



BIOPHARMA

Advanced Optimization of Photochemical Reactions Using Flow Chemistry Reactor and Benchtop NMR

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Innovation with Integrity

This white paper showcases effective monitoring and optimization of a photochemical transformation via a Syrris Asia Flow Chemistry System and an in-line Bruker Fourier 80 benchtop nuclear magnetic resonance (NMR) spectrometer. The combination of instrumentation is a powerful framework that enhances and streamlines reaction optimization to improve product yield, which is demonstrated with the flow photooxygenation of 1,5-dihydroxynaphthalene to obtain Juglone. The precise control over reaction parameters from the flow chemistry system used and the real-time monitoring of the reaction from in-line NMR analysis led to more reliable and efficient fine-tuning of reaction parameters and output. The results from this reaction optimization demonstrate the value of integrating benchtop NMR into process chemistry development for improved process control and optimization.

1 Introduction

1.1 Flow Chemistry

Flow chemistry offers a unique approach to chemical and pharmaceutical development and manufacturing. Reactions using flow chemistry take place in a continuous flowing stream where reactants and solvent are pumped through a flow reactor, which improves the precision of reaction parameter controls, throughput efficiency, operational safety, and manufacturing scalability. The evolution of flow chemistry has therefore helped unlock unprecedented advancements in process chemistry that are difficult or unsafe to achieve in traditional batch reactions. High-temperature and high-pressure conditions, for example, can be precisely controlled in flow systems, enabling reactions that were previously impractical, unsafe, or even impossible^{1,2}. The expansion of operational parameters allows chemists to access faster, more selective, and often more environmentally friendly reactions. The surge in related published works highlights the rapid expansion of flow chemistry and scope of synthetic possibilities as new protocols are released on a regular basis. This trend reflects not only growing academic interest in flow chemistry but also increasing adoption in industrial settings, where flow processes are leveraged for their scalability, efficiency and cost-effectiveness^{1,3}.

The field of **Flow Photochemistry**, as an extension of flow chemistry that incorporates photochemistry principles and offers similar advantages over traditional batch photochemical methods, specifically its precise control over reaction parameters. In flow photochemical reactors, uniform light distribution and precise exposure times ensures consistent reactions and minimizes degradation and side reactions. For instance, accurate wavelength selection from

monochromatic LED light sources results in better reaction selectivity and yields.⁴ Additionally, the increased reaction rates and throughput from optimized photon flux flow systems offer more efficient and more environmentally favorable processes because of the improved heat management and scalability, which is consistent with **Green Chemistry** principles^{1,2,5}.

A valuable, comprehensive setup for performing flow chemistry and photochemistry reactions is the **Syrris Asia Flow Chemistry System**. This equipment provides a full platform for standard operations, such as reaction optimization and scale-up, as well as advanced applications, including electrochemistry, photochemistry, multi-step reactions and reactions at cryogenic temperatures. Users benefit from precise control over reaction parameters, which ultimately delivers efficient and reliable synthesis across a wide range of chemical processes. This capability, coupled with automated control and data collection functionalities, makes the Syrris Asia Flow Chemistry System an invaluable tool for both research and industrial applications, especially when high precision and scalability are required.

1.2 Flow Chemistry Analytics

Analyzing reaction mixtures in continuous flow synthesis is necessary to understand the reaction progress and deviations from the ideal trajectory. In laboratory-scale experiments, the most common method is **off-line** analysis where reaction aliquots are extracted from the bulk mixture to be examined elsewhere using techniques like gas chromatography (GC), high-performance liquid chromatography (HPLC) or nuclear magnetic resonance (NMR).² However, off-line measurements insufficient for real-time understanding of reaction kinetics and mechanisms, maintaining continuous process quality control, and dealing with reactive or toxic intermediates. For these operations and for more precise process optimization, on-line or in-line analysis methods are recommended. **On-line** analysis involves periodic automated sampling and transfer through a flow system to analytical instruments, such as HPLC, GC, mass spectrometers, fluorescence spectrometers, or NMR spectroscopy.² **In-line** analysis allows for the probe of a non-destructive analytical instrument (e.g. infrared, Raman, UV-vis or NMR spectroscopy) to be placed directly within the flow process for real-time assessments.²

