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Catalytic Aerobic Phenol Homo- and Cross-Coupling with Copper Complexes Bearing Redox-Active Guanidine Ligands

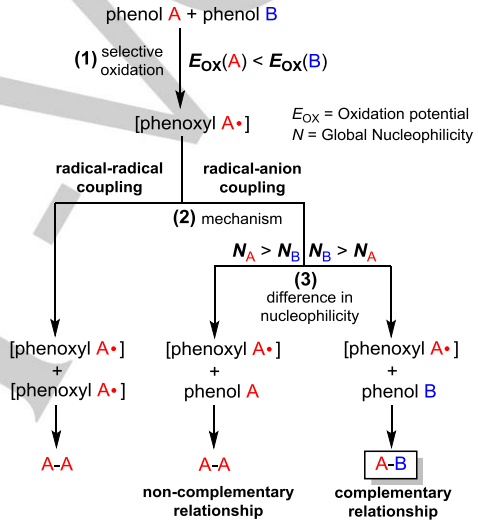
Florian Schön, Elisabeth Kaifer and Hans-Jörg Himmel*[a]

Abstract: Due to their large importance in synthetic chemistry, catalytic *C-C* coupling reactions of phenols are currently intensively studied. Herein we report on new copper catalysts for the *C-C* coupling of phenols using dioxygen as a green oxidizing reagent. By using redox-active guanidine ligands, the activity as well as chemo-selectivity in the cross-coupling of non-complementary phenols (between an electron-rich phenol and a less nucleophilic second phenol) is significantly improved. On the basis of the accumulated data for several test reaction, a reaction mechanism is proposed to explain the high chemo-selectivity.

Introduction

Modern synthetic chemistry strongly depends on the development of strategies for the selective formation of carbon-carbon bonds.[1–9] Symmetric as well as non-symmetric biphenols, traditionally synthesized by coupling of two phenol units, are of high relevance in several research fields such as natural product synthesis,[10] material science,[11] drugs[12,13] as well as the design of advanced molecular catalysts.[14] Motivated by the efficiency and selectivity of metalloenzymes, considerable effort has been devoted to the development of metal complexes that mimic enzymes in mediating the selective catalytic aerobic oxidation of phenols.[15,16]

Traditionally, non-symmetric biphenols are prepared by transition-metal catalyzed cross-coupling of aryl-halides (Ar-X).[17–19] Often, a number of synthesis steps is required, leading to an unfavorable overall atom economy. In seminal work, Pappo *et al.* systematically studied cross-coupling reactions of phenols with a radical-anion coupling mechanism and grouped the phenol cross-coupling reactions in two categories depending on their redox potential and "global nucleophilicity" ***N*** (Scheme 1).[20,21] For practical reasons, the parameter ***N*** of a phenol was simply defined by the authors as the HOMO energy relative to tetrachloro-ethylene, allowing it´s straightforward determination by standard DFT methods.[20] Obviously, for a pair of phenols A and B with $\boldsymbol{E}_{ox}$(A) < $\boldsymbol{E}_{ox}$(B), the oxidation of phenol A to a phenoxyl radical is thermodynamically favored. A spontaneous radical-radical coupling of two phenoxyl radicals leads to the undesirable homo-coupling product A–A (Scheme 1). By contrast, the cross-coupling reaction is favored in a radical-anion coupling mechanism of phenols with a complementary relationship ($\boldsymbol{N}_B$ > $\boldsymbol{N}_A$), leading to a desired high cross-coupling chemo-selectivity. On the other hand, phenols with a non-complementary relationship ($\boldsymbol{N}_A$ > $\boldsymbol{N}_B$) generally display only inferior cross-coupling chemo-selectivity, even for a radical-anion coupling mechanism. Waldvogel *et al*. presented another concept in electrochemical cross-coupling of phenols and anilines, providing high chemoselectivities by shifting the oxidation potential of the phenols in dependence of the substitution pattern in a specific range through addition of water or methanol to the electrolyte.[22,23] Kozlowski *et al.* studied the aerobic cross-coupling of phenols with a complementary relationship with different catalysts (i.e. Cr-salen complexes).[24]



