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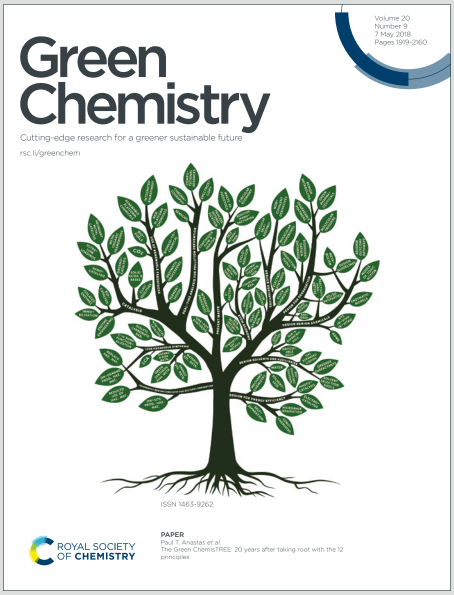

Volume 20
Number 9
7 May 2018
Pages 1919-2160

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Chemistry
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rsc.li/greenchem

ISSN 1463-9262

ROYAL SOCIETY
OF CHEMISTRY

PAPER
Paul T. Anastas *et al.*
The Green ChemisTREE: 20 years after taking root with the 12 principles

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DOI: 10.1039/D6GC02577C

Green Foundation Statement

1. This work aims to circumvent the use of toxic and fossil-fuel derived solvents in the context of Synthetic Organic Electrochemistry, enabling the use of versatile electrochemical reactions on scale. Water and propylene carbonate can be employed to afford sustainable reactions with inexpensive and less wasteful inorganic supporting electrolytes, unlocking the full sustainable nature of the electrochemistry technique.
2. The different case studies demonstrated the environmentally benign replacement of classical solvents with water and propylene carbonate, achieving superior green metrics and excellent productivities.
3. In the future, similar strategies can be envisioned for all the classical electron-mediated transformations, further validating the sustainable nature of electrochemistry.

View Article Online
DOI: 10.1039/D6GC02577C

ARTICLE

Combining Water and Biorenewable Solvents for Sustainable Anodic Reactions

Received,
Accepted

DOI: 10.1039/x0xx00000x

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Enabling technologies are perceived as inherently sustainable, due to the replacement of stoichiometric oxidants and reductants with traceless redox mediators such as photons or electrons. However, the reaction solvent plays a crucial role in the environmental impact of the process. To aspire towards ideal sustainable electrochemical transformations, the use of water as solvent would be the most preferred choice, but poor solubility of organic compounds hinders its employment. Another option could be the use of biorenewable solvents, which require wasteful organic supporting electrolytes. In this work, the application of a solvent mixture of water and propylene carbonate is presented. This media combines the best features of the two chemicals, enabling sustainable electrochemical synthesis without solubility issues of organic material or inorganic salts. The adoption of high mass-transfer electrochemical reactor overcomes the limitations caused by heterogeneous mixtures, streamlining potential industrial applications. The generality of this concept was validated across four different representative anodic reactions, comprising a cross-coupling, a rearrangement, a direct and a mediated oxidation. In all the studies, process scalability could be demonstrated, reaching excellent productivities (from 39 g/day to 3.4 kg/day) with exquisite green metrics (PMI up to 27, Green Score > 84). Finally, guidelines for general application of this approach were outlined.

Introduction

The emergence of enabling technologies in organic synthesis has started a revolution in the way molecular assembly is conceived.[1] By controlling Single Electron Transfer events in a mild fashion, new scenarios have been opened at any level of chemical research, ranging from academic education to fine chemical industry.[2-5] One of the driving forces for the adoption of these techniques is their innate sustainability, unlocking the replacement of toxic and hazardous reagents with traceless redox mediators such as photons or electrons.[6,7] However, this perception of greenness fades away when individual transformations are carefully evaluated, especially for large scale operations.[2] In synthetic organic electrochemistry, the use of wasteful supporting electrolytes, toxic fossil fuel derived solvents, and inaccessible electrode materials critically limits the transfer of these systems to higher regimes (Figure 1, Top).[8] Furthermore, low current densities and prolonged electrolysis time hinder the overall productivity of electrochemical processes. Nevertheless, the transposition of synthetic organic electrochemistry on scale would be highly desirable as it allows the preparation of materials under room temperature, which provides a great operational advantage compared to traditional thermal processes. Ideally, the seamless transposition of electrochemical systems to industrial scale would require the adoption of sustainable and/or biorenewable solvent systems,[9-11] the use of simple inorganic salts as electrolytes, as well as the implementation of widely available and inexpensive electrode materials,[12,13] with proper intensification of current density to maximize throughput. In particular, the selection of reaction medium is of utmost importance to preserve the sustainability of the entire process.[14] Intuitively, the use of water as benign solvent seems the best choice for its non-toxic nature, high dielectric constant and salts solubility,[15,16] with relatively broad stability window (from +1.5 V to −2.3 V *vs* Fc+/Fc).[17]
Unfortunately, aqueous systems are usually impractical due to the poor solubility of organic compounds, which dramatically affects the electrolysis outcome and its reproducibility. For this reason, water as solvent in synthetic organic electrosynthesis was only sporadically employed, with severe limitations on the generality of this approach, mostly circumvented by the addition of surfactants[18] or other classical organic media[19]. On the other hand, the use of biomass-derived solvent obviates the problem of organic compounds' solubility, maintaining a high sustainability profile as well as guaranteeing good conductivity.

