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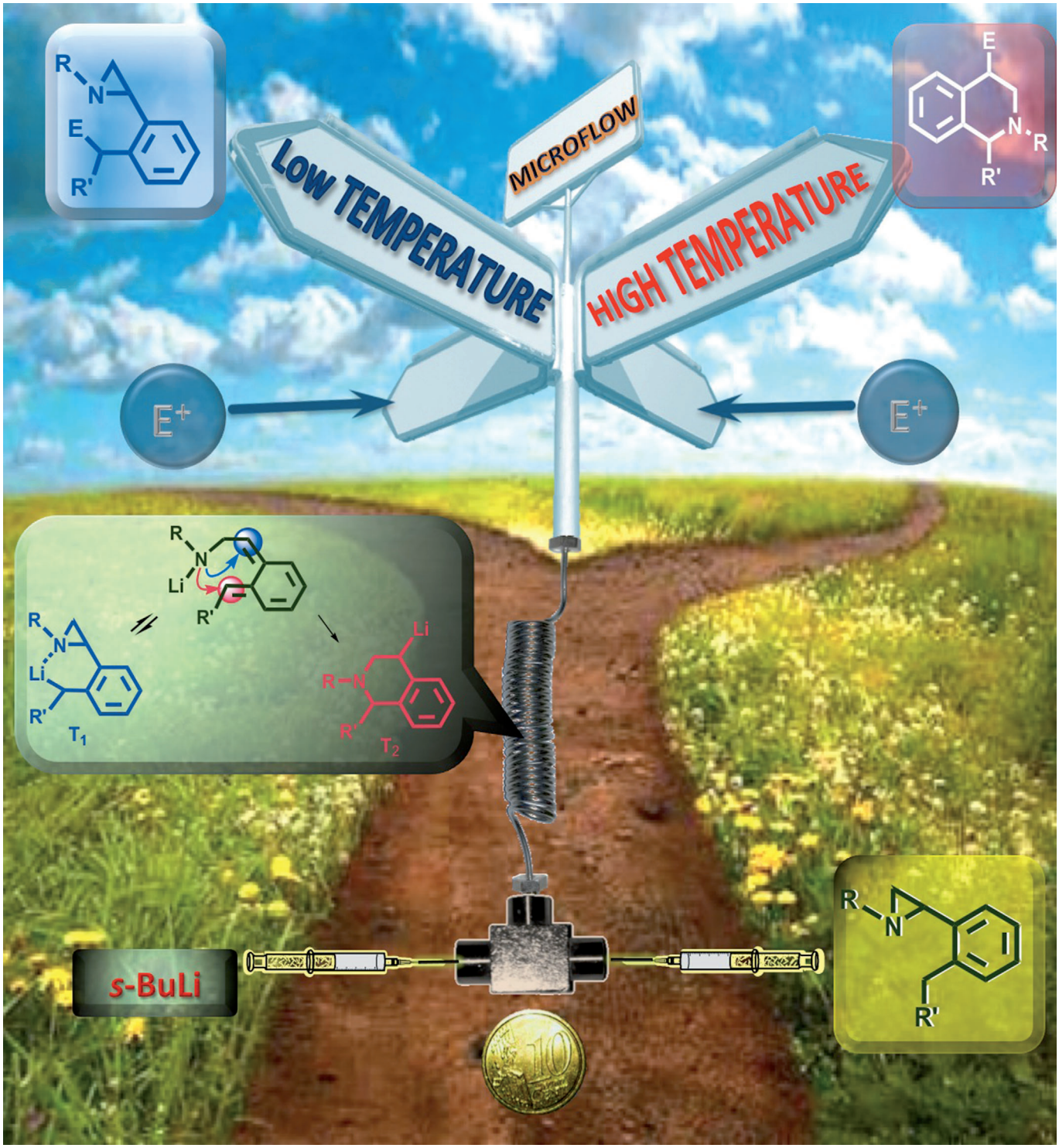
Synthesis of 1,2,3,4-Tetrahydroisoquinolines by Microreactor-Mediated Thermal Isomerization of Laterally Lithiated Arylaziridines

