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Exploiting photooxygenations mediated by porphyrinoid photocatalysts under continuous flow conditions†

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Photooxygenation reactions are a powerful synthetic tool to produce oxidized organic compounds; however, these reactions often exhibit experimental limitations including the production of complex mixtures that hinder desired product isolation and scale-up. Herein, we present a photocatalysed protocol under continuous flow conditions using a simple home built photoreactor and porphyrinoids as photocatalysts. Reaction conditions, long-term experiments, and scope demonstrate a protocol that is cost-effective, safe, reproducible and robust, thus allowing the production of relevant substituted naphthoquinones with interest in natural product synthesis and biological activity.

Introduction

Photooxygenation reactions have an important role in synthetic chemistry due to their high atom-economy and low cost.[1] Over the last five decades researchers have recognized that singlet oxygen is the key excited intermediate for generating oxygenated compounds such as hydroperoxides,[2] peroxides,[3] dioxetanes,[4] endoperoxides[5] and sulfoxides.[6]

The generation of singlet oxygen using photosensitizers is well-known.[7] While many photosensitizers have been described,[8] porphyrin derivatives are one of the most efficient classes of compounds for this purpose as supported by recent and relevant applications in organic synthesis.[5,9]

Since their discovery, photooxygenation processes have presented restrictions for their use in large scale reactors due to limitations imposed by the potential to form explosive intermediates, thus requiring the use of high dilutions and small scales. However, this limitation has recently been addressed by utilization of flow-based approaches to carry out photochemical transformations.[10] Current advances in chemical synthesis under continuous flow conditions have in fact changed the way in which reactions are developed and scaled up in the pharmaceutical industry and research laboratories.[11] Numerous advantages have been provided such as controlled mixing, fast heat transfer, control of residence time and process automation.[12] Particularly, photochemical and photocatalysed transformations accelerated under continuous flow are one of the most prominent processes since significant improvements have been accomplished at the micro- and meso-scale, and successful reaction classes improved using these techniques due to the high efficiency of light irradiation and enhanced safety.[10]

Regarding the photooxygenations of naphthols, previous work performed in batch conditions has been published,[13] as well as preliminary versions of photochemical flow devices. The pioneering work of Oelgemöller[14] and co-workers showed the possibility to use both plug-flow and parallel falling films for photooxygenations under different continuous flow conditions. However, both methodologies and devices of these previous work displayed limitations and required many reaction cycles, high concentrations of photosensitizers (up to 5 mol%) with low conversions in some cases,[14c] inspiring us to explore improved and cost-competitive conditions for this continuous flow photooxygenation.

Herein, we have built and applied a simple, yet effective in-house engineered photoreactor to perform a comprehensive study of the photooxygenation of naphthols (Scheme 1). Different porphyrinoid and phthalocyanine derivatives were evaluated as photosensitizers (0.1–0.5 mol%), achieving high efficiency. Scope, robustness, and most importantly, scalability with a 24 h extended experiment are presented under continuous flow conditions, which allowed the production of relevant substituted naphthoquinones of interest in natural product synthesis and with well-recognized biological activities.[15]

Results and discussion

First, in order to elucidate the best conditions for these photooxygenations, we constructed the photoreactor shown in Fig. 1 and S1 (ESI†). We used a reflexive aluminium-plate adapted with connections for a lamp with fan cooling, and a glass cylinder to coil the PFA (perfluoroalkoxy) tubing (for

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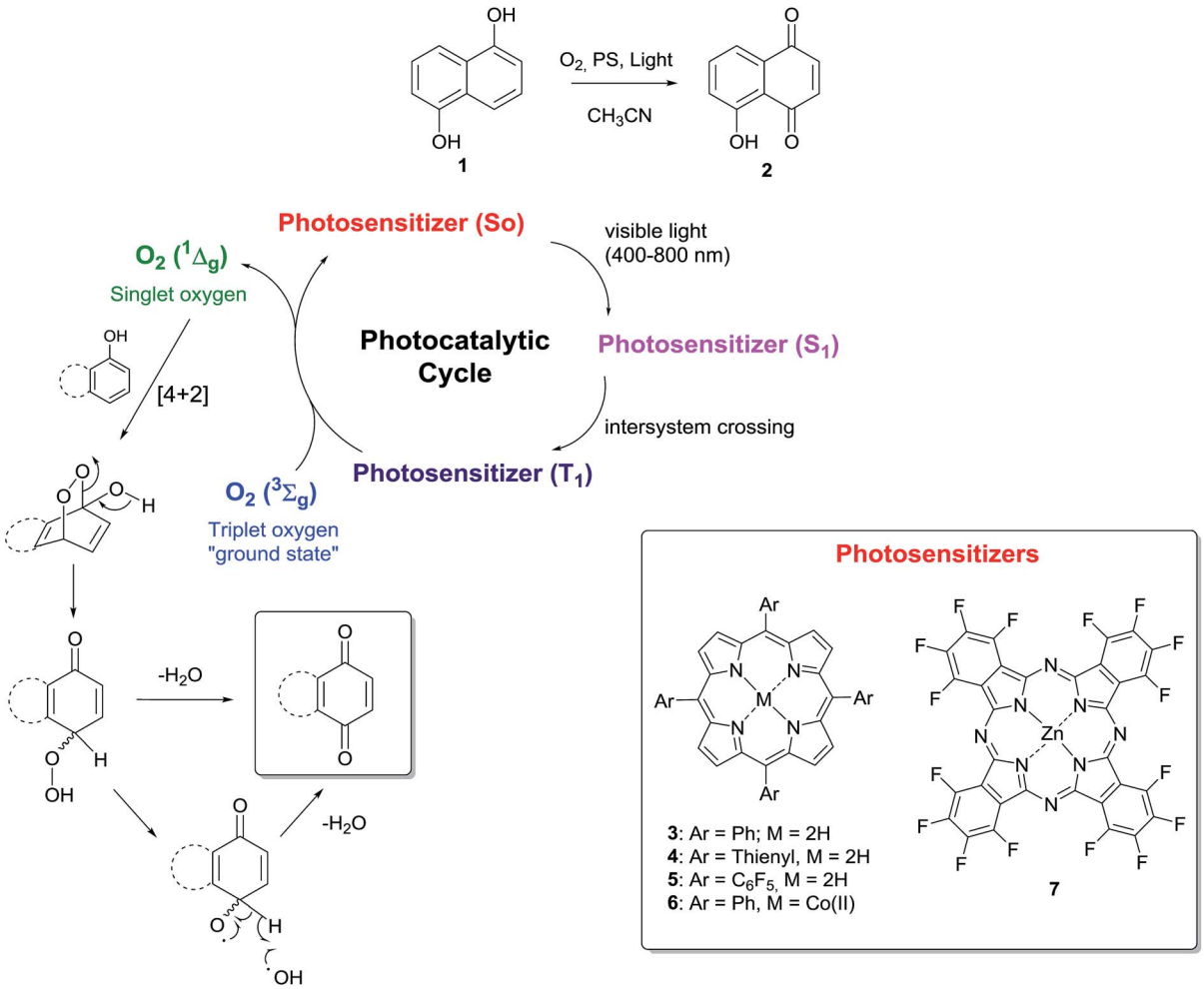


