Supporting Information

Towards a Scalable Synthesis of 2-Oxabicyclo[2.2.0]hex-5-en-3-one Using Flow Photochemistry

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1. General information

1.1. Materials and Methods

All solvents and chemicals were obtained from standard commercial vendors (Sigma-Aldrich or TCI) and were used without any further purification, unless otherwise noted.

**NMR spectra:** $^1$H NMR spectra were recorded on Bruker 300 or 400 MHz instruments. $^{13}$C NMR spectra were recorded on the Bruker 300 or 400 MHz instrument at 75 or 100.6 MHz respectively. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, dd, t, q, and m are used to indicate singlet, doublet, doublet of doublets, triplet, quadruplet, and multiplet respectively.

**Low field NMR:** reactor output was analyzed by $^1$H NMR, using a low field benchtop NMR (Magritek Spinsolve Ultra, running proton experiments at 43 MHz).

**UV/Vis:** spectra were recorded using a fiber-coupled Avantes Starline AvaSpec-2048 spectrometer, with an Avantes AvaLight-DHc lamp as the light source. These spectra were manipulated using Avasoft 8.7 software.

**Light source characterization:** emission spectra were recorded using a fiber-coupled Avantes Starline AvaSpec-2048 spectrometer, and were manipulated using Avasoft 8.7 software.

**Flash column chromatography:** Automated flash column chromatography was performed on a Biotage Isolera system using columns packed with KP-SIL, 60 Å (32–63 μm particle size) silica.
1.2. Flow Reactor Setup

1.2.1. Corning Lab Photo Reactor system (375 nm high power LEDs)

This commercial setup was used for triplet-sensitized experiments presented in manuscript Scheme 2.

A glass plate-based Corning Advanced-Flow Photo Reactor system was used as shown in Figure S1. The emission spectra of the light source is indicated in manuscript Scheme 2 and Figure S2. The volume of the flow path exposed to the light source was 2.77 mL.

Figure S1. Corning Advanced-Flow Photo Reactor setup used for experiments with high power LEDs.

Figure S2. Emission spectrum of high power 375 nm LEDs, used for experiments using the Corning Photo Reactor setup (Figure S1).
1.2.2. 8 W lamp home-made setup (254, 365, 303 nm tube lamps)

This setup was used for the exploratory experiments presented in Table S2 and for manuscript Table 1, entries 1-3.

A flow photoreactor made using a 8W T5 UV-C lamp (254 nm), 8W T5 UV-B lamp (303 nm) or 8W T5 UV-A lamp (365 nm) with PFA tubing (o.d. 1/16 in, i.d. 1/32 in, 0.8 mm) was constructed as shown in Figure S3. The emission spectra of these light sources are shown in Figure S4, Figure S5 and Figure S6. A length of the PFA tubing (2 mL) was wrapped around the light source. A Syrris Asia syringe pump was used to pump solvent through the home-made reactor. 5 mL of reactant solution was injected through a sample loop for each experiment, using a 2-position, 6-port injection valve assembly (V-450, IDEX Health and Science).

Figure S3. Flow chemistry setup for reactions using T5 lamps (254, 303, or 365 nm).
**Figure S4.** Emission spectrum of 254 nm 8W T5 UVC lamp.

**Figure S5.** Emission spectrum of 303 nm 8W T5 UVB lamp.

**Figure S6.** Emission spectrum of 365 nm 8W T5 UVA lamp.
1.2.3. Vapourtec UV-150 system (setup for optimization experiments)

This setup was used for the optimization experiments presented in manuscript Table 1, entries 4-10, as well as Table S3 and Table S4.

A Vapourtec UV-150 photochemical reactor system, equipped with 3 × V-3 peristaltic pumps, was used as shown in Figure S7. A medium pressure mercury lamp and band-pass filter (#2) were installed in the UV-150 reactor system, in the center of a 10 mL coil of PFA tubing (see Figure S16). The emission spectra of this light source is shown in Figure S8. 5 mL of reactant solution was injected through a sample loop for each experiment, using a 2-position, 6-port injection valve assembly (V-450, IDEX Health and Science).

Figure S7. Vapourtec UV-150 setup used for optimization experiments.

Figure S8. Emission spectrum of medium pressure Hg lamp with band-pass filter #2.
Figure S9. Transmission spectra of band-pass filters. Image courtesy of Vapourtec Ltd. (https://www.vapourtec.com/products/flow-reactors/photochemistry-uv-150-photochemical-wavelength-filters/)
1.2.4. Vapourtec UV-150 system (setup for scale-out experiments)

This setup was used for the scale-out experiments presented in manuscript Figure 2a.

