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Dehydrogenative Anodic C–C Coupling of Phenols Bearing Electron-Withdrawing Groups

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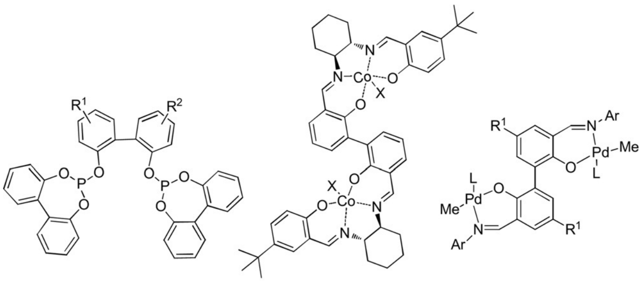
Abstract: *We herein present a metal-free, electrosynthetic method that enables the direct dehydrogenative coupling reactions of phenols carrying electron-withdrawing groups for the first time. The reactions are easy to conduct and scalable, as they are carried out in undivided cells and obviate the necessity for additional supporting electrolyte. As such, this conversion is efficient, practical, and thereby environmentally friendly, as production of waste is minimized. The method features a broad substrate scope, and a variety of functional groups are tolerated, providing easy access to precursors for novel polydentate ligands and even heterocycles such as dibenzofurans.*



1 2 3

Scheme 1. Important ligands for transition metal catalysis involving the 2,2′-biphenol motif.

2,2′-Biphenols are an important structural feature of a variety of ligands in transition metal catalysis.[1] Phosphite ligands **1** are used on the industrial scale in the hydroformylation process.[2] The biphenols carrying electron-withdrawing groups are excellent precursors for salen-type ligands **2**, which can be employed in various polymerization reactions, such as in the asymmetric copolymerization of CO$_2$ with *meso*-epoxides to give optically active polycarbonates, and in neutral nickel and palladium complexes **3** used as precatalysts for norbornene polymerization (Scheme 1).[3]

The dehydrogenative coupling plays an important role in modern organic chemistry, since it is a very efficient way to selectively form C–C bonds.[4] Therefore, numerous studies on the syntheses of biaryls have been reported, but the direct synthesis of 2,2′-biphenols exhibiting electron-withdrawing moieties in 3,3′-positions have been rarely reported. A very efficient copper-catalyzed reaction providing symmetrical and unsymmetrical 2,2′-BINOL derivatives in $>90\%$ *ee* in the presence of O$_2$ was developed by Kozlowski et al.[5] The protocol tolerates a variety of electron-withdrawing groups in position 3 and proceeds in good yields and high selectivity. However, the synthesis of cross-coupled naphthols proceeded with low selectivity. Furthermore, this method seems to be limited to naphthols as substrates. To the best of our knowledge, only substrates carrying electron-releasing groups or halogens have been successfully converted by electrochemistry so far.[6] Halo-2,2′-biphenols have been successfully synthesized via anodic oxidation of *o,o*′-dihalogenated phenols by the Nishiyama group.[7] The reaction was conducted at a very low current density and using undesirable LiClO$_4$ as an additional supporting electrolyte provided the coupled product in only 25 % yield (Scheme 2).

In previous work, our group was also able to access 3,3′-dihalo-2,2′-biphenols.[8] When trifluoroacetic acid in combination with methyltriethylammonium methylsulfate as the supporting electrolyte is used, 2-halophenols can be converted in high current efficiency when a high current density is applied. Noteworthy are the high yields of 76 % for the 3,3′-dibromo-2,2′-biphenol and 47 % for the 3,3′-dichloro-2,2′-biphenol. However, this methodology is still limited to substrates equipped with electron-releasing substituents. As a complementary method, the anodic C–C coupling of phenols with electron-withdrawing groups is presented here for the first time. This electrolytic conversion represents an efficient, metal-free route to symmetric 2,2′-biphenols having electron-withdrawing groups in good yields and high selectivity. Coupling these phenols with naphthalenes leads to polycyclic intermediates, which can be further oxidized to dibenzofurans or cleaved to access the desired cross-coupled

