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COMMUNICATION

The Right Light – De Novo Design of a Robust Modular Photochemical Reactor for Optimum Batch and Flow Chemistry

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Abstract: Having identified inconsistencies when repeating literature examples of photochemical transformations and difficulties recreating experimental setups, we devised several criteria that an ideal lab-scale reactor should achieve. Herein, we introduce a versatile photoreactor for high throughput screening, preparative scale batch reactions and continuous processing, all with a single light source. The reactor utilizes interchangeable arrays of pseudo-monochromatic high-power LEDs in a range of synthetically useful wavelengths, combined with excellent temperature control. Moreover, light intensity can be modulated in an accurate and straightforward manner. This system has subsequently been tested on a range of literature methodologies.

In recent years there has been a resurgence of interest in photochemical reactions from academia and industry, with light acting as an economical and renewable alternative to traditional methods of radical formation, leading to more sustainable processes.[1] Of these, visible light (400-700 nm) mediated photoredox transformations have attracted a significant amount of attention.[2-8] However, it has been found that these reactions are not always reproducible. As a result, much of the current literature is not easily scalable from an industrial perspective as key details critical to process understanding are absent e.g. the effect of light intensity on a reaction (Bunsen-Roscoe Law) and the internal reaction temperature. Attempts have been made to address some of these issues, yet, at present there is no standardized platform that enables scale-up from laboratory screening to plant manufacturing using a single light source.[9,10]

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Supporting information (SI) for this article is given *via* a link at the end of the document.

Our preferred strategy would be to have a well-characterized LED light source. To scale-up, the number of LEDs per surface area would simply be increased.

The main deterrent from the ubiquitous adoption of photochemistry is the perceived 'non-scalability' that arises in batch because of the exponential decrease in light transmittance with distance from light source. Continuous processing presents itself as a solution, with light penetration consistent regardless of reaction scale.[1,11] A number of photoredox reactions in flow have been reported, but from a pharmaceutical process chemistry perspective there remains insufficient understanding to enable direct adoption by industry.[11]

With an increasing number of light sources and photoreactors available, the need for a standardized photochemistry platform has never been more prevalent. It is exceptionally challenging to make direct comparisons between two light sources due to the cumulative effects of all components of a light source that can vary marginally during manufacture, especially with domestic light sources; even two seemingly identical lights can differ as a result of batch-to-batch variability.[12] The wattage of a light source gives little information relating to its efficiency or its performance in a photochemical reaction. With a view to overcoming the limitations of equipment described in the literature, a lab-scale photoreactor was developed to satisfy the following criteria:

1) The LEDs must be as monochromatic as possible so that the specific wavelength required for a transformation can be identified.
2) The equipment must offer flexibility in reaction scale from screening to batch and continuous flow with a single light source.
3) The equipment must allow for a detailed understanding of the light source; therefore, the light intensity must be variable. This will also allow the optical power requirements of a reaction system to be more thoroughly understood.
4) The system must have a powerful cooling system so that photochemical and thermal processes can be decoupled.

A photoreactor meeting these criteria will enable optimization of the light to the chemistry as opposed to optimizing the chemistry to several different light sources, as the process transfers through various stages of development, ensuring consistent results regardless of reaction scale.[13] Herein, we introduce a standardized photochemical platform that has been deployed across GSK, which enables results to be reliably reproduced.

