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Continuous Processing of Concentrated Organolithiums in Flow Using Static and Dynamic Spinning Disc Reactor Technologies

Ulrich Wietelmann,* Johannes Klösener, Peter Rittmeyer, Stefan Schnippering, Henk Bats, and Wouter Stam

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ABSTRACT: Organometallic reactions involving highly reactive organolithium reagents are widely used in organic synthesis. However, the use of such organometallics in batch mode on a pilot and industrial scale is challenging for safety reasons and frequently requires expensive cryogenic process conditions. A change to continuous processing in flow mode can provide major advantages for process safety and economics. In this study, we compare static and dynamic flow reactor technologies for two important organolithium (butyllithium and hexyllithium)-enabled transformations: deprotonations and bromine/lithium exchange reactions. Using higher concentrated (≥3 M) butyllithium (BuLi) solutions, that is, reaction mixtures with reduced hydrocarbon content, decreases the risk of reactor fouling and allows for increased space/time yields. In the flow mode, the observed reactions could be carried out under more convenient conditions, that is, at higher temperatures compared to the batch mode, and the deprotonation reaction even at ambient temperature instead of −78 °C. The formation of precipitates with the risk of clogging can be further reduced by changing from static flow to dynamic spinning disc reactor technology. The SpinPro reactor system from Flowid has been identified to ensure robust performance, as it tolerates salt precipitations and can provide excellent mass transfer conditions. Flow process technology using concentrated organolithium products can provide unique benefits for the manufacturing of pharmaceutical intermediates, agrochemical products, and specialty chemicals.

KEYWORDS: *concentrated butyllithium, flow process, spinning disc reactor, clogging*

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■ INTRODUCTION

Organometallic species of the 1st main group, in particular, organolithium compounds, are indispensable tools for organic synthesis, as they serve as carbanion equivalents and are used directly or indirectly for various C-C cross-coupling reactions. The main reactions are additions to unsaturated functional groups, for example, 1,2-additions to carbonyl compounds or CN double and triple bonds. Other important organolithium reactions involve deprotonation reactions and halogen/metal exchange reactions. In addition, organolithium compounds are used for metal-exchange reactions (e.g., production of organozinc or organocopper compounds) and finally for direct transition metal-catalyzed C-C coupling reactions (*Murahashi−Feringa* couplings[1]). Most of these reactions have long been known and are summarized in corresponding textbooks.[2]

Organolithium compounds RLi with R = saturated alkyl groups are preferably produced and used as solutions in hydrocarbon solvents, as those solvents provide high solubility and the best possible thermal stability. Many such organolithium products, especially the butyllithium isomers *n*-butyllithium, *sec*-butyllithium, and *tert*-butyllithium, as well as hexyllithium, are available on an industrial scale as solutions in hexane, heptane, cyclohexane, toluene, and so forth. The most popular commercial solutions are between 1.5 and 2.5 M in hexanes or heptanes: 15 or 23 wt % in the case of *n*-butyllithium and ca. 33 wt % for *n*-hexyllithium.[3]

All these solutions have in common that they do not contain a donor solvent, such as an ether or an amine. Although lithium alkyls are very soluble in donor solvents like tetrahydrofuran (THF) or other ether compounds, these formulations exhibit only unsatisfactory thermal stability. For example, *n*-butyllithium decomposes at 0 °C in THF with a half-life of 23.5 h.[4] Decomposition takes place with the formation of ethylene and the Li-enolate of acetaldehyde

$$C_4H_8O + C_4H_9Li$$
$$\rightarrow H_2C]CH_2 + LiO - CH]CH_2 + C_4H_{10}$$

However, donor solvents are indispensable for many reactions with RLi compounds, as they can positively influence both reactivity and selectivity. In hydrocarbons, *n*-butyllithium is mainly present as a hexameric aggregate. Such oligomerization phenomena provide stabilization of the electron-deficient carbon−lithium interactions, but at the same time, it reduces the oligomer's nucleophilicity and its desired reactivity for chemical conversions, for example in halogen−metal exchange

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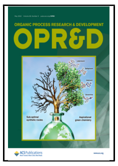

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reactions.[5] By adding Lewis bases, these oligomers are broken down, and significantly more reactive dimers and monomers form.[6,7] Therefore, donor solvents, in most cases THF, are required for practical organolithium conversions, and they are typically introduced together with one of the substrates. Some deprotonation reactions even need stronger donor additives, typically amines such as TMEDA, in order to generate the most reactive monomeric RLi species. Recently, it has been reported that the addition of those strong donor bases is not needed to deprotonate fluorinated aromatic compounds when the more reactive *sec*-butyllithium isomer is applied instead of *n*-BuLi.[8]

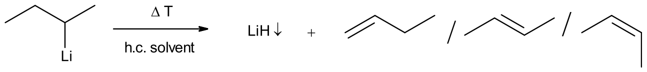
The reaction temperature is chosen so that the desired reaction is much faster than the attack on the donor solvent. Many reactions using organolithium compounds are carried out at low temperatures (often in the temperature range between −100 and 0 °C). It is known that, for example, bromine/lithium exchange reactions in the presence of THF or diethyl ether occur very quickly even at low temperatures like −78 °C, so that the undesired side reaction—the attack onto the donor solvent—does not occur.

