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Finding the Perfect Match: A Combined Computational and Experimental Study Towards Efficient and Scalable Photosensitized [2+2] Cycloadditions in Flow

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ABSTRACT

With ever-evolving LED technology, classical photochemical transformations are becoming accessible with more efficient and industrially viable light sources. In combination with a triplet sensitizer, we report the detailed exploration of [2+2] cycloadditions, in flow, of various maleic anhydride derivatives with gaseous ethylene. Using a flow reactor capable of gas handling and LED wavelength/power screening, an in-depth optimization of these reactions was carried out. In particular, we highlight the importance of matching substrate and sensitizer triplet energies, alongside light source emission wavelength and power. Initial triplet sensitized reactions of maleic anhydride were hampered by benzophenone's poor absorbance at 375 nm. However, DFT calculations predicted that derivatives such as citraconic anhydride have low enough triplet energies to undergo triplet transfer from thioxanthone, whose absorbance matches LED emission at 375 nm. This observation held true experimentally, allowing optimization and further exemplification in a larger scale reactor, whereby >100 g of material was processed in 10 hours. These straightforward DFT calculations were also applied to a number of other substrates, showing a good correlation with experimental data, implying a powerful strategy in targeted reaction optimization for future substrates.

KEYWORDS flow photochemistry; DFT calculations; cycloadditions; photosensitizers; gasliquid reactions

INTRODUCTION

A recent surge in efforts towards new photochemical methodologies for organic synthesis¹ has also brought about renewed interest in "classical" photochemical transformations, such as the synthesis of cyclobutanes by [2+2] cycloaddition.² Although photochemical [2+2] cycloadditions have been continually studied since their discovery in 1877,^{2a} their applications have remained almost exclusively academic. In recent years, though, the modern "Escape from Flatland" era of medicinal chemistry has driven a paradigm shift, favoring sp³-rich compounds with an increased number of chiral centers and more three-dimensional complexity.³ Within this framework, building blocks with distinct and varied expansion vectors are highly desirable, which has driven synthetic research in synthesis of compounds such as cubanes⁴ and bicyclo[1.1.1]pentanes.⁵ The cyclobutane moiety, however, also fulfils these prerequisites, as a saturated linking motif with multiple distinct expansion vectors. In contrast to more complex building blocks, cyclobutanes may be accessed by means of [2+2] cycloaddition; a route which instils modularity, or adds complexity, depending upon the degree of starting material functionalization.

Maleic anhydride (1) is a cheap and widely available bulk chemical (EUR13.40 per kg),⁶ which has been demonstrated to undergo photochemical [2+2] cycloaddition with ethylene, furnishing a cyclobutane-based cyclic anhydride.^{7,8} This 5-membered anhydride can be opened (in a symmetric or asymmetric fashion), revealing two carboxylic acid moieties, with many possible modes of further functionalization such as reductions, esterification or amidation. Furthermore, many recent cross-coupling methodologies have begun to invoke carboxylic acid-derived electrophiles,⁹ making maleic anhydride derivatives versatile cyclobutane synthons, towards a vast range of diversely functionalized molecules (Scheme 1).^{2b} Synthesis of these building blocks on small scale may be readily achieved in medicinal chemistry labs using modern synthetic photochemistry equipment, yet performing the same chemistry on larger scales is expected to become problematic due to issues with light penetration and gas-liquid mixing.



Scheme 1. Depiction of possible uses for maleic anhydride-derived cyclobutanes in API synthesis.

Implementation of flow technology has been identified as the most practical solution to performing photochemical reactions in a scalable manner¹⁰ and, accordingly, there are many examples of photochemical [2+2] reactions performed in flow.^{8,11,12} These include very few examples of large scale processing,¹² and almost all employ UV light sources such as pressurized mercury lamps. These light sources suffer from numerous drawbacks that make them unsuitable for large scale applications. High energy consumption coupled with low efficiency results in an immense heat output, requiring substantial cooling. Furthermore, the lifetime of these lamps is unpredictable, and relatively short, requiring regular replacement and hence, material "sent to waste" in a manufacturing setting. Finally, these lamps consist of multiple discrete energy bands across the entire UV-visible spectrum, exacerbating energy wastage by unused light and introducing issues with reaction selectivity, particularly in molecules containing delicate functionalities, such as APIs (active pharmaceutical ingredients).^{10a,b} LED light sources offer an excellent alternative; incorporating improved efficiency, predictable performance over long lifetimes and a narrow pseudo-monochromatic light output.¹³ In addition, LED technology is developing at a fast rate, implying that their use will continue to become more widespread within all areas of synthetic photochemistry.¹⁴ Indeed, the use of LEDs in place of higher energy (or other broad-emission light sources) has already been reported in numerous cases¹⁵ and this trend is ever increasing.13

