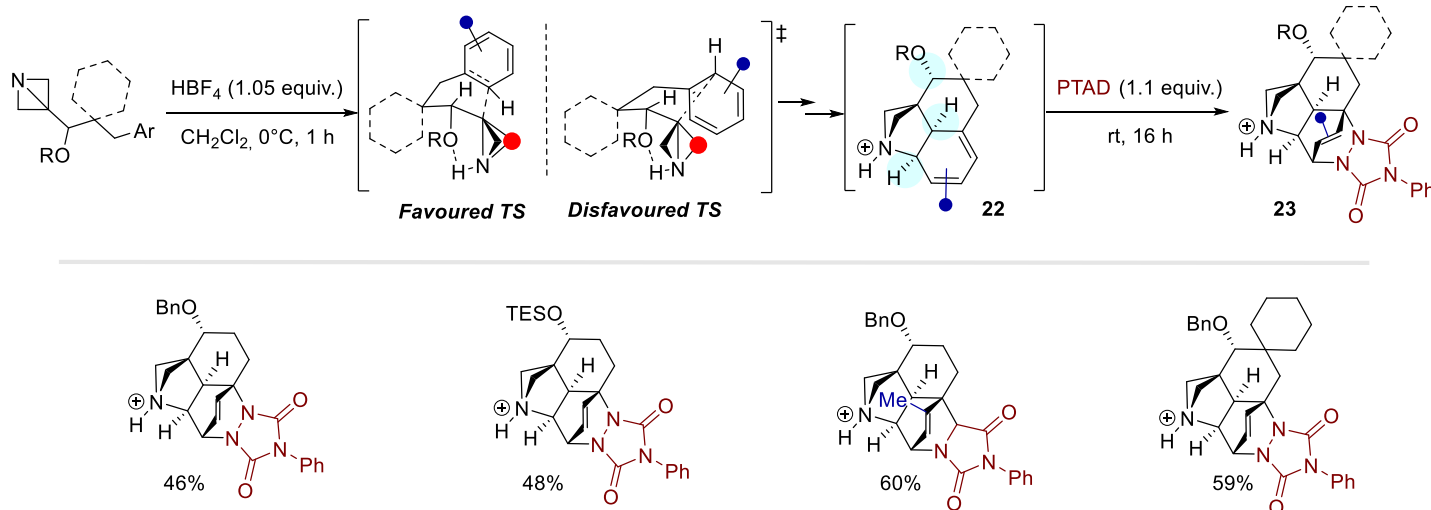
Scheme 9. Strain-release-driven Friedel-Crafts spirocyclization of ABBs.

The transformation of ABB-carbinols with sodium hydride and an alkyl or silyl halide furnished the corresponding ethers **18** that were used for the exploitation of the strain-release transformation. In the optimized conditions, the Friedel-Crafts-driven spirocyclization of **18** proceeded smoothly with HBF_4 followed by the addition of a base and Boc_2O . According to the proposed mechanism, tetrafluoroboric acid activates the C3-N bond by protonation of the nitrogen, and the aryl fragment can add to the C3 of ABB system according to a Friedel-Crafts reaction (Scheme 9). The rapid proton shift and intramolecular addition of the nitrogen to the cationic ring lead to the formation of a bicyclic intermediate, that affords the final product after treatment with Boc_2O and the final base-promoted rearomatization. A range of substituted β -(hetero)aryl aldehydes could be efficiently transformed *en route* to spirocyclic compounds **19** (Scheme 9). Moreover, the authors envisioned that they could harness the use of other electrophiles aside from the Boc anhydride for the functionalization of the nitrogen atom in the second step of the transformation (Scheme 10, A). Interestingly, a selection of substituents such as strongly deactivated aryls, a sulfonyl, and an acyl group could decorate the azetidine nitrogen atom affording the corresponding products **21**.