Arianna Giovine,[a] Biagia Musio,[a] Leonardo Degennaro,[a] Aurelia Falcicchio,[b] Aiichiro Nagaki,[c] Jun-ichi Yoshida,*[c] and Renzo Luisi*[a]

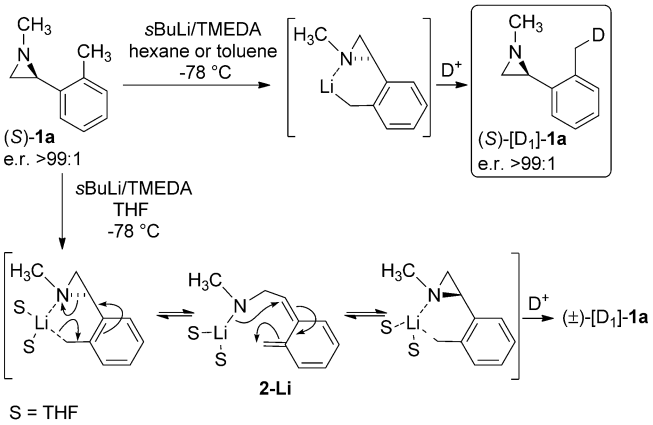


Nitrogen-containing heterocycles are ubiquitous in natural products, as well as in drugs and drug candidates.[1,2] Among nitrogenous heterocycles, the tetrahydroisoquinoline (THIQ) core represents a relevant structural motif frequently found in natural products and biologically active compounds.[3] Of the various synthetic approaches to nitrogenous heterocycles, the use of organometallic compounds has recently emerged as a particularly robust methodology.[4] Our recent studies on the chemistry of lithiated three-membered nitrogenous heterocycles[5] demonstrated the importance of this methodology to the preparation of other nitrogen-containing heterocycles, such as piperazines,[6] phthalanes,[7] and isochromanes.[8]

Herein, we report a new synthetic strategy for the preparation of C4-functionalized 1,2,3,4-tetrahydroisoquinolines, which exploits the chemistry of lithiated aziridines and the advantages of flow-microreactor technology.[9] It is worth mentioning that, because of their biological relevance, new synthetic routes to substituted THIQs are desired.[10]

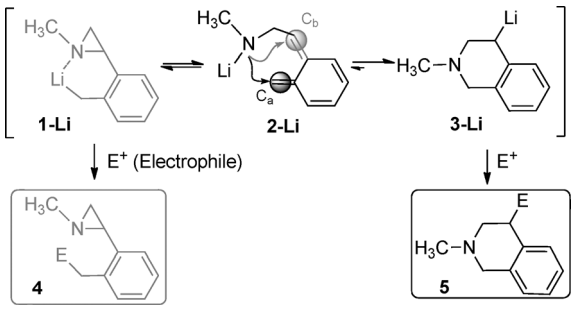
During previous work evaluating the reactivity of laterally lithiated 1-methyl-2-(*ortho*-tolyl)aziridine, we reported the solvent-dependent stereochemical outcome of the lithiation reaction. In fact, when enantioenriched (e.r. > 99:1) aziridine (*S*)-**1a** was subjected to a lithiation–electrophilic-trapping protocol in THF at −78 °C, racemic (±)-[D_1]-**1a** was obtained upon quenching with a deuterium source. In striking contrast, in a less polar solvent, such as hexane or toluene, highly enantioenriched (*S*)-[D_1]-**1a** was recovered (Scheme 1). This result could be ascribed to the effect of the solvent on the nature and aggregation state of the lithiated intermediate.[11]

It has been proposed that a more polar solvent, such as THF, could promote an aziridine ring opening with the formation of the *ortho*-quinodimethane intermediate, **2-Li**. This intermediate promptly undergoes a reclosing reaction on either enantiotopic face of the double bond, leading to the observed epimerization (Scheme 1).[12] With the aim of demonstrating the intermediacy of the *ortho*-quinodimethane, **2-Li**, strong dienophiles, such as maleic anhydride and tetracyanoethylene, were added to the reaction mixture as trapping agents, but without any satisfactory outcome. The inability of a strong dienophile to trap **2-Li** is likely to be



