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Synthesis of 2-(Trifluoromethyl)Azetidines by Strain-Release Reactions of 2-(Trifluoromethyl)-1-Azabicyclo[1.1.0]Butanes

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Substituted azetidines are privileged heterocyclic scaffolds in medicinal chemistry and have become synthetic targets of high interest in recent years. With the goal of developing a new access to azetidines incorporating the pharmaceutically relevant trifluoromethyl group, the reactivity of 2-(trifluoromethyl)-1-azabicyclo[1.1.0]butanes was investigated in polar strain-release reactions. By using benzyl chloroformate or trifluoroacetic anhydride as reacting partners, diversely substituted 3-chloroazetidines, 3-substituted azetidines and azetidin-3-ols bearing a trifluoromethyl group at C2 could be readily synthesized. In addition, palladium-catalyzed hydrogenolysis reactions provided an entry to *cis*-3-aryl-2-trifluoromethyl azetidines.

1. Introduction

Nitrogen heterocycles are prominent motifs in marketed drugs.[1] Since increasing saturation was found to correlate with a higher success rate of drug candidates in the preclinical development phases,[2] scaffolds rich in sp^3-hybridized carbons have attracted considerable interest.[1,3] Compared to piperidines and pyrrolidines, four-membered nitrogen heterocycles are much less encountered, except as components of β-lactam antibiotics.[1] However, azetidines are emerging as privileged heterocycles in medicinal chemistry, with potentially improved pharmacokinetic properties compared to their higher homologs.[4] Examples of drugs incorporating an azetidine include baricitinib, used in the treatment of rheumatoid arthritis,[5] and the anticancer agent cobimetinib.[6] Replacement of a biaryl motif in the identified lead compound by an (aryloxy)azetidine led to the discovery of the oxytocin receptor antagonist PF-3274167 and fluorescent probes were further devised based on the structure of this latter compound.[7] The introduction of fluorinated groups is classically used to optimize the physicochemical and pharmacokinetic properties of lead compounds.[8] In particular, fluorinated groups in the vicinity of an amine can lower the basicity of the nitrogen atom,[9] which is often responsible for off-target effects.[10] Hence, trifluoromethyl-substituted nitrogen heterocycles constitute an interesting class of compounds[11] and 2-(trifluoromethyl)-azetidines have been considered as motifs for structure–activity relationships studies, as illustrated with the $\alpha4\beta7$ integrin inhibitor **I**[12] and the ketohexokinase inhibitor **II**[13] (Figure 1).

Despite their potential interest, 2-(trifluoromethyl)azetidines **A** constitute an underexplored class of nitrogen heterocycles and most of the strategies for their synthesis[14–20] rely on the formation of the C4—N bond (Scheme 1). One straightforward route is based on the intramolecular nucleophilic substitution of γ-chloro-(trifluoromethyl)amines (prepared from ethyl trifluoroacetoacetate) (Scheme 1, route *a*).[14] Intramolecular nucleophilic substitution of a tosylate by the potassium salt of sulfonamides, arising from regioselective ring-opening of the corresponding CF_3-aziridines with potassium phenoxides, was also reported (Scheme 1, route *b*).[15] Other examples include the intramolecular ring-opening of an α-(trifluoromethyl)-α-amino epoxide (Scheme 1, route *c*)[16] or the cyclization of an α-trifluoromethyl homoallylic amine induced by electrophilic activation of the double bond (Scheme 1, route *d*),[17] both substrates arising from diastereoselective addition of organometallic reagents to chiral imines derived from phenylglycinol and fluoral.[16,17] One example of C2—N bond formation by intramolecular nucleophilic substitution of a (trifluoromethyl)carbinyl mesylate was also disclosed (Scheme 1, route *e*).[18] Recently, a highly functionalized 2-(trifluoromethyl)azetidine was prepared by hydrogenation of the corresponding 2-(trifluoromethyl)azetine, produced from diethyl acetylenedicarboxylate and trifluoroacetyl *N*-Boc carbamate by a phosphine-promoted aza-Michael addition and subsequent intramolecular Wittig olefination (stepwise formation of C4—N and C3—C2 bonds) (Scheme 1, route *f*).[19]

Alternatively, 2-(trifluoromethyl)azetidines **A** can be obtained by reduction and/or functionalization of (trifluoromethyl)azetidinones **B**,[21] the synthesis of which can be

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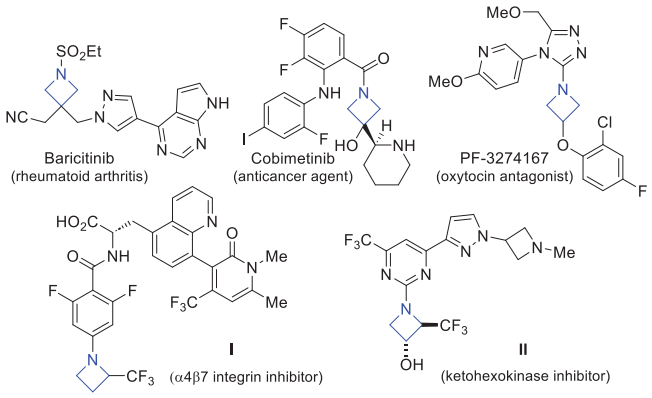
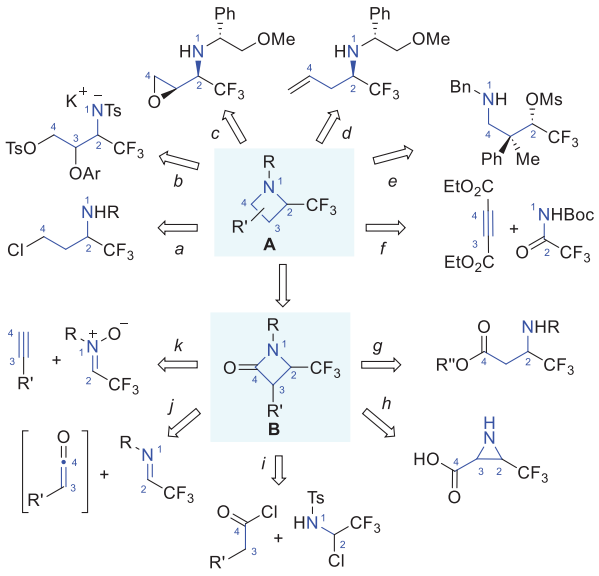


