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Communication

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Supporting Electrolyte-free and Scalable Flow Process for the Electrochemical Synthesis of 3,3',5,5'-Tetramethyl-2,2'-biphenol

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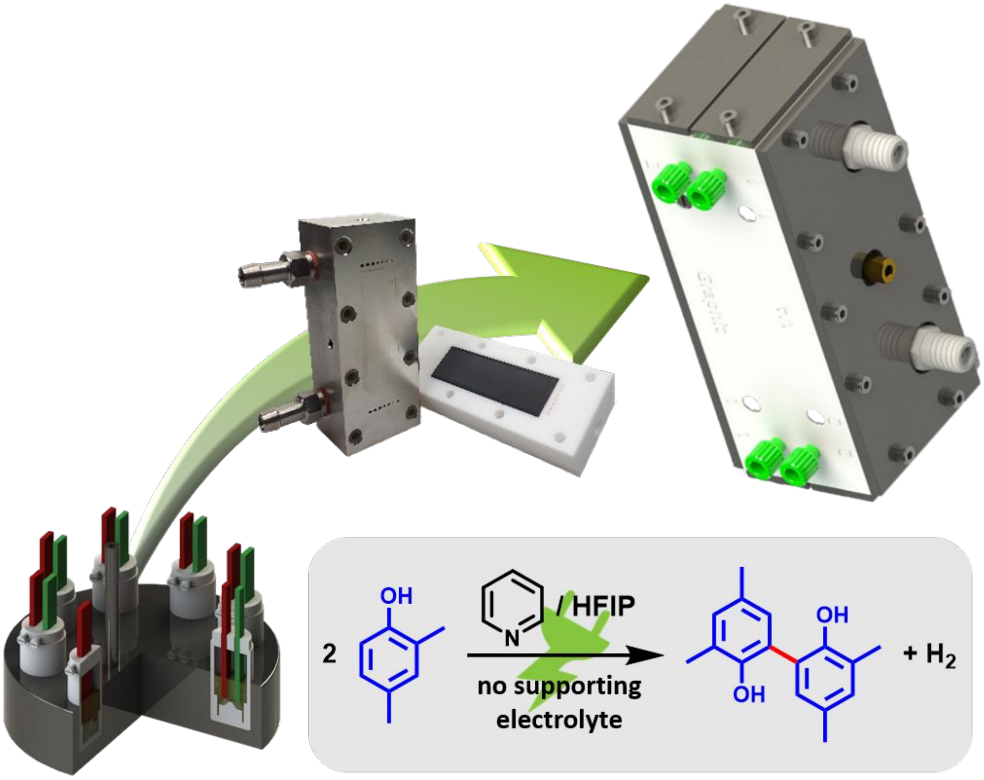
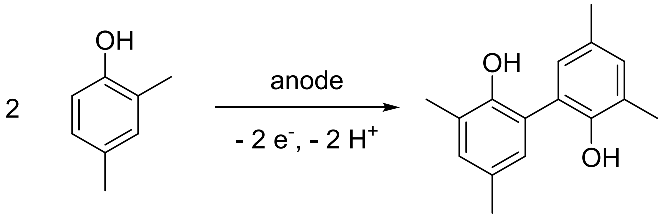


KEYWORDS. Electro-organic synthesis – flow cell – biphenol – oxidation – dehydrogenative coupling

ABSTRACT. The most efficient electrochemical synthesis of 3,3',5,5'-tetramethyl-2,2'-biphenol by dehydrogenative coupling is reported. The electrolysis is performed supporting electrolyte-free in 1,1,1,3,3,3-hexafluoroisopropanol and at carbon electrodes, whereby glassy carbon electrodes turned out to be superior. To provide sufficient conductivity pyridine is added, which can easily be recovered by evaporation and reused. This facilitates the downstream process tremendously making it simple, economic and technically viable. The scalability was proven by establishing a flow electrolysis in differently sized narrow gap flow electrolyzers. By carrying out a multi-step cascade electrolysis, the challenging hydrogen evolution could be successfully addressed. The scaled-up electrolysis provided an isolated yield of 59% biphenol.

Introduction

The significance of 2,2’-biphenols relates to their application as ligand building blocks in transition metal catalysis.[1] In the hydroformylation reaction, one of the largest product branches in the field of homogeneous catalysis, 2,2’-biphenols play an important role as entity of biphosphite ligands.[2] The pioneering work of Union Carbide is a prominent example of this.[3–6] A good impression of catalytic properties in the hydroformylation of ligands containing 2,2'-biphenols as building blocks is given by the work of van Rooy et al.[7] In particular, 3,3',5,5'-tetramethyl-2,2'-biphenol (**2**) is a remarkable example for such ligand building blocks.[8] In recent years, the focus has increasingly shifted to a more sustainable industrial manufacturing. This is also reflected in the strong alignment with environmental issues at this year's World Economic Forum in Davos.[9] To follow this trend, green chemical methods must more and more replace conventional synthetic pathways in the production of chemicals.[10] One way to keep up with this demand is electrochemistry, since it is considered as an intrinsically green method.[11–16] In the classical way, the synthesis of **2** requires either transition metal catalyst[17–23] or stoichiometric or over-stoichiometric amounts of oxidants, whereas the electrochemical route relies solely on electrons as reagent. Thus, toxic and/or expensive reagents can be avoided and the amount of reagent waste produced can be significantly decreased.[12,24] The electrochemical synthesis of 3,3',5,5'-tetramethyl-2,2'-biphenol (**2**) by anodic treatment of 2,4-dimethylphenol (**1**) has been a subject of research for some time (Scheme 1).[25–31]



1 **2**

Scheme 1: Electrochemical synthesis of 3,3',5,5'-tetramethyl-2,2'-biphenol (2) by direct dehydrogenative C-C homo-coupling reaction of 2,4-dimethylphenol (1).

