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Facile and Selective Cross-coupling of Phenols Using Selenium dioxide

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Abstract: Non-symmetric biphenols are important structural motifs in organic chemistry. Therefore, an easy and versatile protocol for oxidative cross-coupling is essential to generate these so called "privileged ligands". We developed an efficient and selective oxidative pathway to synthesize 2,2'-biphenols as well as 2,4'- or 4,4'-biphenols. The use of selenium dioxide, a stable, powerful and commercially available oxidizer, in 1,1,1,3,3,3-hexafluoroisopropanol allows the oxidative coupling of alkyl, alkoxy and halogen substituted phenols.

Biphenols are well-known structures in organic chemistry due to their widespread applications. Symmetric and nonsymmetric biphenols are present in various natural products,^[1] drugs^[2] and in material sciences.^[3] Their outstanding significance as ligand building blocks for catalytic systems underlines the importance for scientific and industrial applications.^[4] Therefore, the selective synthesis of biphenols is of utmost interest.

Transition-metal catalyzed C-C cross-coupling reactions give access to biphenol structures, but they need highly functionalized compounds and costly catalysts.^[5] In particular, the introduction of specific leaving groups enhances the synthetic effort of this method to synthesize non-symmetric biphenols. Oxidative coupling reactions by direct C-H activation avoid these disadvantages. Recent investigations are dealing with chromium,^[6] vanadium,^[7] copper^[8] or iron^[9] based catalytic systems, using oxygen or difficult to handle peroxides to generate the desired biphenols. A very prominent method uses hypervalent iodine reagents to synthesize biphenyls.^[10] Other oxidants, like potassium persulfate and copper(II)-chloride, are less expensive, but require additives to increase the selectivity.^[11] Anodic cross-coupling to non-symmetric biphenols is a cutting-edge sustainable concept of contemporary research.^[12] However, a rather specific laboratory set-up including electrode materials and supporting electrolyte is necessary. This might be a barrier for the applicability in standard laboratories.[13]

Especially, the selective cross-coupling of phenols is still challenging because of broad scope of possible by-products. In

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particular, homo-coupling products, C-O-coupled structures, or polycyclic by-products may occur.^[14] In order to circumvent this kind of structural diversity, ^[15] template concepts were established increasing the number of synthetic manipulations.^[16] Employing solvents with a high capability for hydrogen bonding and outstanding stability towards oxidation turned out to be the key for the selective cross-coupling reactions of phenols, phenol-aniline, or phenol-arene substrate combinations. Particularly, 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP), a highly fluorinated solvent with a high capability for hydrogen bonding, is able to stabilize reactive intermediates like radicals or radical cations. ^[17] Additionally, the solvent is highly stable under oxidative conditions and can be recycled after the reaction.^[12,18] Selenium dioxide is a versatile, easy to handle and in each synthetic laboratory readily available oxidizer which is obtained by roasting of copper, lead, zinc or iron ores.^[19] In the course of oxidative transformations elemental selenium is generated. This can be reoxidized by heating at aerobic conditions.^[20] Therfore it is an excellent oxidizer for scientific and industrial applications. Recently, we reported the first selective oxidative homo-coupling of phenols using selenium dioxide as oxidizer.^[21] In that study, solvent turned out to be crucial for the transformation to obtain selectively either the diaryl selenides or the 2,2'-biphenols.

Here, we report the first, selenium dioxide-mediated, phenolphenol cross-coupling. Initially, we determined the best solvent system for a selective cross-coupling process.



Scheme 1. Test substrate combination for cross-coupling.

Therefore, we tested the conversion of 2,4-bis(1,1dimethylethyl)phenol (1) and 2,6-dimethoxyphenol (2) in acetic acid at 85 °C (Scheme 1). However, gas chromatographic analysis of those runs indicated no significant selectivity for the formation of mixed biphenols. Instead, the homo-coupling products (4, 5) were preferentially obtained. Similar solvents like formic acid^[12,18] generated further by-products, but not the displayed biphenol structures (3-5). However, 1,1,1,3,3,3hexafluoropropan-2-ol (HFIP) yielded the desired product (3).For better reaction rates, we performed the reaction at 55 °C. In addition, other fluorinated solvents like trifluoroacetic acid lead to very sluggish reaction. Next, we optimized the ratios of the phenolic components 1 and 2 with respect to yield and selectivity. Former studies indicated that the oxidation of 1 is

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more facile than $2^{[21]}$ Thus, we decided to use component 1 in excess compared to phenol 2. Table 1 summarizes the results of this study: The use of equimolar amounts of 1 and 2 lead to acceptable ratios of the desired product 3 compared to the undesired homo-coupling products 4 and 5. However, the yield was rather low. (Table 1, entry 1).

offer subsequent options for functionalization. The use of halogen-equipped starting materials in oxidative coupling reactions is very challenging. These substituents (particularly iodine is a good leaving group) and oxidative treatment in the presence of water can lead to quinone formation.

 Table 1. Selectivity of phenol-phenol cross-couplings dependent on the component ratio.

