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CASE STUDY

Mitigating chemical hazards via continuous flow

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Customer
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Application
Synthesis of a nitroarene bearing an acid-sensitive functional group on a decagram scale and the safe reaction of neopentyl iodide with t-butyllithium.

Requirements
A versatile chemistry platform that gives greater control over delicate process and offered effective scale-up over traditional batch reactors, and reduced the cost and risk associated with these applications.

Solution
Syrris Asia Flow Chemistry System.

Results
Safe and successful scale-up of both processes.

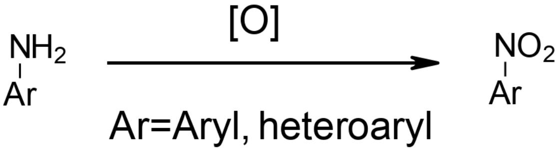
Introduction

Sygnature Discovery prides itself on offering a unique, high-quality, distinctive and tailored integrated drug discovery service to their clients. They have a proven track record of solving challenging synthetic chemistry problems in new and creative ways, opening the scope of chemical space available for projects and generating novel intellectual property.

In this case study, **Dr. Raminder Mulla, Lead Scientist at Sygnature Discovery**, presents recent work that required the use of two hazardous reagents on a considerable scale using the Asia Flow Chemistry System from Syrris. The first is mCPBA, which was employed in the oxidation of an acid-sensitive arene:

Case study 1: Oxidation of an aniline to a nitroarene

Nitroarenes can be prepared from anilines using a variety of oxidising agents (Scheme 1)[1]. For a recent synthesis of a nitroarene bearing an acid-sensitive functional group on a decagram scale, we found from screening experiments that a set of conditions using mCPBA in DCE as oxidant were the most promising for scale-up[2].



Scheme 1: An aniline to nitroarene oxidation.

Our initial risk assessment concluded that the quantities of mCPBA required (hundreds of grams) coupled with the process temperature (> 80°C) presented a substantial explosion risk,[3,4] if a conventional batch reactor were used. This prompted us to investigate a flow chemistry approach based around the Syrris Asia Flow Chemistry System.

The Asia system was selected for several key reasons: its use of open standards for fluidic fittings, which allowed easy interfacing with non-Syrris equipment; the syringe pumps' ability to handle the high back-pressures associated with superheated solvents; its comprehensive emergency cut-out features; and the highly accurate, consistent dosing of the pump heads, which we had independently validated.

To make our identified conditions better suited to flow, some adjustments were necessary: In our initial screening, we observed that a suspension was formed when running the reaction in DCE and that the reaction was slow (>10 hours before completion). Therefore, we assessed different solvents to keep the reaction completely in solution as well as higher operating temperatures to minimise the residence times required.

From solvent screens, we identified isopropyl acetate (iPrOAc) as a good solvent for our aniline and a 90:10 v/v mixture of iPrOAc and MeCN for the mCPBA used (commercial, 70wt% mCPBA). The high proportion of the iPrOAc in the reaction mixture meant that the output of any flow reaction could be continuously quenched and partitioned, thereby limiting the amount of active oxidant. Furthermore, the mixture could be superheated with a manageable back pressure that was set via an adjustable steel check valve to 6 bar (Figure 1).

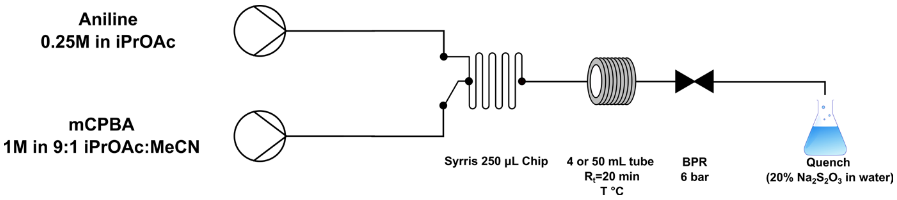


Figure 1: A representative flow system for oxidation of an aniline to a nitroarene.

With solvents defined, we deployed the Asia system to rapidly optimise our key reaction parameters with a view to scaling up: equivalents of mCPBA, operating temperature, concentration and residence time (Table 1).

