# Selective and Scalable Dehydrogenative Electrochemical Synthesis of 3,3',5,5'-Tetramethyl-2,2'-biphenol

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**Abstract** 3,3',5,5'-Tetramethyl-2,2'-biphenol is a compound of high technical significance, as it exhibits superior properties as building block for ligands in the transition-metal catalysis. However, side reactions and overoxidation are challenging issues in the conventional synthesis of this particular biphenol. Here, an electrochemical method is presented as powerful and sustainable alternative to conventional chemical strategies, which gives good yields up to 51%. Despite using inexpensive and well-available bromide-containing supporting electrolytes, the issue of bromination and general byproduct formation is effectively suppressed by adding water to the electrolyte. Additionally, the scalability of this method was demonstrated by conducting the electrolysis on a 122 g scale.

**Key words** electrosynthesis, oxidation, phenol, anode, biphenol, sustainable synthesis

Biphenols represent a very frequently appearing structural motif in many organic compounds. They play a significant role in natural products,<sup>1</sup> in technical applications,<sup>2</sup> and most importantly in ligand systems.<sup>3</sup> In particular, 3,3',5,5'-tetramethyl-2,2'-biphenol (2) shows an outstanding behaviour as powerful ligand building block in transition-metal catalysis.<sup>4</sup> Therefore, an efficient and sustainable way of synthesizing 2 is highly desired. Most commonly, methods based on transition-metal catalysis,<sup>5,6</sup> or stoichiometric and over stoichiometric amounts of oxidants are used.<sup>6-8</sup> However, these strategies suffer from several disadvantages: Many of the reagents applied are costly and/or toxic.8 Additionally, a significant amount of reagent waste is created, which subsequently has to be disposed or recycled laboriously. Facing a rising need in sustainability as one of the largest global challenges, the methods mentioned above are not contemporary and appropriate anymore. An approach reported by Easwaramoorthy claims to



obtain the biphenol **2** in yields of 72% by simply applying sodium hypochlorite as oxidizer.<sup>9</sup> However, it could be proven that instead of a C–C homocoupling solely chlorinated byproducts occur (see section 7 in the Supporting Information). The action of hypochlorite as chlorinating agent of phenols was found also by Beifuss et al.<sup>10</sup>

In contrast, electroorganic chemistry as part of green chemistry offers a potent alternative over conventional chemical approaches.<sup>11</sup> Since only electrons serve as reagent, no terminal oxidant is required. Consequently, the formation of reagent waste is effectively avoided. In addition, electrochemical methods are inherently safe. When using renewable energy sources and in particular temporary electricity surplus, electrochemical methods are even more sustainable and contribute to a stable electrical grid.<sup>12</sup>

There have been several approaches for an electrochemical synthesis of **2**. However, these methods either cause low yields<sup>13,14</sup> or need in most labs not readily available supporting electrolytes like methyltriethylammonium methylsulfate.<sup>15,16</sup> Another approach is an template-directed coupling reaction via a tetraphenoxy borate derivative.<sup>17</sup> Even though, this method is very selective, there are several drawbacks. First, it is a multistep reaction, which is very laborious, time consuming, and atom inefficient. Secondly, boron-containing intermediates are used. This leads to problematic boron contents in wastewater. Consequently, a scalable process for electrochemical synthesis of **2** is highly desired.

A general challenge in electrochemical coupling reactions is overoxidation. In particular, methylated phenols such as 2,4-dimethylphenol (1) face this issue. Consequently, usually a complex mixture of several products are formed within the oxidation process (Scheme 1).<sup>18,19</sup> Especially noteworthy byproducts are some pentacyclic scaffolds like **7–10**, whereby **9** and **10** represent secondary products of dehydrotetramer **7**.<sup>14,20</sup> Depending on the con-

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ditions of the electrolysis different products can be dominant. In alkaline media with  $Ba(OH)_2$  as supporting electrolyte a derivative of the Pummerer ketone **3** and the spirolactone **7** are the main products of the electrolysis. Whereas, the target compound **2** appears with a yield of 3% only as byproduct. Therefore, a further improvement of the electrochemical synthesis of **2** is still strongly required.

