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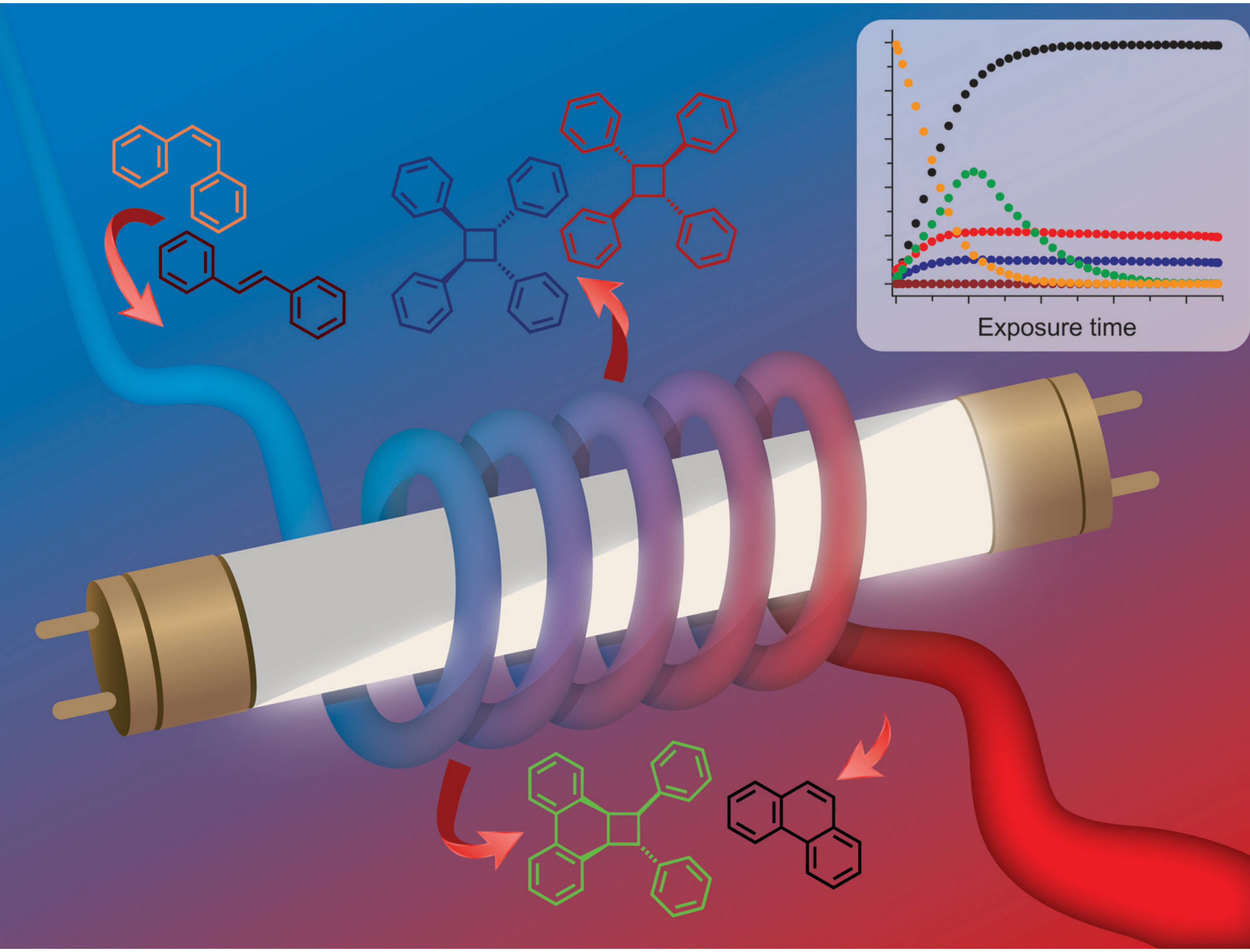

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The switch-off method: rapid investigation of flow photochemical reactions†

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In a flow photochemical process switching off the light source and monitoring the reaction composition as it leaves the photoreactor allows the effect of all irradiation times up to a maximum to be analysed in a single experiment. The switch-off method was illustrated using three reactions: [2 + 2] intermolecular photocycloadditions between an alkene and alkyne, and between two alkenes, and a Mallory photocyclization of *cis*-stilbene.

