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FULL PAPER

Design of a mesoscale continuous flow route toward lithiated methoxyallene

Sofie Seghers, Thomas S. A. Heugebaert, Matthias Moens, Jolien Sonck, Joris W. Thybaut, and Christian V. Stevens*

Abstract: The unique nucleophilic properties of lithiated methoxyallene allow for C-C bond formation with a wide variety of electrophiles, thus introducing an allenic group for further functionalization. This approach has yielded a tremendously broad range of (hetero)cyclic scaffolds, including API precursors. To date, however, its valorization at scale is hampered by the batch synthesis protocol which suffers from serious safety issues. Hence, the attractive heat and mass transfer properties of flow technology were exploited to establish a mesoscale continuous flow route toward lithiated methoxyallene. An excellent conversion of 94% was obtained, corresponding to a methoxyallene throughput of 8.2 g/h. The process is characterized by short reaction times, mild reaction conditions and a stoichiometric use of reagents.

Introduction

Allenes, with their curious arrangement of cumulated double bonds, display unique reactivity. They have been exploited in many promising transformations, *e.g.* to build diverse (hetero)cyclic compounds.[1] The reactivity of an allene moiety can strongly be influenced by functional groups. In this respect, alkoxyallenes are claimed to display chameleon type reactivity. Whilst the double bond bearing this substituent preferentially reacts with electrophiles, reaction with nucleophiles at the two terminal carbons (C^1 and C^3 position) may also occur. Extremely useful, however, is the smooth metalation at the carbon bearing the alkoxygroup. Lithiation induces *umpolung* and generates a fairly strong nucleophile at the C^1-position. (Lithiated) methoxyallene, has been used extensively in all kinds of transformations, serving as a versatile C_3-building block.[2] Among others, the pioneering work of Arens *et al.*[3] and the efforts of the Reissig group are acknowledged for demonstrating its wide potential. A tremendously broad spectrum of (heterocyclic) scaffolds was accessed via lithiated methoxyallene,[2],[4] such as alkylated derivatives,[3b] α,β unsaturated α'-ketols,[3a] dihydropyranones and tetrahydropyran-4-ones,[5] 2,5-dihydrofuranes and the corresponding 3-oxotetrahydrofuranes,[3c],[6] 1,2-oxazines,[7] lactones,[8] pyrrolines, pyrroles and pyrrolidinones,[9] β-ketoenamides,[10],[11],[12] oxazoles,[10] imidazoles,[13] furanylideenamines,[14] 2,3-dihydropyridines and pyridines,[11],[15] pyrimidines,[12] thiophenes,[16] azepines[17] and diverse large mono- to even pentacyclic structures.[6d],[6f],[18]

Without exception, these abundant applications of lithiated methoxyallene **4** all rely on the originally reported batch synthesis protocol (Scheme 1). Methoxyallene **3** is generated from methyl propargyl ether **2**, obtained from propargylic alcohol **1**, in a high yielding base-catalyzed isomerization after which it is distilled. Lithiation affords a nucleophilic 1-position which then readily reacts with electrophiles, introducing an allenic group for further functionalization. Unfortunately, these academic efforts cannot be valorized, as the synthesis and distillation of methoxyallene suffers from serious safety issues. Even when its use provided the most efficient API (Active Pharmaceutical Ingredient) synthesis route, it was abandoned due to the lack of scalability.[5] Low molecular weight ethers and acetylenes (**2**) are known for their alarming thermal instability, resulting in a highly energetic and potentially explosive decomposition. While the small scale performance – certainly up to 10 g – can be safely operated, the exothermicity of the isomerization limits the implementation scale to 200 g. An extremely violent reaction resulting in complete destruction of the internals of a calorimeter was reported by Anderson *et al.* Dilution in THF as a heat sink was imperative and further risk reduction was pursued by an addition-rate controlled reaction. The authors state to operate this procedure up to 2 L scale (330 g).[5] The further lithiation steps face similar challenges and are essentially performed under cryogenic conditions in view of the reactive nature of alkyl lithium reagents and the instability of lithiated methoxyallene.

