



Cite this: *Chem. Commun.*, 2015, 51, 11041

Received 13th March 2015,
Accepted 1st June 2015

DOI: 10.1039/c5cc02153g

www.rsc.org/chemcomm

Photoredox catalysis under shear using thin film vortex microfluidics†‡

Michael N. Gandy,^a Colin L. Raston^{*b} and Keith A. Stubbs^{*a}

A microfluidic vortex fluidic device (VFD) operating in either confined or continuous mode is effective in high yielding photoredox reactions involving Rose Bengal, with short reaction times. This processing can be translated to multi-components reactions, also with significantly reduced processing times relative to batch processing and channel microfluidic processing, with comparable or improved yields.

Developing new synthetic methods lies at the heart of organic chemistry. They require the detailed understanding of a chemical reaction at the molecular level for gaining access to new molecules for therapeutic or materials applications. In addition, they require developing new technologies that allow for the rapid synthesis of such molecules. Flow chemistry has been developed to meet this challenge, and is now commonplace in industry, having advanced since the advent of smaller-sized reactors that allowed researchers to work in laboratory settings.^{1,2} Advantages of the use of flow chemistry lie in controlling chemical reactions at various levels including reagent quantities, surface area of reactions and the ability to automate the processes.³ The microfluidic platforms^{4–11} used in flow chemistry are successful in the synthesis of a wide variety of molecules. In terms of their design they commonly rely on the use of channels^{6,9,12} where there is laminar flow, or more recently rotating surfaces^{8,11} where dynamic thin films are not restricted to diffusion control of the reactions.¹¹

One research area that has benefited from the use of flow methodology is that of photoredox chemistry.^{13,14} Coupling the high throughput nature of channel flow reactors with the mild reactions conditions invoked in photoredox chemistry has resulted in a large number of different chemical transformations having been achieved using this technology.¹⁵

An interesting paradigm for photochemistry under flow would be the use of devices which incorporate intense micro-mixing in thin films of the reaction medium. Here the thin films would allow for (i) rapid heat transfer and no large temperature isotherms, (ii) uniform mixing of reagents, and (iii) introducing new compounds quickly without disturbing the concentrations of the reagents in an unbiased manner. Applying such thin film processing in photo-based reactions overcomes a fundamental problem associated with batch processing where the irradiating source is impeded by the bulk solution which can result in reduced yields and mixtures of products. Thin films have a larger volume to surface area so that the irradiating source becomes much more effective and homogenous, approaching a uniform flux per molecule as the liquid transverses the light source. We recently developed a thin film microfluidic vortex fluidic device (VFD), which is an efficient platform for preparing organic molecules, controlling chemical reactivity and selectivity⁸ and has been used in a wide variety of synthetic applications,^{16–18} along with protein folding¹⁹ and materials processing.²⁰

The utility of the VFD relates to the generation of a thin film in the rapidly rotating reaction tube at a tilt angle above the horizontal position⁸ with the thickness of the thin film exquisitely controlled primarily by varying the speed of rotation of the tube and the tilt angle. The VFD is usually operated in one of two modes, the so called confined mode for a finite volume of liquid and the continuous flow mode.⁸ For the confined mode the mixing is dependent on Stewartson/Ekman layers²⁰ and for continuous flow jet feeds direct reacting liquids to the base of the tube where there is intense micro-mixing as the liquids move in the tube. Furthermore the VFD is robust and simple to operate and maintain, and does not suffer from clogging which can occur for flow chemistry using channel reactors.^{3,9} Herein we describe the use of the VFD as part of our program towards developing efficient synthetic protocols for organic reactions, in performing photoredox reactions in both the confined and continuous flow modes, with an emphasis placed on the use of this device as a simple flow reactor. We note that the confined mode is suitable for small scale processing, and the continuous flow mode

^a School of Chemistry and Biochemistry, The University of Western Australia, Crawley, WA 6009, Australia. E-mail: keith.stubbs@uwa.edu.au

^b Centre for NanoScale Science and Technology, School of Chemical and Physical Sciences, Flinders University, Bedford Park, SA, 5042, Australia. E-mail: colin.raston@flinders.edu.au

† Dedicated to the memory of Professor Jack Cannon, AO.

