Application Note 58:

Visible-Light Singlet Oxygen Generation using Heterogeneous Photosensitisers in Continuous Flow

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Abstract

A selection of polymeric materials designed as heterogeneous photosensitizers for the production of singlet oxygen under continuous flow conditions is described. The photosensitizers all absorb in the visible spectrum (420 – 530 nm) and were employed either as a dispersion within the reaction mixture or immobilized in a transparent glass column. The studies demonstrate the efficiency of these materials and the ability to use them in complex flow streams consisting of solid, liquid and gas components.

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This application note describes:

- Production of singlet oxygen using polymeric heterogeneous photosensitizers
- Implementation of UV-150 Photochemical reactor for heterogeneous dispersions
- Immobilized photosensitizers in column photoreactors
- Easy handling of a complex flow stream consisting of solid, liquid and gas

Background

Heterogeneous photosensitizers in flow.

Singlet oxygen ($^1O_2$) is a highly energetic electronic state of oxygen which has been studied extensively for over 100 years. Due to its wide range of synthetic, environmental and biological applications, $^1O_2$ continues to be examined and the materials and methods used to produce it improved upon.[1] The production of $^1O_2$ in continuous flow was first reported in 2002 using Rose Bengal as a homogeneous photosensitiser.[2] In fact, the vast majority of literature employing flow chemistry for $^1O_2$ production has continued to

use similar homogeneous materials (organic dyes and metal complexes).2-4 While heterogeneous photosensitizers, such as immobilized dyes and fullerenes, have been implemented in flow, only small scale microphotoreactors (or microfluidic chips) were utilised.[3] These reactors typically have a volume <1 mL resulting in lower productivity as there are upper limits to how much reactant, and subsequent product, can pass through the system. In order to increase this productivity, flow systems with greater volume (larger scale) can be used. Therefore, these issues have spurred the development of new heterogeneous photosensitizers for flow systems at a larger scale.

Generation of $^1O_2$ using heterogeneous photosensitizers has clear advantages such as ease of recovery and subsequent reusability. However, due to photon penetration depth and excessive irradiation, the significance of these advantages is lessened at larger scales.[5] Continuous flow addresses these issues through higher surface area to volume ratios and more efficient light penetration due to shorter path lengths compared to batch procedures.

Herein we present a range of polymeric materials that have been successfully employed as heterogeneous photosensitizers for the production of singlet oxygen ($^1O_2$) in flow using the Vapourtec easy-Photochem E-Series apparatus or a bespoke continuous flow set up. We demonstrate these materials to be photoactive in the visible spectrum and outline the use of synthetic design to alter the conditions under which they are utilized as photosensitizers. As depicted in Figure 1, production of $^1O_2$ was indirectly detected through a chemical reaction whereby α-terpinene was converted to ascaridole. This reaction was chosen as it only proceeds in the presence of $^1O_2$ and is inert to other reactive oxygen species.[6]

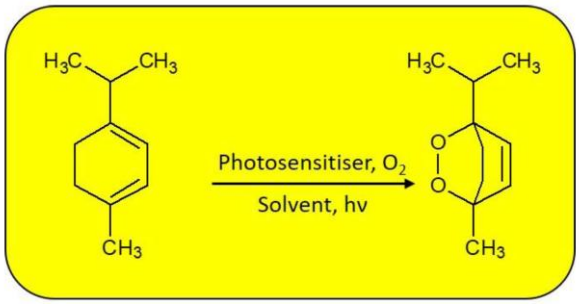

Figure 1: Synthesis of ascaridole from α-terpinene via the photosensitization of $^1O_2$ under visible light irradiation.

Setup

All of the reactions were carried out using a Vapourtec easy-Photochem E-Series (or equivalent instrument) in one of two ways: (*i*) as a heterogeneous suspension through a UV-150 photochemical reactor equipped with an LED module irradiating light at the appropriate wavelength (Figure 2a); (*ii*) as an immobilized photosensitizer trapped in a transparent glass column fitted to a photochemical reactor through which the reaction mixture is allowed to flow (Figure 2b). The PTFE tubing used within the systems had a 1 mm bore and oxygen was provided from either ambient air or from an oxygen cylinder equipped with a low-pressure regulator. The reagent mixture generally consisted of a 1.0 M solution of the target molecule and was stirred continuously to ensure even distribution of the reagent and a uniform suspension. The mixture was pumped at a constant flow rate (0.1 – 1.3 mL min^{-1}) through the photoreactor. Air (or oxygen) was pumped at the same (or higher) flow rate (0.1 – 10.0 mL min^{-1}) and met the reaction mixture at the T-junction prior to entering the photoreactor. For suspension reactions, the mixture was cycled through the photoreactor until full conversion of the starting material was