A. Electrophile-induced rearomatization



B. PTAD interrupted Friedel-Crafts/Diels Alder dearomatization reaction



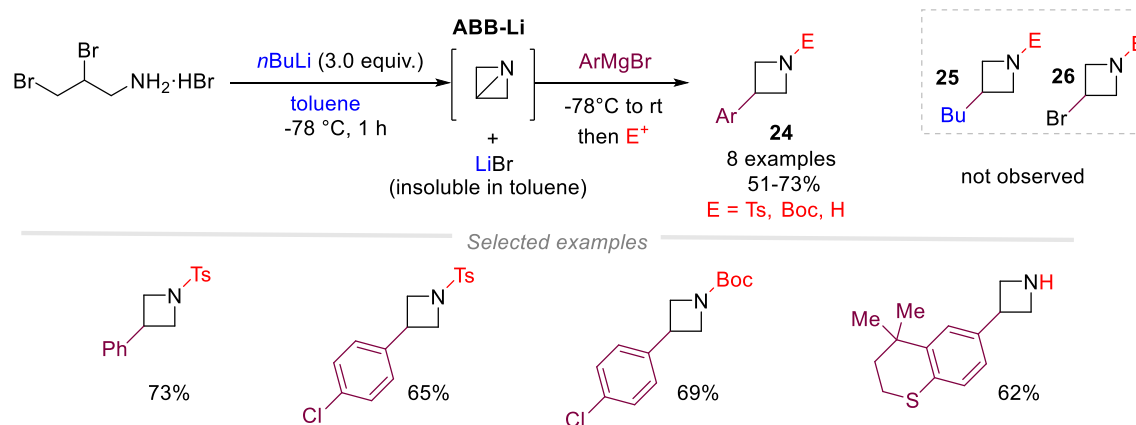
Scheme 10. Further Friedel-Crafts spirocyclization of azabicyclo[1.1.0]butyl carbinol ethers.

Finally, the authors could interrupt the reaction before the rearomatization step by exploiting the addition of PTAD (4-Phenyl-1,2,4-triazole-3,5-dione) as a suitable dienophile for the Diels-Alder transformation of the intermediate **22** (Scheme 10, B). It is worth noting that the corresponding products **23** were obtained as a single diastereoisomer. The stereoselectivity has been explained considering the existence of a preferred transition state as shown in Scheme 10, B.

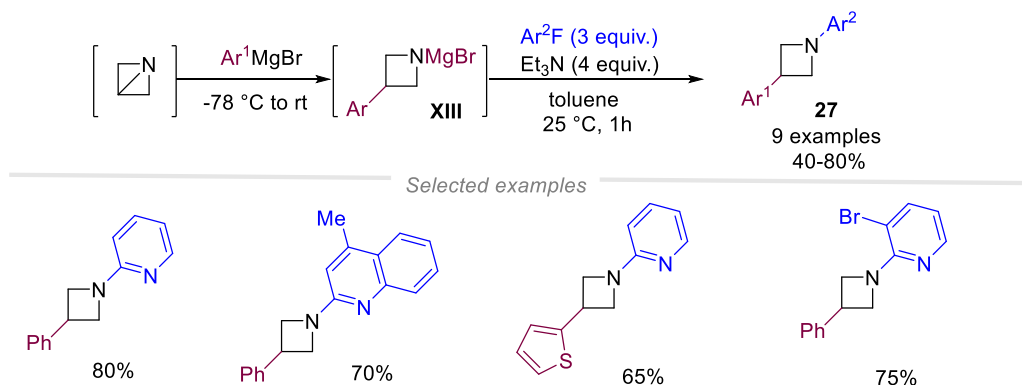
4. Synthesis of 1,3-Bisarylazetidines from ABBs

In 2022, a strain-release arylation approach was exploited by Didier and coworkers for the efficient preparation of 1,3-bisarylated azetidines, which are scarcely explored motifs in the literature.¹⁸ At first, the C3 functionalization of ABB through nucleophilic ring-opening with aryl Grignard reagents was examined. In comparison with previous reports, the ABB system was generated by using the less nucleophilic *n*-BuLi as the lithiation agent instead of PhLi to suppress the by-product **25** derived from the addition of the organolithium reagent to the ABB system. Furthermore, toluene was selected as the solvent to precipitate LiBr, generated after the Li/Br exchange reaction, which was responsible for the formation of the by-product **26**. Adopting these modifications, a series of *ex situ* generated aryl Grignard reagents were found to be suitable for the strain-release producing a series of 3-arylated azetidines **24** (Scheme 11, A).