Scheme 1 Photocatalytic cycle and photosentizers for the photooxygenation of 1.

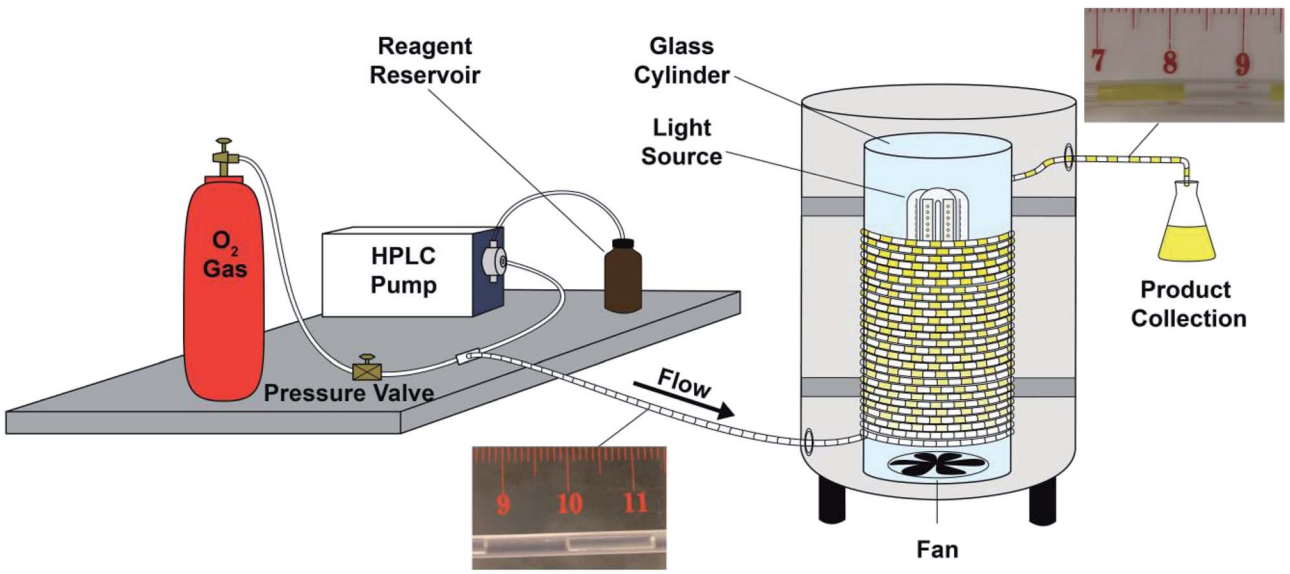


Fig. 1 Flow chemistry setup for photooxygenations.

details, Fig. S1†). For process optimization we selected 5-hydroxynaphthol (**1**) to yield juglone (**2**) (Scheme 1).

We began the optimization by pumping of 100 mL of 3 mM solution of **1** with 0.1 mol% of the photocatalyst tetraphenylporphyrin (**3**) under three different plug-flow conditions (Table 1) in order to select the best flow rate and light source for the transformations (Scheme 1 and Fig. 1).

Using the FLC lamp (45 W) the best result was obtained with a flow rate of 0.75 mL min^{-1} (entry 2, Table 1) considering the yield, residence time, and space-time yield (STY). Similarly, the use of white LED lamp (24 W) and a flow rate of 0.75 mL min^{-1} (entry 5, Table 1) produced the best result in terms of yield, residence time and STY, and requiring approximately half of the energy compared to the FLC source (24 W *vs.* 45 W). The superiority of the white LED lamp can be explained by the comparison of the emission and absorption spectra (Fig. 2) for each light source and the porphyrin **3**. Specifically, the broad emission band of white LED source (480–700 nm) encompasses the entire visible region of the absorption spectrum of **3** (500–670 nm).

Thus, from the first six experiments it was possible to suggest the flow rate of 0.75 mL min^{-1} as the most adequate due to the productivity, and also because the most significant increase of STY was found in the range of 0.5 to 0.75 mL min^{-1}. It is important to highlight that the reproducibility was also evaluated by performing each reaction twice (Table 1) with only minor variations of 1–3% yield, as observed in Table 1.

After establishing the best light source, different photocatalyst concentrations were examined from 0.1 to 0.5 mol% at three different flow rates (Table 2). From the results we conclude that 0.3 and 0.5 mol% are the best photosensitizer concentrations, but it was not clear if the use of 0.5 mol% would furnish the best cost-benefit.

Subsequently, different concentrations of substrate **1** (Table 3) were assessed from 3.0 to 12.0 mM while maintaining the flow rate at 0.75 mL min^{-1} and employing two different photocatalyst concentrations (0.3 and 0.5 mol%). Comparing the experiments from entries 1–5 and 6–9, very similar yields and STY were observed between all comparable entries, however, the use of lower amounts of photocatalyst (0.3 mol%, entries 1–5, Table 3) were decisive for the choice of 0.3 mol% as the most ideal catalyst loading.

