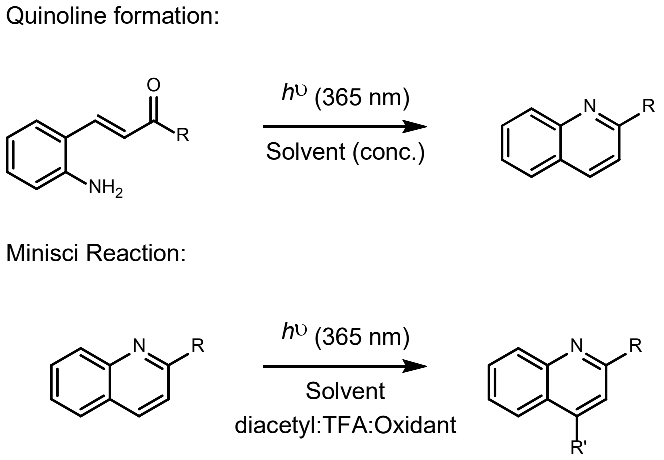
Solstice™ Application Note 34:



Scheme 1 – Reaction schemes for the photochemical quinoline formation and Minisci reaction.

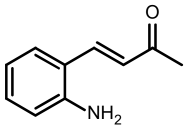
Introduction:

Commercial benchtop photoreactor packages offer users the ability to expedite the translation from batch to continuous flow. **Uniqsis** have developed the Solstice™ 12-position batch (***Fig 2.***) and Borealis Flow™ continuous flow (***Fig 3.***) devices to enable fast optimisation workflows and scalable photochemistry.

Direct absorption of reagents is the most straightforward photochemical pathway, and this area of research is continually expanding for constructing novel and known heterocyclic molecules. In this application note we show how the batch 12-position photoreactor was used to screen optimal conditions for two photochemical transformations: Quinoline formation and a Minisci reaction. Using a 365 nm lamp, optimal conditions for solvent and concentration were quickly evaluated using the batch reactor. These optimal conditions were carried forward in continuous flow to allow for scale up of the processes, presented also is a comparison between batch and flow in terms of productivity.

Method:

For the quinoline formation reaction the model substrate chosen is shown below in *Figure 1.*



Scheme 2 – model substrate (E)-4-(2-aminophenyl)but-3-en-2-one.

Unless otherwise stated, cooling was monitored directly using a digital thermometer (K-type coupling). For the batch reactions the digital thermometer probe fed into one of the reaction tubes (filled with solvent) to give the most accurate temperature reading. For the flow experiments, the thermometer recorded the temperature of the coil housing and is positioned as close as possible to the reactor tubing to afford an accurate measure of the flow reaction temperature. The temperature was controlled by altering the water flow rate provided by the house supply.

Optimisation experiments for quinoline formation reaction:

(E)-4-(2-aminophenyl)but-3-en-2-one (0.15 mmol, 24.2 mg) was charged into separate 8 mL reaction tubes equipped with a stir bar. To each tube was added acetonitrile, acetone, or ethanol (50 mM, 3 mL). These solutions were placed inside the Uniqsis Solstice multi-position photoreactor (***Fig 2.***) and irradiated with a 365 nm lamp (input power set to 60%; 72 W) for the stated reaction time, cooling was provided by the house water supply with the reactor and lamp connected in series. The solvent was then removed under reduced pressure and quantitative ^{1}H-NMR analysis was performed.

Optimisation experiments for Minisci reaction:

Quinaldine (50 mM, 250 mM, or 500 mM) was charged into separate 8 mL reaction tubes with a stir bar with the volume fixed at 3 mL. These solutions were placed inside the Uniqsis Solstice multi-position photoreactor (***Fig 2.***) and irradiated with a 365 nm lamp (input power set to 60%; 72 W) for the stated reaction time, cooling was provided by the house water supply with the reactor and lamp connected in series. The solvent was then removed under reduced pressure and quantitative ^{1}H-NMR analysis was performed.

