

CONTINUOUS FLOW INTENSIFICATION OF ORTHO-LITHIATION AT AMBIENT CONDITIONS

Ruili Feng, Newcastle University, r.feng2@newcastle.ac.uk
Sushil Rajan Ramchandani, Institute of Chemical and Engineering Sciences
Balamurugan Ramalingam, Institute of Chemical and Engineering Sciences
Song Wei Benjamin Tan, Institute of Chemical and Engineering Sciences
Chuanzhao li, Newcastle University
Soo Khean Teoh, Institute of Chemical and Engineering Sciences
Kamelia Boodhoo, Newcastle University
Paul Sharratt, Institute of Chemical and Engineering Sciences

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Ortho-lithiation is an important class of reaction for the synthesis of regiospecifically substituted aromatics and it is an emerging method to prepare phthalides which are common pharmaceutically active compounds.¹ This reaction is typically conducted in batch mode under cryogenic temperatures (-78 to -40 °C)² to tame the high reactivity of the organolithium intermediates. Scaling up batch cryogenic organolithiation chemistry has traditionally proven to be a significant challenge. This involves the need to handle large quantities of hazardous lithium reagents and excessive costs associated with cryogenic technology at scale. These challenges make ortho-lithiation reaction an ideal candidate in deploying continuous flow processing as a process intensification (PI) technique. Continuous flow processing offers several 'green' benefits in the case of ortho-lithiation reaction where the use of highly energy-intensive refrigeration to -78 °C may be avoided. This offers the prospect of considerable energy savings at industrial scale, leading to reduced greenhouse gas emissions. It can also achieve high purity product stream so the downstream processing steps may be simplified. This minimizes the amount of solvent used and increases productivity due to higher selectivity. In addition, the use of continuous flow processing lowers the risk of accidental releases arising from the lower inventories of hazardous material.

Pioneering contributions from the Yoshida group demonstrated that sequential lithium-halogen exchange protocols with in situ trapping of aryllithium intermediate by different electrophiles in microstructured flow devices (consists of micromixers and microtube reactors) are superior to batch protocols.³ However, a significant area of concern in adopting flow processing in enclosed channels is the possibility of precipitation of the intermediate lithium salts,⁴ which can lead to clogging of such flow reactors. There are numerous reported solutions to circumvent this issue, such as lowering the product concentration,⁵ the use of acoustic irradiation with a sonication bath⁶ and the multijet oscillating disc (MJOD).⁷ Other concerns involve scalability and accurate temperature control.

In recent years, spinning disc reactors (SDR) have been developed as a process intensification technology, where rapid mixing and high mass and heat transfer rates can be achieved in the free flowing thin film of liquid produced due to centrifugal acceleration created by rotation.⁸ There are a number of characteristics of the SDR which make it a potential process intensification option for ortho-lithiation reaction, one of which is that it can avoid the issue of clogging as the stream flows freely over the disc surface instead of through an enclosed channel. The study of ortho-lithiation reaction in a SDR has yet to be reported.

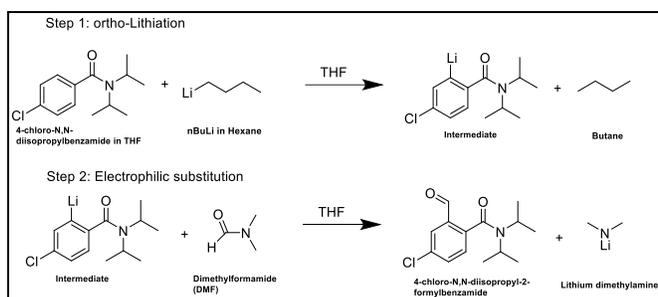
The present work aims to investigate the effect of the key operating parameters in the SDR (disc rotational speed and flow rate) and tubular reactors (flow rate and residence time) on the reaction and make comparison to the stirred tank reactor (STR) and T-reactor at 20°C based on power dissipation. Table 1 presents a summary of the equipment used in this study, their respective operating conditions and the maximum crude yield obtained. Ultimately, the potential green benefits (energy usage, Process Mass Intensity (PMI), etc.) of adopting the different intensified technology will be illustrated for the whole process (including workup) at industrial scale.

Table 1 Summary of the equipment used in this study.

	Microchip 1	Microchip 2	T-reactor	SDR	STR
Material of construction	Glass	Glass	PTFE	Stainless steel	Glass
Nominal cross section area	0.075 mm ²	1 mm ²	2.56 mm ²	N.A.	N.A.