Entry	[Aniline] /mol dm^{-3}	[mCPBA] /mol dm^{-3}	Equiv. mCPBA /No units	Aniline flow rate /cm^3 min^{-1}	mCPBA flow rate /cm^3 min^{-1}	Mixer	Reactor coil	T /°C	Rt /min	Analytical conversion /%
A	0.25	1	4	0.1	0.1	Syrris chip (250 µL)	Syrris tube (4mL)	125	20	100[a]
B	0.25	1	2.5	0.12	0.08	Syrris chip (250 µL)	Syrris tube (4mL)	125	20	33
C	1	2	0.99	0.13	0.07	Syrris chip (250 µL)	Syrris tube (4mL)	125	20	78[b]
D	0.05	0.2	4	0.25	0.25	Syrris chip (250 µL)	Syrris tube (4mL)	120	8	25
E	0.25	1	4	0.25	0.25	CSTR[c]	N/A	140	20	100
F	0.25	1	4	0.25	0.25	CSTR	N/A	140	20	100
G	0.25	1	4	0.5	0.5	CSTR	N/A	130	10	66
H	0.25	1	4	1.25	1.25	Syrris chip (250 µL)	50mL tube (custom)	120	20	93[d]

Table 1: Optimisation of an mCPBA-mediated aniline to nitroarene oxidation. a) Conditions nominated for scale-up as entry H. b) System blocked. c) Asynt fReactor Continuous Stirred Tank Reactor (CSTR) used. d) 83% isolated yield, prior to recrystallisation.

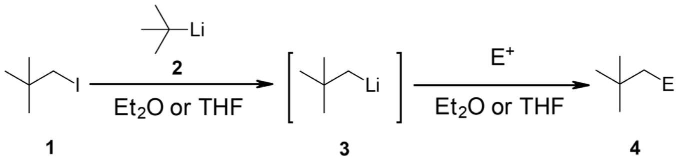
We found that a residence time of at least 20 minutes was necessary to achieve full conversion with our system even at the temperatures studied (cf. Table 1 entries A and D) and that 4 equivalents of mCPBA were required for satisfactory conversion (cf. Table 1 entries A and B). Because of blockages, increasing process concentration was not a suitable way to improve throughput (Table 1 entry C).

Equipped with this data, improving throughput for final scale-up was simply a matter of increasing flow rates while preserving the 20 minute residence time. We achieved this by moving from the Syrris 4mL tube reactor to a custom 50 mL reactor (Table 1 entry H).

Scale up was successfully run, across 10 hours, affording our nitroarene on the desired decagram scale in 83% yield after workup.

Case study 2: t-Butyllithium

Our second case study describes the safe reaction of neopentyl iodide **1** with t-butyllithium **2** (Scheme 2), a reagent with significant safety and handling concerns.[5] As part of a synthesis requiring reaction of a neopentyl organometallic with an unreactive electrophile on a decagram scale, we deemed the use of t-butyllithium necessary after attempts to generate a neopentyl organometallic that was sufficiently reactive with the electrophile using organosodium, zinc and magnesium chemistry were unsuccessful. This meant that utilisation of a more reactive organometallic, i.e. the organolithium was necessary to drive the reaction. Although neopentyl lithium **3** may be generated using lithium sand, we favoured lithium-halogen exchange given that the generation of lithium powder is not trivial.



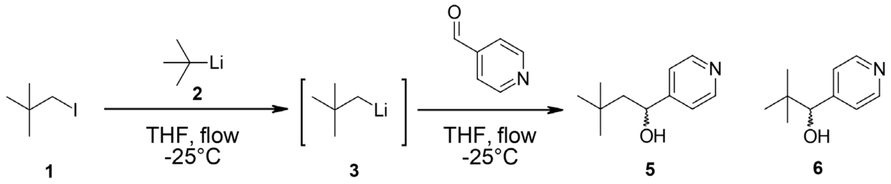
Scheme 2: Lithium-halogen exchange to generate neopentyl lithium and its reaction with an electrophile.

Even though lithium-halogen exchange to form neopentyl lithium **3** proceeded well in batch[6], subsequent reaction with our electrophile suffered from poor reproducibility, product purity and yield, meaning that handling large quantities of t-BuLi would be necessary to furnish the product in sufficient quantity for any scale-up work in batch.