Here we describe an electroorganic method for the selective synthesis of 3,3',5,5'-tetramethyl-2,2'-biphenol (**2**) by direct dehydrogenative homocoupling of **1**. The method is metal- and reagent-free, and only readily available and inexpensive electrolyte components are employed and can be recycled as well.

For the development of new electrosynthetic protocols we start with a screening and optimization of the electrolytic conditions. These screening experiments are conducted in small electrolysis cells with a volume up to 5 mL<sup>21</sup> To keep the optimization process as less time consuming as possible quantification of the screening results is performed by gas chromatography using an internal standard method (see section 2 in the Supporting Information). Thus, it is possible to determine the yield of **2** directly from the crude product without conducting complete workup. When the optimal conditions are identified by screening experiments, the electrolysis is performed in larger electrolysis cells with a volume of 25 mL to obtain reliable isolated yields.<sup>22</sup> This should demonstrate that scale-up is then viable.

In the synthesis of **2**, the electrolyte consists of the starting material **1**, 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as solvent, and benzyltriethylammonium bromide

(NBnEt<sub>3</sub>Br) as low-cost organic supporting electrolyte. In a preliminary study, a variety of different quaternary ammonium salts were tested for their suitability in this electrolysis, with NBnEt<sub>3</sub>Br providing the best results (see section 4 in the Supporting Information). HFIP turns out to be an ideal solvent for electrochemical coupling reactions.<sup>23,24</sup> This is dedicated to its high stability under electrolytic conditions,<sup>25</sup> its outstanding radical stabilizing properties,<sup>26</sup> and its unique behavior of building a micro-heterogeneous structure.<sup>27</sup> Even though HFIP is a rather expensive solvent, almost quantitative recycling is feasible. Contrary to expectations indicated by the literature,<sup>28</sup> NBnEt<sub>3</sub>Br as supporting electrolyte did not lead to bromination as dominant reac-





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tion pathway. Brominated phenol derivatives just occur as byproducts in small quantities, whereas the biphenol 2 is the major product of the electrolysis (Figure 1).

As first parameter, the concentration of the supporting electrolyte was studied (Table 1).

Table 1	Optimization fo	r the Concentration of	Supporting	Electrolyte <sup>a</sup>
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Entry	Concentration of NBnEt <sub>3</sub> Br (mol.1 <sup>-1</sup> )	Yield of <b>2</b> (%) <sup>b</sup>
	(	
1	0.04	41
2	0.08	41
3	0.12	41
4	0.16	42
5	0.20	42

<sup>a</sup> Electrolytic conditions: glassy carbon electrodes, undivided cell (5 mL), HFIP, constant current conditions,  $j = 7.2 \text{ mA} \cdot \text{cm}^{-2}$ , Q = 1.0 F per mol of 1, 0.44 mol·L<sup>-1</sup> of 1, 50 °C

<sup>b</sup> Yield was determined from crude product by GC using an internal standard (IK1).

The concentration of the supporting electrolyte has virtually no influence onto the performance of the reaction. The vields stay more or less constant. Hence, the use of small amounts of supporting electrolyte for the electrolysis is viable without corrosion of yield (Table 1, entry 1). This is of benefit for a technical application of this reaction, because it minimizes the costs and facilitates downstream processing.

The theoretically required amount of applied charge is 1 F per mol of 1. However, side reactions can cause a higher demand of electricity. Therefore, the influence of the applied charge was investigated (Table 2).

Table 2 Optimization of Applied Charc
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Entry	Applied charge (F per mol <b>1</b> )	Yield of <b>2</b> (%) <sup>b</sup>	
1	1.0	40	
2	1.1	42	
3	1.2	44	
4	1.3	44	
5	1.4	42	
6	1.5	42	
7	1.6	38	
8	1.7	36	

<sup>a</sup> Electrolytic conditions: glassy carbon electrodes, undivided cell (5 mL), HFIP, constant current conditions, j = 7.2 mA·cm<sup>-2</sup>, 0.04 mol·L<sup>-1</sup> of NBnEt<sub>3</sub>Br, 0.44 mol·L<sup>-1</sup> of **1**, 50 °C

<sup>b</sup> Yield was determined from crude product by GC using an internal standard (IK2).