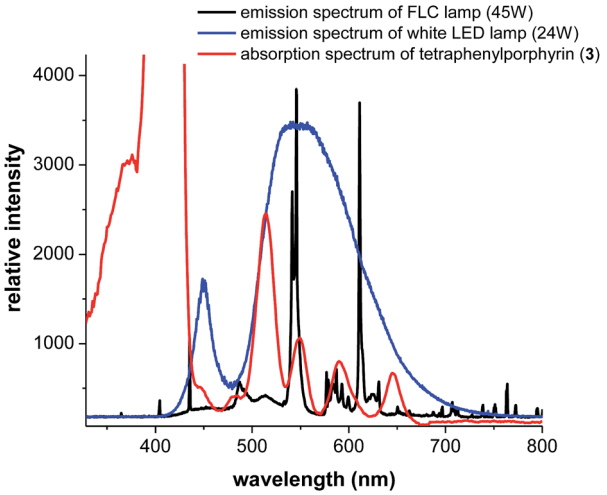


Fig. 2 Comparison between the emission spectra of light sources and absorption spectra of **3**.

Another parameter which highlights this preference is the productivity of the photocatalyst which is almost two times greater for 0.3 mol% photocatalyst loading. The selected conditions to proceed with the methodology study are shown in entry 4, Table 3, since greater concentrations of substrate (up to 10 mM) required amounts of photocatalyst **3** (mol%) which caused precipitation to occur (entries 5, 8 and 9, Table 3). It is important to highlight that this optimized amount of TPP (**3**) (0.3 mol%, US dollars 33.1 $mmol^{-1}$)[16] is advantageous compared to similar photooxygenation procedures found in the literature[14] using bengal rose (≥5 mol%, US dollars 40.4 $mmol^{-1}$).[16]

After screening to find the best flow rate and substrate/photocatalyst concentrations we decided to evaluate different photocatalysts including additional porphyrinoids **4–6** and the phthalocyanine **7** (Table 4). Different photoactivities were observed most likely due to the different ability of these photosensitizers (**3–7**) to produce singlet oxygen since nearly the entire absorption spectra of **3–7** (Q-bands, 500–700 nm) were covered by the emission spectra of the LED lamp (430–700 nm). Clearly, the simplest and most cost-competitive photocatalyst **3** proved to be the most efficient giving us all of the

Table 1 Screening of light source and flow rate for the continuous flow photooxygenation of **1**[a,b]

Entry	Visible light source	Solution flow rate (mL min^{-1})	Juglone (**2**) yield (%) 1st	2nd	Avg	Residence time (min)	STY (**2**)[c] (g per day)
1	FLC, 45 W	0.50	52	55	53	25.0	0.20
2	FLC, 45 W	0.75	58	60	59	16.7	0.33
3	FLC, 45 W	1.00	48	49	48	12.5	0.36
4	LED, 24 W	0.50	75	72	74	25.0	0.28
5	LED, 24 W	0.75	58	56	57	16.7	0.32
6	LED, 24 W	1.00	43	43	43	12.5	0.32

[a] Reactions performed by using 100 mL of a solution of the substrate **1** at 3.0 mmol L^{-1}, photocatalyst **3** at 0.1 mol% in CH_3CN : CH_2Cl_2 (95 : 5), 1 cm plug-flow (regular oxygen and solution) in a 25 mL PFA tubing photoreactor (0.125 in (OD) × 0.065 in (ID)). [b] Isolated yield by column chromatography. [c] Considering the average yield (Avg).

Table 2 Screening of photocatalyst **3** mol% by using 24 WLED lamp for the continuous flow photooxygenation of **1**[a]

Entry	Solution flow rate (mL min^{-1})	Juglone (**2**) yield (%) using TPP (**3**) at 0.1 mol%	Juglone (**2**) yield (%) using TPP (**3**) at 0.2 mol%	Juglone (**2**) yield (%) using TPP (**3**) at 0.3 mol%	Juglone (**2**) yield (%) using TPP (**3**) at 0.5 mol%
1	0.50	73	81	85	85
2	0.75	57	71	80	83
3	1.00	43	60	75	81

[a] Reactions performed by using 100 mL of a solution of the substrate **1** at 3.0 mmL L^{-1}, photocatalyst **3** in different concentrations in CH_3CN : CH_2Cl_2 (95 : 5), 1 cm plug-flow (regular oxygen and solution) in a 25 mL PFA tubing photoreactor (0.125 in (OD) x 0.065 in (ID)).

Table 3 Screening of the substrate concentration using LED 24 W lamp for the continuous flow photooxygenation of **1**[a]

Entry	Substrate **1** mmol L^{-1}	TPP (**3**) as photocatalyst (mol%)	Juglone (**2**) yield (%)	STY (**2**) (g per day)	Productivity mmol product per mmol catalyst per h
1	3.0	0.3	80	0.45	120
2	6.0	0.3	85	0.96	128
3	9.0	0.3	85	1.44	128
4	10.0	0.3	82	1.54	123
5[b]	12.0	0.3	78	1.76	117
6	3.0	0.5	83	0.47	75
7	6.0	0.5	83	0.93	75
8[b]	9.0	0.5	83	1.41	75
9[b]	12.0	0.5	78	1.76	70

[a] Reactions performed by using 100 mL of a solution of the substrate **1**, photocatalyst **3** at 0.3 mol% or 0.5 mol% in CH_3CN : CH_2Cl_2 (95 : 5), solution flow rate (0.75 mL min^{-1}), 1 cm plug-flow (regular oxygen and solution) in a 25 mL PFA tubing photoreactor (0.125 in (OD) × 0.065 in (ID)). [b] In these conditions it was observed a small amount of TPP (**3**) as a precipitate after the experiment with no serious blockage of the pump system.

