Solvent-Dependent Facile Synthesis of Diaryl Selenides and Biphenols Employing Selenium Dioxide

Thomas Quell,[a] Michael Mirion,[a] Dieter Schollmeyer,[a] Katrin M. Dyballa,[b] Robert Franke,[b, c] and Siegfried R. Waldvogel*[a]

Biphenols are important structure motifs for ligand systems in organic catalysis and are therefore included in the category of so-called "privileged ligands". We have developed a new synthetic pathway to construct these structures by the use of selenium dioxide, a stable, powerful, and commercially available oxidizer. Our new, and easy to perform protocol gives rise to biphenols and diaryl selenides depending on the solvent employed. Oxidative treatment of phenols in acetic acid yields the corresponding biphenols, whereas conversion in pyridine results in the preferred formation of diaryl selenides. As a consequence, we were able to isolate a broad scope of novel diaryl selenides, which could act as pincer-like ligands with further applications in organic synthesis or as ligands in transition metal catalysis.

The use of selenium dioxide as catalytic or stoichiometric reagent is currently experiencing a renaissance.[1] Selenium dioxide is a readily available and stable selenium reagent, which is commonly employed for oxygenation reactions.[2] Remarkably, the product distribution in stereoselective selenation reactions seems to be strongly solvent dependent.[3] The chemistry of diaryl selenides is only moderately explored despite the stable molecular entity and interesting structural feature.[4] In particular, hydroxy-substituted compounds have potential use as ligands or building blocks.[5] However, the synthesis requires a multistep approach usually starting with aryl halides, selenium, and a reducing agent, for example, sodium.[6] The employment of phenols would require a set of protective groups. Interestingly, the direct conversion of 2,4-di-tert-butylphenol with selenium dioxide to the corresponding diaryl selenide seems

to be the singular example of commercial interest.[5j] Recently, a few examples for the conversion of phenols using SeOCl$_2$ or SeCl$_2$/AlCl$_3$ mixtures were reported.[7] Consequently, a facile synthetic approach to such diaryl selenides would be of general interest. The oxidative treatment of phenols can provide biphenols,[8] which are of tremendous academic and industrial significance as building blocks for ligands in homogenous catalysis,[9] building blocks for material science,[10] or in natural product synthesis.[11] In particular, the conversion of simple methyl substituted phenols, that is 2,4-dimethylphenol, has turned out to be challenging.[12] The formation of polycyclic by-products is very dominant and can lead to high structural diversity.[13] Several concepts were elaborated to obtain the interesting 2,2'-biphenol in acceptable selectivity.[14] However, most of them require an electrochemical setup.[15] Therefore, a simple and easy-to-perform method to access the 2,2-biphenols is also highly desired.

Here, we report a solvent-dependent conversion of simple phenols with selenium dioxide, yielding the corresponding biphenols or diaryl selenides (Scheme 1).
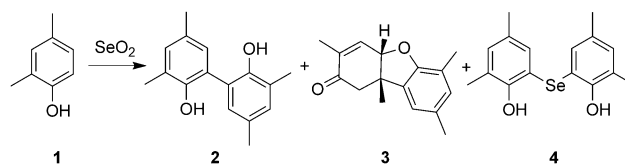
Scheme 1. Test reaction using selenium dioxide.

Initial studies were performed with 2,4-dimethylphenol (1) as test substrate, since we already have experience with the complex product diversity formed in this particular conversion to biphenol 2.[12] The analysis of the reaction mixtures revealed that indeed, the desired biphenol 2 was formed. In addition, two by-products were identified: First, a derivative of Pummerer's ketone (3) which is an isomer to 2 and often preferentially formed upon oxidative treatment.[16] Secondly, a previously not observed by-product in the oxidation of 1 was isolated. Mass spectrometric analysis of the gas chromatography (GC) peak clearly indicated the typical isotope pattern of selenium. Based on NMR spectroscopic data, the structure of 4 could be proposed, wherein two phenolic moieties are tethered by a selenium atom. X-ray analysis of suitable single crystals verified the molecular structure of bis(3,5-dimethyl-2-hydroxyphenyl)selenium (Figure 1.). Therein the C—Se—C motif has an angle of 97.(22)° with a distance of 0.28 nm between both oxygen