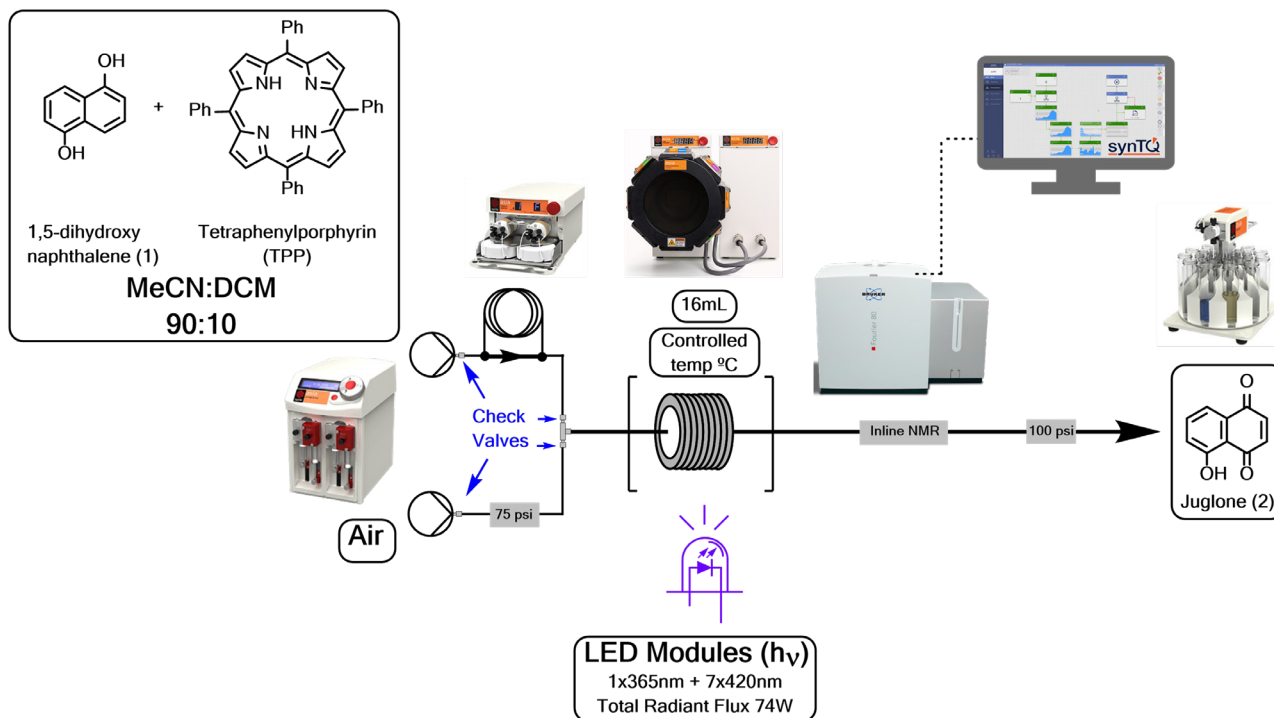
The **Bruker Fourier 80 benchtop NMR** is one such tool spectrometer that can be extremely valuable for flow chemistry analysis because it delivers high-quality structural and quantitative data with better resolution than in-line Raman and IR spectrometers. Additionally, NMR can be used to calibrate other techniques for more efficient quantitative measurements because it does not need to be tediously calibrated like other spectroscopic and chromatographic techniques. The instrument can be installed in standard laboratory environments, including fume hoods and benches, without the need for expensive infrastructure, cryogenics, or complex installation procedures. These features, combined with an intuitive and user-friendly setup, drive the accessibility of NMR and facilitate its integration into process laboratories. In effect, the Bruker Fourier 80 benchtop NMR enables operators to perform detailed molecular analysis without requiring specialized training.

The simple addition of **an InsightMR Flow Unit** to the Bruker Fourier 80 NMR, part of the compact **Fourier RxnLab** setup, enables on-line or in-line NMR measures for enhanced real-time monitoring of chemical processes. providing, i.e. on a bench or the fume hood. As a result, process chemists can benefit from fast, reliable, and actionable insights of the reaction kinetics next to where the reaction is happening for effective and informed decision-making, which ultimately reduces downstream risk and costs. Additionally, the system streamlines the analytical process by generating on-the-fly quantitative concentrations curves of the reaction components without the need for time-consuming calibrations.

While flow chemistry and benchtop NMR technology can support efficient and in-depth process and product understanding, these can be further enhanced through the adoption of a Process Analytical Technology (PAT) framework. A PAT knowledge management and orchestration software facilitates the creation of datasets, analytical insights, predictive models and advanced control systems. This framework connects analytical instruments (e.g., NMR spectrometer), sensors, reaction condition control systems, and statistical analytical software within a unified environment to synchronize their data streams in a single interface for comprehensive key process and product insights. synTQ is a leading process analytical technology (PAT) software platform designed to facilitate real-time data acquisition, analysis, and control in manufacturing and research environments. Bruker offers a complete PAT solution through its synTQ-based **Fourier PAT** to help NMR users optimize real-time monitoring and data-driven decision-making.

1.3 Evaluating the synergy between flow chemistry and in-line NMR

This study was designed to evaluate the effectiveness of a flow chemistry system and a benchtop NMR spectrometer for real-time monitoring and control of a photochemical reaction. Complementary high-field NMR measurements will be conducted to demonstrate that the benchtop instrument provides comparable information. The objective is to use this combination of technologies to drive process optimization and improve product quality. The model reaction used as a case study was a photooxygenation reaction of 1,5-dihydroxynaphthalene (**1**) to obtain the natural product Juglone (**2**)⁶ through real-time process analysis via a flow Bruker RxnLab Fourier 80 spectrometer (**Scheme 1**). In addition, the study aimed to demonstrate the ability to fine-tune reaction parameters of the Syrris Asia Flow Chemistry System from real-time NMR analytics to improve product yield.



Scheme 1. Fluidic setup for the synthesis of juglone (**2**).

2 Methodology

This study was carried out in collaboration with **Syrris** (www.syrris.com), **DReaM Facility** (<https://www.bath.ac.uk/research-facilities/dynamic-reaction-monitoring-facility/>) at the **University of Bath** under coordination of **Dr. Ulrich Hintermair**, and **Bruker Biospin** (www.bruker.com).