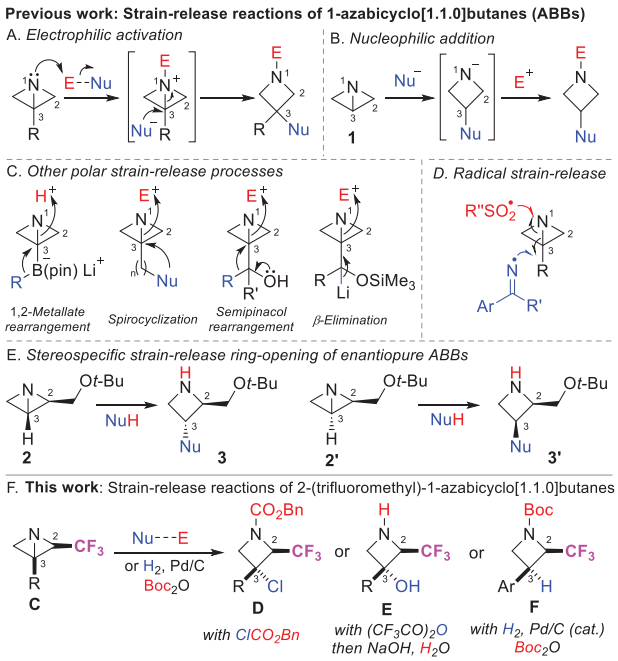
Figure 1. Examples of bioactive azetidines.



Scheme 1. Synthetic approaches toward 2-(trifluoromethyl)azetidines. Boc = *t*-BuOC(= O), Ms = $MeSO_2$, Ts = *para*-$MeC_6H_4SO_2$.

accomplished by cyclization of β-amino-β-trifluoromethyl esters (C4—N bond formation), accessible by different methods (Scheme 1, route *g*).[22] Some ring-expansion reactions involving (trifluoromethyl)aziridine carboxylic acid derivatives have also been reported (Scheme 1, route *h*).[23] Formation of both the C4—N and C2—C3 bonds can be achieved in a one-pot manner by treatment of α-chloro-α-trifluoromethyl sulfonamides with enolizable acid chlorides in the presence of a tertiary amine (Scheme 1, route *i*),[24] by classical Staudinger cycloaddition between ketenes and trifluoromethyl imines (Scheme 1, route *j*)[25] or copper-promoted Kinugasa reaction between alkynes and trifluoromethyl nitrones (Scheme 1, route *k*).[26]

In recent years, strain-release ring-opening reactions of 1-azabicyclo[1.1.0]butanes (ABBs) have emerged as an appealing strategy for the synthesis of azetidines (Scheme 2).[27] Besides the classical ring-opening mode triggered by electrophilic activation of the nitrogen atom with concomitant nucleophilic attack of the resulting 1-azoniabicyclo[1.1.0]butane intermediate (Scheme 2A), nucleophilic additions to azabicyclobutane **1**, followed by functionalization of the nitrogen atom with an



Scheme 2. Strain-release reactions of 1-azabicyclo[1.1.0]butanes leading to azetidines. pin = Pinacolato.

electrophilic agent, have been disclosed (Scheme 2B).[28] The possibility to generate and functionalize 1-azabicyclobut-3-yllithium[29] has resulted in the development of new strain-release processes capitalizing either on 1,2- metallate rearrangement, spirocyclization, semipinacol rearrangement or Brook rearrangement followed by β-elimination (Scheme 2C).[29–31] Recently, the first radical strain-release reaction was reported, featuring addition of a sulfonyl radical to the nitrogen atom and subsequent coupling of the resulting radical at C3 with an iminyl radical. Both reactive radical species were generated from sulfonylimines through a catalytic photosensitized process (Scheme 2D).[32] Polar strain-release reactions have been classically achieved with ABBs devoid of substituents at C2, besides a few examples of hydration and hydrohalogenation involving 2,3-disubstituted ABBs.[27,33] Recently, Baran et al. disclosed the enantiocontrolled synthesis of an azetidine library by strain-release functionalization of ABBs substituted at C2.[34] Gram-scale syntheses of diastereomeric ABBs **2** and **2′** (and their enantiomers), followed by stereospecific strain-release reactions with a variety of nucleophiles (promoted by protonation of the nitrogen atom), delivered the corresponding azetidines **3** and **3′**, respectively (Scheme 2E).[34] The possibility to achieve the double functionalization of **2** (or stereoisomers thereof) by deprotonation–electrophilic trapping at C3, followed by ring-opening, was also demonstrated.[34]

