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Synthesis of *meta*-Terphenyl-2,2″-diols by Anodic C–C Cross-Coupling Reactions

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Abstract: *The anodic C–C cross-coupling reaction is a versatile synthetic approach to symmetric and non-symmetric biphenols and arylated phenols. We herein present a metal-free electrosynthetic method that provides access to symmetric and non-symmetric meta-terphenyl-2,2″-diols in good yields and high selectivity. Symmetric derivatives can be obtained by direct electrolysis in an undivided cell. The synthesis of non-symmetric meta-terphenyl-2,2″-diols required two electrochemical steps. The reactions are easy to conduct and scalable. The method also features a broad substrate scope, and a large variety of functional groups are tolerated. The target molecules may serve as [OCO]$^{3-}$ pincer ligands.*

Since the first report on the synthesis and application of pincer ligands in the late 1970s, the interest in these compounds has steadily increased.[1] In particular, their exceptional properties as ligands in molecular catalysis have been exploited.[2,3] Their tridentate coordination mode leads to unusally stable metal complexes,[2,3] and by involving the metal–carbon bond, metallacycles are generated that provide additional stabilization of the complex and allow for the use of harsh conditions for catalysis.[2,3] Furthermore, the high structural variability enables the distinct control of the properties at the metal center. OCO pincer ligands based on *meta*-terphenyl-2,2″-diols have been used in various complexes with different metal centers such as Cr,[4–6] Mo,[7,8] W,[9–11] Ti,[12,13] Zr,[13,14] Ta,[15] Sm,[16] and Yb.[17,18] These complexes have been used in various catalytic reactions, such as oxygen[4] and nitrogen[19] atom transfer reactions, acetylene[9,11] and olefine[20] polymerization, alkene isomerization,[21] nitrene[22] and carbene[23] transfer, O_2[5] and C–H activation,[24] disulfide reduction,[25] and aerobic oxidation.[6] They have also been employed for the synthesis of crown ethers[26] and in modern gas sensors,[3] molecular switches,[3] and photosensitization.[3] Unfortunately, in most cases for the cross-coupling reaction, expensive transition-metal catalysts and stoichiometric amounts of waste-generating leaving groups or oxidizers are required.[27,28] Recently, Kita and co-workers described an elegant synthesis of an *ortho,ortho*-diarylated phenol in an iodine(III)-catalyzed oxidative coupling.[29] A practical synthesis of biphenols was established by Kürti et al., which proceeded by mixed-acetal formation and a subsequent [3,3]-sigmatropic rearrangement upon initial oxidative formation of a quinone ketal.[30] An alternative efficient oxidative route to non-symmetric biphenols was described by Jeganmohan and co-workers.[31] More recently, Kita et al. also reported an iodine-catalyzed oxidative pathway for the coupling of phenols in the *para* positions.[32] In 2011, they had already developed a similar method for the synthesis of naphthalene–benzene biaryls in cross-coupling reactions.[33] To obtain *meta*-terphenyl-2,2″-diols, however, several classical coupling steps are necessary for the desired regioselectivity.[27] Despite considerable work, all of these systems require leaving groups and expensive catalytic systems. Furthermore, these methods only provide access to symmetric *meta*-terphenyl-2,2″-diols in total yields of up to 30%. The synthesis of non-symmetric *meta*-terphenyl-2,2″-diols using these pathways would be even more challenging. Therefore, a novel and innovative approach that provides more efficient access to these compounds is highly desired.

The arylation of phenols can also be conducted by anodic cross-coupling reactions.[34] However, the anodic conversion of phenols may lead to complex product mixtures.[35] Consequently, the electrolytic conversion has to be controlled.[36] Yoshida and co-workers have reported an elegant cation-pool method, wherein radical cations are generated and accumulated by electrolysis at low temperature,[37] which prevents the formation of the undesired homocoupling products. Finally, our group has developed a method that provides defined access to non-symmetric 2,2′-biphenols and phenol-substituted arenes in an anodic cross-coupling.[38,39] Electrochemical reactions can be easily scaled up,[40,41] and the transformations can be precisely controlled by switching the electric current on or off. Therefore, this method is inherently safe. The recovery and recycling of non-converted substrates and the electrolyte render the electrochemical C–C coupling reactions attractive in terms of ecological and economical considerations.[42,43]