Introduction

Photochemical transformations performed using continuous flow have been an area of increasing interest in recent years,[1–6] due to the simplicity of reactor design and higher and more homogeneous photon flux in photochemical flow processes.[7] One such design was described by Booker-Milburn *et al.*[8] consisting of coils of UV transparent tubing wrapped around an immersion well with a high-pressure mercury UV lamp contained within. This design has been adapted with the use of low-power, wavelength-selective fluorescent tube bulbs[9] to allow operational simplicity, albeit with limited scale. A second design involves placing UV LEDs over a microfluidic chip[10] which has the benefit of being able to choose wavelength-specific LEDs to irradiate the sample, but the drawback is that UV LEDs below 300 nm are currently expensive. These designs are advantageous as they provide a small, precisely defined depth of reaction solution that the light must penetrate through in order to fully irradiate the solution.[11] This combined with the control of the irradiation time, *via* changing the flow rate or reactor size, and the uniformity of irradiation,[11] allows the user excellent control over the reaction conditions which can prevent over-irradiation to side products. Calculation of the quantum yield and thermal back reaction of photochemical reactions has also been demonstrated using flow photochemistry methods combined with modelling tools using a spiral-shaped microreactor and UV LEDs.[12] Additionally, the benefits[13] of performing reactions using flow chemistry are still present such as ease of using high pressure and temperatures,[14,15] faster heat transfer, and improved mixing.[16]

One of the drawbacks of flow chemistry is that reaction time is determined by flow rate so that, unlike batch chemistry where a reaction can be sampled at many time points to determine optimum reaction times, in flow separate experiments are required for each time point. An elegant solution has been developed based on introducing a step-change[17,18] or continuous change[19] in flow rate to allow many timepoints for a reaction to be observed in a single run, termed the 'push out' method. The use of multivariate analysis of continuously acquired data (for example IR[19] or UV-vis[17,20]) is particularly useful for the extraction of reaction data when these methods are used.

Herein we present an operationally simple method to obtain information on all irradiance times in a single flow photochemistry experiment by switching off the light source during a run (Fig. 1) and utilizing continuous in-line or off-line analysis of collected reaction fractions.[21,22] It has an advantage over the 'push out' method in that a step change in flow rates, which most commercial flow systems cannot automate, is not required and that exposure times from zero are captured.

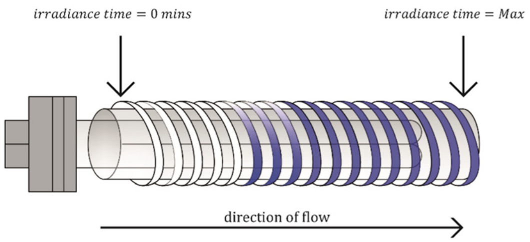

Fig. 1 Diagram of flow photochemical reactor after light source has been switched off showing the gradient of irradiance times throughout the reactor.

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Results and discussion

Reactor design

The photoreactor consisted of a single layer of PFA tubing (1 mm internal diameter) coiled around a quartz tube long enough to fit a 36 W fluorescent lamp inside. UV-A, B, C, and visible light bulbs at this power are cheap and easy to purchase and install. K-type thermocouples were installed at the beginning, centre, and end of photoreactor tubing, then aluminium foil was layered over, followed by a layer of tubing for water flow to cool the reactor if needed.[9]

Methodology

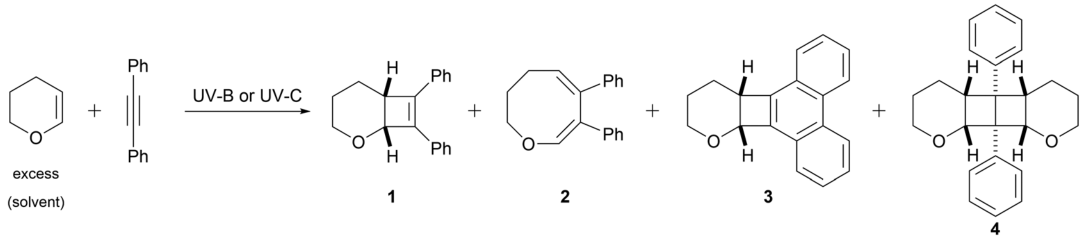
The study of the effect of irradiance time was achieved by pumping the reagent solution through the photoreactor until a steady state of the reaction mixture is reached. At this point, the reactor light is switched off creating a gradient of effective exposure time throughout the photoreactor from the maximum time, down to zero. This gradient can then be analysed as the reaction leaves the reactor either using in-line monitoring or by collecting fractions for analysis using off-line techniques.