The main drawback of LEDs in synthetic photochemistry is the fact that those with synthetically useful light output are currently limited to wavelengths >340 nm. Therefore, in order to carry out most cycloadditions, an added photosensitizer is required, due to the short absorption wavelength of most organic substrates. However, this targeted excitation of a photocatalytic species can also allow for more efficient reactions under milder conditions. Since triplet photosensitizers typically have high attenuation coefficients (efficient light absorption) and an intersystem crossing (ISC) yield close to unity,¹⁶ even a small quantity of sensitizer can enhance the rate at which the reaction substrate reaches its required excited state, when compared to direct irradiation. Triplet-sensitized organic transformations have seen significant interest in recent years, as alternative or complimentary methods to the more common single electron transfer (SET) photoredox catalysis.¹⁷ It is also envisioned that computational methods may be used to assist in identifying suitable triplet sensitizers to be paired with different reaction substrates through simple comparison of triplet energies.¹⁸ Therein, it may be possible for a powerful predictive method to be developed, allowing expeditious reaction optimization.

Within our interests to develop and showcase scalable flow photochemistry towards API synthesis, the formation of cyclobutanes is of significant interest. To our knowledge, scale-up of photosensitized cycloadditions has very little literature precedence thus far,⁸ and so a detailed study into this type of synthetic methodology would prove to be of interest to process development chemists within the pharmaceutical and fine chemical industries. Ethylene is an excellent choice as an alkene cycloaddition partner to further explore this reaction, since it acts as a reactive and cheap route into simple cyclobutanes, but also further exemplifies the benefits of performing gas-liquid reactions under flow conditions. Inspired by recent work examining the scalability of the cycloaddition of maleic anhydride (1) with ethylene, using ketone photosensitizers,⁸ we opted to undertake a broader study of this class of reactions. The aforementioned study initially employed a medium pressure Hg lamp, but later moved on to LED irradiation to achieve a more energy-efficient and industrially-applicable transformation, assumedly for the reasons mentioned above.

RESULTS AND DISCUSSION

Optimization of Maleic Anhydride Cycloaddition

Our studies using the same substrate began using a commercially available plate based photoreactor (Corning Advanced-Flow Lab Photo Reactor).¹⁹ This reactor implements two LED panels to irradiate the reaction plate and uses integrated pumps, mass flow controller and back pressure regulator, along with temperature regulators for both the reaction plate and LED panels (Scheme 2). Initial reactions were performed using 1-hexene as a model liquid olefin, in order to explore reaction parameters, prior to involving a gaseous reagent feed. These studies showed that temperature had no significant effect on reaction rate and that almost complete reaction could be achieved in a 10 min residence time, using an excess of 1-hexene (4 equiv) and an elevated loading of benzophenone (see Supporting Information, Table S5-S7 for details of reaction optimization with 1-hexene). Our attention then shifted to introducing ethylene as a gaseous alkene. In this case it was expected to be less straightforward to apply such an excess of the alkene partner, since the concentration in solution is solubility-limited. Nevertheless, it was found that by applying a moderate pressure of 12 bar to these reactions using the in-built back pressure regulator (Zaiput BPR-10) the ethylene stream was entirely dissolved in the reaction medium, resulting in simpler monophasic fluid behavior. Surprisingly, a single phase was observed in all reactions, even those at elevated temperatures and when using 2.5 equiv of ethylene. Although multiphasic flow regimes have been shown to improve productivity in some cases.²⁰ having all of the input gas dissolved in the reaction medium allows a longer irradiation time (based on the same flow rates), hence improving overall productivity (see Supporting Information, Table S8 for details of reaction optimization with ethylene). Based on the optimized conditions (Scheme 2) a greatly increased space-time-yield was calculated in comparison to the previously reported procedure (301 g L⁻¹ h⁻ ¹ vs 90 g L⁻¹ h⁻¹).⁸ This can be attributed to the increased light intensity provided by the LED arrays and smaller reactor size (2.77 mL vs previously reported 20 mL reactor).



Scheme 2. Flow schematic showing the optimal reaction conditions for the cyclization of maleic anhydride (1) with ethylene. GC yield is shown in the scheme and an 84% isolated yield was achieved.