Organolithium compounds, predominantly *n*-butyllithium and *n*-hexyllithium, are increasingly used in continuous processes carried out in micro and mesoreactors ("flow processes"). This trend is mainly due to safety considerations, as organolithium compounds are regarded as dangerous substances due to their high reactivity and potential pyrophoricity in air. Furthermore, savings are possible through process intensification and lower energy consumption. Owing to the dramatically improved mixing conditions, the faster heat dissipation, and lower residence times in the flow mode, reactions can often be performed at higher (noncryogenic) temperatures than is the case for the classical batch process.[9,10]

However, the much higher specific surfaces of microflow reactors than that of batch reactors and the small diameters of their channel structures also provide challenges in reactions with butyllithium. Many users observed decreasing flow rates and finally blockages, so-called "reactor fouling," in the course of time. These clogging phenomena are attributed to various reasons, such as the precipitation of salt-like or polymeric solids. Clogging has been found to be the largest obstacle restricting a smooth and continuous operation.[11] As a result, flow reactions with organolithium compounds can frequently not be run stable for longer periods of time. Cleaning and deblocking cycles have to be applied regularly. This counteracts the principal advantages of continuous reaction process technology.

Reactor fouling may be caused by insolubles being already present in the starting materials or solids generated by side or main reactions during organolithium conversions. Normally, liquid raw materials, including RLi solutions, are pumped through filters to ensure supply with a perfectly clear feed. Depending on the RLi manufacturing method and its storage history, these organometallics may be contaminated with gelly-like solids, formed by prior contact with air and/or due to contaminations from the organolithium synthesis process. Organolithium synthesis makes use of Li metal dispersion. This reactive form of finely divided lithium can be prepared either by spraying bulk molten Li into an argon atmosphere[12] or by an emulsion process in hydrocarbon solvents. The material from the latter process contains oils and decomposition products stemming from the dispersing agent, which may contaminate commercial solutions.

Furthermore, longer storage of RLi compounds, esp. *sec*-BuLi, leads to thermal decomposition under the formation of olefins and finely dispersed insoluble LiH



During the flow process, additional solids may be formed by hydrolysis of RLi compounds due to humidity traces in the raw materials, esp. the solvents, according to

$$\mathrm{RLi} + \mathrm{H_2O} \rightarrow \mathrm{H} + \mathrm{LiOH}\downarrow$$

Lithium hydroxide is virtually insoluble in nonpolar organic solvents such as hydrocarbons.

Rigorous drying of solvents can improve the situation, but conventional methods like water adsorption with solid drying reagents like alumina, sodium sulfate, calcium hydride, and so forth, are either inconvenient or/and do not ensure perfect drying to deliver water levels <ca. 35 ppm. As an alternative, a recently published chemical drying method using calculated amounts of iPrMgCl allows quick and complete drying but still needs a membrane filtration step to remove insoluble Mg salts formed upon the hydrolysis reaction.[13]

Another source for undesired precipitation is presented by lithiated organic intermediates, might it be alkoxides, halides, or compounds with direct C−Li bonds, which exhibit low solubility in the hydrocarbon-containing solvent blends applied.

Static mixing devices, which are characterized by miniaturized flow paths, are especially vulnerable to clogging processes. For example, conventional mixing tees containing glass or metal frits with a typical pore size of 10 μm are quickly blocked by any solids, especially gelly-type precipitates. On the contrary, mixing elements containing less tortuous flow paths, such as Koflo static tube mixers, comprise less severe constriction and pressure drop conditions and may thus improve the robustness of the flow process.[14]

Another option is to make use of mixing technologies and devices which can tolerate the presence or generation of solids. One of these technologies is presented by the spinning disc reactor (SDR) system. Such a system has been successfully applied, for example, for ortho-lithiation reactions, which could be carried out at ambient instead of cryogenic (−70 °C) temperatures for the case of conventional stirred tank reactor (STR) setup.[15]

In this paper, the advantages of using concentrated butyllithium and hexyllithium products in different flow reaction setups are outlined.

■ USE OF CONCENTRATED BUTYLLITHIUM PRODUCTS IN THE CONTINUOUS FLOW SETUP

This study aims to avoid solid precipitation by reducing the concentration of nonpolar hydrocarbons in the reaction mixtures. It is assumed that the hydrocarbon solvents automatically introduced by commercial 12−23 wt % butyllithium (BuLi) solutions may act as antisolvents for polar compounds or lithiated intermediates. Therefore, higher concentrated (30, 50, and 75%) BuLi solutions in hexanes were used, and benchmarked with the 15% standard commercial solution. Two exemplary types of reaction were selected for the most important BuLi applications, which are bromine−lithium exchange and deprotonation reactions. Beneath butyllithium, the performance of concentrated hexyllithium (HexLi) in comparison to the standard 33% solution was also assessed.

In order to carry out these reactions in static flow, a lab Vapourtec R2/R4 installation was used, as shown in Figure 1.

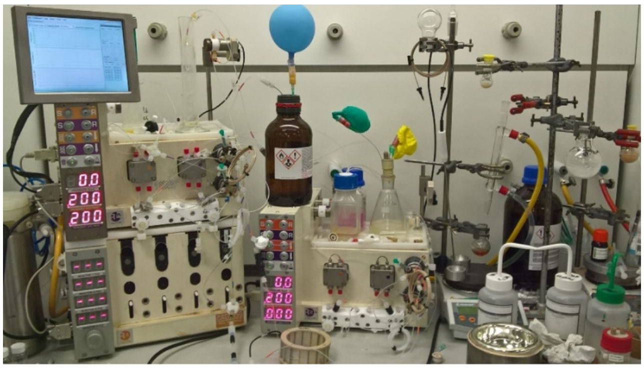


Figure 1. Vapourtec R2/R4 static flow system.

This equipment is very useful for first screening and process optimization tests, as the R-series is a modular flow chemistry system allowing to conduct almost all chemical conversions on a convenient, small scale down to <1 mL. It is equipped with 2 resp., 4 pumps, and an autosampler. Mixing of substrate/reagent can be achieved in the easiest way by combining their flows in a simple T-shaped mixer. However, if a reaction needs quicker/more turbulent homogenization, miscellaneous static mixers are applied. For reactions needing longer residence time for completion than provided within the mixing aggregate, a dwell time module is interpositioned before the next reaction step.