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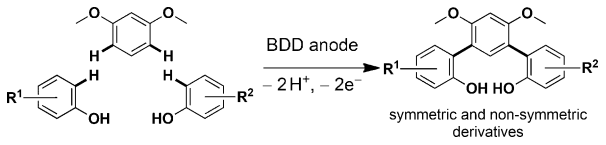
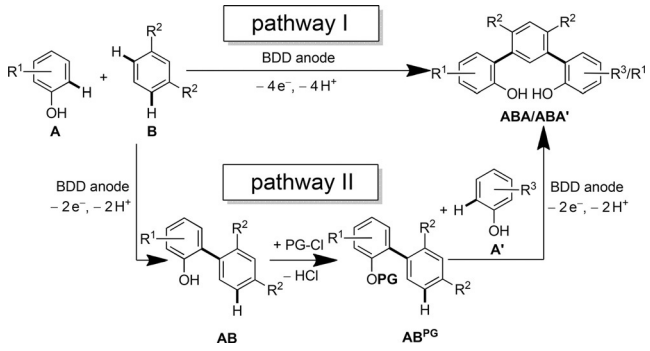
Herein, we report the first direct cross-coupling of symmetric and non-symmetric *meta*-terphenyl-2,2″-diols that does not require leaving groups or chemical oxidants. As shown in Scheme 1, these diols are accessible by the twofold anodic oxidation of two phenols and a single arene. For the anodic coupling, we used the powerful combination of boron-doped diamond (BDD) as the elecrode and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), which has already been used for anodic cross-coupling reactions of phenols and phenol-arenes.[38,39] HFIP has a stabilizing effect on the intermediate radicals; it also exhibits an extraordinary stability under electrolytic conditions,[44] and decouples nucleophilicity from oxidation potential.[45] Furthermore, it can be fully recovered by distillation.



Scheme 1. General electroorganic synthesis of *meta*-terphenyl-2,2″-diols.

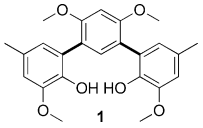
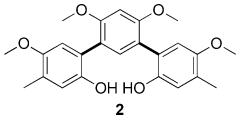
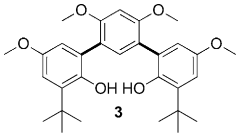
For the electrochemical synthesis of *meta*-terphenyl-2,2″-diols, two general pathways were developed (Scheme 2). Pathway I provides direct access to symmetric *meta*-terphenyl-2,2″-diols. Phenol **A** and arene **B** are coupled in a one-pot electroorganic process. Pathway II was developed for the synthesis of non-symmetric *meta*-terphenyl-2,2″-diols, wherein the phenol-substituted arene **AB** is initially synthesized by anodic cross-coupling and then isolated. Subsequently, a protecting group is installed to generate intermediate $\mathbf{AB^{PG}}$, which turned out to be essential for successful cross-coupling. Initial coupling experiments using unprotected **AB** only led to poor yields of up to 17%. We assume that the non-protected system underwent several side reactions, in particular over-oxidation. Upon installation of a suitable protecting group, these side reactions should be circumvented. When protected $\mathbf{AB^{PG}}$ is used for a second selective cross-coupling reaction with a different phenol (**A′**), the non-symmetric target molecule is obtained. To favor cross-coupling of the radical of **A′** with $\mathbf{AB^{PG}}$, 2.5 to 3.0 equivalents of $\mathbf{AB^{PG}}$ were used, which also reduced the formation of undesired side products and oligomerization products. A detailed mechanistic proposal can be found in the Supporting Information.



Scheme 2. Anodic pathways to symmetric and non-symmetric *meta*-terphenyl-2,2″-diols. PG = protecting group.

The symmetric *meta*-terphenyl-2,2″-diols that were thus synthesized are shown in Table 1. For the phenolic component, alkyl groups, such as methyl or *tert*-butyl, and electron-releasing groups, such as methoxy moieties, in the 2- and 4-position were found to be beneficial. We have thus developed a facile method to access these products by one-pot electrolysis with an option to recover the solvent and non-converted substrate. Compared to the conventional coupling pathway describe above,[27,28] which starts from the same simple phenols but requires the introduction of protecting and leaving groups and a mandatory methylation, this sequence offers a much more competitive way in terms of total yields, effort, and sustainability.

