Selective Formation of 4,4′-Biphenols by Anodic Dehydrogenative Cross- and Homo-Coupling Reaction


Abstract: A simple and selective electrochemical synthesis by dehydrogenative coupling of unprotected 2,6- or 2,5-substituted phenols to the desired 4,4′-biphenols is reported. Using electricity as the oxidizing reagent avoids pre-functionalization of the starting materials, since a selective activation of the substrates takes place. Without the necessity for metal-catalysts or the use of stoichiometric reagents it is an economic and environmentally friendly transformation. The elaborated electrochemical protocol leads to a broad variety of the desired 4,4′-biphenols in a very simplified manner compared to classical approaches. This is particular the case for the cross-coupled products.

The selective formation of a carbon–carbon bond is an important issue for contemporary organic chemistry. Numerous and often complex scaffolds can be accessed using such transformations.

In particular, asymmetric biaryls show interesting structural features, since they give access to products of great value in pharmaceutical or material science, biochemistry or in the application as precursors for ligands. In particular, para-linked biphenols show interesting properties as anti-oxidants or building blocks for small molecule protein–protein interaction (PPI) inhibitors (Figure 1).

Hamilton and co-workers demonstrated that a trisubstituted linear teraryl, as displayed in Figure 1 (right side), is a potential and hydrolytically stable α-helix mimic.

The orange dots in Figure 1 are indicating amino acid side chains of the helical structure through two turns. The substituents of the linear teraryl are in sufficient accordance in angle and distance to these amino acid side chains to successfully mimic the α-helix. Further, these linear teraryls are more stable regarding to conformational and proteolytic stability than peptide based drugs.

We could show that such teraryl peptide mimetics can be assembled in a modular way using aryltriflates via Pd-catalyzed cross-coupling reactions. For the extension of our program of synthesizing α-helix mimetics to quateraryls featuring four amino acid residues, we required suitable substituted 4,4′-biphenols as building blocks for core fragments. Upon triflation, these structure motifs could be connected with pyridine boronic acids via Pd-catalyzed cross-coupling reactions.

However, classical approaches for the synthesis of 4,4′-biphenols precursors are quite tedious. Using a transition-metal-catalyzed synthetic pathway requires pre-functionalization of the starting materials as well as inert conditions, since the used substrates are often sensitive to water or air.

The functionalization of the starting materials can include the transformation to boronic esters or the installation of halo substituents as well as organometallic moieties. This leads to a limited tolerance of various functional groups. Another approach is the direct C–H activation by the means of chemical oxidizers to create the desired aryl C–C bond (Scheme 1). Recently, Kita and co-workers reported an organo-iodine(III)-catalyzed pathway to access the desired cross-coupling products. Unfortunately, this method is very tedious and needs Oxone™ as a terminal oxidant. Furthermore, the reported scope for 4,4′-biphenols in that work was rather limited. An alternative synthetic approach was published by Pappo and co-workers. To access the para-biphenols a meso-tetrathenylporphyrin iron chloride catalyst and peroxides as the stoichiometric oxidant was employed. Using peroxides as reagent is involving potential safety risks at least on technical-scale operations. Moreover,
these strategies create additional waste which has to be disposed upon synthesis. Hence, it is desirable to establish an easy and flexible protocol to access the desired 4,4′-biphenols (Scheme 1, bottom).

It was previously shown by Waldvogel and co-workers, that several aromatic compounds can be synthesized utilizing electricity to form the desired carbon–carbon bond by dehydrogenative coupling. Furthermore, the electrochemical approach represents a remarkably simple, inherently safe and sustainable method to form the desired aryl–aryl C/C bond, since the coupling reaction is essentially reagent- and metal-free.

Here, we present a simple protocol for the anodic dehydrogenative coupling reaction of 2,5- or 2,6-substituted phenols to access a broad variety of the desired 4,4′-biphenols (Schemes 2 and 3). In Scheme 2, the product range of the selective anodic cross-coupling between 2,5- or 2,6-substituted phenols in isolated yields up to 77% is displayed. To enable the selective cross-coupling reaction to the desired 4,4′-biphenols, over-oxidation as well as homo-coupling has to be prevented. It is well known, that the para-connected structure motifs are likely to be over-oxidized to the corresponding diphenoquinones. Since the reaction is carried out in an undivided cell, it should be taken into account that an undesired formation of a redox shuttle may occur since the diphenoquinone can be effectively reduced at the cathode. Additionally, this redox-system most likely promotes further side reactions such as oligo- or polymerization, as the final product is not sufficiently stable. Thus, the electric current is consumed in a non-productive process and limits the yields. A promising strategy to prevent this pathway is to force a twist along the newly formed carbon–carbon bond. Therefore, a planar arrangement of the aromatic rings, which is necessary to form the corresponding diphenoquinone, is not possible anymore. A suitable approach is the use of a 2,5-disubstituted phenol as coupling component. A sterically demanding moiety in position 5 of the corresponding phenol is likely to push the system out-of-plane so as to reduce steric tension along the newly formed carbon–carbon bond and therefore prevents over-oxidation. Evidence of the molecular structures is given by X-ray analysis of the non-symmetric cross-coupling products 11 and 15 (Figure 2, more details in Supporting Information). For 15, exhibiting a methyl group in position 5, the torsion angle is

Figure 2. Single crystal X-ray analysis of 15 (on the left) and 11 (on the right). The torsion angle for molecule 11 amounts to –33° that of molecule 15 to –88°. Hydrogen atoms were omitted for clarity.
licity from the oxidation potential by means of different solvolytic media.

