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A synthetic toolbox for sustainable methods in porphyrin chemistry

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Greener synthesis for red dyes. As the days of chlorinated organic solvents are numbered, we propose a sustainable synthetic protocol for porphyrin synthesis to facilitate the transition into a more viable, safer and greener lab. Here we present a facile flow-assisted method for the sustainable synthesis of 40 *meso*-substituted planar porphyrins of the A_4-, A_2-, and *trans*-A_2B_2-type, including 10 examples of dodecasubstituted nonplanar porphyrins. We set forth a sustainable approach towards porphyrin synthesis, saving up to 90% of chlorinated solvents and drastically limiting waste generation by merging a flow synthesis process *via* a continuous stirred tank reactor (CSTR) with a traditional batch oxidation method.

Sustainability spotlight

"A synthetic toolbox for sustainable methods in porphyrin chemistry" falls into goal 12 of the UN Sustainable Development Goals (Sustainable consumption and production patterns). One of the targets of chapter 20 of Agenda 21 is preventing or minimizing the generation of hazardous waste. In porphyrin chemistry, the bulk of hazardous waste generated during porphyrin synthesis consists of chlorinated solvents. We aim to limit the generation of hazardous waste in porphyrin synthesis by reducing the volume of solvent required for the synthesis. This is enabled by continuous flow; merging a flow synthesis process *via* a continuous stirred tank reactor (CSTR) with a traditional batch oxidation step, we reduced the volume of chlorinated solvent required for the synthesis by up to 90%.

Introduction

Minimising solvent use in chemical reactions is one of the twelve principles of green chemistry[1] and the ten objectives of green and sustainable chemistry, proposed by the United Nations.[2] Specifically, seeking alternatives to chlorinated solvents was identified as one of the key green chemistry research areas by the ACS Green Chemistry Institute in 2005.[3] While a suitable drop-in replacement for dichloromethane (DCM) and its homologues has not yet been identified,[4] limiting their use is strongly encouraged. This is exemplified by the restriction for specific industrial applications of DCM in the European Union since 2010 (ref. 5) and most uses of DCM introduced in the United States by the Environmental Protection Agency in 2024.[6]

Macrocycles constitute a class of functional molecules applied in sensing, catalysis, medicine, cosmetics, agriculture and nanotechnology.[7] Their synthesis requires high dilution to promote cyclisation over formation of linear products.[8] This is called the high dilution principle, and its implications can be circumvented by experiment design,[9] pseudodilution[10] and catalysis.[11]

Porphyrins are aromatic tetrapyrrolic macrocycles. *meso*-Substituted porphyrins, such as 5,10,15,20-tetraphenylporphyrin (H_2TPP, Fig. 1) are artificial dyes, counterparts to naturally occurring porphyrinoids, like heme B, chlorophyll a, or vitamin B12 (Fig. 1).[12] Due to the ease of their synthesis and versatile chemical and physical properties, *meso*-substituted porphyrins are highly sought after as feasible targets for research areas including catalysis,[13] quantum technologies,[14] molecular probes[15] and supramolecular assemblies,[16] applications in dye-sensitised solar cells,[17] remediation,[18] imaging, photodynamic therapy,[19] and other areas of biomedicine.[20]

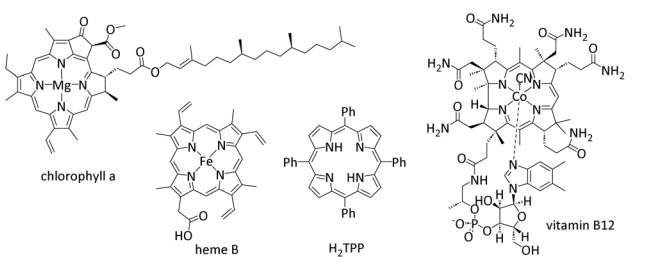

Fig. 1 Structures of chlorophyll a, heme B, 5,10,15,20-tetraphenylporphyrin (H_2TPP) and vitamin B12.

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Table 1 Comparison of synthetic methods in porphyrin synthesis

Protocol	Rothemund	Adler–Longo	Lindsey
Steps	1	1	2
Concentration	High 3.6 M	High 0.1–0.3 M	Low 0.001–0.1 M
Temperature	220 °C	140 °C	20 °C
Solvent	Pyridine	Propionic acid	Chlorinated
Catalyst	None	cat. = solvent	$BF_3 \cdot Et_2O$, TFA
Conditions	sealed vessel	Aerobic	Inert
Oxidant	None	Nitrobenzene	Quinone
Yields	<10%	<30%	35–60%

Perhaps the most thoroughly studied and certainly most frequently applied method for porphyrin synthesis is a two-step protocol involving a condensation of aldehydes with pyrroles under acidic conditions, followed by an oxidation of the tetrapyrrolic macrocycle.[21] The first general method toward porphyrin synthesis was initially reported by Rothemund[22] and further developed by Adler,[23] and called for harsh conditions, such as high temperatures and acidic or basic solvents (Table 1).

Porphyrins synthesised *via* either Rothemund or Adler protocols were contaminated with the corresponding chlorins (<10%); this could be evaded by treatment with a strong quinone oxidant, such as 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). In Lindsey's method, oxidation is an inherent step following the mild, room temperature cyclisation carried out in acidified chlorinated solvents, at low concentrations.[24] Currently, the Lindsey protocol is the mildest and most effective method for the synthesis of *meso*-substituted porphyrins, both A_4 5,10,15,20-tetra-[25,26] (Fig. 2) and 2,3,5,7,8,10,12,13,15,17,18,20-dodecasubstituted.[27,28] The higher yields and wider functional group tolerance are related to the mild reaction conditions.

The Lindsey protocol is currently the standard method for porphyrin synthesis in academia and industry.[29] One major drawback of this method is the requirement for large volumes of chlorinated solvents for the reaction, which calls for 1–100 mM reactant concentrations to promote macrocyclisation over formation of linear side products.[30,31] This constitutes a sustainability issue and improvements to the current methods or development of new protocols for porphyrin synthesis are needed to overcome this problem.

Protocols employing microwave irradiation and mechanochemistry, as well as the use of ionic liquids as solvents, have been developed over the past two decades to increase the sustainability of *meso*-substituted porphyrin synthesis.[32]

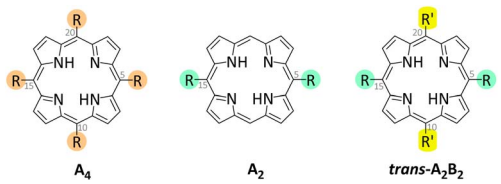


Fig. 2 *meso*-Substitution patterns in 5,15- and 5,10,15,20-substituted porphyrins.