A Vapourtec UV-150 photochemical reactor system, equipped with 3 × V-3 peristaltic pumps, was used as shown in Figure S10. A medium pressure mercury lamp and band-pass filter (#2) were installed in the UV-150 reactor system, in the center of a 10 mL coil of PFA tubing (see Figure S16). The emission spectra of this light source is shown in Figure S8. Reactor cooling was achieved using a stream of compressed air. When set to 10 °C, cardice was used to precool this stream.

Figure S10. Vapourtec UV-150 setup used for scale-out experiments.
2. DFT Assessment of 2-Pyrone Triplet Energy

Computational methods:
Calculations were carried out on a standard desktop computer (Intel Core i5-4590 3.30 GHz processor, 8 GB RAM); no specialist hardware was required. Density functional theory (DFT) calculations were carried out using the Gaussian09 software package. M06-2X/TZVP basis set on all atoms was chosen for all further calculations. Solvation was modelled implicitly, using a conductor-like polarizable continuum model (CPCM) with Et₂O (“DiethylEther”, ε = 4.240) assigned as the solvent. All structures were found as energy minima, with frequency calculations performed, to verify zero imaginary frequencies. GaussView 5.0.9 was used for the visualization of structures. Details of optimized structures are presented below. The quoted triplet energy was calculated by simply subtracting the ground state singlet energy (multiplicity 1) from the ground state triplet energy (multiplicity 3).

Figure S11. Representation of optimized singlet and triplet state structures of 2-pyrone 1.
Table S1. Summary of DFT calculations used to estimate triplet energy of 2-pyrone 1.

|                      | Singlet state | Triplet state |
|----------------------|---------------|---------------|
| Route                | Opt Freq M062X/TZVP FormCheck scrf=(CPCM,solvent=DiethylEther) | Opt Freq M062X/TZVP FormCheck scrf=(CPCM,solvent=DiethylEther) |
| Charge               | 0             | 0             |
| Multiplicity         | 1             | 3             |
| Gibbs energy (a.u.)  | –343.301575   | –343.208019   |
| Gibbs energy (kcal/mol) | –216279.9923 | –216221.052   |
| # Imaginary frequencies | 0            | 0             |

Optimized coordinates:

**Singlet**

| Symbol | X      | Y      | Z      |
|--------|--------|--------|--------|
| C      | 0.2553440 | 1.2523850 | -0.0000110 |
| C      | -1.0923080 | 1.1996280 | 0.0000100 |
| C      | -1.7687500 | -0.0621450 | 0.0000020 |
| C      | -1.0193730 | -1.1732620 | 0.0000100 |
| C      | 1.0455080  | 0.0383200  | -0.0000440 |
| H      | 0.8075360  | 2.1805860  | 0.0000080 |
| H      | -1.6715600 | 2.1145040  | 0.0000180 |
| H      | -2.8451220 | -0.1335580 | 0.0000050 |
| H      | -1.3982420 | -2.1850010 | 0.0000000 |
| O      | 0.3266340  | -1.1434050 | -0.0000060 |
| O      | 2.2464740  | -0.0448560 | 0.0000270 |

**Triplet**

| Symbol | X      | Y      | Z      |
|--------|--------|--------|--------|
| C      | -0.2258260 | 1.2484400 | -0.0000710 |
| C      | 1.2300790  | 1.1664970 | 0.0000390 |
| C      | 1.7693250  | -0.0697750 | -0.000050 |
| C      | 0.9482970  | -1.2362880 | 0.0000250 |
| C      | -1.0401910 | 0.0706180  | -0.0003540 |
| H      | -0.7548660 | 2.1886770  | 0.0000900 |
| H      | 1.8268540  | 2.0653000  | 0.0002920 |
| H      | 2.8398510  | -0.2268700 | 0.0000900 |
| H      | 1.3169920  | -2.2475120 | 0.0001160 |
| O      | -0.4155310 | -1.1683350 | 0.0000330 |
| O      | -2.2493360 | 0.0612670  | 0.0001970 |
3. Procedure for Triplet-sensitized Reaction (manuscript Scheme 2)

Scheme S1. Reaction scheme depicting the setup used for triplet-sensitized reaction of 2-pyrone 1.

The reaction setup detailed in Figure S1 was used. See above for further details.

A solution of pyrone 1 (240 mg, 2.5 mmol) and thioxanthone (10.6 mg, 0.05 mmol) was made up in MTBE (100 mL) which had been degassed by sparging with argon for 15 minutes prior to use. The reactor temperature was set to 20 °C and the array of 375 nm LEDs was turned on at 100% power.