Table 4 Screening of the different photocatalysts **3–6** in the photooxygenation of **1**[a]

Entry	Photocatalysts at 0.3 mol%	Juglone (**2**) yield (%)	STY juglone (**2**) (g per day)	Productivity mmol product per mmol catalyst per h
1	**3**	82	1.54	123
2	**4**	15	0.28	22
3	**5**	72	1.35	108
4	**6**	6	0.11	9
5	**7**	18	0.34	27

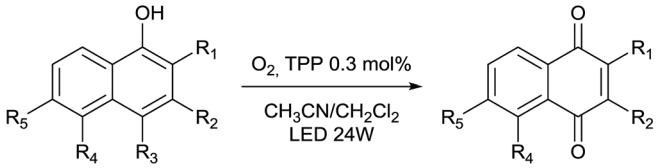
[a] Reactions performed by using 100 mL of a solution of the substrate **1** at 10.0 mmol L^{-1}, different photocatalysts at 0.3 mol% in CH_3CN : CH_2Cl_2 (95 : 5), solution flow rate (0.75 mL min^{-1}), 1 cm plug-flow (regular oxygen and solution) in a 25 mL PFA tubing photoreactor (0.125 in (OD) × 0.065 in (ID)).

optimized parameters required to advance the scope of this photooxygenation protocol. Before continuing with the scope of this protocol, we decided to showcase the robustness of this method and performed two 24 h experiments using the optimized conditions (substrate **1** at 10 mM, TPP **3** at 0.3 mol%, flow rate at 0.75 mL min^{-1} in CH_3CN : CH_2Cl_2 95 : 5, and 1 cm plug-flow of oxygen and solution). Juglone (**2**) was obtained in both experiments in 72% (1.35 g) and 74% (1.40 g) yield, respectively, proving this protocol as reproducible and in agreement with STY (1.54 g) for these conditions (entry 4, Table 3).

In order to evaluate the scope, we selected different naphthol derivatives **8–17** containing various substituent groups in different positions (Table 5). The first general result is that naphthol derivatives containing electron-donating groups are invariably more reactive than the ones with electron-withdrawing groups, which is consistent with the accepted [4 + 2] pericyclic mechanism for this photooxygenation.[1,13]

Comparing entries 1 and 3 (Table 5) the starting materials **1** and **8** yielded the expected corresponding naphthoquinones **2** and **19**, respectively, with the same yield (82%) under continuous flow conditions, compared to 59% yield obtained for **18** (entry 2, Table 5). Also, the yields for batch conditions (using the same residence time, 16.7 min) were substantially lower than under continuous flow, providing a real advantage with the use of this photoreactor.

Table 5 Scope of the photooxygenations under continuous flow and batch conditions[a]



1: $R_1 = R_2 = R_3 = H$; $R_4 = OH$; $R_5 = H$
8: $R_1 = R_2 = R_3 = R_4 = R_5 = H$
9: $R_1 = CH_3$; $R_2 = R_3 = R_4 = R_5 = H$
10: $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = OH$
11: $R_1 = R_2 = R_3 = H$; $R_4 = NH_2$; $R_5 = H$
12: $R_1 = R_2 = R_3 = R_4 = NHAc$; $R_5 = H$
13: $R_1 = Ac$; $R_2 = R_3 = R_4 = R_5 = H$
14: $R_1 = CH(OH)CH_3$; $R_2 = R_3 = R_4 = R_5 = H$
15: $R_1 = NO_2$; $R_2 = R_3 = R_4 = R_5 = H$
16: $R_1 = R_2 = H$; $R_3 = Cl$; $R_4 = R_5 = H$
17: $R_1 = R_2 = H$; $R_3 = Br$; $R_4 = R_5 = H$

2: $R_1 = R_2 = H$; $R_4 = OH$; $R_5 = H$
18: $R_1 = R_2 = R_4 = R_5 = H$
19: $R_1 = CH_3$; $R_2 = R_4 = R_5 = H$
20: $R_1 = R_2 = R_4 = H$; $R_5 = OH$
21: $R_1 = R_2 = H$; $R_4 = NHAc$; $R_5 = H$
22: $R_1 = CH(OH)CH_3$; $R_2 = R_4 = R_5 = H$
23: $R_1 = H$; $R_2 = Br$; $R_4 = R_5 = H$

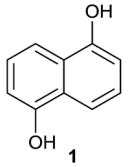
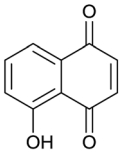
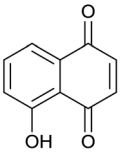
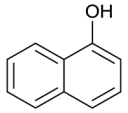
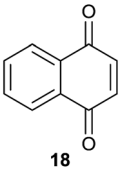
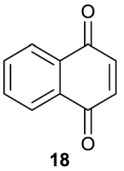
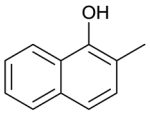
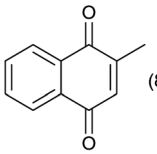
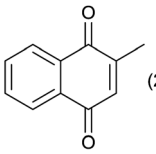
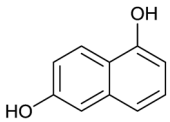
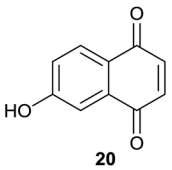
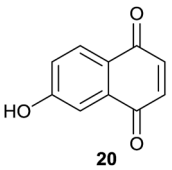
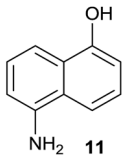
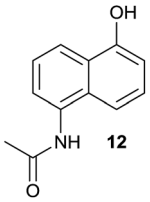
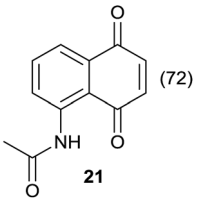
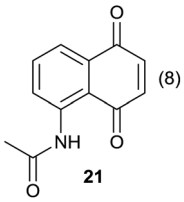
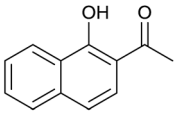
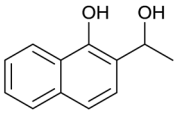
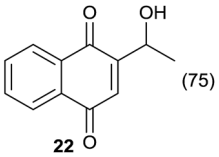
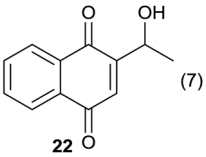
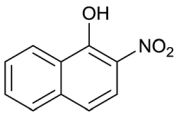
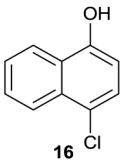
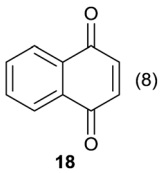
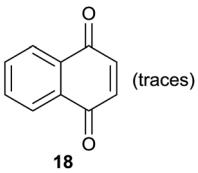
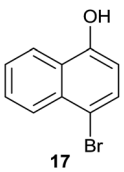
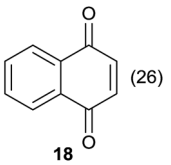
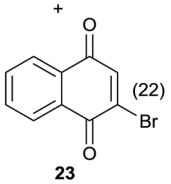
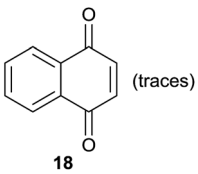
Entry	Substrate	Product and yield (%) under continuous flow conditions[b]	Product and yield (%) in batch conditions[b,c]
1	 **1**	 (82) **2**	 (11) **2**
2	 **8**	 (59) **18**	 (7) **18**
3	 **9**	 (82) **vitamin K_3 (19)**	 (20) **vitamin K_3 (19)**
4	 **10**	 (46%) **20**	 (traces) **20**
5	 **11**	No reaction[d]	No reaction[e]
6	 **12**	 (72) **21**	 (8) **21**