The same reactions were also investigated under dynamic flow conditions. Such an approach can be realized with an SDR system, which is commercially available from Flowid. Figure 2 shows the experimental setup with the Flowid SpinPro R10 installation as a key component.

The SpinPro dynamic reactor technology was specially developed for:

- Exothermic reactions, as it provides excellent heat transfer.
- Multiphase reactions (G/L, L/L) involving viscous liquids. High shear forces of >1.000.000 Reynolds number allow an excellent mass transfer.
- Reactions involving solids, especially those generated by an in situ-precipitation process. The very high shear forces counteract solid deposition and blocking of the flow channels.

A key feature of SpinPro is the creation of two mixing regimes in the reactor: both plug flow (PFR) regimes and continuously stirred tank reactor (CSTR) regimes are generated in distinct reactor zones, as seen in Figure 3 below.

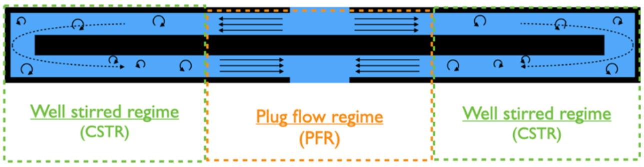


Figure 3. Flowid SpinPro mixing regimes.

The high shear forces in the CSTR zone create small vortices (micromixing zones), thus ensuring the high Reynolds numbers of >1.000.000. The alternation of PFR and CSTR will also avoid any backmixing in the SpinPro, as outlined in Figure 4.

The SpinPro R10 allows for production volumes in the range from 70 L/h down to the mL/min scale, while the larger SpinPro R300 is designed for up to 1,000 L/h throughputs. The reactor system allows for running a 24/7 operation for production under GMP- and ATEX-conformal conditions. It is equipped with integrated pumps, process control, process computer, and support. On this background, it has already been established in the industry for many applications in pharma, specialty chemicals, and the food industry.

■ HALOGEN–METAL EXCHANGE REACTIONS

Reaction in Vapourtec Static Flow Equipment. In order to evaluate the effect of BuLi concentration (and hence that of hexane content in the reaction mixture) on the efficiency of the lithiation reaction, very basic reactions were first carried out: two different aryl bromides were lithiated and quenched with methanol to obtain the dehalogenated products (see Scheme 1).

Since the quenching reaction is fast and quantitative, the amount of the dehalogenated product (anisole resp. pyridine) reflects the success of lithiation. The following Figure 5 displays the experimental setup for the lithiation of 4-bromoanisole.

The substrate was dissolved in THF (0.3 mmol in 1 mL) and placed in a 1 mL loop. *n*-BuLi from different stock solutions was then injected into the next loop, which had a

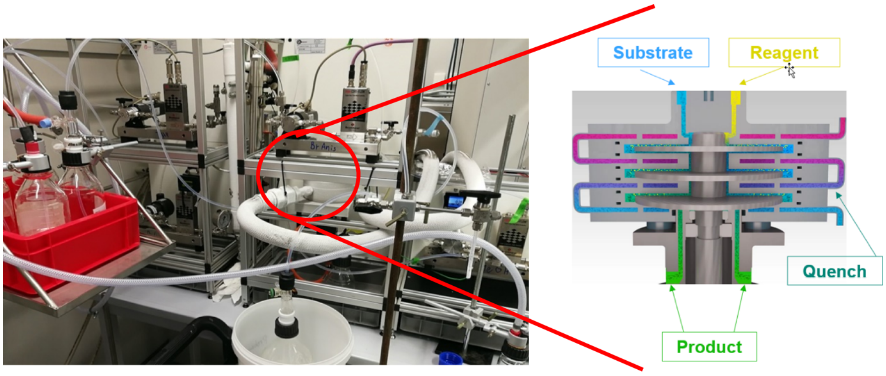


Figure 2. (a) Flowid SpinPro R10 setup for RLi conversions (left) and (b) drawing of SpinPro reactor (right).

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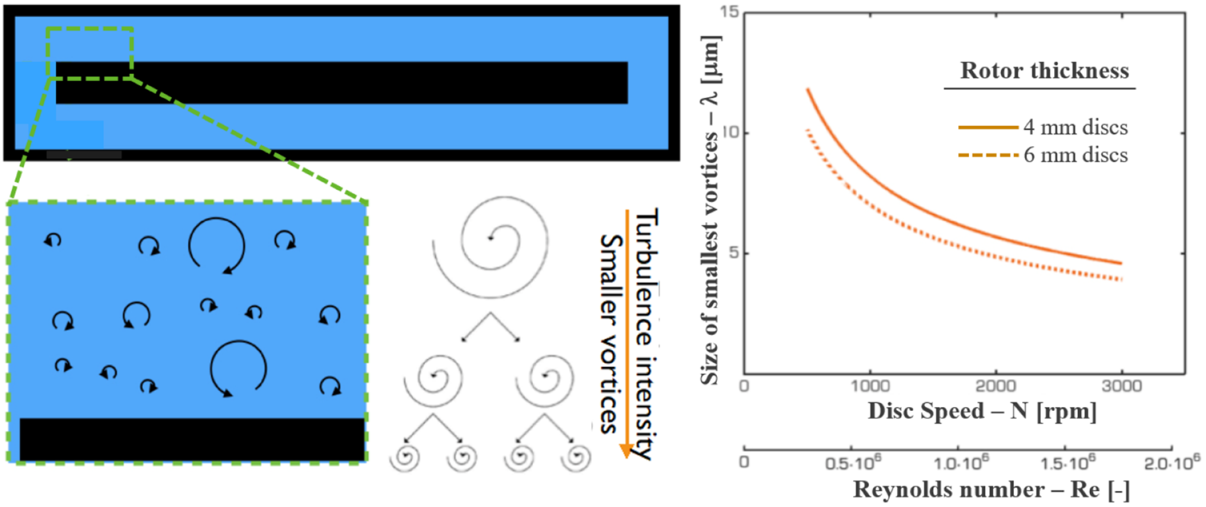
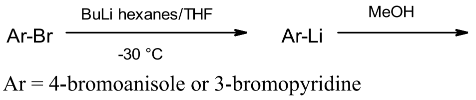


Figure 4. Flowid SpinPro mixing vortices.