A. Ring opening of azabicyclo[1.1.0]butanes with aryl Grignard reagents



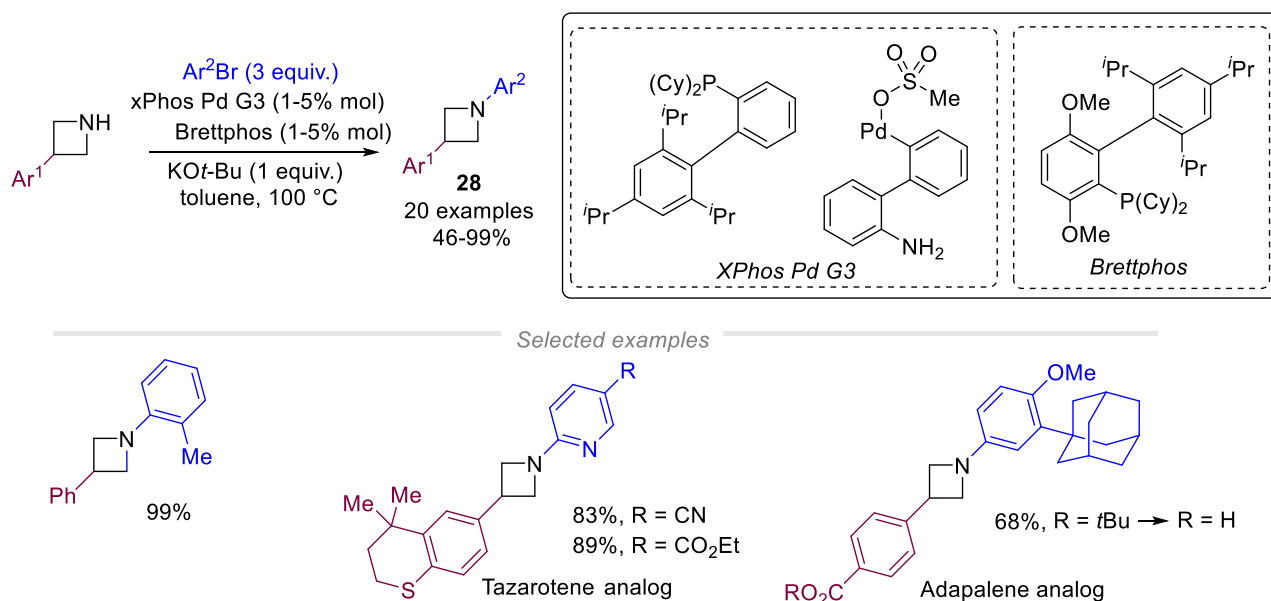
B. S_NAr of C3-aryl azetidines



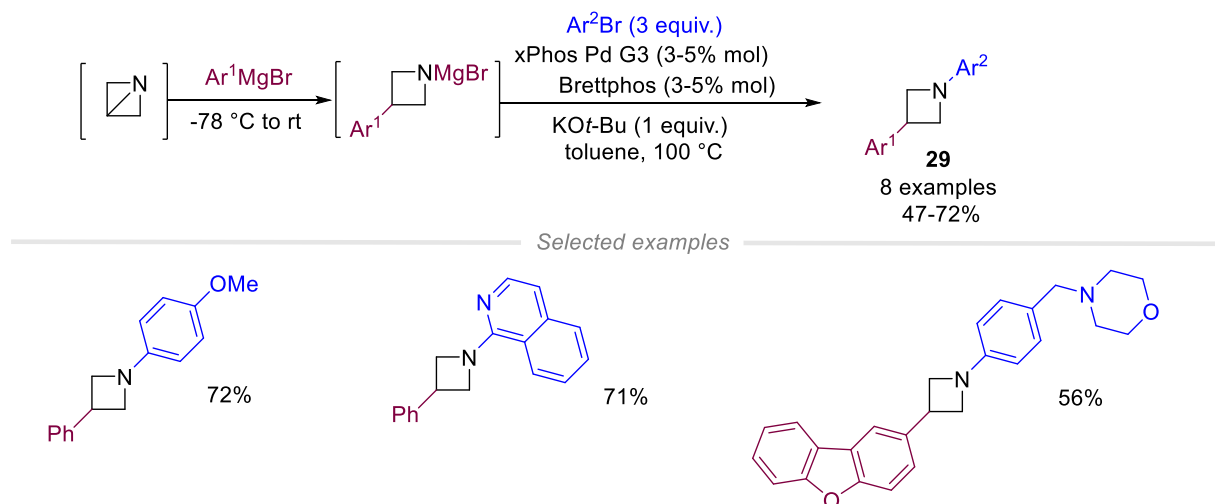
Scheme 11. Ring opening of ABB with aryl Grignard reagents and arylation through nucleophilic aromatic substitution (S_NAr).

Subsequently, the *N*-arylation of obtained azetidines was studied. In particular, the authors demonstrated how the *N*-azetidylmagnesium intermediate **XIII** could undergo a nucleophilic aromatic substitution (S_NAr) using 2-fluoropyridines in the presence of triethylamine (Scheme 11, B) to produce the desired 1,3-bisarylated azetidines **27**. Although this approach was proved to be efficient, it was limited to the use of fluorinated pyridines. Hence, aiming for a more a general strategy to prepare 1,3-bisarylated azetidines, the functionalization of the nitrogen through a Buchwald-Hartwig coupling was investigated. According to the optimized reaction conditions, free 3-arylazetidines were successfully coupled with various aryl and heteroaryl bromides using xPhosPdG3/Brettphos ([[(2-Di-cyclohexylphosphino-3,6-dimethoxy-2',4',6'- triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate) as the catalytic system in the presence of *t*-BuOK as the base (Scheme 12, A).

A. Preparation of 1,3-bisarylated azetidines through Buchwald-Hartwig coupling



B. One-pot strain-release/Pd-coupling sequence



Scheme 12. Preparation of 1,3-bisarylated azetidines through Buchwald-Hartwig coupling.