In essence, all associated safety hazards involve a lack of control over the reaction environment. Therefore, the translation of this synthesis route into continuous flow production was envisioned, including the synthesis of methyl propargyl ether **2**. Owing to the large surface-to-volume ratio, an efficient heat transfer is observed in micro- and even mesoreactors. The outstanding control of stoichiometry and reaction parameters and the small hold-up of the critical intermediates improve process safety. Straightforward scalability opportunities offer a safe and less time- and money consuming route toward industrial production.

Results and Discussion

Preparation of methyl propargyl ether

The methylation of propargylic alcohol **1** was initiated in batch, varying the methylation reagent and base (Tables 1 and S1). The Williamson ether synthesis using methyl iodide, catalyzed by potassium *tert*-butoxide, showed promise. A commercially

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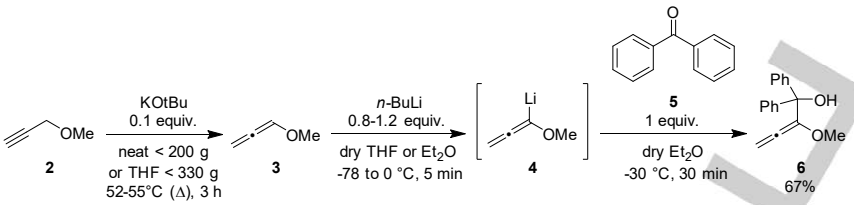
Supporting information for this article is given via a link at the end of the document.



Scheme 1. Batch synthesis pathway toward lithiated methoxyallene **4** and nucleophilic addition to benzophenone **5**

available dry solution of KOtBu in THF yielded methoxyallene **3** efficiently in a single reaction step (Table 1, entry 2). Turbid reaction mixtures, however, were obtained due to the formation of KI salt crystals which would cause clogging of the flow reactor. Attempts were made to prevent precipitation of the salt using additives such as 18-crown-6 ether, HMPT (tris(dimethylamino)phosphine), HMPA (hexamethylphosphoramide) and DMF. Aside from persistent turbidity, methylation was hampered and the allene formation was no longer observed in the presence of these additives.

The evaluation of a variety of common bases failed to offer an efficient methylation step free of precipitate. Both LiOtBu and NaOtBu delivered methyl propargyl ether **2**, but inhibited further reaction (Table 1, entries 3 and 4). Even after additional dosage of KOtBu, the isomerization to **3** did not occur. Again, the methylation was partially suppressed by the addition of 18-crown-6, 12-crown-4, EDTA (ethylenediaminetetraacetic acid), TMEDA (tetramethylethylenediamine), HMPT or HMPA and allene **3** was still not observed. In a reaction with Et_3N, the nucleophilic behaviour of the base lead to the formation of the quaternary ammonium salts. Reaction with *n*-BuLi lead to an unidentified complex reaction mixture and, although the use of LiH or LiHMDS lead to good conversion to the ether **2** (Table 1, entries 5 and 6), turbid reaction mixtures were again observed. The alternative methylation reagents dimethylcarbonate and methyl triflate were rejected respectively because of reactivity and turbidity issues (Table S1).

None of the water-free methylation routes could provide a good way to telescope the methylation of the alcohol with the synthesis of lithiated methoxyallene due to turbidity and/or reactivity limitations. In batch, methyl propargyl ether **2** is efficiently synthesized using dimethyl sulfate and sodium hydroxide in water (Table 1, entry 1).[19] In our hands, performing this aqueous batch procedure at a 1 L scale showed highly exothermic behaviour. As such, the incontrollable heat of reaction and the toxicity of the methylating agent were an additional driving force to transfer the aqueous procedure into continuous flow (Scheme 2). Using a residence time of 30 min, 96% conversion was obtained, which corresponds to a throughput of 12.8 g/h. A liquid liquid separator was used to isolate the ether phase in continuous mode. Fouling of the membrane was avoided by feeding water downstream of the reactor. The end product **2** was obtained in 77% isolated yield via distillation.

