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VIP Oxidative Phenol Cross-Coupling Very Important Paper

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# Metal- and Reagent-Free Highly Selective Anodic Cross-Coupling Reaction of Phenols

*Bernd Elsler, Dieter Schollmeyer, Katrin Marie Dyballa, Robert Franke, and Siegfried R. Waldvogel**

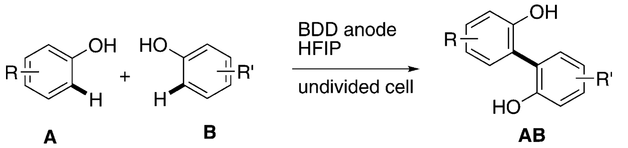
***Abstract:*** *The direct oxidative cross-coupling of phenols is a very challenging transformation, as homo-coupling is usually strongly preferred. Electrochemical methods circumvent the use of oxidizing reagents or metal catalysts and are therefore highly attractive. Employing electrolytes with a high capacity for hydrogen bonding, such as methanol with formic acid or 1,1,1,3,3,3-hexafluoro-2-propanol, a direct electrolysis in an undivided cell provides mixed 2,2′-biphenols with high selectivity. This mild method tolerates a variety of moieties, for example, tert-butyl groups, which are not compatible with other strong electrophilic media but vital for later catalytic applications of the formed products.*

**N**onsymmetrical biaryls are important structural units in organic chemistry,[1] natural product synthesis,[2,3] molecular catalysis,[4] and material science.[5] C–C cross-coupling reactions provide highly versatile and applicable transformations for their synthesis.[3,6] Typically, such coupling reactions require leaving groups and complex catalysts that are often based on toxic transition metals, for example, palladium.[7] Selective functionalization of arenes by direct C–H activation is consequently one of the hot topics in contemporary organic synthesis. A variety of efficient protocols for this modern strategy have recently been developed, allowing a catalytic approach to the active transition-metal species in the presence of only one activated coupling partner.[8] C–H activation of one reaction partner can also be achieved by an organocatalytic pathway.[9] In particular, 2,2′-dihydroxybiaryls play an important role in ligand development for transition-metal catalysis. They are widely employed as structural units of sterically hindered diphosphate ligands for rhodium-catalyzed hydroformylation, one of the largest homogeneously catalyzed reactions in industry. In general, these phosphorous acid triesters are manufactured from substituted biphenols. Their catalytic properties are strongly dependent on the nature of the substituents.[10] Therefore, universal synthetic protocols for the coupling of substituted phenols are highly significant.

A considerably improved atom economy results from the direct oxidative coupling of arenes.[6,11] This excludes the necessity of leaving functionalities and thus represents an important breakthrough. A prior oxidation of one component and subsequent coupling under strongly electrophilic conditions provides access to a variety of biaryl derivatives.[12] Unfortunately, most of the currently known and established methods require very costly catalyst systems and produce large quantities of reagent waste.

Electroorganic synthesis is an attractive method for the formation of organic compounds,[13] including C–C coupling reactions.[14] Because only electrons serve as reagent and the employed carbon electrodes are of sustainable origin, electrochemistry complies with the conditions of “green chemistry”.[15] Direct electrochemical cross-coupling faces the challenge that the individual oxidation potential of the components usually directs the selectivity. This results in a strong predominance of homo-coupling products, whereas only traces of the desired cross-coupling products are generated. Recently, Yoshida et al. circumvented this dilemma with the cation-pool method and established an elegant electroorganic access to biaryls.[14d,16] So far, this method cannot be extended to biphenols and is not scalable. Consequently, a direct electrolysis to selectively afford the cross-coupled 2,2′-biphenols is highly desirable. Here, we report the first cross-coupling of phenol and naphthol derivatives without using leaving functions, protecting groups, or reagents in an undivided electrolysis cell (Scheme 1).

