



Syrris Tech Note - Bicyclo[1.1.1]pentanes through photoredox catalysis

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1 Summary

This technical note demonstrates the use of Asia Photochemical Reactor to carry out the light driven photoredox reactions for the synthesis of bicyclo[1.1.1]pentane derivatives. The results of the Asia Photochemical Reactor are compared with an in-house customer set up which was previously being used to develop the photoredox reactions.

The use of the Asia Photochemical Reactor for this application shows both an increased efficiency and a safer practical method for this transformation.

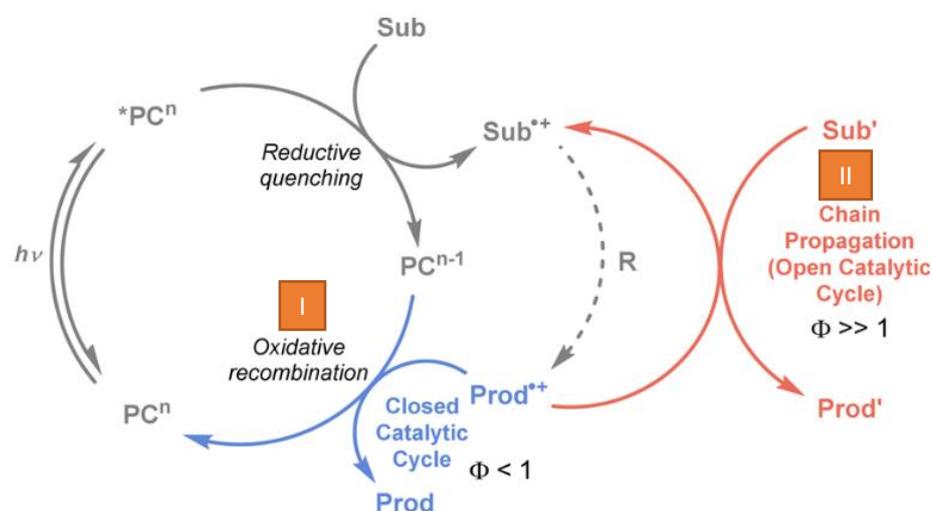
2 Introduction

Photochemistry has emerged as an alternative or complementary technique to promote chemical reactions and employs photons to drive chemical transformations. Traditional approaches rely on the direct excitation of bonds with high intensity UV light sources such as low and medium pressure mercury lamps. These have limitations due to the broad-spectrum light they emit making selectivity of reactions difficult. The need to employ cooling of the light source by external means and adequate shielding to protect the user from high energy UV light add to these limitations.

More recent photochemistry applications use visible light activation, generally delivered by LED light sources making the application more selective and safer. This has allowed the development of photoredox catalysis which uses a photosensitizer (photocatalyst) to facilitate electron transfer, generating reactive intermediates under milder conditions.¹

The use of transition metal complexes in photoredox catalysis has increased over the past decade where ruthenium and iridium complexes have played the main role in the photoredox applications.²

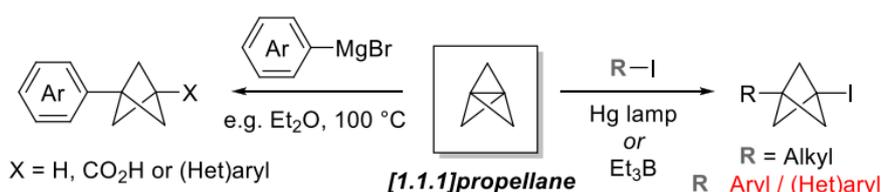
There are some controversies around the mechanism of these reactions, closed catalytic cycles are considered as the mechanistic path to the final neutral product. Recent in-depth studies demonstrate that radical chain propagation cycles might play a major role in the mechanism of certain photocatalytic reactions (Scheme 1).²



Scheme 1. Proposed mechanisms for photoredox reactions

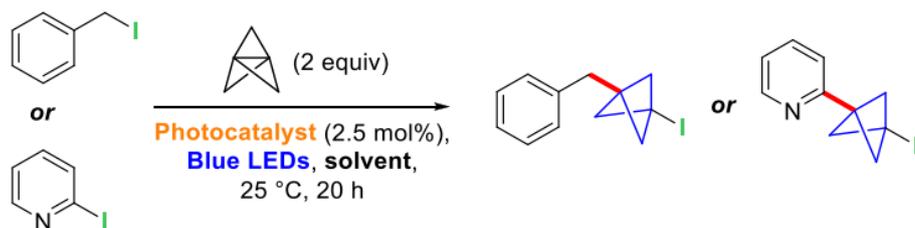
The experiments highlighted within this application note were conducted at Vernalis Research, Cambridge, UK (<https://www.vernalis.com/>) and have successfully demonstrated the use of photoredox catalysis to promote the addition of organic halides to the carbocycle [1.1.1]-propellane.

