ELECTROCHEMISTRY

Unexpected high robustness of electrochemical cross-coupling for a broad range of current density

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Electro-organic synthesis is a powerful technique for the sustainable preparation of compounds. However, many electrosynthetic reactions require complex equipment, are limited to a very narrow current density range, or have very long reaction times; some also involve nonselective transformations and bad scalability. The robust and selective synthesis of nonsymmetric biphenols and partially protected derivatives is established by anodic C–C cross-coupling. The setup is simple, involving constant current conditions and undivided cells. Its key is a unique electrolyte system based on fluorous alcohols and mixtures, particularly 1,1,1,3,3,3-hexafluoroisopropanol. This allows variations of the current density of more than two orders of magnitude without decreasing selectivity or product yield. This exceptional effect is unknown for electro-organic synthesis of products that have similar oxidation potentials as the starting materials. It potentially paves the way for industrial electrolyzers with variable current consumption, which could enable the flexible use of energy surplus in the electricity supply.

INTRODUCTION

Preparative electrochemical synthesis is a versatile method for establishing green, sustainable processes. The major benefits of electrochemical methods over conventional chemical synthesis are the avoidance of reagent waste and the mild reaction conditions. In addition, electrochemistry benefits from chemoselective transformations in combination with high functional group tolerance (1). In the industrial context, electrochemistry offers a way to design economic, inherently safe, and scalable processes that do not generate uncontrollable situations because they can easily be switched off. However, electrochemistry is an interdisciplinary field mostly dominated by physical chemists. Many synthetic chemists are reluctant to consider this technique either because they lack experience or because they incorrectly assume that specific equipment is needed.

Many electro-organic protocols focus on the use of a three-electrode setup for constant potential conditions (2). Although these experimental setups offer the possibility of achieving the selectivity of desired transformation by specific adjustment of the electric potential, they exhibit significant disadvantages over a constant current two-electrode setup. A significant drawback is the cost of a three-electrode setup based on the reference electrode and the sophisticated electronic periphery required. However, another serious disadvantage of this method is that because of the depletion of the starting material, the current continuously decreases in the course of conversion. Consequently, for a complete conversion, prolonged electrolysis times have to be encountered.

The most practicable experimental electrochemical setup is a galvanostatic two-electrode arrangement in an undivided cell. This configuration enables operation with an affordable current source and good electrochemical conversion in acceptable time scales. For the synthesis of large quantities of product by electrochemical techniques or even an industrial application, this cell design, in combination with high applicable current density, would be the optimum in terms of cost and time saving, as well as sustainability of the process.

However, a survey of the research literature reveals that most electro-organic transformations are limited to a low current density of 0.5 to 5 mA/cm^2 or less (3–5). In addition, most of these protocols only operate successfully in a rather restricted current density window, with a substantial drop in yields and selectivity when this window is exceeded (5, 6). The main reason for this can be attributed to the direct correlation of applied current density to the electrode potential. Only a few electrochemical transformations can be found, which are operated at high current densities of $\geq$20 mA/cm^2. Thus far, the crucial requirement for successful applications of high current density has been the inherent electrochemical stability of products formed, as can be found, for example, for Kolbe electrolysis (7) and for the Monsanto's Baizer process (8). At the same time, the need for robust electrochemical reaction conditions is clear from the number of strategies that has been developed in an attempt to realize high current electrolysis. The main approaches are the use of macroporous electrodes to maximize the available electrode surface (9–13), electrolysis in biphasic systems (14, 15), and utilization of mediating systems in equimolar quantity (16). Each of these strategies has its own drawbacks, mostly related to their unpredictable scalability, insufficient effectiveness, or high substrate specificity.

Here, we report a unique robust electrochemical synthesis of phenols and arenes to nonsymmetric biphenols, partially protected nonsymmetric biphenols, and m-terphenyl-2,2″-diols by anodic C–H activating cross-coupling reaction. The selective formation of C–C bonds is of general interest in modern organic chemistry for the construction of complex carbon architectures. In particular, 2,2′-biphenols and m-terphenyl-2,2″-diols have exceptional properties as building blocks for ligands in molecular catalysis, bioactive materials, and natural products (17). Classically, C–C cross-coupling of phenols and arenes is carried out under transition metal–catalyzed reaction conditions. To follow this strategy, substrates have to be activated by installation of specific leaving functionalities. Both these sacrificial groups and the complex and costly catalysts, which are often palladium-based, result in a large amount of reagent waste over a multistep synthesis (18). Therefore, a direct oxidative C–H activating protocol for this synthesis is of high interest. However, oxidation of mixtures of phenols or phenols with arenes results in the unselective formation of homocoupling products (Fig. 1, AA and BB), desired cross-coupling products (Fig. 1, AB), and a variety of overoxidation products in a statistical manner (19).