Recently, two contributions describing the use of continuous flow in porphyrin synthesis were reported. These involve the Gonsalves protocol,[33,34] and a process for Lindsey synthesis of *meso*-substituted porphyrins.[35] Both articles constitute landmarks in porphyrin synthesis in continuous flow; however, there is still room for improvement in the sustainability-related aspects of porphyrin synthesis. Reduction of solvent volume required for the synthesis, application of green solvents and finally, generalisation of solventless methods are green directions in porphyrin synthesis. In this contribution we build up on the preliminary studies reported for application of continuous flow in porphyrin synthesis to achieve improved sustainability (*E*-factor) and propose a universal method for porphyrin synthesis. We present a semi-continuous protocol for porphyrin synthesis under Lindsey conditions, incorporating a continuous stirred tank reactor (CSTR) at the condensation step. In this approach, we show that a significant (10×) increase in reactant concentration is not only beneficial for the reaction yield, but it also allows reduction in the volume of chlorinated solvents required for macrocyclisation by up to 90%.

Experimental

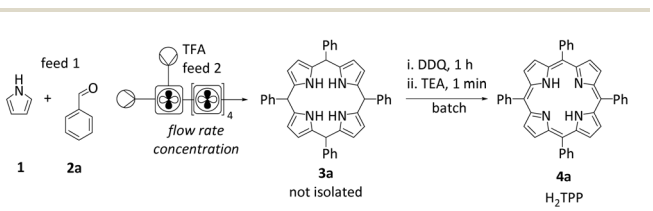
Materials and methods

Dipyrromethanes **5c** and **5d** (Scheme 4) were purchased from Frontier Scientific. Column chromatography was carried out using Supelco Silica Gel (pore size 60 Å, 230–400 mesh; Merck). CSTR-assisted synthesis was carried out using Asynt fReactor with five 2 mL modules (total reactor volume 10 mL). Detailed description of the experimental setup, including photographs, is provided in SI (page S6). Full compound characterisation data and ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, HRMS, IR, UV/vis spectra are provided in SI.

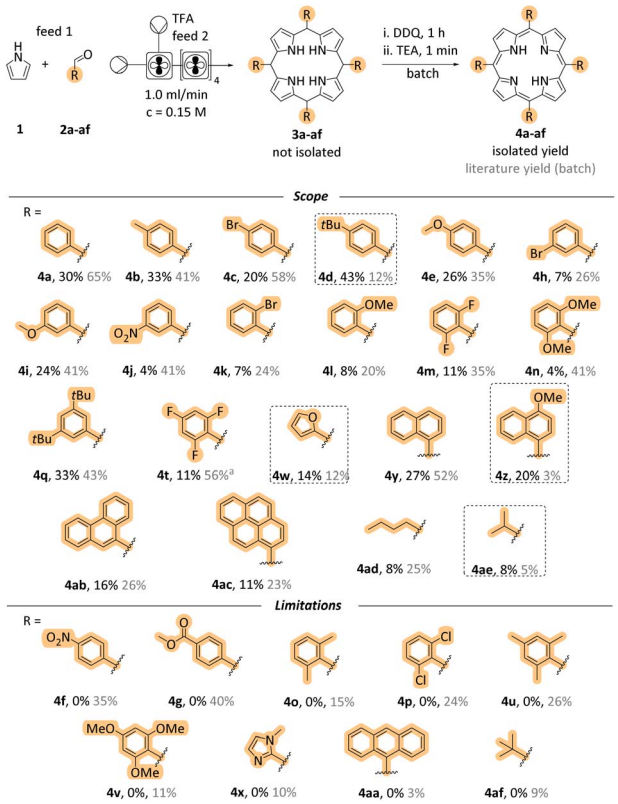
Synthetic procedures

Dipyrromethanes **5a**, **5b**, **5e**, **5f** (Scheme 4) and 3,4-diethylpyrrole **9** (Scheme 5) were prepared according to literature procedures.[36–38]

General procedure A: flow-assisted synthesis of A_4 porphyrins. A solution of pyrrole **1** (155 μL, 2.25 mmol, Scheme 1) and aldehyde **2a–af** (2.25 mmol, Fig. S1, SI) in DCM (15 mL) and a solution of trifluoroacetic acid (TFA, 170 μL, 2.25 mmol) in DCM (15 mL) were taken up in syringes and injected into fReactor at equal flow rate of 1 mL min^{-1}. After injection was completed, an additional 10 mL of DCM was pumped through the reactor to wash fully wash out the crude porphyrinogen **3a–af** (Scheme 2) into a round bottom flask equipped with a stir bar



Scheme 1 CSTR-assisted synthesis of **4a**.



Scheme 2 Scope and limitations of CSTR-assisted synthesis of A_4 porphyrins. Yields in grey were reported in literature for batch syntheses.[44] [a]Literature yield for Alder–Longo method.

and shielded from light. DDQ (450 mg, 2.00 mmol) was added to the crude mixture as powder and the mixture was stirred at RT for 1 h, neutralised with triethylamine (TEA, 300 μL, 2.25 mmol) and poured onto a short silica gel plug. Porphyrins **4a–af** (Scheme 2) were eluted with DCM (50 mL) and precipitated with *n*-hexane or methanol to afford purple crystals. The yields were determined based on two experiments.

General procedure B: flow-assisted synthesis of A_2 and *trans*-A_2B_2 porphyrins. A solution of dipyrromethane **5a–f** (0.75 mmol, Scheme 4) and aldehyde **2a–af** (0.75 mmol, Fig. S1, SI) in DCM (15 mL) and a solution of TFA (57 μL, 0.75 mmol) in DCM (15 mL) were taken up in syringes and injected into fReactor at equal flow rate of 1 mL min^{-1}. After injection was completed, an additional 10 mL of DCM was pumped through the reactor to wash fully wash out the crude porphyrinogen **6a–af** (Scheme 4) into a round bottom flask equipped with a stir bar and shielded from light. DDQ (136 mg, 0.60 mmol) was added to the crude as powder and the mixture was stirred at RT for 1 h, neutralised with TEA (100 μL, 0.75 mmol) and poured onto a short silica gel plug. Porphyrins **7a–af**, and **8c–e** (Scheme 4) eluted with DCM (30 mL) and precipitated with *n*-hexane to afford purple crystals. The yields were determined based on two experiments.