Scheme 1. Br/Li Exchange Reactions with Methanol Quench[a]



[a]Ar = 4-bromoanisole or 3-bromopyridine.

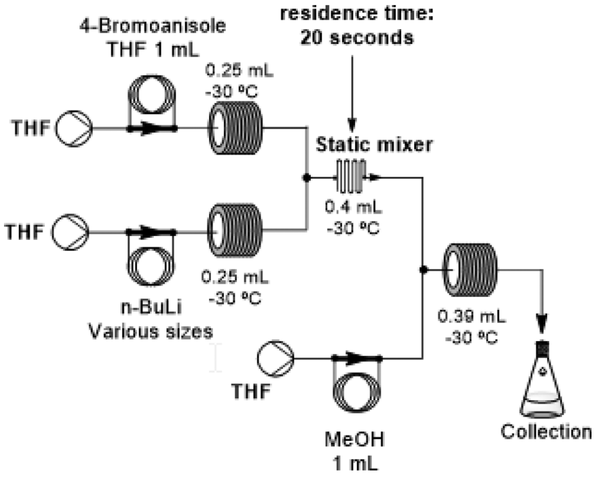


Figure 5. Experimental setup for the Br/Li exchange reaction of 4-bromoanisole.

volume of 0.250 mL. Since *n*-BuLi was applied in excess −1.33 equiv, 0.40 mmol of it was needed. This means that 0.25 mL from the 1.6 M stock solution were directly injected into the 0.25 mL loop without further dilution. From the 3.2 M sample, 0.125 mL BuLi solution was diluted with 0.125 mL of THF and injected into the loop, and from 5.8 M stock, 0.069 mL of BuLi was diluted with 0.181 mL of THF. The reagents were pumped at rates that resulted in 20 s residence time in the reactor (static mixer) before being quenched by methanol. The collected mixture was analyzed by HPLC for the ratio of the dehalogenated product, that is, starting material.

Table 1 shows that by reducing the concentration of the nonpolar solvent hexane, the conversion is significantly increased. No hints of reactor fouling or blockage were observed in any case.

In the next step, the reaction concentration was stepwise increased by diluting the substrate 4-bromoanisole with less and less THF. The butyllithium solutions were used with a 1.6 M concentration containing different hexanes/THF ratios. The results are summarized in Table 2.

Table 2. Lithiation of 4-Bromoanisole with *n*-BuLi Using Different Substrate Concentrations in THF

	conversion (%) using different 4-bromoanisole concentrations (mol/L)					
stock BuLi sln (mol/L)	0.3 M in THF	0.5 M in THF	1.0 M in THF	2.0 M in THF	2.5 M in THF	5 M in THF
1.6	27	30	blockage			
3.2[a]	35	44	80	95	blockage	
5.8[a]	49	83	86	68	75	blockage
8.8[a]	35	43	40	68	69	65

[a]Diluted with THF to 1.6 M before use.

Table 1. Br/Li Exchange Using 0.3 M Solution of 4-Bromoanisole in THF, Effect of Hexane Concentration

n-BuLi/hexane stock solution concentration	hexane concentration of BuLi feed solution (%)	hexane concentration of reaction mixture (%)	conversion to dehalogenated product (%)	reactor status
1.6 M	85	17	27	no blockage
3.2 M[a]	43	8	35	no blockage
5.8 M[a]	24	5	49	no blockage

[a]Diluted with THF to 1.6 M before use.

Three trends can be clearly remarked:

- Increasing the THF/hexanes ratio in the BuLi feed solution has a positive effect on the conversion in the case of low substrate concentrations.
- Increasing the 4-bromoanisole concentration for a given BuLi solvent composition increases the conversion, at least up to an optimum.
- Most importantly, reducing the concentration of hexanes helps to avoid clogging! The highest yields are obtained when using the 3.2 or 5.8 M BuLi stock solutions and high substrate concentrations.

Similar trends are observed in the lithiation of 3-bromopyridine (see Table 3). In this case, only the run with the lowest hydrocarbon concentration allows for a high substrate concentration of 0.75 M.

Table 3. Lithiation of 3-Bromopyridine with BuLi Using Different Substrate Concentrations in THF

	conversion (%) using different 3-bromopyridine concentrations (mol/L)	
stock BuLi sln (mol/L)	0.5 M in THF	0.75 M in THF
1.6	38	Blockage
3.2[a]	66	blockage
5.8[a]	86	97

[a]Diluted with THF to 1.6 M before use.

It is assumed that the lithiated reaction intermediates Ar−Li are much better soluble in THF than in hexanes; thus, they are kept in solution even at high reaction concentrations but provided low hydrocarbon concentration.

These trends can also be confirmed with a more useful chemical reaction comprising a bromo−lithium exchange step. Fenarimol (1) is a pyrimidinylcarbinol fungicide, and it acts by inhibition of ergosterol biosynthesis by inhibiting the P450 enzyme responsible for 14-demethylation. A key step is the C-C coupling of the lithiated pyrimidine synthon with the ketone (2) (see Scheme 2).

This reaction has been carried out in the classical semibatch mode by adding 1.6 M *n*-BuLi in hexanes to a solution of the substrates in THF at −95 °C.[16] The yield under these conditions was reported to be 34% and the approximate percentage of hexane in the solvent blend applied was 16%.