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RESULTS AND DISCUSSION

We have developed a selective, reagent- and metal-free protocol for the electrochemical C–H activating synthesis of these substance classes. By this approach, the selective synthesis of nonsymmetric biphenols (20, 21), partially protected nonsymmetric biphenols (17), and *m*-terphenyl-2,2″-diols was established (Fig. 2) (18). This protocol allows the formation of desired cross-coupling products in high yields and selectivity, by direct electrolysis of simple starting materials, and without the necessity of either a previous installation of leaving groups or the use of costly catalysts.

The best yield and selectivity for the oxidative cross-coupling are achieved in fluorinated solvents, such as 1,1,1,3,3,3-hexafluoroisopropanol (HFIP). This specific role can be attributed to strongly different solvation of the individual coupling partners and stabilization of reactive intermediates (22–24). Recent investigations of HFIP reveal a heterogeneity on nanoscale (25). The possibility of applying a broad range of current density was not observed in former studies using other fluorinated solvents, such as trifluoroacetic acid or 1,1,1-trifluoroethanol (26, 27).

Crucially, our studies reveal that HFIP acts both in the stabilization of reactive intermediates and in the stabilization of the desired products of the electrochemical cross-coupling of arenes. Because of this combined effect, the anodic C–C cross-coupling in HFIP proves unusually robust in a broad applicable variety of current densities. A series of electrolyses were performed for each of the three product classes to observe robustness in terms of yield and selectivity of the anodic cross-coupling. We used simple undivided beaker-type cells, equipped with boron-doped diamond (BDD) electrodes. Although other electrode materials can also be used in these electroconversions, BDD turned out to be the best inert electrode material for these electrosynthetic applications. The combination of electrochemically very stable HFIP and electrochemically robust BDD anodes prompted us to apply an unusually high current density. Electrochemical cross-coupling was carried out at 1, 5, 10, 20, and 25 mA/cm^2 and even extended to 35, 50, 75, and 100 mA/cm^2. The results are shown in Figs. 3 and 4.

The anodic C–C cross-coupling is remarkably robust and can be reliably carried out with the current density varied over two orders of
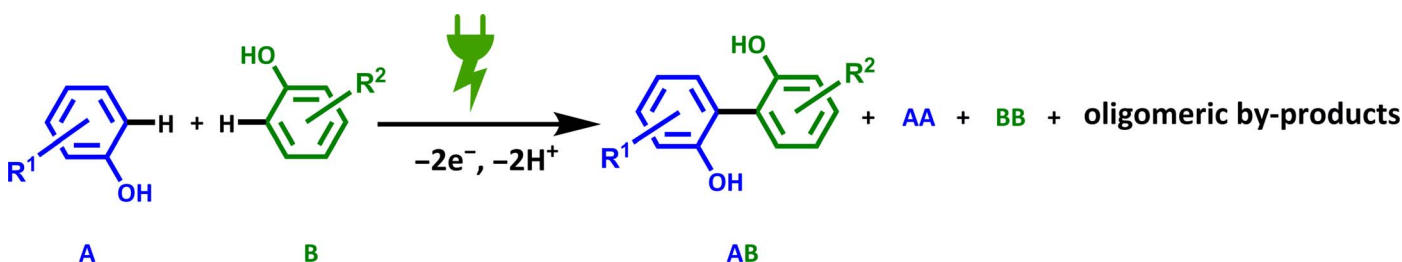