General procedure C: flow-assisted synthesis of 2,3,5,7,8,10,12,13,15,17,18,20-dodecasubstituted porphyrins. A solution of 3,4-diethylpyrrole **9** (135 mg, 1.10 mmol, Scheme 5) and aldehyde **2a–af** (1.10 mmol, Fig. S1, SI) in DCM (10 mL) and a solution of *p*-toluenesulfonic acid (TSA, 209 mg, 1.10 mmol) in DCM/MeOH (10 mL, 99 : 1, v/v) were taken up in syringes and injected into fReactor at equal flow rate of 1 mL min^{-1}. After injection was completed, an additional 10 mL of DCM was pumped through the reactor to wash fully wash out the crude porphyrinogen **10a–af** (Scheme 6) into a round bottom flask equipped with a stir bar and shielded from light. DDQ (750 mg, 3.30 mmol) was added to the crude mixture as powder and the mixture was stirred at RT for 1 h, then neutralised with TEA (150 μL, 1.1 mmol). The crude porphyrins **11a–s** (Scheme 6) were isolated as green solids by precipitation with methanol. Recrystallisation from KOH/EtOH 0.4% w/v afforded 'free base' dodecasubstituted porphyrins as brown/purple crystals. Porphyrin **11d** (Scheme 6) was isolated as a dication salt, in the form of a green solid. The yields were determined based on two experiments.

Results and discussion

A_4 porphyrins

With the goal to limit the volume of chlorinated solvents required for porphyrin synthesis, we envisioned a semi-continuous process, aided by a CSTR reactor (continuous stirred tank reactor). In the first step, an in-flow condensation of aldehydes **2a–af** (Fig. S1) with pyrrole **1** was performed. Due to the poor solubility of DDQ in chlorinated solvents, in-line oxidation would be counterproductive to the goal of limiting the need for chlorinated solvents in porphyrin synthesis.[39] DDQ was selected as the oxidant for this method (rather than its weaker tetrachlorinated derivative *p*-chloranil) in order to eliminate the need for heat supply during the oxidation step[40] and to comply with principle 6 of green chemistry ("design for energy efficiency").[1] Hence, both the oxidation and neutralisation steps were conducted in-batch.

Optimisation. The model reaction selected for optimisation was a condensation of pyrrole **1** with benzaldehyde **2a**, catalyzed by TFA, followed by an oxidation with DDQ and neutralisation with TEA, to yield 'free base' 5,10,15,20-tetraphenylporphyrin (**4a**, Scheme 1). The reagents (pyrrole **1** and aldehyde **2a**) were used in 1 : 1 molar ratio. The optimisation of in-flow condensation conditions involved the flow rate and the concentration of the reactants. The concentration range investigated started at 0.02 M, (a typical concentration for in-batch condensation)[24] and was increased up to c = 1.00 M (50 times more concentrated). For each concentration, we examined four different flow rates to assess the influence of residence time on the yield. Isolated yields listed in Table 2 were determined for the pure isolated product of condensation, oxidation and neutralisation (*i.e.*, 'free base' porphyrin **4a**).

Overall, the yields obtained in this optimisation varied from 9 to 30% (Table 2, entry 4 and entries 13 and 14, respectively). Interestingly, increasing the concentration of the reactants from standard batch conditions (c = 0.02 M) up to 10 times (c = 0.15, 0.20 M) returned best results; the highest yield recorded for c = 0.02 M was 15% (entry 1), and the best yield overall was 30% (c = 0.15 M, entries 13, 14). No further improvement was observed increasing the reactant concentration to c = 1.00 M –

Table 2 Optimisation of CSTR-assisted synthesis of **4a**

Entry	Conc. [M]	Flow rate [mL min^{-1}]	Yield [%]
1	0.02	0.5	15
2	0.02	1.0	12
3	0.02	1.5	10
4	0.02	2.0	9
5	0.05	0.5	22
6	0.05	1.0	16
7	0.05	1.5	15
8	0.05	2.0	11
9	0.10	0.5	27
10	0.10	1.0	24
11	0.10	1.5	23
12	0.10	2.0	20
13	0.15	0.5	30
14	**0.15**	**1.0**	**30**
15	0.15	1.5	29
16	0.15	2.0	29
17	0.20	0.5	28
18	0.20	1.0	28
19	0.20	1.5	27
20	0.20	2.0	25
21	0.30	0.5	27
22	0.30	1.0	26
23	0.30	1.5	24
24	0.30	2.0	24
25	0.50	0.5	22
26	0.50	1.0	20
27	0.50	1.5	20
28	0.50	2.0	19
29	1.00	0.5	12
30	1.00	1.0	12
31	1.00	1.5	13
32	1.00	2.0	13

unsurprisingly, a gradual drop in isolated yields to 28% (0.20 M, entry 17), 27% (0.30 M, entry 21), 22% (0.50 M, entry 25) and 13% (1.00 M, entries 31, 32) was observed. The optimal concentration of reactants for the in-flow condensation reaction was 0.15 M.

The impact of flow rate and residence time on the yield of 5,10,15,20-tetraphenylporphyrin **4a** was well-pronounced at low concentrations (0.02–0.10 M, entries 1–12, Table 2). Here, decreasing the flow rate from 2.0 mL min^{-1} to 0.5 mL min^{-1} contributed to 6, 12 and 7% yield increase at 0.02, 0.05 and 0.10 M, respectively. The maximum yields obtained for this range of concentrations were 15, 22 and 27%, increasing with the reactant concentration and residence time (entries 4, 8, 12). The influence of residence time on the isolated yield of H_2TPP (**4a**) was negligible in more concentrated reaction mixtures (0.15–1.00 M), with 3–8% differences in isolated yields. At the most effective reagent concentration of 0.15 M, both 0.5 mL min^{-1} and 1.0 mL min^{-1} returned the same highest yield of 30%. Thus, we concluded that the optimal flow rate for in-flow condensation of aldehydes and pyrroles under acid catalysis is 1.0 mL min^{-1}, translating to 15 min residence time.

Having established the optimal concentration and flow rate of the reactants for condensation, we examined other solvents commonly used in porphyrin synthesis – acetonitrile (MeCN), as a non-chlorinated alternative, and $CHCl_3$ (Table 3). The reactions were carried out at c = 0.3 M concentrations at 1.0 mL min^{-1} flow rate. No product was detected in the reaction in MeCN (entry 1), and in $CHCl_3$ the yield was 10% – over 2.5 times lower than in DCM (entries 2 and 3, respectively). While DCM is more volatile than $CHCl_3$, the latter is classified as significantly more hazardous for health according to the CLP Regulation.[41,42] Thus, we selected DCM as the more promising choice of solvent for this synthetic method.