Unfortunately, the limit of productivity for this reaction quickly became apparent and the optimal conditions (Scheme 2) could not be improved upon further. Our optimal conditions closely reflected those used in the aforementioned publication,⁸ with the main deviation being the use of ambient temperature, which avoids energy costs associated with cooling the reactor. Using a panel of 375 nm LEDs, very high loadings (40-60%) of the sensitizer benzophenone (2) were required to achieve a fast rate of reaction, leading to poor atom-economy. Recovery and reuse of the sensitizer is possible (see Supporting Information Section 1.5.1), yet this purification process would add multiple unit operations to the process and is undesirable when considering large scale processing, particularly in recovering a commercially available material. Of particular interest in this case, was the comparative performance of differing LED wavelengths under these conditions. The absorption spectrum of benzophenone peaks at ~340 nm ($\lambda_{maz} = 343$ nm) and the efficacy of pseudo-monochromatic LEDs at multiple wavelengths was examined (Table 1). LEDs with a maximum emission at 343 nm were found to be ineffective in this transformation (Table 1, entry 1), likely due to their poor photon flux, which is substantially lower than that of other wavelengths examined. As noted previously, the development of UV LEDs is a rapidly advancing area of research and as a result it is expected that this power will improve in the coming years.¹⁴ LEDs of 365 nm and 375 nm showed roughly equal yield, despite benzophenone's significantly higher

absorbance at 365 nm. This higher absorbance at 365 nm may bring the reaction into a regime where all light is absorbed before penetrating the entire reaction medium, hence showing only limited improvement. As expected, irradiation at 385 nm shows very little conversion and 405 nm is completely outside of benzophenone's absorbance range, so no reaction was observed.

Table 1. Results of Benzophenone-sensitized Reaction Protocol at varying LED Wavelengths,Including a Graphical Representation of Benzophenone Absorption Spectrum with theExamined LED Wavelengths Appended.



The UV/vis spectrum was measured in ethyl acetate at a concentration of 12.5 mM. ^aWavelengths listed are the maximum output wavelength, as taken from the LED specification sheet; the actual value may vary by ± 5 nm. ^bRadiant flux values were obtained from the LED specification sheets for a single LED, then multiplied by 40 (the total number of LEDs irradiating the reactor plate). Note: Two separate panels were used for various experiments in this study (panel 1 = 340, 375, 395, 422, 450, 540 nm; panel 2 = 365, 385, 405, 485, 610 nm and "4000K" white light; see

Supporting Information Figure S2 and Figure S3 for emission spectra). °Yield was calculated by the ratio of starting material to product by GC, since only one product was observed.

Since the reaction performance could not be improved by selecting a different LED wavelength, six alternative photosensitizers were examined, in attempt to achieve better overlap with the available LED output (Table 2). None gave a comparable level of conversion, with only a small extent of reaction observed with 4,4'-dimethoxybenzophenone (entry 4) and thioxanthone (entry 6). This can easily be explained by the poor spectral overlap (when a sensitizer's triplet energy is high), or by insufficient triplet energy (when good spectral overlap is achieved). In order to enable a predictive method of matching substrates and sensitizers, the triplet energies of these sensitizers were obtained using DFT calculations and compared to literature values. A screen of methods and basis sets revealed M06-2X at a TZVP level of theory to be most suitable, whilst still allowing these calculations to be completed quickly on a standard desktop computer.²¹ Experimental determination of triplet energies requires specialized equipment,²² so these data are not readily available. Accordingly, this method of comparison will be especially beneficial, particularly for reaction substrates and more exotic sensitizers. The trend between sensitizer triplet energy and absorption spectrum can be seen clearly and, as would be expected, higher triplet energies require absorption of more energetic (shorter) wavelengths.

Table 2. A Selection of Triplet Sensitizers, Displaying their Triplet Energies as Found Using DFT Calculations Compared with Experimental Literature Values, Alongside their Wavelength of Maximum Absorption (λ_{max}), and Extent of Reaction of Maleic Anhydride (1) with Ethylene.

Entry	Sensitizer	Calculated ET ₁ [kcal mol ⁻¹] ²³	Experimental ET ₁ [kcal mol ⁻¹]	λ _{max} [nm]	Experimental yield 3 [%] ^a
1	Xanthone (4)	74.6	74.2 ^{22a}	338	0
2	Acetophenone (5)	72.4	73.6 ^{22a}	318	0
3	Benzaldehyde (6)	70.7	71.9 ^{22a}	325	0
4	4,4'-Dimethoxy benzophenone (7)	72.7	69.4 ^{15c}	335	4
5	Benzophenone (2)	69.2	68.5 ^{22a}	343	12
6	Thioxanthone (8)	65.5	65.5 ^{22a}	377	4
7	Fluorenone (9)	54.8	53.3 ^{22a}	397	0

Reaction conditions: 0.05 equiv sensitizer loading, 0.5 M concentration in EtOAc, 0.5 mL/min substrate flowrate, 1.25 mL/min ethylene flowrate. ^aYield was calculated by the ratio of starting material to product by GC, since only one product was observed.