Recently, we published a selective and scalable electrochemical method for the synthesis of 3,3',5,5'-tetramethyl-2,2'-biphenol (**2**) using inexpensive and readily available bromide containing supporting electrolytes.[32] However, the common necessity of supporting electrolytes often can be a drawback of electrochemical conversions, because it has to be removed and recovered elaborately. Regarding a technical application of the process, this can be problematic. Therefore, waiving off a supporting electrolyte is highly favourable. One way to get rid of supporting electrolytes in HFIP-based electrolytes is the addition of an amine base like *N,N*-diisopropylethylamine (DIPEA). The effectiveness of adding a base instead of a solid supporting electrolyte was demonstrated by Waldvogel and co-workers for the electrochemical functionalization of electron rich compounds with 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) and its subsequent aryl coupling,[33–35] or for electrochemical cross-coupling of phenols with an electron-withdrawing group.[36]

Here, we report the development of a new method for the electrochemical dehydrogenative homo-coupling of 2,4-dimethylphenol (**1**) to 3,3',5,5'-tetramethyl-2,2'-biphenol (**2**). By using amine-based bases, salt-based additional supporting electrolytes can be avoided. This provides an advantage over the previously published systems, since no more supporting electrolyte must be recovered at great expense, e.g. by washing using water. Instead, it has the benefit that it can be completely evaporated and reused.

In order to demonstrate the technical applicability of this reaction, the electrolysis was scaled-up via a flow electrochemical process.

Results

At first, different amine-based additives were studied for their suitability for the electrochemical homo-coupling of 2,4-dimethylphenol (**1**). In all cases (except for the solid DMAP) a volume fraction of 5 vol % of the amine was added to the electrolyte (Table 1). For this initial study, the screening approach developed in our group, using small batch electrolysis cells with a volume of 5 mL, was applied.[37] The reaction conditions were chosen on the basis of previous publications.[32] Boron-doped diamond (BDD) as anode material has proven its outstanding performance in the anodic C–C coupling in many cases.[13,38–48] Additionally, the use of HFIP as solvent is mandatory in electroorganic coupling reactions, as it is considered essential for obtaining the desired reaction selectivity.[46,49–53] By hydrogen bonding the oxygen functionality is blocked avoiding the typical C–O bond formation and/or the generation of polycyclic molecular architectures.[26,54–56]

Table 1: Screening of different amine-based additives for the electrochemical synthesis of 3,3',5,5'-tetramethyl-2,2'-biphenol (**2**).[a]

Entry	Amine	Volume fraction (vol %)	Concentration (mol·L^{-1})	Yield of **2** (%)[b]
1	DIPEA[c]	5	0.29	57
2	pyridine	5	0.62	69
3	2-picoline	5	0.52	54
4	2,6-lutidine	5	0.44	47
5	2,4,6-collidine	5	0.37	51
6	DMAP[d]	-	0.65	46

[a]**Reaction conditions:** 2,4-Dimethylphenol (**1**) c = 0.5 mol/L in HFIP, cathode: BDD, anode: BDD, electrode surface: 7 cm^2, current density: 7.2 mA/cm^2, applied charge: 1.0 F, T = 50 °C. [b]Isolated yield. [c]DIPEA = *N,N*-Diisopropylethylamine. [d]DMAP = 4-Dimethylaminopyridine.

The electrolyses were successful with all tested amines, but the yields vary. With pyridine as additive the best yield of 69% (Productivity: 0.08 g/h) was achieved (Table 1, entry 2). This is contrary to the results for coupling of phenols bearing electron-withdrawing groups.[36] Here, pyridine as additive led primarily to O–C coupling instead of the desired

C–C coupling of the phenols. Since pyridine is a liquid with a boiling point of 115 °C, it can easily be removed from the reaction mixture by distillation. Noteworthy, the use of pyridine in HFIP does not lead to the pyridination reaction of electron-rich arene substrates forming the Zincke salts.[57–61]

Since this work is also addressing the scale-up of this electrolysis, the reaction was then transferred to a flow cell. Flow electrolysis is particularly well suited for a scale-up, as it represents a continuous process, whereas batch processes are typically restricted to a volume of a few litres.[62–74] Additionally, in flow electrolysis cells the heat management is much easier and the electrode surface-to-volume ratio is superior compared to batch-type cells.[75] For the screening of proper conditions for the homo-coupling of 2,4-dimethylphenol the 2 cm × 6 cm-flow cell was used, which was developed by us recently.[74] However, unlike the previous publication the electrochemical cell used here was equipped with a temperature-controlled stainless steel cathode. The use of this cathode enabled cooling or heating of the electrolysis (Figure 1).[76] Furthermore, the current density was set on 30 mA/cm². It already has been demonstrated, that dehydrogenative coupling reactions in HFIP are very robust against high current densities.[43,77] This makes screening more time-efficient, because high current densities are associated with a shorter electrolysis time.