Boron-doped diamond (BDD) has recently attracted considerable attention as a novel electrode material and is readily available by chemical vapor deposition methods.[17] Because of its unique electrochemical properties,[18] BDD electrodes enable new synthetic strategies in electroorganic synthesis.[19] Owing to the unusually high over-potentials for oxygen evolution in protic media, the oxyl radicals are directly generated with high efficiency.[20] These outstandingly reactive spin centers are exploited in wastewater treatment or constructive synthesis.[21] Fluorinated alcohols such as



***Scheme 1.*** Direct anodic cross-coupling of phenols.

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[*] B. Elsler, Dr. D. Schollmeyer, Prof. Dr. S. R. Waldvogel
Institut für Organische Chemie
Johannes Gutenberg-Universität Mainz
Duesbergweg 10–14, 55128 Mainz (Germany)
E-mail: waldvogel@uni-mainz.de
Homepage: http//www.chemie.uni-mainz.de/OC/AK-Waldvogel/

Dr. K. M. Dyballa, Prof. Dr. R. Franke
Evonik Industries AG
Paul-Baumann-Straße 1, 45772 Marl (Germany)

Prof. Dr. R. Franke
Lehrstuhl für Theoretische Chemie, Ruhr-Universität Bochum
44780 Bochum (Germany)

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1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) seem to have an extraordinary stabilizing effect onto these intermediates, avoiding mineralization of employed substrates.[22,23] Recently, we found the first direct anodic phenol–arene cross-coupling.[24] Both yields and selectivity were dramatically enhanced when water or methanol were added to the electrolyte.[25] Although an electrolyte-dominated process, the best performance was achieved at BDD anodes. The employed HFIP can be quantitatively recovered as this alcohol exhibits outstanding electrochemical stability.[26] Despite the fact that simple phenols tend to form wide polycyclic scaffolds upon anodic treatment,[27] we were pleased to find that this concept can be extended to the cross-coupling of phenols.

In the previously studied phenol–arene cross-coupling, guaiacol derivatives turned out to be suitable phenolic components,[24,26] which form nonsymmetric homo-dehydrodimers in the absence of another coupling partner.[28] 4-Methylguaiacol exhibits a lower oxidation potential and therefore represents component **A**, which initiates the cross-coupling sequence (see the Supporting Information). The electrolysis was performed in an undivided cell with a BDD anode and a nickel cathode. As an electrolyte, either HFIP or HFIP/methanol were used in which methyltriethylammonium methylsulfate was dissolved as a supporting electrolyte. The scope of desired 2,2′-biphenols obtained through cross-coupling of 4-methylguaiacol with simple phenols and the variation in substitution patterns are displayed in Table 1. In all examples except entry 10, no homo-coupling products of the individual components were detected. The electrochemical protocol does not require blocking of all activated positions. However, *p*-cresol provides the mixed 2,2′-biphenol in 36 % yield, while a larger alkyl substituent in position 4 of component **B** provides similar yields of isolated products (entries 1–3). It is noteworthy, that these products exhibit a free and activated position 3. The products are readily isolated despite the formation of some oligomeric material. Using *m*-cresol as the phenolic component, **B** leads exclusively to two different cross-coupling products (entry 4). Because positions 4 and 6 of *m*-cresol are the more easily accessible and activated positions, both coupling products are found in almost equal amounts. The use of substrates with sterically more demanding substituents not only enhances the

***Table 1:*** Scope of direct anodic phenol cross-coupling reactions.[a,b]

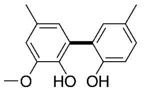
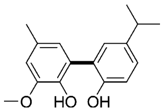
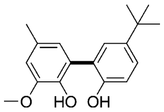
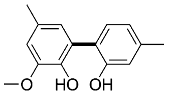
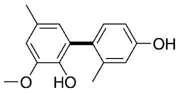
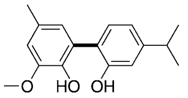
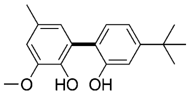
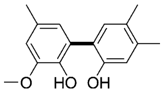
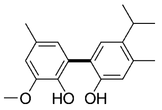
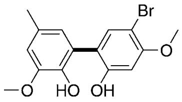
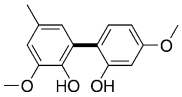
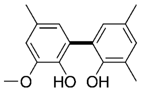
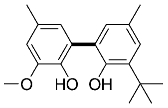
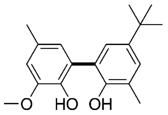
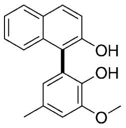
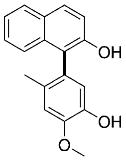
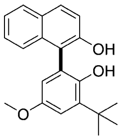
| Entry | Cond.[c] | Product(s) | | Yield[d] |
|---|---|---|---|---|
| 1 | I |  | **1** | 36 % |
| 2 | I |  | **2** | 39 % |
| 3 | I |  | **3** | 34 % |
| 4a | II |  | **4a** | 21 % |
| 4b | |  | **4b** | 23 % |
| 5 | II |  | **5** | 52 % |
| 6 | II |  | **6** | 63 % |
| 7 | I |  | **7** | 52 % |