Table 3 Solvent screening for **4a** synthesis

Entry	Conc. [M]	Flow rate [mL min^{-1}]	Solvent	Yield [%]
1	0.30	1.0	MeCN	0
2	0.30	1.0	$CHCl_3$	10
3	**0.30**	**1.0**	**DCM**	**26**

Next, we carried out experiments with other acids used as catalysts in the Lindsey method of porphyrin synthesis, *i.e.*, boron trifluoride diethyl etherate ($BF_3 \cdot Et_2O$) and *p*-toluenesulfonic acid (TSA). Both acids promoted the condensation, however neither performed as well as TFA: $BF_3 \cdot Et_2O$ yielded 17% of H_2TPP (entry 1, Table 4) and TSA 25% (entry 2). Additionally, we examined the influence of the amount of acid catalyst used on the yield, on the example of TFA. Reducing the amount of acid to 0.5 eq. resulted in a yield decrease to 8% (entry 4), while using 2.0 eq. of TFA only slightly increased the yield from 30 to 34% (entry 5). This result is in line with the 31% yield of **4a** reported by Parveen *et al.*[35] Given the modest improvement in yield triggered by the 100% increase in TFA quantity (entry 5), we concluded that TFA in 1.0 eq. is the optimal catalyst for condensation of aldehydes with pyrrole in a CSTR reactor. Taken together, the optimised conditions used for the determination of scope of flow-assisted synthesis of porphyrins under Lindsey conditions at high concentrations were a c = 0.15 M concentration of reagents in DCM with 1.0 eq. of TFA, at 1.0 mL min^{-1} flow rate. These optimised conditions require 7.5 times less DCM for porphyrin synthesis (c = 0.15 M). Additionally, a further decrease in solvent requirement is possible with a negligible drop in yield (from 30 to 28%), to 10 times less DCM than in batch conditions (using c = 0.20 M).

Scope and limitations. With the optimised conditions in hand, we moved on to scope determination. We selected a broad range of mono-, oligo- and per substituted benzaldehydes bearing electron donating and withdrawing groups, as well as polyaromatic, heterocyclic and aliphatic aldehydes (Fig. S1, Scheme 2).

Table 4 Optimisation for acid

Entry	Conc. [M]	Flow rate [mL min^{-1}]	Acid	Acid eq.	Yield [%]
1	0.15	1.0	$BF_3 \cdot Et_2O$	0.1	17
2	0.15	1.0	TSA	1.0	25
3	**0.15**	**1.0**	**TFA**	**1.0**	**30**
4	0.15	1.0	TFA	0.5	8
5	0.15	1.0	TFA	2.0	34

The best yields were obtained for condensations involving activated benzaldehydes, 4-*tert*-butylbenzaldehyde **2d** (**4d**, 43%), 4-tolualdehyde **2b** (**4b**, 33%) and 3,5-di-*tert*-butylbenzaldehyde **2q** (**4q**, 33%). **4a** was obtained in 31% yield from **2a**. Condensations with isomeric anisaldehyde **2e** and **2i** yielded 5,10,15,20-tetrakis(4-methoxyphenyl)porphyrin (**4e**, 26%) and 5,10,15,20-tetrakis(3-methoxyphenyl)porphyrin (**4i**, 24%). The presence of a bulky substituent in the *ortho* position of a benzaldehyde negatively impacts the yield,[43] as evidenced by 5,10,15,20-tetrakis(2-methoxyphenyl)porphyrin **4l** and 5,10,15,20-tetrakis(2,6-dimethoxyphenyl)porphyrin **4n**, which were formed in low yields of 8 and 4%, from aldehydes **2l** and **2n**, respectively. While *p*-bromobenzaldehyde **2c** gave 20% yield of the corresponding porphyrin **4c**, *meta* and *ortho* isomers both yielded 7% yield of porphyrins **4h** and **4k**, respectively. Interestingly, **4f** and **4g** were not isolated despite moderate yields reported in literature for batch synthesis of these porphyrins under Adler–Longo and Lindsey conditions, respectively.[44j,k] *ortho*-Substituted 2,6-difluorobenzaldehyde **2m** and 2,4,6-trifluorobenzaldehyde **2t** produced porphyrins (**4m**, 13%) and (**4t**, 11%) in yields lower than reported in literature for batch synthesis. The low yields of condensation observed for benzaldehydes bearing bulky substituents at the *ortho*-positions in comparison to H_2TPP result directly from the steric hindrance caused by bromine and fluorine atoms and methoxy groups, compared to a hydrogen atom.[43] Porphyrins **4k** and **4l** were obtained as mixtures of atropisomers.[45]

Polycyclic aromatic aldehydes, naphthaldehyde **2y**, 4-methoxynaphthaldehyde **2z**, 9-phenantrenecarbaldehyde **2ab**, 9-antracenecarbaldehyde **2aa** and 1-pyrenecarbaldehyde **2ac** were subjected to condensations with pyrrole to yield π-rich porphyrins which have previously found applications in two-photon absorption[46] and nanomaterials,[47] with moderate results. 5,10,15,20-Tetrakis(1-naphthyl)porphyrin **4y** and 5,10,15,20-tetrakis(4-methoxy-1-naphthyl)porphyrin **4z** were isolated in 27 and 20% yields, while phenanthrene and pyrene carbaldehydes **2ab** and **2ac** produced porphyrins **4ab** and **4ac** in 16% and 8% yields, respectively. Not surprisingly, the sterically hindered 5,10,15,20-tetrakis(9-anthryl)porphyrin **4aa** was not isolated out of the reaction mixture. Previous efforts to synthesise this porphyrin resulted in only 0.2% yield for Rothemund conditions,[48] 0.4% for modified Rothemund conditions (in pyridine and glacial acetic acid)[49] and 2.6% and 4% for the carbinol route.[50,51] Among heterocyclic derivatives, tetrakis(2-furyl)porphyrin **4w** was obtained in 14% yield, while 5,10,15,20-tetrakis(1-methyl-2-imidazolyl)porphyrin **4x** was not isolated. To further demonstrate the wide applicability of this method, three aliphatic aldehydes were included in the scope. These typically produce lower yields than their aromatic counterparts.[52] Valeraldehyde **2ad** and *iso*-butylaldehyde **2ae** formed porphyrins **4ad** and **4ae** in 8% yields, but pivaldehyde **2af** did not produce the 5,10,15,20-tetrakis(*tert*-butyl)porphyrin **4af**. Porphyrins **4d**, **4w**, **4z** and **4ae** (Scheme 2, framed) were isolated in yields surpassing those reported in literature for batch methods.[53–55] Yields determined for **4b**, **4i**, **4q**, **4ab** and **4ac** were comparable with those reported in literature for conventional methods of porphyrin synthesis according to the Lindsey protocol.[56–59] The detailed comparison of the yields obtained with this method and those reported previously in literature is presented in Scheme 2.

