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A sustainable and chemoselective continuous flow hydrogenation of functionalized 2-azetines to azetidines

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ABSTRACT

The synthesis of functionalized azetidines from azetines is poorly explored. Here, we report the safe and sustainable continuous flow hydrogenation of 2-azetines using ethyl acetate and CPME as environmentally responsible solvents. The chemoselective saturation of the endocyclic double bond of 2-azetines bearing additional functional groups sensitive to hydrogenation has been additionally disclosed. Moreover, the protocol has been successfully combined with the continuous flow preparation of the substrates, accessing to a bio-relevant azetidine through a telescoped multistep approach.

1. Introduction

The saturated four-membered azacycles, azetidines, are of profound relevance in medicinal chemistry [1–4]. The azetidine ring can be found in several biologically relevant compounds showing a wide range of activities (Scheme 1, A) [5]. In addition, the rigidity and the small size of the ring have been disclosed as a source of favorable physicochemical properties. The synthesis of such azacycles is commonly achieved through two main approaches. For instance, azetidines can be obtained through cyclization or cycloaddition reaction of acyclic precursors [6–10]. Alternatively, the preparation of densely functionalized azetidines can be achieved via the functionalization of a preformed ring [11–16], or via strain-release transformations of 1-azabicyclo [1.1.0] butanes [17–21]. In this context, minor attention has been dedicated to the preparation of azetidines from azetines, the mono-unsaturated four-membered aza-cycles. The chemistry of azetines is severely underdeveloped but their use in organic synthesis has been recently under the spotlight.

In 2014 Hodgson reported the easy preparation of N-Boc-2-lithio-2-azetine and their transformation to N-Boc-2-substituted azetines from N-Boc-3-methoxyazetidine (Scheme 1, B) [22]. Subsequently, Didier reported the preparation of 2,3-disubstituted 2-azetines from 3-oxo-N-Boc-azetidine in a one-pot multistep approach [23,24]. It is worth mentioning that the subsequent reduction with hydrogen upon Pd (0) catalysis furnished challenging 2-functionalized azetidines (Scheme 1, C). Hence, 2-azetines are valuable precursors of azetidines, but very little information can be found in the literature. We recently contributed to the topic reporting the high-yielding preparation of 2-substituted azetines in continuous flow starting from commercially available N-Boc-3-iodoazetidine [25]. Considering these results, we aimed at developing a sustainable, safe, and selective protocol for the hydrogenation of such unsaturated azacycles *en route* to valuable 2-functionalized azetidines which are otherwise hardly accessible by α-lithiation–electrophile trapping methodology from unsubstituted N-Boc azetidine [26]. The common batch hydrogenation protocols present several hazards and disadvantages. For instance, these strategies require the use of hydrogen gas, specific reactors, and often autoclave conditions. Secondly, the hydrogenation of double bonds is an exothermic reaction, and efficient heat exchange is generally needed, especially for large-scale transformations. To overcome such limitations, hydrogenation under continuous flow conditions can be exploited. In this approach, the reagent solution and hydrogen gas pass through an immobilized metal catalyst cartridge, and the product can be subsequently collected. It is worth mentioning that the use of reusable catalyst cartridges reduces considerably the amount of catalyst to be disposed, and the cartridges can be regenerated several times until substantial loss of catalytic activity [27]. Moreover, the generation and use of hydrogen in a confined space allow for overcoming the safety issues related to gas-liquid transformations, making the flow protocol appealing for industrial applications. Considering these