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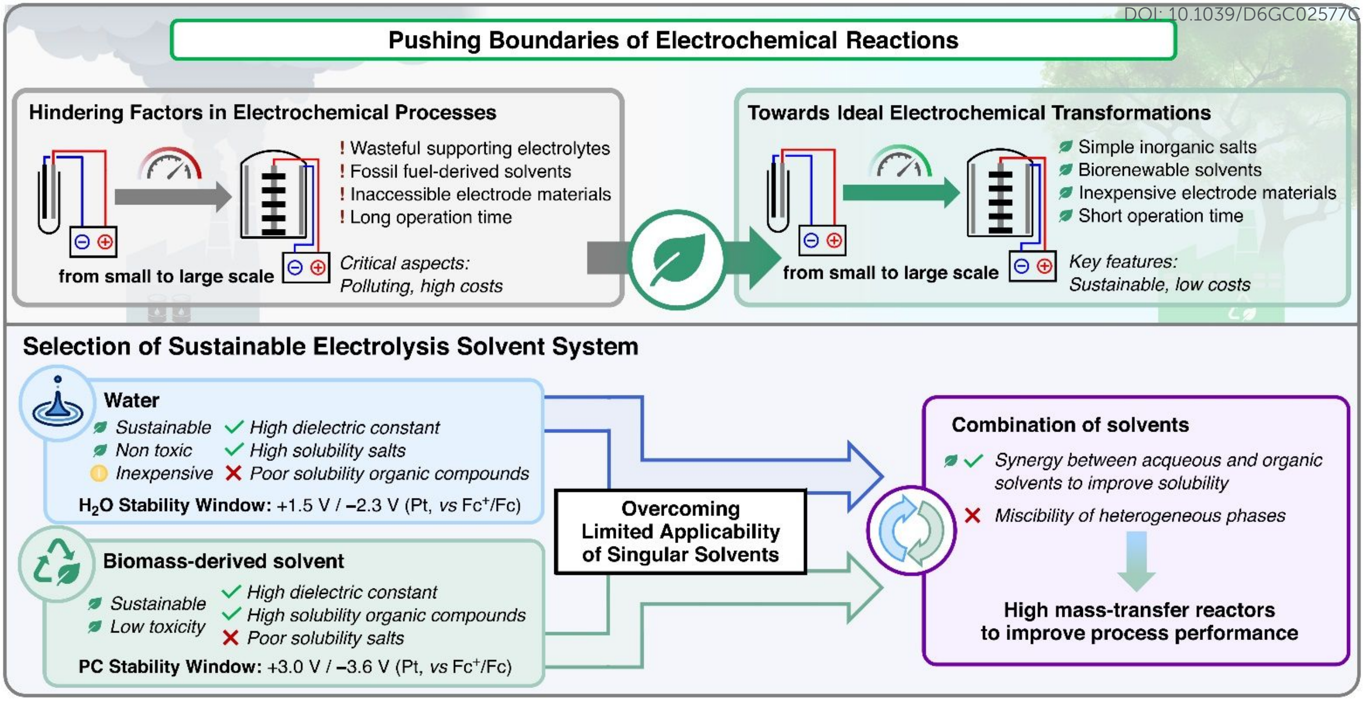

Figure 1. Pushing boundaries of electrochemical reactions. Top: Hindering factors and ideal solutions for more sustainable electrochemical reactions. Bottom: The impact of solvent selection in electrochemical reaction design. Features of water and biomass-derived solvent systems. Combination of the two-reaction media for enhanced sustainability. Redox potentials for stability window refer to literature data (Ref. 17).

In particular, organic carbonate solvents are one of the most promising candidates,[20] with propylene carbonate (PC) as their most renown member, owing to their high dielectric constant, excellent solubility properties, moderate viscosities,[9,10] and a broad redox potential windows.[17] Nevertheless, the employment of these solvents generally requires organic supporting electrolytes to compensate for poor solubility of inorganic salts (Figure 1, Bottom). In order to overcome the limitations of these classes of solvents, we wondered if they could be combined, leading to the ideal merger of their beneficial features. Their synergy would enable the perfect solubility of inorganic salts and organic materials, sustaining conductivity and electrolysis.[21] This approach was rarely reported and exploited in specific cases, employing solvents such as methyl tert-butyl ether (MTBE)[22,23], ethyl acetate (EtOAc),[24] or dichloromethane (DCM)[25-27]. The limited application of this concept lays on the heterogeneous nature of these mixtures, which would compromise the feasibility of this approach. Employing water soluble organic systems such as ethanol or acetone may mitigate this issue, but hinders the solubility of organic compounds.[16] Furthermore, the recovery of PC can be envisioned at the end of the process by simple aqueous-organic separation and recovered by photoresist stripping,[28] or directly employed for other purposes.[29,30] Tackling this challenge, it was reasoned that the application of high mass-transfer reactors could improve the reaction performance owing to the more intimate mixing of the two phases.[31,32] In this work, a strategy to execute electrochemical oxidative reactions employing water/propylene carbonate as sustainable solvent system is reported, overcoming the limitations of previous approaches towards the development of a reliable and scalable electrochemical process. By the use of this mixture, intensified electrolysis on scale was successfully carried out employing simple inorganic salts as supporting electrolytes in a Spinning Cylinder Electrochemical Reactor (SCER), available in different sizes, from 50 mL to 1.25 L.[33] The rotating electrode of this reactor generates sufficient shearing forces to guarantee intimate mixing of the heterogeneous solution.[33] The generality of this approach was validated by four case studies, with excellent productivity and exquisite green chemistry metrics. This solvent mixture obviates the longstanding problem of adapting small-scale electrolysis to more processable settings without compromising the reaction performance and the innate sustainability typical of synthetic organic electrochemistry.

Results and Discussion

Case Study 1: C–H Amination of Phenols

The investigation was commenced by selecting a compelling transformation for the synthesis of C–N bonds via amination of phenols, reported by Lei and coworkers.[34] These oxidations have wide application in the synthesis of valuable biaryl cores, present in many natural products and fundamental materials.[35] In the original work, the authors employed MeCN / MeOH as electrolysis solvent, with substoichiometric amounts of ^{n}Bu$_4$NBF$_4$ as supporting electrolyte. Starting from these conditions, phenothiazine **1a** and 4-methoxyphenol **2a** were selected as model substrates for the reaction.

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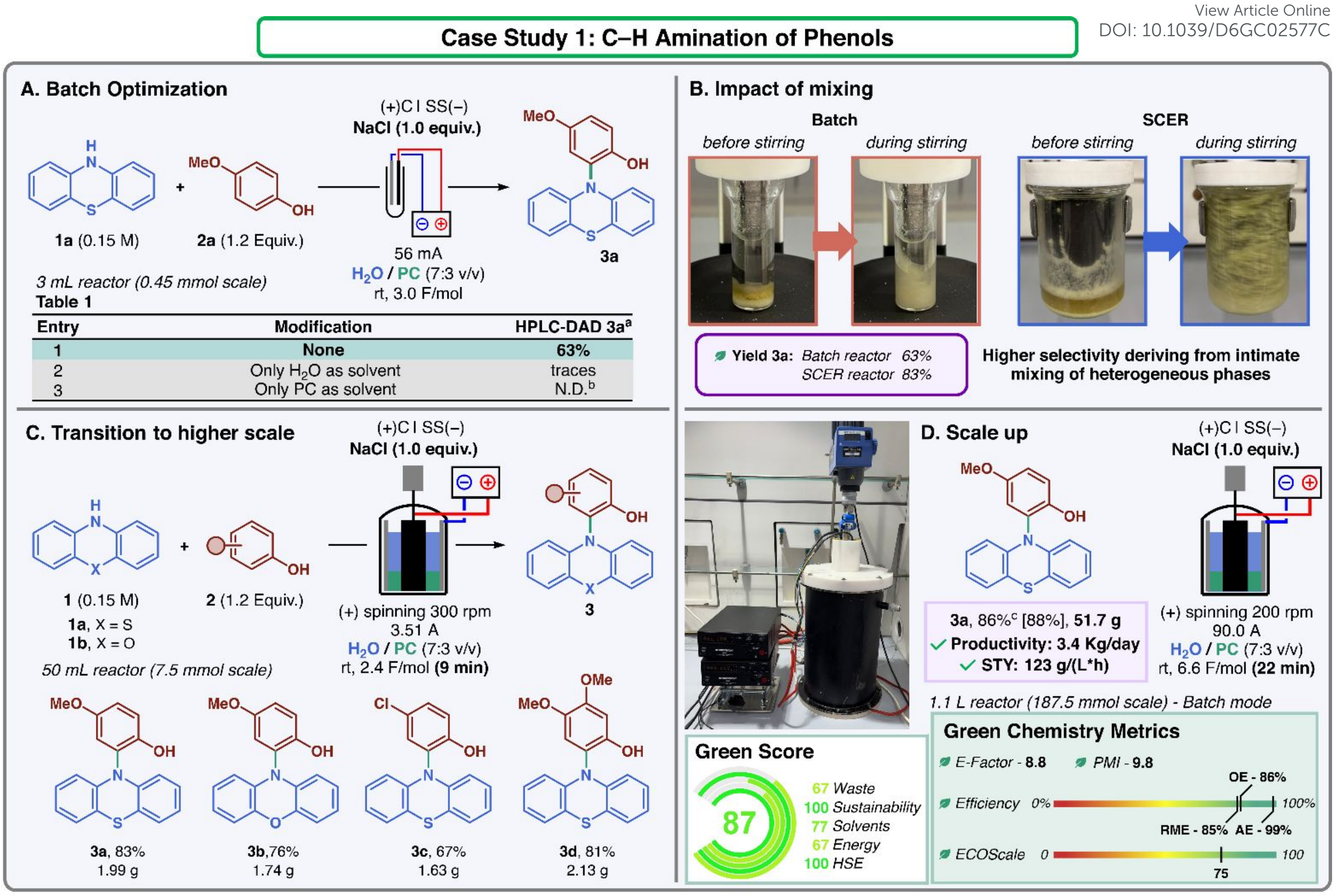