Table 5 (*Contd.*)

Entry	Substrate	Product and yield (%) under continuous flow conditions[b]	Product and yield (%) in batch conditions[b,c]
7	 **13**	No reaction[f]	No reaction[f]
8	 **14**	 (75) **22**	 (7) **22**
9	 **15**	No reaction[f]	No reaction[f]
10	 **16**	 (8) **18**	 (traces) **18**
11	 **17**	 (26) **18** +  (22) **23**	 (traces) **18**

[a] All the reactions under continuous flow conditions were performed using the optimized conditions: LED lamp 24 W, 10 mM solutions of the substrates in $CH_3CN : CH_2Cl_2$ (95 : 5) (100 mL), TPP (**3**) at 0.3 mol%, solution flow rate = 0.75 mL min^{-1}, 1 cm plug-flow (oxygen-solution), residence time = 16.7 min, 25 mL photoreactor. [b] Isolated yields by using column chromatography. [c] Reactions performed using the residence time of the comparable continuous flow conditions (16.7 min). [d] An attempt to run this reaction under continuous flow conditions was performed, but due to the low solubility of the starting material it was not possible to finish it because the blockage of the system. [e] An attempt to perform this reaction in batch conditions was performed but no products were observed after 1 h. [f] Starting material totally recovered.

The activated 6-hydroxynaphthol (**10**) (entry 4, Table 5) yielded **20** in 46% yield under continuous flow conditions together with minor by-products which were difficult to separate. In an identical reaction performed using batch conditions only traces of **20** could be identified.

Compound **11** was submitted to photooxygenation under both flow and batch conditions, but unsuccessfully, most likely due to the very low solubility of this compound (entry 5, Table 5). On the other hand, the corresponding acetylated compound **12** yielded the corresponding naphthoquinone **21** in both flow (72% yield) and batch (8% yield) conditions (entry 6, Table 5). Similarly, the deactivated naphthol **13** (entry 7, Table 5) was unreactive in both flow and batch reactions, but the equivalent reduced compound **14** furnished the corresponding product **22** under both flow (75% yield) and batch (7% yield) conditions (entry 8, Table 5). The deactivated compound **15** also did not react (entry 9, Table 5), however, both compounds **16** and **17** yielded the corresponding naphthoquinone **18** (8 and 26% yield, respectively) under continuous flow conditions together with many by-products (entries 10 and 11, Table 5). It is important to highlight in entry 11 (Table 4) that we were able to isolate the brominated derivative **23** in 22% yield under continuous flow conditions, and we conclude that this was most likely possible *via* reaction of **18** and HOBr produced during the process.

Conclusions

In summary, we have developed an optimized protocol for photooxygenation of activated naphthols, screening some porphyrinoids as photocatalysts and many parameters under continuous flow conditions. In addition, we have shown the applicability and safety of this very simple device in process intensification by using mild and cost-competitive conditions to produce valuable compounds in gram-scale. Previous efforts described in the literature presented limitations requiring many reaction cycles due to the engineered devices or the photocatalysts which were used. Herein we have presented a simple and efficient solution for these problems allowing the production of relevant naphthoquinone derivatives in only one reaction cycle with short optimized residence time (16.7 min).

Experimental section

All reagents and solvents were purchased from Aldrich or national US suppliers. When necessary, solvents and reagents were purified using standard procedures.[17] Porphyrins **3–6** were obtained as described in the literature.[7f,11r] Phthalocyanine **7** was purchased from Sigma-Aldrich.

^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance 600 spectrometer at 600 and 150 MHz, respectively. $CDCl_3$ or DMSO-d_6 was used as solvent and TMS (tetramethylsilane) as the internal reference. The chemical shifts are expressed in δ (ppm) and coupling constants (J) are given in Hertz (Hz). The UV-vis spectra were recorded with a Perkin-Elmer Lambda 25 spectrophotometer using 1 cm optical length quartz cuvettes at 25 °C and dichloromethane as solvent. Emission spectra of FLC and LED lamps were recorded an Ocean Optics Spectrometer HR2000CG-UV-NIR. MS analysis were performed using HP model 5973 mass selective detector with HP model 6890 + gas chromatograph; scanned from 50 to 550 amu; T = 70 °C for 3 min and then to 300 °C at 30 °C min^{-1}.

All continuous flow experiments were carried out using a micro HPLC pump from ThalesNano and an in-house engineered photoreactor as specified in the ESI.† Analytical thin-layer chromatography was performed on glass plates (3 × 6 cm, 1 mm thick), Merck TLC silica-gel 60 F254.

General procedure for experiments under continuous flow conditions

A solution of naphthol (**1** or **8–17**) (0.3–1.2 mmol) was prepared in 10 mL of acetonitrile and sonicated for 2 min. After this was completed, 85 mL of oxygenated acetonitrile (previously bubbled with oxygen for 10 min) was added, and a solution of photocatalyst (0.1–0.5 mol%) in 5 mL of CH_2Cl_2 was added last. The reaction mixture was protected from light with an aluminium foil and the solution pumped into the photoreactor in different flow rates, as specified. The plug-flow was performed using a commercial oxygen cylinder adapted with a manometer (0–250 bar) and an intermediate valve for the fine adjustment of oxygen pressure (1.5–2.0 bar depending on the solution flow). All reactions were started only after previous stabilization of the plug-flow (*ca.* 1 cm each) using the desired flow rate of acetonitrile and oxygen. The product was also protected from external light and collected until the end of pumping process, when pure acetonitrile was used to clean the photoreactor maintaining the same initial flow rate. After recovering all of the reaction mixture, acetonitrile was distilled off under vacuum followed by purification by simple silica-gel plug filtration using CH_2Cl_2 as eluent or mixtures of solvents as specified in each example. In general, 50–70% of the photocatalyst was recovered, and the main product was easily isolated after the solvent evaporation.