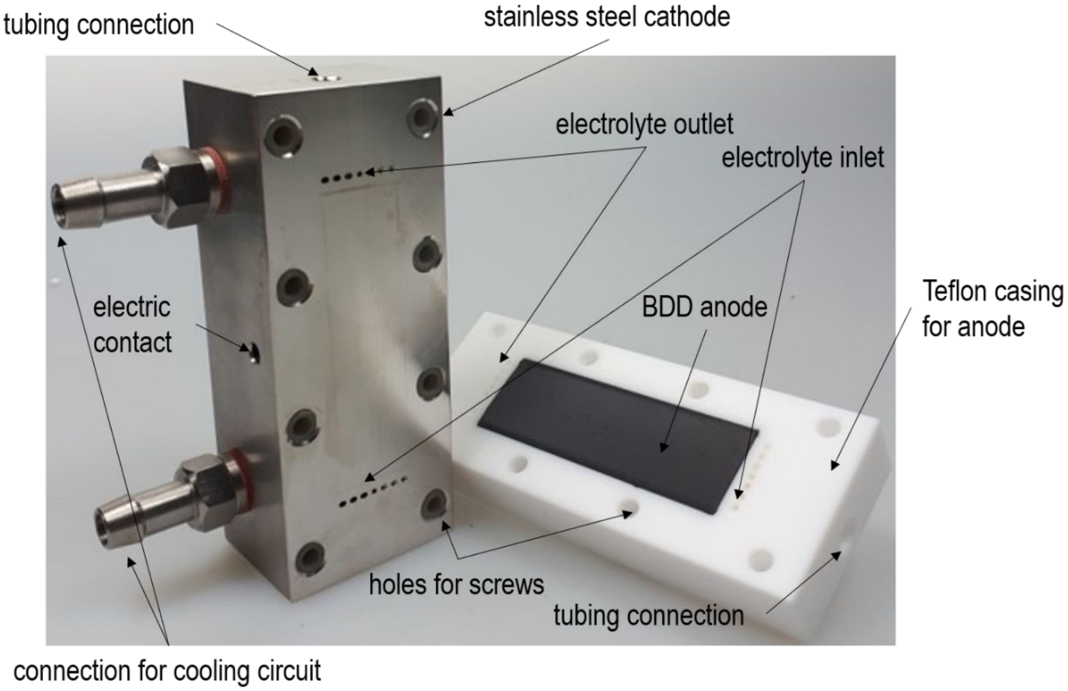


Figure 1. 2 cm × 6 cm-flow cell with a temperature-controlled stainless steel and a Teflon-cased cell.

In order to optimize the process, the composition of this solution used for the electrolysis was examined. First, the volume fraction of pyridine was altered (Table 2).

Table 2: Screening of the volume fractions of pyridine for the electrochemical synthesis of 3,3',5,5'-tetramethyl-2,2'-biphenol (**2**) in the 2 cm × 6 cm-flow cell.[a]

Entry	Volume fraction (vol %)	Yield of **2** (%)[b]
1	1.0	25
2	2.5	24
3	5.0	26
4	7.5	26
5	10.0	25
6	12.5	24
7	15.0	20

[a]**Reaction conditions:** 2,4-Dimethylphenol (**1**) c = 0.5 mol/L in HFIP, cathode: stainless steel, anode: BDD, electrode surface: 12 cm^2, current density: 30 mA/cm^2, applied charge: 1.0 F, T = 20 °C, flow rate: 0.45 mL/min. [b]Isolated yield.

The highest yield of 26% each was achieved with 5.0 vol % and 7.5 vol %, respectively (Table 2, entries 3 and 4). In order to keep the amount of additive as low as possible and at the same time ensure a sufficiently high conductivity, 5 vol % of pyridine was used for the further reactions (Table 2, entry 3). Higher as well as lower volume fractions of pyridine in the electrolyte lower the yields. However, it is apparent that the yields are almost three times lower than in the batch process (Compare Table 2, entry 3 with Table 1, entry 2). This is mainly due to unconverted starting material. But over-oxidation of the product to oligomeric compounds can also partly be a reason for the moderate yields.[32,78] This reveals that a further optimization of the reaction is of utmost necessity. Hence, additional parameters were screened, beginning with the concentration of the starting material 2,4-dimethylphenol **1** (Table 3). In order to keep the applied charge constant at 1.0 F, the flow rate had to be adjusted to the respective concentration. Thus a high flow rate was used for low concentrations and vice versa.

Table 3: Screening of the concentration of **1** for the electrochemical synthesis of 3,3',5,5'-tetramethyl-2,2'-biphenol (**2**) in the 2 cm × 6 cm-flow cell.[a]

Entry	Concentration of **1** (mol/L)	Flow rate (mL/min)	Yield of **2** (%)[b]	Productivity (g/h)
1	0.25	0.90	21	0.34
2	0.50	0.45	26	0.43
3	0.75	0.30	37	0.61
4	1.00	0.22	37	0.59
5	1.25	0.18	39	0.64

6	1.50	0.15	37	0.61
7	1.75	0.13	39	0.64
8	2.00	0.11	30	0.48

[a]**Reaction conditions:** 5 vol % pyridine in HFIP, cathode: stainless steel, anode: BDD, electrode surface: 12 cm^2, current density: 30 mA/cm^2, applied charge: 1.0 F, T = 20 °C. [b]Isolated yield.