There is some drop-off in irradiation intensity at the ends of the reactor which can be dealt with by only using data from the central 90% of the tube. An alternative method was to correct for any inhomogeneity using the results from a standard reaction to give effective exposure times – *i.e.* what the exposure time would be for a homogeneous light source (see ESI†).

Three model reactions have been investigated using this methodology.

[2 + 2] photocycloaddition of alkene and alkyne

[2 + 2] photocycloadditions are an important set of reactions forming cyclobutene compounds using relatively mild conditions[23,24] which can then be used as synthetic intermediates to form many different compounds,[25–27] natural products,[28,29] and biologically active molecules[30–32] containing the cyclobutene motif. Additionally, [2 + 2] photocycloadditions have been performed under continuous flow conditions by several groups[33–37] demonstrating the reactions suitability towards study *via* the switch-off methodology. The photochemical reaction between diphenylacetylene and 3,4-dihydro-2*H*-pyran[38] to form 7,8-diphenyl-2-oxabicyclo[4.2.0]oct-7-ene **1** was chosen as a first model reaction due to previous reports[39] that have shown that **1** can, upon further irradiation, undergo either an electrocyclic ring opening into oxocine **2**, or a Mallory reaction proceeding *via* 6π electrocyclic ring closure and formal oxidation to form phenanthrene based compound **3** with a loss of H_2 (Scheme 1). The switch-off methodology was applied with the UV-C and UV-B light sources with the effective exposure time gradient being analysed using



Scheme 1 The [2 + 2] photocycloaddition of diphenylacetylene and 3,4-dihydro-2*H*-pyran.

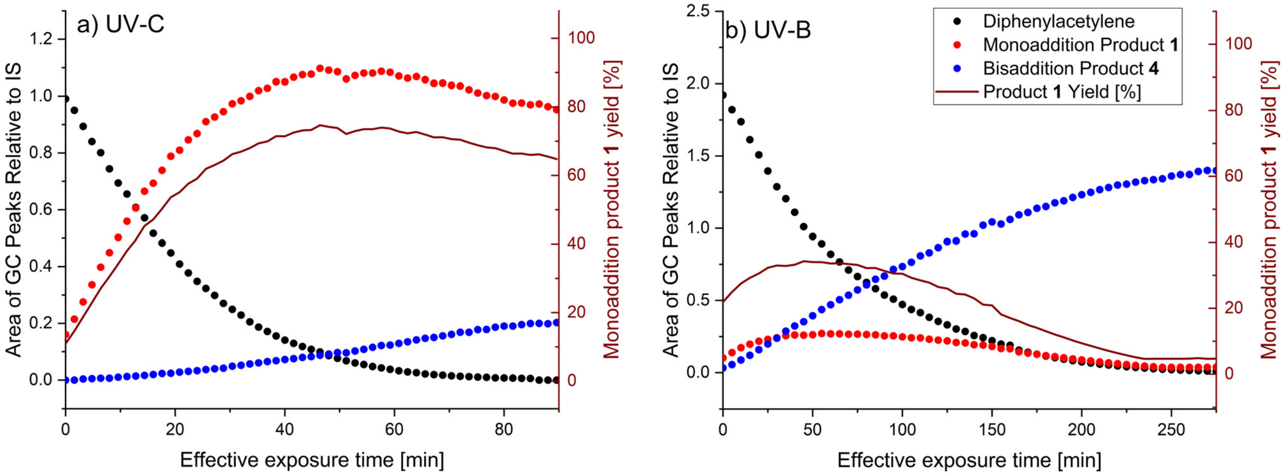


Fig. 2 Results obtained from switch-off experiments of [2 + 2] photocycloaddition between 3,4-dihydro-2*H*-pyran and diphenylacetylene. Left axis corresponds to dotted lines representing area of GC peaks relative to internal standard and right axis corresponds to solid line representing percentage yield of compound **1**. Relative GC areas of compounds **2** and **3** are not shown due to the low amounts formed.