Scheme 1. Solvent dependent lithiation–deuteration of 1-methyl-2-(*ortho*-tolyl)aziridine.

caused by the instability of **2-Li** with respect to **1-Li**. Nevertheless, assuming the presence of the equilibrium depicted in Scheme 2, we reasoned that the nucleophilic nitrogen



Scheme 2. Reaction pathways for laterally lithiated aziridine **1-Li**.

(N–Li) could attack either C_b, leading to **1-Li**, or C_a, giving access to **3-Li**, a tetrahydroisoquinoline scaffold lithiated at C4 (Scheme 2).[13] This strategy would allow, starting from the same parent aziridine, the preparation of either functionalized aziridines **4** or THIQs **5** upon electrophilic trapping.

After a thorough screening of the reaction parameters, we were happy to find evidence of the presence of **3-Li** by warming a sample of **1-Li**, generated in toluene at −78 °C, to a temperature in the range −30 to −40 °C. With $ClSiMe_3$ as the electrophile, the trapping product **5a** was obtained in modest yield.[14] However, this optimization study furnished evidence of the intermediacy of **2-Li**, as well as demonstrating the crucial role of the temperature for reproducibility of the reaction outcome.

The critical importance of reaction temperature to the outcome of the reaction prompted us to investigate this process by using the microreactor technology. The main advantages of flow microreactor procedures are exquisite thermal control and efficient heat transfer derived from the increased surface-to-volume ratio possible on the microscale.

[a] Dr. A. Giovine, Dr. B. Musio, Dr. L. Degennaro, Prof. R. Luisi
Department of Pharmacy, University of Bari "Aldo Moro"
Via E. Orabona 4, 70125 Bari (Italy)
Fax: (+39) 080-5442539
E-mail: renzo.luisi@uniba.it

[b] Dr. A. Falcicchio
Istituto di Cristallografia (IC-CNR)
Via Amendola 122/o, 70125 Bari (Italy)

[c] Dr. A. Nagaki, Prof. J.-i. Yoshida
Department of Synthetic Chemistry and Biological Chemistry
Graduate School of Engineering, University of Kyoto
Nishikyo-ku, Kyoto, 615-8510 (Japan)
E-mail: yoshida@sbchem.kyoto-u.ac.jp

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It is also noteworthy that residence time in the reactor can be precisely adapted to achieve maximum yield and selectivity.[15] These features have made flow-microreactor systems excellent alternatives to traditional batch chemistry, even in the case of moisture sensitive, unstable, and highly reactive organometallic intermediates such as oxiranyllithiums and aziridinyllithiums.[16] The reaction of an intermediate can also be switched by precise control of residence time and temperature in the flow-microreactor system.[17] The lateral-lithiation–isomerization reaction of **1a** was optimized in a flow-microreactor system consisting of two T-shaped micromixers (M1 and M2), two tube reactors (R1 and R2) and three precooling units (P1, P2 and P3) with $ClSiMe_3$ as the electrophile.[18] As shown in Figure 1, at $T<-48\,°C$ the main