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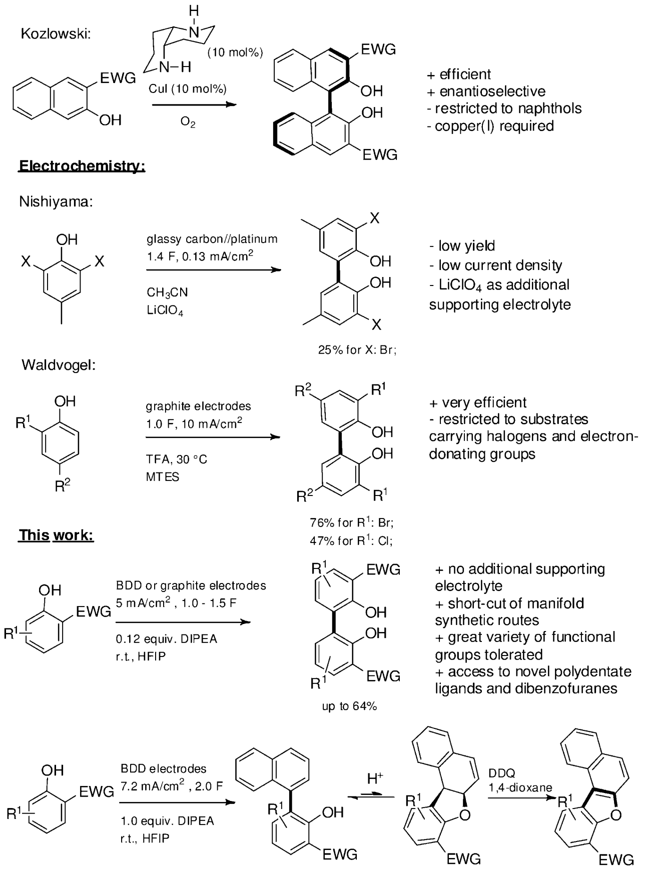


Scheme 2. Synthetic strategies to 2,2′-biphenols incorporating electron-withdrawing groups. EWG = electron-withdrawing group; TFA = trifluoroacetic acid; MTES = methyltriethylammonium methylsulfate; BDD = boron-doped diamond; DIPEA = diisopropylamine; HFIP = 1,1,1,3,3,3-hexafluoroisopropanol.

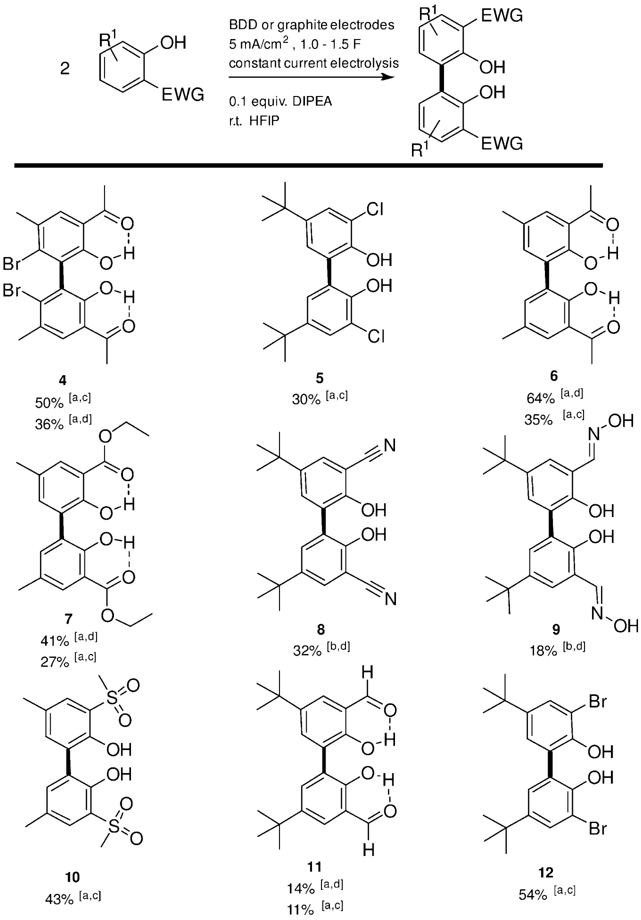
products. The use of base as an additive in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) obviates additional supporting electrolyte. The reactions are easy to conduct and scalable.