Fig. 1. Potential products for oxidative cross-coupling reaction of anodic phenol-phenol coupling. Besides the desired cross-coupling product, both homo-coupling products AA and BB will be obtained in a statistical manner. In addition, numerous oligomers may form.
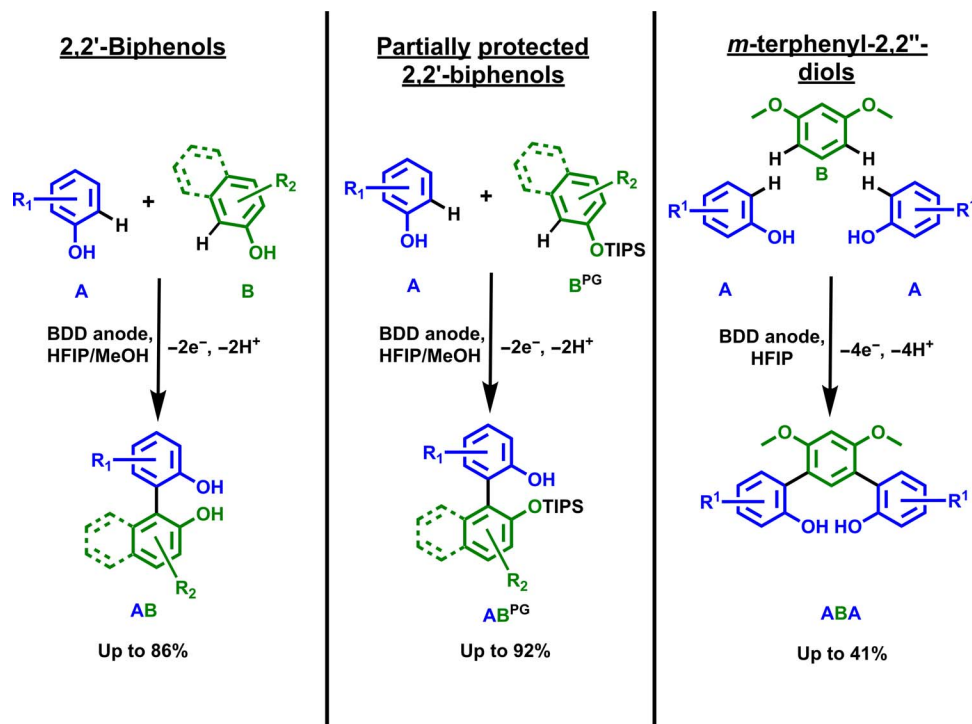