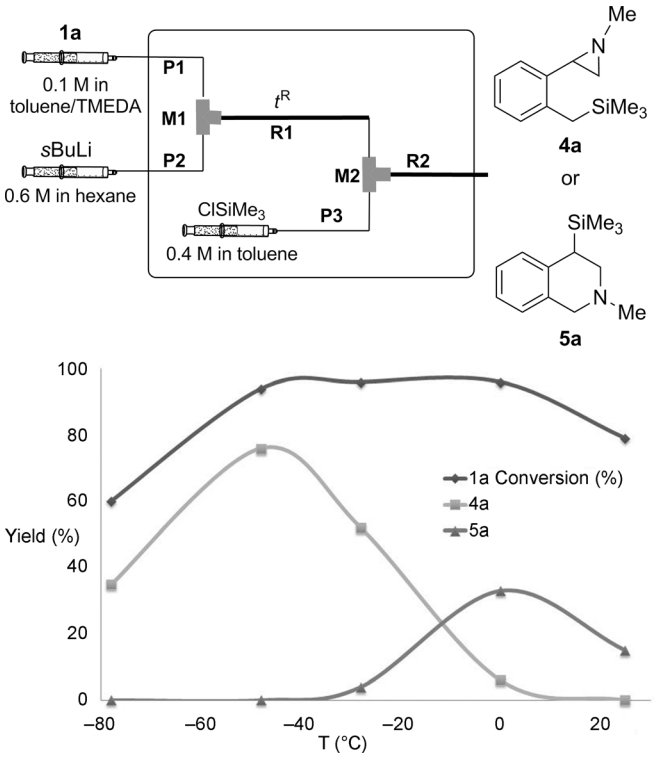
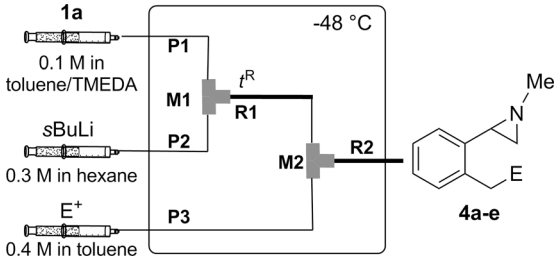


Figure 1. Flow microreactor for optimization of lateral lithiation and isomerization of **1a**. Reaction conditions: $t^R=23.56$ s; flow rates: aziridine **1a** 3, *s*BuLi 1, electrophile 2 mL min^{-1}.[18]

product was the laterally substituted aziridine **4a**, whereas the silylated tetrahydroisoquinoline **5a**, likely derived from the isomerization of **1-Li**, was obtained as the main product when the reaction was run at 0 °C. Reduced yields were observed at higher temperatures. Starting from the reaction conditions described in Figure 1, aziridine **1a** was lithiated at −48 °C in M1 (250 μm) and, after a residence time of 20.9 seconds in R1, **1-Li** was successfully trapped with several electrophiles in M2 (500 μm) to furnish aziridines **4a–e** (Table 1).

Regardless of the diastereomeric ratio of the products observed from the reactions with prochiral carbonyl compounds, the lithiation–trapping sequence worked quite well, giving yields comparable to or even better than those obtained from batch procedures.[8] In addition, the reactions occurred faster and at higher temperature (−48 °C vs. −78 °C).

Table 1. Flow-microreactor system for the lateral-lithiation–electrophilic-trapping sequence of **1a**.



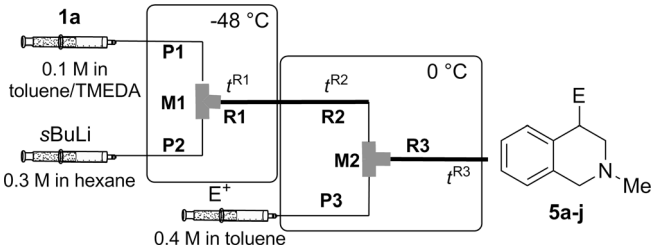
Product **4**[a]	Electrophile	Yield [%][b]	d.r.[c]
4a	$SiMe_3Cl$	90	–
4b	cyclohexanone	48	–
4c	propiophenone	77[c]	82:18
4d	*t*BuCHO	70	70:30
4e	2,6-$(CH_3)_2$-C_6H_3NCO	58	–

[a] See the Supporting Information for full technical details. Reaction conditions: $t^R=20.9$ s; flow rates: aziridine **1a** 3, *s*BuLi 1.5, electrophile 1.5 mL min^{-1}. [b] Yields of the isolated product. [c] Diastereoisomeric ratio calculated on the basis of ^{1}H NMR spectra of the crude reaction mixtures. [d] Only the major diastereoisomer was isolated.