The fluidic setup used in this study is shown in **Scheme 1** and **Figure 1**. Tetraphenylporphyrin was used as a photocatalyst⁶ and aliquots of the reagent solution were injected using an Asia Reagent Injector. The Asia Pump was used to deliver a mixture of acetonitrile and dichloromethane (MeCN:DCM 90:10) (carrier fluid) and atmospheric air (source of O₂). The Asia Reagent Injector (RIM) was used to introduce aliquots of the reagent solution (10 mL) into the fluidic network, which were then combined with the carrier solvent and air using the Asia Gas Introduction kit. The reaction mixture passed through the Asia Photochemistry Reactor into the 16 mL Asia Tube Reactor and exposed to 1x365 nm and 7x420 nm LED modules housed on the Asia Cryo Controller. A residence time of 16 min to 128 min and the temperature at 25°C and 75°C were evaluated against the product yield. The outlet of the reactor was directed to the Fourier 80 flow cell and resonances of ¹H were recorded at 80 MHz to track the quantity of reactants and product. Reaction slugs were collected using the Asia Product Collector. Note that IDEX check-valves were positioned according to **Scheme 1** and used to prevent back flow while ensuring the pressurization of the system. In-line analyses were carried out with both a Bruker 80 MHz and 500 MHz NMR spectrometers using an internal standard (dimethylsulfone) for the quantitative investigation of the substrate and product of the photochemical reaction.

The methodologies adopted for this research are based on a protocol described by De Oliveira *et al.*, 2016.⁷

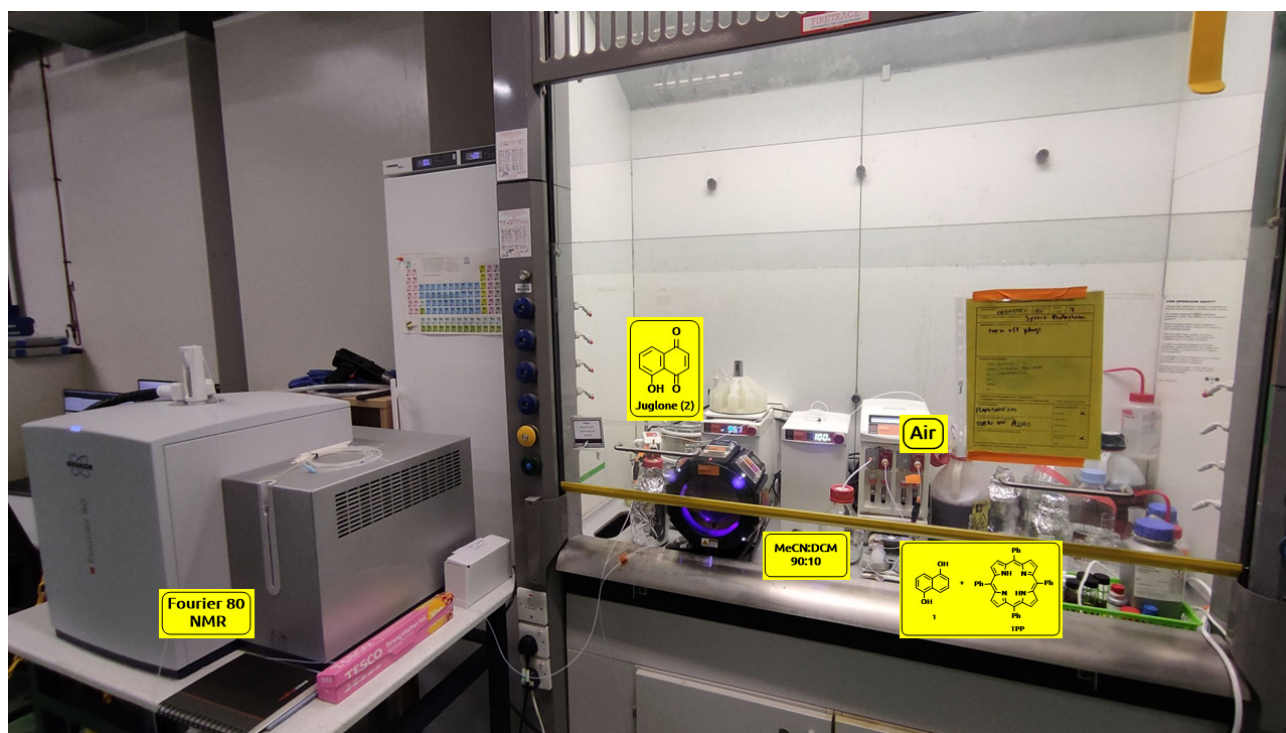


Figure 1. Fluid setup for the photooxygenation reactions.

A series of eight experiments were conducted using the Asia Photochemical Reactor for method development and optimization purposes. Light intensity was adjusted by varying the power of LED modules at 0, 50 and 100%. The residence times were varied by changing the substrate flow rates while atmospheric air was pumped constantly at 1500 µL/min. The temperature was altered by turning off the Cryo controller and allowing the incident light from the LED Modules to raise the temperature of the reactor. In this case, the temperature rose up to 75°C and stabilized after 40 min. Negative controls of the reactions were performed without irradiation, oxygen or catalyst.

The reactions conditions are shown in **Table 1**.

a) 1x365 nm+7x420 nm

b) No catalyst

Entry	LED Modules Power (%) ^(a)	Total Radiant Flux (W)	Temperature (°C)	Substrate Flow rate (μL/min)	Air Flow Rate (μL/min)	Residence Time (min)
A	100	74	75	1000	1500	16
B	100	74	25	500	1500	32
C	100	74	75	500	1500	32
D ^(b)	100	74	75	500	1500	32
E	100	74	75	500	0	32
F	50	37	75	500	1500	32
G	0	0	75	500	1500	32
H	100	74	75	250	1500	64
J	100	74	75	125	1500	128

Table 1. Experimental conditions used for reaction optimization.