Fig. 2. Overview of selective anodic C–C cross-coupling reactions of phenols with arenes. HFIP is a major component of the electrolyte, and BDD is the inert anode material.
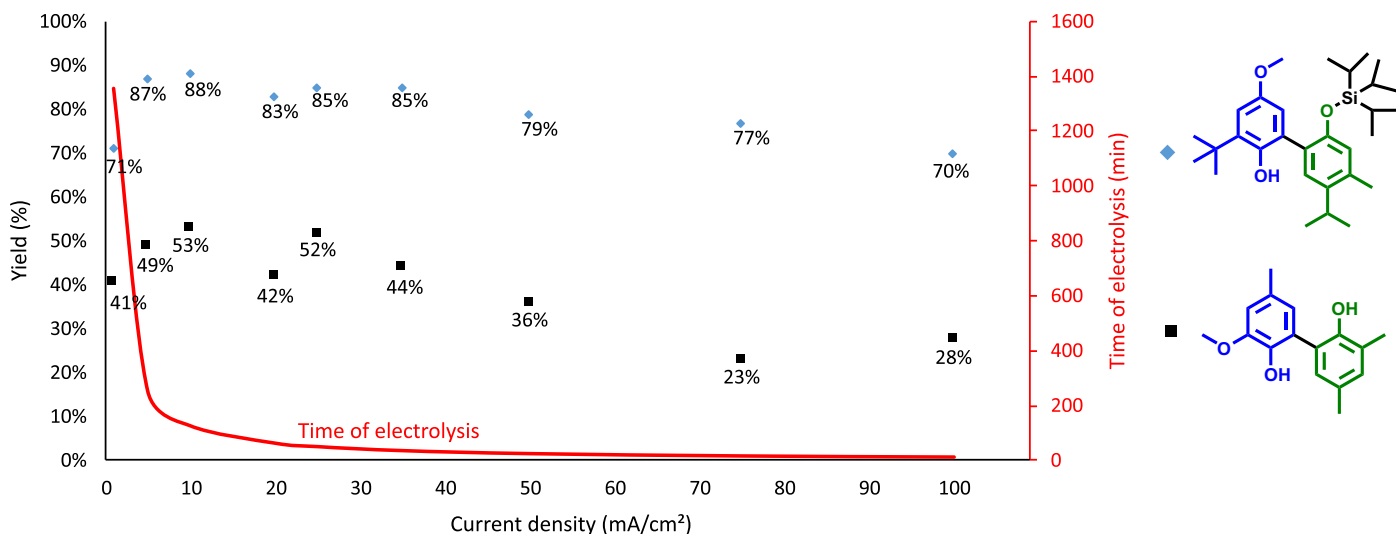
Fig. 3. Variation of current density for single anodic C–C cross-coupling reaction. Synthesis of 2,2′-biphenols (AB; black) and partially protected nonsymmetric 2,2′-biphenols (AB[TIPS]; blue). Each data point represents electrolysis on a scale of 3.8 mmol for the limiting coupling partner **A**. Isolated yields are given. Details for the protocols are provided in the Supplementary Materials. The red line represents the time of electrolysis required for the full conversion (2 F) of 3.8 mmol of **A**.
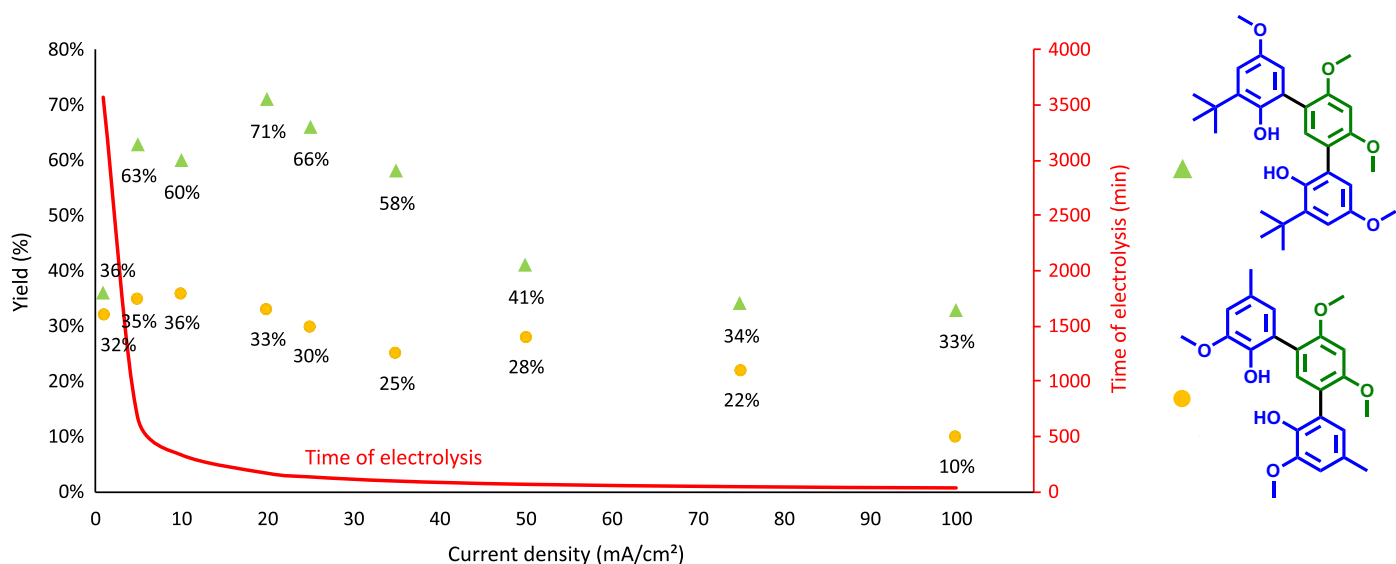

Fig. 4. Variation of current density for twofold anodic C–C cross-coupling reaction. Synthesis of *m*-terphenyl-2,2″-diols (ABA; yellow and green). Each data point represents electrolysis on a scale of 5.0 mmol for the limiting coupling partner **B**. Isolated yields are given. Details for the protocols are provided in the Supplementary Materials. The red line represents the time of electrolysis required for the full conversion (4 F) of 5.0 mmol of **B**.

magnitude, from 1 up to 100 mA/cm^2. With increasing current density, the electrolysis time can be significantly reduced, as illustrated by the red line in Figs. 3 and 4. When carried out at 1 mA/cm^2, full conversion (2 F) of approximately 3.8 mmol of coupling partner **A** takes more than 22 hours, whereas full conversion can be reached in less than 13 min at 100 mA/cm^2 with our elaborated setup.