This observation appears to limit the synthetic application of light sources emitting at wavelengths >340 nm, since longer wavelengths only allow lower energy triplet states to be achieved. From the obtained UV-vis absorption spectra (Table 2), thioxanthone (8) (entry 6)²⁴ appears to provide a good overlap with the output of several available LEDs (365, 375, 385 nm), with an appreciably high triplet energy. Furthermore, multiple recent publications have found thioxanthone and its derivatives to be effective triplet sensitizers, at low loadings, for a range of transformations including intra-²⁵ and intermolecular²⁶ [2+2] cycloadditions, halogenations²⁷ and radical polymerizations.²⁸ Accordingly, further DFT calculations were undertaken, in order to guide the choice of substrate towards one which might undergo effective triplet transfer with thioxanthone (8). The addition of a single methyl group to the backbone of maleic anhydride (1) was calculated to reduce the triplet energy by 3.2 kcal/mol, which prompted experimental

examination of its performance in this [2+2] cycloaddition reaction. Pleasingly, the observation held true experimentally and complete conversion to the cyclobutane product was observed within a short residence time, using a significantly lower sensitizer loading (Scheme 3Error! Reference source not found.). The lower sensitizer loading can be explained by comparing the extinction coefficients of both sensitizers, since poorer light absorption will ultimately result in a lower triplet state population. Benzophenone (2) has a very low coefficient of 34 M⁻¹ cm⁻¹, whilst that of thioxanthone (8) is 6265 M⁻¹ cm⁻¹ (roughly 200 times higher),²⁹ meaning that a far lower sensitizer concentration is required in the reaction mixture to absorb all of the incident light.



Scheme 3. Modification of starting material from maleic anhydride (1) to citraconic anhydride (10), and accompanying improvement in reaction performance, when using a low loading of thioxanthone (8) as a photosensitizer.

A detailed examination of the reaction parameters was carried out (Table 3), following complete conversion observed at 0.5 mL/min (entry 1). The residence time could not be reduced any further, as shown by the incomplete conversion observed at higher flow rates (entry 2 and 3),

and use of acetone as an alternative solvent resulted in no change (entry 4). Increasing the concentration was attempted to improve productivity, but was observed to reduce conversion (entry 5), thought to be due to the shorter residence time caused by the increased ethylene flow rate. Accordingly, the ethylene flow rate was reduced to provide only 1.5 equiv, yet this further reduced the reaction yield (entry 6). A lower photosensitizer loading gave a slightly reduced yield (entry 7 vs entry 2), yet a higher loading also gave a decrease in yield (entry 8 vs entry 2), implying that complete light absorbance within this channel depth (0.4 mm) is achieved between 2.5-5 mol% sensitizer loading (12.5 to 25 mM concentration). Furthermore, the same quantity of thioxanthone 8 was observed by GC before and after the reaction, so no decomposition or photobleaching occurred under the reaction conditions. Direct translation to the more widely available 385 nm LEDs showed a slight decrease in yield (entry 9), so a lower flow rate of 0.45 mL/min was necessitated to achieve full conversion (entry 10). To test the influence of incident oxygen upon the reaction, it was performed without degassing the reaction mixture (entry 11). The resulting lack of any reaction (all starting material remained unchanged) clearly demonstrates the importance of excluding oxygen from these reactions; assumedly due to competitive deactivation of the excited thioxanthone species. These studies led to the optimal conditions for this transformation, providing an exceptional space-time-yield of 759 g L^{-1} h⁻¹ (productivity of 2.1 g h^{-1}) with complete starting material conversion.

Table 3. Optimization of the [2+2] Photocycloaddition of Citraconic Anhydride (10) withEthylene.