‡ Electronic supplementary information (ESI) available. See DOI: 10.1039/c5cc02153g

addresses scalability, allowing higher volume processing using parallel arrays of the microfluidic device, as for channel based microfluidic systems.⁹ The application of the VFD centred on the use of organic dyes because of their green chemistry credentials. Recently it has been demonstrated that such molecules, especially Eosin Y and Rose Bengal (RB), can be used in photoredox reactions,^{21–24} with multiple groups demonstrating their utility in both batch and channel based flow chemistry conditions.^{13,25–38}

Initially we chose to assess the applicability of using the VFD in C–C and C–P bond forming reactions using tetrahydroisoquinoline derivatives as substrates in model reactions noting that these types of reactions have been conducted previously^{26,29,30,32,35} using other conditions. Molecules based on the tetrahydroisoquinoline scaffold are important synthetic intermediates to a variety of important compounds in medicinal chemistry, especially in cancer and antibiotic discovery.³⁹ We chose initially to use the confined mode of operation of the VFD to first demonstrate if the reactions could be carried out in the device, and to then refine the processing parameters as a prelude for the continuous flow mode of operation. All the studies were conducted using a 10 mm OD borosilicate glass NMR tube (Scheme 1).

At the outset we used *N*-phenyltetrahydroisoquinoline and nitromethane as their reaction enjoys high yields and has been widely used as a model visible light catalysed reaction, utilising both metal-based catalysts^{13,40–42} and organocatalysts.^{26,29,30} To optimise the operating parameters of the VFD, we measured the percentage conversion for the model reaction under various settings of tilt angle and rotational speed. In all cases the reaction was deemed complete after only 90 minutes and overall this established that operating the VFD at 4000 rpm and 45° produced the highest conversion, at 78% yield (Table 1).

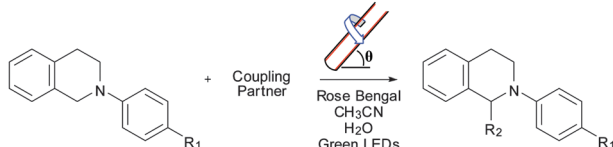
Although the model reaction has been previously conducted using only nitromethane as solvent,^{26,36} other workers³⁵ have also included water and acetonitrile as co-solvents, presumably to improve the solubility of the RB. In our hands, to achieve complete dissolution of the RB in a reaction medium containing

water and acetonitrile as co-solvents, it was necessary to reduce the final concentration of RB from 5 mol% to 1 mol%. Remarkably, using this solution together with the optimised VFD parameters, we found that we could effect 98% conversion and 80% isolated yield after chromatography with a significantly reduced reaction time of 75 min. Compared to literature flow reactor conditions,³⁵ where the reaction was run for 5 h for a yield of 92%, these optimised conditions are able to effect a >3-fold reduction in reaction time with comparable yields as well as a 80% reduction in catalyst loading.

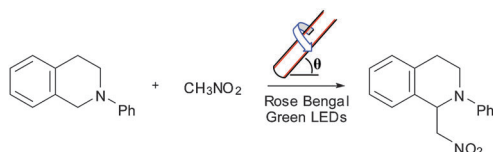
With suitable reaction conditions established using the reaction of *N*-phenyltetrahydroisoquinoline and nitromethane as a model, we expanded the repertoire of coupling partners to demonstrate the widespread utility of the method (Table 2). In all cases the yields were comparable to literature preparations of the respective compounds for other flow chemistry conditions, but achieved in a considerably shorter time, as demonstrated for nitromethane.

With these results in the confined mode in hand we sought to extend the strategy to the continuous mode of operation of the 10 mm glass tube VFD. Of note is that the reaction time used in the confined mode (75 minutes) was highly commensurate with a flow rate of 0.05 mL min^{−1} that can be delivered by the jet

Table 2 Synthesis of various coupling partners using the VFD operating at 4000 rpm and 45° tilt angle at room temperature in confined mode for 75 minutes. All reactions were conducted in triplicate with the average shown. Errors were within ±2%. Literature yields for other flow chemistry reactions are shown in brackets^{26,30,35,36}