Table 1

Entry	Modification	HPLC-DAD 3a[a]
1	None	63%
2	Only H_2O as solvent	traces
3	Only PC as solvent	N.D.[b]

Figure 2. Case study 1: Amination of phenols. A. Batch reaction validation under the H_2O / PC solvent mixture. B. Impact of higher mixing regimes in the biphasic system. C. Evaluation of different substrates in the new conditions employing SCER. D. Scale up in a 1.25 L reactor, with scale and green metrics. PMI: Process Mass Intensity. RME: Reaction Mass Efficiency. OE: Overall Efficiency. AE: Atom Efficiency. Chromatographic separation not included in the metrics calculations. [a]HPLC-DAD area percentage. [b]Maximum voltage reached during the experiment. [c]Isolated yield based on a 10% aliquot (analytical yield in backets).

After a brief optimization employing commercially available batch cells (3 mL, 0.45 mmol scale), an optimal solvent mixture consisting of 7:3 H_2O / PC led to 63% analytical yield of the desired coupled product **3a** (Figure 2A, Table 1, Entry 1). Notably, high current (56 mA) could be employed, corresponding to the maximum current density applicable in the large SCER system. Furthermore, simple NaCl could be successfully selected as competent supporting electrolyte, with graphite as anode and stainless steel as cathode. The singular use of either water or PC as solvent did not lead to formation of the desired product (Figure 2A, Table 1, Entry 2-3). Upon running the 3 mL batch reaction, it was noticed that the two phases remained completely separated throughout the entire time of the electrolysis. By subjecting the same reaction mixture to the cylindrical stirring system, a much more finely dispersed suspension could be observed (Figure 2B, a glass vessel was used for visual analysis, see Supplementary Information for further details). With this experimental observation in hand, the reaction was promptly transferred to the SCER maintaining the same current density (50 mL, 7.5 mmol scale, batch mode, see Supplementary Information for further details). As a result, the electrolysis was successfully conducted in approximately 9 minutes, obtaining the desired compound **3a** in 83% yield, corresponding to almost 2 g of product. The higher yield observed compared to the traditional 3 mL batch system was attributed to the improved mixing, which guaranteed a more efficient and selective reaction. Furthermore, the shortened electrolysis time is caused by the larger electrode-surface-to-reaction mixture-volume ratio characteristic of this reactor design. The reaction was then tested with different coupling partners to further ensure the generality of the newly optimized method (Figure 2C). Phenoxazine **1b** was found to be a competent partner, obtaining 76% of **3b**. Other phenols such as 4-chlorophenol and 3,4-dimethoxyphenol led to similar results, obtaining compounds **3c** and **3d** in 67% and 81% yield respectively. Once the reaction was established, the attention was turned to further intensifying the process. The electrochemical protocol was transferred to a larger version of the SCER system, having a 1.25 L capacity, used in batch mode.[33] This time a 90 A electrolysis was carried out, accomplishing a 187.5 mmol scale reaction (1.15 L stock solution) in less than 23 minutes (6.6 F/mol to accomplish full conversion Figure 2D). The reaction mixture was simply composed of 37.3 g of **1a**, 27.9 g of **1b**, 10.9 g of NaCl, dissolved in 770 mL of tap H_2O and 330 mL of PC. This remarkably rapid reaction led to an 88% analytical assay yield and confirmed by 86% isolation of a 10% aliquot. Upon surveying the scale metrics, a throughput of 141 grams per hour was obtained, leading to a projected productivity of 3.4 kg of product per day. Further scale-up could be envisioned by adopting a semi-continuous recirculation system.[33] The Space-Time-Yield (STY) of the reaction was 123 g/(L*h). The evaluation of the green chemistry metrics also reflected the overall benignity of the process.[36,37] The calculated E-Factor for this scale-up resulted in a score of 8.8, while the Process Mass Intensity (PMI) resulted in a value of 9.8. Regarding the efficiency metrics, aside from the 99% Atom Efficiency (AE) due to the nature of the cross-dehydrogenative coupling transformations, Reaction Mass Efficiency (RME) was 85%, and Overall Efficiency (OE) was 86%. In the ECO Scale metrics, the proposed reaction obtained a score of 75, positioning as a sustainable transformation.[37] Notably, a Green Score of 87 could be calculated for the proposed method, with maximum evaluation for sustainability and Health, Safety and Environmental (HSE) components leading to a more sustainable profile than the original electrochemical route,[34] as well as other photochemical[38] or thermal[39] alternatives (see Supplementary Information for the detailed comparison). Finally, the reaction was tested in more extreme conditions, employing untreated snow as water source together with defrosting urbanistic salt as electrolyte, obtaining satisfactory results (see Supplementary Information for further details). These results demonstrated the efficacy of the H_2O / PC approach not only in terms of reaction transformation, but also as dramatic improvement in the environmental impact of the approach greatly enhancing the throughput of the process.

