2,2′-Biphenols **Very Important Paper**

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Selective Synthesis of Partially Protected Nonsymmetric Biphenols by Reagent- and Metal-Free Anodic Cross-Coupling Reaction

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Abstract: *The oxidative cross-coupling of aromatic substrates without the necessity of leaving groups or catalysts is described. The selective formation of partially protected nonsymmetric 2,2′-biphenols via electroorganic synthesis was accomplished with a high yield of isolated product. Since electric current is employed as the terminal oxidant, the reaction is reagent-free; no reagent waste is generated as only electrons are involved. The reaction is conducted in an undivided cell, and is suitable for scale-up and inherently safe. The implementation of O-silyl-protected phenols in this transformation results in both significantly enhanced yields and higher selectivity for the desired nonsymmetric 2,2′-biphenols. The use of a bulky silyl group to block one hydroxyl moiety makes the final product less prone to oxidation. Furthermore, the partially silyl-protected 2,2′-biphenols are versatile building blocks that usually require tedious or low-yielding synthetic pathways. Additionally, this strategy facilitates a large variety of new substrate combinations for oxidative cross-coupling reactions.*

Selective formation of carbon–carbon bonds between two distinct substrates is of high interest in modern organic chemistry.[1] This transformation is exploited for the construction of complex carbon architectures. Therefore, C–C cross-coupling reactions are essential chemical transformations in a large variety of disciplines like biochemistry[2,3] and materials[4] and pharmaceutical sciences.[5,6] In particular, nonsymmetric 2,2′-biphenols have exceptional properties as building blocks for ligands in molecular catalysis,[7] bioactive materials,[3] and natural products.[5] Accordingly, an efficient and selective route to these structural entities attracts considerable attention within the chemical community.[8,9] Classically, nonsymmetric 2,2′-biphenols are prepared via transition-metal-catalyzed coupling reactions.[8,10] Following this strategy, the substrates are activated by introduction of specific leaving groups and this requires much effort and often harsh reaction conditions. The leaving-group chemistry along with complex and costly catalysts (e.g. palladium based) generate a large amount of toxic waste in this approach. Therefore, oxidative coupling reactions by direct C–H activation are of high current interest for sustainable processes.[11–15] This approach has been addressed by a variety of efficient protocols.[12,16] For instance, single or twofold C–H bond activation can be carried out in the presence of directing groups by transition-metal catalysis.[16,17] The indirect (two-step) oxidative cross-coupling can be achieved by prior oxidation of one coupling partner, which is separated in time and space from the coupling event. For mixed 2,2′-biphenols, initially quinone monoacetals are fashioned which are subsequently coupled with the other partner in a second step.[18] An elegant electroorganic alternative is described by the cation pool method established by Yoshida et al. to prevent undesired homocoupling products.[13] The best direct oxidative cross-coupling of aryls is achievable in stabilizing media like 1,1,1,3,3,3-hexafluoroisopropanol (HFIP).[19] The role of this specific solvent and source of selectivity can be attributed to the strongly different solvation of the individual coupling partners and therefore the decoupling of oxidation potential from nucleophilicity.[20] Solvents with a similar performance require a strong hydrogen-bonding capability, for example, formic acid.[11,21] However, the oxidative stability of HFIP is unique. The oxidative generation of phenoxyl radicals can be effected using, for example, hypervalent iodine reagents,[22] iron-catalyzed decomposition of peroxides,[14] and direct electrolysis.[11,20,23] However, because of safety issues only the latter method is considered for technical scale-up since the process can be easily controlled by switching off the electricity. The generation of reactive intermediates by electrolysis is extremely attractive as it displays excellent atom economy and cost efficiency.[24] However, simple phenols tend to form complex and diverse mixtures upon anodic treatment.[25] Recently, we developed a selective method for the C–C cross-coupling of nonprotected phenols to form 2,2′-biphenols by anodic oxidation in undivided cells using HFIP.[11]