[a] T. Quell, Dr. M. Mirion, Dr. D. Schollmeyer, Prof. Dr. S. R. Waldvogel
     Department of Organic Chemistry, Johannes Gutenberg University Mainz
     Duesbergweg 10–14, 55128 Mainz (Germany)
     E-mail: waldvogel@uni-mainz.de

[b] Dr. K. M. Dyballa, Prof. Dr. R. Franke
     Evonik Performance Materials GmbH
     Paul-Baumann-Straße 1, 45772 Marl (Germany)

[c] Prof. Dr. R. Franke
     Department of Theoretical Chemistry, Ruhr-Universität Bochum, 44780
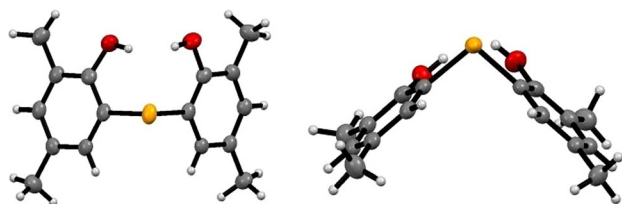   Bochum (Germany)

Figure 1. Molecular structure of bis(3,5-dimethyl-2-hydroxyphenyl)selenium (**4**) as top and side view.

atoms and 0.31 nm between the selenium and oxygen atoms. This gap specifies the size of a complexation center.

Next, the influence of the solvent onto the product distribution was studied. Since 2,4-dimethylphenol is liquid, the conversion was carried out neat. Although a pronounced selectivity for the biphenol is apparent, significant amounts of the organoselenium species are observed (Table 1, entry 1). Most importantly, only traces of the common by-product **3** are detected. During the course of reaction, the mixture solidifies and therefore, the use of solvents was indicated. The conversion in cyclic ethers rendered both lower selectivity and productivity. Interestingly, the earlier report employed such solvents,[17] and this might explain why this conversion was not studied further because of the sluggish reaction mixture.

The absence of the desired product in tetrahydrofuran (THF) can be attributed to the oxidation of the solvent. Conducting the reaction in aromatic solvents like toluene did not improve the reactivity. Interestingly, the use of xylene lead to a change in selectivity with **3** becoming more dominant. A protic polar solvent such as dimethylformamide (DMF) led to almost no selectivity between **2** and **4**. Switching to protic media changed the situation dramatically. Acetic acid at 85 °C promoted the formation of the desired biphenol **2** in high selectivity. Formic acid turned out to be also a suitable solvent, but the instability towards selenium dioxide required a lower temperature, and the hazard of spontaneous decomposition is still a hazard challenge. 1,1,1,3,3,3-Hexafluoropropan-2-ol (HFIP) represents a protic solvent with high capability for hydrogen bonding, which turned out to be useful in phenol-coupling reactions.[18] In this media, almost exclusively 3,3′,5,5′-tetramethyl-2,2′-biphenol (**2**) was formed in high quantity. Both by-products were only detected in trace amounts. When switching to the basic solvent pyridine, a complete reversal of selectivity in favour of **4** was observed. The selenium compound is by far the major product.

The optimal reaction temperature was 55 °C. Higher temperatures led to decreased selectivity, and operation at lower temperature required significantly prolonged reaction times. It is noteworthy, that other nitrogen-based basic solvents showed very low or almost no conversion. The lack of product formation in the presence of triethylamine could be attributed to the oxidation of the solvent by the selenium reagent. The low costs, good environmental footprint, and simple-to-perform work-up when using acetic acid prompted us to conduct the studies for biphenol synthesis with this particular solvent.

On a preparative scale (81 mmol), the generation of **2** was achieved in 61% isolated yield. The reagent waste selenium

Table 1. Solvent-dependent product distribution in the conversion of **1**.

Solvent	T [°C]	t [min]	Yield [%][a]		
			2	3	4
None	85	340	45	4	22
1,4-Dioxane	85	300	36	9	8
THF	65	450	–	–	–
Toluene	85	120	21	2	10
Xylene	85	300	48	19	4
DMF	85	1380	22	5	25
Acetic acid	85	300	84	1	3
Formic acid	60	300	88	Traces	1
HFIP	55	90	81	1	1
Pyridine	55	4320	2	Traces	85
Quinoline	60	1440	Traces	Traces	9
1-Methylimidazole	60	5760	–	–	–
Triethylamine	60	180	–	–	–

[a] Data were obtained by gas chromatographic analysis.

was obtained in its black elemental modification, which can be directly filtered off from the reaction mixture for recycling pur-

Table 2. Substrate scope of the selenium-dioxide-mediated phenol coupling.