Static elements	No	Yes (step and rotating)	No	N.A.	N.A.
In-process volume	250 μL	300 μL	130 μL - 2.1 mL	1.2-6.7 mL	20 mL
DMF addition	Via external T-joint	Via third inlet in the microchip	Via T-joint	On the disc	Semi-batch
Range of total flow rate	0.01-3 mL min ⁻¹	0.01-9 mL min ⁻¹	20-310 mL min ⁻¹	60-310 mL min ⁻¹	N.A.
Disc/Impeller speed	N.A.	N.A.	N.A.	400-2400 rpm	50-400 rpm
Temperature control	Direct contact with cooling plate	Submerged in cooling bath	Submerged in cooling bath	Coolant circulating under the disc surface and reactor wall	External cooling bath
Best crude yield (%)	No (clogging)	90 at 20°C	99 at 20°C	92 at 20°C	94 at -75°C
Throughput at best yield (ton/year)	No	0.32	3.2	3.2	Depends on reactor size
Experimental constraint	Clogging due to narrow channel	Flow rate limited by pump	Flow rate limited by pump	Residence time limited by size of disc	Small STR volume

In this work a typical procedure^{1b} was employed according to Scheme 1. Step 1 is the reaction of interest in this study as it is reported that most decomposition of lithiated intermediate and side product formation occur in this step.⁹



Scheme 1 Model reaction: ortho-lithiation reaction of 4-chloro-N,N-diisopropylbenzamide in THF using n-BuLi in hexane followed by reaction with DMF^{1b}

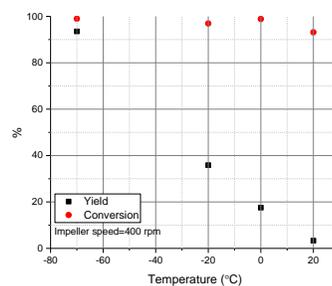


Figure 1 Semi-batch ortho-lithiation at 20, 0, -20 and -75 °C at constant agitation speed of 400 rpm

A laboratory stirred-tank reactor (STR) of 50 mL capacity and a 2-blade impeller of 1.2 cm diameter was used as a benchmark. The n-BuLi was added semi-batchwise to the solution of 4-chloro-N,N-diisopropylbenzamide (amide) in THF. The influence of temperature on reaction yield is presented in Figure 1. The maximum yield obtained is 94% at -75 °C and a fixed impeller speed of 400 rpm. Attempts were made to perform the reaction at -20, 0 and 20 °C but the yields were very low. At 20 °C the reaction produced almost no desired product; rather it formed a darkly coloured solution. Similar visual observation has been made by Ley and co-workers which they attributed to the decomposition of the aryllithium species via a benzyne intermediate.¹⁰

For the flow study, Microchip 1 with nominal cross sectional area of 0.075 mm², shown in Figure 2, was initially employed. The initial experiments resulted in blockage in the mixing channel (pre-reaction region) where the two streams first contacted. The mixing channel was not thermally controlled as this region was not in contact with the cooling plate. Stephan and co-workers⁴ have reported similar problem of clogging and proposed several possible reasons for this, i.e.; the formation of solids due to moisture in feed streams, impurities, formation of salt as byproduct, solid formation in the hot spots and polymerisation. It was hypothesized that the blockage was largely attributed to the narrow diameter of the microchip channel and the insufficient cooling in the mixing

channel, causing it to be very susceptible to accumulation of the fine precipitate.

Indeed, the use of Microchip 2, as shown in Figure 3, with a larger cross sectional area channel of 1mm^2 circumvented the issue of clogging. Without the problem of clogging, a crude yield of 90% and at a throughput of 40 g h^{-1} was achieved at $20\text{ }^\circ\text{C}$, which is a significant improvement from the stirred-tank reactor at the same temperature. For scale up, we developed a flow setup, with even larger diameter (2.56 mm^2) and used higher flow rates, by employing two PTFE Tee-joints connected by PTFE tube, as shown in Figure 4. High crude yield of 99% and throughput of 400 g h^{-1} were obtained at $20\text{ }^\circ\text{C}$.

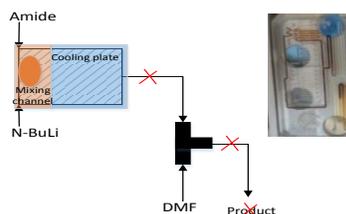


Figure 2 Schematic of glass Microchip 1 ($\phi=0.075\text{ mm}^2$) setup with clogging issue.