By increasing the concentration of 2,4-dimethylphenol (**1**), higher yields between 37% and 39% of 3,3',5,5'-tetramethyl-2,2'-biphenol (**2**) were obtained. A concentration of 1.25 mol/L can be regarded as the best result, as it delivers the highest yield of 39% (Productivity: 0.64 g/h, Table 3, entry 5). At a concentration of 1.75 mol/L the same values for yield and productivity are achieved (Table 3, entry 7). However, the flow rate is with 0.13 mL/min lower than at 1.25 mol/L (0.18 mL/min). Therefore, a concentration of 1.25 mol/L was chosen for the upcoming experiments because it is more time efficient.

Testing different carbon-based anode materials showed that when using glassy carbon (GC) instead of BDD the yield can be increased slightly (Table 4). This is of benefit for a technical process, because glassy carbon is less expensive than BDD. However, much less expensive graphite is not suitable for this reaction, as it only gives a yield of 35%

(Table 4, entry 3). In general, the electrocatalytic activity of carbon electrodes is low. However, graphite, GC and BDD differ in their structure and characteristics. In contrast to BDD, graphite and GC both consist of sp^2 carbon. In GC, however, the graphite structure is strongly disordered and interlinked, providing GC an increased stability over graphite. This may be one reasons for the better performance of GC compared to graphite in electrolysis (yield: graphite 35%, GC 43%). The difference in yield with BDD (40%) and GC (43%) as electrode material is not large. Both are electrochemically stable, which is why the stability can be considered a decisive effect. The slightly better yields with GC are therefore probably due to the increased sp^2 content.

Table 4: Screening of anode materials for the electrochemical synthesis of 3,3',5,5'-tetramethyl-2,2'-biphenol (**2**) in the 2 cm × 6-cm-flow cell.[a]

Entry	Anode material	Yield of **2** (%)[b]
1	BDD	40
2	Glassy carbon	43
3	Graphite	35

[a]**Reaction conditions:** 2,4-Dimethylphenol (**1**) c = 1.25 mol/L and 5 vol % pyridine in HFIP, cathode: stainless steel, electrode surface: 12 cm^2, current density: 30 mA/cm^2, applied charge: 1.0 F, T = 20 °C, flow rate: 0.18 mL/min. [b]Isolated yield.

A common issue of narrow gap flow electrolysis is hydrogen evolution as counter reaction of the phenol coupling. The formed gas disturbs the electrolyte flow, occupies a substantial part of the electrode surface thus can lead to uncontrollable fluctuations in the local current density and voltage. To prevent this, higher flow rates of the electrolyte are beneficial, as so the electrolyte together with the hydrogen gas is pumped out of the cell faster and cannot cause so much interference. However, higher flow rates are interconnected with a lowering of the applied charge per pass through the electrolysis cell. To ensure that a sufficient amount of charge is applied to the electrolyte at higher flow rates, the electrolyte must be pumped through the cell repeatedly. This can be done in form of a cascade, in which the electrolyte is pumped through the cell several times in succession (several cascade steps), whereas the flow rate for each step increases with the number of steps. For example, in a cascade with two steps, the overall process is divided into two electrolysis units that operate at twice the flow rate compared to the corresponding electrolysis with only one pass. In each stage, only half the charge of the corresponding electrolysis is applied in a single pass because the flow rate is twice as high. After the two steps had been carried out, the completely required charge was applied. First the electrolysis was conducted in form of a cascade with five steps. Therefore, the electrolyte was pumped through the cell five time in a row with a five times higher flow rate. So, with every cascade step another 0.2 F was applied. By that adaption, the yield was increased drastically up to 57% (Table 5, entry 1). Consequently, cascades with 10 (Table 5, entry 2), 15 (Table 5, entry 4) and 20 (Table 5, entry 6) cascade steps were tested. However, the yield has not increased further, but corroded moderately.

Table 5: Cascade electrolysis for the electrochemical synthesis of 3,3',5,5'-tetramethyl-2,2'-biphenol (**2**) in the 2 cm × 6 cm-flow cell.[a]

Entry	Cascade steps	Flow rate (mL/min)	Applied charge (F)	Yield of **2** (%)[b]
1	5	0.90	1.0	57
2	10	1.79	1.0	58
3	8	1.79	0.8	57

4	15	2.67	1.0	52
5	12	2.67	0.8	58
6	20	3.58	1.0	56
7	16	3.58	0.8	58

[a]**Reaction conditions:** 2,4-Dimethylphenol (**1**) c = 1.25 mol/L and 5 vol % pyridine in HFIP, cathode: stainless steel, anode: glassy carbon, electrode surface: 12 cm^2, current density: 30 mA/cm^2, T = 20 °C. [b]Isolated yield.