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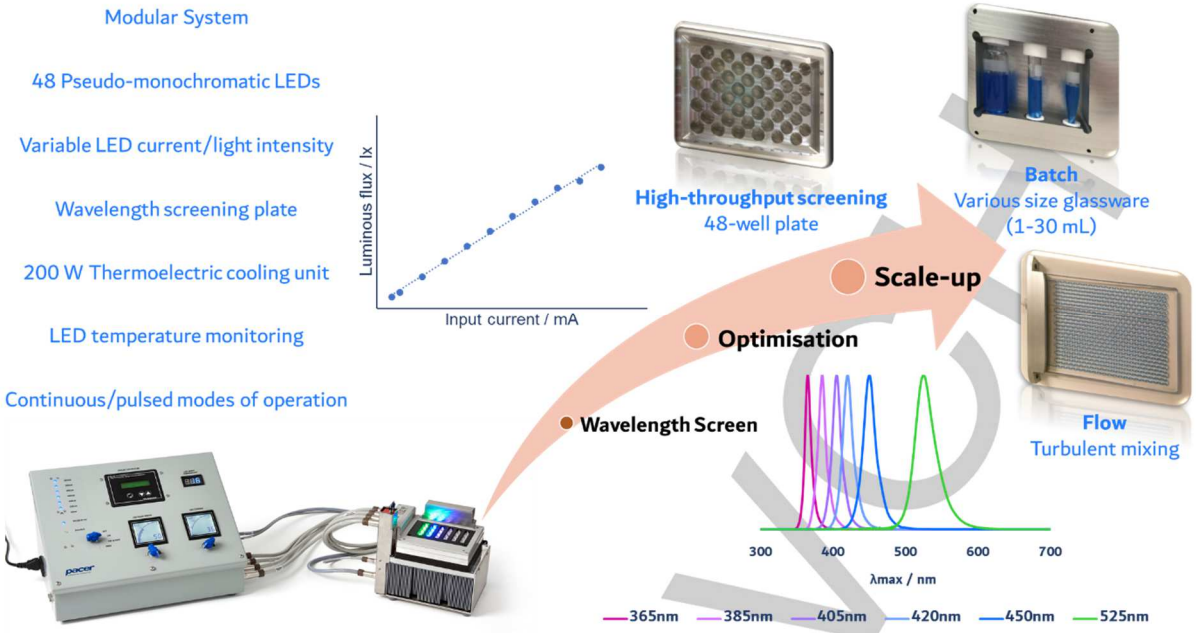


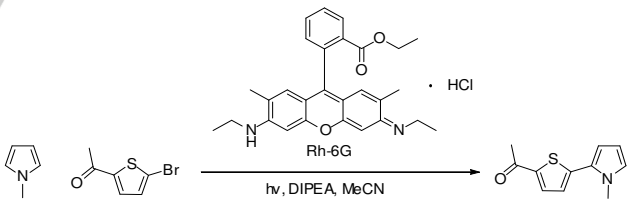
Figure 1. Recommended and standardized workflow for photochemical reactions: 1) perform a wavelength screen in the Photochemistry LED Illuminator; 2) optimize reaction using optimum wavelength; 3) scale-up reaction in batch or flow.

The Photochemistry LED Illuminator

The Photochemistry LED Illuminator (PHIL, see SI for full characterization) is a photoreactor with the capability to screen reactions (up to 48 HPLC vials) and scale-up in batch (3 x 1-30 mL vials) or flow (4.09 mL reactor volume) all with the same light source (Figure 1). Initial validation of this system demonstrated that by utilizing this technology, a more efficient route to scale-up is achieved as optimization only needs to be performed once.[13] Efficient wavelength optimization is achieved by utilizing a 24-well screening plate, containing a range of pseudo-monochromatic wavelengths (365, 385, 405, 420, 450 and 525 nm). Further reaction optimization can then be performed by high-throughput screening (HTS) using a 48-well single wavelength LED plate corresponding to the optimum wavelength identified by the wavelength screen. For reaction screening each narrow angle LED (20°) aligns with one of the wells in the 48-well screening plate, ensuring each vial is exposed to the same light intensity, at a constant distance (3 mm). Temperature control of the system is achieved by a 200 W thermoelectric cooling unit and using a specific vial type.[14] With this setup it is possible to evaluate and decouple the thermal contribution to the photochemical process to gain a deeper understanding of the whole process. Easy interchangeability between all modes of operation ensures the system can adapt to the needs of the user. As the specific light intensity needed for a transformation is currently undefined across the literature, the system also boasts the ability to change the LED current and thereby light intensity (30-1000 mA per LED depending on the wavelength) and to alternate between constant wave (CW) or a pulsed width mode (PWM) of operation.[15]

Heteroaromatic coupling

Initially, the photoredox transformation in Scheme 1 was being used as an actinometry reaction to compare commercially available in-house light sources.[16-18] The developed reaction was used to validate the 24-well wavelength screening plate in PHIL. Surprisingly, the reaction could be performed successfully at almost all wavelengths, including those at which the catalyst does not absorb (Figure 2a). Parallel reactions performed in the absence of catalyst identified a catalyst-free cross-coupling regime (Figure 2b) presumed to result from direct homolytic cleavage of the C-Br bond in **2**.[19] The two mechanisms take place concurrently and so are difficult to decouple. This highlights the importance of performing control reactions in the absence of photocatalyst simultaneously with wavelength screening investigations to determine if background reactions are occurring. Consequently, a standard workflow was designed for any literature reaction to be repeated (Figure 1). To date, we have not been able to find a suitable actinometry reaction that is fit for both batch and flow photochemistry.