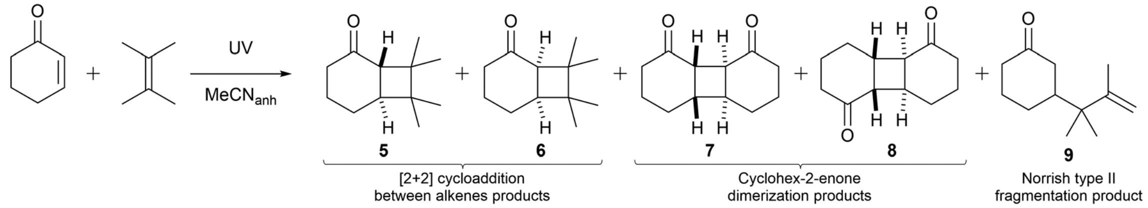
calibrated offline gas chromatography. With UV-C light it showed that in our system diphenylacetylene had all been consumed after 80 minutes and a maximum effective exposure time of 43 minutes was suitable for maximized formation of desired cycloaddition product **1** while simultaneously limiting the formation of side-products (Fig. 2a). Further irradiation causes **1** to convert into the *bis*-addition compound **4** formed from a second addition of 3,4-dihydro-2*H*-pyran to **1** which has not been reported before. Only low amounts of **2** and **3** were detected using GC analysis. Changing the irradiation wavelength to UV-B (Fig. 2b) lowered the rate of the reaction taking approximately 225 minutes to reach >99% conversion. However, it also changed the selectivity of the reaction forming **4** as the major product of the reaction at effective exposure times longer than 30 minutes. The selectivity is due to low absorption of light by diphenylacetylene at the wavelengths used by the UV-B lamp (305 to 315 nm), whereas **1** has a broad absorption across those wavelengths ($\lambda_{\max}$ = 298 nm), so **1** will become the main activated species and due to the large excess of 3,4-dihydo-2*H*-pyran in the reaction, **4** becomes the major product.

Two test reactions were performed with conditions obtained in switch-off experiments for both light sources to validate the results. Reaction utilizing UV-C light and effective exposure time of 43 minutes delivered product **1** in 71% isolated yield, whereas using UV-B light and 50 minutes effective exposure time delivered monocyclization product **1** in 37% isolated yield. Both results are in good agreement with result of the switch-off experiment.

[2 + 2] photocycloaddition of alkenes

A second model reaction tested was a [2 + 2] photocycloaddition between cyclohex-2-enone and tetramethylethylene (Scheme 2). In this reaction a number of compounds can be formed, including the substituted cyclobutane in a [2 + 2] photocycloaddition between alkenes (**5** and **6**), cyclohex-2-enone dimerization products (**7** and **8**), and cyclohexane (**9**) formed *via* the Norrish type II fragmentation of compounds **5** or **6**.[40–43]

The switch-off experiments were performed using UV-A, B, and C light sources and showed that maximum yields of cyclobutane products **5** and **6** of 65%, 30%, and 22% are obtained after 49, 25, and 20 minutes of effective exposure times, respectively for UV-A,



Scheme 2 The [2 + 2] photocycloaddition between cyclohex-2-enone and tetramethylethylene.

