Development of a Continuous Flow Synthesis of 2-Substituted Azetines and 3-Substituted Azetidines by Using a Common Synthetic Precursor

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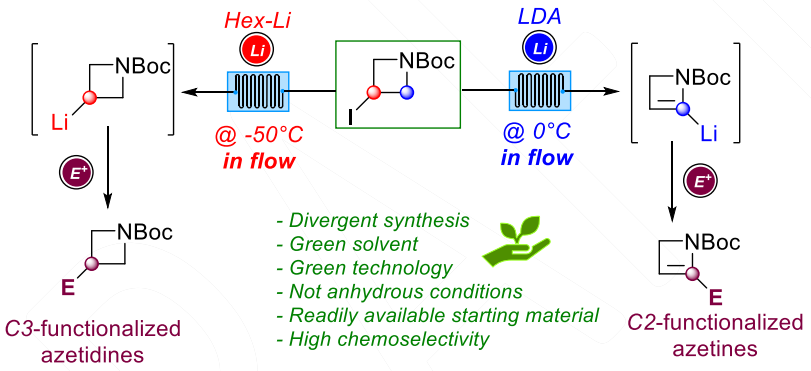


Abstract. The generation and functionalization, under continuous flow conditions, of two different lithiated four-membered aza-heterocycles is reported. *N*-Boc-3-Iodoazetidine acts as a common synthetic platform for the genesis of C3-lithiated azetidine and C2-lithiated azetine depending on the lithiation agent. Flow technology enables easy handling of such lithiated intermediates at much higher temperatures compared to batch processing. Flow technology combined with cyclopentylmethylether (CPME) as an environmentally responsible solvent allows obeying sustainability concerns.

Introduction

Nitrogen-bearing heterocycles are ubiquitous and essential in a plethora of biologically relevant molecules and natural products.[1] Piperidines and pyrrolidines are in the top-five among the 25 most frequently employed nitrogen heterocycles, respectively at the first and fifth position. In this ranking, the four-membered heterocyclic core is represented by the well-known β-lactams (i.e. azetidine-2-ones), especially as bicyclic fused systems mostly employed as antibacterial agents. However, although less investigated than the corresponding higher homologs belonging to the class of *N*-containing heterocycles, the azetidine ring is present in several biologically relevant compounds.[2,3] The peculiar molecular rigidity and robustness (e.g. chemical stability) are the main features that justify the introduction of azetidine motifs in medicinal chemistry design. Moreover, beneficial effects on the pharmacokinetic profile after the introduction of this strained ring have also been reported.[4] The importance of the azetidine ring is showcased by the recent introduction into the market of several medicines such as Azelnipidine (Calblock®),[5] Cobimetinib (Cotellic®),[6] Baricitinib (Olumiant®),[7] and others (Figure 1).[8, 9]

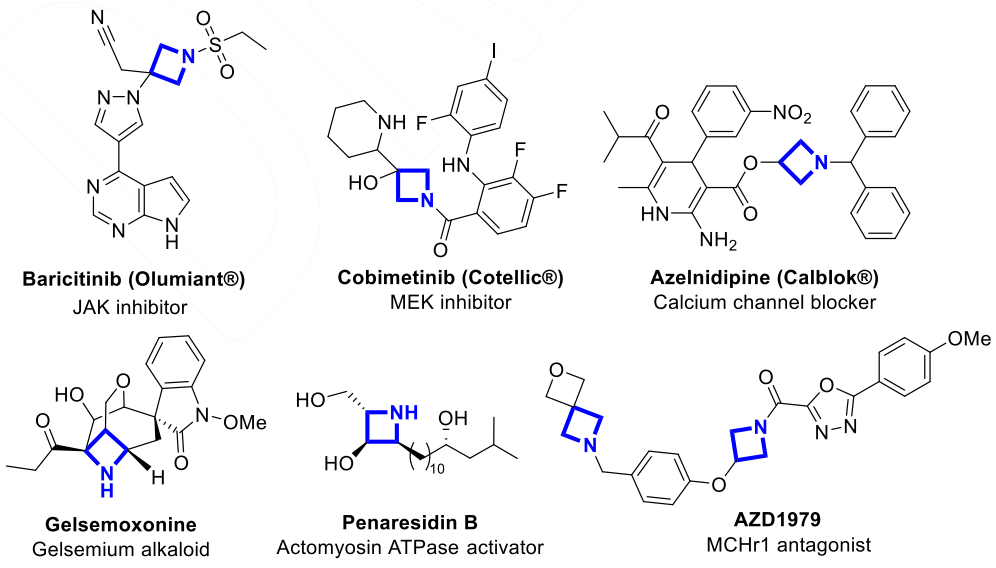
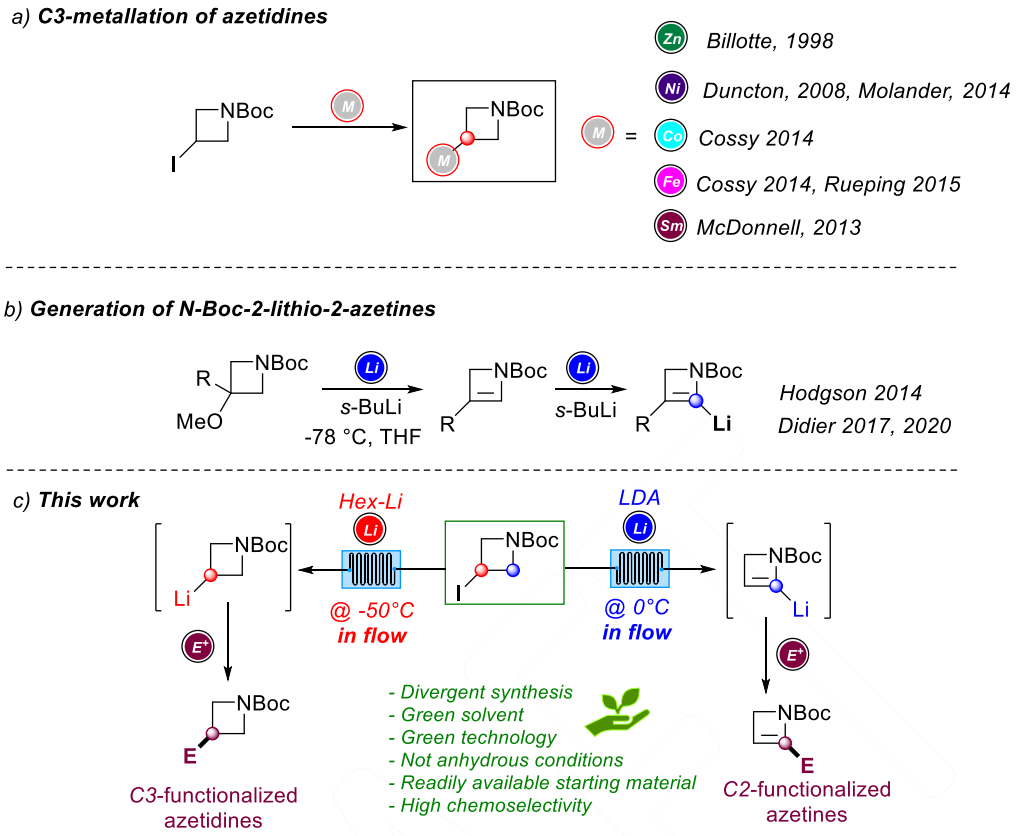


***Figure 1**. Examples of azetidine-containing biologically active compounds.*

The first reported synthesis of the azetidine ring dates to 1888,[10] but the interest in developing efficient synthetic methodologies for creating functionalized azetidines raised only recently. On the other hand, such a relatively unexplored motif continues to stimulate organic chemists' creativity.[11] Our research group is involved in developing synthetic tactics involving metallated (i.e. lithiated) azetidines as useful intermediates for creating molecular diversity.[12,13] In addition, we became interested in the use of flow technology as a tool for taming, controlling, and using highly reactive organometallic intermediates.[14] The benefits of flow microreactor technology as a pivotal synthetic "toolbox" for enabling new and previously inaccessible reactivity patterns, or for controlling safety concerns of old-fashioned chemistry are nowadays well-documented.[15,16] Furthermore, the flow technology holds the potential to be a green technology addressing the quest for sustainability coming from modern society.[17] Leveraging on our experience in the field, we report herein a greener and more sustainable approach for the functionalization of the azetidine ring under continuous flow conditions. [18] Examples of C3-functionalization of azetidines, via the corresponding C3-metallated intermediates, have been reported by several authors (Scheme 1, a) that, however, used this strategy in cross-coupling reactions in the presence of transition metals. [19, 20, 21, 22, 23] The C2-functionalization of 2-azetines has been exploited only recently by Hodgson[24] and Didier[25] that generated the corresponding 2-lithium azetine intermediates under cryogenic conditions and without using a green solvent. Herein, a sustainable continuous flow protocol has been developed starting from a common readily available precursor, to access C3-functionalized azetidines and C2-functionalized 2-azetines. Both synthetic sequences foresee a metalation (lithiation) step (Scheme 1, c) and employed cyclopentylmethyl ether as green solvent.[26]

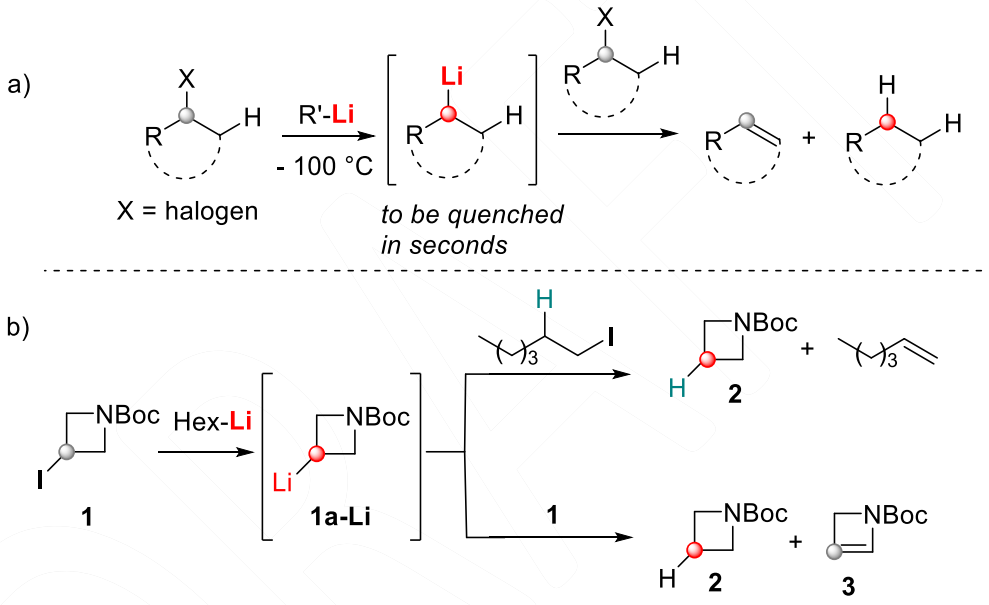


Scheme 1.

Results and Discussion

We started our investigation by using 1-Boc-3-iodoazetidine **1** as a cheap (2.7 eur/g)[27] and readily available starting material, evaluating the lithium/iodine exchange reaction leading to **1a-Li**. Quenching of **1a-Li** with an electrophile gives access to C3-functionalized 1-Boc-azetidines. To the best of our knowledge, protocols for the generation of azetidine lithiated at C3 have not been reported. A possible reason could be ascribed to the expected high reactivity of the putative secondary organolithium generated by lithium/iodine exchange. Knochel recently reported the generation of secondary alkyllithium reagents employed in very elegant stereocontrolled processes. Moreover, it was reported that the generation and use of secondary akyllithiums requires a precise control of the reaction parameters (i.e temperature as low as -100 °C), rapid quenching in the order of seconds, and precise order of addition of reactants to avoid undesired side reactions.[28] With this

in mind, we envisaged that the lithiated species **1a-Li**, generated by iodine-lithium exchange from **1** using hexyllithium,[29] would undergo protonation (i.e. quenching) by reaction with **1** itself or with 1-iodohexane, furnishing side products **2**, **3**, and 1-hexene respectively (Scheme 2, b). According to Knochel's report, such side-reaction pathways could be favored generating **1a-Li** in the presence of an excess of **1**. Hence, an inversion addition protocol, in which **1** is added to an organolithium solution, was fundamental. Moreover, the process needed to be conducted at low temperatures (< -78 °C).

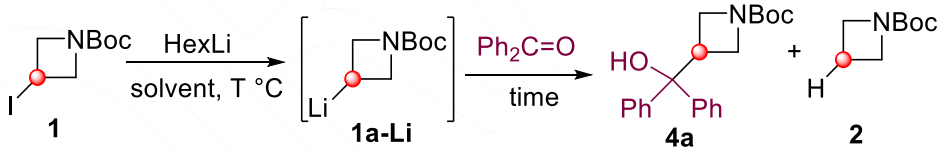


Scheme 2. Self-quenching of secondary alkyllithiums.