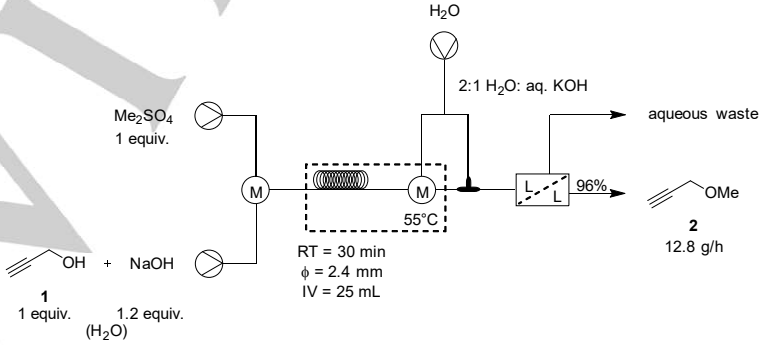
Table 1. Selected experiments of the batch optimization of the methylation of propargylic alcohol **1**[a]

	Methylation reagent[b]	Base[c]	Solvent	t (h)	^{1}H-NMR (%)		
					1	2	3
1	Me_2SO_4	NaOH	H_2O	2	5	95	0
2	MeI	KOtBu	THF	2	2	2	96
3	MeI	LiOtBu	THF	1	5	95	0
4	MeI	NaOtBu	THF	1	1	99	0
5	MeI	LiH	THF	3	5	95	0
6	MeI	LiHMDS	THF	1	18	82	0

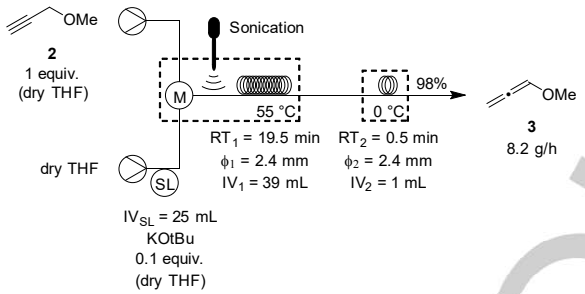
[a] Full data of all optimization experiments can be found in the Supporting Information [b] 1 equiv. [c] 1.2 equiv.

Isomerization to methoxyallene

The continuous flow isomerization was next addressed, using a catalytic amount of potassium *tert*-butoxide (Scheme 3). In batch, 98% conversion of **2** toward methoxyallene **3** was observed after 45 min at reflux temperature in dry THF, using 0.1 equiv. KOtBu. Preliminary optimization experiments were performed in a tubular reactor using syringe pumps and a standard T-connector (Table S2). A strictly dry environment was found to be crucial, as in the presence of moisture KOH debris caused clogging of the reactor. As such, the KOtBu solution was provided through a sample loop (SL). Several precautions were taken to overcome clogging. In



Scheme 2. Continuous flow synthesis of methyl propargyl ether **2** from propargyl alcohol **1** using a 5 port mixer and a tubular reactor



Scheme 3. Overview of the optimized continuous flow isomerization of **2** to methoxyallene **3**, using a 5 port mixer and a tubular reactor

Table 2. Key experiments in the optimization of the continuous flow isomerization of methyl propargyl ether **2** to methoxyallene **3**[a]

Entry[b]	Pump type	IV (mL)	Φ (mm)	RT (min)	T (°C)	RT_{cool} (min)	Conv.[c] (%)
1[d]	peristaltic	10	2	15	50	0	61-98
2[d]	peristaltic	40	2.4	20	45	0	44-98
3	HPRP	40	2.4	20	45	0	77-97
4	HPRP	40	2.4	20	45	2.5	92-96
5	HPRP	40	2.4	20	55	2.5	96-98