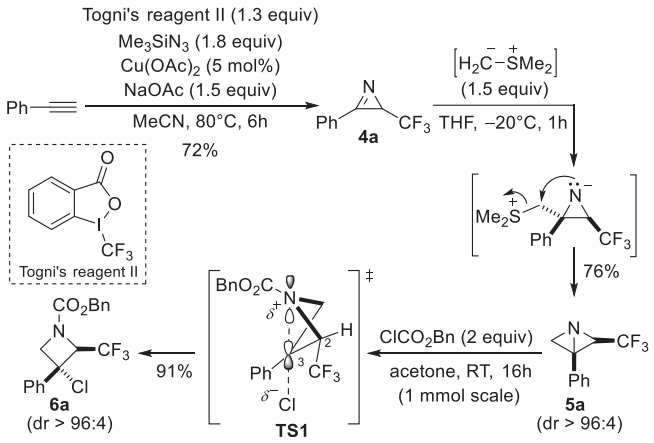
In conjunction with our interest in ring-expansion reactions leading to nitrogen heterocycles incorporating the pharmaceutically relevant trifluoromethyl group at C2,[35] we would like to report herein the first examples of strain-release reactions involving a new class of ABBs **C**, possessing a trifluoromethyl group at C2, promoted either by electrophilic reagents (benzyl chloroformate, trifluoroacetic anhydride) or under palladium-catalyzed

hydrogenolysis conditions, as a route to diversely substituted 2-(trifluoromethyl)azetidines **D**–**F**, respectively (Scheme 2F).

2. Results and Discussion

With the goal of harnessing strain-release reactions for the synthesis of 2-(trifluoromethyl)azetidines, several issues had to be addressed. The first one was related to the accessibility of the requisite substrates, i.e., 2-(trifluoromethyl)-1-azabicyclo[1.1.0]-butanes **C**, the preparation of which had never been reported. By analogy with known routes toward ABBs,[27c,36] cyclopropanation of 2-(trifluoromethyl)-2*H*-azirines[37,38] with sulfur ylides emerged as a viable option. Azirine **4a** was prepared from phenylacetylene according to a known copper-catalyzed azido-trifluoromethylation, accompanied by loss of nitrogen gas, using 1-trifluoromethyl-1,2-benziodoxol-3-(1*H*)-one (Togni's reagent II) and Me_3SiN_3, in the presence of NaOAc and $Cu(OAc)_2$ (5 mol%) (MeCN, 80°C, 6 h, 72% yield).[37a] Azirine **4a** was then involved in a cyclopropanation by treatment with (dimethylsulfonium)methylide (generated by deprotonation of Me_3SI with *n*-BuLi, THF, −20°C, 1 h) which afforded the desired 2-trifluoromethyl ABB **5a** (76%) as a single detectable diastereomer (dr > 96:4, by ^{1}H NMR spectroscopy). As previously reported for other substituted azirines,[27c] addition of the sulfur ylide preferentially occurred on the less hindered face of the C═N bond of **4a** (opposite to the CF_3 group). The second issue was related to the reactivity of ABB **5a** in strain-release reactions. Indeed, the CF_3 substituent is sterically hindered (size ranging in between ethyl and isopropyl groups)[39] and its electron-withdrawing effect could decrease the ability of the nitrogen atom to react with electrophilic species. However, treatment of **5a** with benzyl chloroformate (2 equiv) triggered the expected strain-release reaction under mild conditions (acetone, RT, 16 h) and afforded the desired 3-chloro-2-(trifluoromethyl)azetidine **6a** in good yield (91%), as a single detectable diastereomer (dr > 96:4). The relative stereochemistry of **6a** was assigned at this stage by analogy with literature results concerning the stereochemical outcome of polar strain-release reactions involving ABBs[27,33,34] and was later confirmed in our studies (vide infra). Thus, electrophilic activation of the nitrogen atom of **5a** by the chloroformate should produce a 1-azoniabicyclo[1.1.0]butane intermediate and nucleophilic addition of the released chloride ion should proceed through a reactant-like transition state **TS1** in which a 2p-orbital at C3 lies along the C3—N axis, with concerted C3—Cl bond formation and concurrent C3—N bond cleavage (Scheme 3).[27d]

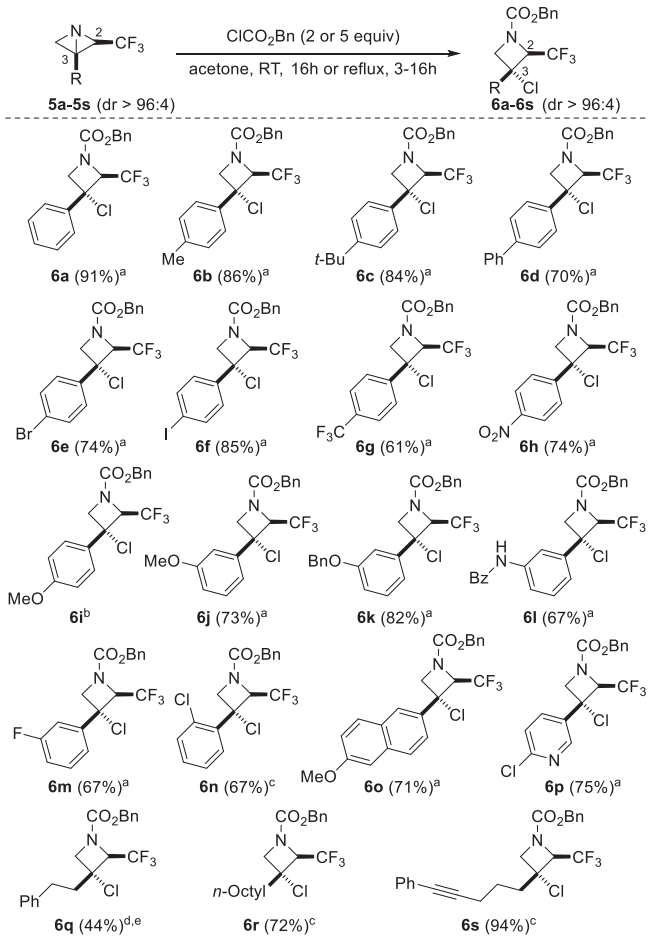
The scope of the ring-opening with benzyl chloroformate was examined with different substituted 2-(trifluoromethyl)ABBs **5b**-**5s** (Scheme 4). Alkyl substituents (Me, *t*-Bu) or a phenyl group could be present at the *para* position of the aromatic ring at C3, as illustrated with the isolation of the 3-chloroazetidines **6b** (86%), **6c** (84%) and **6d** (70%), respectively. The azabicyclic substrates **5e**-**5h**, possessing an electron-withdrawing substituent at the *para* position of the phenyl group all reacted smoothly with benzyl chloroformate and delivered the corresponding 3-chloro-azetidines **6e**-**6h** (61%–85%). It is noteworthy that ABB **5h**, incorporating a *p*-nitrophenyl group, reacted equally well