					
Entry	Substrate		Coupling partner		Yield (lit. yield)
	R ₁	R ₂	R ₁	R ₂	
1	CH ₃	CH ₃ NO ₂	CH ₃	CH ₂ NO ₂	79(85) ³⁵
2	OMe	CH ₃ NO ₂	OMe	CH ₂ NO ₂	81(86) ³⁵
3	Br	CH ₃ NO ₂	Br	CH ₂ NO ₂	83(89) ^{a,26}
4	H	EtNO ₂	H	MeCHNO ₂	78(82) ^{a,26}
5	CH ₃	EtNO ₂	CH ₃	MeCHNO ₂	72(78) ³⁰
6	OMe	EtNO ₂	OMe	MeCHNO ₂	74(97) ^{a,36}
7	Br	EtNO ₂	Br	MeCHNO ₂	76(64) ³⁰
8	H	ProNO ₂	H	EtCHNO ₂	71(95) ^{a,26}
9	CH ₃	ProNO ₂	CH ₃	EtCHNO ₂	76(91) ^{a,36}
10	OMe	ProNO ₂	OMe	EtCHNO ₂	77(95) ^{a,36}
11	Br	ProNO ₂	Br	EtCHNO ₂	74(91) ^{a,36}
12	H	TMSCN	H	CN	83(87) ³⁵
13	CH ₃	TMSCN	CH ₃	CN	81(77) ³⁵
14	OMe	TMSCN	OMe	CN	69(64) ³⁵
15	Br	TMSCN	Br	CN	87(75) ³⁵
16	H	DEM	H	CH(CO ₂ Et) ₂	81(71) ³⁵
17	CH ₃	DEM	CH ₃	CH(CO ₂ Et) ₂	74(53) ³⁵
18	OMe	DEM	OMe	CH(CO ₂ Et) ₂	77(51) ³⁵
19	Br	DEM	Br	CH(CO ₂ Et) ₂	78(55) ³⁵
20	H	DEP	H	PO(CO ₂ Et) ₂	81(59) ³⁵
21	CH ₃	DEP	CH ₃	PO(CO ₂ Et) ₂	82(56) ³⁵
22	OMe	DEP	OMe	PO(CO ₂ Et) ₂	84(60) ³⁵
23	Br	DEP	Br	PO(CO ₂ Et) ₂	71(56) ³⁵

DEM = Diethyl malonate. DEP = Diethyl phosphite. ^a Batch reaction yield.



Scheme 1 Model reaction for investigating the utility of the VFD for photoredox reactions in the confined mode.

Table 1 Percentage conversion for the reaction between *N*-phenyltetrahydroisoquinoline and neat nitromethane in the presence of Rose Bengal and green LED light for 90 min, when varying the rotational speed and tilt angle of the VFD. All reactions were conducted in triplicate with the average shown. Errors were within ±2%

Tilt angle (°)	Rotational speed (rpm)		
	2000	4000	7000
15	57%	77%	59%
45	25%	78%	77%
75	18%	57%	60%



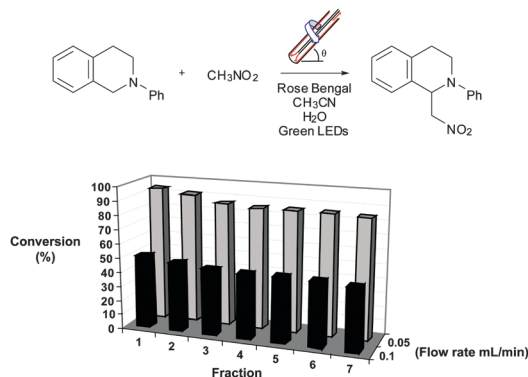


Fig. 1 Synthesis of 1-nitromethyl-2-phenyltetrahydroisoquinoline using the VFD operating at 4000 rpm and 45° tilt angle at room temperature in the continuous flow mode. Fractions (2 mL) were collected in a continuous fashion from when the reaction mixture began to elute from the device. All reactions were conducted in triplicate with the average conversion shown (errors within $\pm 2\%$) as determined using ^1H NMR.

feeds in the VFD and so this results in a similar residence time for the reaction mixture.⁸ Again using *N*-phenyltetrahydroisoquinoline and nitromethane as a model example we exposed a working solution of the reagents used in the confined mode experiments to the continuous mode conditions. Fractions of the reaction mixture were then collected and gratifyingly we found that high conversion had indeed been achieved (Fig. 1). Of note is that the initial fractions have a higher conversion than fractions collected later, implying that there is a need for establishing a steady state conversion of the starting material. Based on these results the flow rate was increased to ascertain what effect this would have on the percentage conversion. An increased flow rate would result in a reduced residence time and so if a reduced conversion was observed it would establish the practical lower level flow rate required for conversion. Indeed, at a flow rate of 0.1 mL min^{-1} there was a reduction in conversion which demonstrates that the residence time of 75 minutes is critical to the conversion. We then expanded the study to *N*-phenyltetrahydroisoquinoline and other coupling partners that were used earlier and saw similar results (See ESI†). Overall this demonstrates the utility of the VFD in both modes of operation of the device for preparing these types of compounds.