However, if you look at the progression of the GC yield over the individual cascade steps for the 10, 15 and, 20 step cascade, it becomes apparent that the GC yield decreases after the application of about 0.8 F (Figure 2). This effect is due to over-oxidation of the 3,3',5,5'-tetramethyl-2,2'-biphenol (**2**).[32,78]

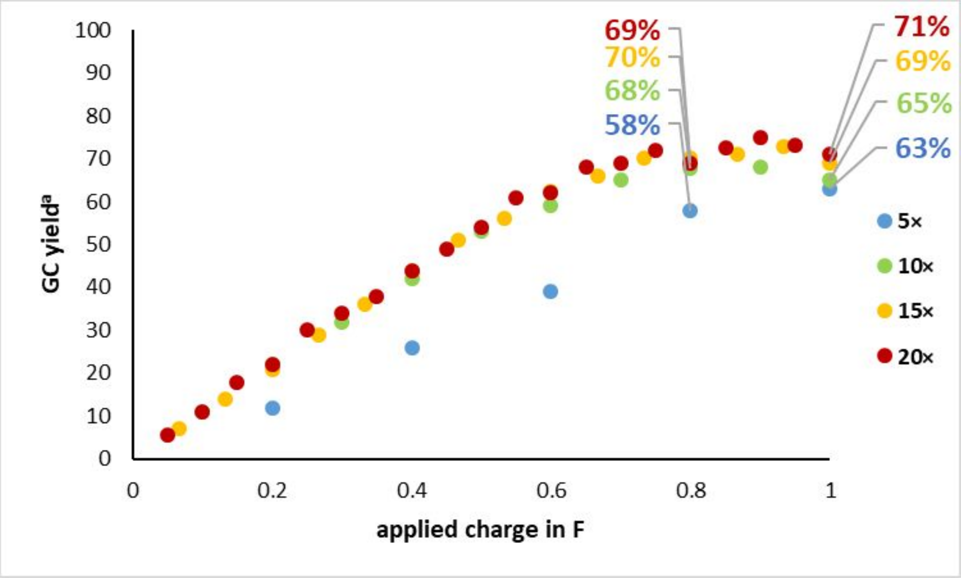


Figure 2. GC yields for the individual cascade steps. ^{a}Determined by GC using an internal standard.

Therefore, all but the five-step cascade was interrupted after 0.8 F or respectively after 8 steps for the 10-step cascade (Table 5, entry 3), 12 steps for the 15-step cascade (Table 5, entry 5) and, 16 steps for the 20-step cascade (Table 5, entry 7) and the product was isolated. The isolated yields are all similar (57% – 58%) and, in the case of the 15- and 20-step cascade, are above the yields of the reaction after 1.0 F. For the 10-step cascade the yield does not substantially change (57% after 0.8 F and 58% after 1.0 F), but the current yield is higher when the reaction is terminated after 0.8 F (current yield: 71%).

Cascade electrolyses with more steps do not deliver higher but similar yields (12 steps and 16 steps both 58%, Table 5, entries 5 and 7). However, they are associated with an increased workload compared to a cascade of 8 steps. Therefore, the 10-step cascade that is stopped after 8 steps (0.8 F) is the most efficient way of electrolysis and the experiments that followed were continued with this configuration.

Subsequently, the current density was studied. Since it is a well-known fact that electrochemical coupling reactions are stable under a wide range of current densities, the current density was varied between 10 mA/cm² and 80 mA/cm² (Table 6).[43]

Table 6: Screening of the current density for the electrochemical synthesis of 3,3',5,5'-tetramethyl-2,2'-biphenol (**2**) in the 2 cm × 6 cm-flow cell via a cascade electrolysis.[a]

Entry	Current density (mA/cm²)	Flow rate (mL/min)	Yield of **2** (%)[b]
1	10	0.60	53
2	20	1.19	53
3	30	1.79	57
4	40	2.39	61
5	50	2.98	59
6	60	3.58	61

7	70	4.18	57
8	80	4.78	57

[a]**Reaction conditions:** 2,4-Dimethylphenol (**1**) c = 1.25 mol/L and 5 vol % pyridine in HFIP, cathode: stainless steel, anode: glassy carbon, electrode surface: 12 cm^2, cascade electrolysis with 8 steps of 0.1 F, total applied charge: 0.8 F, T = 20 °C. [b]Isolated yield.

Indeed, in the studied range the yield does not change a lot: The yield is in the range of 53% and 61%. However, there is a plateau of high yields (59% – 61%) in the range of 40 mA/cm^2 to 60 mA/cm^2 (Table 6, entries 4 – 6), with the best time efficiency being achieved at 60 mA/cm^2.

The last parameter that was studied during the optimization was the temperature, which was altered between 0 °C and 50 °C (Table 7).

Table 7: Screening of the temperature for the electrochemical synthesis of 3,3',5,5'-tetramethyl-2,2'-biphenol (**2**) in the 2 cm × 6 cm-flow cell via a cascade electrolysis.[a]

Entry	Temperature (°C)	Yield of **2** (%)[b]
1	0	59
2	10	59
3	20	58

4	30	58
5	40	56
6	50	57

[a]**Reaction conditions:** 2,4-Dimethylphenol (**1**) c = 1.25 mol/L and 5 vol % pyridine in HFIP, cathode: stainless steel, anode: glassy carbon, electrode surface: 12 cm^2, current density: 60 mA/cm^2, cascade electrolysis with 8 steps of 0.1 F, total applied charge: 0.8 F, flow rate: 3.58 mL/min. [b]Isolated yield.

The influence of the temperature can generally be considered as low. However, there is a minor trend that the yield increases with decreasing temperature. Since the required energy for an active cooling of the process gets higher at lower temperature and the yield does not increase significantly at the same time, cooling the process is unfavourable. So, the electrolysis´ performance is with a yield of 58% (Productivity: 2.37 g/h) still best at 20 °C (Table 7, entry 3).