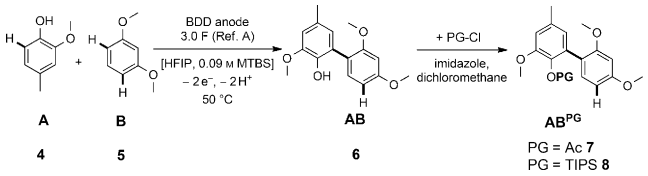
Table 1: Scope of symmetric *meta*-terphenyl-2,2″-diols.[a]

Entry	Product	Applied current	Yield[b]
1	 1	4.0 F	38%
2	 2	4.0 F	41%
3	 3	3.5 F	28%

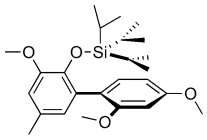
[a] Electrolysis conditions: 50 °C, constant current ($j = 2.8$ mA cm^{-2}), BDD anode, nickel-net cathode, undivided cell, solvent: 33 mL HFIP, 1.02 g methyltributylammonium methylsulfate. [b] Yields of isolated products.

For the synthesis of non-symmetric *meta*-terphenyl-2,2″-diols, a suitable phenol-arene component has to be made and isolated in satisfactory yield in a facile work-up process. Therefore, the anodic cross-coupling reaction of 4-methylguaiacol and 1,3-dimethoxybenzene was performed. Simple work-up by short-path distillation provided the desired compound in an acceptable yield of 29%. Non-converted starting materials and the solvent could be completely recovered. The electrolysis was run in a simple beaker-type cell with a stack of 10 BDD electrodes at constant current conditions (see Figure S3 in the Supporting Information).

Next, an appropriate protecting group had to be identified that tolerates the required electrochemical parameters and has sufficient electrolytic stability. Initial studies were performed with silyl ether protecting groups (Scheme 3). Fortunately, these substrates are accessible in almost quantitative yield under standard conditions and show sufficient stability at the anode during electrolysis.[46] In line with our experience with the synthesis of non-symmetric biphenols, the best results were obtained with triisopropylsilyl (TIPS) as the



Scheme 3. Synthesis of phenol-arene **6** and subsequent protection.



Scheme 4. Protected phenol-arene with a bulky TIPS group.

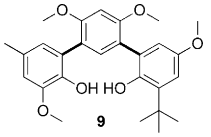
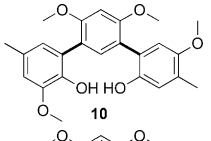
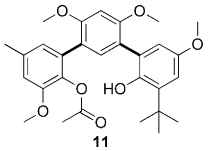
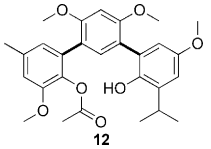
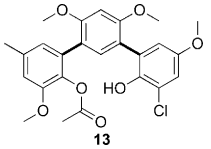
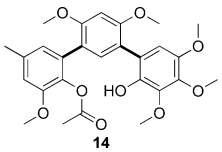
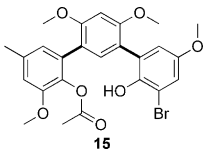
protecting group as it is relatively bulky and serves as an apolar and twist-inducing structural feature (Scheme 4).[47] Thereby, the two π-systems are not in conjugation.

Therefore, the aryl moiety acts as an electron-withdrawing group that does not generate an extended π-system.[48] Furthermore, the electron-rich methoxy groups on both aryl moieties are strongly solvated by HFIP, which is intensified by the hydrophobic nature of the TIPS group. This solvent effect reduces the nucleophilicity of the substrate, and strong electrophiles are thus required.

To quickly establish electrolysis conditions and suitable coupling partners, we performed several screening experiments.[49] As the desired cross-coupling products could be readily identified by GC-MS, the test reactions were performed on preparative scale. All reactions were carried out in an undivided cell equipped with a BDD anode and a nickel cathode (see Figure S1). HFIP was used as the electrolyte with 0.09 M methyltributylammonium methylsulfate (MTBS) as a supporting electrolyte.