The flow experiments were executed in the Vapourtec R2/R4 device; 2 mL injection loops were used in the configuration shown in Figure 6. Loop 1 and loop 2 contained the ketone resp., 5-bromopyrimidine in THF solution, and these were mixed in a simple T-piece. It was found that simply metering a small volume of *n*-BuLi into the much larger volume of ketone/bromide gave unsatisfactory results, probably due to poor mixing. Therefore, THF was used to dilute the BuLi stock solutions to the same volume/concentration as the other reagents to give a 1:1:1 stoichiometry and then added to loop 3. The reaction mixture was fed into a static mixer and then into a 5-min residence coil. Both mixer and coil were cooled to −78 °C in a dry ice/acetone bath. The outflow of the residence coil was quenched using a known volume of saturated ammonium chloride brine, and an aliquot of the solution was injected into an HPLC system to measure conversion. The results are shown in Table 4.

The results show increasing conversion to the desired product with decreasing percentage of hexanes in the reaction mixture. In this test series, no blockage has been observed in any case. Please note that no further optimization experiments were carried out to increase the mediocre reaction results.

Reactions in the Dynamic Spinning Disc (Flowid SpinPro R10) Reactor Setup. The experimental setup is displayed in Figure 7.

The raw material feed was accomplished with gear pumps (Tuthill Pumps, U.K.); Coriolis flow meters (Bronkhorst, NL) were used for metering the respective flow rates. 4-Bromoanisole was supplied to the pumps from storage bottles at 3 ± 2 °C and *n*-butyllithium (applied with ca. 30% excess, see Table 5) and THF were cooled down to −20 ± 2 °C with heat exchangers before entering the SpinPro reactor, which itself was kept at −20 ± 1 °C by a Huber thermostat. Methanol, which was used as quench, was supplied at room temperature to the third stage of the reactor.

At first, screening experiments were performed to evaluate the optimal rotational speed; 3000 rpm was selected for all further trials. Following this, the optimal residence time was determined by using different total pump flow rates. Residence time of 20, 10, 5, and 3.3 s was applied, and the flow rates of the compounds used are found in Table 5.

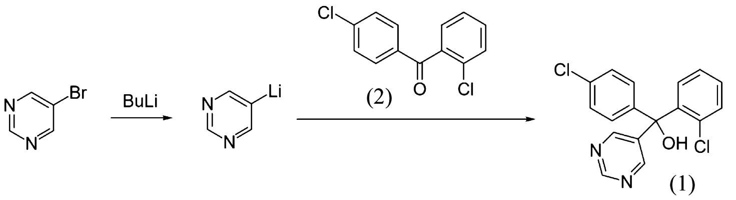
The residence time aforementioned is based on a volume of 10 mL since the methanol quench is performed on the third disc (see Figure 7), which has a volume of 9 mL, granting a total reactor volume of 19 mL for the SpinPro R10.

All experiments showed almost quantitative conversion, as bromoanisole has been converted to anisole with min. yields of 98%. As the sampling at high flow rates has been regarded to be unsafe for the case of highly concentrated reactants, a residence time of 5 s (corresponding to the respective flow rates mentioned in Table 5), which provided excellent results, was selected.

The first set of experiments was conducted with 15% (1.6 M) *n*-BuLi solution in hexanes and a 0.5 M solution of the organic substrate in THF. The conversion slightly increased with residence time; in line with the results obtained with the Vapourtec reaction system, no hints of reactor fouling or blockage were observed.

With these optimized conditions, the next set of experiments with increased concentrations of reactants was carried out. Please note that the higher concentrated *n*-butyllithium stock solutions were diluted with THF directly before the start of an

Scheme 2. Bromo-Lithium Exchange Test Reaction with Subsequent C-C Coupling 34% in Batch



34 % in batch

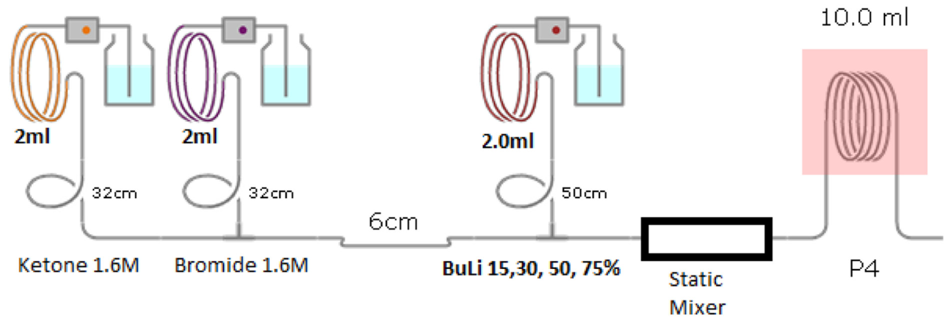


Figure 6. Bromine−lithium exchange reaction at −78 °C in flow.

Table 4. Variation of Conversion Depending on Hexane Concentration and Reaction in the Static Flow Mode

experiment no.	compound	concentration	loop size (ml)	conversion by HPLC (%)	approximate wt % hexanes
1	ketone	1.6 M in THF	2	22	28
	bromide	1.6 M in THF	2		
	n-BuLi	1.6 M in hexanes	2		
2	ketone	1.6 M in THF	2	34	12
	bromide	1.6 M in THF	2		
	n-BuLi	3.2 M in hexanes (1 mL) diluted with 1 mL THF	2		
3	ketone	1.6 M in THF	2	42	5
	bromide	1.6 M in THF	2		
	n-BuLi	5.3 M in hexanes (0.6 mL) diluted with 1.4 mL THF	2		