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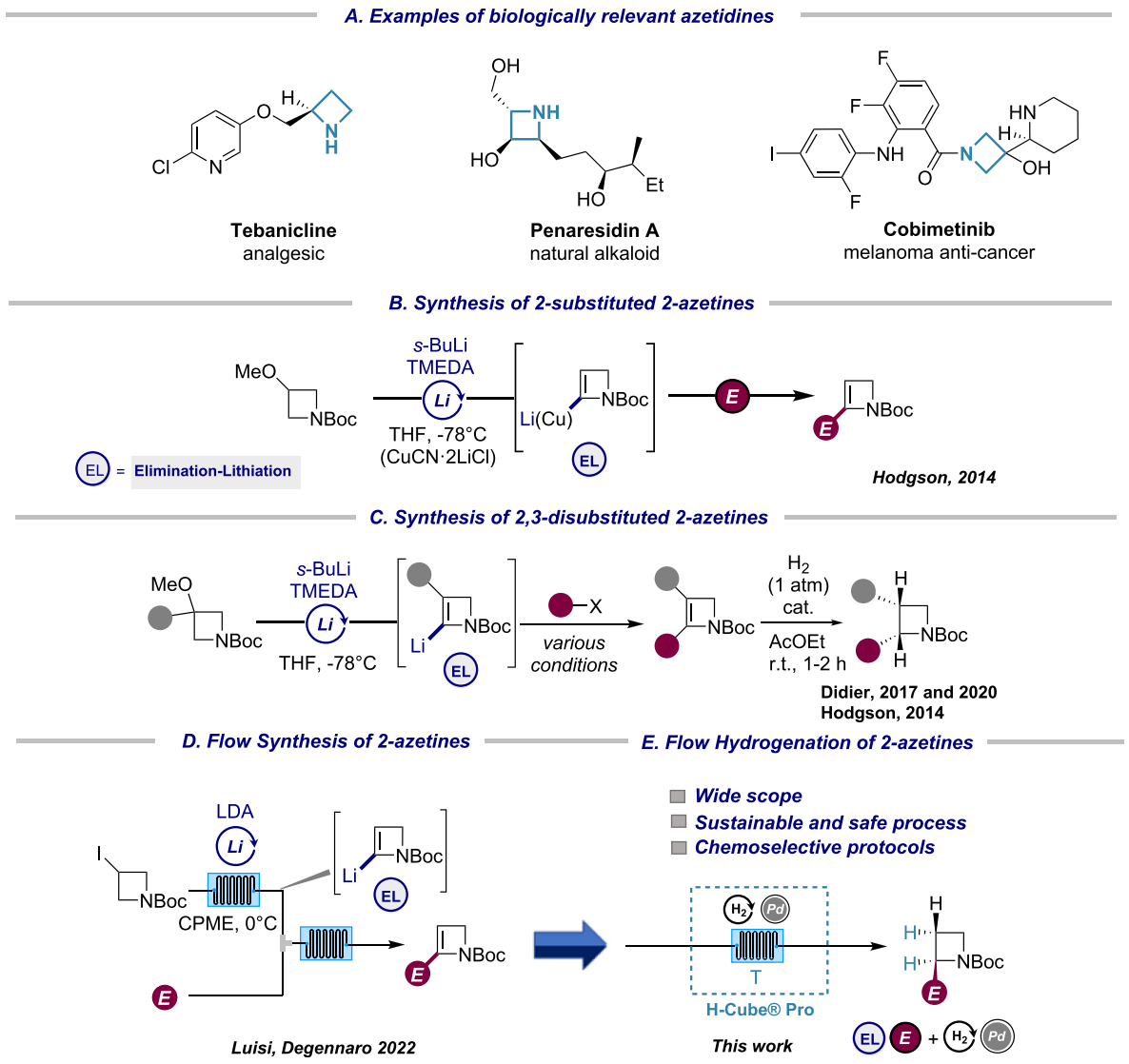


Scheme 1. A) Selected biologically active azetidine; B) preparation of 2-substituted-2-azetines; C) preparation of 2,3-disubstituted-2-azetines; D) continuous flow synthesis of 2-azetines; E) this work.

aspects, we studied the hydrogenation of 2-azetines in flow, employing a ThalesNano H-Cube®Pro apparatus. In addition, we explored the possibility of overcoming chemo-selectivity issues by tuning the reaction parameters when 2-azetines bearing reduction-sensitive functionalities were employed.

2. Experimental

2.1. General experimental information

All the azetines used in this work were prepared according to a reported procedure [25]. The continuous flow synthesis of azetines was performed using a stainless-steel microfluidic system. The reagent solutions were injected into the flow system using Harvard PHD 2000 syringe pumps equipped with gastight syringes. Continuous flow hydrogenation reactions were performed on an H-Cube® Pro (ThalesNano) apparatus employing a sealed catalyst cartridge 10%Pd/C (CatCarts®). NMR spectra were recorded on an Agilent 500 spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C, 470 MHz for ^{19}F) or a Varian Mercury 300 spectrometer (282 MHz for ^{19}F). Chemical shifts are reported in ppm (δ), and the residual solvent signal was used as the internal standard which was related to TMS with δ 7.26 ppm (^{1}H in $CDCl_3$), δ 4.87 ppm (^{1}H in CD_3OD) δ 77.00 ppm (^{13}C in $CDCl_3$), δ 49.00 ppm (^{13}C in CD_3OD). The signal multiplicity is reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), bs (broad signal), m (multiplet). Spin−spin coupling constants (J) are given in hertz. As far as possible, the unambiguous assignment of resonances was performed by combined HSQC and COSY experiments. Infrared spectra (FT-IR) were registered with a PerkinElmer 283 Spectrometer. High-resolution mass spectrometry experiments (HRMS) were performed on an Agilent 6530 accurate mass Q-TOF instrument. TLC analyses were performed on 0.25 mm precoated silica gel thick plates (Merck) using a fluorescence indicator F-254. The spots were visualized under UV light ($\lambda = 254$ nm) and/or using $KMnO_4$ (aq) as the revealing agent.