Entry	Reaction	Sensitizer	Solution	Ethylene	Residence	Irradiation	Yield	Productivity	Space
	conc.	loading	flow rate	flow rate	time	wavelength	11	[g h ⁻¹]	time
	[M]	[mol%]	[mL/min]	[mL/min]	[min] ^a	[nm]	[%] ^b		yield
				/ equiv					[g h⁻
									L-1]
1	0.5	2.5	0.5	1.25 / 2.5	5.2	375	>99	2.10	759
2	0.5	2.5	1	2.5 / 2.5	2.6	375	69	2.90	1 047
3	0.5	2.5	0.6	1.5 / 2.5	4.3	375	97	2.45	883
4 ^c	0.5	2.5	1	2.5 / 2.5	2.6	375	69	2.90	1 047
5	0.6	2.5	0.5	1.5 / 2.5	5.2	375	96	2.42	874
6	0.6	2.5	0.5	0.9 / 1.5	5.2	375	87	2.19	792
7	0.5	1.25	1	2.5 / 2.5	2.6	375	59	2.48	896
8	0.5	5	1	1.5 / 1.5	2.6	375	64	2.69	972
9	0.5	2.5	0.5	1.25 / 2.5	5.2	385	95	2.02	729
10	0.5	2.5	0.45	1.13 / 2.5	5.7	385	>99	1.89	683
11d	0.5	2.5	0.45	1.13 / 2.5	5.7	385	0	-	-

used as reaction solvent ^dReaction was run without prior degassing.

Application to Other Substrates

Having previously observed an excellent correlation between calculated and experimental triplet energies of triplet sensitizers (Table 2), it was decided that a useful expansion of this computational system would be to include reaction substrates for comparison and choice of sensitizer. In this manner a sound estimate can be made, of which triplet sensitizer is suitable to undergo triplet transfer towards a chosen substrate. Following this strategy could have a significant impact upon the time and resource spent optimizing a [2+2] cycloaddition (or other triplet sensitized reaction). Furthermore, an estimate of the most applicable triplet sensitizers will help guide the choice of light source, potentially limiting wasted investment in poorly-matched equipment. A range of substrates known to undergo [2+2] cycloadditions were selected, and their triplet energies calculated by DFT, by the same method and basis set used previously (M06-2X/TZVP). Subsequently, their reactivity was examined using two sets of conditions, similar to those described in the benzophenone-sensitized reaction of maleic anhydride (1) and the thioxanthone-sensitized reaction of citraconic anhydride (10) (Table 4). Due to the low extinction coefficient of benzophenone (2) at 375 nm (see discussion above), a far higher loading (40 mol% vs 2.5 mol%) was used, as decided upon in previous optimization studies (see Supporting Information Table S8).

Of the substrates examined, maleimides **12** and **13** (entry 1 and 2) had the lowest triplet energies, and were both observed to undergo complete conversion under both sets of reaction conditions. The triplet energies of *N*-phenylmaleimide was also calculated, but was found to be insoluble under the standard conditions, so could not be examined experimentally. Citraconic anhydride (**10**) (entry 3) was found to have a very similar triplet energy to maleimide (**13**) and was already been shown to react smoothly under sensitization by thioxanthone (**8**), but also undergoes effective cycloaddition under benzophenone-sensitized conditions. Isophorene (**14**) (entry 4) was calculated to have a significantly higher triplet energy of 72.1 kcal/mol, yet undergoes a reasonable extent of reaction (52% conversion) with thioxanthone sensitization. This result implies that the calculated triplet energy in this case could be significantly erroneous, particularly when considering the lower triplet energy of cyclohexanone (**15**) (entry 5). Based on previous trends and the observed experimental results, the inclusion of a methyl group at the enone carbon should lower the triplet energy. Some reaction of cyclohexanone (**15**) was still observed using

thioxanthone, but far lower than the corresponding benzophenone-sensitized reaction. Finally, the triplet energy of maleic anhydride (1) was too higher for effective reaction with thioxanthone, but, as discussed earlier, underwent productive reaction with benzophenone.

Table 4. Calculated Triplet energies of Selected Substrates Compared with their ReactionPerformance, Using Thioxanthone (2.5 mol%) or Benzophenone (40 mol%) as thePhotosensitizer

Entry	Substrate	Calculated E _{T1} [kcal mol ⁻¹] ^a	Conversion with thioxanthone 8 $(E_T = 65.5) [\%]^b$	Conversion with benzophenone 2 $(E_T = 68.5) [\%]^{\circ}$
1	0 0 Bn 12	60.0	>99	>99
2	0 N H 13	62.5	>99	>99
3	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	62.6	>99	>99
4		72.1 ^d	52	84
5	O 15	65.2	12	72
6		65.8	4	89

^aTriplet energies calculated by DFT: M06-2X/TZVP. Conditions: LED irradiation at 375 nm, ^bthioxanthone conditions: 2.5 mol% sensitizer, 0.5 mL/min solution flow rate, 1.25 mL/min (2.5 equiv) gas flow rate, residence time \approx 5.2 min. ^cbenzophenone conditions: 40 mol% sensitizer, 0.25 mL/min solution flow rate, 0.625 mL/min (2.5 equiv) gas flow rate, residence time \approx 10.4 min. ^dCalculated triplet energy is likely erroneous, particularly when considered with the experimental conversion observed and versus entry 5.