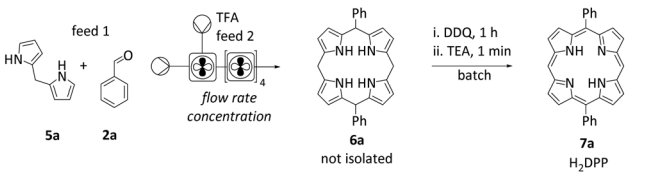
The limitations of this method correspond with those observed in traditional porphyrin synthesis. Bulky substituents installed near the formyl group of the aldehyde can hamper or preclude condensation.[43] This was observed for mesitylaldehyde **2u**, 2,6-dimethylbenzaldehyde **2o**, 2,6-dichlorobenzaldehyde **2p** and 2,4,6-trimethoxybenzaldehyde **2v** as corresponding porphyrins **4u**, **4o**, **4p** and **4v** were not isolated.

In summary, we prepared 21 5,10,15,20-tetrasubstituted porphyrins in 4–43% yields. The yield range in this library is in line with that reported by Parveen *et al.*, albeit exact comparison of numerical values cannot be made due to negligible overlap in scopes.[35]

A_2 and *trans*-A_2B_2 porphyrins

Optimisation. A_2B_2 porphyrins (including A_2 porphyrins, Fig. 2) are highly sought after for their applications in nonlinear optics,[60] dye-sensitised solar cells[61] and photodynamic therapy.[62] The reduced symmetry of A_2B_2 porphyrins compared to A_4 enables incorporation of substituents and functional groups with distinct chemical character, leading to remarkable properties. This comes at the cost of more laborious, multi-step synthesis. *trans*-A_2B_2 porphyrins are synthesised in a [2 + 2] condensation, known as MacDonald condensation, in which *meso*-free or *meso*-substituted dipyrromethane (*e.g.*, **5a** in Scheme 3) undergoes an acid catalyzed condensation with an aldehyde to form porphyrinogen **6a**, which is then oxidised to porphyrin **7a**.[63] We tested the applicability of our flow-assisted method, developed for A_4 porphyrins, for the synthesis of a model A_2 porphyrin, 5,15-diphenylporphyrin (**7a**, H_2DPP). Without deviation from the optimised conditions (c = 0.15 M, flow rate 1 mL min^{-1}, cat. 1.0 eq. TFA) we isolated H_2DPP **7a** in 27% yield (Scheme 3).

As [2 + 2] condensations are typically carried out at higher dilutions,[64] we anticipated an improvement in the isolated yield of H_2DPP upon decreasing the reagent concentration. Indeed, at concentrations c = 0.10, c = 0.07 and c = 0.05 M the recorded yields gradually increase to 29, 31 and 35%, respectively (Table 5, entries 2, 3 and 4). Further dilution to c = 0.03 and c = 0.01 M resulted in yield drop to 19 and 17%, respectively (entries 5 and 6). Similarly to the case of A_4 porphyrins described above, deviation from 1.0 eq. of TFA brought no improvement to the yield, as 0.5 eq. of acid produced 26% of H_2DPP (entry 7), and 2.0 eq. of TFA yielded only 9% of the porphyrin (entry 8). Taken together, under the best yielding conditions for [2 + 2]



Scheme 3 CSTR-assisted synthesis of **7a** (H_2DPP).

Table 5 Optimisation of **7a** (H_2DPP) synthesis

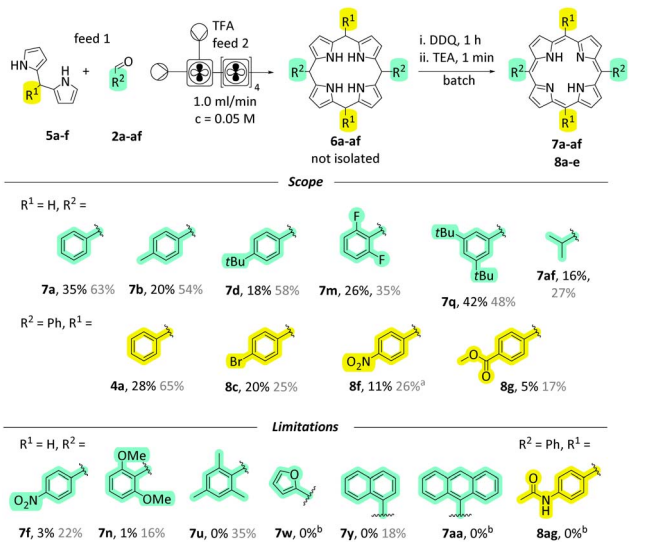
Entry	Conc. [M]	Flow rate [mL min^{-1}]	TFA eq.	Yield [%]
1	0.15	1.0	1.0	27
2	0.10	1.0	1.0	29
3	0.07	1.0	1.0	31
4	**0.05**	**1.0**	**1.0**	**35**
5	0.03	1.0	1.0	19
6	0.01	1.0	1.0	17
7	0.05	1.0	0.5	26
8	0.05	1.0	2.0	9

condensation of *meso*-unsubstituted dipyrromethane **5a** and benzaldehyde **2a**, catalyzed by TFA, at $c = 0.05$ M concentration in dichloromethane, at 1.0 mL min^{-1} flow rate, H_2DPP **7a** was isolated in 35% yield. These conditions were used for scope determination for [2 + 2] condensations producing A_2 and *trans*-A_2B_2 porphyrins. While the isolated yield of H_2DPP is lower than that obtained under traditional batch conditions, our optimised CSTR-assisted method uses only 10% of the DCM volume, comprising a significant reduction of the environmental cost of porphyrin synthesis.

Scope and limitations. The conditions optimised for flow-assisted variant of MacDonald [2 + 2] condensation of dipyrromethanes and aldehydes were used in the synthesis of two libraries of porphyrins with distinct substitution patterns: A_2 porphyrins, obtained through a condensation of aldehydes with *meso*-free dipyrromethane **5a**, and *trans*-A_2B_2 porphyrins, formed from *meso*-substituted dipyrromethanes **5b–f** (Scheme 4).