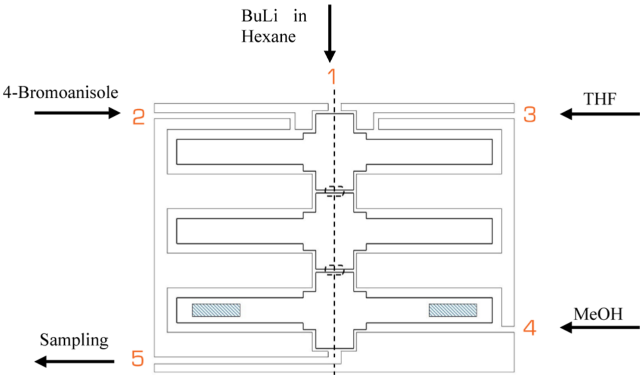


Figure 7. Experimental setup for the Br/Li exchange reaction of 4-bromoanisole in the dynamic flow mode.

experiment in order to assure a constant BuLi concentration of 1.6 M for all experiments. An aliquot of each entry was worked up, salts were removed, and the filtrate was subsequently analyzed by HPLC and NMR.

Again, in most experiments, quantitative yields (>98%) were obtained, as shown in Table 6, where the results of the reactions in the static flow equipment from Vapourtec are also tabulated for comparison purposes. In dynamic flow experiments, using the most concentrated bromoanisole feed solutions (3 resp. 4 M), only mediocre product conversions of 88 resp. 53% were observed when using the hexane-rich

Table 6. Reaction of 1.6 M *n*-BuLi/hexanes/THF with 0.3−4.0 M 4-Bromoanisole Solutions in THF with 5 s Residence Time[a]

n-butyllithium stock solution in hexanes (M)	4-bromoanisole in THF (M)	product conversion in static flow reactor (%)	product conversion in dynamic SDR (%)
1.6	0.3	27	N/A
3.2*	0.3	35	N/A
5.8*	0.3	49	N/A
1.6	0.5	30	98
3.2*	0.5	44	N/A
5.8*	0.5	83	N/A
1.6	1.0	blocked	100
3.2*	1.0	80	99+
5.8*	1.0	86	99+
1.6	2.0	N/A	99+
3.2*	2.0	95	99+
5.8*	2.0	68	99+
1.6	3.0	blocked	88
3.2*	3.0	91	**
5.8*	3.0	99+	99+
1.6	4.0	N/A	53
3.2*	4.0	N/A	98
5.8*	4.0	N/A	99+

[a] * Diluted in SpinPro R10 with THF to 1.6 M; N/A = no experiment conducted; ** 99%, but with an erroneous *n*-butyllithium flow rate of 85 instead of 43 mL/min.

Table 5. Reaction of 1.6 M *n*-BuLi/hexanes with 0.5 M 4-Bromoanisole Solution in THF

n-butyllithium stock solution in hexanes (M)	flow rate *n*-butyllithium (mL/min)	flow rate 4-bromo-anisole (mL/min)	flow rate MeOH (mL/min)	product conversion (%)	residence time (s)	T_{outlet} (°C)
1.6	9	21	3	99+	20	−6
1.6	17	43	6	99+	10	0
1.6	35	85	11	98	5	20
1.6	58	142	19	98	3.3	27

https://doi.org/10.1021/acs.oprd.2c00007
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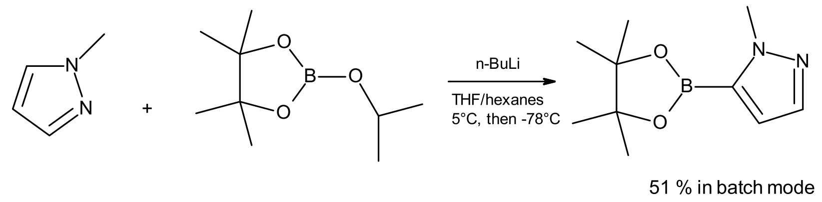
Scheme 3. Deprotonation/Borylation Reaction of *N*-Methylpyrazole in the Batch Mode



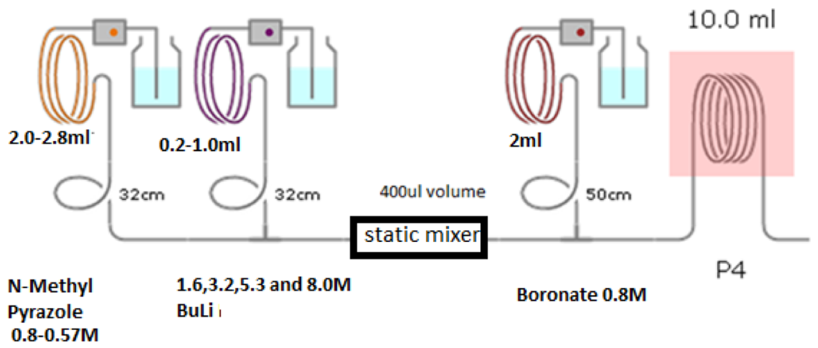


Figure 8. Schematic for deprotonation–borylation reaction at an ambient temperature in flow.

Table 7. Variation in Conversion with Approximate wt % Hexanes in the Reaction Mixture for a Deprotonation–Borylation Reaction at Room Temperature

experiment no.	compound	concentration (M)	loop size (mL)	conversion by HPLC (%)	approximate hexanes content (%)
1	pyrazole	0.8 in THF	2	29	17
	boronate	0.8 in THF	2		
	BuLi	1.6 M in hexanes	1		
2	pyrazole	0.8 M in THF	2.5	45	8
	boronate	0.8 M in THF	2		
	BuLi	3.2 M in hexanes	0.5		
3	pyrazole	0.59 M in THF	2.7	66	2.5
	boronate	1.6 M in THF	2		
	BuLi	5.3 M in hexanes	0.3		
4	pyrazole	0.8 M in THF	2	78	3.4
	boronate	0.8 M in THF	2		
	BuLi	5.3 M in hexanes	0.3		
5	pyrazole	0.57 M in THF	2.8	51	1
	boronate	1.6 M in THF	2		
	BuLi	8 M in hexanes	0.2		

standard 15% BuLi solution. In contrast and in accordance with the results obtained in the static flow reactor, the hexane-deficient reaction mixtures afforded perfect conversion (min. 99%). Please note that in no case reactor fouling or blockage was observed, as it had been observed in the case of the static flow experiments.