From the examined substrates, it was observed that maleimides generally have a lower triplet energy than their anhydride analogues. Accordingly, further optimization using *N*-benzylmaleimide (**12**) was carried out to determine the maximum productivity which could be achieved with this substrate. Analogous to the example described earlier, multiple LED wavelengths were examined for their efficacy in this thioxanthone-sensitized reaction (Table 5), using a faster flowrate to improve the impact of different wavelengths on these incomplete reactions. 365 nm LEDs displayed a reasonable rate of reaction, yet this was surpassed by both 375 nm and 385 nm. A wavelength of 385 nm provides a poor overlap with catalyst absorbance, yet the LED power is considerably higher. On the other hand, 375 nm lies close to the catalyst's λ_{max} and these LEDs still provide a high radiant flux. Following additional optimization experiments (see Supporting Information, Table S13) almost complete conversion (98% yield) was still observed at a minimum residence time of ~2.23 min (1.15 mL/min substrate flow rate, 2.88 mL/min ethylene flow rate), yielding an impressive space-time-yield of 2285 g L⁻¹ h⁻¹.

Table 5. Results of Thioxanthone-sensitized Reaction Protocol at Varying LED Wavelengths at 1.5 mL/min Flowrate, Including a Graphical Representation of Thioxanthone Absorption Spectrum with the Examined LED Wavelengths Appended.



The UV/vis spectrum was measured in ethyl acetate at a concentration of 0.225 mM. Conditions: 2.5 mol% thioxanthone, 1.5 mL/min solution flow rate, 3.75 mL/min (2.5 equiv) gas flow rate, residence time ≈ 1.7 min. ^aWavelengths listed are the target maximum output wavelength, as taken from the LED specification sheet; the actual value may vary by ±5 nm. ^bRadiant flux values were obtained from the LED specification sheets for a single LED, then multiplied by 40 (the total number of LEDs irradiating the reactor plate). Note: Two separate panels were used for various experiments in this study (panel 1 = 340, 375, 395, 422, 450, 540 nm; panel 2 = 365, 385, 405, 485, 610 nm and "4000K" white light; see Supporting Information Figure S2 and Figure S3 for emission spectra). °Yield was calculated by the ratio of starting material to product by GC, since only one product was observed.

Scale-up

With the optimal conditions for the cycloaddition of citraconic anhydride (**10**) in hand (Table 3), our interest turned to the scalability of this system, due to its improved commercial availability versus maleimides. Flow chemistry is known to be an enabling technology for a wide variety of chemical transformations, as exemplified in numerous cases.³⁰ However, the use of photochemistry introduces further complexity, and these processes have only scarcely been demonstrated on industrially relevant scales. The Corning Advanced-FlowTM Lab Photo Reactor, utilized in these small scale trials, has an irradiated volume of only 2.77 mL. In order to produce material to satisfy demands, for use in API synthesis for example, a system with a larger irradiated volume must be introduced to implement faster flow rates. To tackle this issue, the Corning G1 Photo Reactor suggests to provide seamless scale up from the "Lab" model, by allowing the placement of multiple plates in series.¹⁹ For initial scale-up endeavors, five "low flow" plates (2.77 mL volume each, as used in the optimization experiments) were connected in series, essentially elongating the reactor to give a total irradiated volume of 13.85 mL (Scheme 4, Figure 1).



Figure 1. Reaction setup for larger scale demonstration, using a Corning G1 Photo Reactor, with 5×2.77 mL reaction plates installed.

The reaction conditions from the lab scale optimization were maintained by simply scaling the flow rates by a factor of 5 for the G1 experiments (2.5 mL/min), providing a consistent irradiated residence time of \sim 5.5 min (an estimate, due to changes in volume caused by dissolution

and consumption of ethylene gas along the reaction pathway). Gratifyingly, the reaction performed to an identical standard when compared with the lab scale results. Complete conversion of the starting material was observed in all of the eleven analytical samples, taken at increments across a 10 h runtime (see Supporting Information, Figure S5). In this time, 1.5 L of reaction mixture was processed, resulting in 101.3 g (96%) of the desired product, after evaporation of solvent. Aside from the added triplet sensitizer (2.5 mol%), this material was found to be pure by NMR analysis.