Scheme 1. Flow-chart for general principles in the phenol cross-coupling. Adapted from Pappo *et al.* **2015**.[20]

Due to the resulting limited scope of cross-coupling reactions, several research groups took up the challenge to disclose new concepts for highly chemo-selective cross-coupling reactions of phenols with a non-complementary relationship (Scheme 2). Waldvogel *et al.* reported the cross-coupling of phenols at boron-doped diamond (**BDD**) anodes in 1,1,1,3,3,3-hexafluoropropan-2-ol (**HFIP**) as solvent.[25-29] Using this electro-chemical approach, a variety of phenol cross-coupling reactions was reported. The oxidation potential of phenol A needs to be significantly lower and a one- to twofold excess of phenol B has to be applied to achieve a high chemo-selectivity. In addition, Waldvogel *et al.* used stoichiometric amounts of SeO_2 as oxidant for the cross-coupling of phenols in high yield.[30] The best results were obtained if phenol A is applied in a fivefold excess and HFIP as solvent. More recently, Pappo *et al.* reported an iron catalyst with a tetraphenylporphyrin ligand (**TPP**) for selective oxidative cross-coupling of phenols.[31] This work relied on ^{t}BuOOH as oxidizing reagent and HFIP as solvent. This time, phenol B was applied in threefold excess in the experiments with highest chemo-selectivity. Very recently, Waldvogel *et al.* also succeeded in the electrochemical cross-coupling of 2,6-dimethoxyphenol with 2,6-diisopropylphenol at a BDD anode.[32]

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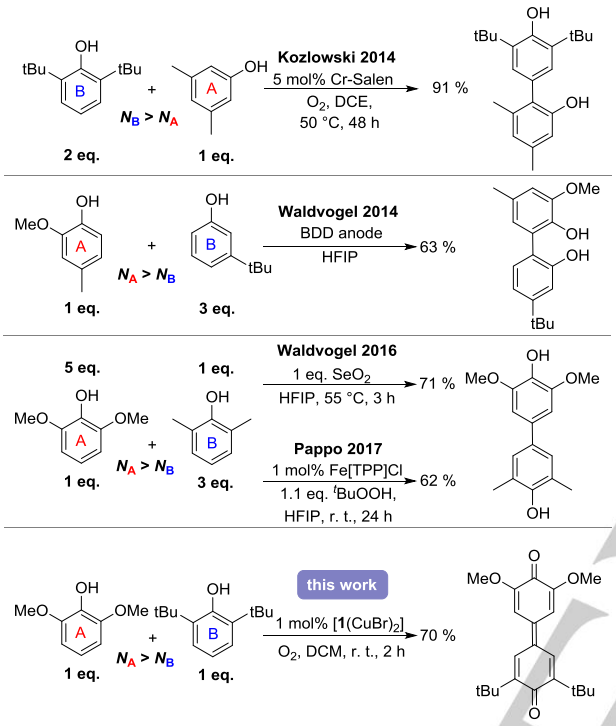
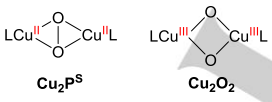
Itoh *et al.* studied the mechanism of oxidative homo-coupling reactions of phenols with dioxygen in the presence of copper catalysts that initially react with dioxygen to dinuclear (side-on) peroxo complexes (**Cu_2P^S**) or bis-μ-oxo-complexes (**Cu_2O_2**), sketched in Scheme 3.[33] They suggest the **Cu_2O_2** complex to be the active species, leading to *C-C* coupling products by a proton-coupled electron transfer (**PCET**) from the phenol to the **Cu_2O_2** complex, producing phenoxyl radicals which then spontaneously dimerize.