Bicyclo[1.1.1]pentanes (BCPs) are motifs of high importance in the pharmaceutical industry and materials chemistry as surrogates for arene,¹ tertbutyl,² and acetylene groups. The synthesis of carbon-substituted BCPs typically requires harsh reaction conditions, such as heating with organometallic reagents, or high-pressure mercury lamp irradiation. This is incompatible with the synthesis of complex targets containing this motif and limit the use of BCPs in medicinal and agrochemistry.



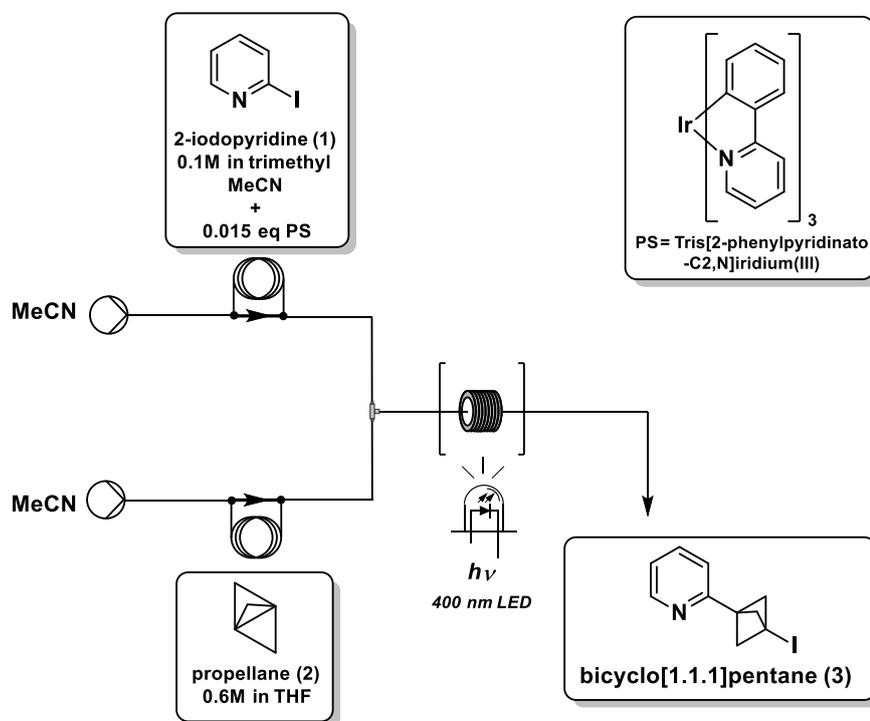
Scheme 2. Traditional anionic and radical additions of [1.1.1]propellane

Researchers at the University of Oxford and Pfizer have reported the use of photoredox catalysis to promote the addition of organic halides to the carbocycle [1.1.1]-propellane to produce (BCPs).³



Scheme 3. Addition of [1.1.1]propellane using photoredox catalysis

Using the Asia system chemists at Vernalis Research wanted to explore the development of a continuous flow methodology using this chemistry. Initial results using a home-made flow photochemical reactor limited to 20W radiant flux output showed moderate results. The flow methodology was developed further using the Asia Photochemistry reactor enabling an increase in radiant flux resulting in shorter reaction times and an improved conversion.



Scheme 4. Flow schematic of the synthesis of bicyclo[1.1.1]pentane (3) via photoredox reactions.