The two pincer ligands **9** and **10** were obtained when TIPS-protected **8** was used as the coupling partner. We were surprised that the TIPS group is not removed from the phenol-arene starting material whereas it is fully cleaved as soon as the electrochemical synthesis of the *meta*-terphenyl-2,2″-diol is completed. When the synthesis of **10** was performed without a protecting group at the phenol-arene, the yield was only 17%. Upon installation of the TIPS group, the yield increased by 250%, and **10** was isolated in 43% yield. As the TIPS moiety is considered to be a rather unsustainable and more expensive protecting group, we screened for other suitable protecting groups. It turned out that the installation of an acetyl ester also led to very promising results. The *meta*-terphenyl-2,2″-diols **11**, **12**, **13**, **14**, and **15** were thus synthesized with the acetyl-protected phenol-arene system. Compared to the direct electrochemical cross-coupling of non-protected or TIPS-protected phenol-arenes, the coupling products were obtained in significantly higher yields under the same electrolysis conditions (Table 2). For comparison, when product **9** was synthesized by using the TIPS group, it was formed in 40% yield. With the acetyl protecting group, however, we achieved a further increase in yield of 25% by using inexpensive acetyl chloride. Whereas **8** was used in an excess of 3.0 equivalents, products **11**, **12**, **13**, **14**, and **15** were synthesized by using a reduced amount of 2.5 equivalents of **7**. No decreases in yields were observed.

Table 2: Scope of non-symmetric *meta*-terphenyl-2,2″-diols.[a]

Entry	Cond.[b]	Product	Yield[c]
1	I	 **9**	40%
2	I	 **10**	43%
3	II	 **11**	65%
4	II	 **12**	63%
5	II	 **13**	21%
6	II	 **14**	84%
7	II	 **15**	16%

[a] Electrolysis conditions: 50 °C, constant current ($j = 2.8$ mA cm^{-2}), BDD anode, nickel-net cathode, undivided cell, solvent: 33 mL HFIP, 1.02 g methyltributylammonium methylsulfate. [b] $Q = z n$ F, PG; I: 2.0 F (**A**), **AB**^{TIPS}, 3.0 equiv; II: 2.2 F (**A**), **AB**^{Ac}, 2.5 equiv. [c] Yields of isolated products.

Furthermore, the applied electric current was optimized from 2.0 F to 2.2 F.

The highest yield of 84% was obtained for the coupling of 2,3,4-trimethoxyphenol. In analogy to the synthesis of symmetric *meta*-terphenyl-2,2″-diols, phenols with alkyl or electron-releasing groups in the 2- and 4-position turned out to be particularly suitable couplings partners. *tert*-Butyl moieties, which play a decisive role for later catalytic applications, were also tolerated. The coupling of phenols with chloro or bromo substituents in the 2-position was also possible, but gave the corresponding products in lower yields. Bromo substituents, in particular, allow for subsequent transformations by classical organic coupling reactions. The significantly improved yields achieved upon using the acetyl-protected intermediate can be rationalized by the oxidation potential of involved components (see the Supporting Information). According to our postulated mechanism, phenol oxidation has to occur

first, which is then followed by nucleophilic attack by the phenol-arene derivative. Cyclovoltammetric measurements indicate that the oxidation potential of the phenol-arene system is very similar to or slightly lower than the oxidation potential of commonly used phenols. Upon installation of the acetyl group, the oxidation potential is significantly increased, and the phenolic component is preferentially oxidized.

In conclusion, we have developed an innovative method for the synthesis of *meta*-terphenyl-2,2″-diols by electrochemical C–C cross-coupling. By using differently substituted phenols, compounds with great structural diversity were obtained. High yields were achieved through the use of protecting groups, which lead to a twisting of the biaryl intermediate or an increase in the oxidation potential. Symmetric products are accessible by facile one-pot-electrolysis in good yields, whereas the non-symmetric ligands could be obtained in a two-step coupling sequence. The possibility to recycle solvent and unconverted reactants renders this method highly innovative and sustainable so that this electrochemical method fulfils the conditions for "green chemistry".

Acknowledgments

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Keywords: C–C coupling · electrochemistry · *meta*-terphenyl compounds · pincer ligands · protecting groups

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