2.1 Experimental

Stock solutions were prepared by dissolving TPP (5.8 mg; 0.009 mmol; 0.003 eq.) in DCM (10 mL). This was then added to a solution of substrate **1** (515 mg; 3.2 mmol, 1.0 eq.) and dimethylsulfone (630 mg; 6.69 mmol) in MeCN (90 mL). Thus, the stock solution contains [substrate] = 32.2 mM and [dimethylsulfone] = 66.9 mM

For each experiment, 10mL were introduced into the sample loop of the Asia Reagent Injector. The reaction was carried out by pumping MeCN:DCM (90:10) and air according to the specific residence times.

2.2 NMR acquisition

Low-field NMR spectra were recorded using a Bruker Fourier 80 MHz NMR with z-gradients and a probe with dedicated ¹H and ¹³C channels, while high-field NMR spectra were acquired using a Bruker 500 MHz Avance III HD Ultrashield equipped with a nitrogen-cooled BBO Prodigy CryoProbe. The reaction monitoring software used was InsightMR 2.0, while data processing was performed with TopSpin 4.4.1 and Dynamics Center 2.8.3. synTQ 5.1 PAT knowledge management platform connected to an NMR adapter was used as the orchestration software. For low-field NMR acquisition in flow conditions, ¹H NMR experiments were interleaved in each cycle and continuously executed every 2 minutes (wetdc: NS = 32, D1 = 1 s, RG = 1, L30 = 1, O1P = 4.7 ppm, SW = 40 ppm, Expt = 1 min 32 s). For high-field NMR acquisition in flow conditions, ¹H NMR experiments were also interleaved in each cycle and continuously executed every 2 minutes (zg30: NS = 16, D1 = 1 s, RG = 1, L30 = 1, O1P = 6.175 ppm, SW = 40 ppm, Expt = 52 s). Static calibration spectra were recorded for both frequencies (80 MHz and 500 MHz) with the same parameters as flow conditions but with a longer D1 of 45 s for ¹H NMR spectra.

The ¹H NMR 80 MHz and 500 MHz spectra were analyzed with Topspin models to effectively detect the NMR peaks for raw materials, i.e. naphthalene and juglone products (**Figure 2, 3 and 4**). A difference in resolution was observed, with the 80 MHz NMR showing lower yet sufficient resolution, particularly with overlapping aromatic peaks. The 500 MHz NMR provided higher resolution and better separation.

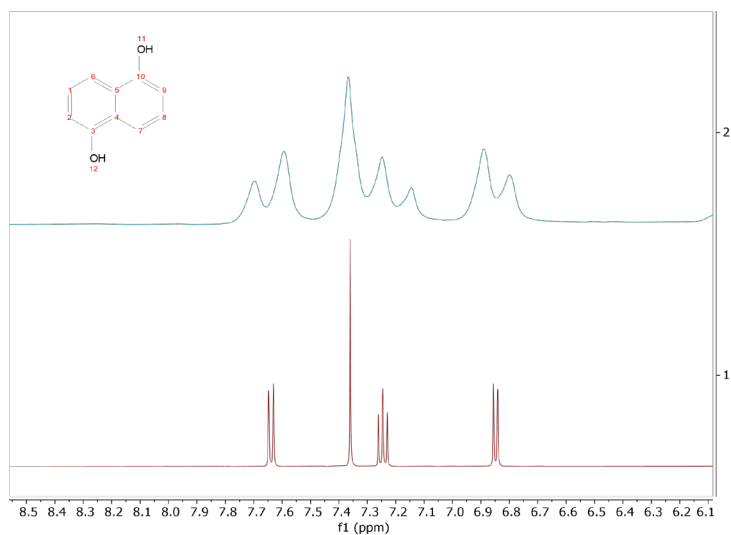


Figure 2. 500 and 80 MHz ¹H NMR spectra of 1,5 dihydroxynaphthalene (**1**) in non-deuterated MeCN:DCM (90:10) under air at 25°C. The red spectrum was recorded at 500 MHz while the blue one was recorded at 80 MHz.

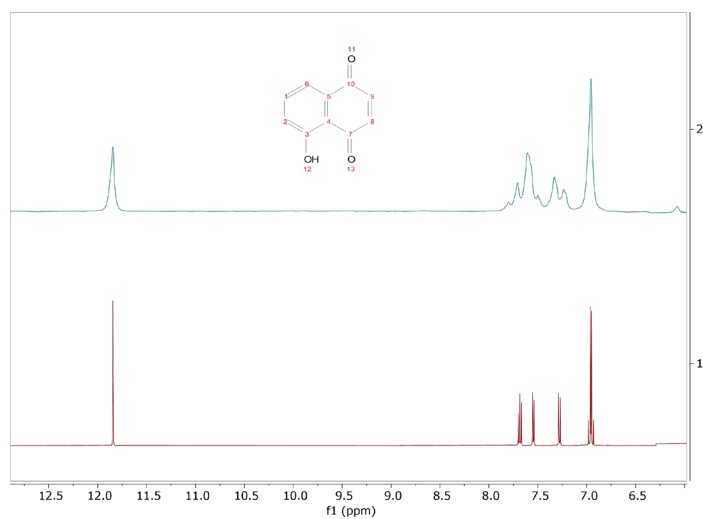


Figure 3. 500 and 80 MHz ¹H NMR spectra of Juglone in non-deuterated MeCN:DCM (90:10) under air at 25°C. The red spectrum was recorded at 500 MHz while the blue one was recorded at 80 MHz.