***Table 1:*** (Continued)

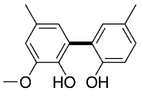
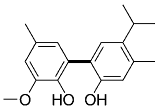
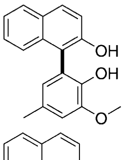
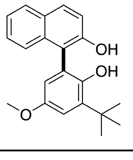
| Entry | Cond.[c] | Product(s) | | Yield[d] |
|---|---|---|---|---|
| 8 | II |  | **8** | 50 % |
| 9a | II[e] |  | **9a** | 39 % |
| 9b | |  | **9b** | 19 % |
| 10[f] | I |  | **10** | 52 % |
| 11 | I |  | **11** | 36 % |
| 12 | I |  | **12** | 46 % |
| 13a | I |  | **13a** | 61 % |
| 13b | |  | **13b** | 7 % |
| 14 | I |  | **14** | 63 % |

[a] Electrolysis conditions: 50 °C, constant current ($j = 2.8$ mA cm$^{-2}$), BDD anode, nickel-net cathode, undivided cell, $Q = 2$ $F{\cdot}n$(phenol **A**), supporting electrolyte: 0.68 g $Et_3NMe$ $O_3SOMe$. [b] Ratio of cross-coupling product(s) **AB** to homo-coupling products **AA** or **BB** (determined by GC) is > 100:1, with the exception of entry 10. [c] Solvent: I: HFIP + 18 vol % MeOH; II: HFIP. [d] Yields of isolated products. [e] BDD anode und cathode. [f] **AB**/**BB** = 9:1.

yield, but exclusively provides the desired 2,2′-biphenol with 52% and 63% yield, respectively (entries 5 and 6). A 3,4-disubstituted phenolic component **B** reliably provided the cross-coupling products with yields higher than 50% (entries 7–9). When bromo substituents were involved, the coupling also occurred, accompanied by a partial dehalogenation at the cathode. Interestingly, upon debromination **9b** was formed without any traces of the isomeric **9** (entry 9). Consequently, bromo substituents can be removed without a trace and can therefore be used in this transformation as protecting groups. 2,4-Dimethylphenol also undergoes the cross-coupling sequence with 52% yield (entry 10). Replacing a methyl group either in *ortho* or *para* position by a *tert*-butyl moiety results in the cross-coupling with lower yield, but unique selectivity (entries 11 and 12). 2-Naphthols are also suitable substrates for this electroorganic coupling. With 4-methylguaiacol only cross-coupling products are found. The desired 2,2′-dihydroxy biaryl **13a** was isolated with a good yield of 61%. From the electrolysis mixture 7% of an isomeric structure was found (entry 13). Switching to a more electron-rich substrate for **A**, led to the formation of a sole cross-coupling product in 63% yield (entry 14). All structures were thoroughly characterized and most of the described compounds are new (see the Supporting Information). The structural elucidation was verified by X-ray analysis of suitable single crystals.

Despite the potential efficiency of the recycling of HFIP, the environmental footprint of highly fluorinated media cannot be denied. Therefore, an alternative solvent would be highly desirable. Initial studies on the phenol–arene coupling in micro flow electrolysis indicated that formic acid has similar solvent properties to HFIP.[29] Applicative screening on the phenol–phenol cross-coupling showed the same solvent effect (Table 2).