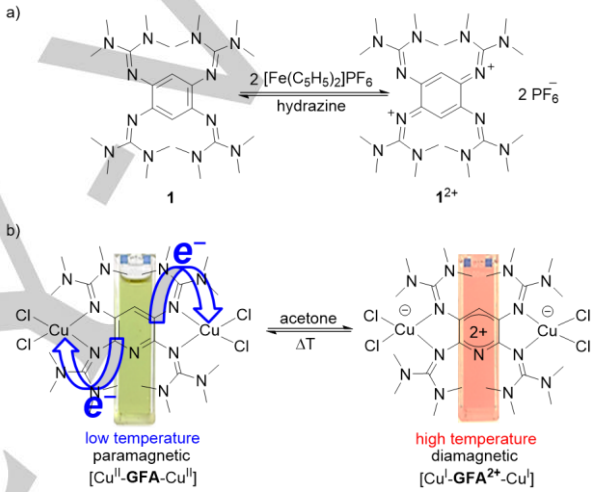


Scheme 2. Selection of catalysts and conditions used in phenol cross-coupling reactions in the literature and one of the catalytic reactions reported in this work.



Scheme 3. Cu_2P^S and **Cu_2O_2** complexes.

Herein we report on the influence of redox-active ligands in new copper catalysts for the homo-coupling reactions of 2,6-di-*tert*-butylphenol and 2,4-di-*tert*-butylphenol. On the basis of these results, the oxidative cross-coupling of phenols with a non-complementary relationship is studied in detail. The oxidant, dioxygen, is activated by copper complexes bearing the redox-active guanidino-functionalized aromatics (**GFA**) 1,2,4,5-tetrakis-(tetramethylguanidino)benzene (**1**) as ligand (see Scheme 4a). This ligand, that is oxidized reversibly at low potential ($E_{1/2}$ = –0.7 V vs. Fc^+/Fc in DCM solution for the redox couple $\mathbf{1}^{2+}$/**1**),[34] supplies the metal atom with extra electron-density, up to the point of full transfer of two electrons from the ligand to the two copper atoms. A number of studies [35–41] has shown that the particularly low barrier for intramolecular ligand-metal electron transfer in guanidine-copper complexes is due to the structural harmonization between Cu^{II} and Cu^{I} complexes caused by the π-donor properties of the guanidine ligands (see also work by Herres-Pawlis *et al.* on the entatic state concept in this context [42–46]). Hence it was possible to shift electrons between the redox-active guanidine ligand and the copper atom in a complex by changing the counter-ions,[35] the solvent [36–38] or the temperature.[37,39–41] An example for a thermally induced intramolecular electron transfer in a dinuclear copper complex with a related bridging redox-active tetrakis-guanidine ligand is given in Scheme 4b.[41] The high electron-donor capability of the ligand warrants an efficient dioxygen activation or O-O bond cleavage reaction to give **Cu_2O_2** complexes.



Scheme 4. a) Lewis structures of the redox-active tetrakisguanidine **1** before and after reversible two-electron oxidation. b) Valence-tautomerism with the redox-active ligand 1,2,4,5-tetrakis(tetramethyl-guanidino)pyridine.[41]

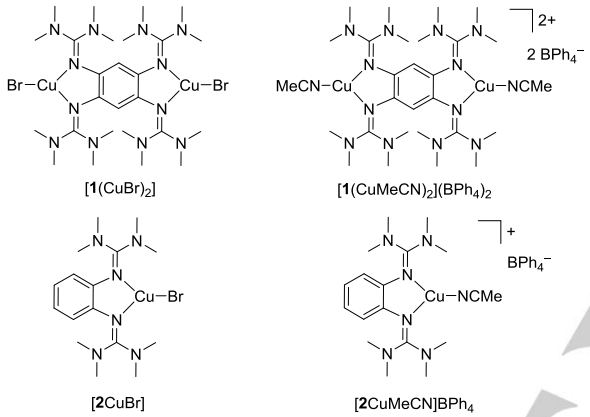
The advantages/peculiarities of the cross-coupling reactions presented herein with respect to previous work are (I) the use of dioxygen as oxidant, (II) fast reaction under mild conditions (room temperature, 1 atm. of dioxygen), (III) use of standard organic solvents (i. e. DCM) in place for 1,1,1,3,3,3-hexafluoropropan-2-ol (**HFIP**), (IV) the use of an equimolar ratio of both phenols and (V) a novel mechanistic option, leading to high chemo-selectivity for phenols with a non-complementary relationship.