observed. For reactions utilizing an immobilized photosensitizer, the solution was allowed to flow through the column (not cycled) after which no starting material remained. The product was collected manually and analyzed via ^{1}H NMR spectroscopy to determine conversion to the desired product.

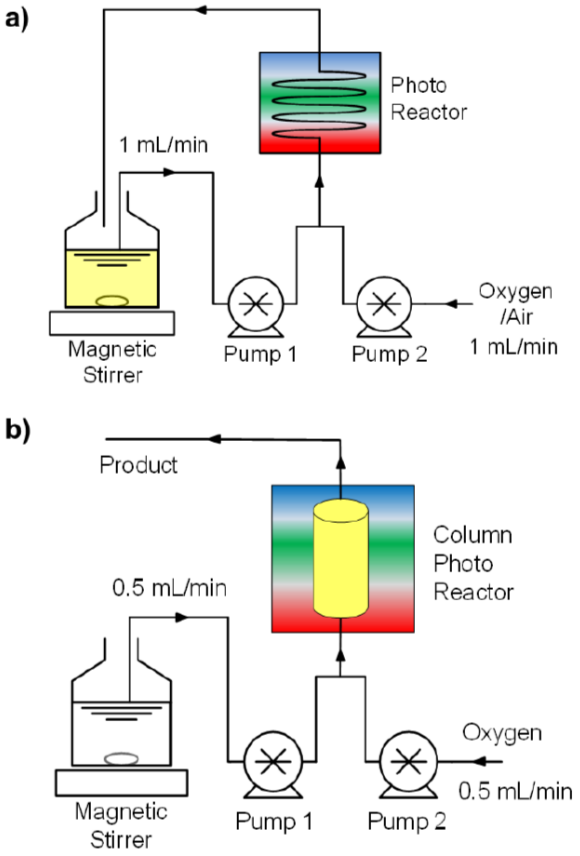

Figure 2: Schematic representation of the experimental flow setup for (a) a heterogeneous suspension of the photosensitizer and (b) an immobilized photosensitizer.

Results

BTZ-based Conjugated Microporous Polymers

Conjugated microporous polymers (CMPs) are fully crosslinked polymer networks characterized by their extended π-conjugation and high surface area. Due to their insoluble nature and ability to act as light harvesters, they make ideal candidates as heterogeneous photocatalysts.[7] Two CMPs based around an electronic 'push-pull' system between benzene (weak electron donor) and 2,1,3-benzothiadiazole (BTZ, strong electron acceptor) were designed as depicted in Figure 3. These materials were fully characterized and subsequently implemented as heterogeneous photosensitizers under continuous flow conditions combined with a visible light LED module as the source of photons.