At Sygnature, we routinely run organolithium chemistry in flow, finding that yields, reproducibility and scalability are improved relative to working in batch in doing so. We therefore transitioned the generation of neopentyl lithium **3** and its reaction with an electrophile into flow, hoping to avail of the same benefits that we did in previous campaigns involving organolithium chemistry. However, use of t-BuLi in flow is not well exemplified, with only a few reports of its use in flow to date[7–9]. This meant that some initial development was necessary.

To minimise the likelihood of blockage in flow, the cloud point of reaction mixtures of neopentyl iodide **1** and t-BuLi **2** in either THF or Et$_2$O were assessed in batch, allowing us to establish temperature (no lower than -30°C) and concentration (no greater than 0.15 M neopentyl iodide) limits for both solvents.

Moving into flow, we conducted some initial experiments assessing the formation of neopentyl lithium in THF as a function of t-BuLi equivalents on an aldehyde electrophile to form an alcohol (Scheme 3).



Scheme 3: Optimisation reactions reacting neopentyl lithium 3 with an electrophile to form secondary alcohols.

These experiments suggested that using 2 equivalents of t-BuLi with respect to neopentyl iodide **3** gave the most favourable ratio of neopentylation to tert-butylation (Table 2). For all experiments, including the scale-up work, we used a microfluidic mixer with a wide central channel (the LTF HTM-ST 3-1) to minimise fouling-related blockage.

Equivalents t-BuLi, 2 /No units	**T /°C**	**Neopentylated product 5**	**t-Butylated product 6**
2	-25	70	30
2.2	-25	80	20
2	20	77	23

Table 2: Neopentylation to t-butylation ratios as a function of equivalents of t-Buli delivered in flow. All ratios determined via LC-MS.

We then moved to the synthesis of our target compound which required the use of a different electrophile. In doing so, we committed to the use of 2 equivalents of t-BuLi with respect to **1**, and proceeded to assess the effect of process temperature and solvent on crude product purity. We also found that using diethyl ether in place of THF improved the reaction profile, but reaction with the electrophile took longer. We also found that the reaction profile was the same when the run at -25°C or 0°C meaning that simple cooling of our reactor under ice was sufficient for our process.

The Asia system was nominated for our scale-up work because of its open framework, the ability to dose t-BuLi directly from the bottle and comprehensive safety features like the ability to stop dosing all reagent streams in case of blockage. In combination with the leak and air-tight valve system the Asia syringe pump provided a good basis of safety. The open framework allowed us to make a few modifications to the liquid lines to prevent exposure of active, pyrophoric t-BuLi to air for the final process (Figure 2).

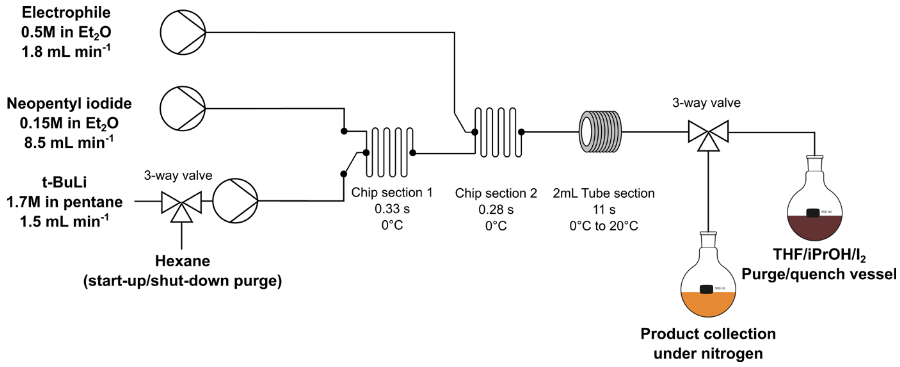


Figure 2: Flow diagram for a t-BuLi mediated lithium halogen exchange using the Syrris Asia system. Key integrations into the fluid path include a hexane purge line for priming and decontamination use, and separate collection and quench vessels for streams that could contain active organometallic.

Scaling up was a simple matter of running the system for longer periods than were used for the test chemistry. Shut-down after runs were complete was trivial due to the almost complete infusion of the contents of each syringe mounted to the Asia pump making for efficient purging of the residual reagents with hexane, an inert solvent, allowing for a highly controlled, productive synthesis.

References

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Dr. Raminder Mulla shown with Sygnature Discovery's Asia Flow Chemistry System.

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