The one-pot lateral-lithiation–isomerization process was then investigated by using a flow-microreactor system consisting of a T-shaped micromixer M1 and a tube reactor R1 ($t^{R1}=20.9$ s) cooled to −48 °C, and a second tube reactor R2 ($t^{R2}=41.9$ s), an additional micromixer M2 and a tube reactor R3 ($t^{R3}=15.7$ s) operating at 0 °C (Table 2). The tube reactor R1 allowed for the generation of **1-Li**, whereas in R2 the isomerization process took place leading to **3-Li**. The results for this microreactor-mediated lithiation–isomerization–electrophile-trapping sequence, leading to THIQs **5a–j** functionalized at C4, are summarized in Table 2. It is worth noting that the generation of THIQs lithiated at C4 is not a simple task and, to the best of our knowledge, only two examples of direct lithiation of THIQs, although with modest yields and at lower temperature (−78 °C), are reported in the literature.[19]

To further demonstrate the strength of this microreactor-mediated methodology for the synthesis of THIQs, the reactivity of the most challenging aziridine **1b**, bearing an *ortho*-allyl substituent, was investigated (Scheme 3).[20] The *ortho*-allyl substituted aziridine **1b** was first lithiated in a macrobatch reactor at −78 °C with *s*BuLi in 5 min, and the corresponding lithiated intermediate **1b-Li** was trapped with a deuterium source to furnish a mixture of two regioisomers, **6** and **7**, in a 4:1 ratio, respectively. The thermally induced isomerization was more difficult for this system and only upon warming of **1b-Li** to 0 °C for 2.5 h was a 30 % yield of THIQ **8** obtained, along with derivatives **6** and **7** and several byproducts. Longer reaction times or higher temperatures

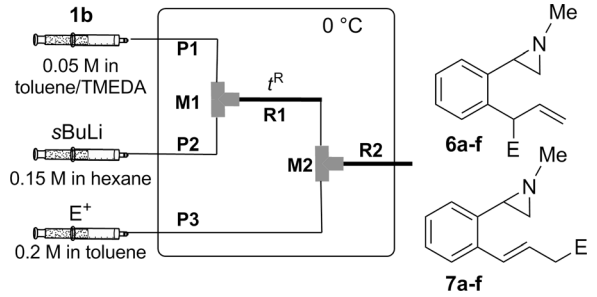
Table 2. Flow-microreactor system for the one-pot lateral-lithiation–thermal isomerization reaction of aziridine **1a**.



Product **5**[a]	Electrophile	Yield [%][b]	d.r.[c]
5a	$SiMe_3Cl$	60	–
5b	cyclohexanone	58	–
5c	*p*-CF_3-C_6H_4CHO	54	45:55[d]
5d	PhCHO	95	45:55
5e	acetophenone	75	52:48
5f	2,4,6-$(CH_3)_3C_6H_2CHO$	63	70:30
5g	*t*BuCHO	90	82:18
5h	Ph_2CO	60	–
5i	$C_6H_{11}NCS$	73	–
5j	2,6-$(CH_3)_2C_6H_3NCO$	95	–

[a] See the Supporting Information for full technical details. Reaction conditions: $t^{R1}=20.9$ s; $t^{R2}=41.9$ s; flow rates: aziridine **1a** 3, *s*BuLi 1.5, electrophile 1.5 mL min^{-1}. [b] Overall yields of the isolated products. [c] Diastereoisomeric ratio calculated on the basis of ^{1}H NMR spectra of the crude reaction mixtures. [d] Structure and stereochemistry confirmed by X-ray analysis (see the Supporting Information).

Table 3. Flow-microreactor system for the lateral-lithiation–electrophilic-trapping sequence of **1b**.