Scheme 3. Synthesis and reactivity of the 2-(trifluoromethyl)ABB **5a**.

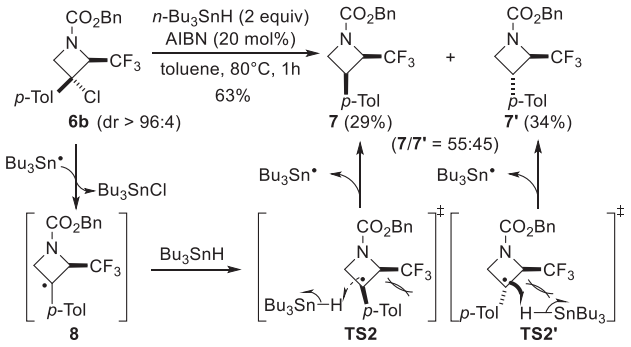
thereby suggesting that there is no significant positive charge build-up at C3 in the transition state. Because of the strong electron-donating character of the *p*-methoxyphenyl group, azabicyclobutane **5i** underwent significant decomposition under the reaction conditions and although azetidine **6i** was effectively detected in the reaction mixture, this compound could not be isolated in pure form. Electron-donating substituents were however well tolerated at the *meta* position of the aromatic ring, as shown with the formation of azetidines **6j**-**6l** (67%–82%). The presence of a fluorine atom at the *meta* position is also possible and azetidine **6m** was isolated in 67% yield. Substrate **5n**, possessing an *ortho*-chlorophenyl group at C3, did not react under the previous conditions, presumably for steric reasons. Fortunately, the use of an excess of $ClCO_2Bn$ (5 equiv) and refluxing the reaction mixture enabled complete conversion of **5n** into 3-chloroazetidine **6n** (67%). Azabicyclobutanes **5o**, substituted by a naphthyl group, and **5p**, by a 2-chloropyridine, afforded azetidines **6o** (71%) and **6p** (75%), respectively. The reactivity of ABBs **5q**-**5s** incorporating an aliphatic chain at C3 was also examined. An excess of $ClCO_2Bn$ (5 equiv) was required to observe complete conversion of **5q** into azetidine **6q** (44%, two steps from azirine **4q**). In the case of **5r** and **5s** bearing a longer and conformationally more mobile alkyl chain at C3, compared to substrate **5q**, refluxing conditions were required to obtain azetidines **6r** (72%) and **6s** (94%) (Scheme 4).

Transformation of the C—Cl bond in the 3-chloro-2-(trifluoromethyl)azetidines resulting from the latter strain-release reaction was investigated. The radical reduction of **6b** with *n*-Bu_3SnH in the presence of AIBN (20 mol%) (toluene, 80°C, 1 h) afforded a mixture of the diastereomeric azetidines **7**/**7′** in a 55:45 ratio (separated by preparative TLC and isolated in 29% and 34% yields, respectively). Abstraction of an hydrogen atom from *n*-Bu_3SnH by the configurationally labile benzylic radical intermediate **8** can occur *trans* or *cis* to the CF_3 group and produce the *cis*- and *trans*-2-(trifluoromethyl)azetidines **7** and **7′**, respectively. The corresponding transition states **TS2** and **TS2′** both suffer from steric interactions, between the CF_3 substituent and the *p*-tolyl group or *n*-Bu_3SnH, respectively, thereby explaining the low diastereomeric ratio (Scheme 5).[40]



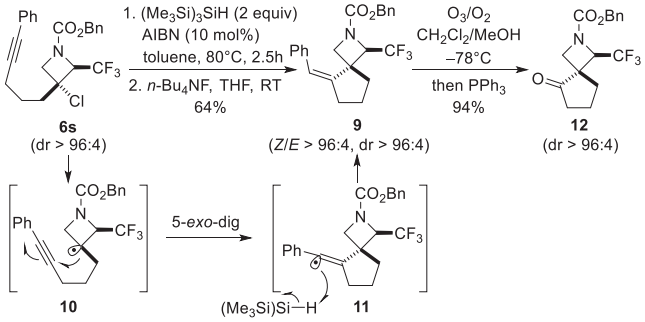
[a] $ClCO_2Bn$ (2 equiv), RT, 16h. [b] Unstable substrate/product. [c] $ClCO_2Bn$ (5 equiv), reflux, 3-16h. [d] $ClCO_2Bn$ (5 equiv), RT, 16h. [e] Yield from azirine **4q** (two steps).

Scheme 4. Scope of the ring-opening of 2-(trifluoromethyl)-1-azabicyclo[1.1.0]-butanes **5a-5s** with benzyl chloroformate. Bn = Benzyl, Bz = Benzoyl.