Results and Discussion

Synthesis of copper complexes

The binuclear complexes [**1**$(CuBr)_2$][47] and [**1**$(CuMeCN)_2](BPh_4)_2$ (Scheme 5 and Figure 1) with the redox-active ligand 1,2,4,5-tetrakis-(tetramethylguanidino)benzene (**1**) were prepared by addition of CuBr respectively $[Cu(CH_3CN)_3]BPh_4$ to the ligand in acetonitrile solutions. The

redox-activity of the ligand should assist in the activation of dioxygen. To elucidate the effect of redox-activity, the ligand 1,2-bis-(tetramethylguanidino)-benzene (**2**) with a similar coordination site, for which irreversible oxidation occurs at much higher potentials of E_{ox} = 0.06 V and E_{ox} = 0.11 V vs. Fc^+/Fc (see SI), was also applied. Both mononuclear Cu^I complexes [**2**CuBr] and [**2**CuMeCN]BPh_4 (Scheme 5) were prepared *in-situ* by addition of one equivalents of CuBr respectively $[Cu(MeCN)_4]BPh_4$ to ligand **2**. The low coordination number of three of the copper atoms in all four complexes should favor the formation of the initial copper-dioxygen complex. A number of oxidative phenol coupling reactions described in the literature employed copper(I) catalysts together with (sub-) stoichiometric amounts of NEt_3.[48] We therefore used catalytic amounts of CuBr in combination with 0.5 eq. NEt_3 for benchmarking.



Scheme 5. Lewis structures of the complexes with 1,2,4,5-tetrakis-(tetramethylguanidino)benzene (**1**) and 1,2-bis-(tetramethylguanidino)benzene (**2**) ligands used in this work as catalysts in oxidative phenol coupling reactions.

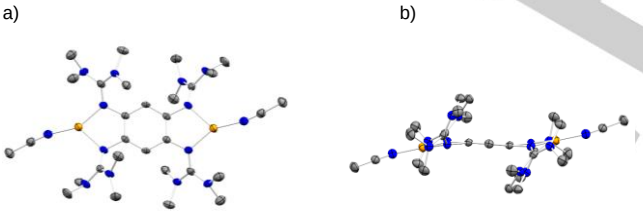
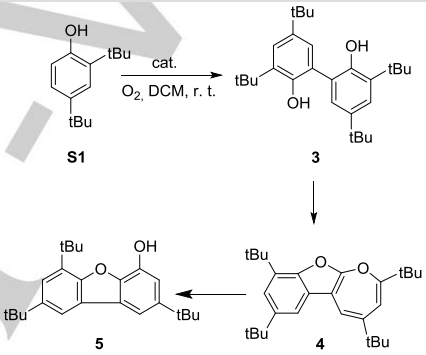


Figure 1. Illustration of the structure of the complex $[\mathbf{1}(CuMeCN)_2]^{2+}$ in crystals of $[\mathbf{1}(CuMeCN)_2](BPh_4)_2$ obtained from a CH_3CN/Et_2O solution (Cu atoms in orange, N atoms in blue and C atoms in grey) from two perspectives. Hydrogen atoms, counterions and solvent molecules were omitted for clarity. a) View perpendicular to the aromatic plane; b) view along the aromatic plane. Thermal ellipsoids are drawn at the 50% probability level.