Scheme 4. Flow schematic showing the conditions used for an extended run in the Corning G1 Photo Reactor.

3. Conclusion

We have demonstrated an in-depth study of photochemical [2+2] cycloadditions, using simple *in silico* calculations to reinforce experimental observations and guide reaction optimization. Initial optimization work using maleic anhydride as a reaction substrate had only limited success, which was caused by a poor overlap of LED output with sensitizer (benzophenone) absorbance. The relatively high triplet energy of maleic anhydride means that other sensitizers were ineffective in triplet transfer, resulting in no reaction – an effect corroborated by DFT-calculated triplet energies. Modification of the reaction substrate was shown to have a dramatic effect on the calculated triplet energy. It was found that addition of a methyl group to the substrate (citraconic anhydride) reduced its triplet energy by 3.2 kcal/mol. Subsequently, this brings the substrate into the range of triplet transfer from thioxanthone, whose absorbance ($\lambda_{max} = 377 \text{ nm}$) overlaps well with available LEDs. This effective overlap allows the sensitizer loading to be lowered to 2.5 mol%, giving complete conversion at higher flowrates up to 0.5 mL/min.

The triplet energies of additional substrates were also examined using DFT calculations, and their reactivities compared with the two distinct sensitizer systems. In general, these calculated energies correlated well with the experimental conversion observed, implying that using a straightforward DFT method (with a very low computational cost) could be very beneficial in the design of this type of chemical system, particularly in the choice of triplet sensitizer. Implementing such computationally-guided sensitizer selection has the potential to speed up development of chemical processes and save a great deal of resource – both material and FTE time. Finally, scale-up of the citraconic anhydride cycloaddition was achieved by simply running the reaction mixture through 5×2.77 mL reactor plates in series, using a Corning G1 Photo Reactor. This strategy enabled production of >100 g of material over 10 h, demonstrating a stable system over a long period of time.

EXPERIMENTAL SECTION

General Procedure for Small Scale [2+2] Cycloadditions Lab Photo Reactor.

Using a Zaiput back pressure regulator, a pressure of 12 bar was set. The array of 40×375 nm LEDs was switched on and its thermal fluid was set to 15 °C. The reaction plate thermostat was set to 25 °C. A solution of citraconic anhydride (**10**) (280 mg, 2.5 mmol) and thioxanthone (**8**) (13.3 mg, 0.0625 mmol) was made up in degassed ethyl acetate (5 mL total volume in a volumetric flask, solvent was degassed prior to use by sparging with argon for 15 min) and loaded into a 5 mL injection loop (with an Upchurch 6-way valve, see Supporting Information for further details). Ethyl acetate was pumped through the 2.77 mL reaction plate at a flowrate of 0.5 mL/min. Simultaneously, ethylene was introduced from a pressurized cylinder, via a Bronkhorst mass flow controller, at a flowrate of 15 mL/min (2.5 equiv, roughly 1.25 mL/min at 12 bar). After allowing the reactor to equilibrate for roughly 15 min, the reaction mixture was injected from the sample loop. The central 1 mL portion of this sample was collected for analysis by gas chromatography.

Long Run Synthesis of 3-Oxabicyclo[3.2.0]heptane-2,4-dione (3) in Lab Photo Reactor, Scheme 2:

Using a Zaiput backpressure regulator, a pressure of 12 bar was set. The 40 LED array was switched on at 375 nm and its thermal fluid was set to 15 °C. The reaction plate thermostat was set to 25 °C. A 0.5 M solution of maleic anhydride (1) (2.45 g, 25 mmol) and benzophenone (2) (2.73 g, 15 mmol) was made up in degassed ethyl acetate (~50 mL) (solvent was degassed prior to use by sparging with argon for 15 min). Reaction solution was pumped through the 2.77 mL reaction plate at 0.2 mL/min. Simultaneously, ethylene was introduced from a pressurized cylinder, via a Bronkhorst mass flow controller, at 0.5 mL/min. After allowing the reactor to equilibrate for roughly 15 min, the processed reaction mixture was collected for 175 min, amounting to a total collected volume of 35 mL. From the resulting solution, solvent was removed in vacuo, yielding a white solid. To this solid was added cyclohexane (5 mL), and the solid collected again by filtration, then washed with further cyclohexane (5 \times 5 mL). The liquor was evaporated in vacuo, yielding recovered benzophenone (2) (1.75g, 92%). The filtered product was identified as 3-oxabicyclo[3.2.0]heptane-2,4-dione (3)⁸ as an off-white solid (1.86 g, 84% yield, adjusted for 5.5% benzophenone content by NMR). ¹H NMR (300 MHz, CDCl₃) δ 3.53-3.43 (m, 2H), 2.79–2.64 (m, 2H), 2.44–2.28 (m, 2H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ 173.6, 38.9, 23.3 ppm.