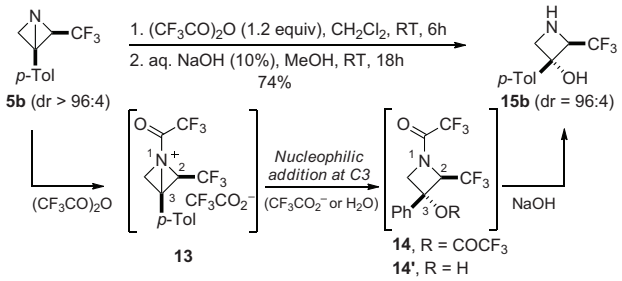


Scheme 5. Radical reduction of the C—Cl bond in azetidine **6b**. AIBN = azobis(isobutyronitrile). *p*-Tol = *para*-Tolyl.

Because spirocycles, especially those incorporating four-membered rings, are scaffolds of interest in medicinal chemistry,[41] the construction of a 2-azaspiro[3.4]octane ring system was explored from 3-chloroazetidine **6s**, possessing an appropriately located remote alkyne. The reductive radical cyclization was achieved by treatment of **6s** with $(Me_3Si)_3SiH$ in the presence of AIBN (10 mol%) (toluene, 80°C, 2.5 h, followed by



Scheme 6. Synthesis of azaspirocyclic compounds **9** and **12**.

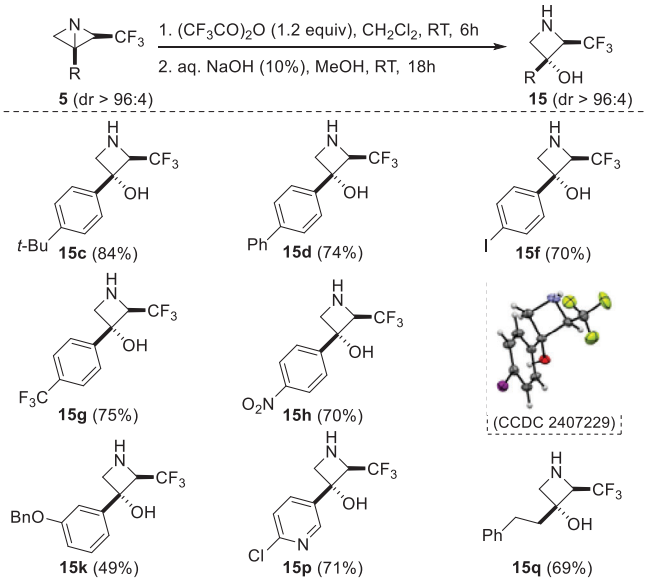


Scheme 7. Strain-release reaction of **5b** with trifluoroacetic anhydride.

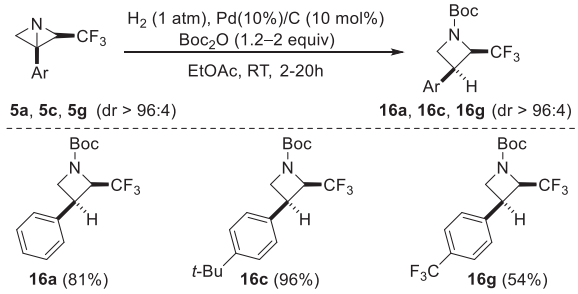
treatment with *n*-Bu_4NF to facilitate separation of the silylated byproducts). Azaspirocyclic compound **9** was formed as a single detectable diastereomer and was isolated in 64% yield. The relative stereochemistry of **9**, assigned by NMR (NOESY),[42] is consistent with a 5-*exo*-dig cyclization of the azetidinyl radical **10** proceeding *trans* to the CF_3 substituent. In addition, the *Z* configuration of the exocyclic alkene was explained by preferential hydrogen atom transfer from the silane on the less-hindered face of the configurationally labile vinylic and benzylic radical intermediate **11**. Cleavage of the benzylidene moiety in **9** was then achieved by ozonolysis, followed by reduction with PPh_3, to afford azaspirocyclic ketone **12** (94%) (Scheme 6).

As a key structural feature of the anticancer drug cobimetinib,[5] the azetidin-3-ol moiety is also employed in structure–activity relationships aimed at tuning the pharmacological properties of lead compounds.[43] With the goal of developing an access to 2-(trifluoromethyl)azetidin-3-ols, the polar ring-opening of 2-(trifluoromethyl)ABBs was investigated with trifluoroacetic anhydride in order to facilitate subsequent cleavage of the acyl residues on the nitrogen atom and the oxygen atom at C3 in the adduct. In addition, this latter reagent has already been employed to trigger strain-release ring-opening reactions of ABBs.[30a] Compound **5b** was reacted with trifluoroacetic anhydride (CH_2Cl_2, RT, 6 h) to trigger the formation of the azonium intermediate **13**, the ring-opening of which was achieved either by the trifluoroacetate anion or adventitious traces of water to provide **14** and/or **14′**. After treatment with a 10% aqueous solution of NaOH (MeOH, RT, 18 h), the desired 2-(trifluoromethyl)azetidin-3-ol **15b** was obtained with high diastereomeric purity (dr = 96:4) in 74% overall yield (Scheme 7).

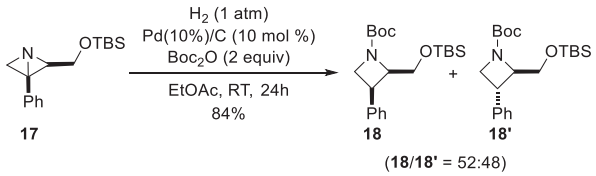
The scope of this formal hydration process was extended to some of the other 2-(trifluoromethyl)ABBs synthesized pre-



Scheme 8. Synthesis of substituted 2-(trifluoromethyl)azetidin-3-ols.



Scheme 9. Palladium-catalyzed hydrogenolysis of 3-aryl-2-(trifluoromethyl)-1-azabicyclo[1.1.0]butanes.