The further chemo- and regioselective transformation of 2,2′-biphenols to nonsymmetric structures, for example, as ligands for catalysis or as inhibitors for protein–protein interactions, is a challenging task, as the two hydroxyl groups react similarly.[26] This issue can be circumvented by blocking a single hydroxyl moiety with an easily removable protecting group (Figure 1). The blocking of one hydroxyl group of nonsymmetric 2,2′-biphenols by standard chemical methods is achieved either by applying minimum amounts of protecting reagent or by partial deprotection of completely

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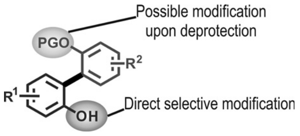
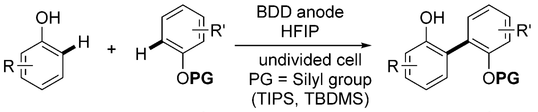


Figure 1. Concept for the selective modification of hydroxyl groups by partial protection of nonsymmetric biphenols.

protected biphenols. This strategy leads to complex product mixtures, requiring tedious workup and resulting in low yields of the desired product.[27] Consequently, a novel powerful and atom-efficient method to such entities is highly desired.

Here, we report the first direct and selective synthesis of partially silyl-protected nonsymmetric biphenols by oxidative cross-coupling. For the direct synthesis of partially protected nonsymmetric biphenols, we electrolyzed an unprotected phenol **A** in the presence of a protected phenol **B** (Scheme 1).



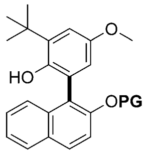
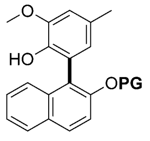
A **B^{PG}** **AB^{PG}**

Scheme 1. General reaction pathway for the anodic synthesis of partially protected nonsymmetric biphenols. PG: protecting group.

Typically, substrate **A** exhibits a lower oxidation potential and is preferentially oxidized at the anode. To statistically favor the cross-coupling sequence starting with **A** over the undesired homocoupling, component **B** is used in a two- to threefold excess. Stabilization of reactive radical intermediates is crucial to avoid uncontrolled mineralization and oligomerization. The unique properties of HFIP and the beneficial effect of protic additives like water and methanol on yield and selectivity was recently described.[11,20,28]

Decisive for the successful synthesis of the desired target is the stability of the respective protecting groups under electrolysis conditions. In addition, the protecting group should have minimal influence on the electronic properties of the corresponding phenol. Only alkyl or silyl moieties will fulfill those requirements. The facile removal of silyl groups prompted us to employ them. Protection of phenols as silyl ethers is a common method. The substrates can be easily prepared in almost quantitative yield from the respective phenols by standard methods.[29] Initial electroorganic screening[30] indicated that trimethylsilyl (TMS) ethers are not stable under electrolysis conditions and only unprotected nonsymmetric biphenols were obtained. However, the bulkier silyl moieties such triisopropylsilyl (TIPS) and dimethyl-*tert*-butylsilyl (TBDMS) exhibit sufficient stability and gave access to the desired partially protected cross-coupling products. However, when the screening hits for the anodic cross-coupling reaction were transferred to a preparatory-scale electrolysis in order to obtain reliable data regarding yield and utility of the methodology, it turned out that phenolic TBDMS ethers give inferior results (Table 1). In general, under identical electrolysis conditions, phenols protected with triisopropylsilyl moiety provide substantially higher yields and this particular protecting group is not lost within the course of electrolysis.