Scheme 1. Photoredox actinometry reaction using Rhodamine-6G (Rh-6G) as a photocatalyst.

[2+2]-cycloaddition

To enable comparison of PHIL with others in the literature a [2+2]-cycloaddition reaction (Scheme 2) was examined.[20-22] This reaction, thought to be UV mediated, typically utilizing a Hg lamp (polychromatic 200-580 nm), has predominately been performed in flow, and so this setup was employed by first intent.[23] Using the proposed workflow (Figure 1) a wavelength screen for the intermolecular cycloaddition of **4** and **5** exhibited slow conversion at all wavelengths available with the system (365-525 nm), although for similar transformations ~310 nm is the optimum wavelength, which would account for this observation.[24,25] Triplet sensitizer benzophenone was introduced to aid energy transfer to **4** at 365 nm; time courses in the presence

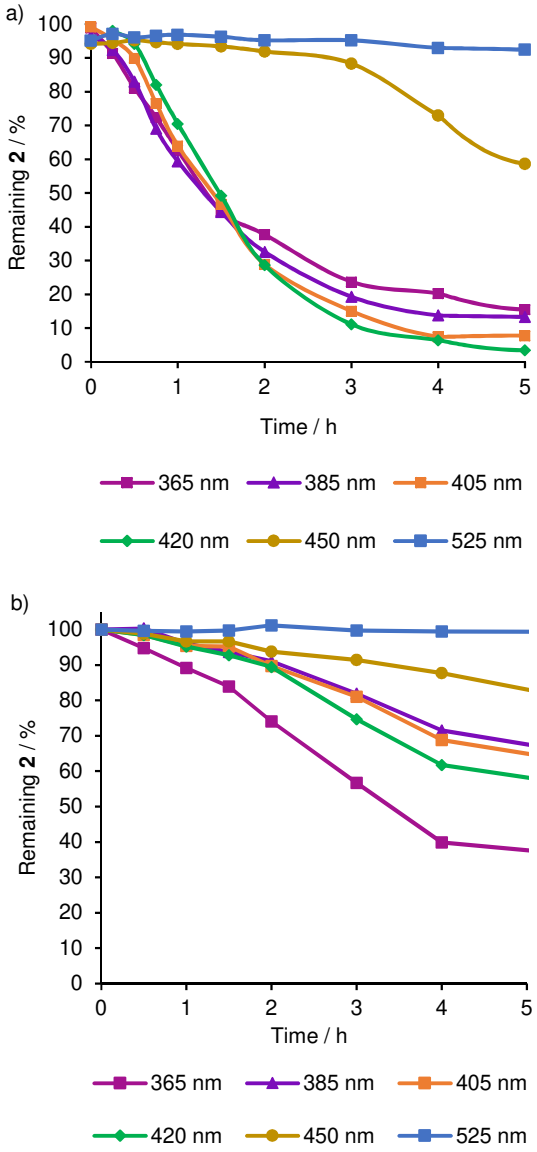
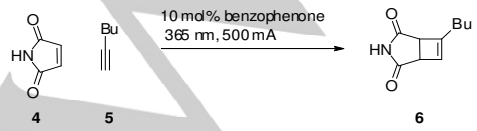


Figure 2. PHIL wavelength screening at 350 mA for the photoredox actinometry reaction: a) with 1% catalyst loading and b) in the absence of catalyst.

of 10 mol% benzophenone exhibited a significant rate increase (Figure 3), with complete conversion in only 10 min compared to 60 min without the additive. Moving the reaction from HTS (1 mL) to the batch setup (5 mL), with the same reaction and equipment settings, verified that consistent results were attained without further optimization (Figure 3).

The reaction rate was again found to increase when this protocol was used to generate **7** (Scheme 3), with a reduction in reaction time from 100 min (without benzophenone) to only 5 min.[26]



Scheme 2. Intermolecular [2+2]-cycloaddition of **4** and **5**.