This approach enabled the high-yielding preparation of a series of 1,3-bisarylated azetidines **28**, among which the azetidine analogs of adapalene and tazarotene are particularly interesting. Furthermore, to circumvent the preparation and purification of free 3-arylazetidines, a convenient one-pot procedure involving the strain-release and the Buchwald-Hartwig coupling was developed. Hence, *N*-azetidinylmagnesium intermediates, generated through the nucleophilic addition of aryl Grignard reagents to the *in-situ* generated ABB, were subjected to Pd-catalyzed C-N coupling with aryl bromides adopting the previously described reaction conditions, to produce the bis-functionalized azetidines **29** (Scheme 12, B).

5. Conclusions

1-Azabicyclo[1.1.0]butanes are useful precursors of functionalized azetidines. Since the late 1960s, several methods allowing for the functionalization at the 1,3 positions, through the cleavage of the C3-N bond, have been reported. However, during the past two years, some novel and interesting transformations of ABBs have been disclosed, accessing an unexplored chemical space. Azabicyclobutanes bearing a saturated heterocycle with C3_(ABB)-C2_(het) connectivity could be easily prepared and further manipulated to furnish diversely functionalized azetidines. In addition, a library of spirocyclic azetidines could be prepared through strain-release spirocyclization of azabicyclo[1.1.0]butyl carbinols and ketones, and the easy preparation of 1,3-diaryl azetidines from azabicyclo[1.1.0]butane were achieved. Considering the growing interest in the exploitation of ABBs as precursors of pharmaceutically relevant azetidines, further advances are expected to come soon.

Acknowledgments

The authors are grateful to all the researchers that developed the interesting transformations of azabicyclo[1.1.0]butanes discussed in this review.