Case Study 2: Aromatization of Heterocycles

Upon completing the first case study, the attention was turned to the aromatization of heterocycles. Owing to the importance of these scaffolds in pharmaceutical and agrochemical compounds, the development of these oxidative methodologies is important in conjugation with classical dihydroheteroarene synthesis[40] including the Biginelli reaction[41] or Hantzsch synthesis[42]. In particular, the electrochemical oxidation of these compounds as sustainable aromatization strategy was originally proposed by Kadysh and corworkers.[43,44] For this investigation, the reaction model reported by Chen, Peng, and Sun was considered.[45] While the electrochemical methodology proposed was extremely robust, several critical parameters were identified in order to translate the reaction into a more sustainable and applicative settings. The classic Biginelli-derived dihydropyrimidone compound **4a** was employed as competent substrate for the reaction (Figure 3A). In the attempt to simplify the reaction conditions, the originally reported platinum anode (Figure 3A, Table 2, Entry 1) was substituted with a more affordable graphite electrode (Figure 3A, Table 2, Entry 2). Replacing the literature solvent mixture with H_2O / PC initially led to poor results (Figure 3A, Table 2, Entry 3). Nevertheless, higher current density could be employed, preserving the reaction performance and validating the possibility of intensifying the process (Figure 3A, Table 2, Entry 4). For this reason, this enhanced current density was chosen for the rest of the optimization. Acknowledging the importance of protons to balance the overall redox reaction (*i.e.*, reduction of protons at the cathode), formic acid was added in the mixture, leading to 54% HPLC yield when a mixture 1:1:1 v/v/v H_2O / HCOOH / PC was tested (Figure 3A, Table 2, Entry 5, see Supplementary Information for further details). As formic acid belongs to the biorenewable feedstock chemical category,[46] its implementation in the solvent system would not affect the overall sustainability, while improving the transformation outcome by improving availability of protons in solution. Upon screening different supporting electrolytes, widely available Na_2SO_4 provided the best performance (Figure 3A, Table 2, Entry 6). As expected, control reactions with only water or propylene carbonate did not lead to any fruitful results. At the end of this optimization, all the critical parameters could be assessed except for the concentration, which could not be intensified more than the 0.025 M in the 3 mL batch setup. This outcome was in line with what was proposed in the original paper for the batch electrochemical cell methodology due to limited solubility (see Supplementary Information for batch concentration survey).[45] With the new conditions in hand, we transferred the protocol to the SCER, obtaining 45% of **5a** using the same current density (Figure 3A, Table 3, Entry 1, 1.88 A). Screening rotation speed different than 300 rpm was not beneficial, as well as further increasing the current density (Figure 3A, Table 3, Entry 2-3). Based on the incomplete reaction profile observed during this initial screening, an optimum of 8.0 F/mol of charge led to similar results obtained in batch (69%, Figure 3A, Table 3, Entry 4). Finally, encouraged by the positive outcome of the first case study, the reaction concentration was reassessed. Indeed, the transformation showed similar performances at much higher concentrations, up to 0.1 M (65%, Figure 3A, Table 3, Entry 5). These new promising conditions further demonstrated the importance of high mass-transfer systems when complex, multiphasic mixtures are involved in electrochemical transformation. In this specific case, the intimate mixing allowed a more efficient reaction in a sustainable environment, incrementing the productivity by a factor 4. Overall, the new reaction design employed biorenewable solvents in synergy with water to deliver the desired aromatized products. Different heterocycles were subjected to the anodic protocol to further probe its robustness (Figure 3B). Under the same conditions, the thiophene-decorated dihydropyrimidone **4b** provided the desired product with good yield (71%). To further expand the application of the H_2O / PC protocol, the commercially available Hantzsch ester **4c** was also tested, leading to the corresponding pyridine in 61% yield. The system was then probed in a higher scale regime using a recirculation setup[33] with a 0.5 L reservoir system at 0.1 M of **4a** (Figure 3C). Within less than 6 hours of electrolysis, product **5a** could be obtained with an assay yield of 84% (see Supplementary Information). The higher yield was attributed to the further improved mixing due to the peristaltic recirculation. This initial scale up attempt gave us confidence in further intensifying the process.

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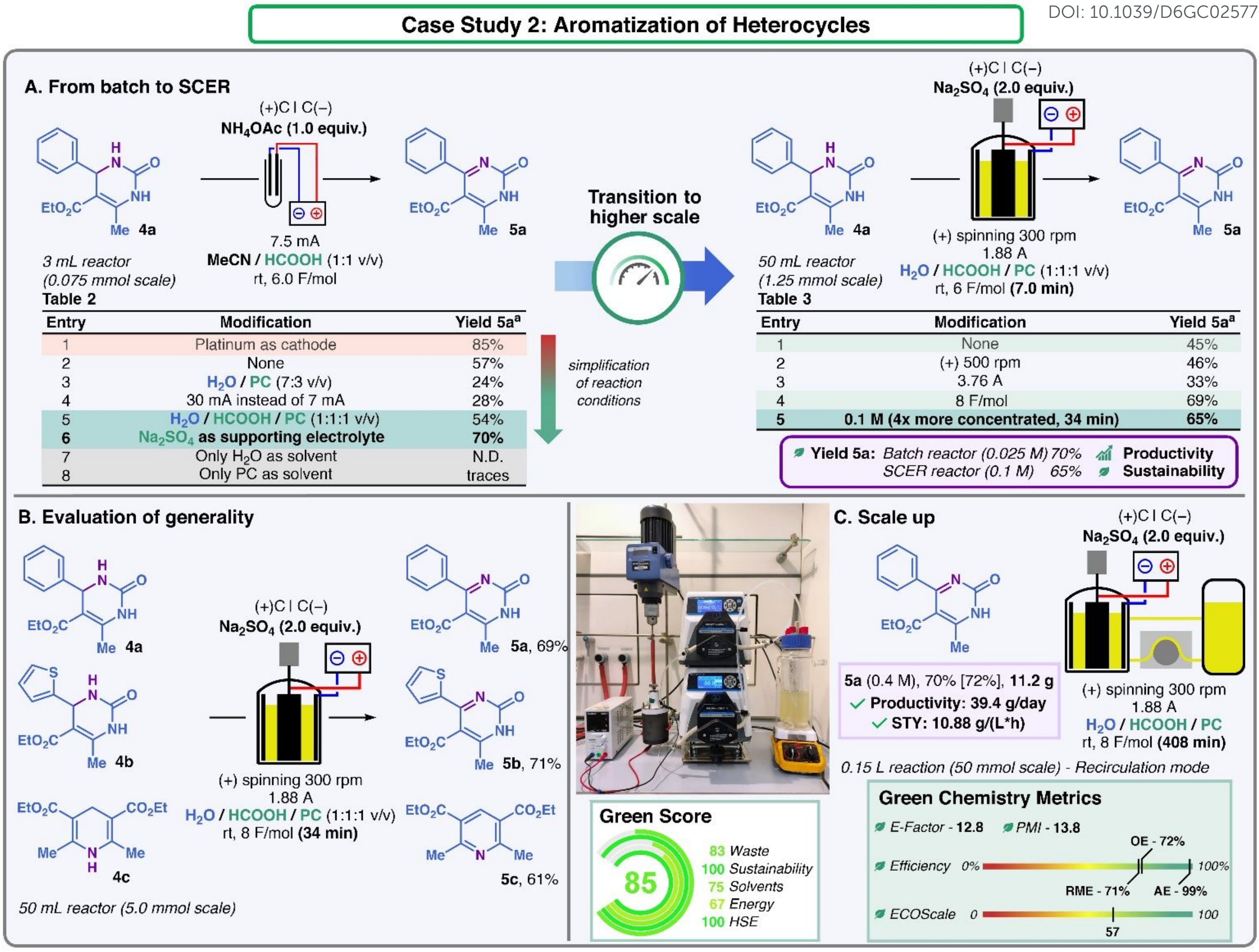