Product	Yield[a] [%]	Product	Yield[a] [%]
2	61[b]	**9**	57[c]
5	38[c]	**10**	33[c]
6	36[b]	**11**	39[b]
7	50[b]	**12**	47[b]
8	41[c]	**13**	47[b]

[a] Isolated yield. All reactions were carried out in acetic acid as solvent with selenium dioxide (0.6 equiv) at [b] 85 °C, [c] 100 °C.
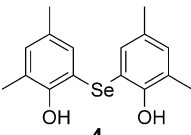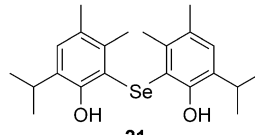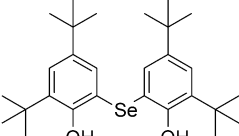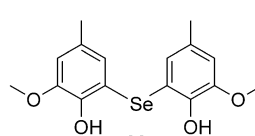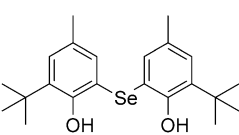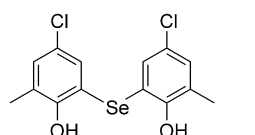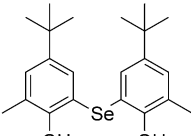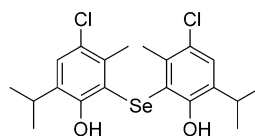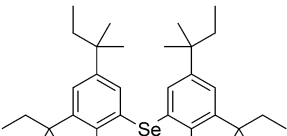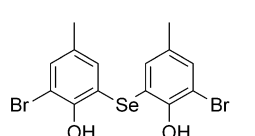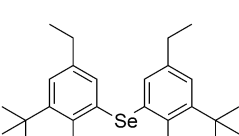
poses. The excellent selectivity for the biphenol in acetic acid allowed the isolation of the desired product by a simple extraction and subsequent crystallization protocol. This simple-to-perform work-up could be the crucial basis for a latter potential scalability. The method was applied to variety of different phenolic substrates to elucidate the scope of this method. Here, we focused on different alkyl substitution patterns on th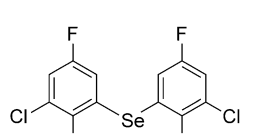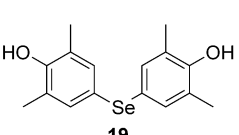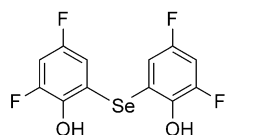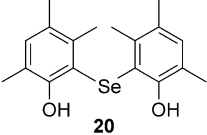e phenolic substrates including methyl, isopropyl, *tert*-butyl, and 1,1-dimethylpropyl fragments. These biphenols play an important role as ligand precursors in homogeneous catalysis.

To generate 2,2′-biphenols selectively, the position 4 should be blocked to avoid the formation of regioisomers. Conversely, blocking of the *ortho*-positions provides synthetic access to 4,4′-biphenols. Oxidation of phenols with a substitution pattern could result in the formation of quinones.[19] The optimized conversions of the different alkyl-substituted phenols required reaction times in the range of 30–300 min (Table 2). The reaction temperatures are as noted either 85 °C or 100 °C and represent optimized conditions. All products were purified by a filtration column and subsequent crystallization. Only biphenol **12** had to be purified by a bulb-to-bulb distillation. In general, a 2,4-disubstituion pattern seems to be suitable for this biphenol synthesis. If the positions *ortho* were blocked, the coupling proceeded in *para* yielding 4,4′-biphenol **10** in 50% yield. The 2,4,5,-trisubstition pattern turned out to be beneficial as well, and the biphenols were reliably isolated in 41–47% yield. The added steric demand of the positions 5 seemed to have no adverse effect.