Electrochemical synthesis of partially protected nonsymmetric biphenols represents the most robust system. Absolutely no loss in selectivity and very high yields of up to 88% can be achieved for the tested current density range. This robustness can be attributed to two complementary effects that we pointed out in our most recent study, Wiebe *et al.* (*17*): The bulky TIPS (triisopropylsilyl) groups at component **B** initiate a strong twist in the biaryl axis of the resulting coupling product. Conse-

quently, the aryl moiety serves as an electron-withdrawing group generating a less expanded π system. This effect, in combination with strong solvation of the product **AB** by HFIP, leads to a significant stabilization and makes the final product less prone to overoxidation. Besides high yields for the synthesis of partially protected nonsymmetric biphenols, we were able to demonstrate that this stabilization is sufficient for the application of an unexpectedly high current density of up to 100 mA/cm^2. The small decrease of product yield to 71% for a low current density of 1 mA/cm^2 can be explained by the displayed mechanism (see fig. S2): For the anodic C–C cross-coupling, two oxidative steps are required. The first step allows the formation of the C–C bond; the second step enables the rearomatization of the coupling product. If the applied current density is too low, then the diffusion of the intermediates formed

will take place before the reaction sequence is accomplished. The contrary applies for high current densities of ≥ 100 mA/cm^2. At this level, diffusion of the sequence starting material **A** onto the electrode surface is insufficient and limited. Therefore, oxidation equivalents are transferred to the electrolyte or initiate side reactions. Consequently, the yields decrease to 70%.

The electrochemical synthesis of nonprotected, nonsymmetric biphenols generally results in lower yields for the isolated products. This can be rationalized by less pronounced stabilization of the final biaryl. Compared to the partially protected biaryl system considered above, strong twists along the biaryl axis are not strongly imposed by steric effects on these coupling products. Therefore, overoxidation to oligomeric by-products can occur and lower the yield. Nevertheless, the electrolyses investigated here still generate robust yields at current densities ranging from 1 to 35 mA/cm^2. The observation of robust and reliable results over such a broad current density window is very unusual for electro-organic synthesis. The same characteristic behavior is observed for nonprotected biphenols, with a low current density of 1 mA/cm^2 leading to slightly lower yields of 41%. Decreasing yields, and therefore, the limit for current density, start with 50 mA/cm^2 for nonprotected, nonsymmetric biphenols. However, the desired product can still be isolated with a remarkable 28% yield at 100 mA/cm^2, whereas in most electro-organic synthesis, only a tarry black residue is obtained under these conditions.

The concept of electrochemical cross-coupling of phenols and arenes was investigated by the direct synthesis of *m*-terphenyl-2,2″-diols. In this twofold coupling sequence, each step represents a phenol-arene cross-coupling. In addition, formation of terphenyls is more complex because of the second coupling to a biaryl system. Because of the huge significance of *m*-terphenyl-2,2″-diols and the bigger challenge, investigations on phenol-arene cross-coupling were focused on the synthesis of symmetric terphenyls.

Robust yields and reliable results can also be observed for the synthesis of *m*-terphenyl-2,2″-diols, which represents an even more complex system. The data obtained furnish evidence that a twofold anodic C–C cross-coupling reaction within one electrolysis is possible with no loss in selectivity and very high yields of up to 71% and demonstrate even higher yields at higher current densities. In general, for both compounds at a current density of about 50 mA/cm^2, yields started to decrease significantly. The lowered yield can be explained again with an insufficient oxidation at the anode, especially for the second cross-coupling reaction.

Recently, cross-coupling reactions of anilines attracted significant attention (*28*). Unfortunately, anilines have a strong tendency for polymerization as a major reaction under electrolytic conditions. Regarding our studies on aniline cross-coupling reactions, deviation from optimum reaction parameters and, therefore, application of such a broad range of current density are not viable. However, these electrolytic conditions in HFIP enable the desired electroconversion to dehydrodimers.