Electro-organic synthesis has become an important part of the synthetic organic toolkit which offers a number of advantages over conventional chemical processes. As well as facilitating novel routes to obtain desired structures, electro-organic synthesis is inherently safe and step-economical.[9] Reaction conditions are typically mild and importantly, electrons can be used as a sustainable reagent. Consequently, no reagent waste is produced. As a result, conventional chemical oxidizers and reducing agents can be replaced by electric current as an inexpensive, renewable, and safe alternative. Usually, electrochemistry is associated with oxidative or reductive transformations, but this mild method to generate radicals from the substrates allows a much broader and versatile scope of reactivity.[11] Moreover, such electrosyntheses may be performed discontinuously or on different power levels,[12] making it compatible with fluctuating renewable energy sources. In our work, the control of selectivity is achieved by HFIP. This solvent is capable of stabilizing reactive intermediates generated at the anode while being very electrochemically stable with a very broad potential window of 4.5 V.[13] Notably, this solvent can be easily recovered and reused. Aside from stabilization, HFIP can decouple nucleophilicity from oxidation potential.[14] For the anodic coupling, it was found that HFIP performed best in combination with boron-doped diamond (BDD) as the electrode material, but here inexpensive graphite serves just as well.

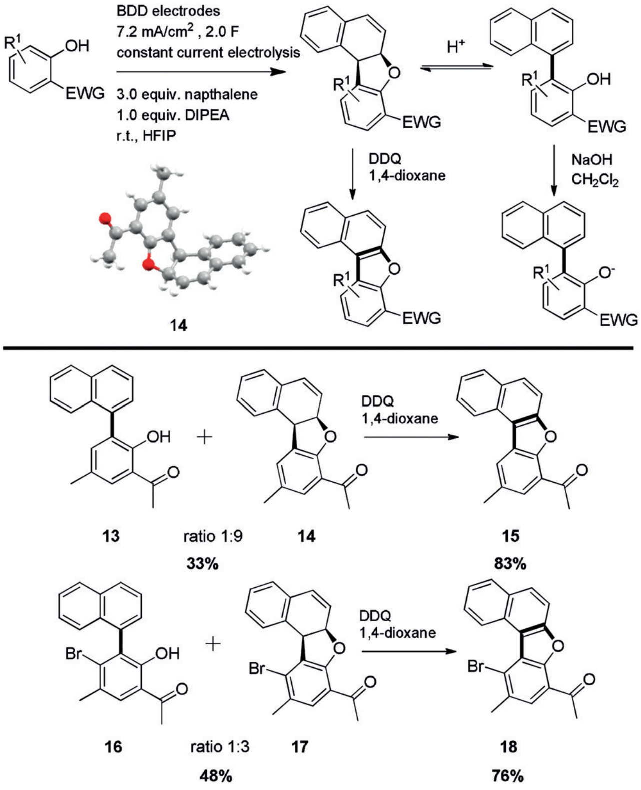
In order to achieve high selectivity in the homo-coupling reaction, the formation of HFIP benzylic ether had to be suppressed.[15] This was accomplished by using a low current density of 5 mA cm^{-2}. The greatest impact on the yield of this reaction was the concentration of starting material. The highest yield of **4** was obtained at a starting material concentration of 0.5 M. However, the solubility limit of the starting material was also reached at this concentration, preventing higher concentrations from being obtained. The minimum amount of diisopropylethylamine (DIPEA) required in this reaction to ensure sufficient conductivity is as low as 0.12 equivalents relative to the phenolic substrate. When other bases such as pyridine are used, O−C coupling becomes dominant and the yield drops dramatically. The applied charge can be as low as 1.0–1.5 F (per mole of phenol), resulting in high current efficiency; when higher charge was applied, over-oxidation and oligomerization took place. The preferred electrode material is BDD, but in some cases, graphite is superior. The low cost of graphite is beneficial for latter technical applications.[16] Additionally, when halogens are present (**4**, **5**, **12**), BDD is preferred as electrode material, because graphite can promote formation of the O−C coupled product (Scheme 3). Other solvents, such as acetonitrile, proved unsuccessful, as they lead to dehalogenation reactions and were not observed to facilitate any C−C or C−O coupling. For ketone (**6**) and ester (**7**) as functional groups, graphite lead to significantly higher yields up to 64%. Halogenated 2,2′-biphenols (**4**, **5**, **12**) can be synthesized yields up to 54%. Nitriles (**8**), oximes (**9**), and sulfones (**10**) are also tolerated, providing polydentate ligand precursors in a straightforward manner in yields up to 43%. Even an aldehyde (**11**) was tolerated to give the product in low yields; the electrode material was not found to play a significant role here. Notably, the very sterically hindered ketone (**4**) was accessible in a yield of 50%. The application of nitro groups yielded only a small amount of biphenol and phosphonates were not tolerated at all.