The reaction solution was pumped through the reactor directly. For the first 10 min the reactor eluent was diverted to waste in order to allow the system to reach steady state. The following 50 mL (36.1 min) of reaction eluent was collected and solvent removed in vacuo. The resulting orange residue was purified by flash column chromatography (0-25% acetone in DCM) to afford dimeric products 3 and 4 as a mixture of diastereomers (77 mg, 64%) in a ratio of 3:1 (3:4) by NMR.

The diastereomers were separated by preparative thin-layer chromatography (solvent system: 25% acetone in DCM) to afford diastereomer 3 (8 mg, 7%) as a pale yellow solid and diastereomer 4 (12 mg, 10%) as a pale yellow solid.
4a,5,8,8a-tetrahydro-1H-8,5-(epoxymethano)isochromene-1,10-dione (3)

\[ \text{Formula} \]

\[ \text{NMR} (300 \text{ MHz, DMSO}) \delta 6.71 - 6.61 (m, 3H, H7 H8 H11), 5.61 (dd, J = 4.6, 1.9, 1.7 Hz, 1H, H2), 5.30 (dd, J = 6.4, 3.7 Hz, 1H, H12), 3.60 - 3.58 (m, 1H, H6), 3.37 (dd, J = 11.5, 1.7 Hz, 1H, H3), 2.80 - 2.75 (m, 1H, H5).

\[ \text{NMR characterization matches that reported in the literature.} \]^{[55]}

4a,5,8,8a-tetrahydro-2H-8,5-(epoxymethano)chromene-2,10-dione (4)

\[ \text{Formula} \]

\[ \text{NMR} (300 \text{ MHz, DMSO}) \delta 6.87 (dd, J = 10.1, 4.1 Hz, 1H, H12), 6.73 (ddd, J = 7.7, 6.2, 1.8 Hz, 1H, H8), 6.55 (ddd, J = 7.7, 5.1, 1.6 Hz, 1H, H7), 5.99 (dd, J = 10.1, 2.1 Hz, 1H, H11), 5.44 - 5.39 (m, 1H, H2), 5.02 (dd, J = 9.9, 1.6 Hz, 1H, H3), 3.70 - 3.64 (m, 1H, H6), 2.99 (dddd, J = 9.9, 4.1, 2.1, 1.6 Hz, 1H, H5).

\[ \text{NMR characterization matches that reported in the literature.} \]^{[55]}
4. General Procedure for Optimization Experiments

Scheme S2. Reaction scheme depicting the setup used for optimization experiments.

The reaction setup detailed in Figure S7 was used. See above for further details.

A solution of pyrone 1 was made up to the desired concentration in degassed MTBE (sparged with argon for 15 minutes prior to use). 5 mL of this solution was loaded into a sample loop, attached to a 6-way valve. The Hg lamp was ignited, reactor temperature set and MTBE was pumped through the photoreactor at the desired flow rate for at least 3 residence times before the sample was injected. To minimize the effect of sample diffusion through the reactor, the central 1 mL portion of reaction mixture output was collected and analyzed directly by low-field $^1$H NMR. Conversion was calculated by comparing the integration of product cyclobutene 2[S4] with unconsumed 2-pyrone 1.
5. Additional Reaction Optimization Data

Table S2. Initial screening of different light sources.

| Entry | Light source | Solvent | Conversion [%] |
|-------|--------------|---------|----------------|
| 1     | 254 nm 8 W UV Lamp (Figure S3, Figure S4) | Et₂O | 0 |
| 2^b   | 303 nm 8 W UV Lamp (Figure S3, Figure S5) | MTBE | 47 |
| 3     | 365 nm 8 W UV Lamp (Figure S3, Figure S6) | THF | 0 |
| 4     | Vapourtec Hg lamp with #2 filter (Figure S7, Figure S8) | MTBE | 56 |

^aConversion was determined by low field NMR, using the ratio of starting material 1 versus product 2. ^bReaction was carried out using an increased residence time of 10 min.

