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Photocatalytic hydroxylation of arylboronic acids using continuous flow reactors†

Inès G. T. M. Penders,^a Zacharias Amara,^a Raphael Horvath,^a Kai Rossen,^b Martyn Poliakoff^{*a} and Michael W. George^{*ac}

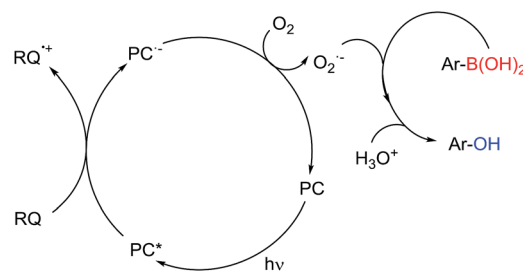
The photocatalytic oxidation of mono- and di-substituted arylboronic acids to phenols has been investigated using a continuous flow photoreactor fitted with white LEDs. An EtOH–H₂O solvent system accelerated conversion at 2 MPa; whereas reactions at atmospheric pressure allowed for moderately efficient desymmetrisation.

Phenols are ubiquitous in organic chemistry and form the central units of many natural products, pharmaceuticals and fine chemicals.^{1,2} However, common strategies for producing phenols use either harsh conditions or metal-catalysed hydroxylation.³ Since the 1930s, boronic acids have been perceived as potential substrates for the development of alternative hydroxylation routes to phenols.^{3–6} Although direct boronic acid hydroxylation has received attention, it often requires the use of strong oxidising agents or toxic metal catalysts.^{3,7–14} Recently, a number of alternative methods have been described, based on the generation of superoxide free radical species (O₂^{•−}).^{15,16} In this context, photocatalysis has emerged as a promising methodology^{17–19} which is compatible with a variety of substrates and catalysts, including metal-free dyes.¹⁷ This procedure is attractive due to its broad applicability with readily available catalysts and mild operating conditions; a general reaction pathway is shown in Scheme 1. Visible light absorption by the photocatalyst is followed by electron transfer from the reductive quencher to the photocatalyst. The reduced photocatalyst transfers an electron to molecular oxygen to generate O₂^{•−} which reacts with the boronic acid. After hydrolysis, the reaction yields phenol with high selectivity.¹⁸ Scaiano and co-workers^{17,20} recently outlined important mechanistic details of the reaction and, in particular, found that organic

dyes such as methylene blue exhibited ×40 higher activity. Even so, the batch photosynthesis of phenols requires relatively long irradiation times (>6 h) using O₂ saturated solutions.

Long reaction times are among the most significant limitations in the scale-up of current batch photochemical processes.^{21,22} This is due to the fact that large volumes of reaction mixtures impede efficient light penetration. The use of molecular O₂ also raises safety issues.²³ Flow chemistry has therefore recently emerged as a promising technology to avoid major problems associated with photochemistry²⁴ and oxygenation reactions.^{25,26} It can operate with a larger surface to volume ratio and enhanced mixing, which leads to more efficient light irradiation and therefore, shorter reaction times are typically observed. The use of O₂ in flow is also safer than in batch because reactions are confined to smaller volumes.^{27,28} The increased performances of flow over batch oxidations can also permit the use of air instead of pure O₂ which leads to inherently safer high pressure processes.²⁷

We have previously reported the continuous photo-oxidation with singlet oxygen (¹O₂) by introducing the use of supercritical CO₂ as a solvent which is non-flammable and non-toxic.^{25,29–33} Here, we report a continuous flow strategy in aqueous mixtures that allows rapid photocatalysed oxidations of arylboronic acids. Our approach combines reactor and process design to



Scheme 1 General photoredox pathway for the hydroxylation of arylboronic acid. PC refers to the photocatalyst and RQ stands for reductive quencher.

^aSchool of Chemistry, University of Nottingham, University Park, Nottingham, NG7 2RD, UK. E-mail: mike.george@nottingham.ac.uk; martyn.poliakoff@nottingham.ac.uk

^bSanofi-Aventis Deutschland GmbH, Industriepark Höchst, 65926 Frankfurt, Germany

^cDepartment of Chemical and Environmental Engineering, University of Nottingham Ningbo China, 199 Talking East Road, Ningbo 315100, China

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offer higher levels of control and thus a more efficient procedure. Finally, selective desymmetrisation of a di-substituted arylboronic acid is investigated.

The flow experiments were carried out in a high pressure tubular sapphire photoreactor with an upflow arrangement, see Fig. 1. The organic feed contained the dissolved substrate, photocatalyst and reductive quencher in a flask open to air. Additional air was dosed into the system using a Rheodyne unit and subsequently mixed with the organics in a micro-mixer before entering the photoreactor. The reactor was filled with 6 mm diameter glass beads to promote mixing and to reduce the optical pathlength to prevent inner filter effects. Three banks of high-power white light emitting diodes (LEDs) provided visible irradiation and the sapphire tube was surrounded by a concentric transparent cooling jacket for temperature control (see ESI†).