2.2. General procedure for azetines hydrogenation

A solution of azetine (0.3 mmol) in AcOEt (15 mL, 0.02 M) was injected on a H-Cube® Pro (ThalesNano) apparatus (operating at 40 °C and 15 bar of hydrogen pressure) equipped with a 10%Pd/C cartridge (CatCarts®) using a BlueShadow Pump 10 P (KNAUER) with a flow rate of 0.5 mL/min. After the complete intake of the reagent solution, AcOEt was fluxed at the same flow rate. The outcoming solution was collected for 45 min. The cartridge was washed by fluxing MeOH for 20 min after

each reaction. The solvent was evaporated under reduced pressure and the desired product was obtained as described for each entry in the Supplementary Information.

2.3. Multistep synthesis of 2-(hydroxy (3-(trifluoromethyl)phenyl)methyl) azetidin-1-ium trifluoroacetate **8**

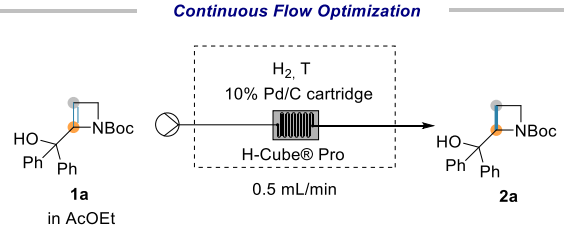
The microfluidic system employed for the preparation of azetine **2o** was made of two stainless steel T-shaped micromixers (M1 φ = 250 μm and M2 φ = 1000 μm), two stainless steel microtube reactors (R1 φ = 1000 μm, L = 100 cm and R2 φ = 1000 μm, L = 200 cm) and three precooling units (φ = 1000 μm, L = 25 cm). Freshly distilled CPME was used. The flow microreactor was cooled with a cooling bath (0 °C). The solution of 1-Boc-3-iodoazetidine (0.0875 M in CPME, 4 mL/min) and the solution of lithium diisopropylamide (0.7 M in CPME, 1 mL/min) were injected into M1, the resulting solution was pushed through R1 (9.4 s) and then introduced to M2, where it was mixed with the solution of 3-trifluoromethylbenzadehyde (0.0875 M in CPME, 4 mL/min). The resulting solution passed through R2 (10.4 s) and was collected, after reaching the steady state regime (1 min), for 1 min in a vial containing 10 mL of water. The upper organic phase was taken, dried over anhydrous sodium sulfate, filtered, and directly injected (8.5 mL) into the H-Cube® Pro apparatus (0.5 mL/min, 40 °C, 15 bar hydrogen pressure) following the general procedure. Azetidine **2o** was purified by column chromatography as described in the Supplementary Information. Azetidine **2o** (84 mg, 0.25 mmol) was dissolved in 1 mL of dichloromethane/trifluoroacetic acid (1:1) mixture and the reaction was stirred at room temperature for 24 h. The solution was concentrated at reduced pressure affording 2-(hydroxy (3-(trifluoromethyl)phenyl)methyl)azetidin-1-ium trifluoroacetate **8** without further purification (see Supplementary Information).

3. Results and discussion

At the starting point of our research, we studied the continuous flow hydrogenation of 2-azetine **1a** employing the H-Cube Pro apparatus equipped with a 10% Pd/C CatCart® cartridge, and focusing on the use of environment-friendly solvents. First, we observed the formation of the desired product **2a** in 67% yield employing a solution 0.1 M of **1a**, 1 bar of H_2 pressure and a flow rate of 0.5 mL/min at room temperature (Table 1, entry 1).