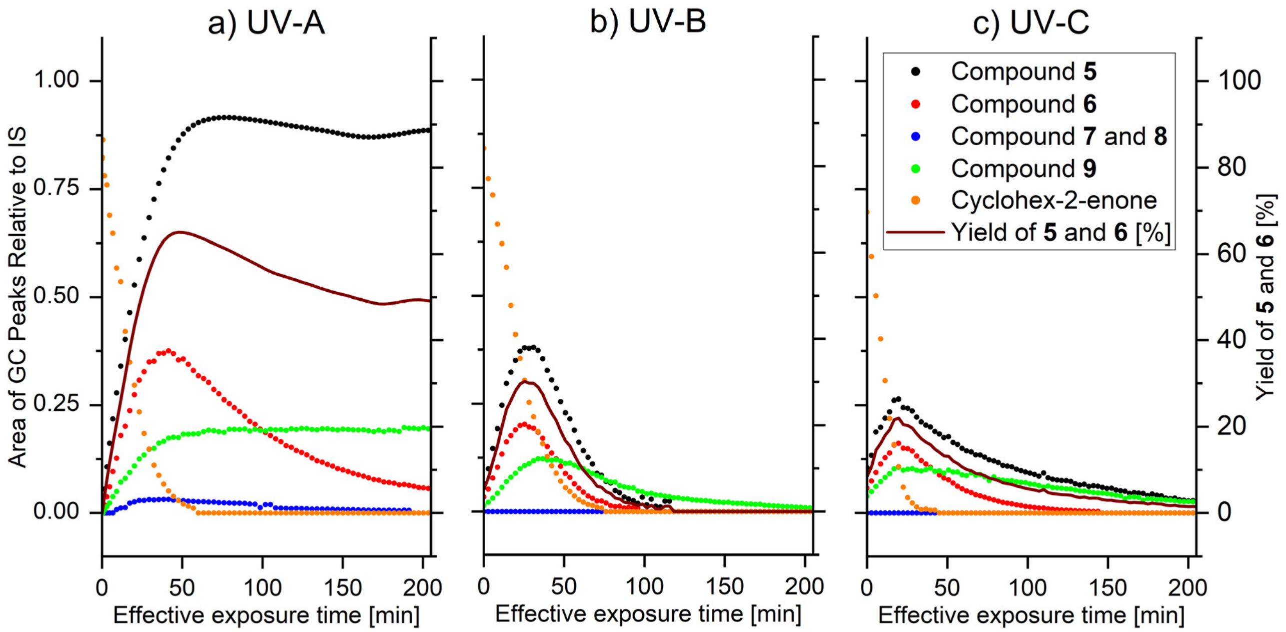


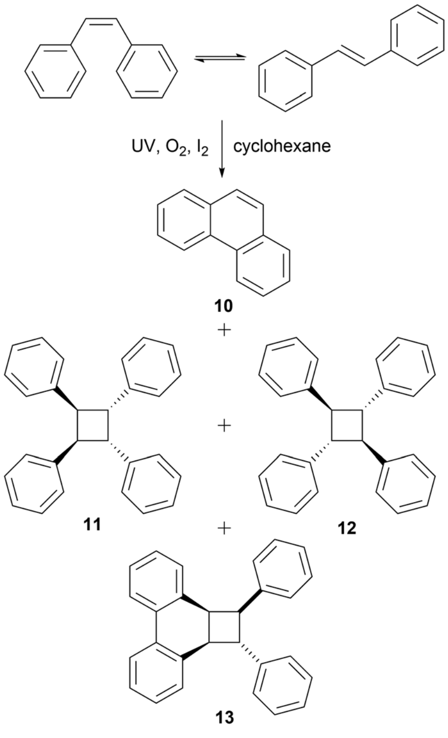
Fig. 3 GC results from switch-off experiments of [2 + 2] photocycloaddition between cyclohex-2-enone and tetramethylethylene. Left axis corresponds to dotted lines representing area of GC peaks relative to internal standard and right axis corresponds to solid line representing percentage yield of compounds **5** and **6**.

B, and C (Fig. 3). In the UV-B and C experiments, complete degradation of the photocycloaddition products was observed for long effective exposure times. The predominant formation for the less stable *trans*-fused cyclobutane isomer **5** is in accord with precedent[40–42] and has been explained.[43] The formation of **9** is precedented by some studies,[41] but not others.[40] Interestingly, when using UV-A light source a specific degradation of the *cis*-diastereoisomer **6** was observed after about 45 minutes of effective exposure time. For comparison, in the studies performed by Batten and Carless,[40] probably using UV-C or broadband UV irradiation, the *trans* isomer **5** underwent light induced Norrish type I fragmentation much faster than the *cis* isomer **6**, and formation of **9** was not observed.

Validation of the results was performed using UV-A light and 50 minutes effective exposure time, which resulted in formation of photocycloaddition products **5** and **6** in 62% yield (45% and 17%, respectively). Side-products **7**, **8**, and **9** were formed in 3%, 2%, and 8% isolated yields, respectively.

Mallory photocyclization

The third model reaction chosen for the switch-off methodology was the Mallory photocyclization of *cis*-stilbene to phenanthrene **10** (Scheme 3). This transformation is a highly studied area[44–46] with a few examples of reactions using continuous flow methods.[47–49] As stilbene absorbs across 240–320 nm, switch-off experiments were attempted using UV-A, B, and C lights and with two concentrations, 5.0 mM and 50.0 mM. In order to achieve oxidative conditions,



Scheme 3 Mallory photocyclization of *cis*-stilbene to phenanthrene **10**, dimerization products **11** and **12**, and phenanthrene–stilbene adduct **13**.