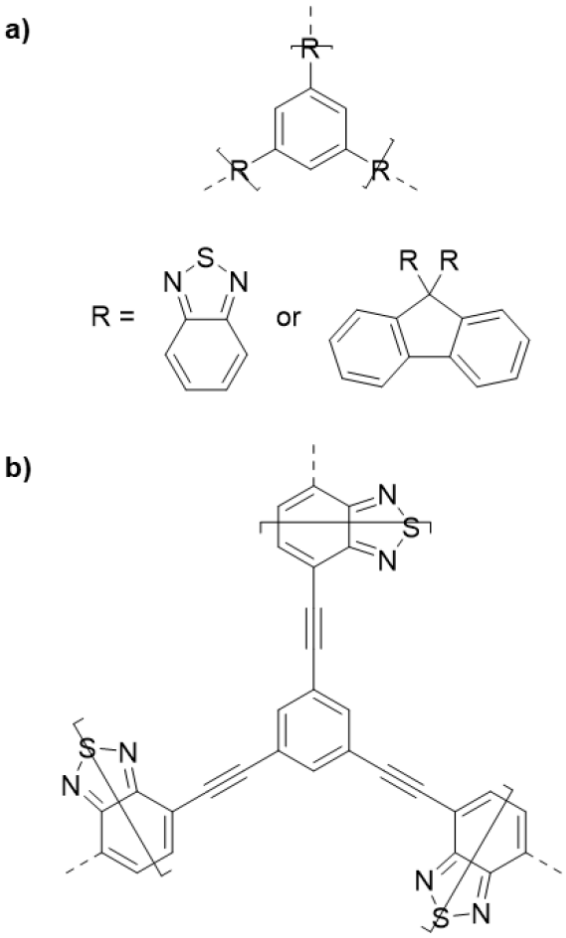

Figure 3: Representative repeat units for two BTZ-based CMPs synthesized via (a) Suzuki and (b) Sonogashira cross coupling.

The first of these materials was synthesized via palladium-catalyzed Suzuki-Miyaura cross-coupling reaction as a polymerized high internal phase emulsion (polyHIPE, Figure 3a). This

strategy enabled the production of a monolithic photoactive polymer that can be used as an immobilized photosensitizer for the production of $^1O_2$ (See Figure 4a).[8] The highly porous CMP-HIPEs were placed in a glass column where a solution of α-terpinene (0.1 M in 10 mL $CHCl_3$), mixed with oxygen, was allowed to flow through the column whilst irradiated at 420 nm. Under these conditions, full conversion to the ascaridole product was observed via ^1H NMR spectroscopy, up to a flow rate of 30 mL h^{-1}. As flow rates increased, contact time between α-terpinene and the $^1O_2$ generated within the column decreased, resulting in lower conversion rates as depicted in Figure 4b. Calculations based on these results translated to a reaction time of approximately 2 minutes. Furthermore, the immobilized polyHIPE showed exceptional photoactivity and photostability as continuous flow of the reagent (10 repeat experiments) at 20 mL h^{-1} resulted in no decrease in conversion to the ascaridole product.

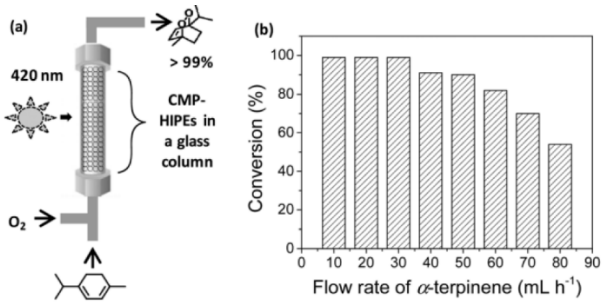

Figure 4: (a) Schematic representation of the continuous flow setup; (b) ascaridole conversion at different flow rates of α-terpinene solution. Reproduced from Ref. 8 with permission from The Royal Society of Chemistry.

The second of these CMP-based materials was designed in a similar fashion. However, in this instance palladium-catalyzed Sonogashira-Hagihara cross-coupling was employed resulting in an alkyne spacer between the BTZ and benzene in the repeat unit (Figure 3b).[9] This study focuses on the photoactivity between structurally identical materials of varying surface areas. Therefore, in order to control for surface area, the polymers were synthesized in the presence of silica nanoparticles and subsequently employed as heterogeneous photosensitizers.

Whilst the reaction flow setup was bespoke, Figure 2a offers a general representation. Since these materials formed insoluble powders, they were used as a dispersion (1 mg mL^{-1}) in a solution of α-terpinene (0.1 M in $CHCl_3$) rather than an immobilized photosensitizer. Again, the reaction mixture was mixed with oxygen, irradiated at 420 nm and allowed to flow at 1 mL min^{-1}. The lowest conversion (26 %) was observed using the untemplated polymer with a relatively low BET surface area (CMP_0, 270 $m^2\ g^{-1}$) while the polymer with the highest surface area (CMP_60, 660 $m^2\ g^{-1}$) presented with near full conversion to the ascaridole product (96 %). Materials with surface areas between these two extremes showed increased photoactivity when compared to the unaltered polymer, but quickly plateaued until CMP_60. Upon doubling the flow rate, the same trend is observed albeit with lower conversions, as expected from the reduced residence time.

While surface area did seem to play a role in the photoactivity of the different materials, this was not the only benefit observed from the templating strategy. Interestingly, the silica templating not only affected the surface areas, but also the mesostructure of the polymers, resulting in distinct morphologies. The more spherical structures showed a greater ability to disperse and were less prone to aggregation, allowing them to be more suitable heterogeneous materials under continuous flow conditions.