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As expected, a slightly higher amount of applied charge is beneficial. With an applied charge of 1.2 F per mol of 1 the yield was increased to 44% (Table 2, entry 3). Although, the starting material is not completely converted, by a distillative recovery of the starting material, the economic efficiency of the process is still warranted.<sup>16</sup> Additionally, when applying higher amounts of charge, overoxidation dominates the reaction which leads to lower yields and the co-formation of oligomers (see section 8.5 in the Supporting Information).

Table 3 shows the influence of the current density onto the conversion. Lower current densities as 7.2 mA·cm<sup>-2</sup> favor the yield of **2**, whereas higher current densities lead to inferior results. In order to have the shortest electrolysis time a current density of 6.1 mA·cm<sup>-2</sup> (Table 3, entry 3) was chosen for the following experiments.

#### Table 3 Optimization of Current Density<sup>a</sup>

Entry	Current density (mA·cm <sup>-2</sup> )	Yield of <b>2</b> (%) <sup>b</sup>	
1	3.9	42	
2	5.6	45	
3	6.1	45	
4	7.2	44	
5	7.8	39	
6	8.3	39	
7	8.9	39	
8	9.4	40	
9	10.0	41	
10	12.9	36	
12	19.4	35	
13	25.6	36	

<sup>a</sup> Electrolytic conditions: glassy carbon electrodes, undivided cell (5 mL), HFIP, constant current conditions, Q = 1.2 F per mol of 1, 0.04 mol·L<sup>-1</sup> of NBnEt<sub>3</sub>Br, 0.44 mol·L<sup>-1</sup> of 1, 50 °C.

<sup>b</sup> Yield was determined from crude product by GC using an internal standard (IK2).

The impact of the temperature was also screened (see section 5 in the Supporting Information). However, no improvement was achieved. Hence, the electrolyses were conducted at a temperature of 50 °C further on.

Previous studies have indicated that adding methanol or water by a volume fraction of 18 vol% or 9 vol% to the electrolyte can have an enormously positive effect onto crosscoupling reactions. For example, in the cross-coupling of 4methylguaiacol with 1,2,4-trimethoxybenzene, the yield of the corresponding biaryl was increased from 21% in pure HFIP to 67% in HFIP with 9 vol% water. This behaviour is attributed to an interaction of the additive within the solvation of the substrates.<sup>24,29</sup> For the C–C homocoupling of **1**, addition of 18 vol% methanol lead to a slight decrease of

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yield (Table 4, entry 1), whereas a volume fraction of 18 vol% of water did not affect the yield (Table 4, entry 1). However, water almost completely suppresses the formation of brominated byproducts (Figure 2). This is probably contributed to a quenching effect of water: Anodically formed highly reactive bromine species may be captured by water and thus are not able to attack the substrate anymore. This indeed, underlines the positive effect of water as additive in electrochemical coupling reactions. Consequently, the purification of the product as well as the recovery of the starting material becomes significantly easier because no brominated by-products have to be separated. This increases the chances for a later application of this electrolysis. The suppression of the bromination reaction might be attributed to the specific hydrogen bonding of HFIP to anions and oxygen termini promoting the C-C bond formation. The addition of water seems to enhance this solvent control, since the protic domains are increased.<sup>27</sup>

 
 Table 4
 Influence of Methanol and Water as Additive onto the Electrochemical Synthesis of 2<sup>a</sup>

Entry	Additive	Volume fra	ction (vol%) GC Yield of $2 (\%)^{b}$
1	MeOH	18	42
2	H <sub>2</sub> O	18	45
3	H <sub>2</sub> O	5	42
4	H <sub>2</sub> O	10	48
5	H <sub>2</sub> O	15	50
6	H <sub>2</sub> O	20	46
7	H <sub>2</sub> O	25	39
8	H <sub>2</sub> O	30	36
9	H <sub>2</sub> O	35	30
10	H <sub>2</sub> O	40	21

<sup>a</sup> Electrolytic conditions: glassy carbon electrodes, undivided cell (5 mL), HFIP + additive, constant current conditions, j = 6.1 mA·cm<sup>-2</sup>, Q = 1.2 F per mol of 1, 0.04 mol·L<sup>-1</sup> of NBnEt<sub>3</sub>Br, 0.44 mol·L<sup>-1</sup> of 1, 50 °C.

b Yield was determined from crude product by GC using an internal standard (IK3).