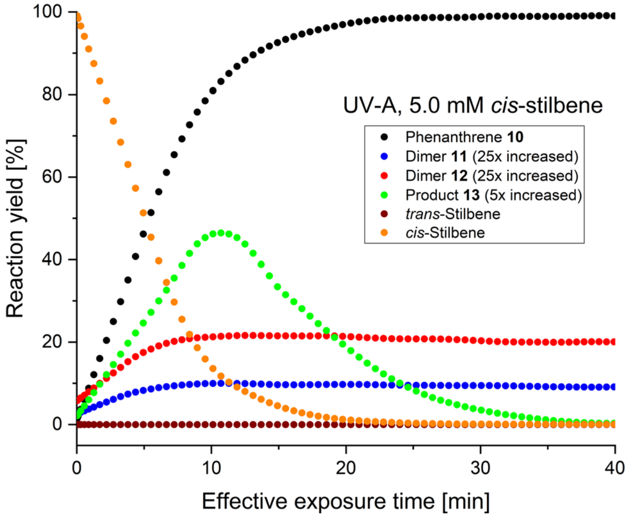


Fig. 4 GC results from the switch-off experiments of Mallory photoreaction using 5.0 mM *cis*-stilbene and UV-A light source.

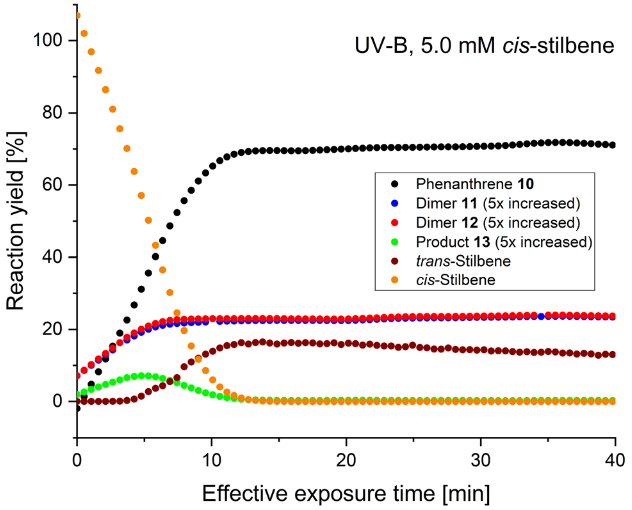


Fig. 5 GC results from the switch-off experiments of Mallory photoreaction using 5.0 mM *cis*-stilbene and UV-B light source.

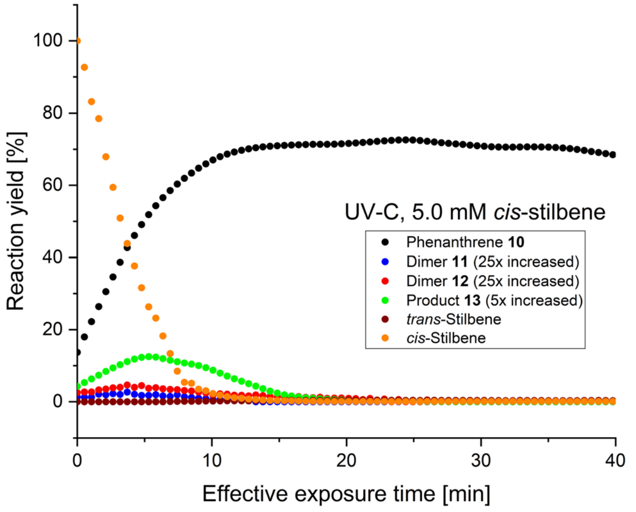


Fig. 6 GC results from the switch-off experiments of Mallory photoreaction using 5.0 mM *cis*-stilbene and UV-C light source.

reaction mixture was bubbled with oxygen stream prior to the reaction.

