Photocatalytic Hydroxylation of Aryl Boronic Acids Using Continuous Flow Reactors

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ELECTRONIC SUPPLEMENTARY INFORMATION

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1. Materials and methods

[Ru(bpy)₃]Cl₂.6H₂O, Rose Bengal, ascorbic acid, *N*,*N*-diisopropylethylamine and phenylboronic acid were purchased from Sigma Aldrich, 1,4-benzenediboronic acid was purchased from Avocado Research Chemicals Ltd. Methanol was purchased from VWR Chemicals and ethanol from Fisher Scientific. All reagents and solvents were used as received, without further purification. Light irradiation was carried out using a bank of Citizen Electronics Co. Ltd 1000 lumen white light LEDs (arranged in 3 sets of 5 diode arrays).

Conversion and selectivity of the reactions were monitored using ¹H NMR. Spectra were recorded on a Bruker AV(III)400 at 400 MHz in dimethyl sulfoxide- d_6 . Spectral analysis was carried out using ACD/SpecManager software and the solvent resonance was used as a reference (DMSO- d_{62} 2.50 ppm for ¹H NMR).

2. General experimental procedures for the hydroxylation of arylboronic acids

2.1 Aerobic hydroxylation of phenylboronic acid (1) in batch



Phenylboronic acid (50 mg, 0.41 mmol, 1 eq), reductive quencher (0.82 mmol, 2 eq) and photocatalyst (8.2 µmol, 2 mol%) were added to 4 mL of methanol. The solution was stirred at room temperature under LED light irradiation in a round bottomed flask equipped with a condenser open to air for 5 hours. The reaction was monitored using ¹H NMR. Aliquots used for analysis were extracted with diethyl ether (3 x 5 mL) followed by washing with brine and drying with Na₂SO₄. ¹H NMR of **2** (DMSO-*d*₆, 400 MHz, ppm): δ 9.34 (s, 1H, Ar-OH), 7.15 (t, *J* = 7.54 Hz, 2H, Ar-H), 6.77 - 6.73 (m, 3H, Ar-H).

2.2 Aerobic hydroxylation of 1,4-benzenediboronic acid (3) in batch



Rose Bengal (10 µmol, 2 mol%) and *i*Pr₂EtN (1.0 mmol, 2 eq) were added to a solution of **3** (83 mg, 0.50 mmol, 1 eq) in EtOH/H₂O (1:1, 10 mL). The solution was stirred at room temperature under LED light irradiation in a round bottomed flask equipped with a condenser open to air for 6 hours. Aliquots for ¹H NMR analysis were quenched with 10% HCl, after which the solvent was evaporated under vacuum to record ¹H NMR spectra afterwards. ¹H NMR of **4** (DMSO-*d*₆, 400 MHz, ppm): δ 9.45 (*br* s, 1H, **4**, OH), 7.60 (d, *J* = 8.53 Hz, 2H, **4**, Ar-H), 6.70 (d, *J* = 8.53 Hz, 2H, **4**, Ar-H). ¹H NMR of **5** (DMSO-*d*₆, 400 MHz, ppm): δ 8.79 (*br* s, 2H, **5**, Ar-OH), 6.55 (s, 4H, **5**, Ar-H).

2.3 Aerobic hydroxylation of arylboronic acids in flow

Continuous flow experiments involving aqueous mixtures were performed using a high pressure photo-oxidation reactor (see Figure S1). The reactor system was operated in upflow mode such that the flow rates of air and the substrate solution are essentially independent. Glass beads (6 mm) were loaded into the sapphire tube (Saint-Gobain crystals, 10 mm o.d., 120 mm long, 1 mm wall thickness).



Figure S1: Reactor schematic for the aerobic hydroxylation of arylboronic acids in flow. **Org 1**: mixture containing the photocatalyst, reductive quencher and substrate, dissolved in the required solvent system, which is pumped by **P:Org 1** (a JascoTM PU-980 HPLC pump); air is added using a modified **Rheodyne** dosage unit. **M**: micromixer (IMM, Mainz) to allow thorough mixing of the reagents solution and air; **R1**: sapphire tube reactor, which is temperature controlled *via* a circulating water/ethylene glycol bath and filled with glass beads (6 mm diameter); **LEDs**: light source ($3 \times 5 \times$ Citizen Electronics Co. Ltd CL-L233-C13 N mounted on water cooled stainless steel blocks); **BPR**: back pressure regulator (model JascoTM BP 1580-81); **TN**: (where N is a number) manual valve.

Arylboronic acid (0.26 mmol, 1 eq, 0.05 M), reductive quencher (0.52 mmol, 2 eq) and photocatalyst (5.2 μ mol, 2 mol%) were dissolved in the organic solvent first (V_{org}/V_{H2O} ratios were calculated to meet the required concentration) and sonicated after addition of water. This solution was pumped into the flow system, mixed with air in a micro mixer **M** (Figure S1) and irradiated in the photoreactor at 25 °C. The air to substrate ratio was maintained during the reaction by a Rheodyne dosage unit. The product was collected at the outlet of the BPR. The product solution collected from the photoreactor was quenched with 10% HCl and a ¹H NMR spectrum was recorded in DMSO- d_6 after evaporating the solvents under vacuum.



Figure S2: Crude ¹H NMR spectrum of hydroxylation of **1** towards **2** (with expanded aromatic region) in EtOH/H₂O (1:1) at 3.2 mL·min⁻¹ at 20 bar in flow (Table 2, entry 10 main paper).

3. Desymmetrisation studies

<u>3.1 Desymmetrisation studies in flow</u>

Following the general flow chemistry procedure, 1,4-benzenediboronic acid (3) was desymmetrised to form 4-hydroxyphenylboronic acid (4) and hydroquinone (5).

Enters	Flow rate /	Calvant	Air:1 (O ₂ :1) ^a Pressure/MPa	Pressure/MPa	Conv. ^b Selectivity to 4	Selectivity
Entry	$mL \cdot min^{-1}$	Solvent				
1	0.8	EtOH/H ₂ Od	67:1 (13:1)	2	>99%	0%
2	2.4	EtOH/H ₂ Od	67:1 (13:1)	2	>99%	0%
3	0.4	EtOH/H ₂ Od	67:1 (13:1)	0.1	26%	78%
4 ^c	0.4	EtOH/H ₂ Od	67:1 (13:1)	0.1	43%	64%
5	0.1	EtOH/H ₂ O ^d	67:1 (13:1)	0.1	78%	38%



Figure S3: Crude ¹H NMR spectrum of the desymmetrisation of **3** (with expanded aromatic region) in EtOH/H₂O (1:1) at 0.4 mL·min⁻¹ at 20 bar (Table S1, entry 4) in flow.

3.2 Desymmetrisation studies in batch

Following the batch chemistry procedure for desymmetrisation, 1,4-benzenediboronic acid (3) was desymmetrised to form 4-hydroxyphenylboronic acid (4) and hydroquinone (5).

Time (hours)	Conv. ^b	Selectivity to 4
0.5	16%	82%
1.5	33%	82%
2.5	52%	80%
3	65%	65%
4	80%	53%
5	90%	37%
6	> 99%	0%