Stimulated by this result, the water content in the electrolyte was systematically varied from 5 vol% up to 40 vol% (Table 4). The conductivity of the solution was increased by this, which led to a lower applied voltage. However, this effect was marginal, since the main part of the conductivity is dominated by the supporting electrolyte. With a yield of 50% the best result was obtained at a volume fraction of 15 vol% water (Table 4, entry 5).

Finally, the concentration of the starting material **2** was optimized, by altering the concentration from 0.40 mol·L<sup>-2</sup> to 2.00 mol·L<sup>-2</sup> (Table 5). Within this screening, the best



**Figure 2** Gas chromatogram of the reaction mixture after electrolysis of **1** with NBnEt<sub>3</sub>Br as supporting electrolyte and 18 vol% methanol (**A**) or 18 vol% water (**B**) as additive. Signal assignment via GC–MS and authentic samples (see section 8.4 in the Supporting Information).

#### Table 5 Optimization of the Concentration of 1<sup>a</sup>

Entry	Concentration of <b>1</b> (mol·L <sup>-1</sup> )	Yield of <b>2</b> (%) <sup>b</sup>	
1	0.40	46	
2	0.50	47	
3	1.00	48	
4	1.50	47	
5	2.00	45	

<sup>a</sup> Electrolytic conditions: glassy carbon electrodes, undivided cell (5 mL), HFIP + 15 vol%  $H_2O$ , constant current conditions, j = 6.1 mA·cm<sup>-2</sup>,

Q = 1.2 F per mol of **1**, 0.04 mol·L<sup>-1</sup> of NBnEt<sub>3</sub>Br, 50 °C.

<sup>b</sup> Yield was determined from crude product by GC using an internal standard (IK4).

yield of 48% was obtained with a concentration 1.00 mol· $L^{-2}$  (Table 5, entry 3).

To validate the screening results, determination of reliable isolated yields on gram scale is crucial. The electrolyses for the product isolation were conducted in 25 mL beakertype cells to also demonstrate a viable scale-up of this electrolysis. Additionally, it was studied if other bromide-containing supporting electrolytes are also suitable for this electrolytic conversion (Table 6). Since NBnEt<sub>3</sub>Br is a comparatively expensive supporting electrolyte (Table 6, entry 4), the application of less expensive supporting electrolytes is advantageous.

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It becomes apparent that the isolated yields are comparable with those yields determined by the internal standard method (Table 6, entry 4). The slightly lower value of the isolated yield is dedicated to the purification process. Clearly, that all four bromide-containing supporting electrolytes are suitable for the electrochemical synthesis of **2**. The isolated yields vary from 46% for NEt<sub>4</sub>Br (Table 6, entry 1) and NBu<sub>4</sub>Br (Table 6, entry 3) to even 51% for NPr<sub>4</sub>Br (Table 6, entry 2), but can be considered as in the similar range. With regards to a scale-up, the replacement of the slightly more expensive NBnEt<sub>3</sub>Br by more inexpensive supporting electrolytes is gratifyingly unproblematic.