Table 2

Entry	Modification	Yield 5a[a]
1	Platinum as cathode	85%
2	None	57%
3	H_2O / PC (7:3 v/v)	24%
4	30 mA instead of 7 mA	28%
5	H_2O / HCOOH / PC (1:1:1 v/v)	54%
6	**Na_2SO_4 as supporting electrolyte**	**70%**
7	Only H_2O as solvent	N.D.
8	Only PC as solvent	traces

Table 3

Entry	Modification	Yield 5a[a]
1	None	45%
2	(+) 500 rpm	46%
3	3.76 A	33%
4	8 F/mol	69%
5	**0.1 M (4x more concentrated, 34 min)**	**65%**

Figure 3. Case study 2: Aromatization of heterocycles. A. Batch reaction validation under the H_2O / PC solvent mixture (Table 2) and transition to higher scale via SCER (Table 3). Tables refer to progressive changes in the reaction conditions. B. Evaluation of different substrates in the new conditions employing SCER. C. Scale up in a with a 0.15 L recirculation system, with scale and green metrics. PMI: Process Mass Intensity. RME: Reaction Mass Efficiency. OE: Overall Efficiency. AE: Atom Efficiency. Chromatographic separation not included in the metrics calculations. [a]HPLC-DAD yield, biphenyl as internal standard. [b]Methyl carbamate product observed. [c]Isolated yield based on a 13% aliquot (analytical yield in backets).

The concentration was increased, leading to a 0.4 M run without loss in performance, 16 times more concentrated than the optimized small scale batch procedure (see Supplementary Information for the scale up assessment). Under these conditions, 70% isolated yield with 150 mL recirculation apparatus was obtained, leading to 1.44 g of **5a** for a 13% aliquot of the reaction mixture. The scale metrics for this campaign showed a throughput of 1.64 grams per hour, corresponding to a productivity of almost 40 grams per day. Furthermore, a STY of 10.88 g/(L*h) could be obtained, superior to the one calculated for other batch setups. In terms of green metrics, the newly developed process obtained an E-Factor of 12.8 and a PMI of 13.8. Regarding efficiency, the calculated RME was 71%, while the OE was calculated as 72%, confronted with an AE of 99%. The Green Score of the reaction also provide valuable insights on the benignity of the process, with particular emphasis on the high sustainability and exceptional HSE features of the transformation. This assessment revealed the possibility of executing these essential redox manipulations in a productive yet sustainable manner. Compared to the original method, the reaction showed similar green metrics with improved productivity and STY (see Supplementary Information for the detailed comparison). This evidence reinforces the idea that intensification of these concentration-dependent reactions can be pursued by adopting a sustainable reaction design where both efficiency and environmental impact can be accounted, without limiting the success of the campaign.

Case Study 3: Synthesis of N-Acylureas

Next, the attention was focused on the industrially relevant Hofmann rearrangement. Historically, this reaction has been extensively investigated and performed in many chemical and electrochemical ways.[47-49] In our laboratories, this reaction was previously executed using an MeCN / MeOH mixture employing the SCER, leading to the transformation of amides to methyl carbamates.[50] Starting with this campaign, it was questioned whether the process could be accommodated in the newly designed solvent system.

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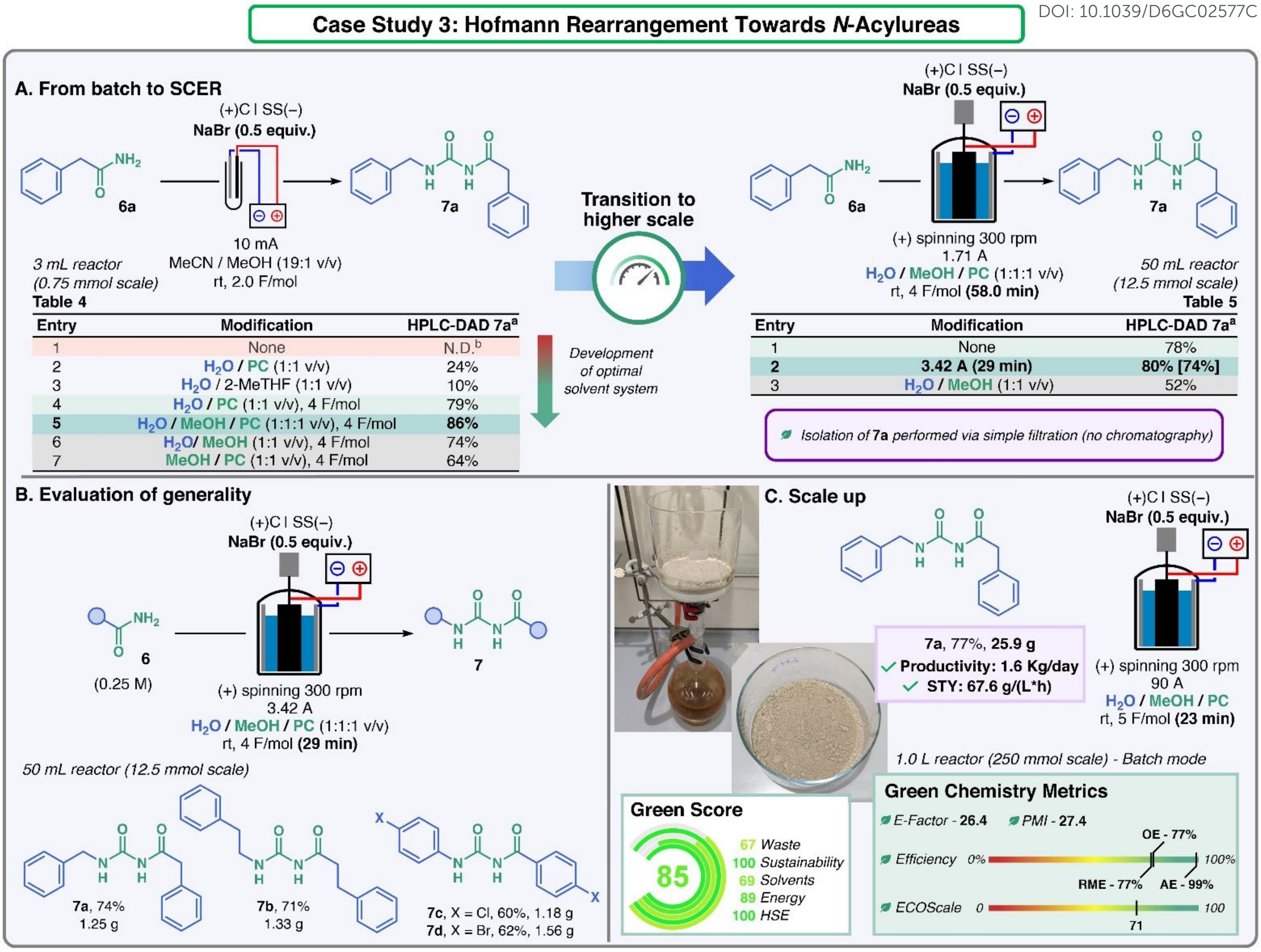