After a successful optimization of the flow process, the electrolysis was scaled-up. For a first attempted the batch process was scaled-up. A beaker-type cell equipped with six glassy carbon electrodes which are polarized alternately (immersed anode surface of 195 cm^2) was used and a volume of 1000 mL electrolyte was electrolyzed under from the

5 mL beaker-type cell adapted conditions. In this context, a purification strategy was used, which is suitable for technical scale.

The first step of this work-up is an evaporative crystallization. While recovering HFIP almost completely *in vacuo*, crystallization of the product occurs, and it can be filtered off with suction. In the second step, the remaining the mother liquor is extracted with boiling *n*-heptane. At last this *n*-heptane solution undergoes a further evaporative crystallization of the product. By this procedure pure product is obtained in 63% yield (Productivity: 2.76 g/h), which allows a reasonable downstream process.

However, this kind of batch reaction reaches its limit with few litres, which makes a further scale-up difficult. Another crucial factor is the productivity of the reaction. By scaling-up the batch process from a volume of 5 mL to 1000 mL, the productivity was increased from 0.08 g/h to 2.76 g/h. However, the small-scale flow processes in the 2 cm × 6 cm-flow cell already gives a productivity of 2.37 g/h. Thus, the scale-up in a continuous flow set-up is essential. For that purpose, the narrow gap 4 cm × 12 cm-flow cell (48 cm² anode surface), which was recently reported by our group, was used (Figure 3).[79]

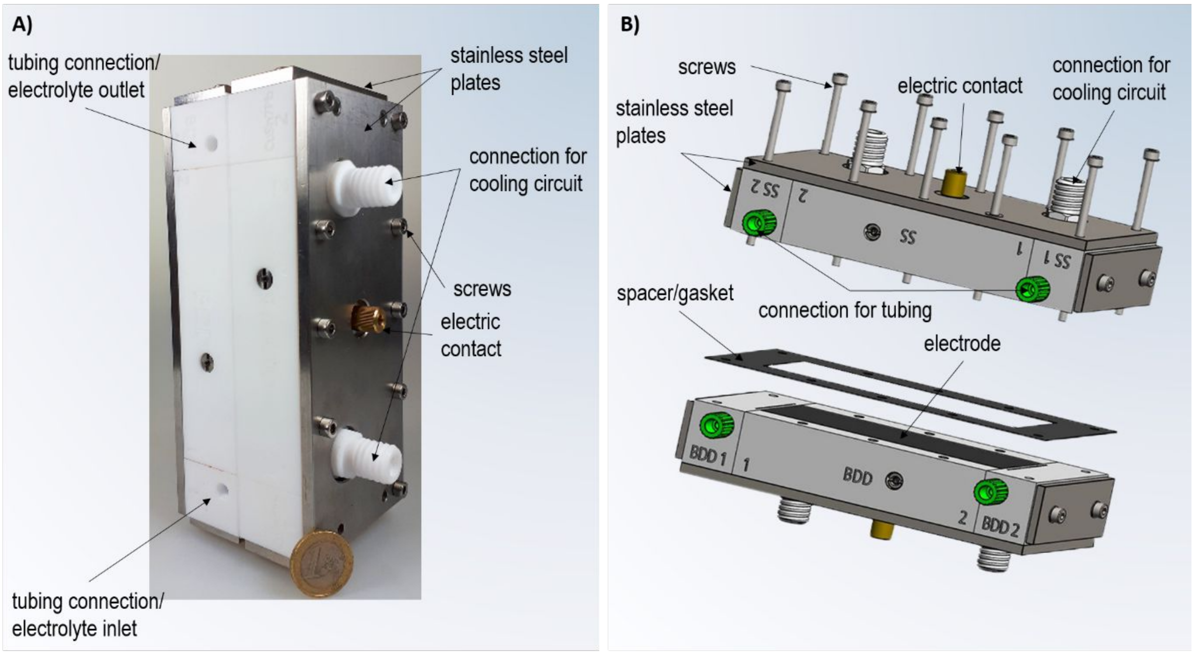


Figure 3. A) Completely mounted 4 cm × 12 cm-flow cell and a one Euro coin (diameter: 23.25 mm) for comparison. B) Explosion drawing of the 4 cm × 12 cm flow cell.

The first experiment in the 4 cm × 12 cm-flow cell was conducted under exactly the same conditions as those optimized in the 2 cm × 6 cm-flow cell (Table 8, entry 1). Although the yield decreased only insignificantly, the temperature of the electrolyte rose. The temperature increase is due to the larger electrode area in connection with the high current density of 60 mA/cm². As a result, a great amount of energy is induced into the electrolyte, causing it to heat up. Therefore, the cell was cooled to 10 °C (Table 8, entry

2) and 0 °C (Table 8, entry 3), respectively. At 0 °C the temperature rising was mastered, and the yield increased to 59%, as well. So, by scale-up the productivity of the reaction was increased from 2.37 g/h (2 cm × 6 cm-flow cell) to 9.60 g/h. Comparing this value with the productivity of the scaled batch process (2.76 g/h), it becomes clear that the developed flow process is superior to the batch process. In addition, the purification strategy used for the batch process can be easily adopted for the flow process, which further advances the technical applicability of the flow process.