General procedure for experiments under batch conditions

A solution of naphthol (**1** or **8–17**) (1.0 mmol) was prepared in 10 mL of acetonitrile and sonicated for 2 min. After this was completed, 85 mL of oxygenated acetonitrile (previously bubbled with oxygen for 10 min) was added, and a solution of photocatalyst (0.3 mol%) in 5 mL of CH_2Cl_2 was added last. The reactions were carried out in a 250 mL Pyrex® round-bottom flask using the same LED lamp (24 W) from the flow photoreactor kept as close as possible to the round-bottom flask (see Fig. S3 – ESI†). A slow magnetic stirring and oxygen bubbling was used and the reaction maintained under irradiation for 16.7 min (the same residence time for comparison – Table 5). After the reaction, acetonitrile was distilled off under vacuum followed by purification by simple silica-gel plug filtration using CH_2Cl_2 as eluent or mixtures of solvents as specified in each example. When obtained, the main product was easily isolated after the solvent evaporation.

General data and yields reported for results from Table 5

5-Hydroxynaphthalene-1,4-dione (2).[14] Purification over silica gel using CH_2Cl_2 as eluent, R_f = 0.52, 82% yield (142.5 mg, 0.819 mmol). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 6.96 (s, 2H); 7.28 (dd, J = 7.8 Hz and J = 1.5 Hz, 1H); 7.62 (dd, J = 7.8 Hz and J = 1.5 Hz, 1H); 7.65 (t, J = 7.8 Hz, 1H); 11.91 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 114.9; 119.1; 124.5; 131.7; 136.5; 138.6; 139.6; 161.4; 184.2; 190.2.

Naphthalene-1,4-dione (18).[18] Purification over silica gel using CH_2Cl_2 : hexanes 6 : 4 as eluent, R_f = 0.38, 59% yield (94.0 mg, 0.594 mmol). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 6.99 (s, 2H); 7.75–7.79 (m, 2H); 8.08–8.12 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 126.4; 131.9; 133.9; 138.7; 185.0.

2-Methylnaphthalene-1,4-dione (19).[19] Purification over silica gel using CH_2Cl_2, R_f = 0.65, 82% yield (141.1 mg, 0.819 mmol). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 2.21 (s, 3H); 6.84–6.86 (m, 1H); 7.71–7.76 (m, 2H); 8.05–8.08 (m, 1H); 8.09–8.12 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 16.4; 126.1; 126.5; 132.2; 132.3; 133.6 (2C); 135.7; 148.2; 185.0; 185.6.

6-Hydroxynaphthalene-1,4-dione (20).[20] Purification over silica gel using CH_2Cl_2 : MeOH 9.5 : 0.5, R_f = 0.50, 46% yield (79.3 mg, 0.455 mmol). ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 6.97 (d, J = 10.2 Hz, 1H); 7.00 (d, J = 10.2 Hz, 1H); 7.18 (dd, J = 8.7 Hz, J = 2.5 Hz, 1H); 7.28 (d, J = 2.5 Hz, 1H); 7.86 (d, J = 8.7 Hz; 1H); 11.0 (br s, 1H). ^{13}C NMR (150 MHz, DMOS-d_6) δ (ppm):

111.6; 120.8; 123.7; 128.9; 133.7; 138.2; 139.0; 162.8; 183.6; 185.0.

***N*-(5,8-Dioxo-5,8-dihydronaphthalen-1-yl)acetamide (21).**[21] Purification over silica gel using hexanes : ethyl acetate 6 : 4, R_f = 0.60, 72% yield (154.9 mg, 0.720 mmol). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 2.31 (s, 3H); 6.93 (d, J = 10.2 Hz); 6.96 (d, J = 10.2 Hz, 1H); 7.74 (dd, J = 8.5 Hz, J = 1.1 Hz); 7.83 (dd, J = 7.5 Hz, J = 1.1 Hz, 1H); 9.09 (dd, J = 8.5 Hz, J = 1.1 Hz); 11.87 (br s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 25.6; 116.0; 121.9; 126.0; 132.2; 135.7; 138.0; 139.9; 141.3; 169.9; 184.4; 189.1.

2-(1-Hydroxyethyl)naphthalene-1,4-dione (22).[22] Purification over silica gel using CH_2Cl_2 : ethyl acetate 9.5 : 0.5, R_f = 0.30, 75% yield (152.1 mg, 0.752 mmol). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 1.52 (d, J = 6.4 Hz, 3H); 2.49 (d, J = 4.9 Hz, 1H); 5.02 (ddq, J = 6.4 Hz, J = 4.9 Hz, J = 1.5 Hz, 1H); 7.01 (d, J = 1.5 Hz, 1H); 7.74–7.78 (m, 2H); 8.06–8.12 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 22.6; 65.3; 126.2; 126.5; 131.9; 132.2; 132.9; 133.8; 134.0; 152.7; 185.3; 185.6.

2-Bromonaphthalene-1,4-dione (23).[23] Purification over silica gel using CH_2Cl_2, R_f = 0.69, 22% yield (42.0 mg, 0.265 mmol). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.53 (s, 1H); 7.75–7.82 (m, 2H); 8.08–8.12 (m, 1H); 8.17–8.20 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 126.9; 127.8; 130.9; 131.7; 134.1; 134.4; 140.1; 140.4; 177.9; 182.4. MS: m/z (relative intensity): [M+] 238 (90); [M+] 236 (90); 157 (100); 129 (90); 101 (70).

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References

1 (*a*) A. Greer, *Acc. Chem. Res.*, 2006, **39**, 797; (*b*) A. Pace and E. L. Clennan, *Tetrahedron*, 2005, **61**, 6665.