No solvation effect comparable to that of HFIP on the phenols and arenes in the anodic cross-coupling has been shown to this day. Usually, very small deviations of current density in electro-organic synthesis have typically been found to result in a significant drop in yield. In addition, high current densities on the level of those described here have successfully been applied only to a very few examples wherein the product cannot be anymore converted at the electrode. The difference in potential between the starting material and the product is in the range of several hundred millivolts. We could prove that the stabilizing solvation by HFIP takes place for all three product classes: nonsymmetric biphenols, partially protected nonsymmetric biphenols, and *m*-terphenyl-2,2″-diols. The general applicability of a current density of up to 100 mA/cm^2 has been shown. The possibility of successfully applying a broad range of current density significantly simplifies the engineering aspects for technical applications. The ability to vary the current density by two orders of magnitude indicates the independence from this parameter and facilitates engineering aspects, such as electrode dimensions and reactor geometry. The precise control of electric current and/or electrode potential, which is challenging for large-scale applications, can be neglected. Moreover, this allows the incorporation of variable power supplies from regenerative sources. The unique solvent effect enables the control of reaction rates. Variation and optimization space-time yields in regard to temporary needs and energy costs are therefore viable without providing electrolyzers or electrodes of different scale. Nevertheless, it must be considered that with increasing current, the open circuit voltage also increases because of ohmic resistance. The energy input will raise the costs in potential synthetic applications, and a compromise between time saving and costs will need to be found. We chose a current density of 35 mA/cm^2 to show the generality of our concept for several derivatives of each product class. This current density is still unusually high for electro-organic synthesis applications, and the full conversion of 3.8 mmol of **A** can be reached within approximately 35 min at acceptable open circuit voltages. The results of that application under these optimum reaction conditions to a variety of derivatives are depicted in Fig. 5.

Therefore, we were able to demonstrate the general applicability of this unique electrochemical robustness by applying the reaction conditions to 12 different substrate combinations. It is striking that compared to previously published results at a current density in the range of 2.8 to 7.2 mA/cm^2, the yields at 35 mA/cm^2 using this new approach are in the same range with markedly shorter reaction times.