Synthesis of 3-Benzyl-3-azabicyclo[3.2.0]heptane-2,4-dione (16) in Lab Photo Reactor, Table 4, entry 1:

Using a Zaiput back pressure regulator, a pressure of 12 bar was set. The array of 40×375 nm LEDs was switched on and its thermal fluid was set to 15 °C. The reaction plate thermostat was set to 25 °C. A solution of *N*-benzylmaleimide (**12**) (468 mg, 2.5 mmol) and thioxanthone (**8**) (13.3 mg, 0.0625 mmol) was made up in degassed ethyl acetate (5 mL total volume in a volumetric flask, solvent was degassed prior to use by sparging with argon for 15 min) and loaded into a 5 mL injection loop (with an Upchurch 6-way valve, see Supporting Information for further details).

Ethyl acetate was pumped through the 2.77 mL reaction plate at a flowrate of 0.5 mL/min. Simultaneously, ethylene was introduced from a pressurized cylinder, via a Bronkhorst mass flow controller, at a flowrate of 15 mL/min (2.5 equiv, roughly 1.25 mL/min at 12 bar). After allowing the reactor to equilibrate for roughly 15 min, the reaction mixture was injected from the sample loop. 10 mL of reaction mixture was collected, to take into account for forward and backward diffusion within the reactor. Solvent was removed *in vacuo* to afford a yellow oil, which was purified by column chromatography; elution gradient 0-50% ethyl acetate in cyclohexane. The appropriate fractions were combined and solvent removed *in vacuo* to afford 3-benzyl-3-azabicyclo[3.2.0]heptane-2,4-dione (16)^{2d} as a pale yellow solid (512 mg, 95% yield). ¹H NMR (300 MHz, CDCl₃) δ = 7.41–7.37 (m, 2H), 7.35–7.26 (m, 3H), 4.70 (s, 2H), 3.30–3.25 (m, 2H), 2.66–2.63 (m, 2H), 2.13–2.10 (m, 2H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ = 179.5, 136.0, 128.7, 128.6, 127.9, 42.5, 38.4, 22.9 ppm.

Scale-up Synthesis of 1-Methyl-3-oxabicyclo[3.2.0]heptane-2,4-dione (11) in G1 reactor, Scheme 4:

Using a Zaiput back pressure regulator, a pressure of 12 bar was set. The arrays of 375 nm LEDs were switched on and their thermal fluid was set to 10 °C. The reaction plate thermostat was set to 25 °C. A solution of citraconic anhydride (**10**) (89.66 g, 800 mmol) and thioxanthone (**8**) (4.29 g, 20 mmol) was made up in degassed ethyl acetate (1.6 L) (sparged with an argon for 30 min). This reaction solution was pumped through the 14 mL series of reaction plates (5×2.8 mL) at a flowrate of 2.5 mL/min. Simultaneously, ethylene was introduced from a cylinder, via a BROOKS mass flow controller, at a flowrate of 74 mL/min (2.5 equiv, roughly 6.2 mL/min at 12 bar). An equilibration period of 15 min was allowed, then the output solution was collected for 10 hours, with samples taken for GC analysis roughly every hour. 1.5 L of product solution was collected and solvent was removed *in vacuo*, yielding 1-methyl-3-oxabicyclo[3.2.0]heptane-2,4-dione (**11**)³¹ as a pale yellow solid (101.3 g, 96% yield, adjusted for 2.5% thioxanthone content by NMR). ¹H NMR (400 MHz, CDCl₃) δ 3.19–3.16 (m, 1H), 2.74–2.69 (m, 1H), 2.59–

2.56 (m, 1H), 2.34–2.27 (m, 2H), 1.52 (s, 3H) ppm. ¹³C NMR (100.6 MHz, CDCl₃) δ 176.3, 173.0, 45.6, 43.3, 30.3, 20.1, 19.3 ppm.

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Supporting Information

Further details of optimization experiments, general experimental procedures, equipment details and setup, NMR and GC data and full details of DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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