Entry	Ratio 1:2	Selectivity 3 to 4 to 5 ^[a]	Yield of 3 /%
1	1:1	77:11:12	21
2	2:1	87:5:8	38
3	3:1	92:4:4	49
4	5:1	94:3:3	74

[a] Data obtained by gas chromatography.

Increasing excess of **1** lead to a preferential generation of the cross-coupling product **3** coming along with enhanced yields (Table 1, entries 2 and 3). The best result was obtained by application of five equivalents of **1** providing good yields up to 74% (Table 1, entry 4). Non-converted phenol **1** can be easily recycled by bulb-to-bulb distillation leading to a quick and synthetically applicable transformation. Consequently, this ratio was employed for the elucidation of the scope. Based on the minor component **2**, only one equivalent selenium dioxide was required, independent from the amount of phenol **1** used. This implies a preferred oxidation of phenol **2** followed by reaction with abundant component **1**. This protocol gave rise to generating selectively a broad scope of non-symmetrical biphenols.

Table 2 displays a variety of novel *ortho-para* coupled products. Therefore, 2,6-dimethoxyphenol (1) turned out to be a suitable phenol in excess since the free position in para acts as preferred reaction site. Conversions with other phenols exhibiting more or less bulky alkyl groups, e.g. methyl, ethyl, 1,1-dimethylethyl, or 1,1-dimethylpropyl, in position 2 and 4 yielded the desired products **3**, **6-10** in moderate to good yields. It is also viable to use other, methoxy substituted, phenols as excess components with a free position in *ortho* (10-13).

The optimized protocol was applied to a broad range of phenols to generate the corresponding *ortho-ortho* cross-coupling products (Table 3). Here, 2-methoxy-4-methylphenol is a versatile excess component providing access to **14-19**. Similar phenols such as 4-ethyl-2-methoxyphenol are also applicable leading to **20**. These methoxy-substituted phenols give rise to a lot of other cross-coupling products. Interestingly, in addition to a wide range of different alkyl substituents, 2,4,5-trisubstitued phenols turned out to be suitable. The additional steric demand in position five seems to have no negative impact (**14-15**).

Since 2,2'-biphenols are the most important derivatives for various applications,^[4] we tried to expand our method in this field. In particular, halogenated products are interesting because they

Table 2. Scope for *ortho-para* coupling to 2,4'-biphenols.



Ratio phenol A (blue) to phenol B (red): 1 : 5.

[a] Isolated yield. All reactions were carried out in HFIP as solvent with 0.6 equivalents of selenium dioxide at 55 $^{\circ}\text{C}$

We applied a variety of halogen-substituted phenols as excess component with good results, yielding the desired products in up to 54% (Table 3). The reaction of 2,4-bis(1,1dimethylethyl)phenol with 3-iodo-4-methoxyphenol yielded a 2,2'-biphenol **21**. But surprisingly the new bond was formed at the more sterically congested position between hydroxyl and iodo substituent. Enlarging the alkyl-substituent from 1,1dimethylethyl to 1,1-dimethypropyl changed the selectivity generating biphenol **22** at the less hindered position. The use of 3-bromo-4-methylphenol in combination with 2-(1,1-

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dimethylethyl)-4-ethylphenol yielded a brominated biphenol **23** comparable to **21**. Additionally, a variety of chlorinated products were isolated in moderate yields using 4-chloro-5-methyl-2-(1-methylethyl)phenol (**24-26**)

Table 3. Scope for ortho-ortho coupling to 2,2'-biphenols.



Ratio phenol A (blue) to phenol B (red): 1 : 5. [a] Isolated yield. All reactions were carried out in HFIP as solvent with 0.6 equivalents of selenium dioxide at 55 °C

Finally, we could show that 4,4'-biphenols by the combination of two 2,6-substitued phenols are accessible. Again, 2,6-dimethoxyphenol was employed as the excess phenolic compound yielding the biphenols **27** and **28** in good yields (Table 4).

 Table 4. Substrate scope of the selenium dioxide-mediated coupling of electron-rich arenes.



Ratio phenol A (blue) to phenol B (red): 1 : 5.

[a] Isolated yield. All reactions were carried out in HFIP as solvent with 0.6 equivalents of selenium dioxide at 55 $^{\rm o}{\rm C}$

In conclusion, we found a very simple to perform and versatile protocol for the oxidative cross-coupling of phenols. By this method selectively either 2,2'-, 2,4'-, or 4,4'- biphenols are accomplished. The substituents on the biphenols range from alkyl to alkoxy, chloro, bromo and iodo. Selenium dioxide as common reagent in organic synthesis laboratories serves as oxidizer and 1,1,1,3,3,3-hexafluoroisopropanol as selectivity directing solvent. By this method, 19 novel biphenols could be quickly generated in very good selectivity. Even if the yield is in the moderate range, the desired products can be easily isolated. The fluorinated solvent can be efficiently recycled and excess phenolic components directly recovered by bulb-to-bulb distillation.

Experimental Section

For experimental details and analytical data see SI.

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Layout 2:

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With a little help from the solvent 1,1,1,3,3,3-hexafluroisopropanol (HFIP) and the common oxidizer selenium dioxide, phenolic substrates are selectively converted into the mixed respective biphenols.

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