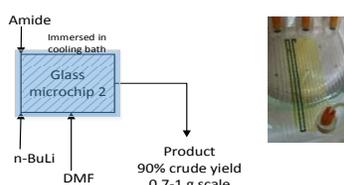


Figure 3 Schematic of glass Microchip 2 ($\phi=1\text{ mm}^2$) setup.

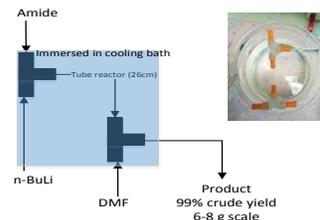


Figure 4 Schematic of T-reactor ($\phi=2.56\text{ mm}^2$) setup.

Figure 5 shows the effect of flow rate in the T-reactor on the yield for a fixed residence time. According to Falk and Commenge,¹¹ increasing the flow rate increases the mechanical energy input for enhanced mixing and shorter mixing time. However, the effect of residence time (0.1, 0.4, 0.8s) on yield was less obvious and less consistent. This may be due to the narrow range of residence time studied.

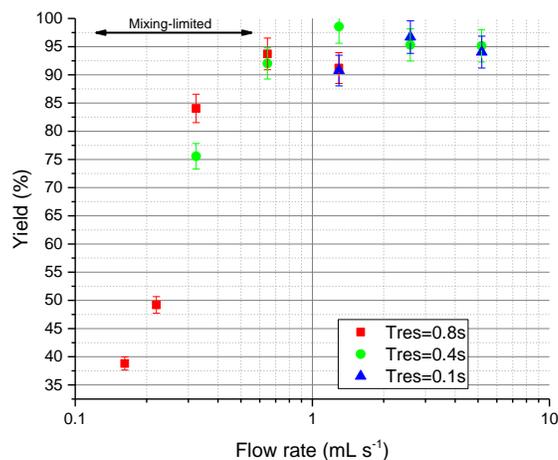


Figure 5 Effect of flow rate on yield at fixed residence time at $20\text{ }^\circ\text{C}$.

Other than the tubular reactors, the SDR was also used as it offered a different mode of mixing in the thin wavy films formed on the rotating surface. Moreover and importantly for this particular process, it can avoid clogging as the reagents flow over the disc instead of an enclosed channel. The amide and n-BuLi were fed onto the rotating disk through two pipes located at the center of the disc, as shown in Figure 6, enabling the two reactants to mix and reactant on a large part of the disc before coming into contact with DMF introduced at the edge of the disc. To control the temperature, coolant was circulated underneath the disc surface and through the side walls. Using similar flow rate as the T-reactor, the SDR also produced high crude yield of 92% and throughput close to 400 g h^{-1} at $20\text{ }^\circ\text{C}$.

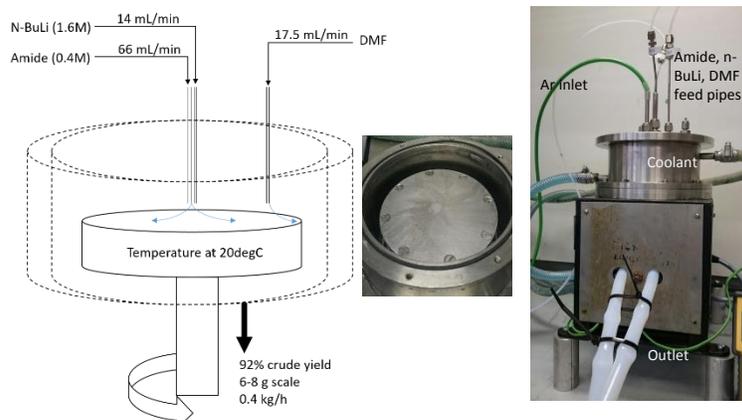


Figure 6 Spinning disc setup and the flow condition of the best run at 20 °C.

The effect of the disc rotational speed on the yield is illustrated in Figure 7. The yield increases with disc rotational speed at 3 and 5 mL s⁻¹ but it is hardly affected by disc speed at 1 mL s⁻¹. This would suggest that at the low flow rate of 1 mL s⁻¹ even relatively low disc speeds achieved sufficient mixing. The effect of film thickness in the mixing process may be considered, as it is dependent on both the flow rate and disc speed. Thin films result in reduced path lengths, across which diffusion occur more rapidly. Figure 8 shows that the lowest flow rate corresponds to the thinnest liquid film on the rotating disc at all disc speeds. This may explain the weak influence of disc speed at 1 mL s⁻¹.