Table 8: Screening of the temperature for the electrochemical synthesis of 3,3',5,5'-tetramethyl-2,2'-biphenol (**2**) in the 4 cm × 12 cm-flow cell via a cascade electrolysis.[a]

Entry	Temperature (°C)	Yield of **2** (%)[b]
1	20	57
2	10	57
3	0	59

[a]**Reaction conditions:** 2,4-Dimethylphenol (**1**) c = 1.25 mol/L and 5 vol % pyridine in HFIP, cathode: stainless steel, anode: glassy carbon, electrode surface: 48 cm^2, current density: 60 mA/cm^2, cascade electrolysis with 8 steps of 0.1 F, total applied charge: 0.8 F, flow rate: 14.33 mL/min. [b]Isolated yield.

In conclusion, we developed a supporting electrolyte-free and scalable flow process for the electrochemical synthesis of 3,3',5,5'-tetramethyl-2,2'-biphenol (**2**). The established method is the most efficient electrochemical way to make this valuable building block by dehydrogenative coupling. The key for this is the use of pyridine as additive in HFIP, which can simply be removed by distillative recovery of the HFIP. With the scale-up into the narrow gap 4 cm × 12 cm-flow cell a yield of 59% of **2** and a productivity of 9.60 g/h was achieved. This underlines a technical applicability of this method, since simple numbering up will provide access to significant amounts. In addition, a purification strategy was developed, which is suitable for larger scales.

Experimental section

General Information:

All reagents were used in analytical grades. Solvents were purified by standard methods.[80] For electrochemical reactions boron-doped diamond (BDD, 15 µm diamond layer on silicon, DIACHEM™ obtained from CONDIAS, Itzehoe, Germany) and glassy carbon (SIGRADUR® G, obtained from HTW Hochtemperatur Werkstoffe GmbH, Thierhaupten, Germany) were applied.

As power supply for the 5 mL beaker-type cells a self-built eight-channel galvanostat with an integrated coulomb counter of the University Bonn (each channel dc output 0 – 50 V and 0 – 50 mA) was used.[37] A similar setup for the 5 mL batch reactions is also commercially available as IKA Screening System (IKA-Werke GmbH & Co. KG, Staufen, Germany, https://www.ika.com/de/Produkte-Lab-Eq/Screening-System-csp-913/, 20.02.2020). As power supply for the 2 cm × 6 cm-flow cell a, self-built one-channel galvanostat (dc output 0 – 70 V and 0 – 1 A) and a self-built coulomb counter of the University Bonn. The electrochemical 2 cm ×6 cm-flow cell is also commercially available as ElectraSyn flow (IKA Werke GmbH & Co. KG, Staufen, Germany, http://www.ikaprocess.de/Produkte/Kontinuierliche-Elektroysenthese-cph-45/, 20.02.2020). For the 4 cm × 12 cm-flow cell a TDK Lambda Z60-3.5 (TDK Lambda, Achern, Germany; dc output 0 – 60 V and 0 – 3.5 A, rated power: 210 W) was used as power supply. The electric current was adjusted for the given current density, whereas the voltage was set freely.

For pumping the electrolytes through the 2 cm × 6 cm-flow cell a Ismatec Reglo ICC Digital Peristaltic Pump MS-2/12 (Cole-Parmer GmbH, Wertheim, Germany; 2 Channels, 12 pump rollers, flow rate: 0.002 – 38 ml/min per channel) with a PharMed® BPT tubing (IDES Health & Science GmbH, Wertheim, Germany; ID: 0.25 mm, wall: 0.90 mm and ID: 2.06 mm, wall: 0.91 mm)), through the 4 cm × 12 cm-flow cell a Fink Ritmo R033/7-16 (Fink Chem + Tec GmbH, Leinfelden-Echterdingen, Germany; flow rate: 0.0417 mL/min – 125 mL/min, maximal pressure: 16 bar, maximal stroke frequency: 190 strokes/min, stroke volume: 0.74 mL) were used.

For external temperature control a Julabo F33-MA refrigerated circulator (Julabo GmbH, Seelbach, Germany; working temperature: −30 °C –200 °C, heating power: 2 kW, cooling power (ethanol): 0.5 kW (20 °C), 0.32 kW (0 °C), 0.12 kW (−20 °C), 0.03 kW (−30 °C), flow rate: 11 L/min – 16 L/min).

^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C by using a Bruker Avance III HD 400 (Bruker, Germany) Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane as internal standard or traces of $CHCl_3$ in the corresponding deuterated solvent. Gas chromatography was performed on a Shimadzu GC-2010 (Shimadzu, Japan) using a ZB-5 column (Phenomenex, USA; length: 30 m, inner diameter: 0.25 mm, film: 0.25 mm, carrier gas: hydrogen).

Column chromatography was performed on a system for preparative chromatography Sepacore® Flash Systems X10 / X50 (Büchi Labortechnik AG, Flawil, Switzerland) with a Büchi Control Unit C-620, a UV detector Büchi UV Photometer C-635, Büchi fraction collector C-660 and two pump modules C-605 to adjust the solvent mixture was used. A 90 g disposable polypropylene cartridge filled with silica gel 60 M (0.060 – 0.200 mm, Macherey-Nagel GmbH & Co., Düren, Germany) was used for column chromatographic separation. Mixtures of cyclohexane purified in the rotary evaporator (solvent A) and ethyl acetate (solvent B) were used as eluents. The following gradient was run at a flow rate of

75 mL/min and a maximum pressure of 10 bar: 12 min 0 s 0% solvent B; 20 min 5 s 0% – 1% solvent B; 15 min 0 s 1% – 2% solvent B; 12 min 5 s 2% – 4% solvent B; 5 min 5 s 4% – 8% solvent B; 5 min 5 s 8% – 16% solvent B; 5 min 5 s 16% – 32% solvent B; 5 min 5 s 32% – 100% solvent B; 5 min 0 s 100% solvent B.