The bromo moiety of **4** is amenable to further derivatizations and X-ray analysis revealed an angle about the aryl–aryl axis of almost 90° (Scheme 5). Conjugation of the π-systems is no longer possible, which makes the product less prone to over-oxidation, as previously investigated by our group.[6c] Also, the product shows strong hydrogen bonds between the keto moiety and the phenolic proton.

In addition, access to cross-coupling employing phenols carrying electron-withdrawing groups was explored using our methodology. When 2-hydroxy-5-methylacetophenone and naphthalene were co-electrolyzed, a polycyclic structure **14** was obtained as the main product, instead of the expected cross-coupled derivative **13** (Scheme 4). The highest yields were obtained at a concentration of 0.1M and with an excess of naphthalene (3.0 equivalents). An applied charge of 2.0 F was sufficient and with BDD electrodes the best yields were



Scheme 3. Scope of the reaction. [a] Electrolysis was carried out in 5 mL HFIP with 2.5 mmol of substrate in an undivided cell and 0.12 equiv DIPEA. [b] Electrolysis was carried out in 5 mL HFIP with 1.0 mmol of substrate in an undivided cell and 0.3 equiv DIPEA. [c] Yield of isolated product obtained using BDD electrodes. [d] Yield of isolated product obtained using graphite electrodes.

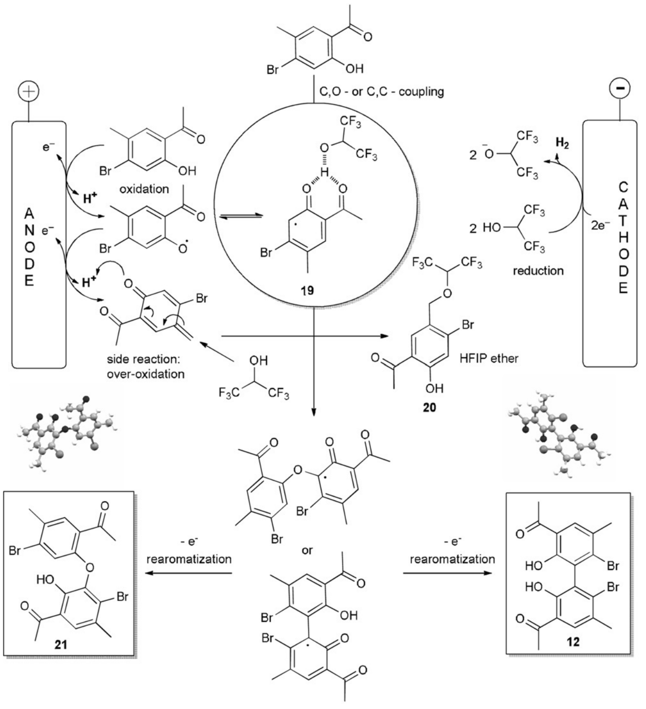


Scheme 4. Reaction pathway of the cross-coupling with naphthalene. Isolated yield are shown. Molecular structure of **14** in *cis*-configuration (*rac.*) determined by X-ray analysis is displayed.