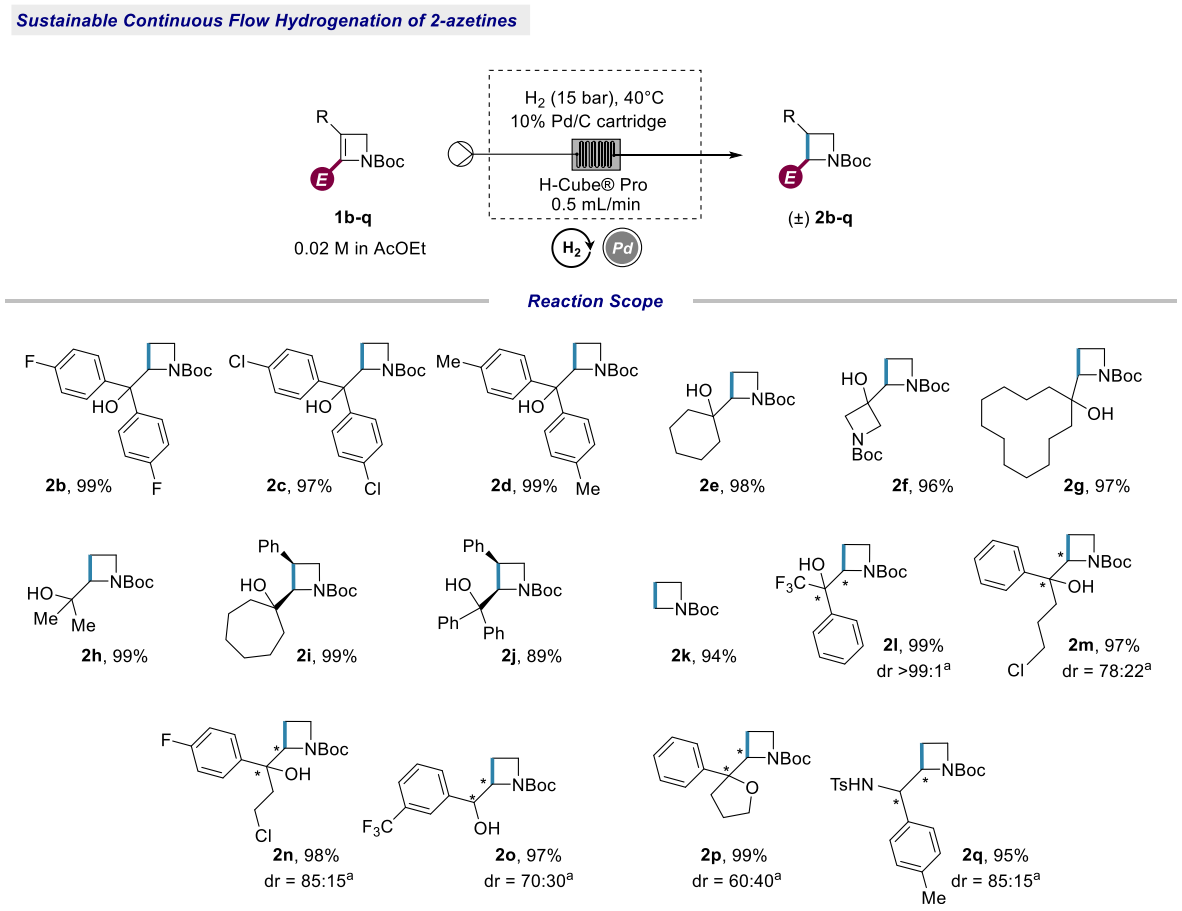
Using a more diluted solution of **1a** (0.02 M, Table 1, entry 2) led to higher conversion (78%), proving that the dilution grade is highly influential. This is reasonably due to the effective capability of the cartridge to catalyze the reaction in a significantly low reaction time. Considering the void volume of the Pd/C cartridge (65 μL), the reaction time is estimated to be around 8 s. Complete conversion towards azetidine **2a** could be achieved by employing 0.004 M and 0.013 M solutions of **1a** (Table 1, entries 3 and 4). We further explored the reaction at higher concentrations employing higher temperatures and hydrogen pressure. To our delight, we observed the complete formation of **2a** using a 0.02 M solution of **1a** at 40 °C and 15 bar of H_2 (Table 1, entry 5). Similarly, full conversion to **2a** was observed when CPME (cyclopentyl methyl ether) was used as the reaction solvent (Table 1, entry 6). Unfortunately, lower conversion was observed when a 0.1 M solution of **1a** in AcOEt was transformed upon 15 bar of H_2 at 40 °C (Table 1, entry 8). Although room temperature and lower hydrogen pressure (Table 1, entries 3 and 4) ensured quantitative conversion to **2a**, 40 °C and 15 bar of H_2 (Table 1, entry 5) were identified as the best reaction conditions to guarantee productivity and sustainability, in terms of reduction of the solvent waste stream, to our process. Furthermore, the use of the H-cube system enables the use of higher hydrogen pressure without affecting operator safety. With the optimized conditions in hand, we explored the reaction scope employing a library of functionalized 2-azetines. First, a selection of substituted 2-hydroxymethyl-2-azetines was hydrogenated *en route* to strained β-amino alcohols bearing the azetidine ring (Scheme 2). Pleasingly, the flow protocol worked efficiently with N-Boc-2-(hydroxydiphenylmethyl)azetine bearing fluorine, chlorine and methyl substituents on the *para* position of the phenyl substituents, furnishing the products in almost quantitative yields (**2b-d**). In the same fashion, several 2-bis-alkylhydroxymethyl-2-azetines could be efficiently hydrogenated to the corresponding saturated products **2e-h**. It is worth noting that the method enabled the preparation of compound **2f** in which two azetidine rings are linked through C2–C3 connectivity, as an example of a rare strained system. Moreover, a 2,3-disubstituted-2-azetine and unsubstituted 2-azetine could be completely reduced affording the corresponding products **2i**, **2j** and **2k**, again in good yields. The use of azetines bearing a stereogenic center needs a separate discussion. When 2-substituted-2-azetines **1l-q** were reacted, the corresponding products were obtained as mixtures of stereoisomers with variable

Table 1
Optimization study for the preparation of azetidine **2a**.