Synthesis of 3,3',5,5'-tetramethyl-2,2'-biphenol (2) in 5 mL beaker-type cell

307 mg (2.5 mmol) 2,4-dimethylphenol (**1**) and 0.25 mL of the amine (DMAP: 396 mg, 3.24 mmol) was dissolved in 4.75 mL HFIP. The solution was transferred into a 5 mL beaker-type cell equipped with BDD electrodes. A constant current electrolysis with a current density of 7.2 mA/cm² (1.8 cm² immersed anode surface, 13 mA) was performed at 50°C. After application of 242 C (1.0 F per mole of **1**) the electrolysis was stopped and the solvent was recovered *in vacuo* (50°C, 200–70mbar). The crude coupling product was purified by column chromatography (SiO_2, cyclohexane/ethyl acetate) and dried under reduced pressure to obtain the pure product.

Synthesis of 3,3',5,5'-tetramethyl-2,2'-biphenol (2) in 1500 mL beaker-type cell

122.3 g (1.0 mol) 2,4-dimethylphenol (**1**) and 50 mL pyridine 830 mL HFIP. The solution was transferred into a beaker-type cell equipped with six glassy carbon electrodes. The electrodes were connected alternating as anode and cathode, leading to five half cells with an immersed anode surface of 195 cm². A constant current electrolysis with a current density of 5 mA•cm^{-2} was performed at 50 °C. After application of 96596 C (1.0 F per mole of **1**) the electrolysis was stopped and the solvent was almost completely recovered *in vacuo* (50 °C, 200 – 70 mbar), just until crystallization of the product occurs. To complete the crystallization, the mixture was placed in the fridge (8 °C) overnight. The product was filtered off with suction and washed with cyclohexane. The solvent of the mother liquor was removed *in vacuo* (50 °C, 200 – 20 mbar) and the residue was boiled three times in 250 mL *n*-heptane to extract remaining product from the mother liquor. The extracts were united, and *n*-heptane was evaporated *in vacuo* (50 °C, 200 – 70 mbar), just until crystallization of the product occurs. To complete the crystallization, the mixture was placed in the freezer (−30 °C) overnight. The product was filtered off with suction, washed with cyclohexane and dried under reduced pressure. Combined product fractions gave 76.0 g (yield: 63%, productivity: 2.76 g/h) of **2**.

Synthesis of 3,3',5,5'-tetramethyl-2,2'-biphenol (2) in flow cells

2,4-Dimethylphenol was dissolved in a solution of HFIP with 1 – 15 vol % pyridine. For a single pass through the flow cell, the solution was pumped once through the electrochemical flow cell at the required flow rate. For a cascade electrolysis, the solution was pumped multiple times with respective multiple times higher flow rates through the cell. In each case, the corresponding electrochemical parameters were applied during electrolysis. Before collecting the electrolyte, a certain volume (2 cm × 6 cm-flow cell: 2 mL, 4 cm × 12 cm-flow cell: 5 mL) was discarded to ensure that the whole collected electrolyte was electrolyzed under the same conditions. An aliquot of 5 mL of the electrolyzed mixture was taken and the solvent was recovered *in vacuo* (50 °C, 200 – 70 mbar). The crude coupling product was purified by column chromatography (SiO_2, cyclohexane/ethyl acetate) and dried under reduced pressure to obtain the pure product.

Synthesis of 3,3',5,5'-tetramethyl-2,2'-biphenol (2) in the 4 cm × 12 cm-flow cell under optimal conditions

2,4-Dimethylphenol (c = 1.25 mol/L) was dissolved in a solution of HFIP with 5 vol % pyridine. The solution was pumped 8 times through the electrochemical flow cell at a flow rate of 14.3 mL/min (in total 0.8 F). The cell was equipped with a glassy carbon anode (48 cm²) and stainless steel cathode and was cooled to 0 °C. A current density of 60 mA/cm² was applied. Before collecting the electrolyte, for each step a volume of 5 mL was discarded to ensure that the whole collected electrolyte was electrolyzed under the same conditions. An aliquot of 5 mL of the electrolyzed mixture was taken and the solvent was recovered *in vacuo* (50°C, 200 – 70 mbar). The crude coupling product was purified by column chromatography (SiO_2, cyclohexane/ethyl acetate) and dried under reduced pressure to obtain 447 mg (yield: 59%, productivity: 9.60 g/h) of the pure product.

ASSOCIATED CONTENT

Supporting Information.

The following files are available free of charge.

General methods, general procedures of electrolyses, GC calibration and analytical

Data. (PDF)

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ABBREVIATIONS

BDD	boron-doped diamond
DIPEA	*N,N*-diisopropylethylamine

DMAP	*N*,*N*-dimethylpyridin-4-amine
GC	gas chromatography
HFIP	1,1,1,3,3,3-hexafluoropropan-2-ol

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