In Figure 7, the disc rotational speed below 1400 rpm has strong influence on the yield at 3 and 5 mL s⁻¹. As seen in Figure 8, the film thickness is relatively thicker at high flow rate and low disc speed, indicating that solely relying on diffusion across the thin film may not provide sufficient mixing. The mixing intensity may be evaluated by examining the maximum shear rate generated in the thin liquid film.¹² Figure 9 demonstrates that the shear rate increases with disc speed and flow rate. Under such conditions, higher shear forces are created within the liquid film which cause more lamellar stretching and increased surface area under laminar flow conditions. The high disc speeds are likely to induce turbulence in the upper layers of the film and contribute to improvement in mixing.

However, in Figure 7, there is no further improvement in yield beyond disc speed of 1400 rpm, especially at 3 and 5 mL s⁻¹. Although increased disc speed improves shear rate and therefore mixing within the film, it shortens residence time proportionally as presented in Figure 10. This may result in incomplete reaction when the residence time becomes shorter than the reaction time. It is likely that beyond a certain disc speed, mixing is no longer the limiting factor but rather the residence time is. Further investigation was made to validate this observation by repeating the experiment with a range of flow rate (1- 5 mL s⁻¹) at constant disc speed of 1400 rpm presented in Figure 11. The result shows that the both conversion and yield are inversely proportional to flow rate. This agrees with our hypothesis that at relatively high disc speed the resultant residence time is too short for complete conversion. This negative effect of incomplete reaction on the yield may have cancelled out with the positive impact of increased shear rate and thus a plateau or a slight dip in the yield was observed beyond disc speed of 1400 rpm.

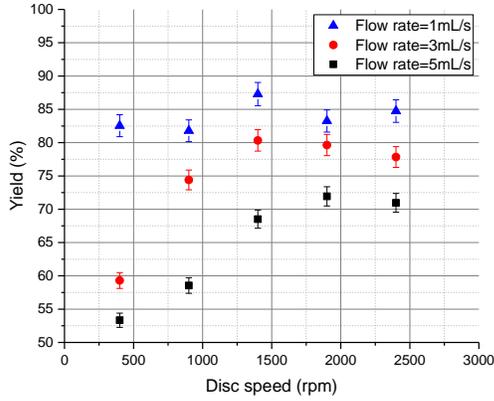
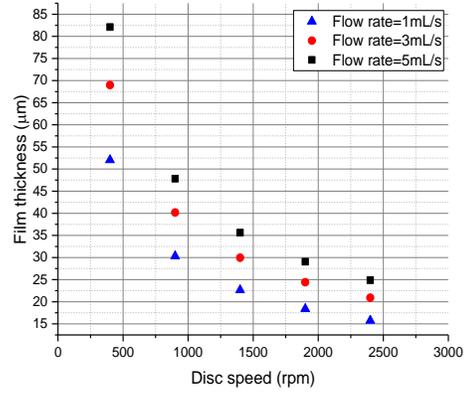
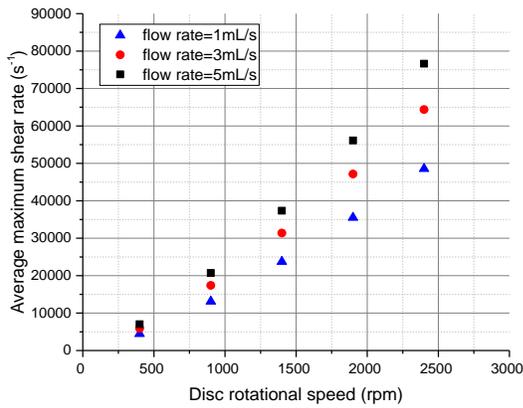


Figure 7 Effect of disc rotational speed on yield at different flow rates at 20°C.