Scheme 10. Palladium-catalyzed hydrogenolysis of azabicyclobutane **17**. TBS = Si*t*-BuMe$_2$.

viously. Azetidin-3-ols **15c**, **15d**, **15f**-**15h** were obtained in good yields (70%–84%) regardless of the electronic properties of the substituent at the *para* position of the phenyl group at C3. Azetidinol **15k**, possessing a benzyloxy group at the *meta* position of the aromatic group, was isolated in moderate yield (49%) but the reaction proceeded well in the presence of a 2-chloropyridine ring, as shown with the isolation of **15p** (71%) (Scheme 8).

An alkyl chain can also be present at C3, as illustrated with the synthesis of **15q** (69%). The relative stereochemistry of the crystalline azetidinol **15f** was determined by x-ray diffraction analysis,[44] showing a *trans* relationship between the hydroxyl and the trifluoromethyl groups, thereby supporting the stereochemical assignments made previously for the polar ring-opening reactions of 2-(trifluoromethyl)ABBs (Scheme 8).

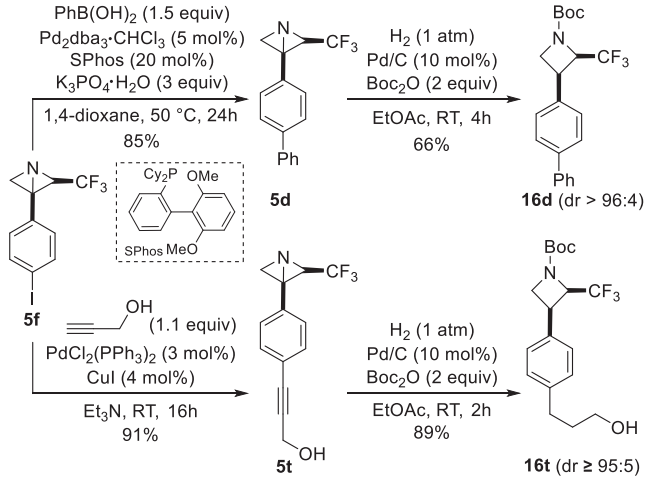
The disappointing stereochemical outcome of the radical hydrodechlorination of 3-chloroazetidine **6b**, which provided a diastereomeric mixture of **7**/**7′** (Scheme 5), led us to investigate an alternative strain-release reductive process. For 2-(trifluoromethyl)ABBs bearing a phenyl group at C3, we reasoned that reductive cleavage of the benzylic C3—N bond could be accomplished by palladium-catalyzed hydrogenolysis. Indeed, treatment of azabicyclobutane **5a** with Pd/C (10 mol%) under an atmosphere of hydrogen gas, in the presence of Boc$_2$O to avoid catalyst poisoning (EtOAc, RT),[45] afforded the *N*-Boc 2-trifluoromethyl-3-phenyl azetidine **16a** (81%), as a single *cis* diastereomer, the configuration of which was assigned by NMR spectroscopy.[42] Similarly, hydrogenolysis of ABBs **5c** and **5g** provided the *cis*-2,3-disubstituted azetidines **16c** (96%) and **16g** (54%).[46] The observed stereochemical outcome is consistent with hydrogenolysis of the C3—N bond occurring with inversion of configuration at C3, as usually observed in the case of benzylic amines (Scheme 9).[47,48]

Furthermore, we demonstrated that the trifluoromethyl group has a remarkable influence on the stereochemical outcome of the latter transformation. Indeed, hydrogenolysis of azabicyclobutane **17**, possessing a silyloxymethyl group at C2, proceeded in a nearly stereorandom manner and afforded a 52:48 mixture of the corresponding diastereomeric *cis*- and *trans*-*N*-Boc azetidines **18** and **18′** (84% combined yield) (Scheme 10).

Because 3-aryl ABBs underwent hydrogenolysis in the presence of the heterogeneous Pd/C catalyst, it was of interest to examine whether the 3-aryl-1-azabicyclobutyl moiety could be compatible with classical palladium-catalyzed cross-coupling reactions. It was demonstrated that ABB **5f**, bearing a *p*-iodophenyl group, could be successfully involved in a Suzuki–Miyaura coupling with phenylboronic acid [Pd_2dba_3.$CHCl_3$ (5 mol%), SPhos (20 mol%), K_3PO_4·H_2O, 1,4-dioxane, 50°C][49] or a Sonogashira coupling with propargyl alcohol [$PdCl_2(PPh_3)_2$ (3 mol%), CuI (4 mol%), Et_3N, RT]. The desired products **5d** (85%) and **5t** (91%), respectively, were isolated in good yields. Subsequent hydrogenolysis of ABBs **5d** and **5t**, catalyzed by Pd/C in the presence of Boc$_2$O, eventually led to the *cis*-2,3-disubstituted *N*-Boc azetidines **16d** (66%) and **16t** (89%), with additional hydrogenation of the disubstituted alkyne in the latter case (Scheme 11).

3. Conclusion

In summary, 2-(trifluoromethyl)-1-azabicyclo[1.1.0]butanes, which are readily available by cyclopropanation of 2-(trifluoromethyl)-2*H*-azirines, can be involved in polar strain-release reactions, despite the presence of the electron-withdrawing and sterically hindered trifluoromethyl substituent. Reaction of this new family of azabicyclobutanes with benzyl chloroformate and trifluoroacetic anhydride provides access to 3-chloroazetidines or azetidin-3-ols, respectively, possessing an (hetero)aryl or an alkyl group at C3 and a trifluoromethyl substituent at C2. In addition, palladium-catalyzed hydrogenolysis of 3-aryl-2-trifluoromethyl-1-azabicyclobutanes enables a convenient access



Scheme 11. Palladium catalyzed cross-coupling and hydrogenolysis reactions from azabicyclobutane **5f**. dba = Dibenzylideneacetone.

to the corresponding *cis*-2,3-disubstituted azetidines. The 2-(trifluoromethyl)azetidines arising from these transformations constitute building blocks of potential interest in medicinal chemistry. These results not only highlight the interest of new families of azabicyclobutanes, as precursors of azetidines, but also complements the repertoire of transformations in which these strained substrates can be involved.