BODIPY-based Conjugate Microporous Polymers

In an attempt to develop materials absorbing at less energetic wavelengths, two CMPs incorporating BODIPY (4,4-difluoro-4-bora-3a,4a-diaza-s-indacene) were designed and synthesized, the final products of which are shown in Figure 5.[10] Designing photocatalytic materials that absorb light at higher wavelengths mitigates issues surrounding the use of highly energetic (UV) light such as photodecomposition of the starting materials and/or products or unwanted side reactions. While both exhibited similar physical properties, their syntheses differed as BDP_CMP used a traditional palladium-catalyzed Suzuki-Miyaura cross-coupling route while PHTT_BDP was post-synthetically modified through a metal-free process. It is important to note that the starting material used to synthesize PHTT_BDP was also made through a metal-free procedure.[11]

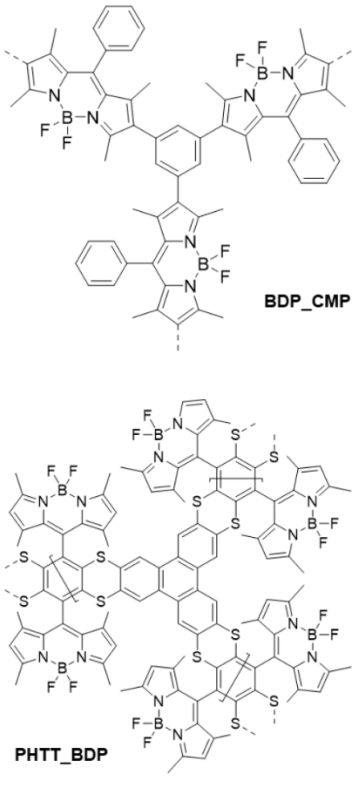

Figure 5: BDP_CMP (top) and PHTT_BDP (bottom) as a powder and dispersed in a solvent.

As these CMPs showed good dispersion in organic solvents (Figure 6), each polymer was added (0.33 mg mL^{-1}) to a solution of α-terpinene (1 mmol in 15 mL $CHCl_3$). Each dispersion was mixed with air, irradiated at 530 nm and allowed to flow at 1 mL min^{-1}. Within 1 hour of circulation, full conversion to ascaridole was observed for both materials. Both also demonstrated a high level of photo and chemical stability, where PHTT_BDP showed only a minor decrease in photoactivity after 6 hours.

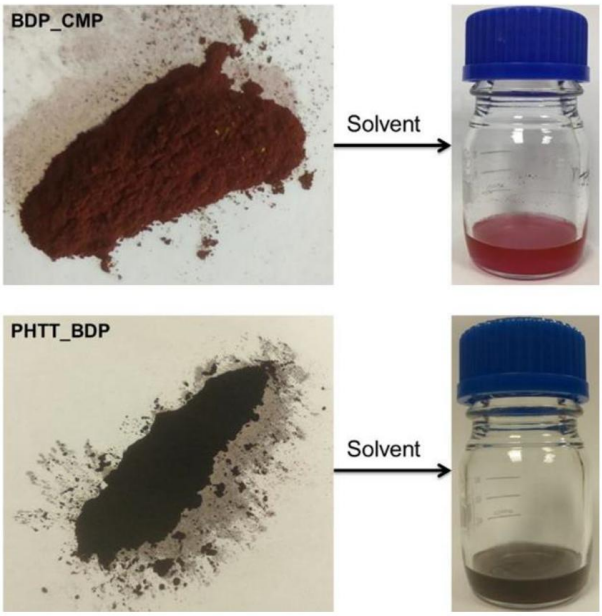

Figure 6: BDP_CMP (top) and PHTT_BDP (bottom) as a powder and dispersed in a solvent. Reproduced from Ref. 10 with permission from The Royal Society of Chemistry.