Entry	Conc. (M)	T (°C)	H_2 (bar)	2a (%)
1	0.100	25	1	67[a]
2	0.020	25	1	78[a]
3	0.004	25	1	99[b]
4	0.013	25	1	99[b]
5	**0.020**	**40**	**15**	**99**[b]
6[c]	**0.020**	**40**	**15**	**99**[b]
7[d]	**0.020**	**40**	**15**	**99**[b]
8	0.100	40	15	81[b]

[a] NMR yield.
[b] Isolated yield.
[c] CPME was used as the solvent.
[d] 1.0 mmol scale.

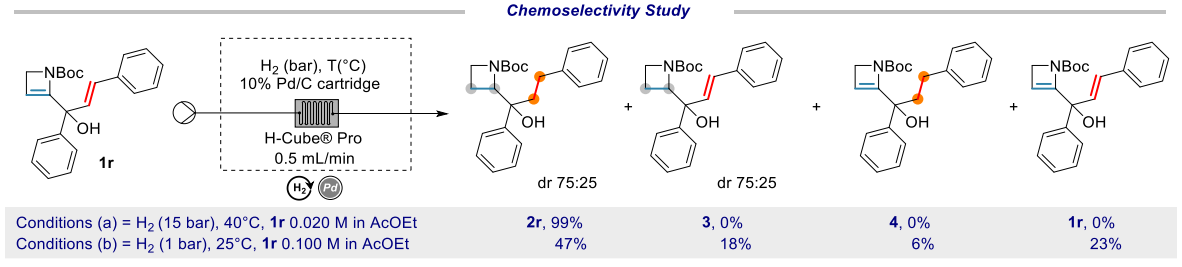


Scheme 2. Preparation of azetidines via hydrogenation of 2-azetines in continuous flow. [a] Relative stereochemistry not assigned.

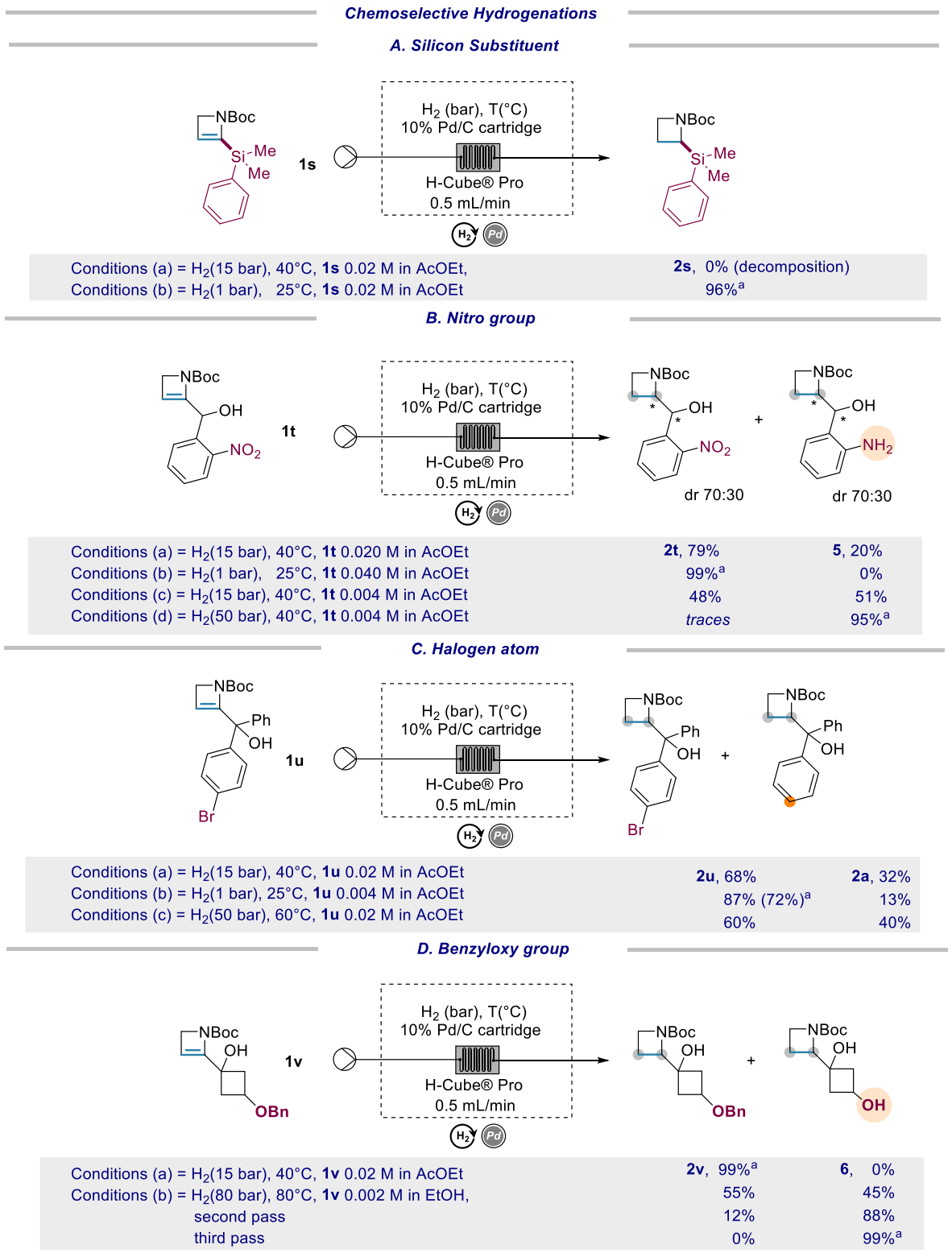
diastereoselectivity (**2l-q**). These results can be explained by considering the coordination of the hydroxyl group, and possibly other functionalities, to the palladium catalyst as previously described by Didier for the reduction of 2,3-disubstituted azetines [22]. As a result, azetidine **2l** bearing a trifluoromethyl and a phenyl group on the tertiary carbinolic fragment could be obtained as a single diastereoisomer ($dr > 99{:}1$). In turn, azetidine **2o** bearing a secondary carbinolic fragment was efficiently hydrogenated and the product was obtained with a 70:30 diastereomeric ratio. 2-Azetines bearing aryl and aliphatic substituents on the tertiary carbinol carbon were also reduced, leading to compounds **2m** and **2n** with around 80:20 diastereomeric ratios. Moreover, the reduction proceeded with poor diastereoselectivity to afford 2-azetidinyl-2-phenyltetrahydrofuran **2p** with a 60:40 diastereomeric ratio. Notably, azetidine **2q** bearing a sulfonamide group has been obtained with a good diastereoselection (dr = 85:15), suggesting that the nitrogen atom could likely coordinate the palladium and affect the diastereoselectivity.