At 5.0 mM, UV-A gave 98% yield of phenanthrene **10** with effective exposure time of 24 minutes (Fig. 4), whereas UV-B and UV-C only went to 70% yield after 12 minutes (Fig. 5 and 6, respectively). The starting *cis*-stilbene was fully consumed after 23, 12, and 12 minutes, for UV-A, B, and C respectively, however when using UV-B light *trans*-stilbene was observed in approximately 16% yield after 12 minutes, which dropped down to 13% at 40 minutes. Moreover, stilbene dimers **11** and **12** were formed when using UV-B light after 5 minutes of effective exposure time in approximately 5% yield each. Experiments with UV-A afforded only traces of the **11** and **12**, whereas UV-C light proved to be ineffective for formation of the dimers. The phenanthrene–stilbene adduct **13** (ref. 50) was formed in approximately 10%, 2.5%, and 1.5% yields after 10, 5, and 5 minutes of effective exposure time, respectively for UV-A, B, and C light. Interestingly, all three experiments showed that at longer exposure times the concentration of **13** drops, suggesting that it decomposes back to phenanthrene **10** and stilbene (which also transforms to **10**), hence the high yield of phenanthrene when using UV-A light for long exposure times.

At 50.0 mM *cis*-stilbene concentration, UV-B (Fig. 8) and C (Fig. 9) gave similar results for phenanthrene formation, affording **10** in 70% yield after 42 minutes, whereas UV-A only went to 56% yield after 150 minutes (Fig. 7). When using UV-B and UV-C light the *cis*-stilbene has been fully consumed after 11 and 10 minutes, respectively, and the *trans*-stilbene was observed only when using UV-B light, affording it in 16% yield after 42 minutes. However, when UV-A light source was used, *cis*-stilbene was fully consumed after 115 minutes and small amounts (<5%) of *trans*-stilbene were detected after 86 minutes of effective exposure time. UV-C light again showed to be ineffective for formation of dimers, however UV-A afforded the dimers **11** and **12** in 6% and 10% yield after 60 minutes, whereas UV-B light afforded the dimers in 2.1% and 4.6% yield after 17 minutes of effective exposure time. The phenanthrene–stilbene adduct **13** was formed in 2.6% yield after 34 and 13 minutes for UV-B and C respectively. Interestingly, when using UV-A light **13** was obtained in 18% yield after 86 minutes, after which the concentration of the **13** was steadily dropping. This is in agreement with the observed *trans*-stilbene formation after 86 minutes, and a conclusion that the adduct **13** decomposes back to phenanthrene **10** and *trans*-stilbene, which can then isomerise to *cis*-stilbene and form second molecule of **10** can be drawn, thus showing why phenanthrene was still formed even though no *cis*-stilbene has been observed after 115 minutes of effective exposure time.

In order to validate the method two test reactions were performed, the first was ran with 5.0 mM concentration, UV-A light, and 24 minutes effective exposure time. Phenanthrene **10** was isolated in 96% yield, which is consistent with the results from the switch-off experiment. Second reaction was performed using 50.0 mM

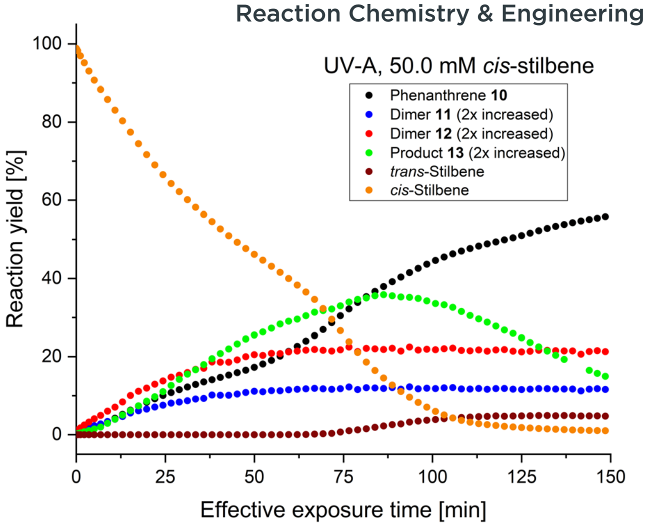


Fig. 7 GC results from the switch-off experiments of Mallory photoreaction using 50.0 mM *cis*-stilbene and UV-A light source.