***Table 2:*** Comparison of HFIP and formic acid for the anodic biphenol synthesis.[a,b]

| Entry | Solvent | Product(s) | | Yield[c] |
|---|---|---|---|---|
| 1a | HFIP + 18 vol% MeOH |  | **1** | 36% |
| 1b | HCOOH + 9 vol% MeOH | | | 13% |
| 2a | HFIP |  | **8** | 50% |
| 2b | HCOOH + 9 vol% MeOH | | | 28% |
| 3a | HFIP + 18 vol% MeOH |  | **13a** | 61% |
| 3b | HCOOH + 9 vol% MeOH | | | 45% |
| 4a | HFIP + 18 vol% MeOH |  | **14** | 63% |
| 4b | HCOOH + 9 vol% MeOH | | | 34% |

[a] Electrolysis conditions: 50°C, constant current ($j = 2.8$ mA cm$^{-2}$), BDD anode, nickel-net cathode, undivided cell, $Q = 2$ $F \cdot n$(phenol **A**), supporting electrolyte: 0.68 g Et$_3$NMe O$_3$SOMe. [b] Ratio of cross-coupling product(s) **AB** to homo-coupling products **AA** or **BB** (determined by GC) is >100:1. [c] Yields of isolated products.

The use of formic acid instead of HFIP resulted in the same exclusive selectivity for cross-coupling reactions, but the yields for the respective 2,2′-dihydroxybiaryls were lower. The reduced efficiency of the electroorganic cross-coupling can be attributed to the significantly lower anodic stability of formic acid. However, the low cost of this electrolyte and the direct process still makes for a synthetically useful reaction conversion, providing compound **13a** with 45% yield (entry 3b) and less negative environmental impact. Compared to traditional approaches to related mixed 2,2′-biphenols, the steps for O protection and installation of leaving functionalities of both compounds, the catalytic coupling, and the deprotection can be cut short by a single electrolytic action.

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**Keywords:** anodic biaryl synthesis · C–C coupling · green chemistry · oxidative coupling · phenol cross-coupling

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[1] a) R. Noyori, *Angew. Chem.* **2002**, *114*, 2108–2123; *Angew. Chem. Int. Ed.* **2002**, *41*, 2008–2022; b) C. A. Mulrooney, X. Li, E. S. DiVirgilio, M. C. Kozlowski, *J. Am. Chem. Soc.* **2003**, *125*, 6856–6857.

[2] a) G. Bringmann, A. J. P. Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem.* **2005**, *117*, 5518–5563; *Angew. Chem. Int. Ed.* **2005**, *44*, 5384–5427; b) G. Bringmann, T. Gulder, T. A. M. Gulder, M. Breuning, *Chem. Rev.* **2011**, *111*, 563–639; c) M. C. Kozlowski, B. J. Morgan, E. C. Linton, *Chem. Soc. Rev.* **2009**, *38*, 3193.

[3] J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359–1470.

[4] a) J. B. Alexander, D. S. La, D. R. Cefalo, A. H. Hoveyda, R. R. Schrock, *J. Am. Chem. Soc.* **1998**, *120*, 4041–4042; b) A. F. Kiely, J. A. Jernelius, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, *124*, 2868–2869; c) R. Singh, C. Czekelius, R. R. Schrock, P. Müller, A. H. Hoveyda, *Organometallics* **2007**, *26*, 2528–2539; d) K. C. Hultzsch, J. A. Jernelius, A. H. Hoveyda, R. R. Schrock, *Angew. Chem.* **2002**, *114*, 609–613; *Angew. Chem. Int. Ed.* **2002**, *41*, 589–593; e) K. Mikami, T. Korenaga, M. Terada, T. Ohkuma, T. Pham, R. Noyori, *Angew. Chem.* **1999**, *111*, 517–519; *Angew. Chem. Int. Ed.* **1999**, *38*, 495–497; f) G. A. Cortez, R. R. Schrock, A. H. Hoveyda, *Angew. Chem.* **2007**, *119*, 4618–4622; *Angew. Chem. Int. Ed.* **2007**, *46*, 4534–4538.