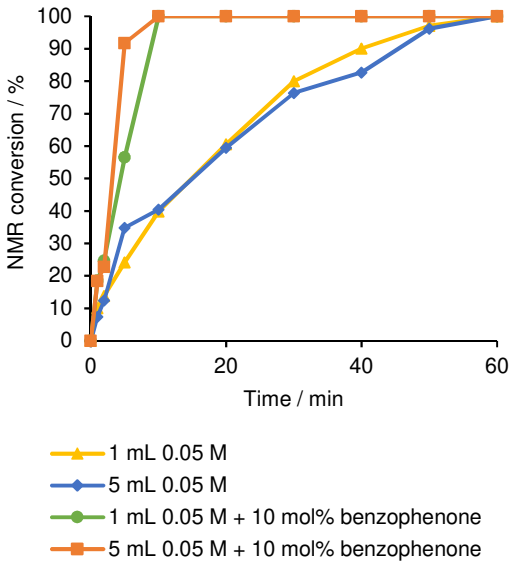
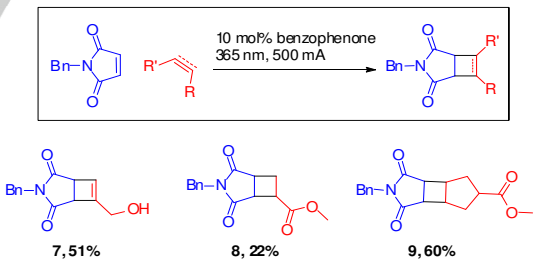


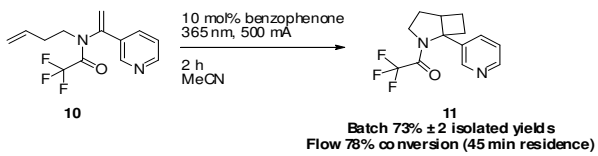
Figure 3. Time course for the intermolecular [2+2]-cycloaddition of **4** and **5** with and without benzophenone at 365 nm, 500 mA in PHIL using HTS and batch setups.

Sensitized intermolecular and intramolecular [2+2]-cycloadditions have recently been reported by Mykhailiuk *et al*.[25,27] Two of the intermolecular substrates (**8** and **9**, Scheme 3) and one of the intramolecular substrates (**10**, Scheme 4) reported were selected for comparison in PHIL. The [2+2]-cycloadditions to prepare **8**, **9** and **10**, which were performed in the batch scale-up setup, showed complete conversion in only 2 h. Formation of **10** was run in triplicate simultaneously in the batch scale-up mode (3 separate vials) and showed consistent yields (±2%) across the batch scale-up module.



Scheme 3. Intermolecular [2+2]-cycloaddition general reaction scheme and scope.

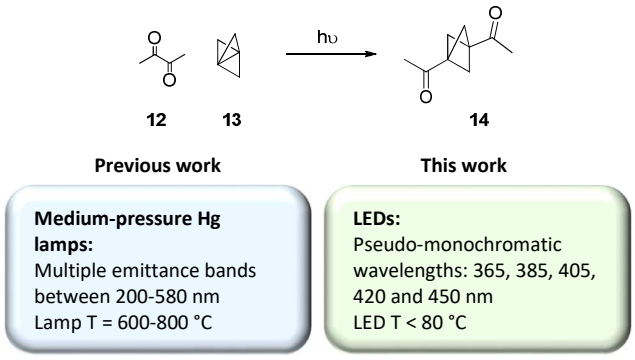
On transferring **10** to flow an optimum flow rate of 0.1 mL min^{-1} (45 min residence time, see SI for optimum residence time determination) at 0.05 M was achieved. These optimized conditions exhibited 78% conversion by ^{1}H NMR to **11**. For this specific example, batch is equivalent to processing 0.208 mL min^{-1} *vs* 0.1 mL min^{-1} in flow. This is likely due to the improved mixing in batch *vs* the mixing speed of the flow reactor at low flow rates .[13]



Scheme 4. Intramolecular [2+2]-cycloaddition.

Norrish Type 1 Rearrangement

Bicyclo[1.1.1]pentanes are non-classical phenyl ring bioisosteres and are therefore of pharmaceutical interest. The Norrish I, previously reported by Booker-Milburn *et al*.,[21] describes the generation of **14** in flow, from which many bicyclo[1.1.1]pentanes are accessed (Scheme 5).[21,28,29] Using PHIL, the photolysis of **12** in the presence of **13** was explored using the wavelength screening plate to determine the optimum wavelength.



Scheme 5. Norrish I of **12** and quench onto **13**.