obtained. Product **14** could only be selectively oxidized to the corresponding dibenzofuran **15** using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in 1,4-dioxane in 83% yield. Further application of current did not yield the desired **15**, contrary to our expectations. The same reaction pathway could be shown for 4-bromo-2-hydroxy-5-methylacetophenone, and gave an even higher overall yield, but a lower selectivity towards the polycyclic intermediate **17**. This mixture was then subjected to further oxidation with DDQ to furnish **18** in 76% yield. When the cyclic product **14** is treated with 1M HCl, a ring opening leading to formation of phenol **16** occurred. After work-up of the mixture, the polycyclic product **17** could again be observed in NMR, which indicates that these two isomers are in equilibrium. This represents an interesting, to our knowledge, previously unknown form of tautomerism. When treated with an excess of 1M NaOH, this equilibrium is completely shifted to the phenolate (Scheme 4). When aldehydes instead of ketones were employed, the yield dropped dramatically, due to over-oxidation (see the Supporting Information).

To demonstrate the scalability of our method, we synthesized compound **6** on a 66.6 mmol scale. The substrates carrying the carbonyl moiety showed not only the highest yield in the 5 mL beaker cells, but they also represent precursors for a variety of polydentate ligands, for example, salen-type ligands (**2**). In addition, these types of structures are used for the synthesis of several binuclear boron[17] and aluminum[18] complexes, for application in optoelectronic devices and as catalysts in polymerization reactions.[3,18] Therefore, a simple and scalable method for the synthesis of these structural motifs is of high interest. The synthesis routes to this structural motif are mostly complicated, multistep, and low-yielding: Compound **6** can be prepared starting from *p*-cresol in a five-step procedure in an overall yield of 1.1%, involving a iodination, *p*-tosyl protection, a reductive coupling using copper, and a Fries-type rearrangement.[19] The electrolysis was scaled up by a factor of 13.3 and was conducted in a 500 mL flask-type cell (Figure S2 in the Supporting Information). The achieved yield of 59% corresponds approximately to the yield in the 5 mL beaker-type cell (64%) and therefore clearly shows the scalability of this method.

Both the O,C- **21** and the C,C-coupled product **12** could be crystallized and their structures were determined by X-ray analysis (Scheme 5). HFIP ether **20** could be observed during the optimization (confirmed by GC-MS and NMR), which is in accordance with observations in our previous work.[15] We therefore propose that an oxidation step and a subsequent deprotonation leads to **19**. This intermediate can either be attacked by the nucleophilic oxygen or carbon, leading, after a further oxidation and subsequent rearomatization, to **21** or



Scheme 5. Proposed mechanisms for the C–C and O–C coupling of phenols carrying electron-withdrawing groups and the formation of HFIP ethers. Molecular structures of **21** and **12** determined by X-ray analysis are displayed.

to the desired product **12**. Further oxidation of **19** provides a quinone methide intermediate which is likely to be attacked by HFIP in a 1,6-addition, leading to **20**. This explains why a lower current density, as well as a higher concentration of phenol, leads to higher yields of desired 2,2′-biphenol. The radical can then be trapped immediately by phenol instead of being further oxidized or undergoing other side reactions. Also, the recombination of such two radicals seems to be a possible pathway to the desired product.

In conclusion, we have established a highly efficient and scalable method for the electrochemical dehydrogenative homo- and cross-coupling of a broad variety of phenols carrying electron-withdrawing groups in good yields. The resulting products represent precursors for polydentate ligands, which have great importance in transition metal catalysis. By electrosynthesis the route towards an important example could be shortened by three steps (when started from *p*-cresol) and the overall yield enhanced by a factor of 50. Cross-coupling reactions with naphthalenes deliver biaryls and precursors for dibenzofurans. The reactions are easy to conduct and no additional supporting electrolyte is needed, since a very low amount of base ensures sufficient conductivity, resulting in a high atom efficiency. In addition, the reaction proceeds with a high current efficiency.

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Conflict of interest

The authors declare no conflict of interest.

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