4. Experimental Section

4.1. General Ethods

Infrared (IR) spectra were recorded with attenuated total reflectance (ATR) sampling technique. ^{1}H NMR spectra were recorded at 400 MHz and data are reported as follows: chemical shift in ppm from tetramethylsilane referenced to the residual isotopomer solvent signal ($CHCl_3$: δ = 7.26 ppm), multiplicity, integration. $^{13}C\{^1H\}$ NMR spectra (broadband ^{1}H-decoupled) were recorded at 100 MHz and data are reported as follows: chemical shift in ppm from tetramethylsilane referenced to the solvent signal ($CDCl_3$: δ = 77.16 ppm), carbon environment (deduced from DEPT experiments). $^{19}F\{^1H\}$ NMR spectra (broadband ^{1}H-decoupled), were recorded at 376 MHz and data are reported as follows: chemical shift in ppm referenced to external $CFCl_3$ (δ = 0 ppm), integration. High resolution mass spectra were obtained by electrospray ionization (ESI) with an orbitrap mass analyzer. Purification by flash column chromatography was performed on silica gel (230-400 mesh).

4.2. Representative Procedures

4.2.1. Synthesis of 2-trifluoromethyl-1-azabicyclo[1.1.0]butanes

(2R*,3S*)-3-Phenyl-2-(trifluoromethyl)-1-azabicyclo[1.1.0]butane (5a): A solution of *n*-BuLi (0.83 mL, 2.5 M in hexanes, 2.07 mmol, 1.5 equiv) was added dropwise to a suspension of trimethylsulfonium iodide (421 mg, 2.07 mmol, 1.5 equiv) in anhydrous THF (20 mL) at −20°C. After 0.5 h stirring at −20°C, a solution of azirine **4a**[37a] (255 mg, 1.38 mmol) was added. The reaction mixture was stirred for 0.5 h at −20°C and was then hydrolyzed with a saturated aqueous solution of NH_4Cl. The resulting mixture was diluted with CH_2Cl_2 and H_2O, the layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were successively washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure (bath temperature < 20°C, volatile compound). The residue was purified by flash column chromatography on silica gel (Pentane/Et_2O, 95:5) to afford 208 mg (76%) of **5a** as a yellow oil. IR (ATR): $\upsilon^{\sim}$ = 1436, 1395, 1288, 1155, 1140, 903, 883, 756, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.43 (m, 2H), 7.40–7.37 (m, 3H), 2.57 (dd, *J* = 2.3, 1.0 Hz, 1H), 2.15 (app. br q, *J* = 5.6 Hz, 1H), 1.68 (d, *J* = 2.4 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 130.0 (C), 129.0 (CH), 128.7 (2 × CH), 128.4 (2 × CH), 121.2 (C, q, $^1J_{C\text{-}F}$ = 275 Hz), 60.7 (CH, q, $^2J_{C\text{-}F}$ = 36.8 Hz), 53.0 (CH_2), 33.4 (C, q, $^3J_{C\text{-}F}$ = 2.3 Hz) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = −67.1 (s, 3F) ppm; HRMS (ESI): *m/z* calcd for $C_{10}H_9F_3N^+$: 200.0682 [*M*+H$^+$]; found: 200.0684.

4.2.2. Ring-opening of 2-trifluoromethyl-1-azabicyclo[1.1.0] butanes with benzyl chloroformate

Benzyl (2S*,3R*)-3-chloro-2-phenyl-2-(trifluoromethyl)azetidine-1-carboxylate (6a): Benzyl chloroformate (0.29 mL, 2.00 mmol, 2 equiv) was added to a solution of azabicyclobutane **5a** (200 mg, 1.00 mmol) in anhydrous acetone (2 mL) at RT. After 16 h stirring at RT, the reaction mixture was hydrolyzed with a saturated aqueous solution of $NaHCO_3$. The resulting mixture was diluted with CH_2Cl_2 and H_2O, the layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were successively washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Petroleum ether/Et_2O, 90:10) to afford 338 mg (91%) of **6a** as a pale yellow oil. IR (ATR): $\upsilon^{\sim}$ = 1724, 1498, 1449, 1406, 1346, 1277, 1225, 1147, 1005, 989, 736, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.31 (m, 10H), 5.25 (d, AB system, *J* = 12.5 Hz, 1H), 5.22 (d, AB system, *J* = 12.5 Hz, 1H), 5.13 (q, *J* = 6.7 Hz, 1H), 5.12 (d, AB system, *J* = 10.3 Hz, 1H), 4.50 (d, AB system, *J* = 10.2 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 156.4 (C), 135.6 (C), 135.4 (C), 129.5 (CH), 128.8 (2 × CH), 128.6 (2 × CH), 128.5 (CH), 128.1 (2 × CH), 127.3 (CH), 122.5 (C, q, $^1J_{C\text{-}F}$ = 282 Hz), 75.3 (CH, q, $^2J_{C\text{-}F}$ = 32.1 Hz), 68.0 (CH_2), 66.2 (C), 62.7 (CH_2) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = −72.3 (s, 3F) ppm; HRMS (ESI): *m/z* calcd for $C_{18}H_{15}ClF_3NO_2Na^+$: 392.0636 [*M*(^{35}*Cl*)+Na$^+$]; found: 392.0638.