Next, we investigated the chemoselective hydrogenation of the azetine's ring in the presence of sensitive functionalities installed on the substituents. Initially, azetine **1r** bearing an additional exocyclic C=C bond was reacted upon the optimized conditions reported in Scheme 4. As expected, we observed the complete reduction of both the double bonds (Scheme 3, A). Notably, the use of a more concentrated solution of **1r** (0.1 M in AcOEt) and milder hydrogenation conditions (1 bar H_2, 25 °C) afforded azetidine **2r** (47%) in a not-separable mixture with the products arising from the exclusive reduction of either the endocyclic (**3**, 18%) either exocyclic (**4**, 6%) double bond, and the starting azetine **1r** (27%). Although the chemoselective hydrogenation of a single double bond is extremely challenging, the results suggest that the hydrogenation of the ene-carbamate double bond of azetine **1r** is slightly favored over the reduction of the exocyclic one (Scheme 3).

The reaction of azetine **1s** bearing a dimethylphenylsilyl group on C2 upon the optimized conditions led to a complex mixture and the expected product could not be detected. However, we were able to obtain the azetidine **2s** in 96% yield by performing the reaction under milder conditions reducing the hydrogen pressure and temperature (Scheme 4, A). In turn, the hydrogenation of the azetine ring of **1t** could be