Due to the compatibility of both polymers in a variety of organic solvents, the same photosensitization reactions were performed for a selection of common solvents as well as a few 'green' solvents (dimethyl carbonate and 2-methyl THF). Each showed comparable conversion to ascaridole, supporting the versatility of these materials under flow conditions. Furthermore, as PHTT_BDP demonstrates nearly identical photoactivity and stability to BDP_CMP, a clear benefit can be ascertained to using PHTT_BDP. As

the synthesis of PHTT_BDP contains no metals throughout the entirety of the process, increasing both environmental and economic sustainability. Any effects regarding photocatalytic performance and toxicity from residual metals is also negated, solving often cited criticisms posed to CMPs used as photocatalytic materials.

The CMPs presented above have been shown as effective and reusable heterogeneous photosensitizers, particularly when employed under continuous flow conditions. While the potential for further exploration of these polymers as photocatalysts is strong, photoactive materials (photosensitizer) designed through different synthetic methodologies, such as free radical polymerization, have proven useful.

Polymer Supported Photosensitizers

Applying the photocatalytic properties and ideas from the BTZ-based CMPs discussed above, two repeat units were designed based on these polymers (Figure 7). These repeat units, either diamine or divinyl-based, were then implemented as photoactive crosslinkers in polyamides or polystyrenes. Furthermore, only a small mol % of monomer was used in each of the polymerization in order to determine the efficacy of the newly synthesized materials with lower concentrations of photoactive material. It should also be noted that these specific polymers do not display the same physical characteristics as the aforementioned CMPs. Most importantly, this means they do not contain extended π-conjugation beyond the photoactive monomer.

The first of the two materials utilized the divinyl monomer (R = $HC{=}CH_2$) which was first tested for photocatalytic performance as a homogeneousphotosensitiser.[12] While the monomer did show full conversion to ascaridole after extended reaction times, it was unstable in the highly oxidative environment. In order to use this monomer in a heterogeneous fashion, it was incorporated as a crosslinker into a polystyrene synthesis at 3-5 mol % via free radical polymerization, resulting in an insoluble gel. While the gel demonstrated a marked improvement in both stability and conversion when compared to the monomer, due to physical limitations this material was not being suitable for implementation in flow chemistry.

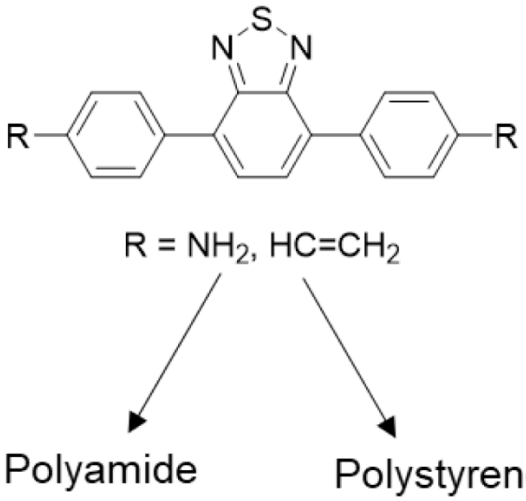

Figure 7: Monomer design for the synthesis of photoactive polyamide and polystyrene materials.

To combat this, well-defined polymer beads (Figure 8, top) and a polyHIPE (Figure 8, bottom) were also synthesized using precipitation and emulsion polymerization techniques, respectively, whilst incorporating the photoactive monomer. This resulted in two materials that were used under flow conditions: (*i*) beads were dispersed in $CHCl_3$ and allowed to flow through the reactor (Figure 2a); (*ii*) polyHIPE was trapped in a transparent column and used as a stationary photosensitizer through which the solution was allowed to flow, similar to the CMP-HIPEs present above (Figure 2b).

Due to their spherical shape, the polystyrene beads demonstrated excellent physical properties as they were easily dispersed (1 mg mL^{-1}) and showed no tendency to aggregate. In a solution of α-terpinene (1 mmol in $CHCl_3$), the dispersion was mixed with air, irradiated at 420 nm and allowed to flow at 1 mL min^{-1}. Within 1 hour of circulation, full conversion to ascaridole was observed.