Similarly to Lindsey condensations, 3,5-di-*tert*-butylbenzaldehyde **2q** produced porphyrin **7q** in the highest yield, 42%, close to the yield reported for batch synthesis (48%).[64] This was the only A_2 porphyrin obtained with higher yield than H_2DPP **7a**, which was formed in 35%. *p*-Tolualdehyde **2b** and *p*-*tert*-butylbenzaldehyde **2d** yielded **7b** and **7d** in 20 and 18%, respectively, while for *p*-nitrobenzaldehyde **2f**, a significant drop in yield was observed (3%). *iso*-Butyraldehyde **2ae** was selected as an aliphatic example and yielded 16% of porphyrin **7ae**. 5,15-Bis(2,6-difluorophenyl)porphyrin **7m** was formed in 26% yield, but condensations with more hindered *ortho*-aldehydes, mesitylaldehyde **2u** and 2,6-dimethoxybenzaldehyde **2n**, did not produce the anticipated porphyrins **7u** and **7n**. In contrast to the A_4 porphyrin **4w**, the heterocyclic 5,15-bis(2-furyl)porphyrin **7w** was not formed. Formation of A_2 porphyrins substituted with polycyclic aromatic hydrocarbons was also impeded, as neither the naphthalene porphyrin **7y**, nor the anthracene derivative **7aa** were isolated.

In the second part of the scope, benzaldehyde **2a** was subjected to [2 + 2] MacDonald condensations with a small library of *meso*-substituted dipyrromethanes, *i.e.* 5-phenyldipyrromethane **5b**, 5-(4-bromophenyl)dipyrromethane **5c**, 5-(4-nitrophenyl)dipyrromethane **5d**, 5-(4-carboxymethylphenyl)dipyrromethane **5e** and 5-(4-acetamidophenyl)dipyrromethane **5f**. However, under the optimised conditions (Table 5), the crude mixtures contained unreacted dipyrromethanes. Thus, flow rate was adapted to 0.5 mL min^{-1} to allow longer residence time, and to drive the reactions to completion. Gratifyingly, this modification helped achieve full consumption of starting materials. Utilising aryl substituted dipyrromethanes **5b–f** the tetrarylporphyrins **4a**, **8c**, **8f** and **8g** were formed in 28, 20, 11 and 5% yields, respectively. These values are lower than those reported previously for batch synthesis of the respective porphyrins **4a**, **8c**, **8f** and **8g**.[59,66] **8ag** was not formed under flow conditions. No scrambling was observed in these experiments.[59]

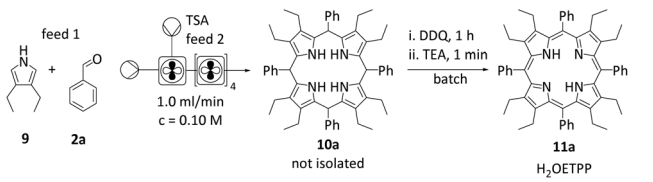


Scheme 4 Scope and limitations of CSTR-assisted synthesis of A_2 and *trans*-A_2B_2 porphyrins. Yields in grey were reported in literature for batch syntheses.[65] [a]Literature yield for Alder–Longo method. [b]Yield not reported in literature.

Dodecasubstituted porphyrins

Recognising the unique properties arising from the shape of dodecasubstituted porphyrins, and their potential for applications in sensing,[67] organocatalysis[68] and photocatalysis[69] we focused on the third library of interest – 5,10,15,20-tetraaryl-2,3,7,8,12,13,17,18-octaethylporphyrins (H_2OETAP). To the best of our knowledge, this is the first flow-assisted method for the synthesis of dodecasubstituted porphyrins.

Optimisation. We optimised the synthetic and process conditions for condensation of benzaldehyde **2a** and 3,4-diethylpyrrole **9**, followed by in-batch oxidation of the porphyrinogen **10a** and neutralisation (Scheme 5). Following the incremental differences in yield of **4a** observed at different flow



Scheme 5 CSTR-assisted synthesis of **11a** (H_2OETPP).

rates within the optimal concentration range (Table 6), here we applied a constant flow rate of 1.0 mL min^{-1}. The synthetic methods for dodecasubstituted porphyrins are significantly less studied than their tetra substituted counterparts.[70] Interestingly, $BF_3 \cdot Et_2O$, which is the standard acid catalyst used for H_2OETAP synthesis,[71] did not promote macrocyclisation to form the desired porphyrinogen **10a** under continuous flow, as evidenced by 0% yield obtained using 0.1 and 0.5 eq. $BF_3 \cdot Et_2O$ at reagent concentrations $c = 0.01$ and $c = 0.1$ M (Table 6, entries 1–3). We then turned our attention to trifluoroacetic acid (TFA); attempts carried out at $c = 0.01$, $c = 0.05$ and $c = 0.1$ M did not result in the formation of the macrocycle (entries 4–6). Gratifyingly, *p*-toluenesulfonic acid (TSA) was found a suitable catalyst for this condensation (entries 7–13).

Using 1.0 eq. of TSA, we observed formation of porphyrin **11a** with 6% isolated yield at $c = 0.05$ M concentration (Table 6, entry 8) and 16% at $c = 0.1$ M (Table 6, entry 9); at $c = 0.01$ M (typical batch concentration) porphyrin **11a** was not isolated (entry 9). The low solubility of TSA in DCM was a significant limitation in these experiments. Hence, we examined the influence of methanol as a solubilising additive. A significant increase in isolated yield, from 6 to 10%, was observed when 0.1% (v/v) of MeOH was used (entries 8 and 10). The yield was increased 2-fold when 1% of MeOH was used (20%, entry 11). With these satisfactory results, we assessed the effect of the concentration of reactants on the yield, keeping in mind our aim to reduce the volume of chlorinated solvents required for porphyrin synthesis. Pleasingly, at $c = 0.1$ M porphyrin **11a** was isolated in 30% yield (entry 12), but at $c = 0.2$ M the yield dropped to 21% (entry 13). Hence, the optimised conditions for the synthesis of dodecasubstituted porphyrins involve TSA as acid catalyst, $c = 0.1$ M in DCM/MeOH, 99 : 1, v/v and 1.0 mL min^{-1} flow rate. As *p*-toluenesulfonic acid has not been used in the synthesis of dodceca substituted porphyrins to date, we carried out batch experiments using TSA for formation of 2,3,7,8,12,13,17,18-octaethyl-5,10,15,20-tetraphenylporphyrin (**11a**, H_2OETPP); however no macrocycle was isolated at low ($c =$ 0.01 M) or high ($c = 0.1$ M) concentrations.