Aimed at developing a more sustainable protocol, our idea was to generate **1a-Li** taking advantage of the flow technology, and by using a primary alkyllithium (i.e. HexLi) for the iodine/lithium exchange reaction using a green solvent (i.e. 2-MeTHF or CPME).[30] We started our investigation by testing the generation of **1a-Li** at -78 °C in batch, under external quenching conditions adding the electrophile after the generation of the lithiated species **1a-Li**. As reported in Table 1, using 2-MeTHF as the solvent (entry 1), **1a-Li** could be efficiently intercepted using benzophenone as the electrophile to furnish adduct **4a** in 64% yield. In striking contrast, the use of CPME resulted in a

modest 18% yield of **4a**, jointly to a predominant 49% of protonated azetidine **2** (entry 2). Another experiment conducted at -50 °C in CPME proved that the process cannot be effectively executed in this solvent (entry 3). Adopting the internal quenching protocol using CPME as the solvent at -78 °C, returned a 62% yield of **4a** and only 10 % of byproduct **2** (entry 4). However, running the reaction at -50 °C under internal quenching mode was detrimental likely because of the thermal sensitivity of **1a-Li** (entry 5). Despite the poor performance of CPME under batch conditions, we reasoned that this might have been the right solvent to be employed under flow conditions for the following reasons. CPME has a high boiling point (106 °C) and low propensity to form peroxides, chemical stability under acidic and basic conditions, is cheaper than 2-MeTHF and can be used as received without anhydrification. In addition, the very low solubility in water allows to reduce the amount of organic solvent for work-up procedures.[31] For these reasons, to develop a greener process, we focused on the use of CPME and flow technology for the C3-functionalization of N-Boc azetidine.

Table 1.



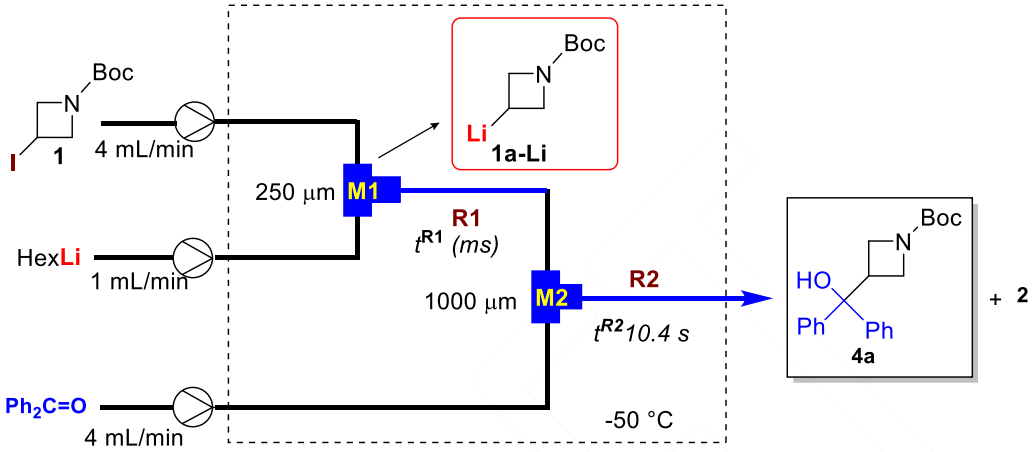
Entry	Solvent	T °C	time[a]	**4a** yield (%)[b]	**2** yield (%)[b,c]
1	2-MeTHF	-78	1 min	64	33
2	CPME	-78	1 min	18	49
3	CPME	-50	1 min	<5	47
4	CPME	-78	0[d]	62	10
5	CPME	-50	0[d]	24	24

[a]Time before quenching with the electrophile. [b]Yields calculated by ^{1}H NMR of the crude reaction mixture using CH_2Br_2 as the Internal Standard. [c]The amount of azetine **3** and 1-hexene was difficult to evaluate due to the volatility of those compounds. [d]Reaction ran in internal quenching conditions.

The continuous flow C3-lithiation/trapping sequence was performed using a flow system consisting of two stainless steel T-shaped micromixers (M1 and M2) and two stainless steel microtube reactors

(R1 and R2), and the CPME solutions of **1**, HexLi and benzophenone were introduced by syringe pumps (Table 2).

Table 2.



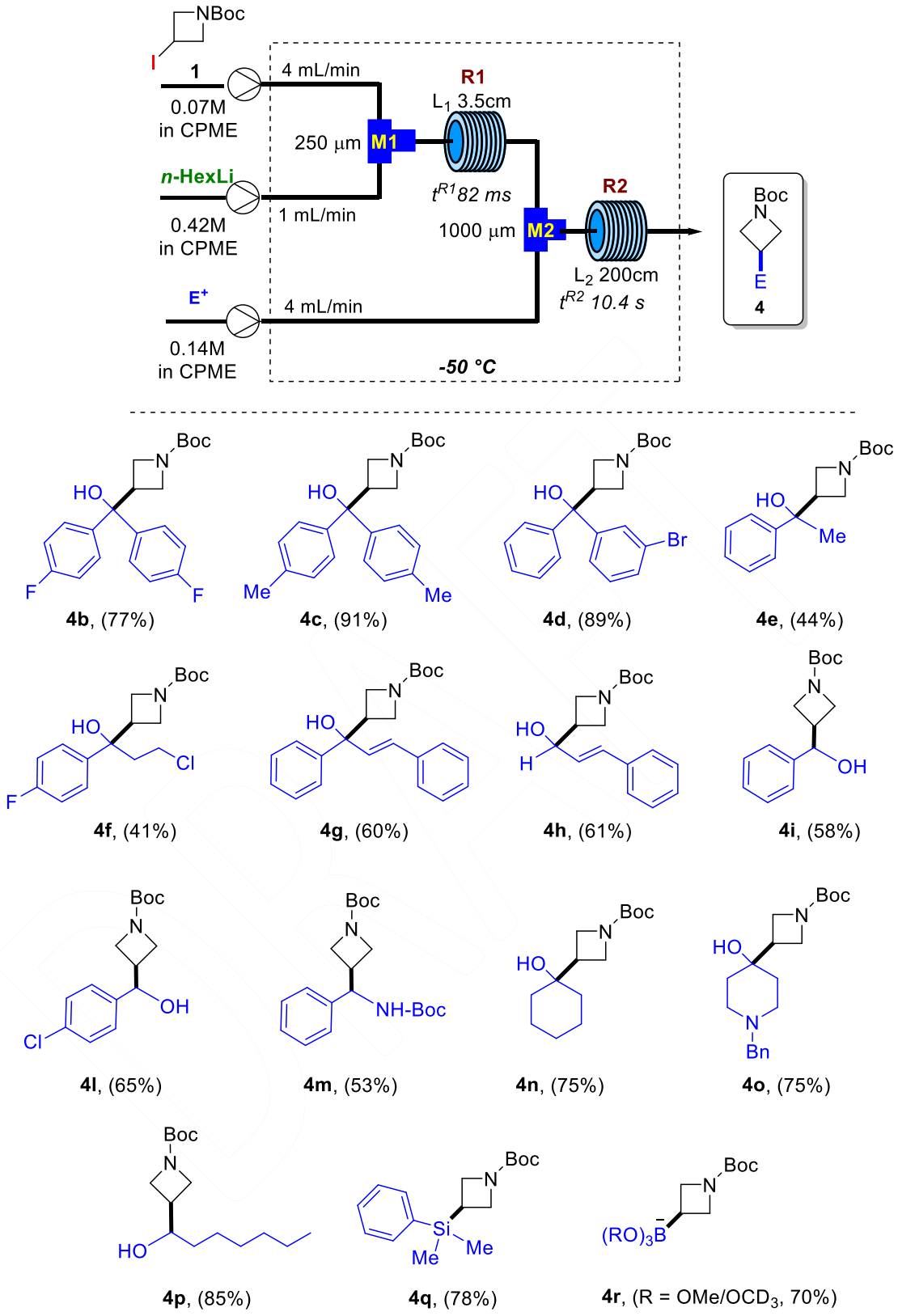
Entry	HexLi (equiv)	Electrophile (equiv)	t^{R1} (ms)[a]	**4a**, yield (%)[b]	**2**, yield (%)[b,c]
1	2	1	330	40	30
2	1.5	1	330	64	10
3	1.5	1	82	52	20
4	1.5	2	82	80	<5

[a]Time before quenching with the electrophile. [b]Yields calculated by ^{1}H NMR of the crude reaction mixture using CH_2Br_2 as the Internal Standard. [c]The amount of azetine **3** and 1-hexene was difficult to evaluate due to the volatility of those compounds.

Initial attempts to conduct the flow sequence in the range of temperatures –30 °C ÷ 25 °C resulted in clogging of the system or low yields of the desired product. To overcome this problem we decided to adopt -50 °C as ideal temperature for the iodine/lithium exchange reaction. As reported in Table 2, by using shorth residence time (in the range of 82 up to 330 ms) we were able to effectively generate and intercept the C3-lithiated azetidine **1a-Li**. Interestingly, **4a** could be obtained in 80% yield using 82 ms as residence time in R1 observing only traces of by-product **2** (Table 2, entry 4). Longer residence times (entries 1 and 2) provided lower yields of **4a** while promoting the protonation of **1a-Li** furnishing **2**. Remarkably, the use of flow technology resulted in a much better

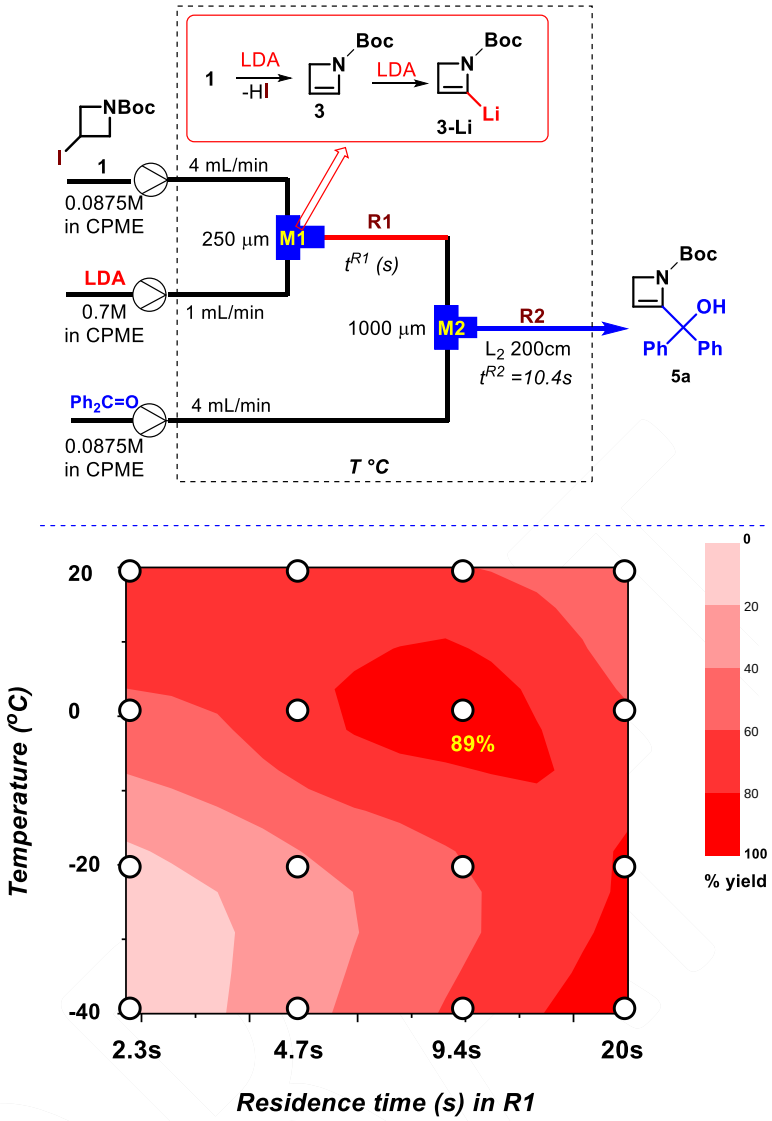
performance of the reaction with respect to batch processing (compare Table 1, entries 3, 5 and Table 2, entry 4). In addition, the short residence time realized in the flow system gives the opportunity to generate a secondary organolithium reagent from the safer (primary) HexLi avoiding the more reactive *t*-BuLi considered the "*must be used*" reagent for this kind of chemistry.

With the optimal condition in hands, the scope of the reaction was investigated. As reported in Scheme 3, the flow set-up allowed to prepare several C3-funtionalized azetidines **4b-r** with good to excellent yields. The flow synthesis was effective with both ketones and aldehydes and occurred with high chemo-selectivity as in the case of **4d** potentially prone to undergoing a competitive Br/Li exchange reaction or as in the case of **4f** susceptible of β-elimination. The use of α,β-unsaturated carbonyls resulted in a chemo-selective 1,2-addition returning products **4g**,**h** in very good yields. The reaction resulted successful with imines (**4m**), carbocyclic and heterocyclic ketones (**4n,o**) as well as with enolizable aldehydes (**4p**). Moreover, compounds bearing a silyl and a boron functionality could be prepared in satisfactory yields (**4q,r**) by silylation and borylation reactions. Under optimized conditions, the process is complete in less than 12 seconds producing 0.224 mmol/min of the desired product. In the case of **4a**, 5 minutes continuous collection furnished 380 mg of the product securing an estimated productivity of 4.56 g/h.