Table S3. Screen of reaction solvents. See Figure S7 for reaction setup.

| Entry | Solvent | Conversion [%]^a |
|-------|---------|-----------------|
| 1     | Et₂O    | 56              |
| 2     | MTBE    | 56              |
| 3     | THF     | 62              |
| 4     | EtOAc   | 61              |
| 5     | MeCN    | 66              |

For these reactions, a back-pressure regulator (Zaiput BPR-10) was used to apply a pressure of 4 bar to the reactor, in order to prevent solvent vaporization. ^aConversion was determined by low field NMR, using the ratio of starting material 1 versus product 2.
Table S4. Full details of concentration, residence time and temperature optimization experiments. See Figure S7 for reaction setup. Highlighted entries are included in manuscript Table 1.

| Entry | Concentration [mM] | Residence time [min] | Temperature [°C] | Conversion [%]a | Precipitation? |
|-------|--------------------|----------------------|------------------|----------------|----------------|
| 1     | 25                 | 5                    | 10               | 59             | -              |
| 2     | 25                 | 10                   | 10               | >95            | -              |
| 3     | 25                 | 20                   | 10               | >95            | -              |
| 4     | 25                 | 60                   | 10               | >95            | observed       |
| 5     | 50                 | 10                   | 10               | 64             | -              |
| 6     | 100                | 10                   | 10               | 37             | -              |
| 7     | 200                | 10                   | 10               | 22             | -              |
| 8     | 5                  | 20                   | 10               | >95            | -              |
| 9     | 100                | 40                   | 10               | >95            | observed       |
| 10    | 100                | 60                   | 10               | >95            | observed       |
| 11    | 200                | 60                   | 10               | 92             | observed       |
| 12    | 25                 | 10                   | 20               | >95            | -              |
| 13    | 25                 | 10                   | 30               | >95            | -              |
| 14b   | 200                | 10                   | 40               | 26             | observed       |
| 15    | 25                 | 5                    | 40               | 56             | -              |
| 16    | 25                 | 10                   | 40               | >95            | -              |
| 17    | 50                 | 20                   | 40               | >95            | -              |
| 18    | 50                 | 30                   | 40               | >95            | -              |
| 19    | 100                | 30                   | 40               | 87             | observed       |
| 20    | 50                 | 10                   | 40               | 58             | -              |
| 21    | 50                 | 15                   | 40               | 82             | -              |
| 22    | 100                | 20                   | 40               | 62             | -              |
| 23    | 100                | 40                   | 40               | >95            | observed       |

aConversion was determined by low field NMR, using the ratio of starting material 1 versus product 2. bReaction was carried out using a different band-pass filter (#5, see Figure S9).
6. General Procedure for Scale-Out Experiments

Scheme S3. Reaction scheme depicting the setup used for scale-out reactions.

The reaction setup detailed in Figure S10 was used. See above for further details.

A 350 mL (or 700 mL) solution of pyrone 1 (1.68 g, 17.5 mmol) was made up to 0.05 M (or 0.025 M) in degassed MTBE (sparged with argon for 15 min prior to use). The Vapourtec Hg lamp was ignited, reactor temperature set to 40 °C (or 10 °C) and the solution was pumped through the photoreactor at 0.5 mL/min (or 1 mL/min). Prior to beginning collection, the reactor output was diverted to waste for 1.5 reactor volumes. The reaction output was then collected in a flask cooled to 0 °C in an ice bath for the reaction duration of 8-10 h. The output stream was collected at intervals and analyzed directly by low-field 1H NMR. Conversion was calculated by comparing the integration of product cyclobutene 2[S1] with unconsumed 2-pyrone 1.

Note: when the reactor was set to 40 °C, dry ice was not used to provide additional cooling. As a result, the reactor temperature equilibrated around 50 °C.
7. NMR Spectra and Fouling Photos from Scale-out Reactions

7.1. 50 mM, 50 °C

Figure S12. Photograph of reactor coil following scale-out reaction at 50 mM concentration and 50 °C.

Figure S13. Stacked low-field NMR spectra, showing the ratio of products throughout a scale-out reaction at 50 mM concentration and 50 °C. See Figure S17 for a representative NMR spectrum of the starting solution.
7.2. 25 mM, 50 °C

**Figure S14.** Photograph of reactor coil following scale-out reaction at 25 mM concentration and 50 °C.

**Figure S15.** Stacked low-field NMR spectra, showing the ratio of products throughout a scale-out reaction at 25 mM concentration and 50 °C. See Figure S17 for a representative NMR spectrum of the starting solution.
7.3. 50 mM, 10 °C

Figure S16. Photograph of reactor coil following scale-out reaction at 50 mM concentration and 10 °C.

Figure S17. Stacked low-field NMR spectra, showing the ratio of products throughout a scale-out reaction at 50 mM concentration and 10 °C.
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9. NMR Spectra

4a,5,8,8a-tetrahydro-1H-8,5-(epoxymethano)isochromene-1,10-dione (3)
4a,5,8,8a-tetrahydro-2H-8,5-(epoxymethano)chromene-2,10-dione (4)