From Figure 4 it is clear that the photolysis of **12** is achieved at a range of wavelengths.[30-33] Most notably, visible light wavelengths (405-450 nm) can be used. This is advantageous over previous literature examples where medium pressure Hg lamps have been employed.[21,34-36] This allows cooler visible light sources to be considered when scaling this transformation, alleviating safety issues that have previously surrounded this chemistry.[15]

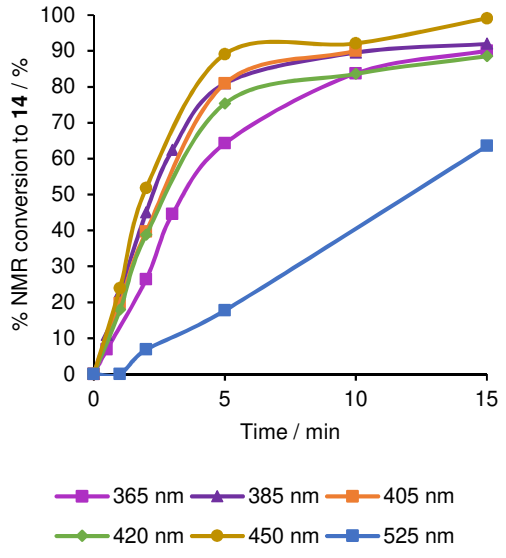


Figure 4. Wavelength screen for the Norrish I of **12** in PHIL at 350 mA.

Matheson *et al.* have reported that the quantum yield for the photolysis of **12** in the vapour phase increases with light intensity.[30] To investigate the effect of light intensity on the generation of **14**, 385 nm was chosen as the LED light intensity can reach 1000 mA (compared to 350 mA and 500 mA respectively for 450 nm and 405 nm LEDs). The rate of

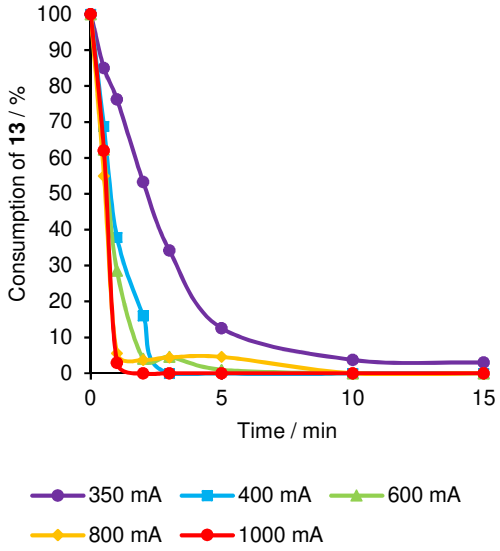
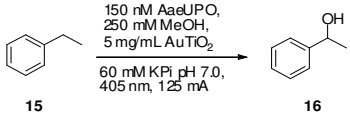


Figure 5. Consumption of **13** as a function of time at varying LED current.

consumption of **13** increased with light intensity, with the effect only becoming limiting above 800 mA (Figure 5).[37]

Hydroxylation

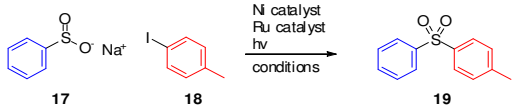
Selective oxyfunctionalizations of ethylbenzene (**15**) have been reported by Hollmann *et al*. using unspecific peroxygenase from *Agrocybe aegerita* (*Aae*UPO) and methanol as a sacrificial reductant for *in situ* H_2O_2 generation from O_2 promoted by an Au-TiO_2 photocatalyst.[38] PHIL wavelength screening identified 405 nm to be the most efficient wavelength for the hydroxylation as this showed the highest conversion after 2 h (Scheme 6).[39,40] Optimization studies were carried out using the 48-well HTS plate. In this case, a lower intensity of 125 mA was shown to be optimum whilst keeping temperatures < 40 °C where the enzyme activity is high. A time course of the reaction at 405 nm, 125 mA showed that the reaction was complete before 21 h (compared to 72 h previously reported).[41] This system was also explored at higher concentrations of **15**, observing that 30 mM substrate was completely converted, and 60 mM substrate gave 93% conversion to **16** after 21 h, whereas 100 mM and 150 mM substrate led to 42% and 6% respectively. Further optimization experiments are under investigation to improve conversion at higher substrate concentrations.



Scheme 6. *Aae*UPO-catalyzed hydroxylation of **15** using Au-TiO_2.