Table 4

Entry	Modification	HPLC-DAD 7a[a]
1	None	N.D.[b]
2	H_2O / PC (1:1 v/v)	24%
3	H_2O / 2-MeTHF (1:1 v/v)	10%
4	H_2O / PC (1:1 v/v), 4 F/mol	79%
5	H_2O / MeOH / PC (1:1:1 v/v), 4 F/mol	86%
6	H_2O/ MeOH (1:1 v/v), 4 F/mol	74%
7	MeOH / PC (1:1 v/v), 4 F/mol	64%

Table 5

Entry	Modification	HPLC-DAD 7a[a]
1	None	78%
2	3.42 A (29 min)	80% [74%]
3	H_2O / MeOH (1:1 v/v)	52%

Figure 4. Case study 3: Electrochemical Hoffmann rearrangement towards N-acylureas. A. Batch reaction validation under the H_2O / PC solvent mixture (Table 4) and transition to higher scale via SCER (Table 5, isolated yield in brackets). Tables refer to progressive changes in the reaction conditions. B. Evaluation of different substrates in the new conditions employing SCER. C. Scale up in a 1.0 L reactor, with scale and green metrics. PMI: Process Mass Intensity. RME: Reaction Mass Efficiency. OE: Overall Efficiency. AE: Atom Efficiency. [a]HPLC-DAD area percentage.

In particular, the use of water was expected to generate the corresponding carbamic acid. Surprisingly, subjecting the amide **6a** to the developed solvent protocol (H_2O / PC) led to the selective formation of a different product (Figure 4A, Table 4, Entry 2). Upon isolation, this unknown species was identified as the *N*-acylurea **7a**. This outcome implied that the isocyanate intermediate underwent quenching with the starting material. While seminally known for chemically induced Hofmann rearrangements,[49,51] this formal dimerization has never been successfully reported in electrochemical settings. Also, these compounds were widely studied as common building blocks for bioactive molecules with pharmaceutical and agrochemical applications.[49,51] Notably, the same product was observed when 2-MeTHF was used in place of PC (Figure 4A, Table 4, Entry 2). During the optimization, higher charge (Figure 4A, Table 4, Entry 4) and the addition of MeOH (1:1:1 v/v/v Figure 4A, Table 4, Entry 5) were found beneficial to improve reaction performance, leading to 86% of desired product on 3 mL scale.[52] The absence of either PC or H_2O led to inferior results (Figure 4A, Table 4, Entry 6-7). Subsequently, several attempts to intercept the electrochemically generated isocyanate with diverse nucleophiles consistently provided the urea **7a** as sole product (see Supplementary Information for comprehensive list of nucleophiles tested). The optimized conditions were then transferred to the SCER, where further intensification could be achieved by progressively increasing the current density until reaching the maximum valuable applicable to the L size reactor (Figure 4A, Table 5, Entry 1-2). Following this protocol, the *N*-acylurea **7a** could be isolated in 80% yield via simple precipitation and aqueous rinse of the product.

Next, these reaction conditions were then applied to different amides (Figure 4B). 3-phenyl propionamide **6b** led to the corresponding urea with 71% yield, while 4-chloro and 4-bromo benzamide (**6c**, **6d**) provided the desired products in 60% and 62% yield respectively.

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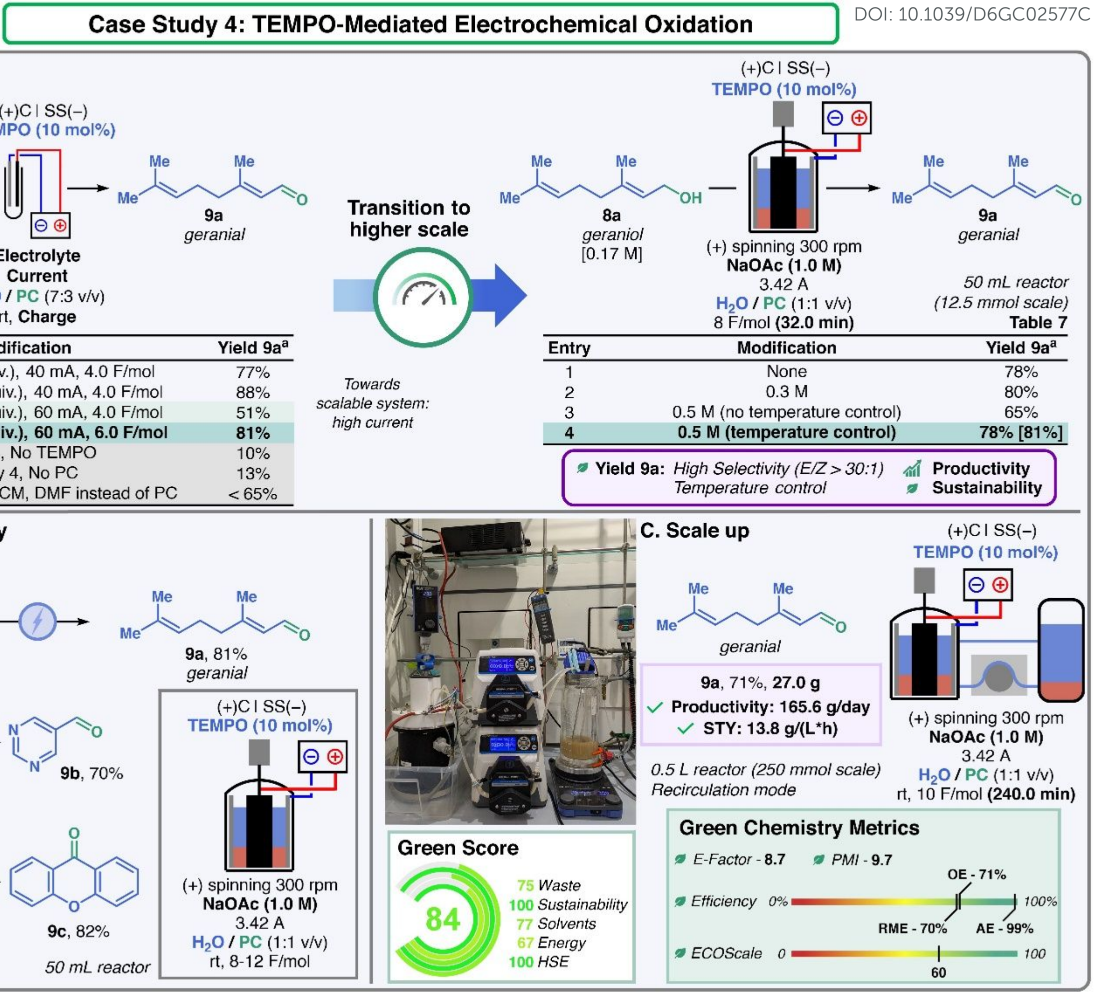