2 C. L. Hugelshofer and T. Magauer, *J. Am. Chem. Soc.*, 2015, **137**, 3807.

3 A. O. Terent'ev, D. A Borisov, V. A. Vil and V. M. Dembitsky, *Beilstein J. Org. Chem.*, 2014, **10**, 34.

4 N. S. Lopes, A. M. Yoshitake, A. F. Silva, V. X. Oliveira Jr, L. S. Silva, A. A. S. Pinheiro and L. F. M. L. Ciscato, *Chem. Biol. Drug Des.*, 2015, **86**, 1373.

5 (*a*) M. Balci, *Chem. Rev.*, 1981, **81**, 91; (*b*) S. T. Staben, X. Linghu and F. D. Toste, *J. Am. Chem. Soc.*, 2006, **128**, 12658; (*c*) K. Gilmore, D. l. Kopetzki, J. W. Lee, Z. Horváth, D. T. McQuade, A. Seidel-Morgenstern and P. H. Seeberger, *Chem. Commun.*, 2014, **50**, 12652; (*d*) L. Novkovic, M. Trmcic, M. Rodic, F. Bihelovic, M. Zlatar, R. Matovic and R. N. Saicic, *RSC Adv.*, 2015, **5**, 99577; (*e*) B. Pieber, T. Glasnov and C. O. Kappe, *Chem.–Eur. J.*, 2015, **21**, 4368; (*f*) T. S. A. Heugebaert, C. V. Stevens and C. O. Kappe, *ChemSusChem*, 2015, **8**, 1648; (*g*) Z. Amara, J. F. B. Bellamy, R. Horvath, S. J. Miller, A. Beeby, A. Burgard, K. Rossen, M. Poliakoff and M. W. George, *Nat. Chem.*, 2015, **7**, 489.

6 J. Dad'ová, E. Svobodová, M. Sikorski, B. König and R. Cibulka, *ChemCatChem*, 2012, **4**, 620.

7 (*a*) A. F. Uchoa, K. T. de Oliveira, M. S. Baptista, A. J. Bortoluzzi, Y. Iamamoto and O. A. Serra, *J. Org. Chem.*, 2011, **76**, 8824; (*b*) C. M. B. Carvalho, T. J. Brocksom and K. T. de Oliveira, *Chem. Soc. Rev.*, 2013, **42**, 3302; (*c*) C. M. B. Carvalho, M. A. Fujita, T. J. Brocksom and K. T. de Oliveira, *Tetrahedron*, 2013, **69**, 9986; (*d*) F. A. B. dos Santos, A. F. Uchoa, M. S. Baptista, Y. Iamamoto, O. A. Serra, T. J. Brocksom and K. T. de Oliveira, *Dyes Pigm.*, 2013, **99**, 402; (*e*) J. C. J. M. D. S. Menezes, M. A. F. Faustino, K. T. de Oliveira, M. P. Uliana, V. F. Ferreira, S. Hackbarth, B. Röder, T. T. Tasso, T. Furuyama, N. Kobayashi, A. M. S. Silva, M. G. P. M. S. Neves and J. A. S. Cavaleiro, *Chem.–Eur. J.*, 2014, **20**, 13644; (*f*) P. B. Momo, C. Pavani, M. S. Baptista, T. J. Brocksom and K. T. de Oliveira, *Eur. J. Org. Chem.*, 2014, 4536; (*g*) M. P. Uliana, L. Pires, S. Pratavieira, T. J. Brocksom, K. T. de Oliveira, V. S. Bagnato and C. Kurachi, *Photochem. Photobiol. Sci.*, 2014, **13**, 1137.

8 (*a*) M. C. De Rosa and R. J. Crutchley, *Coord. Chem. Rev.*, 2002, **233–234**, 351; (*b*) T. Montagon, M. Tofi and G. Vassilikogiannakis, *Acc. Chem. Res.*, 2008, **41**, 1001.

9 J. Park, D. Feng, S. Yuan and H. C. Zhou, *Angew. Chem., Int. Ed.*, 2015, **54**, 430.

10 (*a*) M. Oelgemöller and O. Shvydkiv, *Molecules*, 2011, **16**, 7522; (*b*) J. P. Knowles, L. D. Elliott and K. I. Booker-Milburn, *Beilstein J. Org. Chem.*, 2012, **8**, 2025; (*c*) K. Gilmore and P. H. Seeberger, *Chem. Rec.*, 2014, **14**, 410; (*d*) Y. Su, N. J. W. Straathof, V. Hessel and T. Noël, *Chem.–Eur. J.*, 2014, **20**, 10562; (*e*) M. Hurevich, J. Kandasamy, B. M. Ponnappa, M. Collot, D. Kopetzki, D. T. McQuade and P. H. Seeberger, *Org. Lett.*, 2014, **16**, 1794; (*f*) D. B. Ushakov, K. Gilmore, D. Kopetzki, D. T. McQuade and P. H. Seeberger, *Angew. Chem., Int. Ed.*, 2014, **53**, 557.

11 (*a*) S. Mascia, P. L. Heider, H. T. Zhang, R. Lakerveld, B. Benyahia, P. I. Barton, R. D. Braatz, C. L. Cooney, J. M. B. Evans, T. F. Jamison, K. F. Jensen, A. S. Myerson and B. L. Trout, *Angew. Chem., Int. Ed.*, 2013, **52**, 12359; (*b*) J. C. Pastre, D. L. Browne and S. V. Ley, *Chem. Soc. Rev.*, 2013, **42**, 8801; (*c*) D. T. McQuade and P. H. Seeberger, *J. Org. Chem.*, 2013, **78**, 6384; (*d*) D. Cantillo, O. de Frutos, J. A. Rincón, C. Mateos and C. O. Kappe, *J. Org. Chem.*, 2014, **79**, 8486; (*e*) V. D. Pinho, B. Gutmann, L. S. M. Miranda, R. O. M. A. de Souza and C. O. Kappe, *J. Org. Chem.*, 2014, **79**, 1555; (*f*) B. Gutmann and C. O. Kappe, *Eur. Pharm. Rev.*, 2015, **20**, 37; (*g*) B. J. Deadman, D. L. Browne, I. R. Baxendale and S. V. Ley Chem, *Technol. Eng.*, 2015, **38**, 259; (*h*) J. M. Hawkins, *Nature*, 2015, **520**, 302; (*i*) B. Gutmann, D. Cantillo and C. O. Kappe, *Angew. Chem., Int. Ed.*, 2015, **54**, 6688; (*j*) M. Baumann and I. R. Baxendale, *Beilstein J. Org. Chem.*,