In addition to the biphenol homocoupling, we identified bis(3,5-dimethyl-2-hydroxyphenyl)selenium (**4**) as unexpected by-product. The use of pyridine propelled the organoselenium compound to be the major product. The previous difficulties in preparation of these diaryl selenides could be a reason for the rare use of such compounds. The molecular architecture is very close to the biphenol structure; however, the selenium center may act as an additional complexation position. Thus, these components could be classified as tridentate, pincer-like ligands. Consequently, diaryl selenides could be new and useful building blocks for ligands in homogeneous catalysis.[20] Currently, no general and easy-to-perform synthetic pathway is available. Therefore, the scope was elucidated for the generation of diaryl selenides starting from the simple phenols. As outlined in Table 1, pyridine was stable under oxidative conditions.[21] When conducting the conversion at 55 °C, only traces of the biphenol **2** were detected but no Pummerer's ketone. The outstanding selectivity at lower temperatures caused significantly prolonged reactions times. For an isolated yield of 56% **4**, a reaction time of to three days was required. However, the work-up of the reaction mixture turned out to be reasonably simple and scalable as well. The reaction mixture was subjected to a simple protocol of extraction and crystallization.

With this procedure in hand, we treated a broad variety of phenols in order to elucidate the scope (Table 3). Almost all counterparts of the alkyl-substituted biphenols were generated by switching the solvent to pyridine. The unique selectivity for

Table 3. Substrate scope of the selenium-dioxide-mediated synthesis of diaryl selenides.
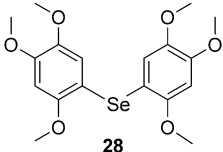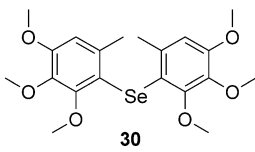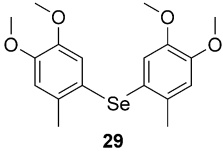
Product	Yield[a] [%]	Product	Yield[a] [%]
4	56[b]	**21**	25[b]
14	38[b]	**22**	36[b]
15	25[b]	**23**	27[b]
16	53[b]	**24**	36[b]
17	39[b]	**25**	19[b]
18	48[b]	**26**	40[b]
19	37[b]	**27**	64[b]
20	40[b]		

[a] Isolated yield. All reactions were carried out in pyridine as solvent with 0.6 equivalents of selenium dioxide at [b] 55 °C, [c] 85 °C.

the diaryl selenides was verified for all of these phenolic substrates. In addition to the alkyl substitution pattern at the phenols, we subjected even more functionalized phenols to this protocol. Interestingly, an additional methoxy group, which increases the electron density on the substrate, was successfully converted, but the reaction rate was dramatically decreased. This seemed to be contradictory for an oxidative process.

Other heteroatoms such as halogens would change the electronic properties, lipophilicity, and might offer subsequent modifications on the diaryl selenides scaffold. We were pleased to see that chloro and bromo substituents were compatible with this transformation leading to the compounds 23–25 in acceptable yield for this simple protocol. However, due to the deactivated nature of the starting materials, reaction times of seven to ten days were required. For the treatment of fluorophenols, elevated reaction temperatures to 85 °C were required but gave access to these highly halogenated diaryl selenides in excellent selectivity.

After the initial success in the conversion of a broad spectrum of phenols, we subjected electron rich arenes to the pyridine-based protocol. However, 1,2,4-trimethoxytoluene in pyridine turned out to be inert to selenium dioxide. Therefore, we switched to the oxidation protocol to acetic acid. Isolation of the product turned out to be the selenium-tethered aryl compound. Other electron-rich aryl substrates confirmed this observation (Table 4). At least two methoxy groups were necessary to be a suitable substrate for this reaction.

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

Product	Yield[a] [%]	Product	Yield[a] [%]
28	42	30	51
29	41		

[a] Isolated yield. All reactions were carried out in acetic acid as solvent with selenium dioxide (0.6 equiv) at 85 °C.

In conclusion, the action of selenium dioxide onto phenols provides solvent-dependent selectively, with access to either biphenols or diaryl selenides. In particular, the generation of diaryl selenides was demonstrated by 15 examples. The protocol is very easy to perform and allows the conversion of a broad scope of different phenols. The established method can be extended to electron-rich arenes as well. Currently, a mechanistic rationale for the diaryl selenide formation has yet to be developed. This is subject of current research.

Experimental Section

For experimental details and analytical data, see the Supporting Information.

Acknowledgements

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