Table 6

Entry	Modification	Yield 9a[a]
1	NaBr (1.2 equiv.), 40 mA, 4.0 F/mol	77%
2	NaOAc (1.2 equiv.), 40 mA, 4.0 F/mol	88%
3	NaOAc (1.2 equiv.), 60 mA, 4.0 F/mol	51%
4	**NaOAc (6.0 equiv.), 60 mA, 6.0 F/mol**	**81%**
5	Entry 4, No TEMPO	10%
6	Entry 4, No PC	13%
7	Entry 4, MeCN, DCM, DMF instead of PC	< 65%

Table 7

Entry	Modification	Yield 9a[a]
1	None	78%
2	0.3 M	80%
3	0.5 M (no temperature control)	65%
4	**0.5 M (temperature control)**	**78% [81%]**

Figure 5. Case study 4: TEMPO-mediated electrochemical oxidation. A. Batch reaction validation under the H_2O / PC solvent mixture (Table 5) and transition to higher scale via SCER (Table 6, isolated yield in brackets). Tables refer to progressive changes in the reaction conditions. B. Evaluation of different substrates in the new conditions employing SCER. C. Scale up in a 250 mL reactor, with scale and green metrics. PMI: Process Mass Intensity. RME: Reaction Mass Efficiency. OE: Overall Efficiency. AE: Atom Efficiency. Chromatographic separation not included in the metrics calculations. [a]HPLC-DAD yield, biphenyl as internal standard.

Finally, the reaction was scaled up to multi decagram quantities in only 23 minutes by employing a 1 L batch SCER setup (77% yield, 5.0 F/mol to accomplish full conversion Figure 4C) using the same purification protocol. A remarkable projected productivity of 1.6 Kg per day was reached under these conditions, with satisfactory green chemistry metrics in line with previous results (Figure 4C). The benignity of this process was also highlighted by the low PMI and E-Factor values, along with good ECO Scale and Green Score numbers obtained. Even in this case, our approach outperforms in terms of sustainability assessment previous chemical routes reported (see Supplementary Information for the complete comparison).[53] This case study highlighted that well-known reactions as the Hofmann rearrangement could be realized and developed on scale, proving that this sustainable solvent system can lead to the controlled formation of non-intuitive and interesting products.

Case Study 4: TEMPO-Mediated Oxidation

To complete the survey around the generality of our approach, it was decided to explore a mediated reaction as final case study for our investigation. Owing to the deep mechanistic understanding of the reactivity as well as its established applicability, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) mediated reactions were selected.[54-56] With this oxidation, most of the possible types of anodic reactions were screened (*i.e.*, cross-coupling, direct oxidation, rearrangement, mediated oxidation). The undeniable volume of literature precedents on these oxidations stretches from pure water as solvent to supported-mediator electrolysis examples.[55] Nevertheless, it was hypothesized that our approach would conciliate sustainability and process intensification, overcoming limitations such as high dilution and potentiostatic operation. This final study began with the oxidation of geraniol **8a**, modifying the conditions reported by Pagliaro and coworkers towards the synthesis of the α,β-unsaturated aldehyde geranial **9a**, commonly used in fragrance industry and detergents.[57]

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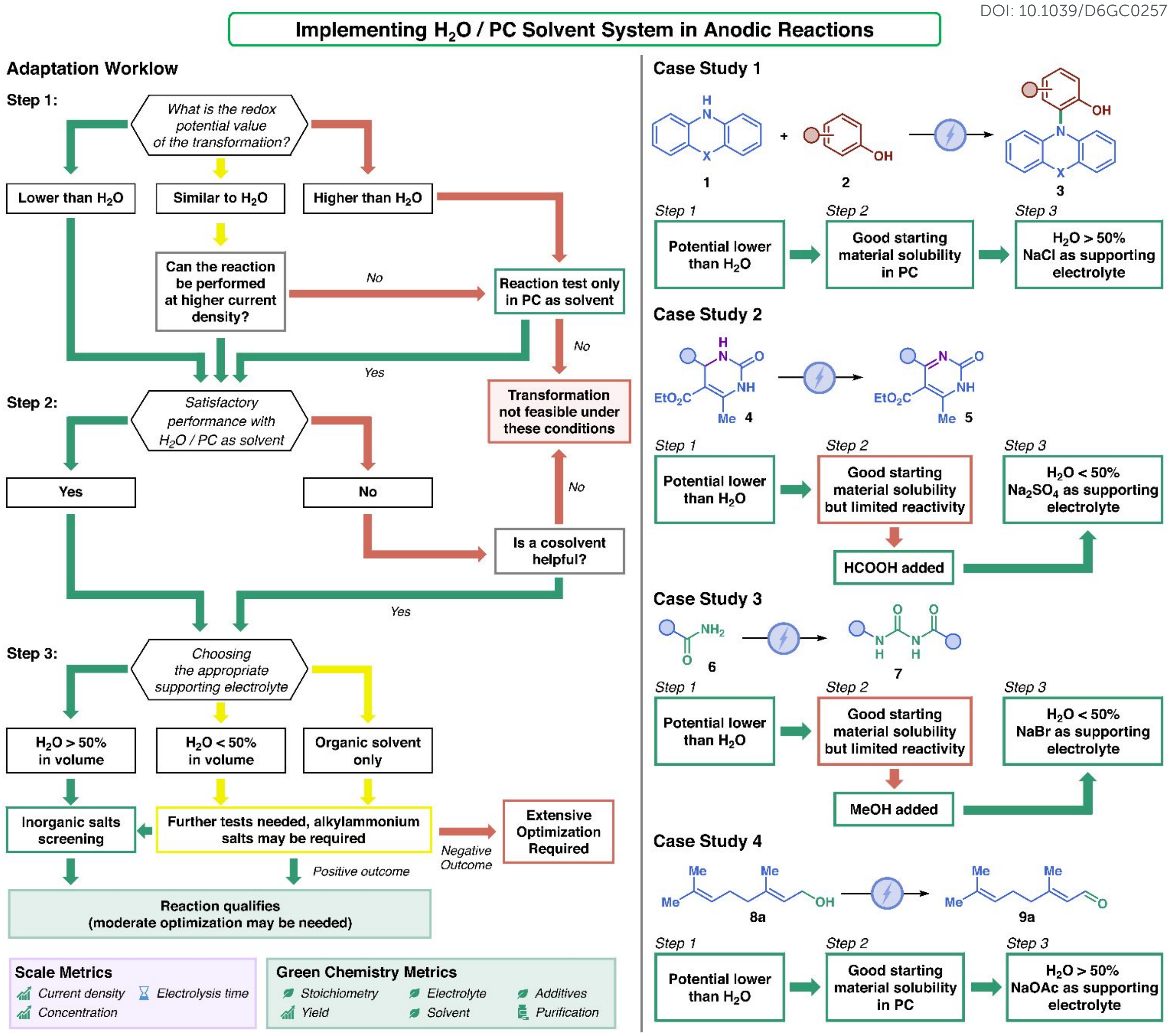

Figure 6. Implementing H_2O / PC solvent system in anodic reactions. Left: workflow of the reaction adaptation. Right: survey of the investigated case studies.