With the success of these reactions we turned our attention to other types of reactions for translational purposes. A recent area of chemical research that has benefited from the use of photoredox catalysis involves multicomponent reactions.³⁵ These involve multiple reactants (≥ 3), where each of these reactants contributes to the product(s), and this type of reaction has had great success in medicinal chemistry.⁴³ Specifically the Ugi multicomponent reaction has been shown to be effectively mediated using an organic dye under photoredox conditions. Unfortunately, low yields and long reaction times, in both batch and channel based flow processing, limit further advances using such processing. The starting material *N,N*-dimethylaniline was incubated with 4-toluenesulfonylmethyl isocyanide in the presence of water under the confined mode of operation of the VFD, using the same optimised parameters described for the

Table 3 Synthesis of various coupling partners using the VFD operating at 4000 rpm and 45° tilt angle at room temperature in the confined mode for 12 hours. All reactions were conducted in triplicate with the average shown. Errors were within $\pm 3\%$. Literature yields for other flow chemistry reactions are shown in brackets^{35,37}

Entry	Substrate		Product		Yield (lit. yield)
	R ₁	R ₂	R ₁	R ₂	
1	H	CH ₂ Ts	H	CH ₂ Ts	83(79) ³⁵
2	Me	CH ₂ Ts	Me	CH ₂ Ts	72(51) ³⁵
3	Br	CH ₂ Ts	Br	CH ₂ Ts	79(83) ³⁵
4	H	C ₄ H ₉	H	C ₄ H ₉	44(60) ³⁵
5	Me	C ₄ H ₉	Me	C ₄ H ₉	53
6	Br	C ₄ H ₉	Br	C ₄ H ₉	48
7	H	CH ₂ CO ₂ Me	H	CH ₂ CO ₂ Me	80(78) ³⁵
8	Me	CH ₂ CO ₂ Me	Me	CH ₂ CO ₂ Me	73(68) ^{a,37}
9	Br	CH ₂ CO ₂ Me	Br	CH ₂ CO ₂ Me	70
10	H	CH ₂ Ph	H	CH ₂ Ph	41(57) ³⁵
11	Me	CH ₂ Ph	Me	CH ₂ Ph	52
12	Br	CH ₂ Ph	Br	CH ₂ Ph	50(57) ^{a,37}

^a Batch reaction yield.

preparation of the tetrahydroisoquinoline derivatives (Table 1). Interestingly, while the reaction proceeded at a lower rate than for the tetrahydroisoquinoline-based reactions, it was complete in a far shorter time period than what has been reported previously for batch and channel flow chemistry processing, indeed up to 300% faster.³⁵ More importantly, the yields of the reactions were greater or at least comparable to those reported previously (Table 3).

We note that the use of the continuous flow mode of operation of the VFD is not viable for these reactions as the lowest practical flow rate deliverable does not result in sufficient residence time to allow for practical levels of substrate conversion.

In conclusion, we have established that the VFD, which is relatively cheap, is an efficient and useful device for photoredox chemical reactions using organic dyes. Due to the nature of the VFD in that the rotational speed and tilt angle of the tube can be varied, thin films can be generated which are highly effective in photochemical reactions, allowing for rapid heat transfer, intense micro-mixing and homogenous irradiation. The VFD is effective for these types of reactions in both the confined and continuous flow modes of operation. The latter is extremely important as conventional channel flow chemistry equipment is expensive to purchase, operate and maintain, and thus the VFD potentially provides a viable alternative, with significantly improved outcomes of the reactions. Matching the residence time of a liquid under continuous flow mode to be equivalent to the processing time for the VFD operating under confined mode (75 minutes), by adjusting the flow rate, results in similar yields. This is consistent with the shear arising from the film instability for droplets of liquid striking the hemispherical base of the NMR tube²³ having no impact on photoredox reactions, as expected, with the reaction occurring in the thin film generated



along the wall of the tube. The results establish the utility of the VFD in photoredox reactions, adding to the expanding capabilities and versatility of the device in controlling chemical reactivity and selectivity, including in the assembly line synthesis of lidocaine in a single pass through a VFD.⁴⁴

Support of this work by the Australian Research Council, the Government of South Australia, and the Centre for Microscopy, Characterisation and Analysis at the University of Western Australia is greatly acknowledged.

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