Phenol is used as a coupling partner. Therefore, over-oxidation can be avoided if a 2,5-substituted phenol is used as a coupling partner.

1,1,1,3,3,3-Hexafluoro propane-2-ol (HFIP) is the solvent of choice. Due to the unique ability of decoupling the nucleophilicity from the oxidation potential by means of different solvation of the substrates the fluorinated alcohol has the ability to promote the desired cross-coupling reaction.\(^{[1,2,4]}\) Furthermore, due to its high dielectric constant and low nucleophilicity, HFIP is able to stabilize the reactive intermediates created at the anode and therefore, reduces undesired side reactions.\(^{[1,2,4]}\)

This is underlined by gas chromatographic analysis of the crude reaction mixtures, wherein no or only traces of the AA homo-coupling products are detected. With these conditions in hand, we were able to electrochemically synthesize a broad variety of non-symmetrical 4,4'-biphenols (Scheme 2). The electrolyses were carried out at constant current in a simple undivided beaker-type cell equipped with planar boron-doped diamond electrodes.\(^{[23]}\) The highest yield of 77\% was obtained by using the electron rich 2,6-dimethoxyphenol as component A and 2-methyl-5-(1-methylethyl)phenol as component B (Scheme 2, 10). This underlines that a sterically demanding substituent in position 5 is able to prevent over-oxidation to the corresponding diphenoquinone and therefore increases the yield of the desired 4,4'-biphenol. When switching the isopropyl substituent in position 5 to a methyl group, three more derivatives in good yields up to 62\% are accessible (Scheme 2, molecules 11–13). Installing a fluoro group in position 5, there is a drop in yield and the desired cross-coupling product 16 was isolated in only 10\% yield. A rationale for this might be, that due to the fluoro group the nucleophilicity of the phenol is lowered and therefore the conversion is hindered. This is in accordance with our anticipated mechanism for anodic cross-coupling reactions, as the B component is acting as the nucleophile (more details in the Supporting Information).\(^{[1,2,4]}\)

Furthermore, the fluoro substituent is less sterically demanding (\(\tau_{\text{w}} = 147\) pm) as a methyl moiety (\(\tau_{\text{w}} = 200\) pm). This means over-oxidation and therefore side-reactions are more likely to occur. Additionally, the scope of the cross-coupling reaction was expanded by two derivatives 14 and 15 in isolated yields of 34 and 32\%, respectively. Furthermore, we present a simple electrochemical protocol for the dehydrogenative coupling reaction of 2,6- or 2,5-substituted phenols to the corresponding homo-coupling products. The desired products can be isolated in yields up to 60\% (Scheme 3). For the homo-coupling it was useful to use HFIP/H\(_2\)O mixtures to increase the yield since the formed products are likely to be less soluble in these mixtures than the corresponding starting materials. This is underlined by 19 and 20, where product precipitation during electrolysis was observed. Promotion of the yields in the anodic generation of electron rich products by precipitation was successfully exploited.\(^{[26]}\) Hence, the formed product is unlikely to be oxidized and therefore unwanted side-reactions are minimized resulting in higher yields. Using different 2,5-substituted phenols as the starting materials leads to the products 22 and 23 in isolated yield 35 and 14\%, respectively. A possible explanation for the lower yields is that the two substituents in position 5 are creating considerable steric tension around the newly formed carbon–carbon bond. Hence, the coupling reaction is less efficient. This is underlined by comparing the isolated yields of 22 and 23. The less sterically demanding fluoro moiety is resulting in a higher yield in contrast to the chloro substituent.

In conclusion, we present a very simple and highly selective electrochemical protocol for the anodic dehydrogenative coupling of 2,5- and 2,6-substituted phenols. This synthetic strategy gives access to a broad range of non-symmetric as well as symmetric 4,4'-biphenols at mild reaction conditions. These products are of great value as antioxidants\(^{[27]}\) or precursors for small molecule protein–protein interaction (PPI) inhibitors.\(^{[30]}\) To successfully prevent over-oxidation and therefore side reactions in case of the dehydrogenative cross-coupling reactions the use of HFIP and 2,5-substituted phenols are a suitable and efficient strategy, resulting in yields up to 77\%. Concerning the dehydrogenative homo-coupling protocol, HFIP/H\(_2\)O mixtures were the key to access the desired symmetrical products in yields up to 60\%. Furthermore, the use of electricity as a reagent is a contribution to the idea of green chemistry since the need for oxidizers or expensive and toxic transition-metal catalysts is avoided.
Experimental Section

The detailed description of electrolytic conversions, the products and their characterization are provided within the Supporting Information.

Acknowledgements

S.R.W. appreciates the financial support by the DFG (Wa 2712/1). R.B. thanks the Austrian Science Fund (FWF) for financial support (Project I-2712).

Conflict of interest

The authors declare no conflict of interest.

Keywords: anode  €• C-H activation  €• cross-coupling  €• dehydrogenation  €• electrochemistry


Manuscript received: November 18, 2018
Revised manuscript received: December 17, 2018
Version of record online: 0000

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Driven by electricity: This work presents an elegant method to synthesize desired 4,4′-biphenols in an oxidative coupling reaction using electrochemical methods. The desired products can be obtained in yields up to 77% without the need for leaving groups or expensive transition-metal catalysts.