In the original report, $NaHCO_3$ was employed as the designated supporting electrolyte, and extended electrolysis time typical of potentiostatic conditions (~100 hours) to convert 0.5 mmol of **8a**. In our case, utilizing NaBr as supporting electrolyte and galvanostatic conditions led to a more efficient formation of the desired product in 77% yield. Yet this system provided lower performance when higher current was applied (Figure 5A, Table 6, Entry 1, see Supplementary Information for the complete survey). During the screening, it was noticed that the presence of chlorides in the reaction mixture dramatically affected the reaction *E:Z* selectivity (see Supplementary Information), which was consistently observed as > 30:1 otherwise. On the contrary, the addition of NaOAc provided the best performance at 40 mA (Figure 5A, Table 6, Entry 2), but a loss in yield was observed when even higher current was tested (Figure 5A, Table 6, Entry 3). Owing to the importance of maximizing the current density to guarantee high throughput, it was observed that increasing the stoichiometry of NaOAc repristinated the original reactivity, obtaining **9a** in 81% yield (Figure 5A, Table 6, Entry 4). Control reactions revealed the fundamental impact of TEMPO mediation (Figure 5A, Table 6, Entry 5), as well as the essential role of PC in the solvent system (Figure 5A, Table 6, Entry 6). Notably, replacing PC with other solvents commonly used in TEMPO-mediated transformations such as MeCN, DCM, and DMF all displayed inferior results (< 65%, Figure 5A, Table 6, Entry 7). With this initial assessment, the transition to larger scale was focused on the maximization of the starting material concentration (Figure 5A, Table 7). Incremental increase of the amount of **8a** held until 0.3 M (Figure 5A, Table 7, Entry 1,2), while the first attempt at 0.5 M did not provide satisfactory results (Figure 5A, Table 7, Entry 3). The decreased reaction performance was attributed to an accumulation of heat during time (~ 70 °C at the end of the electrolysis) caused by prolonged electrolysis (94 minutes). By simply thermostating the

SCER at 20 °C, the original reactivity was recovered, obtaining the desired product **9a** in 81% isolated yield (Figure 5A, Table 7, Entry 4). With these final conditions, the oxidation of the 5-hydroxymethylpyrimidine **8b** was performed, obtaining 70% of the desired carbaldehyde. In addition, the reaction was conducted to synthesize xanthone **9c** via C–H oxidation of xanthene **8c** in 82% yield (Figure 5B).[58] The scale up of geraniol **8a** was conducted in a 250 mL SCER equipped with graphite spinning electrode and stainless-steel static electrode, where 0.5 L of stock solution was electrolyzed under recirculation mode. After 4 hours of electrolysis, 27 g of geranial **9a** could be isolated, corresponding to 71% yield. This mediated reaction provided excellent throughput (6.8 g/h), with a STY of 13.8 g/(L*h). The thorough environmental assessment provided insights in line with the one observed in the previous case studies, underscoring the robustness and generality of our approach.

How to Apply H_2O / PC to Anodic Reactions

Upon completing these studies, a simple yet systematic workflow to accommodate H_2O / PC solvent combination to different anodic reactions emerged from our investigation (Figure 6, Left). In order to apply this approach, several generalizations can be made to secure the seamless solvent transition without tedious trial-and-error, minimizing unnecessary optimization while maximizing the throughput, via following a flow chart.

The first and most crucial step begins with evaluating the redox potential of the desired transformation. If the selected electrochemical reaction presents a potential lower than water oxidation (~ 1.2 V *vs* SHE), it can be forwarded to the second step, as experienced in Case Study 1, 3, and 4 (cf. Figure 6, Right). As mentioned above, in the case of potential higher than water, the process is not applicable, since oxygen evolution reaction (OER) will take place instead. In this eventuality, the reaction might be tested by solely employing propylene carbonate. When the redox potential is close (± 0.2 V), the reactivity must be assessed at high current density to ensure that the desired oxidation is favored. It is important to mention that the increment of current density is essential to guarantee the maximization of throughput as a practical advantage to scale up these transformations. The second step requires the evaluation of the performance of the electrolysis in the H_2O / PC solvent system. If the performance is poor, the employment of a cosolvent must be considered, for example to improve reactivity profile (*e.g.*, hydrogen evolution at the cathode, Case Study 2) or to make the mixture homogeneous (Case Study 3). The third and final step contemplated the choice of an appropriate supporting electrolyte. This selection is closely related to the percentage of water in the solvent mixture. Inorganic electrolytes can be reliably employed when the water content exceeds 50% (Case Study 1 and 4). When the aqueous content is less than half of the solvent mixture, the choice of the appropriate electrolyte should be systematically assessed, starting from more ionic (Na^+, K^+) to generally more soluble salts (Li^+). In the case that these salts are not viable, canonical tetraalkylammonium salts could be added to partially or entirely substitute inorganic material to secure the success of the electrolysis. Upon completing these iterations, the newly designed reaction can be further examined, and other parameters can be explored to improve scalability and sustainability (Figure 6). It is important to mention that different purification techniques may impact the sustainability of the process in an incisive way, and crystallization, extraction, or distillation are generally preferred over chromatography in an industrial setting. Finally, the quantification of green chemistry metrics can provide insight into the achieved improvements.

Conclusions

In conclusion, the development of a sustainable reaction design to translate electrochemical oxidations was developed and validated across four different case studies. The synergy of aqueous systems with biorenewable solvents enabled the use of widely available and atom efficient inorganic salts without compromising organic compound solubility. The successful implementation of this reaction media was guaranteed by the utilization of high mass-transfer electrochemical reactors, which enhance mixing in multiphasic systems improving the overall electrolysis performance. This approach offers a decisive advancement in the design of anodic reactions, enabling the execution of these transformations even at higher scale regimes approaching ideality in sustainable manufacturing.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the Supplementary Information.

Acknowledgements

A.B. and G.L. thank the Institute of Chemistry of the University of Graz for the Doctoral Scholarship.

The Research Center Pharmaceutical Engineering (RCPE) is funded within the framework of COMET - Competence Centers for Excellent Technologies by BMK, BMAW, Land Steiermark and SFG. The COMET program is managed by the FFG.

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DOI: 10.1039/D6GC02577C

Data availability

The data supporting this article have been included as part of the Supplementary Information.