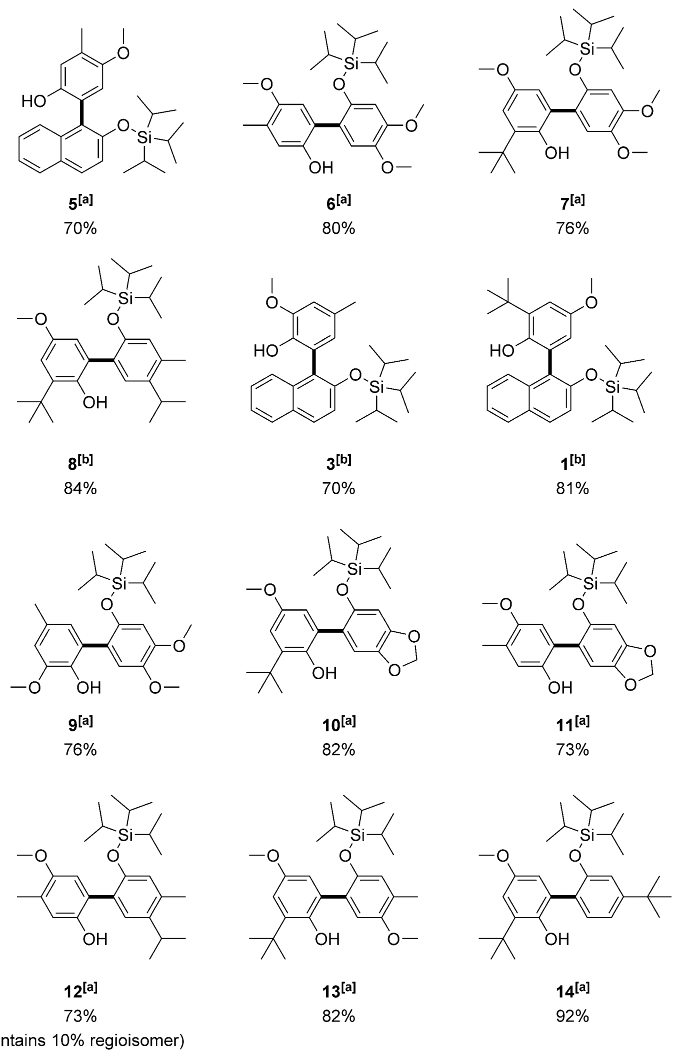
Table 1: Effect of the silyl group on the anodic cross-coupling of phenols on a preparatory scale.

Entry	Product		Yield[c]
1		**1**[b] **2**[a]	81 % (PG = TIPS) 44 % (PG = TBDMS)
2		**3**[a] **4**[b]	70 % (PG = TIPS) 51 % (PG = TBDMS)

[a] Electrolysis conditions: 50 °C, constant current ($j = 2.8\ \mathrm{mA\,cm^{-2}}$), BDD anode, BDD cathode, undivided beaker-type cell, $Q = 2$ F (phenol **A**), supporting electrolyte: 0.09 M $[Bu_3NMe]O_3SOMe$, ratio **A**/**B**^{PG} = 1:3. Homocoupling products were not detected by GC.
[b] Electrolysis conditions: 50 °C, constant current ($j = 2.8\ \mathrm{mA\,cm^{-2}}$), BDD anode, nickel net cathode, undivided L-type cell, $Q = 2$ F (phenol **A**), supporting electrolyte: 0.09 M $[Bu_3NMe]O_3SOMe$. Homocoupling products were not detected by GC. [c] Yield of isolated product.

Anodic cross-coupling reactions of substrates without protecting groups under the same electrolysis conditions were evaluated in earlier studies for the substrate combinations in Table 1.[11] The yields obtained for the TIPS ethers are distinctly higher than in the reaction of the same unprotected substrates. Application of aromatic TIPS ethers has a remarkably positive effect on the performance of electrochemical cross-coupling. The yields achieved for the desired cross-coupling products are exceptionally high. Compared to the yields of the direct electrochemical cross-coupling of unprotected phenols[11] and phenol–arene cross-coupling,[28] the yields of the displayed coupling products (Scheme 2) are significantly higher under identical electrolysis conditions. The rationale for the improved yields is a combination of two complementary effects: The installation of a bulky silyl group on component **B** leads to a strong twist of the biaryl axis. The attractive intramolecular hydrogen bonding between the hydroxyl group and the silyl ether limits the torsion angle to approximately 53° such that the two π-systems are not in conjugation (Figure 2). Consequently, the aryl moiety serves as an electron-withdrawing group generating a less extended π-system in the final product which is therefore less prone to over-oxidation.[31]