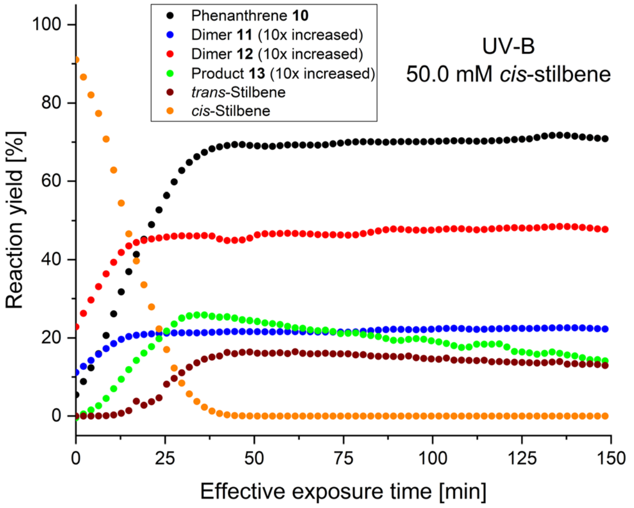


Fig. 8 GC results from the switch-off experiments of Mallory photoreaction using 50.0 mM *cis*-stilbene and UV-B light source.

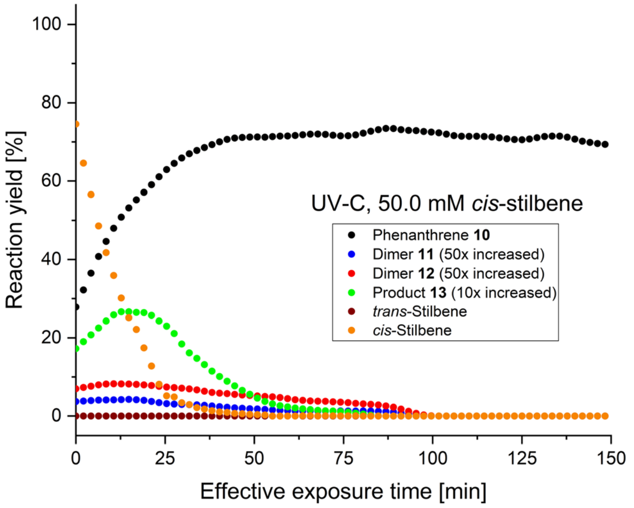


Fig. 9 GC results from the switch-off experiments of Mallory photoreaction using 50.0 mM *cis*-stilbene and UV-C light source.

concentration, UV-A light, and effective exposure time of 50 minutes, and resulted in recovery of 51.6% of *cis*-stilbene and formation of phenanthrene **10** in 10% yield, both cyclobutane dimers **11** and **12** in 8.5% yield, and phenanthrene–stilbene product **13** in 8.7% yield, which again, is consistent with the switch-off results.

Conclusions

A technique was designed to enable the rapid investigation of irradiance time in flow photochemical reactions using a single experiment. Reaction profiles against light exposure are obtained, as opposed to single timepoints, which greatly benefits optimisation as well as kinetic or mechanistic studies of photochemical reactions. The developed methodology was demonstrated on three different chemical systems. The [2 + 2] photocyclization of diphenylacetylene and 3,4-dihydro-2*H*-pyran was optimized for effective exposure time and light source giving best results when using 43 minutes and UV-C light. The selectivity of photochemical reaction was shown with the formation of a novel *bis*-addition product **4** being preferred when changing from UV-C to UV-B irradiation. Optimisation of the [2 + 2] photocycloaddition between cyclohex-2-enone and tetramethylethylene showed that the best results could be obtained when using UV-A light with 49 minutes of effective exposure time. The Mallory photocyclization of *cis*-stilbene was optimized for starting material concentration, irradiation time, and UV type giving an optimum condition of 24 minutes of effective exposure time, 5.0 mM *cis*-stilbene concentration, and UV-A light.

Author contributions

Dawid Drelinkiewicz – conceptualization, formal analysis, investigation, validation, visualization, writing – review and editing; Stephen T. Alston – conceptualization, data curation, formal analysis, investigation, methodology, writing – original draft; Thomas Durand – conceptualization, data curation, formal analysis, investigation, methodology, writing – original draft; Richard J. Whitby – conceptualization, funding acquisition, methodology, resources, supervision, writing – review and editing.

Conflicts of interest

There are no conflicts to declare.

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