3 Material and Method

System Setup

The Asia Flow Chemistry system from Syrris was used to perform the experiments within. Asia is an extremely flexible and modular system and the modules used within this study are as follows:

- Asia Pump (part number 2200292)
- Asia Blue Syringes (part number 2200393)
- Asia Automated Reagent Injector (with 5ml Sample Loops) (part number 2201126)
- Asia Photochemistry Control Module (240V) (part number 2202089)
- Asia Photochemistry Assembly (for Asia Heater) (part number 2202091)
- Asia 450 nm LED modules (Blue) (part number 2202098)
- Asia Heater (part number 2200527)
- Asia Heater Tube Reactor Adaptor (part number 2200530)
- Asia 16 ml Tube Reactor Fluoropolymer (part number 2200542)
- Asia Automated Collector (Mini) (part number 2200535)
- Asia Manager PC Software (part number 2200537)

Reagent Preparation

The following chemicals were needed for the experiments:

- 2-iodopyridine (CAS 5029-67-4) (1)
- Tris[2-phenylpyridinato-C₂,N]iridium(III) (CAS 94928-86-6) (PS)
- Acetonitrile (CAS 75-05-8)
- Trimethylacetonitrile (CAS 630-18-2)
- Tetrahydrofuran (CAS 109-99-9)
- [1.1.1]propellane (CAS 35634-10-7) (2)

A solution of **1** (0.1 M in trimethylacetonitrile, 1 eq.) was mixed with a solution of **PS** (15%mol in trimethylacetonitrile) and the resulting solution was charged in the channel 1 of the AutoRIM. A solution of propellane (**2**) (0.6 M in THF) was charged on the channel 2 of the AutoRIM. Aliquots of 5 mL were pushed to the photochemical reactors by pumping MeCN.

Fluidic Setup

The fluidic setup is shown in Figure 1. The Asia Pump was used to pump acetonitrile (MeCN) as the carrier fluid and the Asia Automated Reagent Injector was used to deliver solutions of the substrate (**1**) and catalyst (**PS**) and the propellane (**2**) into the fluidic network. The system was kept at ambient temperature with no back-pressure regulator applied. Collection was carried out using the Asia Automated Collector. Using both the Vernalis mkII photochemistry reactor and the Asia Photochemistry Reactor both fitted with a 16ml PFA tube reactor a range of experimental conditions were performed. Off-line quantitative analyses were carried out allowing to calculate reaction yields.

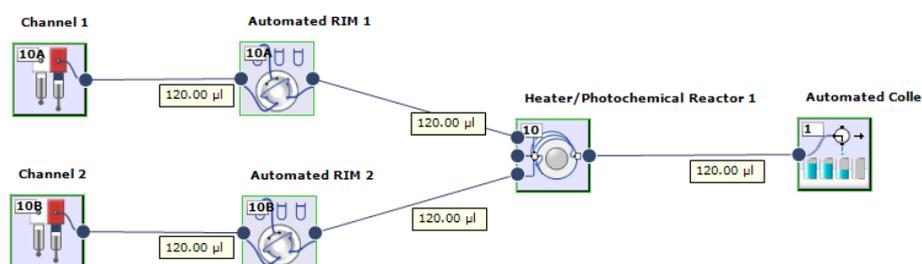
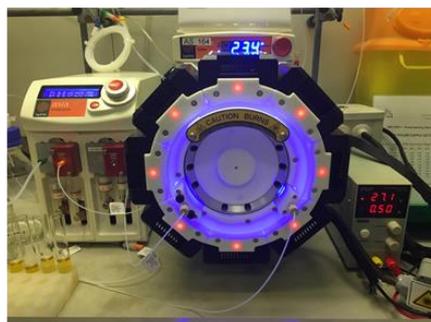


Figure 1 – Fluid network for the photooxygenation reactions.

The Vernalis mkII photochemistry reactor was constructed with a LED strip overing 360° coverage limited to 20W output radiant flux. The Syrris alpha-photochemistry reactor with a variable output radiant flux was used as a comparison (Figure 2).



Syrris α -reactor (variable power)



Vernalis mkII-reactor (20W limit)

Figure 2 – Syrris alpha-photochemistry reactor and Vernalis mkII reactor

System Parameters

The automated experiments were performed using Asia Manager software. The temperature data for experiments was registered and 8 x LED modules (450 nm blue) were used for reaction activation. The radiant power, total flow rate and residence times on the Asia Photochemistry Reactor are disclosed in Table 1.