[5] a) A. C. Grimsdale, K. L. Chan, R. E. Martin, P. G. Jokisz, A. B. Holmes, *Chem. Rev.* **2009**, *109*, 897–1091; b) P. Kirsch, M. Bremer, *Angew. Chem.* **2000**, *112*, 4384–4405; *Angew. Chem. Int. Ed.* **2000**, *39*, 4216–4235; c) L. F. Tietze, G. Kettschau, U. Heuschert, G. Nordmann, *Chem. Eur. J.* **2001**, *7*, 368–373; d) P. W. N. M. van Leeuwen, P. C. J. Kamer, C. Claver, O. Pàmies, M. Diéguez, *Chem. Rev.* **2011**, *111*, 2077–2118; e) S.-J. Su, D. Tanaka, Y.-J. Li, H. Sasabe, T. Takeda, J. Kido, *Org. Lett.* **2008**, *10*, 941–944.

[6] G. P. McGlacken, L. M. Bateman, *Chem. Soc. Rev.* **2009**, *38*, 2447.

[7] a) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196–5217; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094–5115; b) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173–1193; c) L. Ackermann, *Top. Organomet. Chem.* **2008**, *24*, 35–60.

[8] a) L. Ackermann, *Modern Arylation Methods*, Wiley-VCH, Weinheim, **2009**; b) G. Dyker, *Handbook of C-H Transformations*, Wiley-VCH, Weinheim, **2005**; c) J. A. Labinger, J. E. Bercaw, *Nature* **2002**, *417*, 507–514; d) D. Alberico, M. E.

Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174–238; e) K. Godula, *Science* **2006**, *312*, 67–72.

[9] C.-L. Sun, H. Li, D.-G. Yu, M. Yu, X. Zhou, X.-Y. Lu, K. Huang, S.-F. Zheng, B.-J. Li, Z.-J. Shi, *Nat. Chem.* **2010**, *2*, 1044–1049.

[10] R. Franke, D. Selent, A. Börner, *Chem. Rev.* **2012**, *112*, 5675–5732.

[11] a) D. R. Stuart, K. Fagnou, *Science* **2007**, *316*, 1172–1175; b) T. Dohi, M. Ito, K. Morimoto, M. Iwata, Y. Kita, *Angew. Chem.* **2008**, *120*, 1321–1324; *Angew. Chem. Int. Ed.* **2008**, *47*, 1301–1304.

[12] S. K. R. Parumala, R. K. Peddinti, *Org. Lett.* **2013**, *15*, 3546–3549.

[13] a) H. J. Schäfer, A. J. Bard, M. Stratmann, *Organic Electrochemistry, Encyclopedia of Electrochemistry*, Wiley-VCH, Weinheim, **2004**; b) H. Lund, O. Hammerich, *Organic Electrochemistry*, Marcel Dekker, New York, **2001**.

[14] a) H. J. Schäfer, *Angew. Chem.* **1981**, *93*, 978–1000; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 911–934; b) F. Tang, K. D. Moeller, *J. Am. Chem. Soc.* **2007**, *129*, 12414–12415; c) H.-C. Xu, K. D. Moeller, *Angew. Chem.* **2010**, *122*, 8176–8179; *Angew. Chem. Int. Ed.* **2010**, *49*, 8004–8007; d) T. Morofuji, A. Shimizu, J.-i. Yoshida, *Angew. Chem.* **2012**, *124*, 7371–7374; *Angew. Chem. Int. Ed.* **2012**, *51*, 7259–7262.

[15] a) E. Steckhan, T. Arns, W. R. Heineman, G. Hilt, D. Hoormann, J. Jörissen, L. Kröner, B. Lewall, H. Pütter, *Chemosphere* **2001**, *43*, 63–73; b) P. Anastas, N. Eghbali, *Chem. Soc. Rev.* **2009**, *38*, 301–312; c) R. A. Sheldon, *Green Chem.* **2007**, *9*, 1273–1283; d) H. J. Schäfer, *C. R. Chim.* **2011**, *14*, 745–765; e) H. J. Schäfer, M. Harenbrock, E. Klocke, M. Plate, A. Weiper-Idelmann, *Pure Appl. Chem.* **2007**, *79*, 2047–2057; f) B. A. Frontana-Uribe, R. D. Little, J. G. Ibanez, A. Palma, R. Vasquez-Medrano, *Green Chem.* **2010**, *12*, 2099–2119.

[16] a) J.-i. Yoshida, K. Kataoka, R. Horcajada, A. Nagaki, *Chem. Rev.* **2008**, *108*, 2265–2299.