Homo-coupling reaction of 2,4-di-*tert*-butylphenol

The oxidative homo-coupling of 2,4-di-*tert*-butylphenol (**S1**, Table 1) is a well-known reaction, leading to biphenol **3** with subsequent further oxidation to benzoxepine **4**.[48] An additional intramolecular reaction leads to **5** (in analogy to the already reported formation of benzofurans in phenol coupling reactions [49]). Therefore, the work in this article started with a comparison of the performance of several catalysts in the oxidative homo-coupling reaction of 2,4-di-*tert*-butylphenol. The reactions were carried out in a vial with crimp cap and rubber septum under an atmosphere of O_2 (1 atm) to ensure sufficient dioxygen availability. The yields were determined via ^1H NMR integration with an internal standard (hexamethylbenzene) after quenching the reaction with a solution of $NaHSO_4$ in water (10%) and extraction with dichloromethane (details are found in the SI). The variation of the catalysts (Table 1) only led to differences in the reaction rate, but not to different reaction products. Complete consumption of the starting material was reached with 4 mol% $[\mathbf{1}(CuBr)_2]$ in less than 1 h (Table 1, entry 3). With low catalyst loadings, mainly the formation of **3** was observed. For a better comparability, the turnover (*T*) at one copper atom within 1 h reaction time was also estimated with lower catalyst loading (0.4 mol%, Table 1, entry 4).

Table 1. Oxidative homo-coupling of phenol **S1** with different catalysts.



#	catalyst	T [a]	Conversion[b]
1	8 mol% CuBr + 50 mol% NEt_3	1225	98 %
2	0.8 mol% CuBr + 5 mol% NEt_3	0	0 %
3	4 mol% $[\mathbf{1}(CuBr)_2]$	1250*	100 %
4	0.4 mol% $[\mathbf{1}(CuBr)_2]$	6875	55 %
5	8 mol% [**2**CuBr]	1250*	100 %
6	0.8 mol% [**2**CuBr]	38	3 %
7	8 mol% [**2**CuMeCN]BPh_4	325	26 %
8	4 mol% $[\mathbf{1}(CuMeCN)_2](BPh_4)_2$	475	38 %

a) Turnover at one copper atom after 1 h reaction time.

b) After 1 h reaction time.

* Maximum value for the chosen catalyst loading.

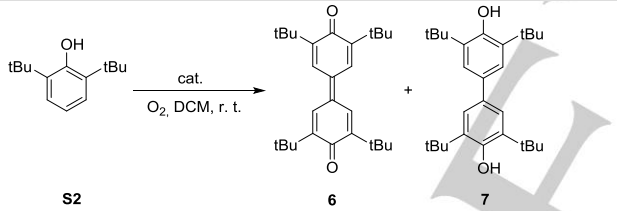
The benchmark catalyst CuBr/NEt_3 displayed a turnover of T = 1225 (entry 1, Table 1) with 8 mol% catalyst loading, whereas a reduction of the catalyst loading to 0.8 mol% resulted in virtually no reaction (entry 2, Table 1). Catalyst $[\mathbf{1}(CuBr)_2]$ with the redox-active ligand showed a significantly higher activity with T = 6875 (entry 4, Table 1). The low catalyst loading of 0.4 mol% was selected due to complete conversion of the starting material in less than one hour with 4 mol% catalyst loading (entry 3, Table