C-S cross-coupling reaction

The cross-coupling of aryl iodides and sulfinic acid salts to generate sulfones has been reported by Manolikakes *et al.*[42,43] An initial wavelength screen in PHIL, for the coupling of **17** and **18** (Scheme 7), identified 525 nm as the optimum wavelength, despite the photocatalyst having a lambda max at 450 nm. A time course of the reaction at 525 nm, 350 mA showed that complete conversion was achieved in only 5 h compared to the previously reported 24 h, allowing a 4-fold increase in throughput. Internal reaction temperatures of ~60 °C were observed during the course of the reaction, whilst the LED temperature was maintained at the



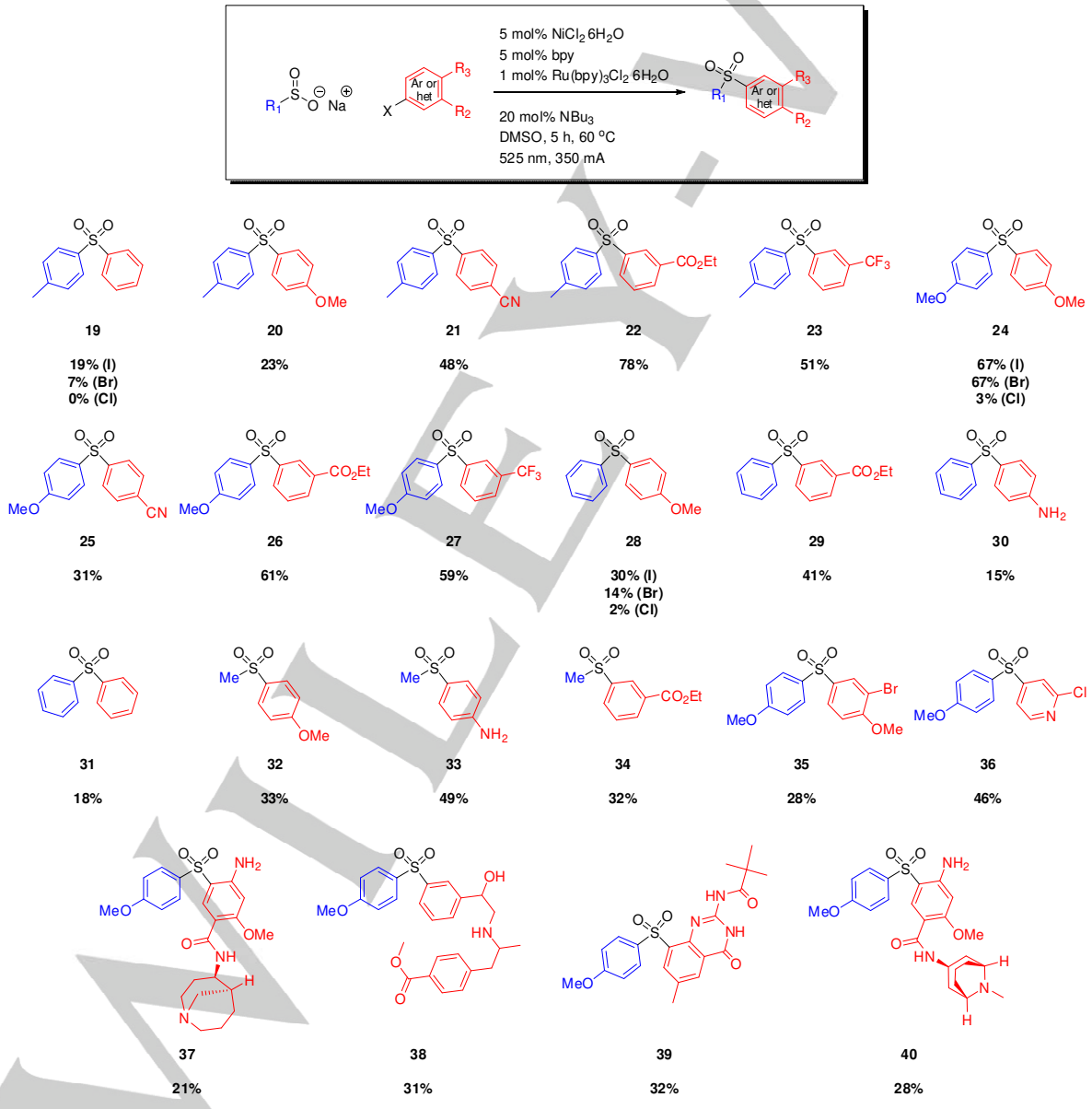
Scheme 7. Aryl iodide and sulfinic acid salt cross-coupling model reaction used for reaction optimization.