Exp #	Radiant Power (W)	Total Flow rate (mL/min)	Residence Time (min)
1*	N/A	0.267	60.0
2**	20	0.267	60.0
3	20	0.250	64.0
4	20	1.000	16.0
5	42	1.000	16.0
6	72	1.000	16.0
7	84	0.615	26.0

*no light; ** Vernalis MKII

Table 1. System parameters.

4 Results

A series of six experiments were used to perform the comparison study reactions on the two photochemistry reactors.

Residence times and LED radiant flux (power) were explored against both reactors. The results are summarized in *Figure 3*.

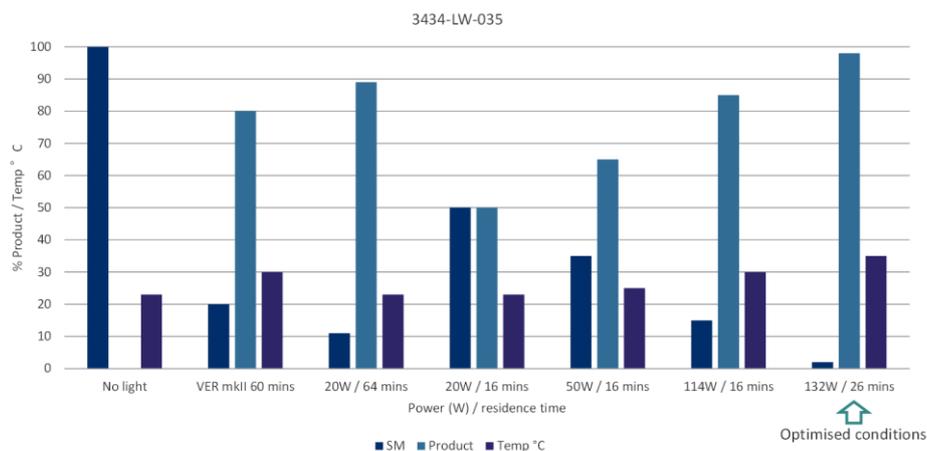


Figure 3. Results of photoredox reaction comparisons. Values stated are input power to the LEDs.

The comparison study showed the direct result of increasing radiant flux (power) to the reaction in both increasing the conversion and decreasing the residence time of the reaction.

Experiment 1 showed that when no light is used the chemical reaction is not triggered and no product is observed.

Experiment 2 shows the benchmark reaction using the Vernalis mkII reactor with a fixed output of 20W and a 60-minute residence time showing a conversion of 80%.

Experiment 3 shows the direct comparison to expt. 2 using the Asia alpha-reactor set to 20W with a 60 minute residence time shows a 89% conversion. This can be attributed to the reactor design allowing better light transmission to the reaction. The temperature profile of the reaction using the Asia reactor also shows a decrease in reaction temperature compared to the Vernalis mkII reactor. Limiting the effects of the heat generated by the light source from the reaction is an important factor in performing selective photocatalysed reactions. The design of the Asia LED modules allows excellent temperature control across all light intensities.

Experiments 4 to 8 show the optimization of the reaction conditions to find a residence time to offer the best throughput by increasing the light intensity to the reaction.

Decreasing the residence time while using the same radiant flux was observed to show a 50% conversion (expt. 5). By increasing the light intensity (expt. 6 and 7) showed that the reaction rate could be increased and the residence time reduced. Expt. 6 showed by increasing the radiant flux from 20 W to 72W the residence time could be reduced to 16mins from 60mins in the original conditions.

The optimum results (expt. 8) showed by increasing the radiant flux to 84W (output power) a near quantitative conversion could be obtained with a 26min residence time.

These results highlight the Asia Photochemistry Reactor design offers advantages over home-made reactors enabling both a variable light intensity to allow optimization of photocatalysed reaction conditions and efficient temperature control.

5 Conclusions

It was shown the safety and capability of the Asia Photochemical Reactor to perform a new class of photoredox reaction where a carbon–carbon σ -bond is functionalized by photocatalyst-generated radicals in a mild and cost-competitive conditions to produce valuable compounds.

The ability to increase radiant flux using the Asia Photochemistry Reactor demonstrates both the increased reaction conversion and the decreased residence times compared with a home-made fixed output reactor and shows the direct scalability of the Asia Photochemistry Reactor design.

6 References

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