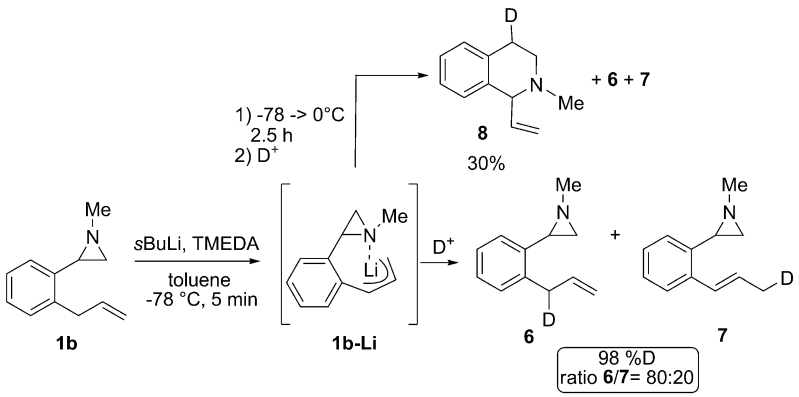
Products **6**,**7**[a]	Electrophile	Yield [%][b]	**6**/**7** ratio
6a, **7a**	CD_3OD	98	80:20
6b, **7b**	EtI	90[c]	62:38
6c, **7c**	acetone	86	65:35
6d, **7d**	*i*PrI	53[c]	93:7
6e, **7e**	Ph_2CO	74	10:90
6f, **7f**	$SiMe_3Cl$	68	5:95

[a] See the Supporting Information for full technical details. Reaction conditions: $t^R=5.24$ s; flow rates: aziridine **1a** 3, *s*BuLi 1.5, electrophile 1.5 mL min^{-1}. [b] Overall yields of the isolated product. [c] Inseparable mixture of regioisomers.

resulted in complex reaction mixtures and only traces of the desired THIQ.

Notwithstanding the above mentioned difficulties, this process was transferred to a microreactor system with the aim of improving the regioselectivity of the lateral-lithiation–electrophilic-trapping sequence, and inducing the isomerization to THIQ. By using a flow-microreactor system consisting of two T-shaped micromixers (M1, M2) of 500 μm inner diameter and two microtube reactors (R1, R2) of 50 and 100 cm length, respectively, the lateral-lithiation–electrophilic-trapping sequence of **1b** was optimized. As reported in Table 3, the trapping occurred in good yields, but with the regioselectivity depending on the electrophile. Subsequently, the isomerization reaction was also optimized by using a flow-microreactor system. We were happy to find that the isomerization occurred in a microtube reactor R2 of 100 cm working at 60 °C with good yields of the THIQs **8a–f** after electrophilic quenching (Table 4). It is also worth noting that all attempts to reproduce this transformation in a macrobatch reactor gave unsatisfactory results.

In summary, a new synthesis of THIQs has been developed starting from laterally lithiated aziridines by a thermally induced isomerization reaction. The use of flow-microreactor technology allowed for precise temperature control, which seems to be crucial for this transformation. Interestingly, a lithiated isoquinoline could be efficiently generated and trapped even at 60 °C. Such conditions were prohibitive in macrobatch reactions. Further work is underway to expand the synthetic applications and control the stereochemistry of this process.



Scheme 3. Lateral lithiation–isomerization of **1b**.

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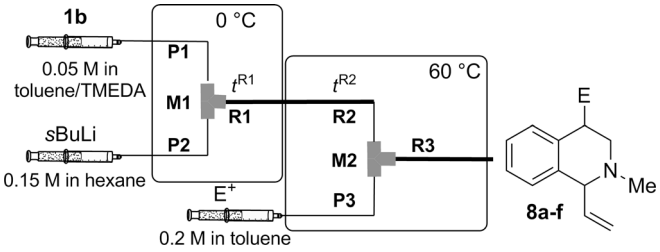
Table 4. Flow-microreactor system for the one-pot lateral-lithiation–thermal isomerization reaction of aziridine **1b**.