Scheme 3. Scope for the Continous Flow Synthesis of C3-Funtionalized Azetidines.

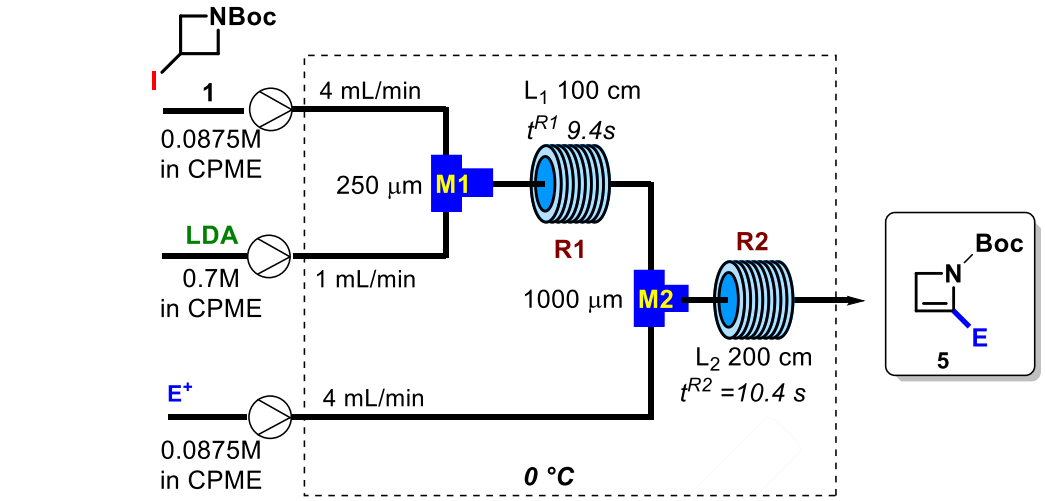
Next, we investigated the possibility to use the same 3-iodo azetidine **1** as a common synthetic platform for a β-elimination/lithiation/electrophilic trapping sequence to access C2-functionalized azetines. Hodgson[23] and Didier[24] demonstrated that azetines could be deprotonated at C2 in THF at -78 °C by using sec-BuLi as lithiation agent. Our idea was to use **1** as starting material for one-pot β-elimination/lithiation sequence. We reasoned that the use of an alkyllithium would have been problematic due to a competitive iodine/lithium exchange reaction. For this reason, we selected, lithium diisopropylammide (LDA, pKa ~ 35) as a suitable non nucleophilic base capable of promoting β-elimination of **1** and C2-lithiation of the resulting azetine **3**.[32] Aimed at developing a sustainable process, the entire sequence was developed under continuous flow conditions and using CPME as the green solvent (Scheme 4).

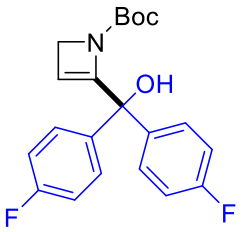


Scheme 4. Optimization of the continuous flow β-elimination/lithiation/electrophilic trapping sequence.

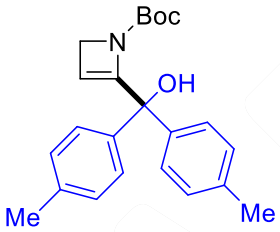
Parameters such as the residence time in R1 and the temperature were evaluated in the optimization study (Scheme 4). Under optimal conditions, the sequence for the conversion of **1** into **3-Li** required 9.4s at 0 °C furnishing, after trapping with benzophenone as the model electrophile, C2-functionalized azetine **5a** in 89% yield. The 3D plot clearly shows that high yields (i.e. > 80%) could be obtained at lower temperature (-40 °C) using longer residence times (up to 20s). In striking contrast, acceptable yields of **5a** (in the range 60-80%) were observed using shorter residence times (2.3s) and higher temperature (20 °C). It is worth pointing out that the same one-pot sequence

performed at 0 °C in batch made returned 60% yield of **5a** and 30% of **3** and required internal quenching conditions.[33] Delighted with the possibility to effectively execute the one-pot β-elimination/lithiation/electrophilic trapping sequence under more sustainable conditions (i.e. continuous flow, 0 °C and using a green solvent), the scope of the synthetic sequence was investigated (Scheme 5). Several C2-functionalized azetines **5b-r** were prepared in good to excellent yields using this one-flow approach from **1** (Scheme 5). Aromatic ketones as well as aldehydes and α,β-unsaturated carbonyls were found suitable reaction partners, and reacted with high chemo-selectivity when in the presence of additional functional groups (namely, halogens as in the case of **5d**, **5f** or **5l**; double bonds as in the case of **5g**,**h**). The use of imines, enolizable aldehydes, strained carbocyclic and heterocyclic ketones was also feasible furnishing respectively azetines **5m-q** in good yields (Scheme 5). Remarkably, silylation reaction occurred with good yield furnishing azetine 5r. This flow process occurred in less than 20 s providing a productivity of 0.3 mmol/min of azetines **5**. By using acetophenone as the electrophile, continuous collection for 5 minutes furnished 525 mg of azetine **5e**, that would correspond to a productivity of 6.3 g/h.

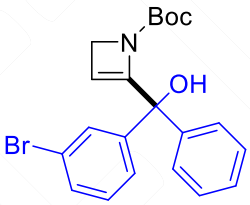




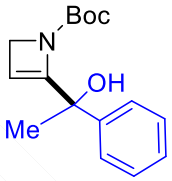
5b, (87%)



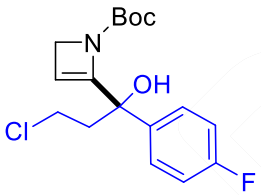
5c, (89%)



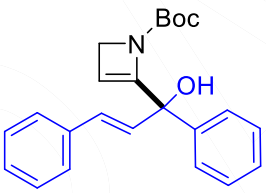
5d, (78%)



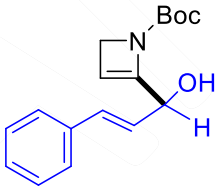
5e, (95%)



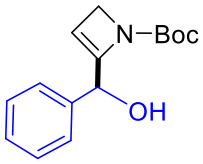
5f, (80%)



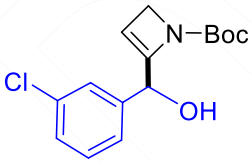
5g, (78%)



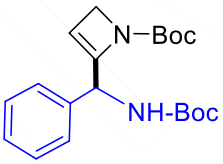
5h, (62%)



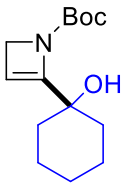
5i, (82%)



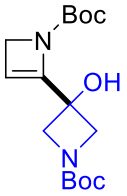
5l, (77%)



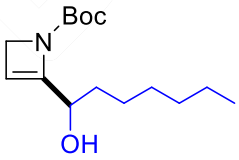
5m, (65%)



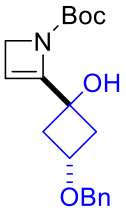
5n, (59%)



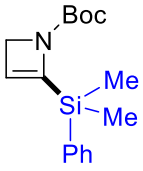
5o, (70%)



5p, (83%)



5q, (85%)
dr >95:5



5r, (55%)

Scheme 5. Scope for the Continous Flow Synthesis of C2-Funtionalized Azetines.

Conclusions

In conclusion, to the best of our knowledges, this work reports the first flow synthesis of C3-functionalized azetidines and C2-functionalized azetines starting from the same precursor, adopting different lithiation conditions. In addition, CPME has been employed as a green and sustainable solvent that could be used as received without requiring additional anhydrification steps. The developed process is safer, robust, and more sustainable if compared to the available batch methods for the preparation of similar molecules. Further use of the prepared molecules will be reported in due course.

Experimental Section

Proton, carbon, and fluorine NMR spectra were recorded on Agilent 500 spectrometer (500 MHz for ^{1}H, 126 MHz for ^{13}C, 470 MHz for ^{19}F), and on Varian Mercury 300 spectrometer (300 MHz for ^{1}H, 75 MHz for 13C, 282 MHz for ^{19}F). Chemical shifts are reported in ppm (δ) and the center of 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 77.00 ppm (^{13}C in $CDCl_3$). The multiplicity of the signals is reported as s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), bs (broad signal), m (multiplet). Spin-spin coupling constants (*J*) are given in Hz. As far as possible, complete and unambiguous assignment of all resonances was performed by combined application of standard NMR techniques, such as HSQC and COSY experiments. To minimize decomposition, NMR spectra of azetines were recorded with $CDCl_3$ aged on solid K_2CO_3. Infrared spectra (FT-IR) were obtained by using a PerkinElmer 283 Spectrometer. High resolution mass spectrometry (HRMS) spectra were recorded on Agilent 6530 accurate mass Q-TOF instrument. CPME was purchased from Merck and employed as received. The solution of lithium diisopropylamide [2M in THF/heptane/ethylbenzene] and the solution of *n*-hexyllithium [2.3M in hexane] were purchased from Merck and titrated prior to use. Other chemicals were purchased from suppliers and used as received. TLCs were carried out on a 0.25mm precoated silica gel thick plates (Merck) with a fluorescence indicator F-254; the spots were visualized under UV light (λ = 254 nm) and/or $KMnO_4$ (aq.) as revealing agent.

Stainless steel T-shaped micromixers and stainless steel microtube reactors were employed. The microtubes were cut into appropriate length and connected to the micromixers with stainless steel

fittings to build customized flow microreactor. Solutions of the reaction components were injected into the flow microreactor system using Harvard PHD 2000 syringe pumps equipped with gastight syringes.

Flow set up A: Two stainless steel T-shaped micromixers (M1 and M2) and two stainless steel microtube reactors (R1 and R2) were employed for the lithiation of azetidine **1** (M1 through hole = 250 μm, R1 inner diameter ϕ = 500 μm, length L = 3.5 cm) and for the quenching step (M2 through hole = 1000 μm, R2 inner diameter ϕ = 1000 μm, length L = 200 cm). Three precooling units (P1, P3 (inner diameter ϕ = 1000 μm, length L = 50 cm) and P2 (inner diameter ϕ = 1000 μm, length L = 25 cm)) were used.

Flow set up B: Two stainless steel T-shaped micromixers (M1 and M2) and two stainless steel microtube reactors (R1 and R2) were employed for the genesis and lithiation of azetine **3** (M1 through hole = 250 μm, R1 inner diameter ϕ = 1000 μm, length L = 100 cm) and for the quenching step (M2 through hole = 1000 μm, R2 inner diameter ϕ = 1000 μm, length L = 200 cm). Three precooling units (P1, P3 (inner diameter ϕ = 1000 μm, length L = 50 cm) and P2 (inner diameter ϕ = 1000 μm, length L = 25 cm)) were used.

General procedure 1 (GP1) for flow synthesis of 3-substituted azetidines 4.

Flow set up A was employed. The flow microreactor was dipped in a cooling bath (-50 °C). The solution of 1-Boc-3-iodoazetidine **1** (0.07 M in CPME, flow rate: 4 mL/min) and the solution of *n*-hexyllithium (0.42 M in CPME, flow rate: 1 mL/min) were delivered into M1 by syringe pumps. The resulting solution passed through R1 (82 ms) and then introduced to M2, where it was mixed with the solution of electrophile. The resulting solution passed through R2 (10.4 s). After the system reached the steady state (1 min), the output solution was collected for 2 minutes while being quenched with water. The aqueous phase was separated, and the organic layer dried on Na_2SO_4, filtered and the solvent removed under vacuum. The yield was determined by NMR using dibromomethane as internal standard. Flash column chromatography (SiO_2) led to the desired product. The employed solution of *n*-hexyllithium (0.42M in CPME) was prepared from the commercial solution of *n*-hexyllithium (2.3M in hexane) and titrated prior to use.

Large scale synthesis of **4a** (>1 mmol): Following the general procedure 1 (**GP1**), continuous collection for 5 minutes furnished, after column chromatography, 380 mg (1.1 mmol) of azetidine **4a**.

General procedure 2 (GP2) for flow synthesis of 2-substituted azetines 5.

Flow set up B was employed. The flow microreactor was dipped in a cooling bath (0 °C). The solution of 1-Boc-3-iodoazetidine **1** (0.0875M in CPME, flow rate: 4 mL/min) and the solution of lithium diisopropylamide (0.7M in CPME, flow rate: 1 mL/min) were delivered into M1 by syringe pumps. The resulting solution passed through R1 (9.4 s) and then introduced to M2, where it was mixed with the solution of electrophile. The resulting solution passed through R2 (10.4 s). After the system reached the steady state (1 min), the outcoming solution was collected for 2 minutes while being quenched with water. The aqueous phase was separated, and the organic layer dried on Na_2SO_4, filtered and the solvent was removed under vacuum. The yield was determined by NMR using dibromomethane as internal standard. To minimize decomposition, NMR spectra were recorded with $CDCl_3$ aged on solid K_2CO_3. Flash column chromatography (SiO_2) led to the desired product. In the case of products **5a-d** and **5f,g**, the crude mixture was washed with hexane/diethyl ether 9:1 (5 mL) and filtrated on Gooch yielding a white powder. The employed solution of LDA (0.7M in CPME) was prepared form the commercial solution of LDA (2M in THF/heptane/ethylbenzene) and titrated prior to use.