4.2.3. Ring-opening of 2-trifluoromethyl-1-azabicyclo[1.1.0] butanes with trifluoroacetic anhydride

(2R*,3R*)-3-Phenyl-2-(trifluoromethyl)azetidin-3-ol (15b): Trifluoroacetic anhydride (12 µL, 0.086 mmol, 1.2 equiv) was added to a solution of azabicyclobutane **5b** (15 mg, 0.070 mmol) in CH_2Cl_2 (1 mL) at 0°C. After 6 h stirring at RT, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in MeOH (0.5 mL) and a 10% aqueous solution of NaOH (0.5 mL) was added to the resulting solution. After stirring for 18 h at RT, the reaction mixture was diluted with water and EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Et_2O) to afford 12 mg (74%) of **15b** as a colorless oil. IR (ATR): $\upsilon^{\sim}$ = 3317 (br), 1615, 1515, 1290, 1206, 1173, 1121, 902, 822, 730, 672 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 4.44 (qd, *J* = 7.6, 0.8 Hz, 1H), 4.17 (d, *J* = 8.4 Hz, 1H), 3.82 (d, *J* = 8.4 Hz, 1H), 2.92–1.92 (m, app. br s, weak intensity, 2H, NH+OH), 2.37 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.5 (C),

135.8 (C), 129.2 (2 × CH), 126.2 (2 × CH), 123.9 (C, q, $^1J_{C\text{-}F}$ = 279 Hz), 69.4 (CH, q, $^2J_{C\text{-}F}$ = 30.5 Hz), 58.4 (CH_2), 21.3 (CH_3) ppm (*one C signal overlaps with those of CDCl$_3$*); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = −73.8 (s, 3F) ppm; HRMS (ESI^+): *m/z* calcd for $C_{11}H_{13}F_3NO^+$: 232.0944 [$M+H^+$]; found: 232.0943.

4.2.4. Representative procedure for palladium-catalyzed hydrogenolysis of 2-trifluoromethyl-1-azabicyclo[1.1.0]butanes

tert-Butyl (2R*,3S*)-3-phenyl-2-(trifluoromethyl)azetidine-1-carboxylate (16a): Pd (10%)/C (96 mg, 0.090 mmol, 10 mol%) and Boc_2O (394 mg, 1.81 mmol, 2 equiv) were successively added to a solution of azabicyclobutane **5a** (180 mg, 0.904 mmol) in EtOAc (7 mL) under an argon atmosphere. The reaction mixture was evacuated under reduced pressure (10 mmHg) and backfilled with argon. The reaction mixture was evacuated again under reduced pressure and backfilled with hydrogen gas (balloon) (this process was repeated three times). After stirring for 2 h at RT, the reaction mixture was evacuated under reduced pressure, backfilled with argon gas and then filtered through Celite (EtOAc). The filtrate was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (Petroleum ether/EtOAc, 90:10) to afford 221 mg (81%) of **16a** as a colorless oil. IR (ATR): $\upsilon^{\sim}$ = 1707, 1380, 1368, 1350, 1282, 1238, 1131, 973, 911, 860, 767, 732, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.38–7.28 (m, 5H), 4.82 (dq, *J* = 9.1, 7.3 Hz, 1H), 4.46–4.41 (m, 1H), 4.31–4.21 (m, 2H), 1.49 (s, 9H) ppm; ^1H NMR (400 MHz, C_6D_6) δ = 7.12–6.93 (m, 5H), 4.41 (m, app. br s, 1H), 4.12 (dd, *J* = 8.7, 7.2 Hz, 1H), 3.79 (app. t, *J* = 9.0 Hz, 1H), 3.34 (m, 1H), 1.44 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 155.6 (C), 134.5 (C), 128.7 (2 × CH), 128.4 (2 × CH), 127.8 (CH), 123.9 (C, q, $^1J_{C\text{-}F}$ = 283 Hz), 81.0 (C), 64.6 (CH, q, $^2J_{C\text{-}F}$ = 31.5 Hz), 52.0 (CH_2), 36.4 (CH), 28.3 (3 × CH_3) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, C_6D_6) δ = 155.5 (C), 134.9 (C), 128.8 (2 × CH), 128.5 (2 × CH), 127.8 (CH), 124.6 (C, q, $^1J_{C\text{-}F}$ = 283 Hz), 80.4 (C), 64.7 (CH, q, $^2J_{C\text{-}F}$ = 31.1 Hz), 52.0 (CH_2), 36.3 (CH), 28.2 (3 × CH_3) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ = −70.9 (s, 3F) ppm. HRMS (ESI): *m/z* calcd for $C_{15}H_{18}F_3NO_2Na^+$: 324.1182 [$M+Na^+$]; found: 324.1181.

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Conflict of Interest Statements

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available in the supporting information of this article.

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[44] Deposition number CCDC 2407229 (**15f**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.
[45] Hydrogenolysis of 3-methyl-ABB in the presence of Raney nickel led to complete ring-cleavage and formation of isobutylamine, see references [27a] and [27b]. Attempted hydrogenolysis of 3-phenylABB in the presence of Pd/C led to poisoning of the catalyst and was accompanied by polymerization, see reference 27c.
[46] Hydrogenolysis of 3-chloroazetidine **6g** [H_2, Pd/C (10 mol%), AcONa, EtOAc, RT] in the presence of Boc_2O was also carried out and afforded the *cis*-2,3-disubstituted azetidine **16g** (dr > 96:4) (83%) (by cleavage of the benzyloxycarbonyl group, acylation of the nitrogen atom with Boc_2O and reduction of the benzylic C–Cl bond with retention of configuration). However, hydrogenolysis of azabicyclobutane **5g** offers a more direct access to azetidine **16g**.
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