In addition, both aryl moieties are still electron rich and experience a strong solvation by HFIP. Therefore, these molecular entities exhibit a strongly reduced nucleophilicity, preventing participation in subsequent dehydrogenative couplings. The outstanding lipophilic characteristics of the TIPS group enhance this solvent effect. This beneficial and unique solvent effect of HFIP should broaden the scope of the anodic cross-coupling reaction and will make novel 2,2′-biphenols accessible. Extremely electron-rich phenols, such as 3,4-dimethoxyphenol and 5-hydroxybenzo-1,3-dioxol, were pre-



Scheme 2. Range of partially protected nonsymmetric biphenols with yields of isolated product. [a] Electrolysis conditions: 50 °C, constant current ($j=2.8$ mA cm^{-2}), BDD anode, BDD cathode, undivided beaker-type cell, $Q=2$ F (phenol **A**), supporting electrolyte: 0.09 M [Bu_3NMe]O_3SOMe, ratio **A**/**B**$^{PG}=1{:}3$. Homocoupling products were not detected by GC. [b] Electrolysis conditions: 50 °C, constant current ($j=2.8$ mA cm^{-2}), BDD anode, nickel net cathode, undivided L-type cell, $Q=2$ F (phenol **A**), supporting electrolyte: 0.09 M [Bu_3NMe]O_3SOMe, ratio **A**/**B**$^{PG}=1{:}3$. Homocoupling products were not detected by GC.

viously very challenging substrates for the electrochemical cross-coupling reaction. Because of their high nucleophilicity, these substrates tend to undergo homocoupling reactions or uncontrolled polymerisation upon electrolysis (Table 2). Only for entry 2 (Table 2) was the cross-coupling product found in trace amounts by GC analysis.

These problems can be circumvented and the scope significantly extended by installation of a TIPS group. Due to solvent effects in HFIP, the silyl ethers are not easily oxidized at the anode. Therefore, these molecules can serve as component **B** and do not undergo homocoupling or electrodegradation.

The residual nucleophilicity is exploited for the nucleophilic attack of protected **B** substrates to form cross-coupling products. Cross-coupling of phenols with TIPS-modified components provided the desired nonsymmetric 2,2′-biphenols in high yields and exclusive selectivity (Scheme 2, substrates **6**, **7**, **9**–**11**). Only for substrate **10** (Scheme 2) were traces of the homocoupling product **BB** observed (3 % by GC analysis). All isolated products were completely characterized and structures were verified by X-ray analysis of suitable single crystals (Supporting Information (SI)).

The electrochemical reaction is very easy to conduct since only a very simple two-electrode arrangement in a beaker-type cell is necessary. In addition, it is performed in a constant current mode, which simplifies the equipment requirements tremendously. In order to test the utility and robust nature of this electroorganic method, we scaled up the reaction of **8** from a 25 mL beaker-type electrolysis cell (using 3.78 mmol **A** and 11.35 mmol **B**) to a 200 mL beaker-type electrolysis cell (30.28 mmol **A** and 60.56 mmol **B**) (Figure 3). This corresponds to a scale-up factor of 8, and also improves the **A**/**B** ratio from 1:3 to 1:2. Application of the same electrolysis protocol gives **8** in the same 84 % yield (12.5 g). Also in this electrochemical conversion, no further side products were detected by gas chromatography.