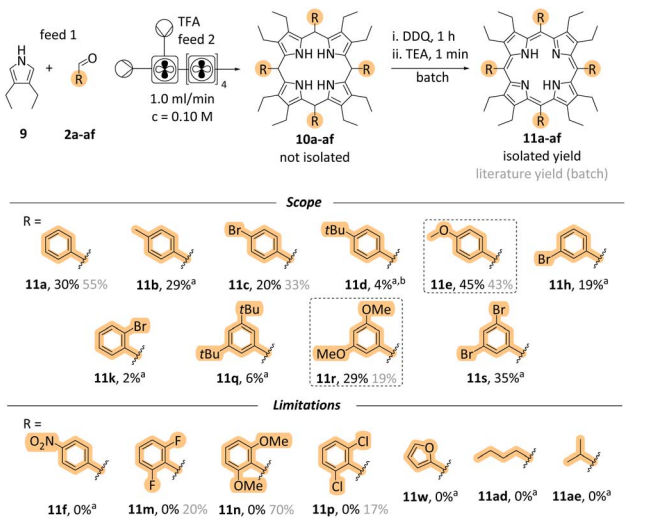
Table 6 Optimisation of CSTR-assisted synthesis of **11a**

Entry	Acid	MeOH [%v/v]	Conc. [M]	Yield [%]
1[a]	$BF_3 \cdot Et_2O$	0	0.010	0
2[a]	$BF_3 \cdot Et_2O$	0	0.100	0
3[b]	$BF_3 \cdot Et_2O$	0	0.010	0
4	TFA	0	0.010	0
5	TFA	0	0.050	0
6	TFA	0	0.100	0
7	TSA	0	0.010	0
8	TSA	0	0.050	6
9	TSA	0	0.100	16
10	TSA	0.1	0.050	10
11	TSA	1.0	0.050	20
12	**TSA**	**1.0**	**0.100**	**30**
13	TSA	1.0	0.200	21

[a] 0.1 eq. of $BF_3 \cdot Et_2O$ was used. [b] 0.5 eq. of $BF_3 \cdot Et_2O$ was used.

Scope and limitations. In comparison to their planar counterparts, dodecasubstituted nonplanar porphyrins are relatively underexplored in terms of synthesis, functionalisation and applications.[70] Additionally, achieving a significant nonplanar distortion in a porphyrin greatly augments the porphyrins basicity.[72,73] This ring contortion makes the pyrrolic imine nitrogen atoms extremely susceptible to core protonation. In practical terms, H_2OETAPs are typically isolated as dication salts, and strong bases are required for isolation of 'free base' ligands.[74,75]

Following the TSA-catalyzed condensation, we synthesised a library of ten dodecasubstituted porphyrins from a range of aldehydes and 3,4-diethylpyrrole **9** (Scheme 6). The highest yield in this library was observed for porphyrin **11e** (45%), 2% higher than previously reported in literature[76a] and 19% higher than the corresponding planar porphyrin **4e** (26%, Scheme 2) under flow conditions. Electronically similar H_2OETPP **11a** and octaethyltetra-*p*-tolylporphyrin **11b** were isolated in 30 and 29% yields, respectively, with the latter having no comparable value in literature.[76b] Both *meta*-disubstituted 3,5-dimethoxybenzaldehyde **2r** and 3,5-dibromobenzaldehyde **2s** produced the corresponding porphyrins **11r** and **11s** in good yields (29 and 35%, respectively). However, the condensation yield determined for the reaction with 3,5-di-*tert*-butylbenzaldehyde **2q** was only 6% for **11q**, a yield 10% lower than reported for batch synthesis.[76c] Similarly, *p*-*tert*-butylbenzaldehyde **2d** only produced 4% of the dication salt of porphyrin **11d**. **11d** was the only porphyrin in this series isolated as a dication, possibly due to an increased basicity of the porphyrin core due to activating electronic effects. *p*- And *m*-bromobenzaldehydes **2c** and **2h** yielded 20% and 19% of **11c** and **11h**, respectively the nonplanar *meta*-derivative was once



Scheme 6 Scope and limitations of CSTR-assisted synthesis of dodecasubstituted porphyrins. Yields in grey were reported in literature for batch syntheses.[76] [a]Yield not reported in literature. [b]Compound isolated as a dication salt. [c]For porphyrins **11a** and **11k**, single crystal X-ray structures were obtained, full refinement details and analysis are provided in the SI (CCDC: 2521006 and 2521007).

again obtained in a higher yield than the planar **4h** (7%, Scheme 2); the *para*-derivative with an isolated with a yield 13% lower than reported for batch conditions.[76d] On the other hand, *o*-bromobenzaldehyde **2k** was the poorest starting material in this library, with only a 2% isolated yield for **11k**. This is likely due to the increased steric hindrance near the reacting atoms.[39] Alkyl groups substituting pyrrole C_β positions may augment this effect significantly; **11k** was the only porphyrin isolated out of five *ortho*-substituted aldehydes investigated. Alkyl aldehydes **2ad** and **2ae**, furfural **2w** and *p*-nitrobenzaldehyde **2f**, and *ortho*-hindered benzaldehydes **2m**, **2n**, **2p** failed to produce the corresponding porphyrins **11f**, **11m**, **11n**, **11p**, **11w**, **11ad** and **11ae** (Scheme 6), contrary to the results reported for batch synthesis.[72]

E-Factors

To validate our methods as sustainable, we calculated *E*-factor (environmental impact factor)[77] for the protocols presented in this manuscript and compare them with corresponding values determined for batch protocols. *E*-Factor is one of the key descriptors used to assess the sustainability of a chemical reaction, considering the effectiveness in product formation over waste produced in the process. We selected *E*-factor as a measure of success in achieving our goal, which was to develop a sustainable and versatile flow-assisted protocol for porphyrin synthesis, reducing the volume of chlorinated solvent required for cyclisation.