[a] Full data of all optimization experiments can be found in the Supporting Information [b] [**2**] = 1.25 M, [KOtBu] = 0.50 M [c] Conversion to **3** via integration on ^{1}H-NMR [d] Clogging

addition to further dilution and a temperature rise, a higher flow rate was applied to increase convective and abrasive forces and mitigate constriction. Sonication was introduced to prevent aggregation and bridging of the solids. Constrictions in the flow channel were avoided by the use of a 5 port mixer with a sufficient internal volume and an increased diameter of the tubular reactor.[20]

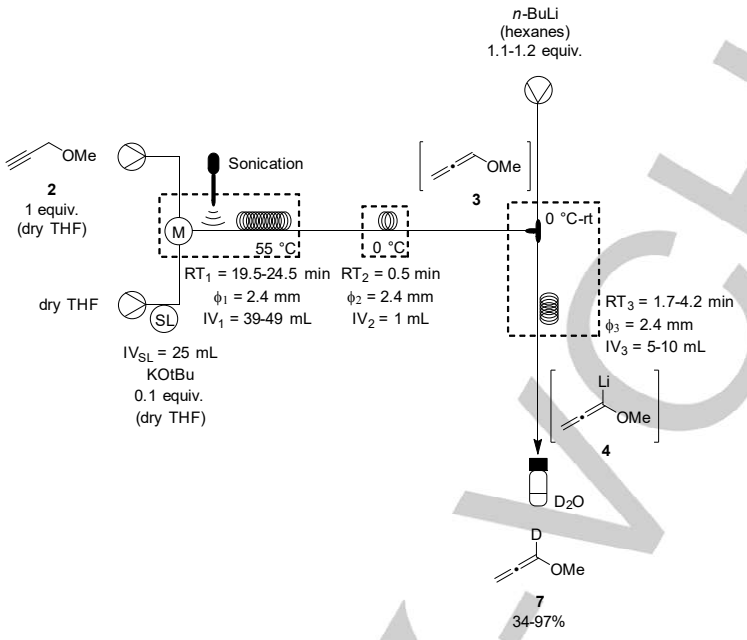
The syringe pumps were replaced by less back pressure sensitive dual piston syringe and peristaltic pumps (Table S3). These pumps are more compatible with suspensions and can be used in a fully continuous mode for injection of larger volumes. Clogging was delayed, but in spite of these efforts still persistent. Upon closer inspection, the non-crystalline but strongly viscous nature of the slurry in a clogged reactor coil suggested beneficial effects of higher pressure pumps. Finally, a switch to high-performance reciprocating pumps (HPRP) appeared crucial to handle the reaction mixture fully continuously.

In this set-up, a good conversion toward methoxyallene **3** was observed in a residence time of 15 min at 50 °C. However, the conversion fluctuated strongly (Table S3). Formation of a gaseous phase was prominent and with regard to the boiling point of methoxyallene **3** (51 °C), the temperature was lowered to 45 °C and the residence time was raised to 20 min (Table 2, entry 3). The gaseous phase and concomitant conversion fluctuations were still observed and a cooling coil was added at the end of the reactor set-up. Superior stability and reproducibility was readily obtained (Table 2 entries 4-5; Table S4).

The established isomerization process is displayed in Scheme 3. The use of a fresh KOtBu solution is essential to ensure absence of KOH in order to obtain high conversion and to avoid reactor clogging. An excellent and steady conversion of 98% toward methoxyallene **3** was observed on ^{1}H-NMR. This corresponds to a throughput of 8.2 g/h.