Table 6	Scope of Different Bromide-C	Containing Supporting Electrolytes	a
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Entry	Supporting electrolyte	Yield of isolated ${\bf 2}$ (%) <sup>b</sup>	Costs (€.500 g <sup>-1</sup> )
1	NEt₄Br	46	64 <sup>30</sup>
2	NPr <sub>4</sub> Br	51	97 <sup>31</sup>
3	NBu <sub>4</sub> Br	46	94 <sup>32</sup>
4	NBnEt <sub>3</sub> Br	47	24833

<sup>a</sup> Electrolytic conditions: glassy carbon electrodes, undivided cell (25 mL), HFIP + 15 vol% H<sub>2</sub>O, constant current conditions, j = 6.1 mA·cm<sup>-2</sup>, Q = 1.2 F per mol of 1, 1.00 mol·L<sup>-1</sup> of 1, 0.08 mol·L<sup>-1</sup> of supporting electrolyte, 50 °C.

<sup>b</sup> Yield of isolated product.

Finally, conduction of the electrolysis in an even larger scale was demonstrated. Therefore, an alternate polarized arrangement of six glassy carbon electrodes (immersed anode surface: 195 cm<sup>2</sup>) was placed into a large beaker-type electrolysis cell filled with a total volume of 1 L electrolyte (122 g starting material **1**). As supporting electrolyte NEt<sub>4</sub>Br was chosen, because of its low costs. With this setup the desired biphenol **2** was obtained in 39% yield. An additional advantage of this system is that workup of the reaction mixture is very simple and allows further scale-up as well as reasonable downstream processing. The pure product is obtained only by extraction and evaporative crystallization.

In conclusion, we developed and optimized an electrochemical method for the synthesis of 3,3'5,5'-tetramethyl-2,2'-biphenol via a simple and fast screening methodology. By the addition of 15 vol% water to the electrolyte the formation of numerous byproducts was effectively suppressed. In particular, the bromination of 2,4-dimethylphenol was inhibited, despite the bromide-containing supporting electrolytes. So far, there are only few examples for electrochemical coupling reactions, where the addition of water to the electrolyte was tested. However, the results of this work could lead to a reinvestigation of other reactions of this kind. In particular, when having technical relevance. Additionally, it was demonstrated that even most common quaternary ammonium salts, such as NEt<sub>4</sub>Br and NPr<sub>4</sub>Br are suitable for this reaction and deliver good yields up to 51%. This is an important prerequisite for the large-scale electroLetter

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chemical production of such components. The synthesis was also successfully transferred into 122 g scale with a yield of 39%. In addition, a purification strategy was developed, which is suitable for larger amounts. This, together with the simple recycling of the starting material as well as the solvent makes the developed method ecological and economical attractive for a technical application.

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# **Supporting Information**

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690706.

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- (21) General Protocol for Screening Reactions
  - A solution of 2,4-dimethylphenol (**1**, 2–10 mmol) and the respective supporting electrolyte (0.2–1.0 mmol) in 5 mL HFIP or HFIP with 18 vol% methanol or HFIP with 5–40 vol% water was transferred into a screening electrolysis cell equipped with a glassy carbon anode and a glassy carbon cathode. A constant current electrolysis with a current density of 3.9–25.6 mA·cm<sup>-2</sup> was performed at 20–60 °C. After application of 1.0–1.7 F per mol of **1**, the electrolysis was stopped, and the solvent mixture was recovered in vacuo (50 °C, 200–70 mbar). Subsequently, the sample was prepared according to the respective internal calibration (IK1–IK4, see section 2 in the Supporting Information).
- (22) General Protocol for the Electrochemical Synthesis of 3,3',5,5'-Tetramethyl-2,2'-biphenol (2)

A solution of 2,4-dimethylphenol (**1**, 3.05 g, 25.0 mmol) and the respective supporting electrolyte (2.0 mmol) in 25 mL HFIP with 15 vol% water was transferred into an undivided beaker-type electrolysis cell equipped with a glassy carbon anode and a glassy carbon cathode. A constant current electrolysis with a current density of 6.1 mA·cm<sup>-2</sup> was performed at 50 °C. After application of 2895 C (1.2 F per mol of **1**) the electrolysis was stopped, and the solvent mixture was recovered in vacuo (50 °C, 200–20 mbar), and the crude product was purified by shortpath distillation (recovery of starting material **1**: 60 °C, 2·10<sup>-3</sup> mbar; sublimation of product **2**: 140 °C, 2·10<sup>-3</sup> mbar).

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