Continuous flow method for quinoline formation reaction:

(E)-4-(2-aminophenyl)but-3-en-2-one (2.5 mmol, 403 mg) was dissolved in EtOH (10 mL, 0.25 M). This was then pumped through the Borealis photoflow reactor (***Fig 3.***) at a flow rate of 1 mL min^{-1} (reactor volume 15 mL) using syringe pumps. One syringe pump delivered the reaction solution while the second contained only solvent to finish the delivery of reaction mixture, both solutions met at a T-piece with non-return valves. The output stream was collected, concentrated *in vacuo* and quantitative ^{1}H-NMR analysis was performed.

Continuous flow method for Minisci reaction:

Quinaldine (2.5 mmol, 358 mg) was dissolved in THF (10 mL, 0.25 M). This was then pumped through the Borealis photoflow reactor (***Fig 3.***) at a flow rate of 1 mL min^{-1} (reactor volume 15 mL) using syringe pumps. One syringe pump delivered the reaction solution while the second contained only solvent to finish the delivery of reaction mixture, both solutions met at a T-piece with non-return valves. The output stream was collected, concentrated *in vacuo* and quantitative ^{1}H-NMR analysis was performed.

Results:

All yields were calculated vs. 1,3,5-trimethoxybenzene as the internal reference standard and representative ^{1}H-NMR spectra were used for quinoline and Minisci product confirmation.[1]

Quinoline formation optimisations:

Initially, lamp input power was investigated, and the results are shown below in *Table 1*.

Table 1 – Lamp input power screen, 50 mM reaction concentration at 3 mL scale, EtOH as the solvent, reaction irradiated for 21 h, reactor temperature 10°C – 15°C (monitored digitally – see method for details).

Entry	Lamp input power (W)	^{1}H-NMR Yield
1	24	77
2	72	**83**
3	120	59

72 W input power (**Entry 2**) gave the best results, and all proceeding optimisation reactions used this power level. Reducing the power (**Entry 1**) resulted in lower conversion, whereas higher power (**Entry 3**) decomposed some of the product.

The optimal solvent and concentration were evaluated, and the results are shown below in *Table 2* and *Table 3* respectively.

Table 2 – Solvent screen, 50 mM reaction concentration at 3 mL scale, 60% input power (72 W), reaction irradiated for 21 h, reactor temperature (monitored digitally – see method for details) 10°C – 15°C .

Entry	**Solvent**	**^{1}H-NMR Yield**
1	Acetonitrile	61
2	Acetone	54
3	EtOH	**83**

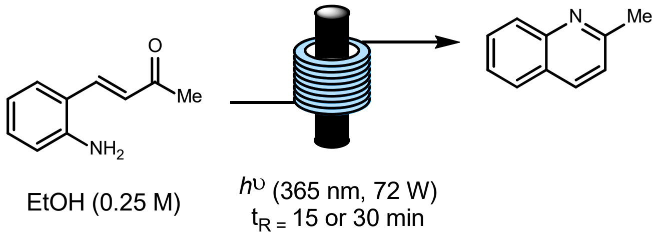
Ethanol (**Entry 3**) proved to be the optimal solvent for this reaction, with acetonitrile and acetone (**Entry 1** and **2**, respectively) giving lower yields of the desired product.

Table 3 – 3 mL scale, acetonitrile as the solvent, 60% input power, reaction irradiated for 21 h, reactor temperature (monitored digitally – see method for details) 10°C – 15°C.

Entry	**Conc (mM)**	**^{1}H-NMR Yield**
1	25	43
2	100	48
3	250	**65**

Continuous flow scale up (2.5 mmol):

(E)-4-(2-aminophenyl)but-3-en-2-one was taken and subjected to the optimised conditions for the photochemical quinoline formation, results shown below in *scheme 2*.



Entry	t_R (min)	Flow rate (mL min^{-1})	NMR Yield (%)
1	15	1.0	32
2	30	0.5	55

Scheme 2 – Continuous flow reaction for the formation of quinolines under UV-A absorption, see method for more information.

Comparison of batch and continuous flow:

Based on the above results, a comparison of batch and flow was carried out at an equal reaction/residence time of 15 minutes, a longer residence time at a lower flow rate was also trialled. The results are presented below in table 4.

Table 4 – Flow conditions for entry 1 see method section. Batch reaction conditions were 3 mL volume, 0.25 M concentration in EtOH, 60% lamp input power, reaction was irradiated for 15 minutes, reactor temperature (monitored digitally – see method for details) 10°C – 15°C.