Lithiation of methoxyallene and trapping of an electrophile

Next, the lithiation of methoxyallene **3** was performed inline with the isomerization, thus avoiding hazardous distillation of the allene (Scheme 4). A 2.5 M *n*-butyllithium solution in hexanes was fed to the reactor using a parallel set-up of two Chemyx® syringe pumps. Many common pump types are incompatible with alkyl lithium solutions. In spite of the limited injection volume, in general syringe pumps or sample loops are preferred for safety and chemical resistance reasons.[21] At the outlet of the reactor, the mixture was quenched at room temperature using D_2O. The distribution of methyl propargyl ether **2**, methoxyallene **3** and deuterated methoxyallene **7** was determined via integration of the ^{1}H-NMR spectra (Table S5). In spite of some very promising results, an unsatisfactory instability of the conversion was observed. This could possibly be attributed to a high deuterium-proton exchange capacity of D_2O, hampering a reproducible quench of the reaction mixture under air. In some of the samples, a large residue of methyl propargyl ether **2** was observed as well, although the initial isomerization conversion of 98% was confirmed. In view of selected samples indicating 97% conversion toward deuterated methoxyallene **7**, it was assumed that the efficiency of the lithiation was not a limiting factor and required only a minimum amount of time. This is typically the case for lithiations and there was no indication that the coupled reaction steps could benefit from an increased residence time.[22] In an attempt to perform an inline quench, 1 equivalent D_2O was fed to the reactor at room temperature and a third tubular reactor was added to the set-up (Table 3). A violent reaction was observed, giving rise to the formation of gas plugs, pressure build-up, flow irregularities and even back flow of the reagent stream.



Scheme 4. Continuous flow isomerization, lithiation and quenching of methyl propargyl ether **2** to deuterated methoxyallene **7**

Hence, process optimization was continued using a less reactive electrophile in flow (Scheme 5 and Table S6). A solution of benzophenone **5** (1 equiv.) was fed to the reactor using a syringe pump and a T-connector. When a T-connector and a tubular reactor were used for the lithiation, the formation of the end product **6** suffered from variable conversion (Table 3). The observed side reactions involved the reversed reaction to methyl propargyl ether **2**, deprotonation of the terminal alkyne and subsequent nucleophilic addition to benzophenone. Clogging only occurred when more than 1.2 equiv. of *n*-butyllithium was used. For fast reactions such as lithiations, mixing efficiency is a critical parameter to ensure a high, stable and selective conversion.

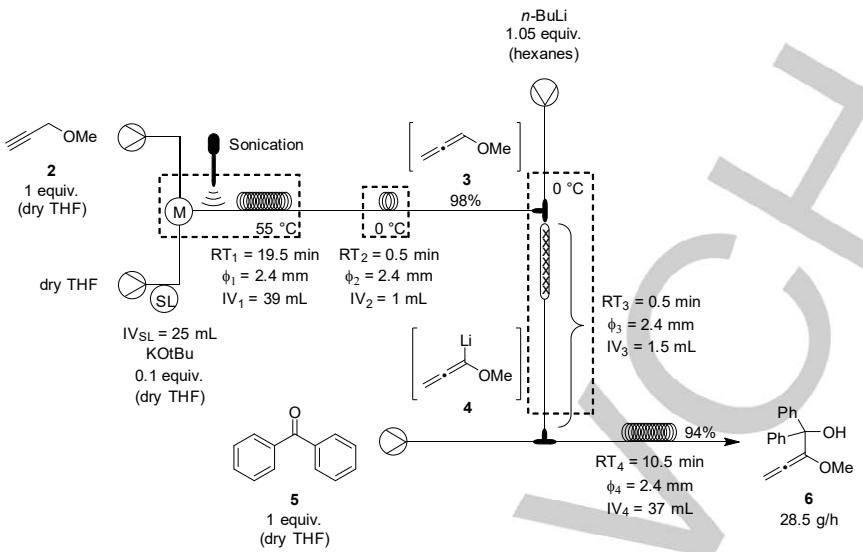
To enhance the lithiation mixing efficiency, a glass static micromixer with a volume of 1.6 mL was used. An excellent and stable conversion, in the 95 to 97% range, and only minimal amounts of side product were observed (Table 3, entry 3). However, frequent clogging of the glass chip was faced. Most likely, the clogging was caused by small amounts of KOH debris formed in the first isomerization reactor. A solubility and pH check of this slurry revealed high water solubility and an alkaline pH. Therefore, we suspected traces of water in the starting materials, causing the formation of KOH. As these plugs only appeared after the 5 port mixer, the water traces originate from the methyl propargyl ether **2** solution. Storage of this solution over molecular sieves improved, but could not overcome clogging of the lithiation reactor. Further efforts were made by lowering the equivalents of *n*-butyllithium and dilution. Clogging was initially avoided by diluting to a 0.2 M solution of methyl propargyl ether **2**. However, a decline in conversion was observed. Although these experiments were unsuccessful, they did show that a slight excess of 1.05 equivalents of *n*-butyllithium was sufficient to obtain an excellent lithiation, given proper mixing.