In conclusion, we established a novel and very efficient strategy to generate partially protected 2,2′-biphenols by the use of a bulky silyl group on one coupling component. The key to the high yield and outstanding selectivity of this process is the twisted biaryl product and solvent effect of HFIP which controls the nucleophilicity of the coupling partner. The use of electric current leads to a metal- and reagent-free conversion that is outstandingly sustainable. The elaborated protocol is very simple to perform since an undivided cell and a two-electrode arrangement is employed. The robust nature of this electrochemical conversion is demonstrated by a simple scale-up to the 30 mmol range. These elaborated substrate combinations might serve as starting materials also for other dehydrogenative cross-coupling reactions based on conventional oxidizers. In addition, this strategy of influencing the oxidation potential of substrates by solvent effects and conformational control seem to be a more general concept and will be studied further.

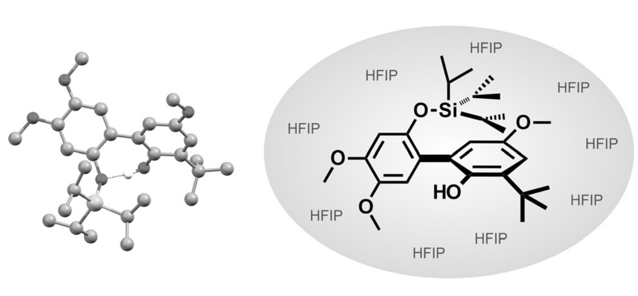
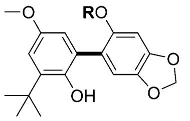
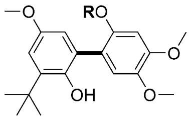
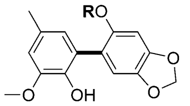
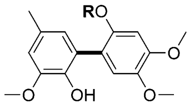


Figure 2. Left: Molecular structure of **7** displaying the twist of the partially protected biphenol due to the bulky TIPS group. Hydrogen bonding is indicated by the dotted line. The data for conformation are obtained from an X-ray analysis (see SI). Right: Solvation of biphenol by HFIP is represented by the sphere.

Table 2: Influence of TIPS group on the anodic cross-coupling of phenols.

Entry[a]	Product	Amount of coupling product by GC analysis[b]
1	 **10**	39% (R = TIPS) – (R = H)
2	 **7**	37% (R = TIPS) 13% (R = H)
3		26% (R = TIPS) – (R = H)
4	 **9**	30% (R = TIPS) – (R = H)

[a] Electrolysis conditions: 50 °C, constant current ($j = 2.8$ mA cm^{-2}), BDD anode, BDD cathode, undivided beaker-type screening cell, $Q = 2$ F (phenol **A**), supporting electrolyte: 0.09 м [Bu$_3$NMe]O$_3$SOMe, ratio **A**/**B**^{PG} = 1:3. [b] GC analysis was performed on crude reaction mixture containing an excess of **B**. GC signals were assigned by GCMS analysis.

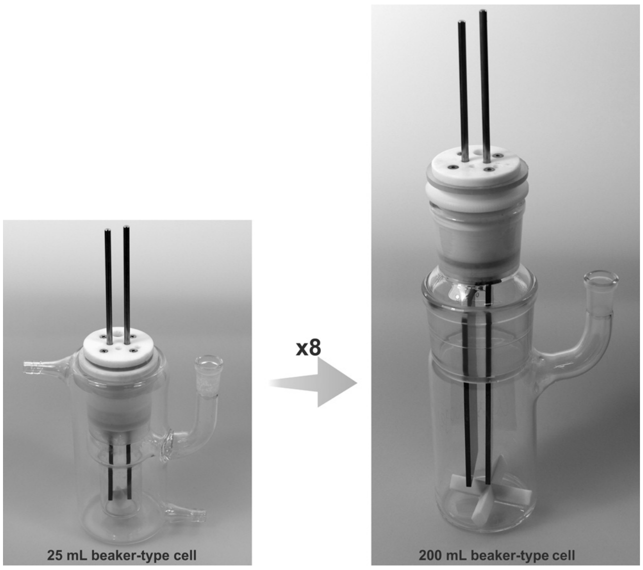


Figure 3. Scale-up of the electrochemical cross-coupling reaction.

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