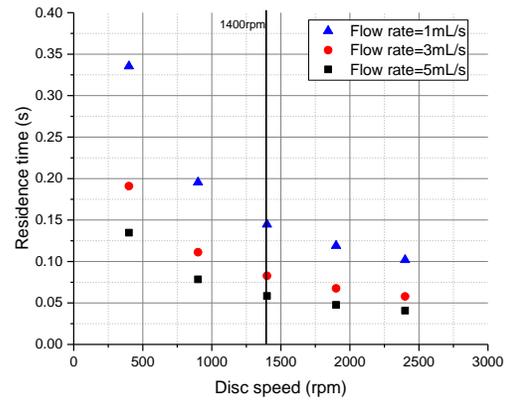
$$\delta(r) = \left(\frac{3vQ}{2\pi\omega^2 r^2} \right)^{\frac{1}{3}}$$

Figure 8 Estimated film thickness at different disc speed at constant total flow rates at 20°C.



$$\dot{\gamma}_{max,average} = \frac{1}{r_o - r_i} \int_{r_i}^{r_o} \left(\frac{3Q\omega^4}{2\pi v^2} \right)^{\frac{1}{3}} r dr$$

Figure 9 Combined effects of disc speed and flow rate on the average maximum shear rate in a thin film on the rotating disc surface at 20°C.



$$t_{res} = \frac{3}{4} \left(\frac{12\pi^2 v}{\omega^2 Q^2} \right)^{\frac{1}{3}} \left(r_o^{\frac{4}{3}} - r_i^{\frac{4}{3}} \right)$$

Figure 10 Estimated residence time at different flow rates at 20°C

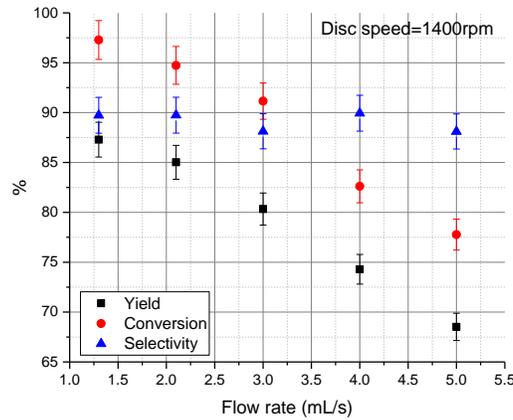


Figure 11 Effect of flow rate on the reaction at 1400 rpm and 20°C

Comparison of reactors

The stirred-tank reactor, spinning disc reactor and the T-reactor are compared based on power dissipation at 20°C in Figure 12. Both the continuous reactors have attained significantly higher yield compared to the stirred-tank reactor. This suggests that the reaction can safely be conducted at ambient temperature in suitable reactors such as the continuous flow systems studied here but it suffers from inadequate mixing in the batch system, which made over-cooling necessary. This indicates a potential for energy saving by avoiding the cryogenic temperature.

The SDR has achieved relatively high yield even at modest power dissipation of about 5 W kg⁻¹. Further increase in the power dissipation did not lead to a significant increase in the yield. In this case, it is beneficial to operate SDR at lower power dissipation/disc rotational speed. Based on the flow rate of the highest crude yield obtained in each system, the estimated throughput for T-reactor and SDR is about 3.2 tons per year (Table 1).

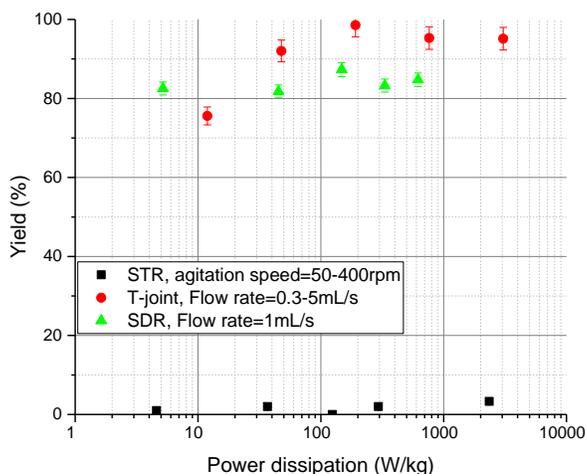


Figure 12 Effect of power dissipation on yield in the STR, SDR and T-reactor at 20°C

Ongoing and future work

Firstly, the heat transfer and temperature control of the T-reactor currently based on PTFE tubes, will be improved by replacing the PTFE sections with stainless steel T-joints, tubes and precooling reagent coils. Secondly, with a high crude yield of 99%, the ortho-lithiation reaction can be telescoped through to the subsequent reaction to minimise the workup steps. Lastly, we will demonstrate the potential green benefits (energy consumption, process mass intensity (PMI)) in the different continuous flow technologies for the whole process at industrial scale.

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