1). In direct comparison, 0.8 mol% of [**2**CuBr] (complete conversion with 8 mol% catalyst loading in one hour, entry 5, Table 1) with the virtually non-redox-active ligand **2** led to a notably smaller turnover of T = 38 (entry 6, Table 1). For [**2**$CuCH_3CN$]BPh_4, a turnover of T = 325 (entry 7, Table 1) was obtained, which can be improved up to 475 h^{-1} (entry 8, Table 1) by using ([**1**$(CuCH_3CN)_2$]$(BPh_4)_2$) with the redox-active ligand **1**. The results demonstrate that the ligands as well as the co-ligands respectively charge of the catalyst have a great impact on the reaction rate. Complex [**1**$(CuBr)_2$] showed the highest activity in the test reaction. The obvious inference is that the redox-activity of ligand **1** supports the activation of dioxygen at the copper atoms due to its electron-donating effect. With 0.4 mol% of catalyst [**1**$(CuBr)_2$], a yield of 97% of **3** was measured after 24 h, indicating no significant catalyst destruction. Moreover, no base addition was required.

Homo-coupling reaction of 2,6-di-*tert*-butylphenol

Next, the oxidative homo-coupling of 2,6-di-*tert*-butylphenol (**S2**) was examined, leading first to biphenol **7**, which rapidly oxidizes further to the *para-para* coupled diquinone (**6**, Table 2). The advantage of this reaction is the clean conversion of **S2** to only one (main) product. According to ^{1}H NMR and GC-MS of the reaction solution, we suggest the formation of 2,6-di-*tert*-butyl-*p*-benzoquinone as by-product (up to 4%) which is primarily

Table 2. Oxidative homo-coupling of phenol **S2** with different catalysts.



S2 **6** **7**

#	catalyst	T [a]	Conversion[b]
1	8 mol% CuBr + 50 mol% NEt_3	75	6 %
2	0.8 mol% CuBr + 5 mol% NEt_3	0	0 %
3	4 mol% [**1**$(CuBr)_2$]	1250*	100 %
4	0.4 mol% [**1**$(CuBr)_2$]	1750	14 %
5	4 mol% [**1**$(CuMeCN)_2$]$(BPh_4)_2$	850	68 %
6	8 mol% [**2**CuBr]	213	17 %
7	8 mol% [**2**CuMeCN]BPh_4	200	16 %
8	0.4 mol% [**1**$(CuBr)_2$] + 50 mol% TEMPO	1650	13 %
9	0.4 mol% [**1**$(CuBr)_2$] + 50 mol% *cis*-stilbene	1650	13 %

[a] Turnover at one copper atom within 1 h reaction time.

[b] After 1 h reaction time.

* Maximum value for the chosen catalyst loading.

observed by using the $CuBr/NEt_3$ catalyst (entry 1, Table 2). The oxidation of phenols to benzoquinones (tyrosinase activity) with copper-dioxygen complexes is typically due to the formation of $\mathbf{Cu_2P^S}$ complexes[50,51] that might be formed in an equilibrium with the $\mathbf{Cu_2O_2}$ complex (well known as key-reactive species in the phenol coupling [33, 52]).In contrast to triethylamine, the electron donating effect of the ligands **1** and **2** shifts the equilibrium to the side of the $\mathbf{Cu_2O_2}$ complex, forming almost no side-products in the phenol coupling reaction. We tested the same catalysts as for oxidative homo-coupling of **S1**, and estimated again the turnover (T) in 1 h reaction time. The catalyst $CuBr/NEt_3$ gave a much lower turnover of T = 75 (entry 1, Table 2) with a catalyst loading of 8 mol%, compared with the homo-coupling reaction of phenol **S1** (T = 1225; entry 1, Table 1). The lower reaction rate can be rationalized by the higher oxidation potential of **S2** (E^0_{OX} = 1.62 V vs. SCE) compared with **S1** (E^0_{OX} = 1.46 V vs. SCE).[33] Complex [**1**$(CuBr)_2$] exhibited a 23 times higher activity with a turnover of T = 1750 (entry 4, Table 2) even with a lower catalyst loading of 0.4 mol%, whereas a conversion of 14% was achieved within 1 h. A longer reaction time of 120 h gave 52% conversion. Complete conversion of the starting material was reached after 1 h by rising the catalyst loading to 4% (entry 3, Table 2). The use of ([**1**$(CuCH_3CN)_2$]$(BPh_4)_2$) reduced the activity (T = 850; entry 5, Table 2) compared with [**1**$(CuBr)_2$]. The application of complexes with the virtually non-redox-active ligand **2** as catalysts resulted in a lower activity, with T = 213 (entry 6, Table 2) for [**2**CuBr] and T = 200 (entry 7, Table 2) for [**2**$CuCH_3CN$]BPh_4, highlighting the advantage of using the redox-active ligand **1** for dioxygen activation.