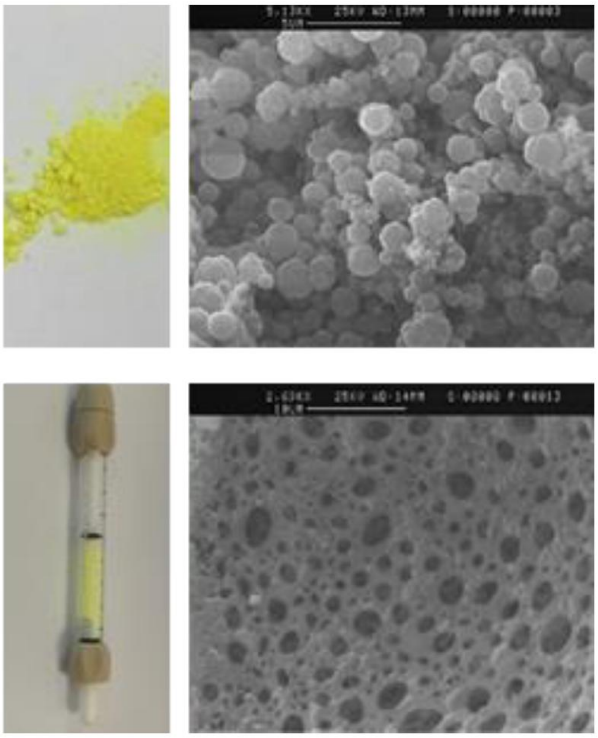

Figure 8: Synthesized polystyrene copolymers and their corresponding SEM images: (top) beads; (bottom) polyHIPE. Adapted with permission from Ref. 12. Copyright 2017 American Chemical Society.

The polyHIPE also showed good photocatalytic activity, however due to the short path and subsequent residence time, the flow parameters needed some adjustment. This included a decrease in concentration of α-terpinene (0.4 mmol in 10 mL $CHCl_3$) and flow rate (0.5 ml min^{-1}) as well as the use of pure oxygen. These changes aided in demonstrating full conversion to ascaridole after a single pass through the polyHIPE. Moreover, the production rate of ascaridole under these parameters was found to be 192 mg h^{-1} or 1.1 mmol h^{-1}.

It should be noted that determination of flow parameters for the polyHIPE underwent many iterations, largely regarding the source of irradiation. Initially a single LED module was used, but proved inadequate. After discussing the issue with Vapourtec Ltd., we tested a set up consisting of 3 modules surrounding the column. This resulted in a great increase in efficiency and was reported back to Vapourtec Ltd. With this data, it aided in the design of a new column photochemical reactor in which the polyHIPE was ultimately employed (Figure 9).

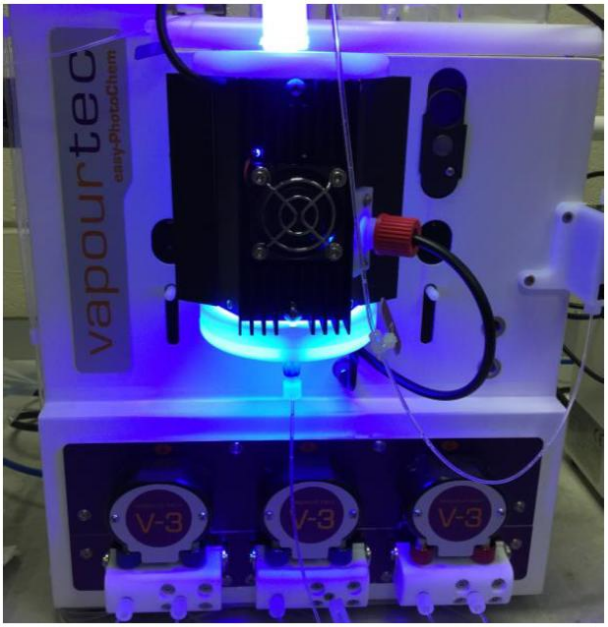

Figure 9: easy-Photochem flow system from Vapourtec Ltd. Equipped with a column photochemical reactor equipped with 420 nm LED lamps. Reprinted with permission from Ref. 12. Copyright 2017 American Chemical Society.

To further demonstrate the versatility of the polystyrene materials as triplet photosensitizers under flow conditions, the aerobic hydroxylation of aryl boronic acids to phenols was investigated (Figure 10). While the reaction conditions were

nearly essentially identical to that of the $^1O_2$ reactions, there were two changes to the reactants. Firstly, phenyl boronic acid replaced α-terpinene as the acceptor for the reactive oxygen species. Secondly, an organic base (N,N'-diisopropylethylamine) was added to facilitate the formation of a super oxide radical anion ($O_2^{\cdot -}$) as opposed to $^1O_2$.