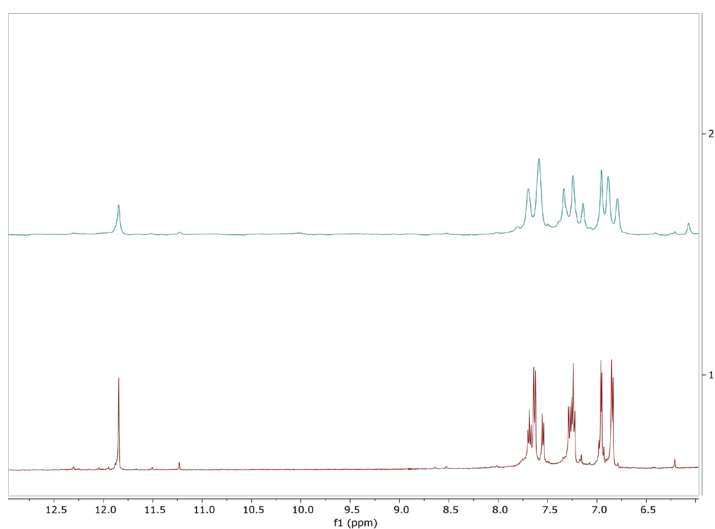


Figure 4. 500 and 80 MHz ¹H NMR spectra of a reaction mixture in non-deuterated MeCN:DCM (90:10) under air at 25°C. The red spectrum was recorded at 500 MHz while the blue one was recorded at 80 MHz.

To monitor the reaction progress, it was necessary to isolate the substrate and product signals for peak integration calculations. The alcohol peak in the juglone spectrum was well-suited for this purpose (**Figure 3**). However, unless the reaction was complete no single peak could be integrated in the naphthalene spectrum (**Figure 2**). The following approach was applied to determine the concentration of naphthalene from peak integration: The total integral of aromatic protons (I_{Ar}) includes contributions from both naphthalene and juglone, while the integral of the alcoholic peak in juglone (I_{OH}) serves as a reference (**Figure 4**). Naphthalene contains 8 aromatic protons, and juglone contains 5 aromatic protons. The juglone OH peak is unique, meaning its integral can be directly correlated with the amount of juglone in the sample. Since the ratio of aromatic to OH protons in juglone is 5:1, the aromatic contribution from juglone can be calculated as $I_{Ar, Juglone} = 5 \times I_{OH}$. To isolate the contribution from naphthalene, the juglone's aromatic contribution is subtracted from the total aromatic integral: $I_{Ar, Naphthalene} = I_{Ar} - I_{Ar, Juglone}$. Since naphthalene has 8 aromatic protons, the concentration of naphthalene is determined by dividing the aromatic integral contribution from naphthalene by 8: $I_{Ar, Naphthalene}/8$.

Quantitative FlowNMR analysis:

Quantitative FlowNMR analysis involved correcting flow effects resulting from different degrees of pre-magnetization by comparing integral values from flow spectra with static reference measurements (**Figure 5**). A correction factor was calculated for each peak by comparing the integral under static and flow conditions. This correction factor was then used for quantitative analysis: $CF = I_{flow}/I_{static}$ and $I_{corrected} = CF \times I$, where I is the integral area of the peak, CF is the correction factor, and N is the number of nuclei contributing to the peak.

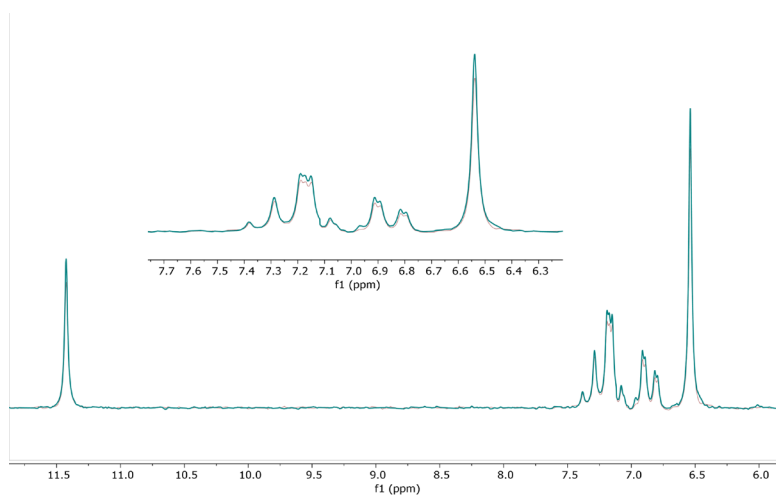


Figure 5. 80 MHz ^1H NMR spectra of 1,5 dihydroxynaphthalene (**1**) in non-deuterated MeCN:DCM (90:10) under air at 25°C. The red spectrum was recorded at 0 mL/min while the blue spectrum was acquired at 1 mL/min.

4. Results

4.1 Effect of Residence Time, Temperature and Light Intensity

During the reactions, the Fourier 80 was directly connected to the reactor (**Scheme 1**). Reagent injections were carried out in 10 mL increments. The reaction volume was monitored by observing a fraction of the solution passing through the spectrometer. The remaining fraction consisted solely of the solvent, which was continuously pumped (**Figure 6**).