We initially studied the reaction of phenylboronic acid (**1**) to phenol (**2**) (Scheme 2), employing an excess of the sacrificial electron donor *N,N*-diisopropylethylamine (iPr₂EtN), as described previously.^{17,18} Rose Bengal (RB) and [Ru(bpy)₃]²⁺ were used as photocatalysts providing an opportunity to compare organic and transition-metal catalysts. We also investigated the use of both iPr₂EtN and ascorbic acid (AA) as reductive quenchers for the photocatalytic cycle. As the reaction requires a highly polar environment, DMF and CH₃CN have been used previously for similar reactions^{17,18} as well as protic solvents such as MeOH, which resulted in similar reaction efficiency. Table 1 summarises our results where **1** (0.05 M in MeOH), the desired photocatalyst (2 mol%) and 2 equivalents of reductive quencher were pumped into the photoreactor. The addition of glass beads had a dramatic effect increasing the reactor efficiency despite the fact that it considerably lowers the internal volume and, hence, the residence time (entries 3 and 4). Rose

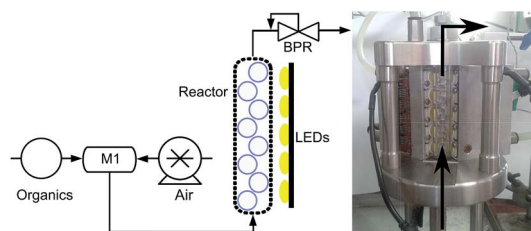
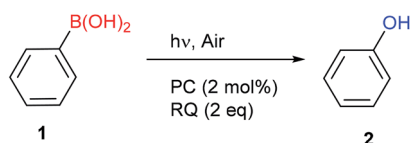


Fig. 1 The sapphire tubular photoreactor in upflow configuration. The organic feed is pumped using a HPLC piston pump and air is dosed via a dosing valve (Rheodyne). Both the liquids and gas are mixed in a static micro-mixer M1 before entering the reactor which contains glass beads. The upflow configuration was chosen to minimise the impact of air dosing on the residence time.



Scheme 2 Continuous flow aerobic hydroxylation of phenylboronic acid (**1**) to phenol (**2**).

Table 1 Conversion of **1** to **2**, in MeOH

Entry	Flow rate ^b / mL min ⁻¹	Photocatalyst	Reductive quencher	Conversion ^c
1	0.1	[Ru(bpy) ₃] ²⁺	iPr ₂ EtN	>99%
2	0.4	[Ru(bpy) ₃] ²⁺	iPr ₂ EtN	27%
3	0.1	[Ru(bpy) ₃] ²⁺	AA	95%
4 ^a	0.1	[Ru(bpy) ₃] ²⁺	AA	43%
5	0.1	RB	iPr ₂ EtN	>99%
6	0.4	RB	iPr ₂ EtN	>99%
7	0.8	RB	iPr ₂ EtN	54%
8	0.1	RB	AA	42%
9	0.8	RB	AA	9%

^a The reactor was not filled with glass beads. ^b Air : **1** is 67 : 1.

^c Measured by ¹H NMR.

Bengal was found to be more efficient in the presence of amine rather than ascorbic acid (entries 5 and 8). With [Ru(bpy)₃]²⁺, the efficiency with both reductive quenchers was high, however, as with Rose Bengal, the amine gave superior conversion (entries 1 and 3). In order to optimise the reaction, we tested the efficiency of both photocatalysts with the amine as the reductive quencher under similar conditions. At 0.4 mL min⁻¹, Rose Bengal gave almost quantitative conversion whereas lower efficiency was obtained with [Ru(bpy)₃]²⁺ (entries 2 and 6). When the conditions from entry 6 in Table 1 were replicated in batch, full conversion was observed only after 5 hours, which suggests that these flow experiments are already 15 times more productive than the batch synthesis.

Interestingly, when the solvent was changed from MeOH to EtOH or EtOH–H₂O (1 : 1) mixtures, the reaction showed increased conversion at fixed flow rates (see Table 2). We investigated the effect of varying the dosing of air. At a reasonably high flow rate the air to substrate ratio was found to be at an optimum at *ca.* 67 : 1. According to previous studies,¹⁷ the use of pure oxygen is expected to increase kinetics. However, increasing the air to substrate ratio led to lower conversion which might be attributed to a decrease in residence time (entry 4). Increasing the system pressure to 2 MPa resulted in full conversion at 0.8 mL min⁻¹ (entry 7). This increase in pressure meant that the flow rate could be increased to 2.4 mL min⁻¹ while maintaining full conversion (entry 8) which gives a productivity of *ca.* 3.4 g of phenol after 5 h. In batch, the full conversion of **1** to **2** took 5 h on a 0.125 g scale.³⁴ A control experiment without photocatalyst resulted in only traces of phenol, demonstrating the need for a photocatalyst in this process. This is consistent with the work of Jiang *et al.*,³⁵ who showed that prolonged UV irradiation is required to carry out this reaction in the absence of a photocatalyst.