CONCLUSION

In conclusion, the use of HFIP-based electrolytes resulted in an outstanding performance with very robust anodic cross-coupling reactions. The selectivity and yield could be maintained in a range of current density of almost two orders of magnitude. When the final products become significantly larger, this unusual robustness narrows slightly. Three major beneficial roles can be attributed to HFIP creating the robust electrosynthesis: first, the stabilization of radical intermediates; second, the prevention of the products from overoxidation by solvation, despite the close oxidation potentials of the product and the starting materials; and third, the support of mass transport by the low viscosity and microheterogeneity of the HFIP/methanol mixture. With three different electrosyntheses to nonsymmetric biphenols, partially protected nonsymmetric biphenols, and *m*-terphenyl-2,2″-diols by anodic cross-coupling, the utility was demonstrated. This type of electrolyte will definitely have a wider application in other electro-organic transformations. Its effectiveness across such a large range of current density will make the electroconversion almost independent of the electrochemical setup used because the geometry and convection do not play a determining role. This should support/facilitate the acceptance of this very sustainable technique in various synthetic fields. The HFIP used is not converted and can be easily recycled. These findings allow for a tremendous reduction of the electrolysis time or the significant downsizing of electrolysis devices. Moreover, the electrolysis can be conducted with variable current densities without significant loss in performance. Future application of electrosynthesis
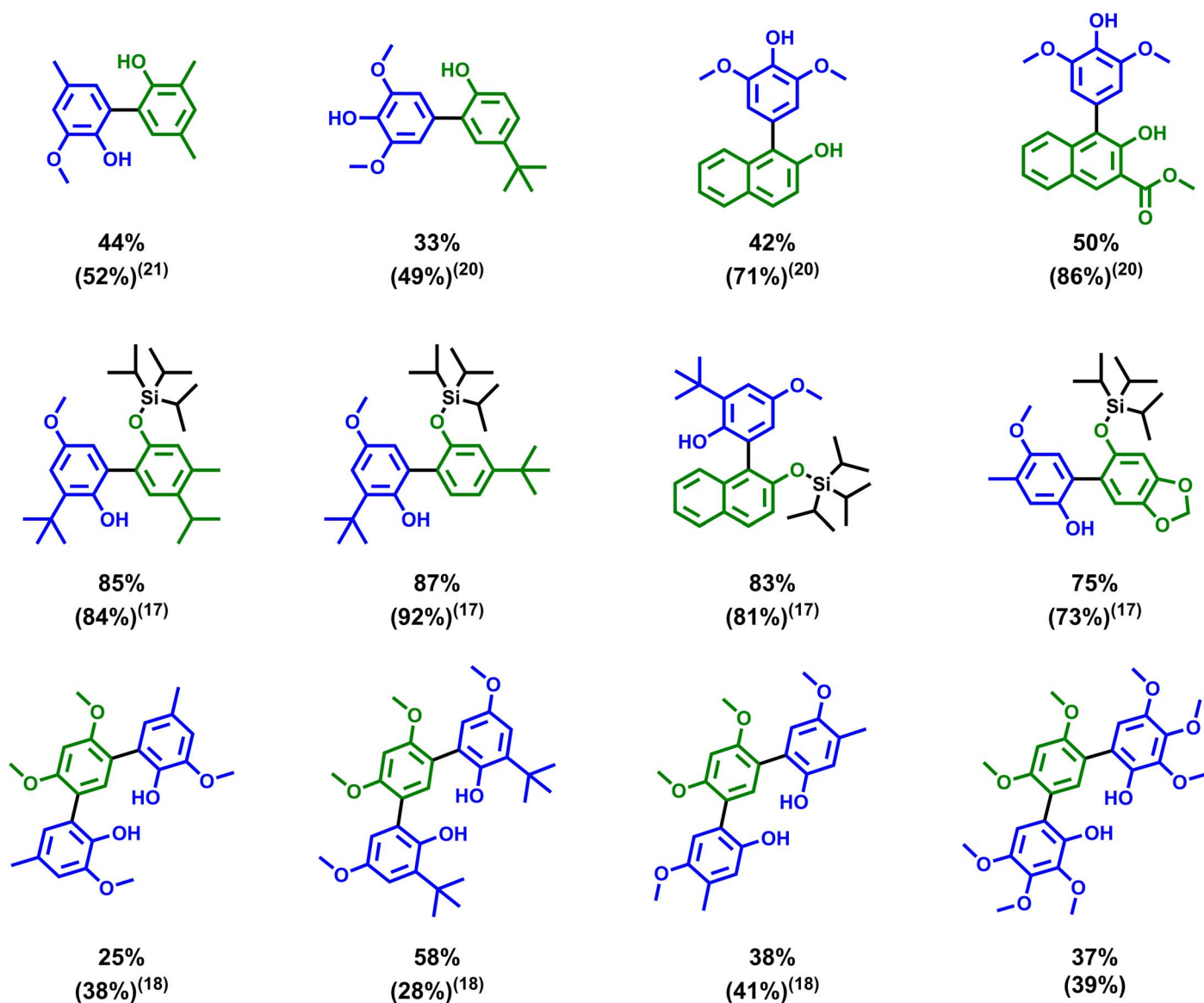
Fig. 5. Scope for the electrochemical C–C cross-coupling at high current density. Reactions were carried out with a current density of 35 mA/cm^2. Isolated yields are given. For comparison, recently published product yields for electrochemical cross-coupling at a lower current density from 2.8 to 7.2 mA/cm^2 are given in parentheses. Exact electrolysis conditions for each substrate combination are given in the Supplementary Materials.

will need robust transformations that can easily adjust to the electricity surplus, which is often generated by renewable energy sources. When integrated into these systems, incomplete electrolytic cells can be left switched on and can simply be operated with higher productivity if excess electricity is available.

MATERIALS AND METHODS
All reagents were used in analytical grades. Solvents were purified by standard methods (*29*). *N*-Methyl-*N*,*N*,*N*-tributylammonium methylsulfate (provided by BASF SE) was used as a supporting electrolyte. Electrochemical reactions were carried out at BDD electrodes. The BDD electrodes obtained were of Diachem quality and were from CONDIAS GmbH. BDD electrodes (15-μm diamond layer) were used on silicon as support.