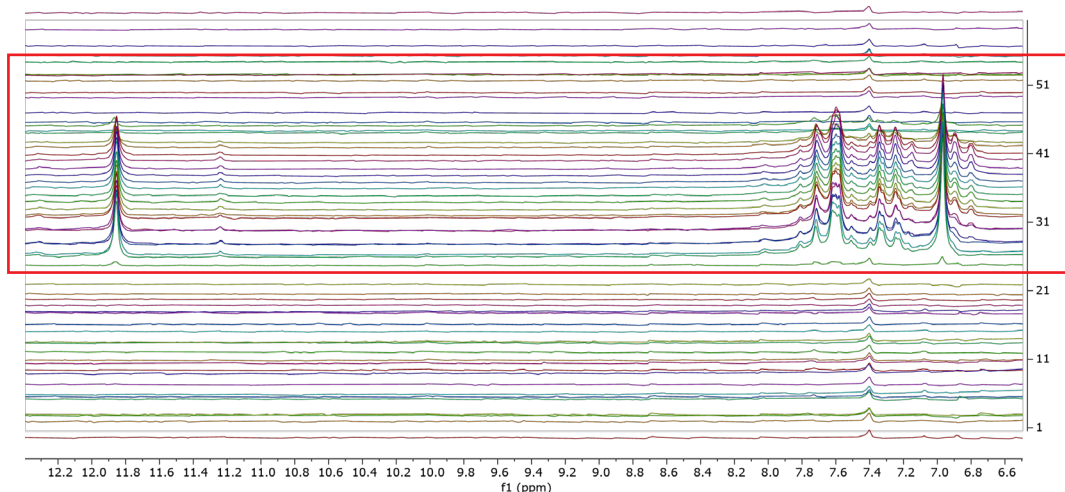


Figure 6. 80 MHz ^1H NMR spectra of a 10 mL plug reaction mixture in non-deuterated MeCN:DCM (90:10) under air at 25°C.

When investigating the effect of temperature on the reaction, the NMR data revealed that temperature played a crucial role in the reaction conversion when residence time and light intensity were held consistent. 75°C was identified as the optimal temperature, providing the best conditions for the reaction without causing side reactions or degradation. (**Figure 7**).

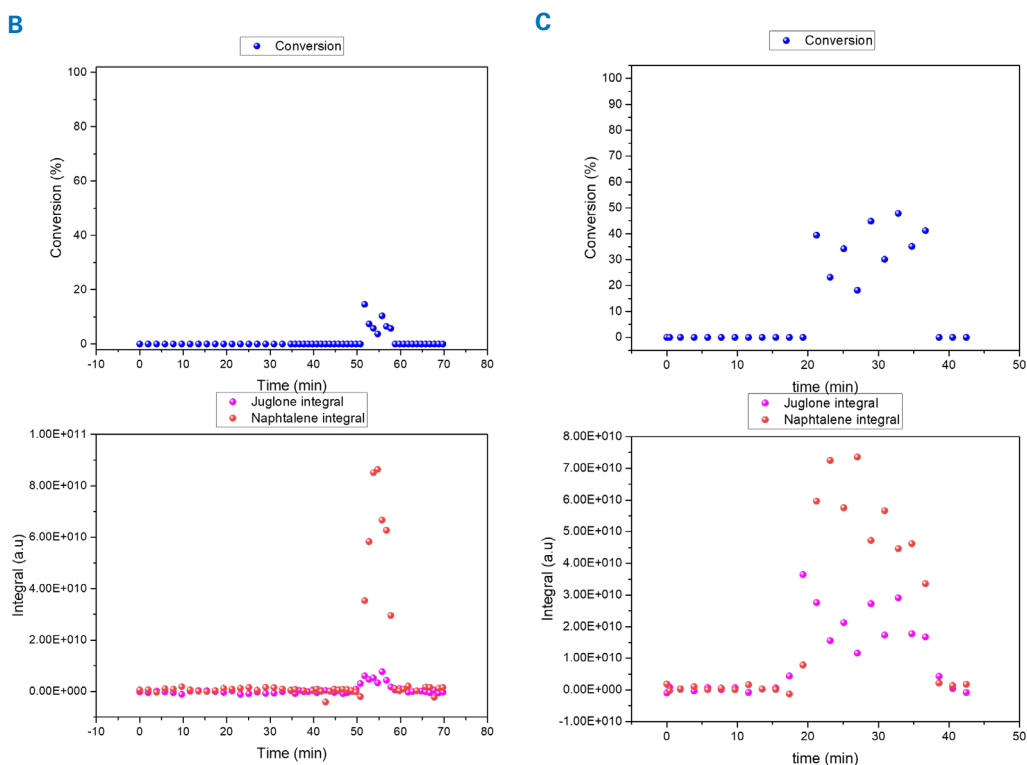


Figure 7. Conversion and integral area of the peak were determined using the Fourier 80 NMR under residence time (32 min) and light intensity (74 W), at 25°C (**B**) and 75°C (**C**).

The effect of residence time was investigated by varying the pump flow rate at 0.125, 0.25, 0.5 and 1 mL/min. As expected, a longer residence time resulted in a higher conversion of naphthalene to juglone. However, the optimum conditions were achieved at a flow rate of 0.25 mL/min, as conversion remained high while the production rate of juglone was high (**Figure 8**).