Large scale synthesis of **5e** (>1 mmol): Following the general procedure 2 (**GP2**), continuous collection for 5 minutes furnished, after column chromatography, 525 mg (1.9 mmol) of azetine **5e**.

***tert*-Butyl 3-(hydroxydiphenylmethyl)azetidine-1-carboxylate 4a.** Following **GP1** with benzophenone as electrophile, compound **4a** was obtained as white waxy solid (80%, 152 mg). Rf = 0.4 (8:2 hexane/ethyl acetate). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33 – 7.19 (m, 10 H, Ar-*H*), 3.98 – 3.85 (m, 4H, 2 x NCH_2), 3.63 – 3.51 (m, 1H, C*H*), 1.41 (s, 9H, 3 x CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 156.5, 145.4, 128.6, 127.5, 126.1, 79.5, 78.4, 50.0, 37.8, 28.6. **IR** (film)/cm^{-1} 3451, 2973, 1689, 1485, 1414, 1365, 1257, 1146, 991, 697. **HRMS** calcd for $C_{21}H_{25}NNaO_3$ $[M+Na]^+$ 362.1732; found 362.1730.

***tert*-Butyl 3-(bis(4-fluorophenyl)(hydroxy)methyl)azetidine-1-carboxylate 4b.** Following **GP1** with 4,4'-difluorobenzophenone as electrophile, compound **4b** was obtained as white waxy solid (77%, 162 mg). Rf = 0.4 (8:2 hexane/ethyl acetate). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.32 – 7.21 (m, 4H, Ar-*H* overlapping $CHCl_3$ signal), 7.05 – 6.93 (m, 4H, Ar-H), 3.95 – 3.82 (m, 4H, 2 x NCH_2), 3.55 – 3.45 (m, 1H, C*H*), 1.41 (s, 9H, 3 x CH_3). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ 162.1 (d, $^1J_{CF}$ = 246.8 Hz), 156.5, 141.1 (d, $^4J_{CF}$ = 3.2 Hz), 127.9 (d, $^3J_{CF}$ = 8.1 Hz), 115.4 (d, $^2J_{CF}$ = 21.4 Hz), 79.7, 76.9, 49.9, 37.9, 28.5. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -114.95 – -115.05 (m, 2F). IR (film)/cm^{-1} 3447, 3404, 2972, 1687, 1602, 1504, 1415, 1147, 991, 828. HRMS calcd for $C_{21}H_{22}F_2NO_3$ $[M-H]^-$ 374.1568; found 374.1570.

***tert*-Butyl 3-(hydroxydi-*p*-tolylmethyl)azetidine-1-carboxylate 4c.** Following **GP1** with 4,4'-dimethylbenzophenone as electrophile, compound **4c** was obtained as white waxy solid (91%, 187mg). Rf = 0.4 (8:2 hexane/ethyl acetate). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.21 – 7.05 (m, 8H, Ar-H), 3.98 – 3.82 (m, 4H, 2 x NCH_2), 3.60 – 3.47 (m, 1H, NCH_2CH), 2.47 (s, 1H, OH), 2.31 (s, 6H, 2 x Ar-CH_3), 1.41 (s, 9H, 3 x CH_3). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ 156.5, 142.7, 137.0, 129.2, 126.0, 79.4, 77.3, 49.9, 37.8, 28.6, 21.1. **IR** (film)/cm^{-1} 3430, 2974, 2923, 1681, 1511, 1420, 1366, 1169, 1145, 1019, 936, 814, 764. **HRMS** calcd for $C_{23}H_{29}NNaO_3$ $[M+Na]^+$ 390.2045; found 390.2038.

***tert*-Butyl 3-((3-bromophenyl)(hydroxy)(phenyl)methyl)azetidine-1-carboxylate 4d.** Following **GP1** with 3-bromobenzophenone as electrophile, compound **4d** was obtained as white waxy solid (89%, 208 mg). Rf = 0.6 (7:3 hexane/ethyl acetate). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.51 (s, 1H, Ar-H), 7.38 – 7.09 (m, 8H, Ar-H), 3.99 – 3.75 (m, 4H, 2 x NCH_2), 3.61 – 3.45 (m, 1H, CH), 2.70 (s, 1H, OH), 1.40 (s, 9H, 3 x CH_3). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ 156.5, 147.7, 144.7, 130.5, 130.1, 129.3, 128.8, 127.9, 126.1, 124.8, 122.8, 79.6, 77.3, 49.8, 37.6, 28.5. **IR** (film)/cm^{-1} 3411, 2975, 1678, 1592, 1565, 1475, 1419, 1366, 1254, 1145, 1075, 995, 781, 767, 700. **HRMS** calcd for $C_{21}H_{24}BrNNaO_3$ $[M+Na]^+$ 440.0837; found 440.0825.

***tert*-Butyl 3-(1-hydroxy-1-phenylethyl)azetidine-1-carboxylate 4e.** Following **GP1** with acetophenone as electrophile, compound **4e** was obtained as white waxy solid (44% yield, 68 mg). Rf = 0.5 (7:3 hexane/ethyl acetate). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 – 7.40 (m, 2H, Ar-H), 7.34 (t, *J* = 7.7 Hz, 2H, Ar-H), 7.27 – 7.24 (m, 1H, Ar-H), 4.03 – 3.93 (m, 2H, NCH_2), 3.75 – 3.65 (m, 2H, NCH_2), 3.00 – 2.94 (m, 1H, CH), 1.49 (s, 3H, CH_3COH), 1.41 (s, 9H, 3 x CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 156.6, 146.0, 128.6, 127.3, 124.8, 79.4, 73.4, 49.8, 39.1, 28.5, 27.4. **IR** (film)/cm^{-1} 3428, 2975, 1682, 1477, 1417, 1367, 1142, 909, 760, 701. **HRMS** calcd for $C_{16}H_{23}NNaO_3$ $[M+Na]^+$ 300.1576; found 300.1571.

***tert*-Butyl 3-(3-chloro-1-(4-fluorophenyl)-1-hydroxypropyl)azetidine-1-carboxylate 4f.** Following **GP1** with 3-chloro-4'-fluoropropiophenone as electrophile, compound **4f** was obtained as white waxy solid (41%, 79 mg). Rf = 0.5 (7:3 hexane/ethyl acetate). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 2H, Ar-H), 7.12 – 6.97 (m, 2H, Ar-H), 4.11 – 3.91 (m, 2H, NCH_2), 3.67 – 3.54 (m, 2H, NCH_2), 3.45 (ddd, *J* = 10.9, 8.5, 7.1 Hz, 1H, CH_2CH_2Cl), 3.26 (ddd, *J* = 10.9, 8.3, 5.8 Hz, 1H, CH_2CH_2Cl), 3.04 – 2.93 (m, 1H, NCH_2CH), 2.70 (bs, 1H, OH), 2.28 – 2.10 (m, 2H, CH_2CH_2Cl), 1.41 (s, 9H, 3 x CH_3). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ 162.2 (d, $^1J_{CF}$ = 246.6 Hz), 156.5, 138.2 (d, $^4J_{CF}$ = 3.1 Hz), 127.0 (d, $^3J_{CF}$ = 8.0 Hz), 115.7 (d, $^2J_{CF}$ = 21.4 Hz), 79.7, 75.6, 49.3, 42.6, 39.9, 39.1, 28.5. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -115.17

(s, 1F). **IR** (film)/cm^{-1} 3401, 1677, 1604, 1508, 1478, 1424, 1367, 1225, 1159, 834, 770. **HRMS** calcd for $C_{17}H_{23}ClFNNaO_3$ $[M+Na]^+$ 366.1248; found 366.1231.

***tert*-Butyl(*E*)-3-(1-hydroxy-1,3-diphenylallyl)azetidine-1-carboxylate 4g.** Following **GP1** with (*E*)-chalcone as electrophile, compound **4g** was obtained as white waxy solid (60%, 123 mg) Rf = 0.26 (8:2 hexane/ethyl acetate). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.37 (dt, *J* = 7.7, 4.0 Hz, 4H, Ar-H), 7.33 – 7.28 (m, 3H, Ar-H), 7.27- 7.23 (m, 1H, Ar-H), 6.66 (d, *J* = 16.0 Hz, 1H, CH=CH), 6.38 (d, *J* = 16.0 Hz, 1H, CH=CH), 4.03 – 3.94 (m, 2H, NCH_2), 3.86 (dd, *J* = 8.7, 6.1 Hz, 1H, NCH_2), 3.79 (t, *J* = 8.6 Hz, 1H, NCH_2), 3.33 – 3.12 (m, 1H, CH), 1.42 (s, 9H, 3 x CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 156.6, 143.7, 136.4, 132.5, 129.5, 128.8, 128.7, 128.1, 127.7, 126.8, 125.6, 79.5, 76.2, 50.4, 49.3, 37.5, 28.5. **IR** (film)/cm^{-1} 3428, 2981,2103, 1649, 1478, 1419, 1265, 1145, 970, 746. **HRMS** calcd for $C_{23}H_{27}NNaO_3$ $[M+Na]^+$ 388.1889; found 388.1892.

***tert*-Butyl (E)-3-(1-hydroxy-3-phenylallyl)azetidine-1-carboxylate 4h.** Following **GP1** with (*E*)-cinnamaldehyde as electrophile, compound **4h** was obtained as white waxy solid (61%, 99 mg) Rf = 0.3 (7:3 hexane/ethyl acetate). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41 – 7.20 (m, 5H, Ar-H), 6.62 (d, *J* = 15.9 Hz, 1H, CH=CH), 6.12 (dd, *J* = 15.9, 6.9 Hz, 1H, CH=CH), 4.38 (t, *J* = 7.1 Hz, 1H, C*H*OH), 4.02 – 3.86 (m, 3H, NCH_2), 3.72 (dd, *J* = 8.7, 5.4 Hz, 1H, NCH_2), 2.71 – 2.60 (m, 1H, NCH_2CH), 2.35 (bs, 1H, OH), 1.43 (s, 9H, 3 x CH_3). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ 156.6, 136.4, 132.2, 129.1, 129.0, 128.8, 128.1, 126.7, 79.6, 74.5, 51.4, 34.1, 28.5. **IR** (film)/cm^{-1} 3400, 2974, 2885, 1677, 1478, 1419, 1366, 1298, 1256, 1143, 968, 858, 750, 693. **HRMS** calcd for $C_{17}H_{23}NNaO_3$ $[M+Na]^+$ 312.1576; found 312.1572.

***tert*-Butyl 3-(hydroxy(phenyl)methyl)azetidine-1-carboxylate 4i.** Following **GP1** with benzaldehyde as electrophile, compound **4i** was obtained as white waxy solid (58% yield, 85 mg). Rf = 0.3 (7:3 hexane/ethyl acetate). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 – 7.19 (m, 5H, Ar-H), 4.74 (d, *J* = 7.9 Hz, 1H, C*H*OH), 4.01 – 3.91 (m, 2H, NCH_2), 3.77 (t, *J* = 8.7 Hz, 1H, NCH_2), 3.63 (dd, *J* = 8.8, 5.7 Hz, 1H, NCH_2), 2.86 – 2.77 (m, 1H, NCH_2CH), 2.70 (bs, 1H, OH), 1.41 (s, 9H, 3 x CH_3). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ 156.6, 142.2, 128.8, 128.2, 126.3, 79.5, 76.0, 51.8, 51.0, 35.6, 28.5. **IR** (film)/cm^{-1} 3403, 2974, 1701, 1677, 1478, 1420, 1366, 1254, 1144, 1053, 992, 859, 770, 756, 701. **HRMS** calcd for $C_{15}H_{21}NNaO_3$ $[M+Na]^+$ 286.1419; found 286.1412.

***tert*-Butyl 3-((4-chlorophenyl)(hydroxy)methyl)azetidine-1-carboxylate 4l.** Following **GP1** with 4-chlorobenzaldehyde as electrophile, compound **4l** was obtained as white waxy solid (65% yield, 108 mg). Rf = 0.4 (6:4 hexane/ethyl acetate). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 – 7.23 (m, 4H, Ar-H), 4.72 (dd, *J* = 7.8, 3.2 Hz, 1H, C*H*OH), 3.95 - 3.90 (m, 2H, NCH_2), 3.76 (t, *J* = 8.7 Hz, 1H, NCH_2), 3.61 (dd, *J* =

8.8, 5.7 Hz, 1H, NCH_2), 3.01 (bs, 1H, OH), 2.80 – 2.71 (m, 1H, NCH_2CH), 1.40 (s, 9H, 3 x CH_3). **$^{13}C\{^1H\}$ NMR** (126 MHz, $CDCl_3$) δ 156.6, 140.8, 133.8, 128.9, 127.7, 79.7, 75.0, 51.5, 35.6, 28.5. **IR** (film)/cm^{-1} 3401, 2975, 1674, 1479, 1417, 1366, 1254, 1145, 1089, 1014, 832, 770. **HRMS** calcd for $C_{15}H_{20}ClNNaO_3$ $[M+Na]^+$ 320.1029; found 320.1024.