In eqn (1) below, waste includes unreacted starting materials, catalysts, solvents, side products formed over the course of the reaction and materials and chemicals used in the work-up. Detailed analysis of waste contributions is disclosed in SI (Table S1).

$$E = \frac{\text{waste[g]}}{\text{product[g]}} \quad (1)$$

Table 7 presents a comparison of *E*-factors calculated for protocols developed in this project and the corresponding values obtained for literature batch protocols. All values are presented for **4a** (H_2TPP), **7a** (H_2DPP) and **11a** (H_2OETPP) syntheses as examples. The range of *E*-factor values for fine chemicals in industry is 5–50.[77a] In porphyrin chemistry, the *E*-factor values for traditional synthesis of **4a** (H_2TPP) range between 158 for Alder–Longo method and 2252 for Lindsey method.[78] Porphyrin synthesis is an environmentally taxing process, which is in part due to high dilutions required for macrocyclisation, combined with the side reactions predominant in acidic conditions.[79] We circumvented some of the problems associated with the synthesis of *meso*-substituted porphyrins. By incorporating flow chemistry at the condensation step, we successfully accessed higher global concentration of reactants, which directly translates to lower demand for chlorinated solvents, and decreasing the volume of waste produced in the process. This effect is quantified by *E*-factor. The comparison of *E*-factors for H_2TPP **4a**, H_2DPP **7a** and H_2OETPP **11a** synthesis in flow and in batch shows significant improvement for all three methods presented in this contribution. The *E* values were reduced by 48% for **4a** (from 2252 to 1180), 38% for **7a** (from 2282 to 1416) and 35% for **11a** (from 2015 to 1314). The reaction yield, type of acid catalyst, oxidant and possible additives have negligible influence on the *E*-factor (Table S1); the major contribution comes from the mass of solvents used for the synthesis and purification. Hence, the 90% decrease in solvent volume required for porphyrin synthesis in our method directly translates to significant improvements in sustainability parameters.

Table 7 *E*-Factors for compounds, **4a** (H_2TPP), **7a** (H_2DPP) and **11a** (H_2OETPP)

Porphyrin	**4a**		**7a**		**11a**	
Method	Flow	Batch	Flow	Batch	Flow	Batch
Scale [mmol]	2.25		0.75		1.10	
Waste [g]	130	495	85	251	92	262
Product [g]	0.11	0.22	0.06	0.11	0.07	0.13
E-Factor[77]	1180	2252	1416	2282	1314	2015

Crystallography

Many examples of X-ray crystal structures of dodecasubstituted nonplanar porphyrins are found in the literature.[74,76,80] However, many H_2OETAP derivatives are often reported in their dicationic form with just one other example of a 'free base' OETAP being previously reported (**11a**, crystallised from ethanolic KOH).[81] Here, the X-ray crystal structures of the 'free base' dodecasubstituted porphyrins **11a** (from deuterated benzene) and **11k** are reported, with **11k** adopting the $\alpha_3\beta$ atropisomeric conformation (Fig. 3).[82]

Analysis of the view of the molecular structures in the crystal of **11a** and **11k** reveals the expected saddled shaped (B_{2u}) nonplanar distortion. For porphyrin **11k** intramolecular hydrogen bonding interactions (2.29–2.34 Å) between both opposing enamine hydrogen atoms (N-21 and N-23) and the adjacent imine nitrogen atoms (N-22) are observed. A

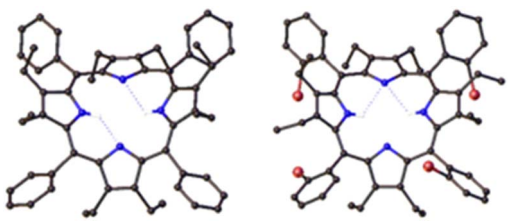


Fig. 3 (Left) View of the molecular structure of **11a** in the crystal, depicting the hydrogen bond interactions in the porphyrin core. Deuterated benzene solvent molecules are omitted for clarity. (Right) View of the molecular structure of **11k** in the crystal, showing the $\alpha_3\beta$ atropisomer and hydrogen bond interactions in the porphyrin core. Solvent molecules and hydrogen atoms on the porphyrin periphery are omitted for clarity.

preferential hydrogen bonding of N-24 with the hydrogen atom of the $CHCl_3$ solvate is noted (Fig. 3). This solvent binding event is not observed in the case of **11a** where enamine hydrogen atoms (N-21 and N-23) hydrogen bond (2.29–2.31 Å) to both adjacent imine nitrogen's (N-22 and N-24).

In contrast to the X-ray crystal structure of **11k**, porphyrin **11a** by when analyzed by NSD analysis has 3.4° greater tilt in the pyrroles from the mean porphyrin plane. Additionally, the total Δ_{oop} distortion of the 'free base' analogue (defined as the average deviation of the 24-atom macrocycle with respect to the mean porphyrin plane, $\Delta z = 0$)[83] is 3.48 Å in porphyrin **11a** compared to 3.13 Å in **11k**.

Comparing the crystal structure of 'free base' **11k** with the analogous Ni(II) metalated *cis*-$\alpha_2\beta_2$ atropisomeric derivative of **11k** from literature[76e] is difficult as conformationally these two porphyrins are quite different, nonetheless, the pyrrole tilt angle for the 'free base' **11k** is 26° almost 3° less than the Ni(II) derivative. The total Δ_{oop} distortion of the 'free base' analogue is 0.64 Å less compared to the Ni(II) counterpart with a total Δ_{oop} distortion of 3.77 Å. Nevertheless, it is very difficult to make a direct comparison between the two structures due to disparate atropisomeric conformations as well differing crystallisation[76d] and crystal packing effects.[84]

Conclusions

In conclusion, we designed and optimised flow-based synthetic methods for *meso*-substituted porphyrin synthesis and demonstrated their applicability to three libraries of porphyrins: A_4, *trans*-A_2B_2 (including A_2) and dodecasubstituted A_4 porphyrins. These sustainable methods were optimised to operate at significantly higher reactant concentrations than traditional batch methods, leading to a dramatic decrease in the volume of chlorinated solvents required for porphyrin synthesis (up to 90% solvent saving), and a significant improvement in *E*-factors over batch conditions (up to 48% reduction of *E* values). The synthesis of 40 porphyrins is disclosed, alongside their structural details. We hope that this contribution proves useful to porphyrin chemists across the globe and prompts the use of sustainable protocols in porphyrin and other chemical laboratories.

Author contributions

Karolina Urbańska – conceptualisation, funding acquisition, methodology, investigation, project administration, writing – original draft; Liam Cribbin – conceptualisation, funding acquisition, investigation, writing – original draft; Brendan Twamley – investigation, formal analysis; Fiach O Ceallaigh – investigation; Mathias O. Senge – resources, supervision, writing – review & editing.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article is included as part of the supplementary information (SI) (compound characterisation, NMR, HRMS, UV/vis and IR spectra and refinement details). References cited in the SI (ref. 85–118) are listed in the article reference list. Supplementary information: compound characterisation data, spectra, CIF files, *E*-factor calculation. See DOI: https://doi.org/10.1039/d6su00176a.

CCDC 2521006 (**11a**) and 2521007 (**11k**) contain the supplementary crystallographic data for this paper.[119a,b]

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