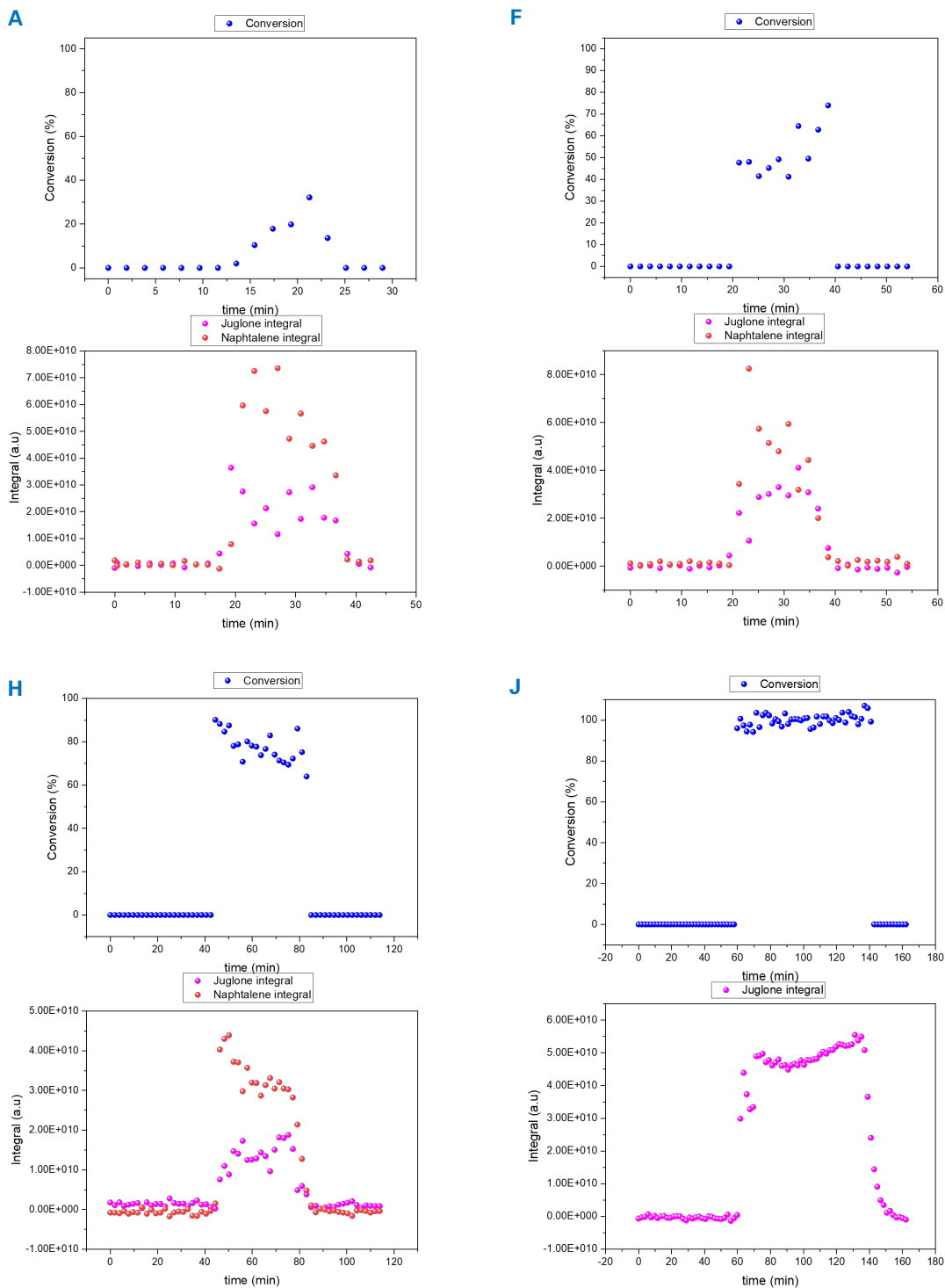


Figure 8. Conversion and integral area of the peak were determined using the Fourier 80 NMR in experiments conducted under temperature (75°C), light intensity (74 W) and 1, 0.5, 0.25 and 0.125 mL/min (**A-F-H-J** respectively)

Experiments were conducted to assess the influence of oxygen, porphyrin and light on the reaction. The absence of light had the most significant impact, as no reaction could occur without it. Since oxygen is a key reactant with naphthalene, no conversion was expected in its absence. However, a 5% conversion was still observed. This was likely due to dissolved molecular oxygen in the solvents. Porphyrin had a minor effect, as the reaction proceeded with a substantial conversion (~40%). This suggests that while the co-catalyst accelerates the reaction, it is not the primary factor in its effectiveness (**Figure 9**).