***tert*-Butyl 3-(((tert-butoxycarbonyl)amino)(phenyl)methyl)azetidine-1-carboxylate 4m.** Following **GP1** with *tert*-butyl (phenylmethylene)carbamate as electrophile, compound **4m** was obtained as white waxy solid (53% yield, 108 mg). Rf = 0.3 (7:3 hexane/ethyl acetate). **^1H NMR** (500 MHz, $CDCl_3$) δ 7.32 (t, *J* = 7.3 Hz, 2H, Ar-H), 7.28 – 7.24 (m, 1H, Ar-H), 7.23 – 7.20 (m, 2H, Ar-H), 4.89 (bs, 1H, C*H*NHBoc), 4.00 (t, *J* = 8.5 Hz, 1H, NCH_2), 3.88 – 3.78 (m, 2H, NCH_2), 3.62 – 3.57 (m, 1H, NCH_2), 2.87 (bs, 1H, NCH_2CH), 1.42 (s, 9H, 3 x CH_3), 1.41 (bs, 9H, 3 x CH_3). **$^{13}C\{^1H\}$ NMR** (75 MHz, $CDCl_3$) δ 156.4, 155.6, 140.5, 129.0, 127.9, 126.7, 80.0, 79.6, 57.1, 51.4, 34.0, 28.5, 28.5. **IR** (film)/cm^{-1} 3330, 2976, 2885, 1704, 1694, 1682, 1410, 1366, 1248, 1166, 1050, 861, 772, 736, 701. **HRMS** calcd for $C_{20}H_{30}N_2NaO_4$ $[M+Na]^+$ 385.2103; found 385.2095.

***tert*-Butyl 3-(1-hydroxycyclohexyl)azetidine-1-carboxylate 4n.** Following **GP1** with cyclohexanone as electrophile, compound **4n** was obtained as white waxy solid (75% yield, 107 mg). Rf = 0.4 (7:3 hexane/ethyl acetate). **^1H NMR** (300 MHz, $CDCl_3$) δ 3.91 – 3.77 (m, 4H, NCH_2), 2.6. – 2.50 (m, 1H, NCH_2CH), 1.66 – 1.36 (m, 7H, CH_2), 1.42 (s, 9H, 3 x CH_3), 1.31 – 1.16 (m, 3H, CH_2). **$^{13}C\{^1H\}$ NMR** (75 MHz, $CDCl_3$) δ 156.6, 79.3, 70.3, 49.5, 38.2, 34.5, 28.6, 25.7, 21.7. **IR** (film)/cm^{-1} 3435, 1682, 1478, 1419, 1366, 1255, 1165, 1140, 994, 962, 859, 771. **HRMS** calcd for $C_{14}H_{25}NNaO_3$ $[M+Na]^+$ 278.1732; found 278.1728.

***tert*-Butyl 3-(1-benzyl-4-hydroxypiperidin-4-yl)azetidine-1-carboxylate 4o.** Following **GP1** with 1-benzyl-4-piperidone as electrophile, compound **4o** was obtained as white waxy solid (75 %, 145 mg). Rf = 0.2 (1:1 hexane/ethyl acetate). **^1H NMR** (500 MHz, $CDCl_3$) δ 7.32 – 7.28 (m, 4H, Ar-H), 7.27 – 7.22 (m, 1H, Ar-H), 3.88 – 3.83 (m, 4H, azetidine NCH_2), 3.53 (s, 2H, CH_2Ph), 2.68 – 2.63 (m, 2H, piperidine CH_2), 2.52 (quin, *J* = 7.1 Hz, 1H, NCH_2CH), 2.33 (td, *J* = 11.4, 3.2 Hz, 2H, piperidine CH_2), 1.58 – 1.47 (m, 4H, 2 x piperidine CH_2), 1.42 (s, 9H, 3 x CH_3). **$^{13}C\{^1H\}$ NMR** (126 MHz, $CDCl_3$) δ 156.6, 138.3, 129.3, 128.3, 127.2, 79.4, 68.5, 63.2, 49.86, 48.99, 48.78, 38.4, 34.1, 28.5. **IR** (film)/cm^{-1} 3430, 2936, 1681, 1416, 1366, 1344, 1255, 1143, 1031, 986, 955. **HRMS** calcd for $C_{20}H_{30}N_2NaO_3$ $[M+Na]^+$ 369.2154; found 369.2146.

***tert*-Butyl 3-(1-hydroxyheptyl)azetidine-1-carboxylate 4p.** Following **GP1** with heptanal as electrophile, compound **4p** was obtained as colourless oil (85%, 129 mg). Rf = 0.3 (7:3 hexane/ethyl acetate). **^1H NMR** (500 MHz, $CDCl_3$) δ 3.91 (q, *J* = 8.4 Hz, 2H, NCH_2), 3.83 (dd, *J* = 8.7, 5.7 Hz, 1H,

NCH_2), 3.71 - 3.63 (m, 2H, C*H*OH and NCH*H*), 2.55 – 2.46 (m, 1H, NCH_2CH), 2.03 (bs, 1H, OH), 1.48 – 1.21 (m, 10H, 5 x CH_2), 1.41 (s, 9H, $OC(CH_3)_3$), 0.87 (t, *J* = 6.9 Hz, 3H, CH_2CH_3). **$^{13}C\{^1H\}$ NMR** (126 MHz, $CDCl_3$) δ 156.6, 79.4, 73.1, 51.4, 50.7, 35.0, 34.6, 31.9, 29.4, 28.5, 25.6, 22.7, 14.2. **IR** (film)/cm^{-1} 3431, 2928, 1705, 1680, 1478, 1416, 1366, 1254, 1143, 998, 943, 860, 771. **HRMS** calcd for $C_{15}H_{29}NNaO_3$ $[M+Na]^+$ 294.2045; found 294.2045.

***tert*-Butyl 3-(dimethyl(phenyl)silyl)azetidine-1-carboxylate 4q.** Following **GP1** with chloro(dimethyl)phenylsilane as electrophile, compound **4q** was obtained as colourless oil (78%, 127 mg). Rf = 0.7 (7:3 hexane/ethyl acetate). **^1H NMR** (500 MHz, $CDCl_3$) δ 7.48 – 7.45 (m, 2H, Ar-H), 7.40 – 7.33 (m, 3H, Ar-H), 4.08 (dd, *J* = 9.9, 8.2 Hz, 2H, NCH_2), 3.85 – 3.81 (m, 2H, NCH_2), 2.13 (tt, *J* = 9.9, 6.9 Hz, 1H, NCH_2CH), 1.41 (s, 9H, $C(CH_3)_3$), 0.33 (s, 6H, $Si(CH_3)_2$). **$^{13}C\{^1H\}$ NMR** (126 MHz, $CDCl_3$) δ 156.4, 137.0, 133.7, 129.6, 128.1, 79.3, 51.1, 49.9, 28.5, 14.9, -5.3. **IR** (film)/cm^{-1} 2930, 2876, 1704, 1478, 1455, 1427, 1391, 1365, 1301, 1251, 1117, 998, 906, 813. **HRMS** calcd for $C_{16}H_{25}NNaO_2Si$ $[M+Na]^+$ 314.1552 ; found 314.1553.

Lithium (1-(*tert*-butoxycarbonyl)azetidin-3-yl)trimethoxyborate 4r. Following **GP1** and using triisopropyl borate as the electrophile, the reaction mixture was concentrated under reduced pressure and the residual solid washed (2 x 2 mL) with a mixture of ethyl acetate/methanol 3:1 (v/v) to afford compound **4r** as insoluble white waxy solid (70 %, 105 mg). **^1H NMR** (500 MHz, CD_3OD) δ 3.92 – 3.79 (m, 4H, NCH_2), 3.35 (s, 9H, 3 x OCH_3), 1.82 – 1.71 (m, 1H, NCH_2CH), 1.41 (s, 9H, 3 x CH_3). **$^{13}C\{^1H\}$ NMR** (126 MHz, CD_3OD) δ 157.0, 78.3, 52.5, 51.2, 47.6, 27.5, 17.1. **^{11}B NMR** (160 MHz, CD_3OD) δ 2.93. **IR** (film)/cm^{-1} 2973, 2935, 2879, 1664, 1478, 1422, 1365, 1137, 916, 860, 768. **HRMS** calcd for $C_{11}H_{23}BNO_5$ $[M-Li]^-$ 260.1675; found 260.1681.

***tert*-Butyl 4-(hydroxydiphenylmethyl)azete-1(2*H*)-carboxylate 5a.** Following **GP2** with benzophenone as electrophile, compound **5a** was obtained as white waxy solid (89%, 210 mg) by treatment of the reaction mixture with hexane/diethyl ether 9:1 (5 mL) and subsequent filtration on Gooch. **^1H NMR** (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.5 Hz, 4H, Ar-H), 7.32 (t, *J* = 7.4 Hz, 4H, Ar-H), 7.26 – 7.25 (m, 2H, Ar-H overlapping $CHCl_3$ signal), 5.09 (s, 1H, NCH_2CH), 4.32 (s, 2H, NCH_2CH), 1.39 (bs, 9H, 3 x CH_3). **$^{13}C\{^1H\}$ NMR** (126 MHz, $CDCl_3$) δ 153.8, 152.7, 143.3, 128.1, 127.5, 127.0, 110.4, 81.5, 76.4, 55.4, 28.3. **IR** (film)/cm^{-1} 3430, 2964, 1720, 1370, 1450, 1263, 1117, 1100, 1018, 727. **HRMS** calcd for $C_{21}H_{23}NNaO_3$ $[M+Na]^+$ 360.1576; found 360.1572.

large scale

***tert*-Butyl 4-(bis(4-fluorophenyl)(hydroxy)methyl)azete-1(*2H*)-carboxylate 5b.** Following **GP2** with 4,4'-difluorobenzophenone as electrophile, compound **5b** was obtained as white waxy solid (87%,

227 mg) by treatment of the reaction mixture with hexane/diethyl ether 9:1 (5 mL) and subsequent filtration on Gooch. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 (dd, J = 8.4, 5.5 Hz, 4H, Ar-H), 7.00 (t, J = 8.7 Hz, 4H, Ar-H), 5.07 (s, 1H, NCH_2CH), 4.31 (s, 2H, NCH_2), 1.40 (s, 9H, 3 x CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 162.3 (d, $^{1}J_{CF}$ = 246.1 Hz), 153.5, 152.7, 139.0 (d, $^{4}J_{CF}$ = 2.5 Hz), 128.8 (d, $^{3}J_{CF}$ = 8.2 Hz), 115.0 (d, $^{2}J_{CF}$ = 21.4 Hz), 110.6, 81.7, 75.6, 55.5, 28.3. ^{19}F NMR (470 MHz, $CDCl_3$) δ -115.34 (s, 2F). **IR** (film)/cm^{-1} 3400, 2985, 2917, 1661, 1601, 1505, 1369, 1223, 1143, 834. **HRMS** calcd for $C_{21}H_{21}F_2NNaO_3$ $[M+Na]^+$ 396.1387; found 396.1385.

***tert*-Butyl 4-(hydroxydi-p-tolylmethyl)azete-1(2H)-carboxylate 5c.** Following **GP2** with 4,4'-dimethylbenzophenone as electrophile, compound **5b** was obtained as white waxy solid (89%, 228 mg) by treatment of the reaction mixture with hexane/diethyl ether 9:1 (5 mL) and subsequent filtration on Gooch. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.2 Hz, 4H, Ar-H), 7.11 (d, *J* = 8.0 Hz, 4H, Ar-H), 5.08 (s, 1H, NCH_2CH), 4.30 (s, 2H, NCH_2CH), 2.32 (s, 6H, 2 x Ar-CH_3), 1.36 (s, 9H, 3 x CH_3). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ 154.1, 152.4, 140.7, 137.0, 128.7, 126.9, 110.2, 81.5, 76.2, 55.2, 28.4, 21.2. **IR** (film)/cm^{-1} 3319, 2977, 2923, 1672, 1510, 1409, 1368, 1176, 1141, 1021, 812, 765. **HRMS** calcd for $C_{23}H_{27}NNaO_3$ $[M+Na]^+$ 388.1889; found 388.1899.

***tert*-Butyl 4-((3-bromophenyl)(hydroxy)(phenyl)methyl)azete-1(2H)-carboxylate 5d.** Following **GP2** with 3-bromobenzophenone as electrophile, compound **5d** was obtained as white waxy solid (78%, 227 mg) by treatment of the reaction mixture with hexane/diethyl ether 9:1 (5 mL) and subsequent filtration on Gooch. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64 (s, 1H, Ar-H), 7.45 – 7.37 (m, 3H, Ar-H), 7.33 (t, *J* = 7.4 Hz, 3H, Ar-H), 7.27 – 7.27 (m, 1H, Ar-H overlapping $CHCl_3$ signal), 7.18 (t, *J* = 7.9 Hz, 1H, Ar-H), 5.12 (s, 1H, NCH_2CH), 4.32 (s, 2H, NCH_2), 1.40 (s, 9H, 3 x CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 153.1, 145.8, 142.7, 130.7, 130.1, 129.6, 128.2, 127.8, 126.9, 125.8, 122.4, 110.8, 81.9, 76.0, 55.2, 28.4. **IR** (film)/cm^{-1} 3307, 1667, 1449, 1409, 1368, 1259, 1207, 1142, 858, 763, 693. **HRMS** calcd for $C_{21}H_{22}BrNNaO_3$ $[M+Na]^+$ 438.0681; found 438.0691.