Whereas the micromixer provided excellent mixing efficiency, the attainable concentration (0.2 M) is considered too low for a commercial process. Our process thus required a larger diameter mixing unit to accommodate higher concentrations while preserving mixing efficiency. A regular T-connector and helical static mixing elements, inserted in a tubular reactor, were used (Table 3). These static mixers were successfully used in literature for pilot scale lithiations.[21],[23] Performing the lithiation at room

Table 3. Key experiments in the optimization of the continuous flow isomerization and lithiation to lithiated methoxyallene **4** and subsequent electrophilic quench[a]

Entry[b]	E[c]	lithiation mixing unit	IV_{lit} (mL)	Equiv. *n*-BuLi	T_{lit} (°C)	IV_{quench} (mL)	RT_{quench} (min)	EP[d] (%)
1	D_2O	T	5	1.2	rt	10	3.3	39-91
2	**5**	T	5	1.2	rt	37	10.2	51-98
3[e]	**5**	MM[f]	2.6	1.05	rt	37	10.5	95-97
4[g]	**5**	MM	2.6	1.05	rt	37	11.7	79-94
5	**5**	T+SM[h]	1.5	1.05	rt	37	10.5	31-82
6	**5**	T+SM	1.5	1.05	0	37	10.5	91-97

[a] Full data of all optimization experiments can be found in the Supporting Information [b] [**2**] = 1.25 M, [KOtBu] = 0.50 M, [**5**] = 3 M [c] Electrophile [d] Distribution via integration on ^{1}H-NMR [e] Clogging at the lithiation mixing unit [f] Glass static micromixer [g] Under diluted conditions: [**2**] = 0.2 M, [KOtBu] = 0.08 M, [**5**] = 0.48 M [h] Helical static mixing elements



Scheme 5. Telescoped 3-step continuous flow process toward lithiated methoxyallene **4** and nucleophilic addition to benzophenone **5**

temperature, however, lead to strong flow irregularities and a prominent presence of gaseous phases, resulting from insufficient heat and reaction control. Again, a strong variation in conversion was observed. Although continuous flow deprotonation and lithium halogen exchange using alkyl lithium reagents are abundantly reported in literature, most results are obtained in a small-scale reactor set-up and a short time-on-stream.[22] Even in a microstructured device, additional cooling is required and as such, the lithiation was next performed in an ice bath. Finally, a mesoscale continuous flow process for the synthesis of lithiated methoxyallene **4** and nucleophilic addition to **5** was established with an excellent average conversion of 94%, with only minor fluctuations (Scheme 5). This corresponded to a throughput 28.5 g/h. Two industrial research groups demonstrated the challenges for continuous flow lithiation scale-up.[23],[21] Similar to our observations, the main issues involved guaranteeing isothermal conditions, even in microstructured reactors, the feedstock quality and exclusion of moisture and operational problems, e.g. pressure built-up in pumps, valves or precoolers and flow pulsations due to the formation of gaseous phases. A critical bottleneck appeared the clogging of micromixers due to deposits of salts, by-products or side products and fouling by polymeric deposits with longer time-on-stream.[21],[23]

Our final process is characterized by short reaction times, mild reaction conditions and an excellent stoichiometric use of reagents. It offers valorization opportunities to the abundant small-scale batch research. By way of example, in need of a large scale synthesis of an API precursor to support drug development, researchers at AstraZeneca identified the lithiated methoxyallene route as the most promising.[5] Using methoxyallene, the number of steps was reduced and an efficient synthesis was demonstrated on a small scale. However, the lack of a safe operation mode forced them to abandon this approach. With the development of a continuous flow process, we have responded to their postulation that such powerful chemistry is in need of a scaled synthesis.