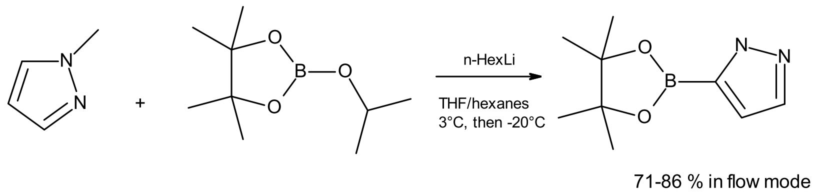
The outflux of the SpinPro R10 was a slurry containing excess starting material, anisole and insoluble lithium methoxide, in THF/hexanes. Optimized experiments with very high substrate concentrations and low hydrocarbon content demonstrate the benefit of using highly concentrated *n*-butyllithium solutions, especially in the dynamic SpinPro R10 reactor system, even dispersions with up to 30% solids content are tolerated, and no clogging or reactor fouling is observed. Thus, very high space/time yields can be realized.

Deprotonation Reaction. The second type of reaction chosen in this study was a deprotonative lithiation, exemplified in the synthesis of a pyrazole boronate, a key intermediate in the synthesis of GSK AKT inhibitor, Afuresertib (Scheme 3).

In batch, this reaction was carried out by adding 1.6 M BuLi in hexanes to a solution of the pyrazole in THF at 5 °C. At this stage, the reaction mixture contains approximately 20% hexanes. The mixture was then cooled to −78 °C, and isopropyl pinacolborate was added.[17] The reported isolated yield is 51%.

Process in Static Flow Equipment. To transfer the reaction to static flow, pyrazole was deprotonated in the first step using a butyllithium stock solution in a static mixer, as shown in Figure 8. In this reaction, the stoichiometry could be controlled using the size of the *n*-BuLi loop, as the reagent ratios are smaller than in the case of the halogen/lithium exchange reaction, and efficient metering and mixing was found. The concentration of the pyrazole in loop 1 was adjusted so that the extrapolated concentration of the lithiated intermediate was always 0.53 M. The outflow was worked up, and the yield was determined by NMR spectroscopy using an internal standard. Interestingly, a design of experiments exercise (results not shown) indicated that the lithiation and borylation reactions could effectively be carried out at room

Scheme 4. Deprotonation/Borylation Reaction of *N*-Methylpyrazole in Flow Using HexLi Instead of BuLi



temperature under flow conditions. Using the commercial standard 15% BuLi solution leads to an overall 17% hexane content in the reaction mass and low conversion of only 29%. This value could be significantly improved by using higher concentrated BuLi solutions, hence by introducing less hexane to the reaction mixture, see data in Table 7.

The experiments again show an increasing conversion to the desired product with decreasing percentage of hexanes in the reaction mixture for the first four entries. The highest yield of 78% was observed for a lithiated pyrazole concentration of ca. 0.7 M, produced with a 5.3 M (ca. 50 wt %) BuLi solution (entry 4). This yield is significantly higher than the 51% obtained in the STR benchmark experiment, which had to be carried out at a cryogenic (−78 °C) temperature. Opposed to this, when using concentrated, nearly solvent-free (>90%) BuLi in entry 5, the yield dropped to only 51%. In this case, the lower-than-expected conversion could be a result of poor metering of the somewhat viscous *n*-BuLi concentrate into the flow reactor.

Only when using the most diluted (1.6 M) BuLi solution, the reaction mixture was significantly turbid due to the precipitation of solids. In contrast, all product solutions produced with higher concentrated BuLi appeared to be clear and homogenous before the acidic aqueous quench with saturated NH_4Cl brine.

Reactions in Dynamic Spinning Disc (SpinPro R10) Reactor Setup. For the deprotonation in dynamic flow, a 33% (2.5 M) hexyllithium solution in hexanes was chosen instead of butyllithium (see Scheme 4). Using the C6 reagent is convenient, as it affords liquid hexane instead of gaseous butane as a byproduct. Thus, the emission of hydrocarbon vapors can be reduced. While the deprotonation was carried out at about 3 °C, the borylation was executed at −20 °C, that is, at considerably more convenient temperatures as in the reference batch experiment.

The raw material feed was accomplished with gear pumps (Tuthill Pumps, U.K.); Coriolis flow meters (Bronkhorst, NL) were used for metering the respective flow rates. The raw materials were supplied to the pumps from storage bottles at 3 ± 2 °C, and hexyllithium and THF/hexane were cooled down to −20 ± 2 °C with heat exchangers before entering the SpinPro reactor, which itself was kept at −20 ± 1 °C by a Huber thermostat. The boronate was supplied at room temperature to the third stage (port 4) of the reactor, which has a volume of 9 mL, granting a total reactor volume of 19 mL for the SpinPro R10, see Figure 9.

Experiments were performed to evaluate the best rotational speed, residence time, and concentrations. Flow rates of the compounds used and the calculated residence times of about 70, 35, and 20 s are found in Table 8. The residence times aforementioned are based on a volume of 10 mL for the pyrazole deprotonation reaction.

Compared with the experiments in static flow, higher conversions to the desired product were generally observed, and in this case, there was no strong influence of the hexyllithium concentration (i.e., the hexanes concentration) on the conversion to product observed. However, the best results of 86% can be noticed with the highest HexLi concentrations of 4.0 and 6.2 M. This 86% conversion is significantly higher than the 51% obtained in the STR benchmark experiment, which had to be carried out at a cryogenic (−78 °C) temperature, and it is also better compared to the best result (78%) obtained in the static flow reactor from Vapourtec.