References

1. Parmar, D. R.; Soni, J. Y.; Guduru, R.; Rayani, R. H.; Kusurkar, R. V.; Vala, A. G. *Archiv der Pharmazie* **2021**, 354, 2100062.
<https://doi.org/10.1002/ardp.202100062>
2. Meanwell, N. A. *Chem. Res. Toxicol.* **2016**, 29, 564.
<https://doi.org/10.1021/acs.chemrestox.6b00043>
3. St. Jean, D. J., Jr.; Fotsch, C. J. *Med. Chem.* **2012**, 55, 6002.
<https://doi.org/10.1021/jm300343m>
4. Galloway, W. R. J. D.; Isidro-Llobet, A.; Spring, D. R. *Nature Commun.* **2010**, 1.
<https://doi.org/10.1038/ncomms1081>
5. Mughal, H.; Szostak, M. *Org. Biomol. Chem.* **2021**, 19, 3274.
<https://doi.org/10.1039/d1ob00061f>
6. Andresini, M.; De Angelis, S.; Uricchio, A.; Visaggio, A.; Romanazzi, G.; Ciriaco, F.; Corriero, N.; Degennaro, L.; Luisi, R. J. *Org. Chem.* **2018**, 83, 10221.
<https://doi.org/10.1021/acs.joc.8b01441>

7. Colella, M.; Musci, P.; Cannillo, D.; Spennacchio, M.; Aramini, A.; Degennaro, L.; Luisi, R. *J. Org. Chem.* **2021**, *86*, 13943.
<https://doi.org/10.1021/acs.joc.1c01297>
8. Musci, P.; Colella, M.; Altomare, A.; Romanazzi, G.; Sheikh, N. S.; Degennaro, L.; Luisi, R. *Molecules* **2022**, *27*, 2847.
<https://doi.org/10.3390/molecules27092847>
9. Musci, P.; Colella, M.; Fanelli, F.; Altomare, A.; Pisano, L.; Carlucci, C.; Luisi, R.; Degennaro, L. *Front. Chem.* **2019**, *7*.
<https://doi.org/10.3389/fchem.2019.00614>
10. Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev.* **2008**, *108*, 3988.
<https://doi.org/10.1021/cr800325e>
11. Andresini, M.; Degennaro, L.; Luisi, R. Azetidines, Azetines and Azetes: Monocyclic. In *Comprehensive Heterocyclic Chemistry IV*, Black, D. ; Cossy, J.; Stevens, C. Elsevier : Oxford, UK, **2022**; Volume 2, pp. 1–115.
<https://doi.org/10.1016/B978-0-12-818655-8.00155-4>
12. Andresini, M.; Degennaro, L.; Luisi, R. *Org. Biomol. Chem.* **2020**, *18*, 5798.
<https://doi.org/10.1039/d0ob01251c>
13. Musci, P.; Keutz, T.; Belaj, F.; Degennaro, L.; Cantillo, D.; Kappe, C. O.; Luisi, R. *Angew. Chem. Int. Ed.*, **2021**, *60*, 6395.
<https://doi.org/10.1002/anie.202014881>
14. Musci, P.; Colella, M.; Andresini, M.; Aramini, A.; Degennaro, L.; Luisi, R. *Chem. Commun.*, **2022**, *58*, 6356.
<https://doi.org/10.1039/d2cc01641a>
15. Gregson, C. H. U.; Noble, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed.*, **2021**, *60*, 7360.
<https://doi.org/10.1002/anie.202100583>
16. Tyler, J. L.; Noble, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed.*, **2021**, *60*, 11824.
<https://doi.org/10.1002/anie.202102754>
17. Tyler, J. L.; Noble, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed.*, **2022**, *61*, e202114235.
<https://doi.org/10.1002/anie.202114235>
18. Trauner, F.; Reiners, F.; Apaloo-Messan, K.-E.; Nißl, B.; Shahbaz, M.; Jiang, D.; Aicher, J.; Didier, D. *Chem. Commun.*, **2022**, *58*, 2564.
<https://doi.org/10.1039/d1cc07053c>

Authors' Biographies



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