Conclusions

Lithiated methoxyallene is an extremely versatile building block in the organic synthesis of (hetero)cyclic scaffolds. Although safety issues limit the batch mode production scale, chemists have relied on this compound for 50 years. Dealing with exothermicity and other challenges, a telescoped mesoscale continuous flow route toward this building block is provided. A single step continuous flow process for the methylation of propargylic alcohol was established first. In a residence time of 30 min, 96% of conversion was reached in water, corresponding to a throughput of 12.8 g/h. After inline removal of water and intermediate distillation, a 3-step continuous flow process was presented, starting with the isomerization and lithiation of methyl propargyl ether to lithiated methoxyallene and its subsequent nucleophilic addition to benzophenone as a model electrophile. The prevention of blockages and preserving the lithiation mixing efficiency and temperature control appeared to be the critical bottlenecks. A break-through was reached when high-performance reciprocating pumps were used and helical static mixing elements were inserted in a tubular reactor to enhance the lithiation mixing efficiency. An excellent conversion of 94% toward the addition product was obtained, using only 1.05 equivalents of *n*-butyllithium and 1 equivalent of the electrophile. In a total residence time of 31 min, a throughput of 28.5 g/h was reached.

Experimental Section

For the fully telescoped continuous flow isomerization and lithiation of methyl propargyl ether **2** to lithiated methoxyallene **4** and subsequent nucleophilic addition to benzophenone **5**, the experiment was performed as follows. A solution **A** of 1.25 M methyl propargyl ether **2** in dry THF was prepared. Under argon atmosphere, 10.56 mL methyl propargyl ether **2** (1 equiv., 8.76 g, 125 mmol) was transferred to a flame-dried 100 mL flask and dry THF was added to reach a 100 mL solution. In a flame-dried 50 mL flask, 15 mL of a commercially available 1 M potassium *tert.*-butoxide

solution in THF (13.53 g, 15 mmol) was diluted with 15 mL dry THF under argon atmosphere to obtain solution **B** of 0.5 M potassium *tert.* butoxide in THF. Solution **D** of 3 M benzophenone **5** was prepared in a 25 mL volumetric flask. Under argon atmosphere, 13.67 g benzophenone (75 mmol) was dissolved in dry THF.

Solution **A** and dry THF, stored under argon atmosphere, were fed to the reactor using two ReaXus® high-performance reciprocating pumps. The inlet tubing of the pumps was inserted in the flasks through the sealing septa. Downstream of pump B, the reactor set up was equipped with a 25 mL sample loop, with an inner diameter of 2.4 mm, to avoid contact of the potassium *tert.*-butoxide solution with the pump flow line. The outlet of pump A and of the sample loop were mixed in a 5 port manifold. The isomerization reaction was performed in a 40 mL PTFE tubular reactor with an inner diameter of 2.4 mm. The 5 port mixing unit and 39 mL of the reactor coil were heated in a water bath at 55 °C. The heated water bath was equipped with a Hielscher® ultrasonic processor. The residual 1 mL tubing of the reactor was passed through an ice bath to condense the gaseous phase. Subsequently, a commercially available 2.5 M *n*-butyllithium solution in hexanes (**C**) was dosed to the outlet of the first isomerization reactor via a T-connector using Chemyx® syringe pumps. During rinsing and equilibration of the isomerization reaction, the inlet channel of the *n*-butyllithium solution was closed via a shut-off valve. Lithiation was performed in a 1.5 mL PTFE tubular reactor with an inner diameter of 2.4 mm at room temperature. The first 0.5 mL of this reactor were equipped with four Nordson® static mixing elements with a diameter of 2.36 mm to enhance the mixing properties. Using a T-connector, the outlet of the lithiation reactor was mixed with solution **D** of 3 M benzophenone **5** in dry THF. Solution **D** was fed to the reactor set-up using a Chemyx® syringe pump. The nucleophilic addition was subsequently performed in a 37 mL PTFE tubular reactor with an inner diameter of 2.4 mm at room temperature. Similar to the *n*-butyllithium solution flow line, the inlet channel of the benzophenone solution could be closed via a shut-off valve during initial rinsing and equilibration of the isomerization and lithiation reactor.