***tert*-Butyl 4-(1-hydroxy-1-phenylethyl)azete-1(2H)-carboxylate 5e.** Following **GP2** with acetophenone as electrophile, compound **5e** was obtained as white waxy solid (95%, 183 mg) after chromatography. Rf = 0.5 (7:3 hexane/diethyl ether + 0.5% triethylamine). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.35 – 7.34 (m, 2H, Ar-H), 7.28 – 7.23 (m, 1H, Ar-H overlapping $CHCl_3$ signal), 5.42 (s, 1H, NCH_2CH), 4.31 – 4.22 (m, 2H, NCH_2), 1.66 (s, 3H, CH_3), 1.38 (s, 9H, 3 x CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 155.4, 152.7, 144.7, 128.2, 127.2, 125.2, 107.0, 81.5, 71.5, 55.5, 28.4, 28.0. **IR** (film)/cm^{-1} 3340, 1668, 1403, 1368, 1205, 1152, 1022, 861, 764, 700. **HRMS** calcd for $C_{16}H_{21}NNaO_3$ $[M+Na]^+$ 298.1419; found 298.1423.

***tert*-Butyl 4-(3-chloro-1-(4-fluorophenyl)-1-hydroxypropyl)azete-1(2H)-carboxylate 5f.** Following **GP2** with 3-chloro-4'-fluoropropiophenone as electrophile, compound **5f** was obtained as white waxy solid (80%, 191 mg) by treatment of the reaction mixture with hexane/diethyl ether 9:1 (5 mL) and subsequent filtration on Gooch. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.47 – 7.42 (m, 2H, Ar-H), 7.07 – 6.99 (m, 2H, Ar-H), 5.43 (s, 1H, NCH_2CH), 4.27 – 4.22 (m, 2H, NCH_2), 3.68 (ddd, *J* = 11.7, 10.9, 4.8 Hz, 1H, CH_2CH_2Cl), 3.28 (td, *J* = 11.3, 5.0 Hz, 1H, CH_2CH_2Cl), 2.55 (ddd, *J* = 13.3, 12.1, 4.8 Hz, 1H, CH_2CH_2Cl), 2.33 (ddd, *J* = 13.4, 12.2, 5.1 Hz, 1H, CH_2CH_2Cl), 1.40 (s, 9H, 3 x CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 162.3 (d, $^1J_{CF}$ = 245.9 Hz), 153.9, 152.9, 137.5 (d, $^4J_{CF}$ = 3.0 Hz), 127.4 (d, $^3J_{CF}$ = 8.1 Hz), 115.2 (d, $^2J_{CF}$ = 21.4 Hz), 107.5, 81.9, 72.8, 55.8, 43.3, 39.7, 28.4. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -115.53 (s, 1F). **IR** (film)/cm^{-1} 3307, 1667, 1600, 1507, 1409, 1369, 1225, 1155, 1139, 1014, 836, 764. **HRMS** calcd for $C_{17}H_{21}ClFNNaO_3$ $[M+Na]^+$ 364.1092; found 364.1087.

***tert*-Butyl (*E*)-4-(1-hydroxy-1,3-diphenylallyl)azete-1(2*H*)-carboxylate 5g.** Following **GP2** with (*E*)-chalcone as electrophile, compound **5g** was obtained as white waxy solid (78%, 198 mg) by treatment of the reaction mixture with hexane/diethyl ether 9:1 (5 mL) and subsequent filtration on Gooch. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.37 (dd, *J* = 14.8, 7.5 Hz, 4H, Ar-H), 7.33 – 7.27 (m, 3H, Ar-H), 7.22 (t, *J* = 7.3 Hz, 1H, Ar-H), 6.68 (d, *J* = 16.0 Hz, 1H, CH=CH), 6.45 (d, *J* = 16.0 Hz, 1H, CH=CH), 5.36 (s, 1H, NCH_2CH), 4.31 (s, 2H, NCH_2CH), 1.40 (s, 9H, 3 x CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 149.8, 142.1, 136.8, 131.5, 130.2, 128.6, 128.3, 127.8, 127.6, 126.9, 126.4, 109.3, 81.6, 74.6, 55.7, 28.4. **IR** (film)/cm^{-1} 3366, 2978, 1667, 1403, 1369, 1144, 903, 859, 770, 746. **HRMS** calcd for $C_{23}H_{25}NNaO_3$ $[M+Na]^+$ 386,1732; found 386.1722.

***tert*-Butyl-4-(1-hydroxy-3-phenylallyl)azete-1(2H)-carboxylate 5h.** Following **GP2** with cinnamaldehyde as electrophile, compound **5h** was obtained as white waxy solid (62%, 125 mg) after chromatography. Rf = 0.4 (7:3 hexane/diethyl ether + 0.5% triethylamine). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.44 – 7.39 (m, 2H, Ar-H), 7.36 – 7.29 (m, 2H, Ar-H), 7.28 – 7.21 (m, 1H, Ar-H), 6.76 (dd, *J* = 16.0, 1.1 Hz, 1H, CH=CH), 6.32 (dd, *J* = 15.9, 6.2 Hz, 1H, CH=CH), 5.40 (s, 1H, C*H*OH), 5.03 – 4.94 (m, 1H, NCH_2CH), 4.31 – 4.24 (m, 2H, NCH_2CH), 1.50 (s, 9H, 3 x CH_3). **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ 152.8, 151.8, 136.7, 132.4, 128.7, 127.9, 126.8, 126.2, 107.3, 81.5, 67.5, 56.2, 28.5. **IR** (film)/cm^{-1} 3370, 2977, 1703, 1672, 1411, 1368, 1203, 1160, 1139, 1048, 967, 754, 964. **HRMS** calcd for $C_{17}H_{21}NNaO_3$ $[M+Na]^+$ 310.1419; found 310.1427.

***tert*-Butyl 4-(hydroxy(phenyl)methyl)azete-1(2H)-carboxylate 5i.** Following GP2 with benzaldehyde as electrophile, compound **5i** was obtained as white waxy solid (82%, 150 mg) after chromatography. Rf = 0.4 (7:3 hexane/diethyl ether + 0.5% triethylamine). **^{1}H NMR** (500 MHz, $CDCl_3$)

δ 7.48 – 7.44 (m, 2H, Ar-H), 7.37 – 7.34 (m, 2H, Ar-H), 7.33 – 7.29 (m, 1H, Ar-H), 5.41 (d, *J* = 1.9 Hz, 1H, C*H*OH), 5.07 (s, 1H, NCH_2CH), 4.29 – 4.19 (m, 2H, NCH_2), 1.49 (s, 9H, 3 x CH_3). **$^{13}C\{^1H\}$ NMR** (126 MHz, $CDCl_3$) δ 152.9, 152.6, 138.6, 128.4, 128.0, 126.9, 108.1, 81.5, 68.9, 55.9, 28.5. **IR** (film)/cm^{-1} 3368, 1705, 1668, 1453, 1409, 1368, 1257, 1159, 1138, 1052, 864, 698. **HRMS** calcd for $C_{15}H_{19}NNaO_3$ $[M+Na]^+$ 284.1263; found 284.1279.

***tert*-Butyl 4-((3-chlorophenyl)(hydroxy)methyl)azete-1(2H)-carboxylate 5l.** Following **GP2** with 3-chlorobenzaldehyde as electrophile, compound **5l** was obtained as white waxy solid (77%, 159 mg) after chromatography. Rf = 0.5 (6:4 hexane/diethyl ether + 0.5% triethylamine). **^1H NMR** (500 MHz, $CDCl_3$) δ 7.48 – 7.46 (m, 1H, Ar-H), 7.34 (ddd, *J* = 5.9, 3.7, 1.5 Hz, 1H, Ar-H), 7.31 – 7.27 (m, 2H, Ar-H), 5.40 – 5.35 (m, 1H, C*H*OH), 5.12 (s, 1H, NCH_2CH), 4.29 – 4.22 (m, 2H, NCH_2), 1.49 (s, 9H, 3 x CH_3). **$^{13}C\{^1H\}$ NMR** (126 MHz, $CDCl_3$) δ 153.0, 151.8, 140.7, 134.3, 129.7, 128.2, 127.0, 125.0, 108.5, 81.8, 68.4, 56.1, 28.4. **IR** (film)/cm^{-1} 3367, 1667, 1598, 1477, 1410, 1368, 1257, 1139, 1054, 861, 765. **HRMS** calcd for $C_{15}H_{18}ClNNaO_3$ $[M+Na]^+$ 318.0873; found 318.0877.

***tert*-Butyl 4-(((tert-butoxycarbonyl)amino)(phenyl)methyl)azete-1(2H)-carboxylate 5m.** Following **GP2** with *tert*-butyl (phenylmethylene)carbamate as electrophile, compound **5m** was obtained as white waxy solid (65%, 164 mg) after chromatography. Rf = 0.5 (6:4 hexane/diethyl ether + 0.5% triethylamine). **^1H NMR** (300 MHz, $CDCl_3$) δ 7.41 – 7.21 (m, 5H, Ar-H), 5.71 – 5.58 (d, *J* = 8.5 Hz, 1H, C*H*NHBoc), 5.51 (s, 1H, NCH_2CH), 4.27 (s, 2H, NCH_2CH), 1.45 (s, 9H, 3 x CH_3), 1.34 (s, 9H, 3 x CH_3). **$^{13}C\{^1H\}$ NMR** (75 MHz, $CDCl_3$) δ 155.3, 151.7, 150.0, 139.1, 128.6, 127.7, 127.0, 108.7, 81.0, 79. 9, 55.5, 52.6, 28.5, 28.3. **IR** (film)/cm^{-1} 3341, 2977, 1704, 1496, 1391, 1367, 1250, 1164, 1017, 861, 699. **HRMS** calcd for $C_{20}H_{28}N_2NaO_4$ $[M+Na]^+$ 383.1947; found 383.1958.

***tert*-Butyl 4-(1-hydroxycyclohexyl)azete-1(2H)-carboxylate 5n.** Following **GP2** with cyclohexanone as electrophile, compound **5n** was obtained as white waxy solid (59%, 105 mg) after chromatography. Rf = 0.4 (7:3 hexane/diethyl ether + 0.5% triethylamine). **^1H NMR** (500 MHz, $CDCl_3$) δ 5.30 (s, 1H, NCH_2CH), 4.20 (s, 2H, NCH_2), 1.82 – 1.63 (m, 6H, 3 x CH_2), 1.56 – 1.39 (m, 3H, CH_2 overlapping 9H, 3 x CH_3), 1.37 – 1.26 (m, 1H, CH_2). **$^{13}C\{^1H\}$ NMR** (126 MHz, $CDCl_3$) δ 157.0, 152.7, 105.3, 81.1, 68.2, 55.8, 35.0, 28.5, 25.8, 22.0. **IR** (film)/cm^{-1} 3391, 2934, 1673, 1478, 1403, 1368, 1257, 1159, 1142, 1026, 1005, 861, 766. **HRMS** calcd for $C_{14}H_{23}NNaO_3$ $[M+Na]^+$ 276.1576; found 276.1572.

***tert*-Butyl 4-(1-(*tert*-butoxycarbonyl)-3-hydroxyazetidin-3-yl)azete-1(2H)-carboxylate 5o.** Following **GP2** with 1-Boc-3-azetidinone as electrophile, compound **5o** was obtained as pale yellow oil (70%, 160 mg). Rf = 0.5 (7:3 hexane/ethyl acetate + 1% triethylamine). **^1H NMR** (500 MHz, $CDCl_3$)

δ 5.51 (s, 1H, NCH_2CH), 4.28 (s, 2H, NCH_2CH), 4.06 and 3.99 (2 x d, AB system, *J* = 9.5 Hz, 4H, 2 x azetidine NCH_2), 1.47 (s, 9H, 3 x CH_3), 1.43 (s, 9H, 3 x CH_3). **$^{13}C\{^1H\}$ NMR** (126 MHz, $CDCl_3$) δ 156.5, 153.0, 151.4, 106.3, 82.0, 79.9, 65.4, 60.8, 59.6, 56.0, 28.5, 28.4. **IR** (film)/cm^{-1} 3338, 2977, 1705, 1672, 1478, 1407, 1368, 1251, 1150, 1080, 999, 862, 769. **HRMS** calcd for $C_{16}H_{26}N_2NaO_5$ $[M+Na]^+$ 349.1739; found 349.1742.

***tert*-Butyl 4-(1-hydroxyheptyl)azete-1(2H)-carboxylate 5p.** Following **GP2** with heptanal as electrophile, compound **5p** was obtained as pale yellow oil (83%, 157 mg). Rf = 0.4 (7:3 hexane/ethyl acetate + 1% triethylamine). **^1H NMR** (500 MHz, $CDCl_3$) δ 5.34 (s, 1H, NCH_2CH), 4.27 – 4.18 (m, 3H, NCH_2 and $CHOH$), 1.73 – 1.66 (m, 2H, hexyl CH_2), 1.48 (s, 9H, $C(CH_3)_3$), 1.34 – 1.27 (m, 8H, 4 x hexyl CH_2), 0.90 – 0.86 (m, 3H hexyl CH_3). **$^{13}C\{^1H\}$ NMR** (126 MHz, $CDCl_3$) δ 153.7, 152.7, 106.1, 81.2, 66.6, 56.0, 33.4, 31.9, 29.9, 29.3, 28.5, 22.8, 14.2. **IR** (film)/cm^{-1} 3400, 2922, 2851, 1709, 1679, 1455, 1409, 1393, 1367, 1258, 1143, 863. **HRMS** calcd for $C_{15}H_{27}NNaO_3$ $[M+Na]^+$ 292.1889; found 292.1896.