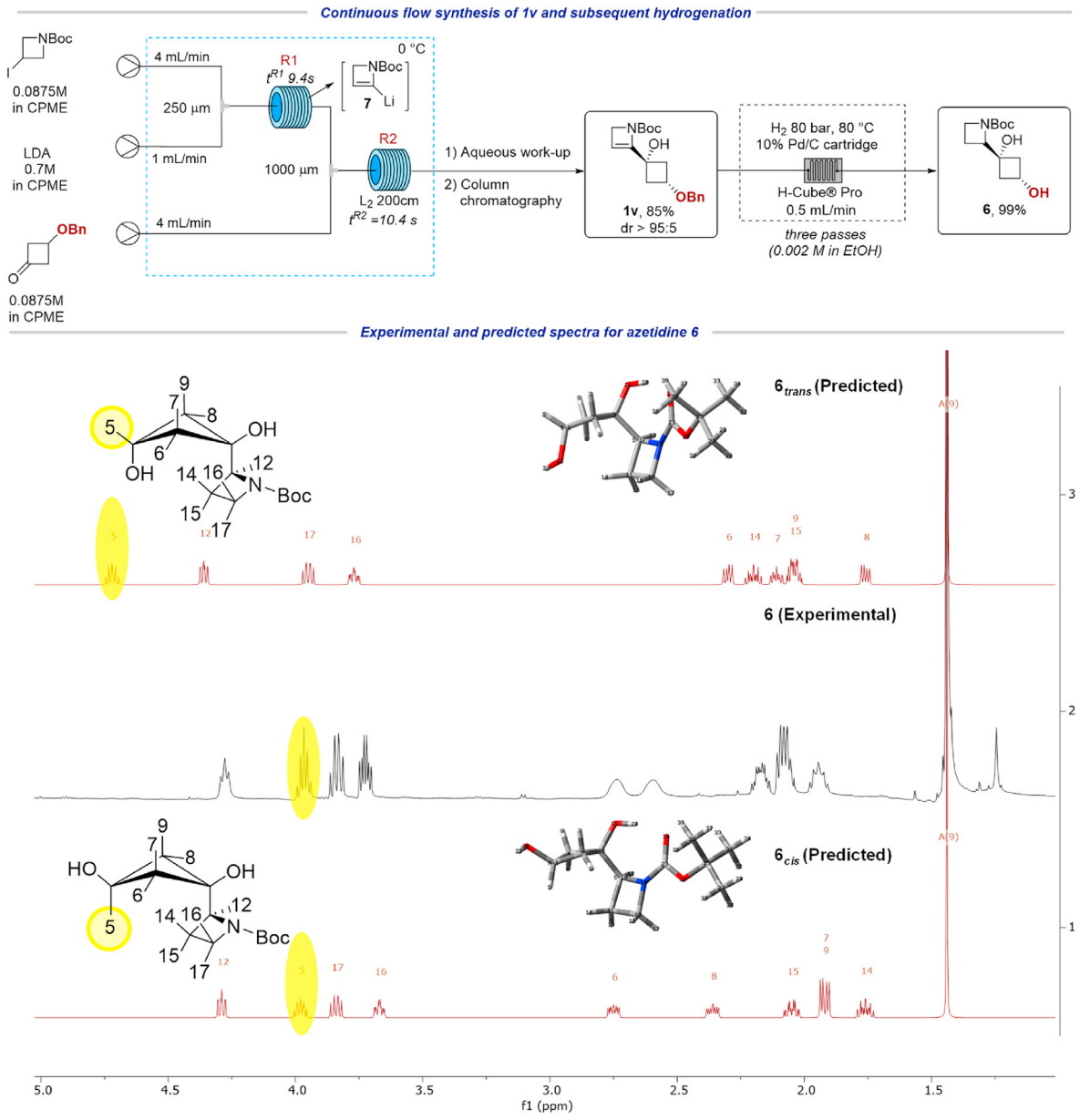


Scheme 3. Continuous flow reduction of azetine **1r**.



Scheme 4. Chemoselective hydrogenation of azetines 1**s-v**. NMR yield. a) Isolated yield of product.

performed chemoselectively while preserving the nitro group installed to the aromatic ring by using 1 bar of H_2 pressure at room temperature (Scheme 4, B). The complete reduction of both the double bond and the nitro group was achieved at higher H_2 pressure (50 bar) and with a more diluted solution of **1t** in AcOEt (0.004 M) leading to aniline **5** in very good yield (Scheme 4, B). On the other hand, the treatment of **1t** upon the standard conditions (Scheme 2) led to a mixture of products **2t** and **5**. The transformation of azetine **1u** bearing a brominated aromatic ring was likewise studied, as a de-halogenation process can be envisaged for these substrates. In this case, the desired halogenated product **2u** could be obtained with good selectivity (87%) from a diluted solution of **1u** upon 1 bar of H_2 and at ambient temperature, while the debromination process



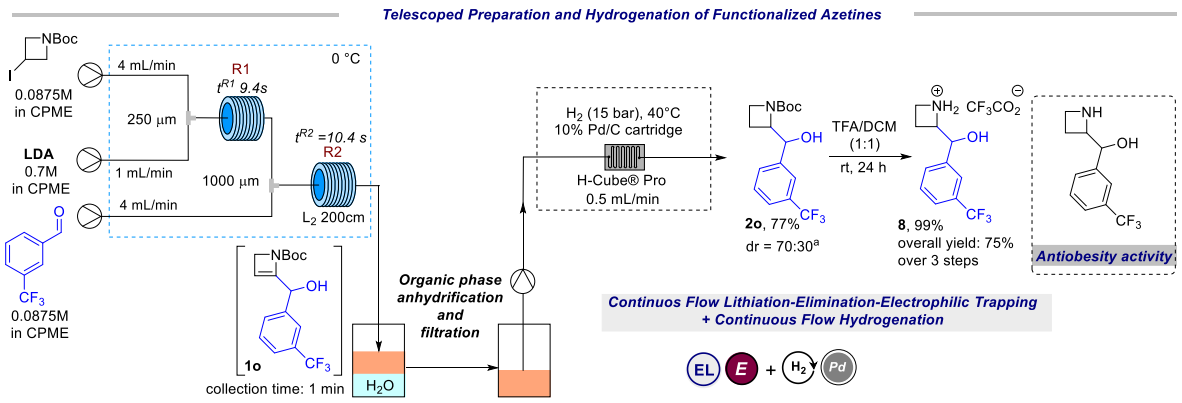
Scheme 5. Top: Continuous flow synthesis of azetine **1v** and subsequent hydrogenation to azetidine 7; Bottom: Comparison between experimental ^{1}H NMR for **6** and predicted spectra for stereoisomers $\mathbf{6}_{trans}$ and $\mathbf{6}_{cis}$.

was assessed to be competitive at higher temperatures and pressures (40 °C, 15 bar) leading to a mixture of **2u** and **2a** (Scheme 4, C).