Next the homo-coupling reaction of phenol **S2** with 0.4 mol% of the catalyst [**1**$(CuBr)_2$] was repeated, but with addition of 50 mol% of a radical scavenger (TEMPO or *cis*-stilbene, Table 2, entries 8 and 9). No significant decrease of the turnover (T) was observed, indicating that no free phenoxyl radicals are formed in the course of the reaction. On the other hand, a radical-radical coupling mechanism with bound phenols is still compatible with these results. This proposal is supported by the ^{19}F NMR spectra taken for the reaction of [**1**$(CuBr)_2$] with 2,3,4,5,6-pentafluorophenol (see SI), displaying a shift in the ^{19}F NMR signal relative to the free phenol, indicating the formation of a complex between the phenol and the copper complex.

Low-temperature UV/Vis experiments

Next, the reactivity of the complexes toward dioxygen was studied. In first experiments, propionitrile solutions of the complexes were cooled to −80 °C, and the changes in the UV/Vis spectra upon addition of a pre-cooled solution of propionitrile, saturated with dioxygen, monitored. Figure 1 visualizes the changes in the UV/Vis spectra upon dioxygen addition.

Since complex [**2**CuMeCN]BPh_4 showed the lowest reactivity in the phenol coupling reactions, one expects this complex to display the lowest reactivity towards dioxygen. The evolution of an intense band at 406 nm (ε = 3300 L mol^{-1} cm^{-1}) was observed in the UV/Vis spectra, with maximum absorbance being reached after 290 s. The wavelength and the high extinction coefficient are characteristic for $\mathbf{Cu_2O_2}$ complexes, and especially comparable to previously reported $\mathbf{Cu_2O_2}$ complexes

with guanidine ligands.[53,54] For prolonged reaction times the bands vanished again, signalling decomposition of this complex even at low temperature of −80 °C. In the case of the reaction of complex [**2**CuBr] as well as both complexes with the redox-active ligand **1** with dioxygen at −80 °C, the UV/Vis spectra gave evidence only for decomposition products, that were responsible for the slow evolution of absorption bands (see SI) that do not vanish at higher temperatures. For [**1**(CuMeCN)$_2$](BPh$_4$)$_2$ and [**1**(CuBr)$_2$] mainly absorption bands at 360 nm and 415 nm were observed upon dioxygen addition. The absorption band at 415 nm was assigned to the twofold oxidized ligand **1**$^{2+}$, in line with the decline of the absorption band at 324 nm due to neutral **1**.[55] The band arises either from the free, oxidized ligand **1**$^{2+}$ or from the oxidized ligand in a copper (dioxygen) complex. Hence the initially formed dioxygen complex is too reactive, even at low temperature, to be spectroscopically studied by the applied methods (e.g. stopped-flow UV/Vis spectroscopy, see SI). Nevertheless, the high electron-density provided by ligand **1** should initially also lead to the formation of **Cu$_2$O$_2$** complexes.