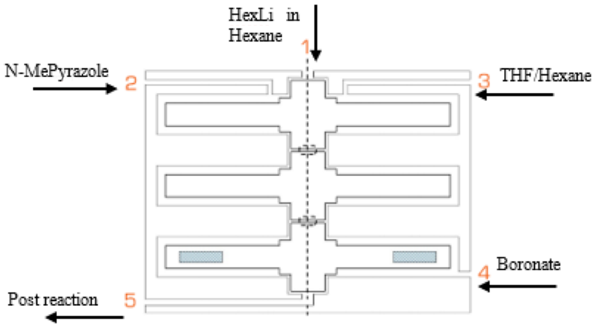


Figure 9. Schematic for deprotonation−borylation reaction at an ambient temperature in SpinPro R10.

■ CONCLUSIONS/SUMMARY

The current study has demonstrated that the presence of hydrocarbon solvents (hexanes) in reaction mixtures in high concentrations (ca. >10%, depending on individual process characteristics) may have a detrimental effect on reactions involving organolithium solutions in continuous flow processes. This could be demonstrated with benchmark reactions involving the two most important applications of RLi reagents: bromine−lithium exchange and deprotonation reactions.

By applying a reduced hydrocarbon concentration in the reaction mixture, which can easily be realized by using highly concentrated (3−6 M) *n*-BuLi or the corresponding concentrated hexyllithium solutions, the yield and the robustness of Br/Li exchange and deprotonation reactions can be significantly improved. In a deprotonation/borylation example (intermediate in the synthesis of GSK's AKT inhibitor, Afuresertib), the semibatch mode literature procedure was carried out at −78 °C and gave a yield of only 51%. The latter could be easily increased to 78% by applying continuous flow conditions at ambient temperatures using static flow reactors. By changing to dynamic SpinPro reactor technology and concentrated hexyllithium solution, a further increase in throughput was observed, reducing the residence time and increasing the conversion to 86%.

Flow chemistry allows to carry out this reaction at convenient temperatures, thus allowing the potential for much more cost-effective syntheses of organic products by lowering the cost of goods, processing time, and consumption of energy. The space/time yield can be maximized by using

Table 8. Reaction of HexLi in Hexanes with Pyrazole and Boronate Using SpinPro R10 at −20 °C

HexLi solution in hexanes (M)	concentration pyrazole/boronate (M)	rotation speed rpm	flow rate HexLi (mL/min)	flow rate pyrazole/boronate (mL/min)	residence time (s)	product conversion (%)
2.5	0.8	3000	5	14	71	84
2.5	0.8	3000	9	29	35	84
2.5	0.8	3000	18	58	18	85
4.0	0.8	3000	18	58	18	71
4.0	0.8	1000	18	58	18	86
4.0	0.8	6000	18	58	18	83
6.2	0.8	3000	18	58	18	86

less solvent if compared to corresponding batch experiments, and thus increased reactant concentrations of, for example, 2 M and higher are enabled. Depending on process/equipment-specific circumstances, the higher concentrated RLi solutions can be fed into the flow reactor device as such, or they can be diluted directly before use by a donor solvent (like THF) to the desired concentration. Higher concentrated BuLi (or HexLi) solutions are nowadays commercially available (Albemarle).

The major issue of the hydrocarbons carried along with the diluted (1.6−2.5 M) standard commercial BuLi solutions is that these act as antisolvents for polar lithiated compounds generated during organolithium-mediated reactions. Thus, solids are formed, which can easily block the channels and pathways of microflow reactor systems. Replacing hydrocarbons with donor solvents such as THF helps to avoid the precipitation of salt-like side products (like Li alkoxides) or other intermediates. As a further advancement, dynamic SDR technology has been found to be a very powerful tool to improve or even overcome any blockage issues. Chemical conversions carried out in the SpinPro R10 reactor available from Flowid/NL are much more tolerant towards solids in the starting materials or generated in situ when compared with the performance in "classical" static flow reactor equipment.

As a result, dynamic SDR technology (SpinPro) used for organolithium processes in flow ensures high process safety and very short residence times due to the highly efficient mixing; the remarkably high shear forces of >1.000.000 Reynolds number allow an excellent mass transfer. On the background of all these positive aspects, many future applications of organolithium processes in continuous flow mode for the manufacture of pharma intermediates, agrochemicals, and specialty chemicals can be expected.

AUTHOR INFORMATION

Corresponding Author

Ulrich Wietelmann − *Albemarle Germany GmbH, D-65926 Frankfurt am Main, Germany;* orcid.org/0000-0002-5909-3411; Phone: 0049-178-3466014; Email: ulrich.wietelmann@albemarle.com

Authors

Johannes Klösener − *Albemarle Germany GmbH, D-65926 Frankfurt am Main, Germany;* Present Address: Albemarle Germany GmbH, Innerstetal 2, 38685 Langelsheim

Peter Rittmeyer − *Albemarle Germany GmbH, D-65926 Frankfurt am Main, Germany*

Stefan Schnippering − *Albemarle Germany GmbH, D-65926 Frankfurt am Main, Germany;* Present Address: Mitsubishi Chemical Europe, Immermannstr. 13, 40210 Düsseldorf, Germany.

Henk Bats − *Flowid, NL-5651 GW Eindhoven, The Netherlands*

Wouter Stam − *Flowid, NL-5651 GW Eindhoven, The Netherlands*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.oprd.2c00007

Author Contributions

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Notes

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ABBREVIATIONS

STR, stirred tank reactor; CSTR, continuously stirred tank reactor; BuLi, butyllithium; HexLi, hexyllithium

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