***tert*-Butyl 4-(3-(benzyloxy)-1-hydroxycyclobutyl)azete-1(2H)-carboxylate 5q.** Following **GP2** with 3-(benzyloxy)cyclobutan-1-one as electrophile, compound **5q** was obtained as pale yellow oil (85%, 197 mg) dr > 95:5. Rf = 0.4 (7:3 hexane/ethyl acetate + 1% triethylamine). **^1H NMR** (500 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 4H, Ar-H), 7.30 – 7.25 (m, 1H, Ar-H), 5.35 (s, 1H, NCH_2CH), 4.43 (s, 2H, OCH_2), 4.22 (s, 2H, NCH_2CH), 3.75 (quin, *J* = 7.2 Hz, 1H, $CHOCH_2$), 2.73 – 2.66 (m, 2H, $COHCH_2$), 2.33 – 2.26 (m, 2H, $COHCH_2$), 1.47 (s, 9H, 3 x CH_3). **$^{13}C\{^1H\}$ NMR** (126 MHz, $CDCl_3$) δ 154.7, 152.7, 138.2, 128.5, 128.0, 127.8, 104.9, 81.6, 70.5, 65.4, 63.2, 55.3, 41.7, 28.5. **IR** (film)/cm^{-1} 3351, 1980, 2938, 1670, 1454, 1410, 1368, 1239, 1173, 1145, 1064, 1026, 860, 698. **HRMS** calcd for $C_{19}H_{25}NNaO_4$ $[M+Na]^+$ 354.1681; found 354.1689.

***tert*-Butyl 4-(dimethyl(phenyl)silyl)azete-1(2H)-carboxylate 5r.** Following **GP2** using chloro(dimethyl)phenylsilane as the electrophile, compound **5r** was obtained as colourless oil (55%, 111 mg). Rf = 0.5 (9:1 hexane/diethyl ether + 1% triethylamine). **^1H NMR** (500 MHz, $CDCl_3$) δ 7.60 – 7.53 (m, 2H, Ar-H), 7.41 – 7.30 (m, 3H, Ar-H), 5.89 (s, 1H, NCH_2CH), 4.55 (s, 2H, NCH_2CH), 1.33 (s, 9H, $C(CH_3)_3$), 0.47 (s, 6H, $Si(CH_3)_2$). **$^{13}C\{^1H\}$ NMR** (126 MHz, $CDCl_3$) δ 158.5, 152.0, 136.5, 134.2, 129.5, 127.9, 126.3, 80.4, 59.8, 28.5, -3.1. **IR** (film)/cm^{-1} 2980, 1689, 1254, 1138, 841. **HRMS** calcd for $C_{16}H_{23}NNaO_2Si$ $[M+Na]^+$ 312.1396; found 312.1402.

Supporting Information

Additional batch and flow procedures and optimization studies, copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at https://www.acs.org.

Notes

The authors declare no competing financial interest.

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REFERENCES

[1] Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem*. **2014**, *57*, 10257−10274.

[2] Yoda, H.; Takahashi, H.; Sengoku, T. Chapter 2, Azetidine and Its Derivates. In Heterocycles in Natural Product Synthesis, 1st ed.; Majumdar, K., Chattopadhyay, S. K., Eds.; Wiley-WCH: **2011**.

[3] a) Matsuura, F.; Hamada, Y.; Shioiri, T. Total Syntheses of Phytosiderophores, 3-Epi-Hydroxymugineic Acid, Distichonic Acid A, and 2'-Hydroxynicotianamine. *Tetrahedron* **1994**, *50*, 265–274. b) Raghavan, S.; Krishnaiah, V. An Efficient Stereoselective Synthesis of Penaresidin A from (E)-2-Protected Amino-3,4-Unsaturated Sulfoxide. *J. Org. Chem*. **2009**, *75*, 748–761.

[4] For recent reviews describing the potential of azetidines and azetines in medicinal chemistry, see: a) Jean D. J. St.; Fotsch, C. *J. Med. Chem*. **2012**, *55*, 6002–6020; b) Melillo, B.; Zoller, J.; Hua, B. K.; Verho, O.; Borghs, J. C.; Nelson, S. D. Jr.; Maetani, M.; Wawer, M. J.; Clemons P. A.; Schreiber, S. L. *J. Am. Chem. Soc*. **2018**, *140*, 11784–11790. b) Reidl, T. W.; Anderson, L. L. Divergent Functionalizations of Azetidines and Unsaturated Azetidines. *Asian J. Org. Chem*. **2019**, *8*, 931–945. c) Bauer, M. R.; Di Fruscia, P.; Lucas, S. C. C.; Michaelides, I. N.; Nelson, J. E.; Storer, R. I.; Whitehurst, B. C. Put a Ring on It: Application of Small Aliphatic Rings in Medicinal Chemistry. *RSC Med. Chem*. **2021**, *12* (4), 448–471. d) Kirichok, A. A.; Shton, I.; Kliachyna, M.; Pishel,

I.; Mykhailiuk P. K. 1-Substituted 2-Azaspiro[3.3]heptanes: Overlooked Motifs for Drug Discovery. *Angew. Chem. Int. Ed*., **2017**, 56, 8865-8869. e) Kirichok, A. A.; Shton, I. O.; Pishel, I. M.; Zozulya, S. A.; Borysko, P. O.; Kubyshkin, V.; Zaporozhets, O. A.; Tolmachev, A. A.; Mykhailiuk, P. K. Synthesis of Multifunctional Spirocyclic Azetidines and Their Application in Drug Discovery. *Chem. Eur. J.* **2018**, 24 (21), 5444–5449.

[5] Gomez-Sanchez, E. P.; Foecking, M. F.; Sellers, D.; Blankenship, M. S.; Gomez-Sanchez, C. E. Is the Circulating Ouabain-like Compound Ouabain? *Am. J. Hypertension* **1994**, *7* (7_Pt_1), 637–646.

[6] Rice, K. D.; Aay, N.; Anand, N. K.; Blazey, C. M.; Bowles, O. J.; Bussenius, J.; Costanzo, S.; Curtis, J. K.; Defina, S. C.; Dubenko, L.; Engst, S.; Joshi, A. A.; Kennedy, A. R.; Kim, A. I.; Koltun, E. S.; Lougheed, J. C.; Manalo, J.-C. L.; Martini, J.-F.; Nuss, J. M.; Peto, C. J.; Tsang, T. H.; Yu, P.; Johnston, S. Novel Carboxamide-Based Allosteric MEK Inhibitors: Discovery and Optimization Efforts toward XL518 (GDC-0973). *ACS Med. Chem. Lett*. **2012**, *3*, 416–421.

[7] Keystone, E. C.; Taylor, P. C.; Drescher, E.; Schlichting, D. E.; Beattie, S. D.; Berclaz, P.-Y.; Lee, C. H.; Fidelus-Gort, R. K.; Luchi, M. E.; Rooney, T. P.; Macias, W. L.; Genovese, M. C. Safety and Efficacy of Baricitinib at 24 Weeks in Patients with Rheumatoid Arthritis who have had an Inadequate Response to Methotrexate. *Ann. Rheum. Dis*. **2015**, *74*, 333−340.

[8] a) Kitajima, M.; Kogure, N.; Yamaguchi, K.; Takayama, H.; Aimi, N. Structure Reinvestigation of Gelsemoxonine, a Constituent Of Gelsemium Elegans, Reveals a Novel, Azetidine-Containing Indole Alkaloid. *Org. Lett.* **2003**, 5, 2075–2078. b) Betz, K. N.; Chiappini, N. D.; Du Bois, J. Intermolecular Sp3-C–H Amination for the Synthesis of Saturated Azacycles. *Org. Lett*. **2019**, *22*, 1687–1691. c) Johansson, A.; Löfberg, C.; Antonsson, M.; von Unge, S.; Hayes, M. A.; Judkins, R.; Ploj, K.; Benthem, L.; Lindén, D.; Brodin, P.; Wennerberg, M.; Fredenwall, M.; Li, L.; Persson, J.; Bergman, R.; Pettersen, A.; Gennemark, P.; Hogner, A. Discovery of (3-(4-(2-Oxa-6-Azaspiro[3.3]Heptan-6-Ylmethyl)Phenoxy)Azetidin-1-Yl)(5-(4-Methoxyphenyl)-1,3,4-Oxadiazol-2-Yl)Methanone (AZD1979), a Melanin Concentrating Hormone Receptor 1 (MCHr1) Antagonist with Favorable Physicochemical Properties. *J. Med. Chem*. **2016**, *59*, 2497–2511.

[9] Selected reviews on the azetidine ring construction and functionalization are listed below: a) Cromwell, N. H.; Phillips, Barry. The Azetidines. Recent Synthetic Developments. *Chem. Rev*. **1979**, *79*, 331–358. b) Singh, G. S.; D'hooghe, M.; De Kimpe, N. Azetidines, Azetines and Azetes: Monocyclic. In Comprehensive Heterocyclic Chemistry III; Stevens, C. V., Ed.; Elsevier: Oxford, U.K., **2008**; Vol. 2, Chapter 2.01, p 1. c) Brandi, A.; Cicchi, S.; Cordero, F. M. Novel Syntheses of Azetidines and Azetidinones. *Chem. Rev*. **2008**, *108*, 3988–4035. d) Couty, F.; Evano, G. Azetidines: New Tools for the Synthesis of Nitrogen Heterocycles. *Synlett* **2009**, *19*, 3053–3064. e) Mehra, V.; Lumb, I.; Anand, A.; Kumar, V. Recent Advances in Synthetic Facets of Immensely Reactive Azetidines. *RSC Adv*. **2017**, *7*, 45763–45783. f) Andresini, M.; Degennaro, L.; Luisi, R. The Renaissance of Strained 1-Azabicyclo[1.1.0]Butanes as Useful Reagents for the Synthesis of Functionalized Azetidines. *Org. Biomol. Chem*. **2020**, *18*, 5798–5810.

[10] Gabriel, S.; Weiner, J. Ueber einige Abkömmlinge des Propylamins. *Ber. Dtsch. Chem. Ges*. **1888**, *21*, 2669–2679.

[11] The use of 1- azabicyclo[1.1.0]butane to access azetidines represent a hot-topic in organic synthesis, see: a) Gianatassio, R.; Lopchuk, J. M.; Wang, J.; Pan, C.-M.; Malins, L. R.; Prieto, L.; Brandt, T. A.; Collins, M. R.; Gallego, G. M.; Sach, N. W.; Spangler, J. E.; Zhu, H.; Zhu, J.; Baran, P. S. Strain-Release Amination. *Science* **2016**, *351*, 241–246. b) Lopchuk, J. M.; Fjelbye, K.; Kawamata, Y.; Malins, L. R.; Pan, C.-M.; Gianatassio, R.; Wang, J.; Prieto, L.; Bradow, J.; Brandt, T. A.; Collins, M. R.; Elleraas, J.; Ewanicki, J.; Farrell, W.; Fadeyi, O. O.; Gallego, G. M.; Mousseau, J. J.; Oliver, R.; Sach, N. W.; Smith, J. K.; Spangler, J. E.; Zhu, H.; Zhu, J.; Baran, P. S. Strain-Release Heteroatom Functionalization: Development, Scope, and Stereospecificity. *J. Am. Chem. Soc*. **2017**, *139*, 3209–3226. c) Fawcett, A.; Murtaza, A.; Gregson, C. H. U.; Aggarwal, V. K. Strain-Release-Driven

Homologation of Boronic Esters: Application to the Modular Synthesis of Azetidines. *J. Am. Chem. Soc*. **2019**, *141*, 4573–4578. d) Gregson, C. H. U.; Noble, A.; Aggarwal, V. K. Divergent, Strain-Release Reactions of Azabicyclo[1.1.0]Butyl Carbinols: Semipinacol or Spiroepoxy Azetidine Formation. *Angew. Chem. Int. Ed.* **2021**, *60*, 7360–7365. e) Musci, P.; Keutz, T.; Belaj, F.; Degennaro, L.; Cantillo, D.; Kappe, C. O.; Luisi, R. Flow Technology for Telescoped Generation, Lithiation and Electrophilic (C3) Functionalization of Highly Strained 1-Azabicyclo[1.1.0]Butanes. *Angew. Chem. Int. Ed*. **2021**, *60*, 6395–6399.

[12] a) Degennaro, L.; Musio, B.; Luisi, R. in *Lithium Compounds in Organic Synthesis From Fundamentals to Applications*, Eds. Luisi, R.; Capriati, V. Wiley-VCH, Weinheim, **2014**, ch. 7, pp. 191- 223; b) Antermite, D.; Degennaro, L.; Luisi, R. Recent Advances in the Chemistry of Metallated Azetidines. *Org. Biomol. Chem*. **2017**, *15*, 34–50. c) Hodgson, D. M.; Kloesges, J. Lithiation-Electrophilic Substitution of N-Thiopivaloylazetidine. *Angew. Chem. Int. Ed.* **2010**, *49* (16), 2900–2903. d) Rayner, P. J.; Smith, J. C.; Denneval, C.; O'Brien, P.; Clarke, P. A.; Horan, R. A. J. Mechanistic Interrogation of the Asymmetric Lithiation-Trapping of N-Thiopivaloyl Azetidine and Pyrrolidine. *Chem. Commun*. **2016**, *52* (7), 1354–1357.