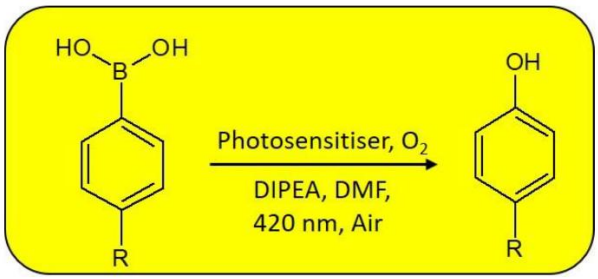

Figure 10: Synthesis phenols from aryl boronic acids via the photosensitization of $O_2^{\cdot -}$ under visible light irradiation.

As seen in Table 1, a scope of aryl boronic acids were tested under batch conditions (Entry 1-6) whereby the reaction time to reach full conversion varied greatly depending on the substituted functional groups present. When performing the model reaction (phenyl boronic acid) with the polymer beads in batch, a dramatic decrease in reaction time was observed (Entry 8). Applying this same reaction to continuous flow, the reaction time required for full conversion was cut in half (Entry 9) compared to the same batch reaction. The polyHIPE was also employed for the same reaction showing good performance (Entry 7), albeit a somewhat longer reaction time required than that of the batch reactions.

The versatility of polystyrene in conjunction with the photoactive monomer is demonstrated through the ability to make highly photoactive polymeric materials for specific reaction conditions in flow. Furthermore, both materials showed tremendous photo and chemical stability. In particular, the polyHIPE was employed for over 80 hours and showed little to no degradation in photocatalytic ability.

The second material used was a photoactive diamine monomer (Figure 5, R=NH_2).[13] Again, while the monomer worked as a photosensitizer under homogeneous conditions, photodegradation was observed. Therefore, the monomer was incorporated into a polyamide polymer matrix in varying concentrations (5 – 75 mol %) through a metal-free polycondensation reaction. Initially, the range of polyamides were added (0.5 mg mL^{-1}) into a 0.1 M α-terpinene $CHCl_3$ solution. The dispersion was mixed with air, irradiated at 420 nm and allowed to flow at 2 mL min^{-1}, recirculating for 120 minutes. The conversion to ascaridole under the stated conditions for each polyamide presented with an upward trend in conversion as the percentage of the photoactive monomer used increases. However, beyond 25%, diminishing returns were observed, particularly when comparing the increase in monomer required for a small increase in conversion.

Table 1: Light-Induced Aerobic Oxidative Hydroxylation of Arylboronic Acids.[a] Adapted with permission from Ref. 12. Copyright 2017 American Chemical Society.

Entry	R Group	Photosensitiser	Time (h)
1	H	Gel	24
2	OCH_3	Gel	72
3	CH_3	Gel	40
4	CF_3	Gel	18
5	$COOCH_3$	Gel	48
6	NO_2[b]	Gel	18
7[c]	H	PolyHIPE	30
8	H	Beads	10
9[c]	H	Beads	5

Reaction conditions: arylboronic acid (0.5 mmol/5 mL DMF), photosensitizer (5 mg), DIPEA (1.0 mmol), DMF (5 mL), 420 nm LED irradiation, air. All reactions reached full conversion as calculated via ^{1}H NMR spectroscopy. Abbreviations: DIPEA = N,N'-diisopropylamine, DMF = N,N'-dimethylformamide. [b]NO_2 at the meta position. cReaction performed under flow conditions.

Unlike most CMPs and the polystyrene described above, these polyamide materials were compatible in water, making them more attractive for both environmental and biological applications. Utilizing their ability to generate $^1O_2$, PA-ABT (25 %) was used for the degradation of two environmental pollutants, bis-Phenol A and cimetidine, under the same flow conditions. Furthermore, the neutralization of Cryptosporidium, a chlorine-resistant water-borne pathogen, was also performed. However, due to technical limitation this could not be performed under flow conditions.

It should be noted that all of the polymer supported photosensitizers presented above were synthesized through metal-free methodologies. As we continue to design and create new photosensitizing materials, it is important to consider both synthetic sustainability and desired applications. By removing metals from these processes, new industrial avenues emerge such as pharmaceutical development, where even trace metal species can be catastrophic.