Product **8**[a]	Electrophile	Yield [%][b,c]	d.r.[d]
8a	$SiMe_3Cl$	78	50:50
8b	MeI	57[e]	56:44
8c	cyclohexanone	50	60:40[f]
8d	acetone	60	50:50
8e	$C_6H_5CON(CH_3)(OCH_3)$	53[e]	55:45
8f	2,6-$(CH_3)_2$-C_6H_3NCO	51	50:50

[a] See the Supporting Information for full technical details. Reaction conditions: $t^{R1}=5.24$ s; $t^{R2}=10.5$ s; flow rates: aziridine **1a** 3, *s*BuLi 1.5, electrophile 1.5 mL min^{-1}. [b] Overall yields of the isolated products. [c] Relative stereochemistry not assigned. [d] Diastereoisomeric ratio calculated from the ^{1}H NMR spectra of the crude reaction mixtures. [e] Inseparable mixture of stereoisomers. [f] Structure and stereochemistry confirmed by X-ray analysis (see the Supporting Information).

Keywords: aziridines · flow microreactor · heterocycles · lithiation · organolithium compounds · stereoselectivity · tetrahydroisoquinolines

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[13] The attack at C_a could be considered an irreversible process because the resulting six-membered heterocycle is not a spring-loaded system like the three-membered aziridine.

[14] A preliminary NMR investigation of the process depicted in Scheme 2 did not give evidence of the presence of **2-Li**, but gave clear signals for **1-Li** at low temperature and **3-Li** at higher temperature. This study is still underway.

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[18] All optimization conditions are reported in the Supporting Information. Selected data have been used for the plot in Figure 1.

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[20] The lithiated intermediate **1b-Li**, thanks to the additional effects of the allylic moiety, was expected to be very stable and hardly prone to thermal isomerization.

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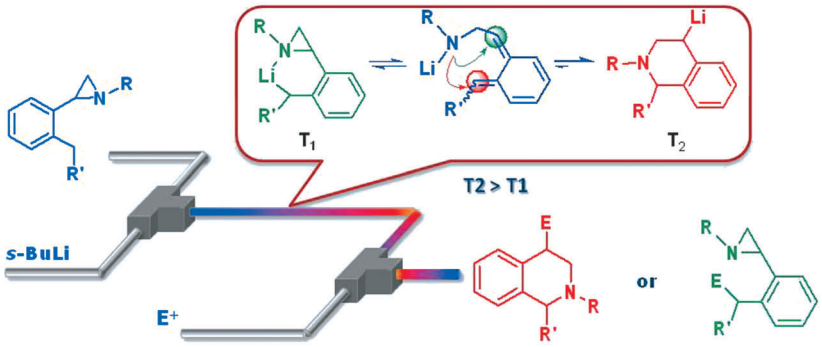
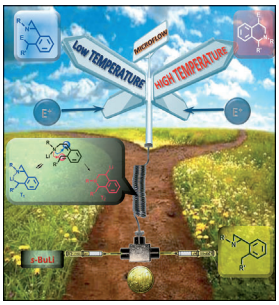
Microreactor Chemistry



Flow chemistry: A flow-microreactor-mediated synthesis of 1,2,3,4-tetrahydroisoquinolines (THIQs) is reported (see scheme). Starting from a laterally lithiated aziridine, a tetrahydroisoquinoline lithiated at C4 was generated by thermally induced isomerization. Because the reaction temperature is a crucial parameter, the exquisite thermal control possible in a flow-microreactor system allowed for fast, efficient, and highly reproducible synthesis of functionalized aziridines or THIQs.



Organolithium Compounds

A flow microreactor system consisting of micromixers and microtube reactors has been used as effective tool for the generation and reactions either of laterally lithiated aziridines or tetrahydroisoquinoline lithiated at C4, depending on the reaction temperature. A thermally induced isomerization process has been *tamed* by exquisite thermal control realized in the flow microreactor system. Trapping with electrophiles of such organolithium intermediates gave access to functionalized aziridines and tetrahydroisoquinolines. Details of these interesting processes are described in the Communication by J.-i. Yoshida, R. Luisi and co-workers on page ■■ff.