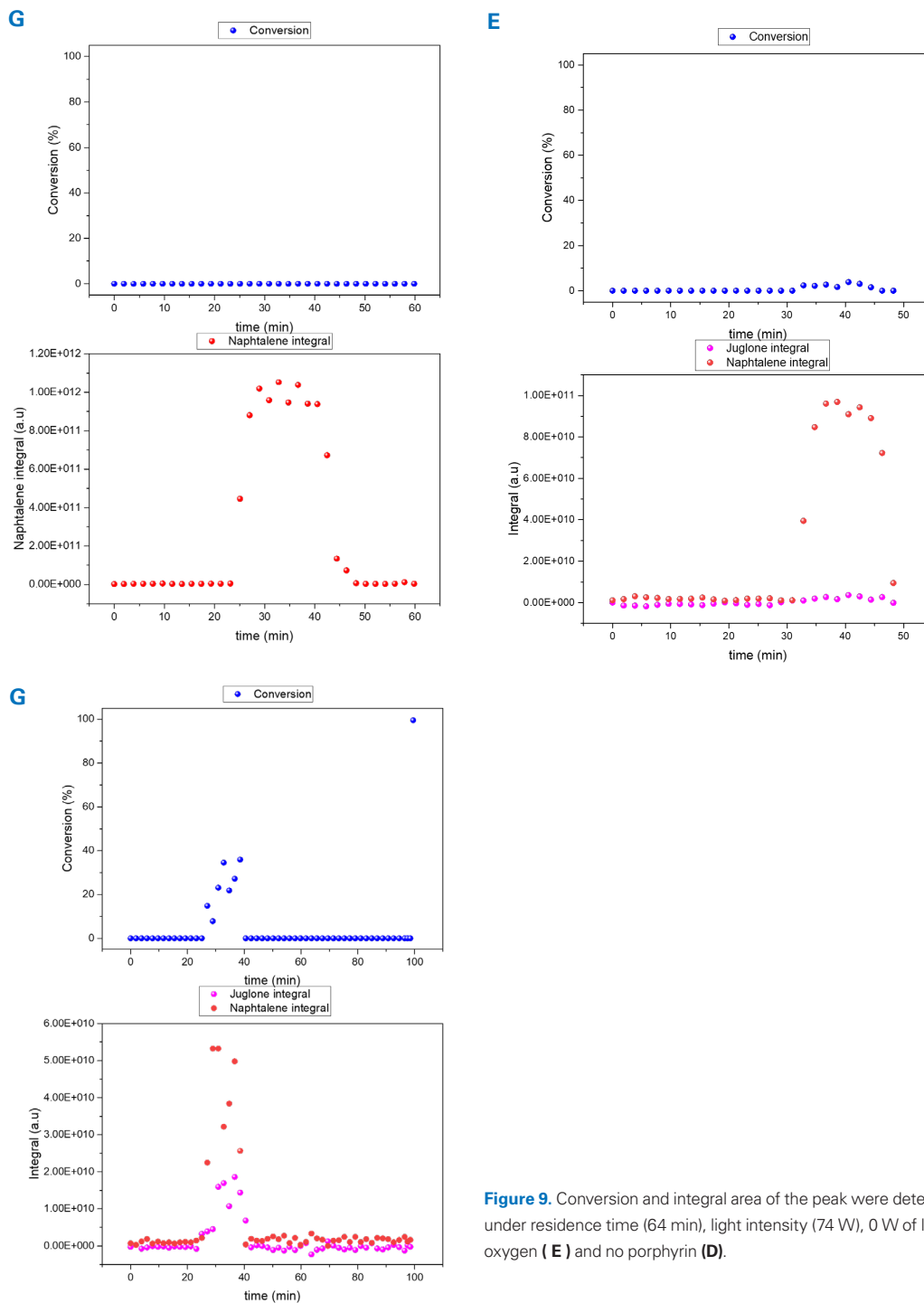


Figure 9. Conversion and integral area of the peak were determined using the Fourier 80 NMR under residence time (64 min), light intensity (74 W), 0 W of light intensity (**G**), 0 mL/min of oxygen (**E**) and no porphyrin (**D**).

Furthermore, the comparison of the 500 MHz and 80 MHz NMR spectra highlighted how the two analyses were aligned and confirmed the same conclusions (**Figure 10**). This demonstrated the ability of the Bruker benchtop NMR system to support accurate continuous monitoring. The 500 MHz high-field NMR provided higher resolution and sensitivity, which is ideal for detailed structural elucidation and complex mixture analysis. However, the 80 MHz benchtop NMR, despite its lower resolution, was able to produce consistent and reliable data that matched the high-field results. This consistency underscores the robustness of the benchtop system for real-time process monitoring, making it a valuable tool for continuous flow chemistry applications.

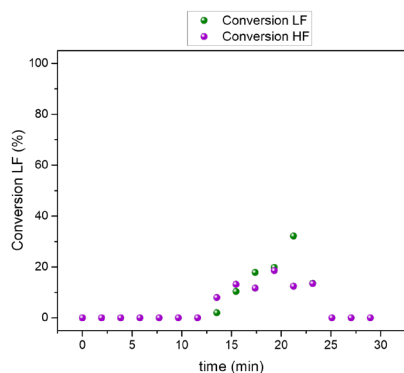


Figure 10. Conversion and integral area of the peak were determined using two NMR instruments: the Fourier 80 and 500 NMR. Spectra were collected under constant residence time (64 min) and light intensity (74 W). LF: Low Field (80 MHz), HF: High Field (500 MHz).

The results obtained from the investigations on the effects of temperature, residence time and light revealed that optimum conditions for reaction productivity are found at 75°C, 74 W light intensity and 64 min of residence time.

5 Conclusions

The study successfully demonstrated how the use of the Bruker Fourier 80 for in-line NMR analytics can support state-of-the-art monitoring and optimization of flow chemical transformations carried out through Syrris Asia Flow Chemistry System reactors. By varying reaction parameters, such as residence time, temperature and light intensity, significant changes in the reaction profile were observed. This work highlights the effectiveness of combining flow chemistry with benchtop NMR for real-time monitoring and optimization. Therefore, this setup provides a powerful and accessible tool for process chemists looking for a compact yet accurate setup to make data-driven strategic decisions that minimize downstream risks and costs.

While it is beyond the scope of this study, it is possible to infer that the use of PAT can enhance the capabilities of the combined flow chemistry setup up, advancing the responsiveness and accuracy when controlling the photochemistry reactions. As a result, users can further optimize cost-reductions, quality, and environmental footprint of their operations.

If you require assistance or further explanation, please contact flow@syrris.com and/or insightMR@bruker.com.

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