After having evaluated the reaction performances of our high pressure continuous flow reactor, we were keen to test whether such a system could also afford improvements in terms of selectivity, by attempting a desymmetrisation reaction. To the best of our knowledge, there have been no previous examples of arylboronic acid desymmetrisations. Furthermore, there have been very few precedents of desymmetrisation reactions carried

Table 2 Screening of reaction conditions using RB and $i\text{Pr}_2\text{EtN}$

Entry	Flow rate/ mL min^{-1}	Solvent	Air : 1 (O_2 : 1) ^a	Pressure/MPa	Conv. ^b
1	0.8	MeOH	67 : 1 (13 : 1)	0.1	54%
2	0.8	EtOH	67 : 1 (13 : 1)	0.1	62%
3	0.8	EtOH- H_2O^d	67 : 1 (13 : 1)	0.1	67%
4	0.8	EtOH- H_2O^d	134 : 1 (26 : 1)	0.1	32%
5	0.8	EtOH- H_2O^d	33 : 1 (6 : 1)	0.1	13%
6	0.8	EtOH- H_2O^d	— ^c	0.1	6%
7	0.8	EtOH- H_2O^d	67 : 1 (13 : 1)	2	>99%
8	2.4	EtOH- H_2O^d	67 : 1 (13 : 1)	2	>99%
9	2.8	EtOH- H_2O^d	67 : 1 (13 : 1)	2	80%
10	3.2	EtOH- H_2O^d	67 : 1 (13 : 1)	2	54%

^a Molar ratio. ^b Measured by $^1\text{H NMR}$. ^c No additional air. ^d Vol. 1 : 1.

out with continuous flow chemistry. Rare examples such as diol mono-functionalisation,^{36,37} or thiophene dissymmetric lithiation were reported.³⁸ We therefore investigated the mono-hydroxylation of 1,4-benzenediboric acid (**3**) (Scheme 3). This symmetrical substrate has two boronic acid functionalities in *para*-positions where steric interactions are minimised and therefore cannot interfere with the second hydroxylation step. At the previously optimised conditions (Table 2, entry 8), the reaction gave almost full conversion to hydroquinone (**5**) and no selectivity to 4-hydroxyphenylboronic acid (**4**). Further experiments at high pressure, using higher flow rates showed low selectivity to **4**. We speculated that this was related to the high efficiency of the process. Indeed, improved selectivity to **4** was achieved when the reaction was run at atmospheric pressure and under stressed flow rate (0.4 mL min^{-1} : 43% conversion and 64% selectivity). These results were compared with batch experiments where a higher selectivity was observed (see Tables S1 and S2 in ESI†). Although the selectivity for the desired product is modest, this serves as a proof of principle for a substrate that does not bear any directing groups to facilitate monofunctionalisation. Future optimisation could address the selectivity and the residual starting material could in principle be separated and recycled.

In conclusion, this study has demonstrated how relatively simple concepts of flow chemistry can be applied to improve the efficiency of the photocatalysed hydroxylation of arylboronic acids. The design of a high pressure flow photoreactor allowed for faster processing with a 90-fold increase in productivity compared to batch experiments, even with the use of air instead of pure oxygen. Our reaction setup also allowed the replacement of conventional polar solvents such as CH_3CN , DMF or DMSO

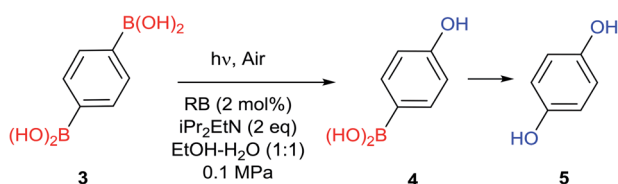
with greener alcoholic aqueous mixtures, the use of non-metallic inexpensive organic dyes and more environmentally friendly reductive quenchers such as ascorbic acid. The overall benefits of flow photochemistry demonstrated here show the importance of such technologies for process development and intensification. Finally, the underdeveloped option of using the photocatalysed hydroxylation in desymmetrisation reactions was assessed with a comparative study. Further work in this area is currently underway in our group.

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Scheme 3 Photochemical desymmetrisation of a *meso*-diboric acid (**3**).

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