Column chromatography
Column chromatography was performed on silica gel 60 M (0.040 to 0.063 mm; Macherey-Nagel GmbH & Co.), with a maximum pressure of 1.6 to 2.0 bar. A preparative chromatography system (Büchi Labortechnik GmbH) with a Büchi Control Unit C-620, a UV detector Büchi UV photometer C-635, a Büchi fraction collector C-660, and two C-605 pump modules was used to adjust the solvent mixtures. Mixtures of cyclohexane and ethyl acetate were used as eluents. Silica gel 60 M on aluminum sheets (F254, Merck Millipore) was used for thin-layer chromatography.

Gas chromatography
Gas chromatography was performed on a Shimadzu GC-2010 using a ZB-5 column (length, 30 m; inner diameter, 0.25 mm; film, 0.25 μm; carrier gas, hydrogen/air; Phenomenex). Gas chromatography–mass

spectrometry measurements were carried out on a Shimadzu GC-2010 (Shimadzu) using a ZB-5 column (length, 30 m; inner diameter, 0.25 mm; film, 0.25 μm; carrier gas, helium; Phenomenex). The chromatograph was coupled with a mass spectrometer (Shimadzu GCMS-QP2010).

Melting points

Melting points were determined with a melting point apparatus, SMP3 (Stuart Scientific) and were uncorrected. The heating rate was 2°C/min.

Spectroscopy and spectrometry

^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were recorded at 25°C using a Bruker Avance III HD 400 (400 MHz) [5-mm BBFO SmartProbe with a z gradient and ATM (automatic tune and match) and a SampleXpress 60-sample changer, Analytische Messtechnik]. Chemical shifts (δ) are reported in parts per million relative to traces in the corresponding deuterated solvent. Mass spectra were obtained by using a MAT 95 (Finnigan) apparatus that uses field desorption. Mass spectra and high-resolution mass spectra were obtained by using a QTof Ultima 3 (Waters) apparatus that uses ESI$^+$ (positive electrospray ionization).

General protocol for electrochemical cross-coupling reactions

A solution of phenolic component **A** (3.8 to 10.0 mmol), component **B** (5.00 to 11.4 mmol), and N-methyl-N,N,N-tributylammonium methylsulfate (0.77 g, 2.25 mmol) in 25 ml of HFIP or HFIP with 18% (v/v) methanol was transferred into an undivided beaker-type electrolysis cell equipped with a BDD anode and a BDD cathode. A constant current electrolysis was performed at 45° to 50°C (reported in the protocol for each product; for electrolysis performed with a current density of 75 and 100 mA/cm^2, the reaction temperature was controlled by a thermostat. After an application of 731°C (2 F per phenol **A**) in regard to the synthesis of biphenols and of 1462° to 1930°C (4 F per arene **B**) in regard to the synthesis of symmetric terphenyl-2,2″-diols, the electrolysis was stopped, and the solvent mixture was recovered in vacuo (50°C; 70 to 200 mbar). The crude coupling products were purified by short-path distillation and column chromatography (SiO$_2$ and ethyl acetate/cyclohexane).

Beaker-type glass cells were homemade by the local mechanical shop at the university. The undivided beaker-type cell is briefly described in the Supplementary Materials, whereas more details are reported in previous literature (30, 31). It was operated with BBD electrodes (0.2 × 2 × 7 cm; 15-μm diamond layer; a support of silicon was used).

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/3/10/eaao3920/DC1

Proposed mechanistic conversion in HFIP

Analytical data of products

NMR spectra

fig. S1. Picture of assembled electrolysis cell and individual parts.

fig. S2. Postulated mechanism for anodic phenol-phenol and phenol–phenolic silyl ether cross-coupling reaction.

fig. S3. Proposed mechanism for the electrochemical formation of m-terphenyl-2,2″-diols by anodic phenol-arene cross-coupling reactions.

table S1. Overview of used chemicals for performed electrolyses.

table S2. Results for anodic cross-coupling to S15 at a different current density.

table S3. Results for anodic cross-coupling to S19 at a different current density.

table S4. Results for anodic cross-coupling to S23 at a different current density.

table S5. Results for anodic cross-coupling to S24 at a different current density.

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