Conclusion

Using the **Vapourtec easy-PhotoChem**, along with other continuous flow apparatus', it has been possible to implement a host of insoluble photoactive polymers for the photosensitization of oxygen under visible light irradiation. The use of two pumps allows for precise control of both the dispersion mixture and introduction of air/oxygen into the system, particularly when compared to more tradition batch methods. As a result, faster conversion rates have been noted along with the potential for scale up procedures. It should also be noted that prior to this work, no literature could be found describing suspension-based photosensitization under continuous flow conditions at this scale.

By pumping the dispersions with air/oxygen through the photochemical reaction module, a greater ratio of surface area to volume is formed, resulting in higher conversion rates. The control afforded with this method allows for fine tuning of the reactions which cannot be easily achieved through other means. Control of the light source (narrow wavelength or broad spectrum) further aids in both material design and optimization of reaction conditions.

While dispersions only require filtration and washing to be reused, the inclusion of a column photoreactor elevates the versatility of this system.

Design and implementation of immobilized photosensitizers introduces another layer of ease to the process. A system whereby the only output from a photochemical process is the desired product is highly coveted within industry.

Comparisons between the work presented here and other flow systems utilizing heterogeneous photosensitizers is rather difficult, primarily due to the difference in scale. While microscale reactions have demonstrated extremely rapid conversion rates (1-2 minutes for full conversion),[3] it is unknown if similar results would be observed on a greater scale with the same materials. However, when comparing the conversion rates of these

heterogeneous materials between batch and flow methods, it is clear that the use of continuous flow techniques has a distinct advantage. This advantage is largely due to the Beer-Lambert law whereby the absorbance of a material is directly proportional to its path length. The irradiation of light through a solution is more efficient under flow conditions due to the shorter path lengths when compared to traditional batch processes.

This application note demonstrates the versatility of the E-Series, photochemical and column photoreactors which have made possible the use of these polymers as photosensitizers under flow conditions. As the materials continue to develop, they do so with an aim towards further flow applications.

Acknowledgements

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References

1. M. C. DeRosa, R. J. Crutchley, *Coord. Chem. Rev.*, **2002**, 233-234, 351-371.
2. D. Cambie, C. Bottecchia, N. J. W. Straathof, V. Hessel, T. Noel, *Chem. Rev.,* **2016,** 116, 10276-10341.
3. A. A. Ghogare, A. Greer, *Chem. Rev.,* **2015,** 116, 9994-10034.
4. M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.,* **2017,** 117, 11796-11893.
5. G. Centi, S. Perathoner, Methods and Tools of Sustainable Industrial Chemistry: Process Intensification. *In Sustainable Industrial Chemistry: Principles, Tools and Industrial Examples;* F. Cavani, G. Centi, S. Perathoner, F. Trifiro, Eds.; Wiley-VCH: Weinheim, Germany, **2009,** 199–256.
6. G. O. Schenck, K. Ziegler, Naturwissenschaften, **1944,** 32, 157.
7. Y.-L. Wong, J. M. Tobin, Z. Xu, F. Vilela, J. *Mater. Chem. A.,* **2016,** 4, 18677-18686.
8. K. Zhang, Z. Vobecka, K. Tauer, M. Antonietti, F. *Vilela, Chem. Commun*., **2013**, 49, 11158-11160.
9. K. Zhang, D. Kopetzki, P. H. Seeberger, M. Antonietti, F. Vilela, Angew. *Chem. Int. Ed.*, **2013**, 52, 1432-1436.
10. J. M. Tobin, J. Liu, H. Hayes, M. Demleitner, D. Ellis, V. Arrighi, Z. Xu, F. Vilela*, Polym. Chem*., **2016,** 7, 6662-6670.
11. J. Liu, J. Cui, F. Vilela, J. He, M. Zeller, A. D. Hunter, Z. Xu, *Chem. Commun.,* **2015,** 51, 12197-12200.
12. J. M. Tobin, T. J. D. McCabe, A. W. Prentice, S. Holzer, G. O. Lloyd, M. J. Paterson, V. Arrighi, P. A. G. Cormack, F. Vilela, *ACS Catalysis,* **2017**, 7, 4602-4612.
13. J. Shen, R. Steinbach, J. M. Tobin, N. M. Mouro, M. Bower, M. R. S. McCoustra, H. Bridle, V. Arrighi, F. Vilela, *Appl. Catal. B. Environ*, **2016**, 193, 226-233.