[13] a) Carroccia, L.; Degennaro, L.; Romanazzi, G.; Cuocci, C.; Pisano, L.; Luisi, R. Straightforward Access to 4-Membered Sulfurated Heterocycles: Introducing a Strategy for the Single and Double Functionalization of Thietane 1-Oxide. *Org. Biomol. Chem.* **2014**, *12*, 2180–2184. b) Degennaro, L.; Zenzola, M.; Trinchera, P.; Carroccia, L.; Giovine, A.; Romanazzi, G.; Falcicchio, A.; Luisi, R. Regioselective Functionalization of 2-Arylazetidines: Evaluating the Ortho-Directing Ability of the Azetidinyl Ring and the α-Directing Ability of the N-Substituent. *Chem. Commun*. **2014**, *50*, 1698-1700. c) Parisi, G.; Capitanelli, E.; Pierro, A.; Romanazzi, G.; Clarkson, G. J.; Degennaro, L.; Luisi, R. Easy Access to Constrained Peptidomimetics and 2,2-Disubstituted Azetidines by the Unexpected Reactivity Profile of α-Lithiated N-Boc-Azetidines. *Chem. Commun*. **2015**, *51*, 15588–15591. d) Zenzola, M.; Degennaro, L.; Trinchera, P.; Carroccia, L.; Giovine, A.; Romanazzi, G.; Mastrorilli, P.; Rizzi, R.; Pisano, L.; Luisi, R. Harnessing Theortho-Directing Ability of the Azetidine Ring for the Regioselective and Exhaustive Functionalization of Arenes. *Chem. Eur. J.* **2014**, *20*, 12190–12200. e) Parisi, G.; Zenzola, M.; Capitanelli, E.; Carlucci, C.; Romanazzi, G.; Pisano, L.; Degennaro, L.; Luisi, R. Exploiting Structural and Conformational Effects for a Site-Selective Lithiation of Azetidines. *Pure and Applied Chemistry* **2016**, *88*, 631–648. f) Andresini, M.; De Angelis, S.; Uricchio, A.; Visaggio, A.; Romanazzi, G.; Ciriaco, F.; Corriero, N.; Degennaro, L.; Luisi, R. Azetidine-Borane Complexes: Synthesis, Reactivity, and Stereoselective Functionalization. *J. Org. Chem*. **2018**, *83*, 10221– 10230. g) Musci, P.; Colella, M.; Fanelli, F.; Altomare, A.; Pisano, L.; Carlucci, C.; Luisi, R.; Degennaro, L. Stereo- and Enantioselective Addition of Organolithiums to 2-Oxazolinylazetidines as a Synthetic Route to 2-Acylazetidines. *Front. Chem*. **2019**, *7*, 614.

[14] a) Degennaro, L.; Fanelli, F.; Giovine, A.; Luisi, R. External Trapping of Halomethyllithium Enabled by Flow Microreactors. *Adv. Synth. Catal*. **2014**, *357*, 21–27. b) Degennaro, L.; Maggiulli, D.; Carlucci, C.; Fanelli, F.; Romanazzi, G.; Luisi, R. A Direct and Sustainable Synthesis of Tertiary Butyl Esters Enabled by Flow Microreactors. *Chem. Commun*. **2016**, *52*, 9554–9557. c) Musci, P.; Colella, M.; Sivo, A.; Romanazzi, G.; Luisi, R.; Degennaro, L. Flow Microreactor Technology for Taming Highly Reactive Chloroiodomethyllithium Carbenoid: Direct and Chemoselective Synthesis of α-Chloroaldehydes. *Org. Lett*. **2020**, *22*, 3623–3627. d) Colella, M.; Tota, A.; Takahashi, Y.; Higuma, R.; Ishikawa, S.; Degennaro, L.; Luisi, R.; Nagaki, A. Fluoro-Substituted Methyllithium Chemistry: External Quenching Method Using Flow Microreactors. *Angew. Chem. Int. Ed.* **2020**, *59*, 10924–10928.

[15] a) J.-i. Yoshida, Flash Chemistry. Fast Organic Synthesis in Microsystems, Wiley-Blackwell, **2008**. b) Yoshida, J.; Nagaki, A.; Yamada, T. Flash Chemistry: Fast Chemical Synthesis by Using Microreactors. *Chem. Eur. J.* **2008**, *14*), 7450–7459. c) Yoshida, J.-I. Flash Chemistry: Flow Microreactor Synthesis Based on High-Resolution Reaction Time Control. *Chem. Rec.* **2010**, *10*, 332–341. d) Yoshida, J.; Takahashi, Y.; Nagaki, A. Flash

Chemistry: Flow Chemistry That Cannot Be Done in Batch. *Chem. Commun*. **2013**, *49*, 9896–9904. e) Nagaki, A.; Yoshida, J.-i. Preparation and Use of Organolithium and Organomagnesium Species in Flow. In: Noël, T. (Ed.) Organometallic Flow Chemistry. Topics in Organometallic Chemistry, **2015**, vol 57. Springer, Cham. f) Nagaki, A. Recent Topics of Functionalized Organolithiums Using Flow Microreactor Chemistry. *Tetrahedron Letters* **2019**, *60*, 150923. g) Colella, M.; Nagaki, A.; Luisi, R. Flow Technology for the Genesis and Use of (Highly) Reactive Organometallic Reagents. *Chem. Eur*. J. **2019**, *26*, 19–32. g) Degennaro, L.; Carlucci, C.; De Angelis, S.; Luisi, R. Flow Technology for Organometallic-Mediated Synthesis. *J. Flow Chem*. **2016**, *6*, 136–166. h) Power, M.; Alcock, E.; McGlacken, G. P. Organolithium Bases in Flow Chemistry: A Review. *Org. Process Res. Dev*. **2020**, *24* (10), 1814–1838.

[16] Sivo, A.; Galaverna, R. de S.; Gomes, G. R.; Pastre, J. C.; Vilé, G. *From Circular Synthesis to Material Manufacturing: Advances, Challenges, and Future Steps for Using Flow Chemistry in Novel Application Area*. *React. Chem. Eng*. **2021**, 6, 756–786.

[17] a) Williams, J. D.; Kappe, C. O. *Recent Advances toward Sustainable Flow Photochemistry*. *Curr. Op. Green Sus. Chem.* **2020**, 25, 100351. b) Gutmann, B.; Cantillo, D.; Kappe, C. O. *Continuous-Flow Technology-A Tool for the Safe Manufacturing of Active Pharmaceutical Ingredients*. *Angew. Chem. Int. Ed*. **2015**, *54*, 6688–6728. c) Fanelli, F.; Parisi, G.; Degennaro, L.; Luisi, R. *Contribution of Microreactor Technology and Flow Chemistry to the Development of Green and Sustainable Synthesis*. *Beilstein J. Org. Chem*. **2017**, *13*, 520–542.

[18] For recent examples of lithiated heterocycles in flow, see: a) Wong, J. Y. F.; Tobin, J. M.; Vilela, F.; Barker, G. Batch Versus Flow Lithiation–Substitution of 1,3,4-Oxadiazoles: Exploitation of Unstable Intermediates Using Flow Chemistry. *Chem. Eur. J*. **2019**, *25*, 12439–12445. b) Kwong, A.; Firth, J. D.; Farmer, T. J.; O'Brien, P. Rapid "High" Temperature Batch and Flow Lithiation-Trapping of N-Boc Pyrrolidine. *Tetrahedron* **2021**, *81*, 131899. c) Colella, M.; Degennaro, L.; Luisi, R. Continuous Flow Synthesis of Heterocycles: A Recent Update on the Flow Synthesis of Indoles. *Molecules* **2020**, *25*, 3242.

[19] Billotte, S. Synthesis of C-Substituted Cyclic Amines Using Azacycloalkyl Organozinc Reagents. *Synlett* **1998**, *4*, 379–380.

[20] a) Duncton, M. A. J.; Estiarte, M. A.; Tan, D.; Kaub, C.; O'Mahony, D. J. R.; Johnson, R. J.; Cox, M.; Edwards, W. T.; Wan, M.; Kincaid, J.; Kelly, M. G. Preparation of Aryloxetanes and Arylazetidines by Use of an Alkyl−Aryl Suzuki Coupling. *Org. Lett*. **2008**, *10*, 3259–3262. b) Molander, G. A.; Traister, K. M.; O'Neill, B. T. Reductive Cross-Coupling of Nonaromatic, Heterocyclic Bromides with Aryl and Heteroaryl Bromides. *J. Org. Chem*. **2014**, *79*, 5771–5780.

[21] Barré, B.; Gonnard, L.; Campagne, R.; Reymond, S.; Marin, J.; Ciapetti, P.; Brellier, M.; Guérinot, A.; Cossy, J. Iron- and Cobalt-Catalyzed Arylation of Azetidines, Pyrrolidines, and Piperidines with Grignard Reagents. *Org. Lett*. **2014**, *16*, 6160–6163.

[22] Parmar, D.; Henkel, L.; Dib, J.; Rueping, M. Iron Catalysed Cross-Couplings of Azetidines – Application to the Formal Synthesis of a Pharmacologically Active Molecule. *Chem. Commun*. **2015**, *51*, 2111–2113.

[23] Connolly, P. J.; Bian, H.; Li, X.; Liu, L.; Macielag, M. J.; McDonnell, M. E. Piperidin-4-il-Azetidinone Diamides As Monoacylglycerol Lipase Inhibitors. US 2013/0102584A1, 2013.

[24] Hodgson, D. M.; Pearson, C. I.; Kazmi, M. Generation and Electrophile Trapping of N-Boc-2-Lithio-2-Azetine: Synthesis of 2-Substituted 2-Azetines. *Org. Lett.* **2014**, *16*, 856–859.

[25] a) Baumann, A. N.; Eisold, M.; Music, A.; Haas, G.; Kiw, Y. M.; Didier, D. Methods for the Synthesis of Substituted Azetines. *Org. Lett*. **2017**, *19*, 5681–5684. b) Music, A.; Baumann, A. N.; Eisold, M.; Didier, D. Regiodivergent Stereoselective Access to Fused Alkylideneazetidines. *J. Org. Chem*. **2018**, *83*, 783–792.

[26] Azzena, U.; Carraro, M.; Pisano, L.; Monticelli, S.; Bartolotta, R.; Pace, V. Cyclopentyl Methyl Ether: An Elective Ecofriendly Ethereal Solvent in Classical and Modern Organic Chemistry. *ChemSusChem* **2018**, *12*, 40–70.

[27] 1-Boc-3-iodoazetidine 1 was purchased from Fluorochem Ltd.

[28] a) Seel, S.; Dagousset, G.; Thaler, T.; Frischmuth, A.; Karaghiosoff, K.; Zipse, H.; Knochel, P. Preparation of Stereodefined Secondary Alkyllithium Compounds. *Chem. Eur. J.* **2013**, *19*, 4614–4622. b) Skotnitzki, J.; Kremsmair, A.; Keefer, D.; Gong, Y.; Vivie-Riedle, R.; Knochel, P. Stereoselective Csp 3 −Csp 2 Cross-Couplings of Chiral Secondary Alkylzinc Reagents with Alkenyl and Aryl Halides. *Angew. Chem. Int. Ed*. **2019**, *59*, 320–324. c) Morozova, V.; Skotnitzki, J.; Moriya, K.; Karaghiosoff, K.; Knochel, P. Preparation of Optically Enriched Secondary Alkyllithium and Alkylcopper Reagents-Synthesis of (−)-Lardolure and Siphonarienal. *Angew. Chem. Int. Ed*. **2018**, *57*, 5516–5519.

[29] Hexyllithium has proved a useful base for lithium/iodine exchange, and potentially a more sustainable and safer alternative to other organolithiums because of the side products (hexane/iodohexane) are less volatile than their butyl counterparts, making them easier to control in flow conditions.

[30] Pace, V.; Hoyos, P.; Castoldi, L.; Domínguez de María, P.; Alcántara, A. R. 2-Methyltetrahydrofuran (2-MeTHF): A Biomass-Derived Solvent with Broad Application in Organic Chemistry. *ChemSusChem* **2012**, *5*, 1369–1379.

[31] Watanabe, K.; Yamagiwa, N.; Torisawa, Y. Cyclopentyl Methyl Ether as a New and Alternative Process Solvent. *Org. Process Res. Dev.* **2007**, 11, 251–258.

[32] Alonso, M.; Garcia, M. C.; McKay, C.; Thorp, L. R.; Webb, M.; Edwards, L. J. Use of Lithium Diisopropylamide in Flow: Operability and Safety Challenges Encountered on a Multigram Scale. *Org. Process Res. Dev*. **2021**, *25* (4), 988–1000.

[33] The one-pot sequence can be effectively executed (93% yield of **5a**) under batch conditions at -50 °C by adopting THF as the solvent and internal quenching methods (See Supporting Information).