Entry	**Reaction mode**	**^{1}H-NMR Yield**	**Spacetime yield (mol L^{-1} day^{-1})**	
			t_R = 15 min	**t_R = 30 min**
1	Continuous	32	7.68	6.60
2	Batch	28	0.0108	

Minisci reaction optimisations:

Initially, lamp input power was investigated, and the results are shown below in *Table 5*. Similarly, the optimal input power was 72 W with higher and lower giving more decomposition and lower conversion, respectively.

Table 5 – Lamp input power screen, 50 mM reaction concentration at 3 mL scale, reaction irradiated for 21 h, reactor temperature (monitored digitally – see method for details) 10°C – 15°C.

Entry	**Lamp input power (W)**	**^{1}H-NMR Yield**
1	24	34
2	72	**56**
3	120	36

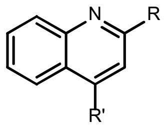
Concentration (mM) was optimised in batch and their results are shown below in *Table 6*.

Table 6 – 3 mL scale, THF as the solvent, 60% input power, reaction irradiated for 21 h, reactor temperature (monitored digitally – see method for details) 10°C – 15°C.

Entry	**Conc (mM)**	**^{1}H-NMR Yield**
1	50	56
2	250	**85**
3	500	71

Minisci reaction batch scope:

Substrate tolerance for the Minisci reaction in batch mode was performed using the conditions optimised above, the results are shown below in *scheme 3.*



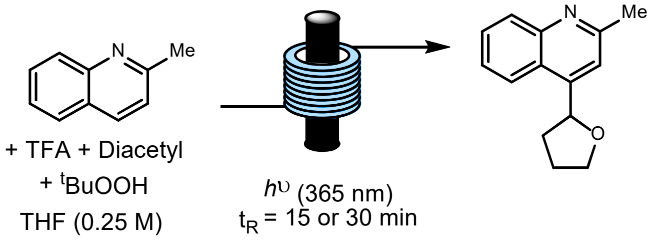
R':
Dioxane = 67%
Et_2O = 46%
MTBE = 46%

NMR yields vs 1,3,5-trimethoxybenzene, R = Me

Scheme 3 – Results for Minisci reaction scope, reaction irradiated for 21 h, 3 mL scale, reactor temperature (monitored digitally – see method for details) 10°C – 15°C.

Minisci reaction scope in continuous flow (2.5 mmol) :

Shown below in *scheme 3* is the finalised flow scheme with the optimised conditions.



Entry	t_R (min)	Flow rate (mL min^{-1})	NMR Yield (%)
1	15	1.0	41
2	30	0.5	69

Scheme 4 - Results for Minisci continuous flow reaction, 2.0 equiv of TFA, Diacetyl, and ^{t}BuOOH used, see method for more information.

Comparison of batch and continuous flow:

Based on the above results, a comparison of batch and flow was carried out at an equal reaction/residence time of 15 minutes. The results are presented below in table 6.

Table 5 - Flow conditions for entry 1 see method section. Batch reaction conditions were 3 mL volume, 0.25 M concentration, 60% lamp input power, reaction was irradiated for 15 minutes.

Entry	**Reaction mode**	**^{1}H-NMR Yield**	**Spacetime yield (mol L^{-1} day^{-1}**	
			t_R = 15 min	**t_R = 30 min**
1	Continuous	41	9.84	8.28
2	Batch	11	0.00422	

As can be seen in *Tables 4 and 6* the productivities of both reactions in continuous flow mode were vastly higher than the batch reaction. The batch reactor exceeded when used for the optimisation of discrete parameters such as solvent and concentrations therefore showing that a combination of both reaction modes can be used in a powerful manner to gain large data sets quickly. This guided the translation to flow mode.

Equipment used in this application note:

Fig 1. *Borealis LED lamps*

Fig 2. *Solstice 12-position BATCH photoreactor*

Fig 3. *Borealis FLOW photoreactor*

References:

[1] R. Crawford, M. Di Filippo, D. Guthrie, M. Baumann, *Chem Commun (Camb)* **2022**, *58*, 13274, DOI: 10.1039/d2cc05601a.