2015, **11**, 1194; (*k*) D. O. Nogueira, S. P. de Souza, R. A. C. Leão, L. S. M. Miranda and R. O. M. A. de Souza, *RSC Adv.*, 2015, **5**, 20945; (*l*) I. I. Junior, E. C. Gaudino, K. Martina, G. Cravotto, R. Luque and R. O. M. A. de Souza, *RSC Adv.*, 2014, **4**, 45772; (*m*) F. G. Finelli, L. S. M. Miranda and R. O. M. A. de Souza, *Chem. Commun.*, 2015, **51**, 3708; (*n*) G. C. O. Silva, J. R. Correa, M. O. Rodrigues, H. G. O. Alvim, B. C. Guido, C. C. Gatto, K. A. Wanderley, M. Fioramonte, F. C. Gozzo, R. O. M. A. de Souza and B. A. D. Neto, *RSC Adv.*, 2015, **5**, 48506; (*o*) L. C. Alves, A. L. Desiderá, K. T. de Oliveira, S. Newton, S. V. Ley and T. J. Brocksom, *Org. Biomol. Chem.*, 2015, **13**, 7633; (*p*) S. Matthies, D. T. McQuade and P. H. Seeberger, *Org. Lett.*, 2015, **17**, 3670; (*q*) C. A. Correia, K. Gilmore, D. T. McQuade and P. H. Seeberger, *Angew. Chem., Int. Ed.*, 2015, **54**, 4945; (*r*) P. B. Momo, B. S. Bellete, T. J. Brocksom, R. O. M. A. de Souza and K. T. de Oliveira, *RSC Adv.*, 2015, **5**, 84350.

12 (*a*) R. J. Ingham, C. Battilocchio, D. E. Fitzpatrick, E. Sliwinski, J. M. Hawkins and S. V. Ley, *Angew. Chem., Int. Ed.*, 2015, **54**, 144; (*b*) S. V. Ley, D. E. Fitzpatrick, R. J. Ingham and R. M. Myers, *Angew. Chem., Int. Ed.*, 2015, **54**, 3449; (*c*) S. V. Ley, D. E. Fitzpatrick, R. M. Myers, C. Battilocchio and R. J. Ingham, *Angew. Chem., Int. Ed.*, 2015, **54**, 10122.

13 (*a*) J. Griffiths, K.-Y. Chu and C. Hawkins, *J. Chem. Soc., Chem. Commun.*, 1976, 676; (*b*) D. Murtinho, M. Pineiro, M. M. Pereira, A. M. d'. A. Rocha Gonsalves, L. G. Arnaut, M. G. Miguel and H. D. Burrows, *J. Chem. Soc., Perkin Trans. 2*, 2000, 2441.

14 (*a*) M. Oelgemöller, N. Healy, L. de Oliveira, C. Jung and J. Mattay, *Green Chem.*, 2006, **8**, 831; (*b*) A. Yavorskyy, O. Shvydkiv, C. Limburg, K. Nolan, Y. M. C. Delauréc and M. Oelgemöller, *Green Chem.*, 2012, **14**, 888; (*c*) O. Shvydkiv, C. Limburg, K. Nolan and M. Oelgemöller, *J. Flow Chem.*, 2012, **2**, 52.

15 For general applications and syntheses see: (*a*) K. W. Wellington, *RSC Adv.*, 2015, **5**, 20309; (*b*) A. K. Jordão, M. D. Vargas, A. C. Pinto, F. C. da Silva and V. F. Ferreira, *RSC Adv.*, 2015, **5**, 67909; (*c*) V. K. Tandon and S. Kumar, *Expert Opin. Ther. Pat.*, 2013, **23**, 1087; (*d*) C. Lisboa, V. G. Santos, B. G. Vaz, N. C. De Lucas, M. N. Eberlin and S. J. Garden, *J. Org. Chem.*, 2011, **76**, 5264; for (S)-espicufolin synthesis, see: (*e*) L. F. Tietze, K. M. Gericke, R. R. Singidi and I. Schuberth, *Org. Biomol. Chem.*, 2007, **5**, 1191; for (±)-γ-indomycinone synthesis, see: (*f*) D.-S. Hsu, T. Matsumoto and K. Suzuki, *Chem. Lett.*, 2006, **35**, 1016; for mensacarcin synthesis see: (*g*) L. F. Tietze, C. Güntner, K. M. Gericke, I. Schuberth and G. Bunkoczi, *Eur. J. Org. Chem.*, 2005, 2459. For (+)-nocardione A synthesis, see: (*h*) D. L. J. Clive, S. P. Fletcher and D. Liu, *J. Org. Chem.*, 2004, **69**, 3282; for rac-Juglomycin A synthesis, see: (*i*) G. A. Kraus and P. Liu, *Synth. Commun.*, 1996, **26**, 4501.

16 http://www.sigmaaldrich.com, accessed in December 21 2015.

17 W. L. F. Armarego and D. D. Perrin, in *Purification of Laboratory Chemicals*, Butterworth-Heinemann, Oxford, UK, 4th edn, 2000.

18 N. Adarsh, M. Shanmugasundaram, R. R. Avirah and D. Ramaiah, *Chem.–Eur. J.*, 2012, **18**, 12655.

19 O. A. Kholdeeva, O. V. Zalomaeva, A. B. Sorokin, I. D. Ivanchikova, C. D. Pina and M. Rossi, *Catal. Today*, 2007, **121**, 58.

20 F. Ameer, I. R. Green, K. Krohn and M. Sitoza, *Synth. Commun.*, 2007, **37**, 3041.

21 E. E. Coyle, K. Joyce, K. Nolana and M. Oelgemöller, *Green Chem.*, 2010, **12**, 1544.

22 Z.-Y. Lin, Y.-L. Chen, C.-S. Lee and C.-P. Chuang, *Eur. J. Org. Chem.*, 2010, 3876.

23 M. Naresh, P. Swamy, M. A. Kumar, M. M. Reddy, K. Srujana and N. Narender, *Tetrahedron Lett.*, 2014, **55**, 3926.