[17] *Diamond Electrochemistry* (Eds.: A. Fujishima, Y. Einaga), BKC Inc., Tokyo, and Elsevier, Amsterdam, **2005**.

[18] *Electrochemistry for the environment* (Eds.: C. Comninellis, G. Chen), Springer, New York, **2010**.

[19] a) *Synthetic Diamond Films—Preparation, Electrochemistry, Characterization and Applications* (Eds.: E. Brillas, C. A. Martínez-Huitle), Wiley-VCH, **2011**; b) S. R. Waldvogel, B. Elsler, *Electrochim. Acta* **2012**, *82*, 434–443; c) S. R. Waldvogel, S. Mentizi, A. Kirste, *Top. Curr. Chem.* **2012**, *320*, 1–31.

[20] B. Marselli, J. Garcia-Gomez, P. A. Michaud, M. A. Rodrigo, C. Comninellis, *J. Electrochem. Soc.* **2003**, *150*, D79–D83.

[21] I. M. Malkowsky, U. Griesbach, H. Pütter, S. R. Waldvogel, I. M. Malkowsky, U. Griesbach, H. Pütter, S. R. Waldvogel, *Eur. J. Org. Chem.* **2006**, 4569–4572.

[22] L. Eberson, M. P. Hartshorn, O. Persson, *J. Chem. Soc. Perkin Trans. 2* **1995**, 1735–1744.

[23] L. Eberson, O. Persson, M. P. Hartshorn, *Angew. Chem.* **1995**, *107*, 2417–2418; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2268–2269.

[24] A. Kirste, G. Schnakenburg, F. Stecker, A. Fischer, S. R. Waldvogel, *Angew. Chem.* **2010**, *122*, 983–987; *Angew. Chem. Int. Ed.* **2010**, *49*, 971–975.

[25] A. Kirste, B. Elsler, G. Schnakenburg, S. R. Waldvogel, *J. Am. Chem. Soc.* **2012**, *134*, 3571–3576.

[26] R. Francke, D. Cericola, R. Kötz, D. Weingarth, S. R. Waldvogel, *Electrochim. Acta* **2012**, *62*, 372–380.

[27] a) J. Barjau, G. Schnakenburg, S. R. Waldvogel, *Angew. Chem.* **2011**, *123*, 1451–1455; *Angew. Chem. Int. Ed.* **2011**, *50*, 1415–1419; b) J. Barjau, P. Koenigs, O. Kataeva, S. R. Waldvogel, *Synlett* **2008**, 2309–2312; c) J. Barjau, G. Schnakenburg, S. Waldvogel, *Synthesis* **2011**, *2011*, 2054–2061; d) J. Barjau, J. Fleischhauer, G. Schnakenburg, S. R. Waldvogel, *Chem. Eur. J.* **2011**, *17*, 14785–14791.

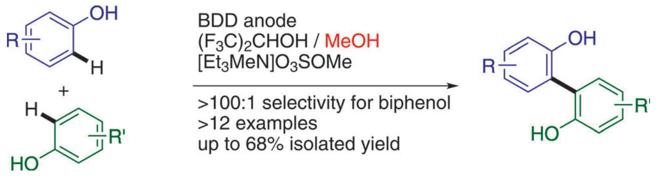
[28] A. Kirste, G. Schnakenburg, S. R. Waldvogel, *Org. Lett.* **2011**, *13*, 3126–3129.

[29] T. Kashiwagi, B. Elsler, S. R. Waldvogel, T. Fuchigami, M. Atobe, *J. Electrochem. Soc.* **2013**, *160*, G3058–G3061.

**Oxidative Phenol Cross-Coupling**

B. Elsler, D. Schollmeyer, K. M. Dyballa,
R. Franke,
S. R. Waldvogel* ———— ■■■■–■■■■

Metal- and Reagent-Free Highly Selective Anodic Cross-Coupling Reaction of Phenols



**Current synthesis**: In a highly sustainable access to mixed biphenols, electric current makes the use of reagents, catalysts, and leaving functionalities obsolete. Solvents with a strong tendency to act as hydrogen-bond donors lead to a unique selectivity for the cross-coupling product.