Similarly, azetine **1v** could be selectively reduced to azetidine **2v** avoiding the deprotection of the hydroxyl function (Scheme 4, D). The hydrogenolysis of the benzyloxy group could be achieved by employing harder conditions (80 bar H_2, 80 °C), leading directly to product **6** from **1v** after three passes of the starting ethanolic solution through the system (Scheme 4, D). The relative configuration of **6** was determined by comparing the experimental ^{1}H NMR spectrum with those calculated in silico. NMR magnetic properties for $\mathbf{6}_{cis}$ and $\mathbf{6}_{trans}$ were calculated employing the DFT-GIAO method after geometry optimization computed at DFT-SMD($CHCl_3$)/b3lyp/6–311++g (d,p) (SM). The predicted spectra for $\mathbf{6}_{cis}$ and $\mathbf{6}_{trans}$ were assembled in MestreNova using the chemical shift values (δ) calculated at DFT-SMD($CDCl_3$)/B3LYP/6-311g(d,p)//MPW1PW91/gen level of theory and the spin-spin coupling constant values (J) calculated at DFT-SMD($CDCl_3$)/B3LYP/6-311g(d,p)//B3LYP/6-311g(d,p) level of theory (SM).

The results suggest that the two hydroxy groups installed on the cyclobutane fragment of azetidine **2v** are most likely in a *cis* relationship, as the experimental ^{1}H NMR analysis for compound **6** is almost superimposable with the predicted spectra for $\mathbf{6}_{cis}$ (Scheme 5). A good agreement has been observed between predicted $\mathbf{6}_{cis}$ and the experimental spectrum relative to the signal assigned to the proton linked to the secondary carbinolic carbon, which is in turn calculated to be de-shielded for about 0.75 ppm for $\mathbf{6}_{trans}$. These results additionally helped in shedding some light on the stereochemical outcome of the reaction of the formation of **1v**. Azetine **1v** was synthesized in continuous flow according to our reported method from commercially available 3-iodoazetidine by treatment with LDA and subsequent capture with the electrophile [25]. The reaction, therefore, is supposed to proceed with excellent diastereoselectivity in favour of the product arising from the attack of transient 2-lithium azetine **7** to the less hindered face of 3-benzyloxycyclobutanone.

Finally, we explored the combination of the two continuous flow



Scheme 6. Telescoped approach *en route* to bio-relevant compound **8**.

processes employed for the formation of azetines and subsequent hydrogenation, avoiding intermediate purification steps. To this end, we focused on the preparation of *tert*-butyl 2-(hydroxy (3-(trifluoromethyl) phenyl)methyl)azetidine-1-carboxylate **2o** as a precursor of pharmaceutically relevant azetidin-2-yl (3-(trifluoromethyl)phenyl)methanol showing antiobesity activity (Scheme 6) [5,28]. According to the reported procedure, the first multistep continuous flow process involved the formation of the transient azetine **2o** from 3-iodoazetidine and *m*-trifluoromethyl benzaldehyde using eco-friendly CPME as the single solvent. The outlet solution was quenched by collection in a vessel containing water. The resulting organic phase was taken, dried over anhydrous sodium sulfate and the solution was filtrated before entering the H-cube system. The reaction crude was then purified by column chromatography furnishing azetidine **2o** in 77% yield. Finally, we performed the Boc-deprotection accessing azetidium trifluoroacetate salt **8** in 75% overall yield over 3 steps starting from N-Boc-3-iodoazetidine.

4. Conclusions

In conclusion, herein we reported the continuous flow hydrogenation of 2-azetines with a ThalesNano H-Cube®Pro apparatus to access functionalized azetidines. The reaction has been optimized using ethyl acetate and CPME as environmentally responsible solvents. As a result, a collection of diversely functionalized azetidines, including a wide library of strained β-amino alcohols, could be prepared in excellent yields from their unsaturated precursors. Moreover, the chemoselective saturation of the endocyclic double bond of a selection of 2-azetines bearing additional groups sensitive to hydrogenation has been disclosed. Finally, we were able to combine two continuous flow processes for the preparation of 2-azetines and subsequent hydrogenation, furnishing a precursor of a pharmaceutically relevant azetidine avoiding intermediate purification steps and employing CPME as the only solvent for the whole manufacturing. Further investigations for the development of sustainable processes for the preparation of strained azacycles are ongoing in our lab and will be presented in due course.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tgchem.2023.100003.

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