Before process start-up, the entire reaction set-up was thoroughly rinsed with dry THF, stored in two flame dried 250 mL flasks under argon atmosphere. The used glass syringes were rinsed with dry THF as well. Next, the 25 mL sample loop was manually loaded with the 0.5 M potassium *tert.*-butoxide solution in THF, using a glass 25 mL syringe. The flow rates of solution **A** and dry THF – the actual flow rate of solution **B** – were set to respectively 1.60 mL/min and 0.40 mL/min, corresponding to 0.1 equiv. of potassium *tert.*-butoxide. The residence time in the heated part of the tubular reactor to carry out the isomerization was 19.5 min, followed by a 0.5 min during cooling phase. After equilibration of the isomerization (2 residence times), the conversion of into methoxyallene **3** was verified via ^{1}H-NMR and the shut-off valve in the *n*-butyllithium flow line was opened. The flow rate of the *n*-butyllithium solution in hexanes was set to 0.84 mL/min, corresponding to 1.05 equiv. of the lithiation reagent. This resulted in a residence time of 0.5 min in the lithiation reactor. After equilibration of the lithiation (5 min), the shut-off valve of the inlet flow channel of the benzophenone **5** solution was opened and the flow rate was set to 0.67 mL/min. This corresponded to the addition of 1 equiv. of benzophenone **5** and a residence time of 10.5 min in the third tubular reactor. During 30 min of monitoring time, multiple samples were collected at the outlet and analyzed via integration of the crude reaction mixtures on ^{1}H-NMR. The obtained 2-methoxy-1,1-diphenyl-2,3-butadien-1-ol **6** is a known compound. Spectral data were in agreement with literature.[24] More experimental details, spectral data, procedures and the results of all optimization experiments can be found in the Supporting information.

Acknowledgements

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Keywords: Allenes • C3 building block • Green chemistry • Microreactors • Telescoping

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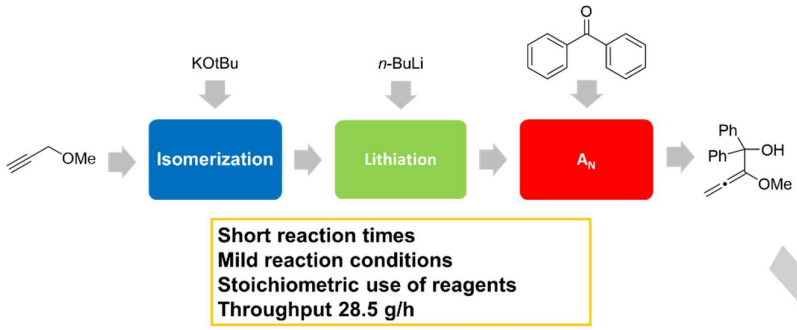

Pumping a chameleon: Lithiated methoxyallene is an extremely versatile building block in the organic synthesis of (hetero)cyclic scaffolds. However, its large scale synthesis pathway suffers from serious safety issues and the abundant small scale batch research cannot be valorized. Hence, the attractive heat and mass transfer properties of flow technology were exploited to establish a mesoscale continuous flow route toward lithiated methoxyallene.

*Sofie Seghers, Thomas S. A. Heugebaert, Matthias Moens, Jolien Sonck, Joris W. Thybaut, Christian V. Stevens**

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Design of a mesoscale continuous flow route toward lithiated methoxyallene