set temperature of 15 °C; we have noted air temperatures 10 °C lower than internal reaction temperatures suggesting the reaction is releasing heat (vibrational relaxation).[44] Other nickel systems infer that the nickel oxidative addition is a thermally governed process,[45-48] so higher temperatures facilitate the cross-coupling cycle in a rate-limiting fashion, whilst the optimization of photochemical conditions facilitates radical formation.[43,49] At a constant current (350 mA) the internal reaction temperature was varied by altering the set point of the thermoelectric cooling unit.

An internal temperature of ~30 °C showed 15% conversion from **18** to **19** in 24 h, whilst at ~35 °C 38% conversion was observed and at ~60 °C an isolated yield of 67% was achieved (64% after only 5 h). As the photochemical conditions remained unchanged in these experiments, thermal and photochemical processes have been successfully decoupled. Therefore, we can clearly state that temperature is the rate-limiting factor in this transformation.

Three methods (A, B and C) were assessed in the HTS mode of PHIL (Scheme 8 shows the results with method C).[50] From a medicinal chemistry perspective, HTS mode allows reaction setup in HPLC vials, thus limiting the amount of material needed, and enables quick purification by mass-directed auto-purification (MDAP).

It was found that electron-rich sulfinic acid salts deliver higher yields when comparing the formation of **19** (Schemes 7 and 8); the reaction is compatible with various aryl halides



Scheme 8. General reaction scheme and substrate scope for the cross-coupling of aryl halides and sulfinic acid salts.

(I, Br and Cl) (compounds **19**, **24** and **28**); coupling aryl iodides and bromides (**24**) proceeded in comparable yield whilst low conversion was observed with aryl chlorides. Moreover, the mild and selective reaction conditions were compatible with additional functional groups for downstream functionalization on industrially relevant substrates (compounds **35** and **36**). Lastly, examples of late stage functionalization were attempted successfully, albeit low yielding due to the structural complexity of these molecules (compounds **37**-**40**).

We have demonstrated that the Photochemistry LED Illuminator is a versatile system that meets the requirements for a photochemical platform by identifying the wavelength and optical power required for photochemical transformations. This commercially available platform is impacting our portfolio by allowing new disconnections that can be utilized by medicinal chemists in an expeditious manner to generate arrays of compounds and understood by process chemists and engineers for efficient transfer to scale-up. Having fully evaluated the system from prototype to commercial unit, we would like future units to have the capability to screen different wavelengths at different light intensities simultaneously. This would be a major advantage to enable rapid development of the photochemical field.

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Keywords

High-throughput screening • Flow • Photocatalysis • Photochemistry

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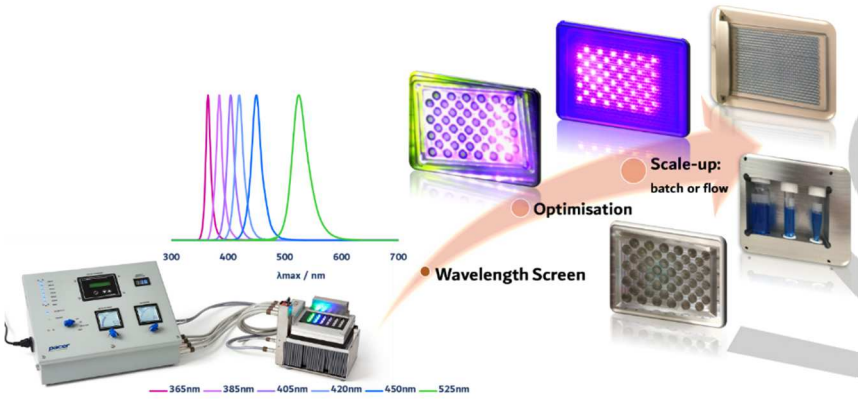

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Title

New commercial photoreactor examined by performing several photochemical literature reactions. Our workflow is presented in the hope that others adopt the same methodology to begin the process of developing a standardized photochemical platform across academia and industry, that can be utilized by chemists to perform photochemistry in a high-throughput manner whilst simultaneously developing the in-depth reaction understanding required.

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