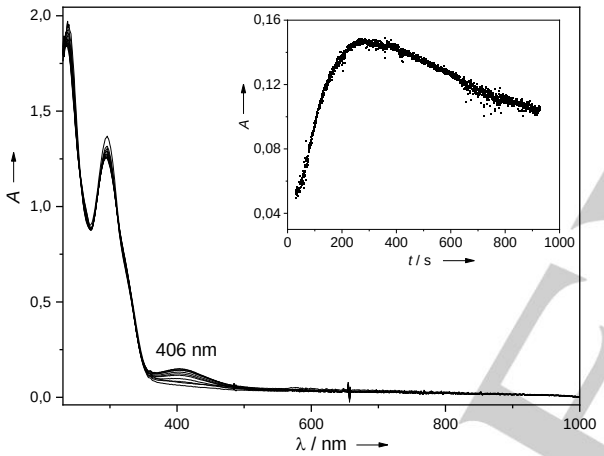


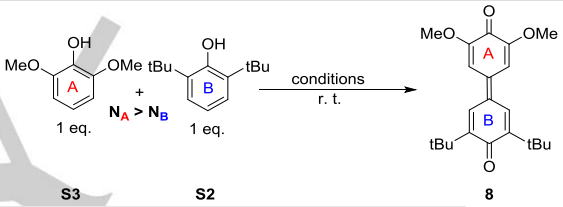
Figure 1. Changes in the UV/Vis spectrum in the first 900 s of the reaction between [**2**CuMeCN]BPh$_4$ ($4.6\cdot10^{-5}$ M) and dioxygen ($6.3\cdot10^{-4}$ M) in propionitrile at −80 °C. Inset: Plot showing the change of absorbance at 406 nm with time.

Chemo-selectivity in the cross-coupling reactions

Next, we studied the oxidative cross-coupling reaction of 2,6-di-*tert*-butylphenol with 2,6-dimethoxyphenol (Table 3) in detail to obtain further insight into the reaction mechanism. Herein, the first step is the formation of the biphenol, which is oxidized for prolonged reaction times to the diquinone as indicated by ^{1}H NMR spectroscopy. According to the literature, one could differentiate between three reaction mechanisms for the oxidative biaryl coupling: 1) the radical-radical coupling ($A^\bullet + B^\bullet$), 2) the heterolytic coupling ($A^+ + B^-$), and 3) the radical-anion coupling mechanism ($A^\bullet + B^-$).[20,24,31,56]

We systematically varied the reaction conditions to elucidate the reaction mechanism (Table 3). For all reactions included in Table 3, the chosen conditions led to quantitative conversion of at least one of the phenols (phenol B). In most cases, quantitative *C-C* coupling (cross- or homo-coupling) was observed. Only in two experiments (entries 1 and 7), side-products were formed. We started our work with the benchmark catalyst CuBr/NEt$_3$ which showed a quite high cross-coupling selectivity of 58% (entry 1, Table 3), but side reactions leading to a low cross-coupling yield of only 38%. Herein, we suggest the formation of 2,6-di-*tert*-butyl-*p*-benzoquinone (~ 8%) as one of the side products, being formed in larger quantities than in the homo-coupling reaction of 2,6-di-*tert*-butylphenol. The complex [**2**CuBr] displayed in the test reaction a cross-coupling selectivity of 54% (entry 2, Table 3) which can be increased further to 70% by using complex [**1**(CuBr)$_2$] (entry 3, Table 3) with the redox-active ligand. Substitution of the bromido ligands by neutral CH$_3$CN, requiring the presence of (weakly coordinating) BPh$_4^-$ counter-ions, did not significantly change the cross-coupling selectivity (entry 4, Table 3), while a slight improvement to 75% cross-coupling selectivity was achieved with HFIP as solvent (entry 5, Table 3).

Table 3. Oxidative cross-coupling reaction between **S2** and **S3** with different catalysts and conditions.



S3 **S2** **8**

#	conditions[a]	selectivity[b] / yield (%)
1	8 mol% CuBr + 50 mol% NEt$_3$, 24 h, DCM, O$_2$	58 / 38[c]
2	8 mol% [**2**CuBr], 24 h, DCM, O$_2$	54 / 54
3	1 mol% [**1**(CuBr)$_2$], 2 h, DCM, O$_2$	70 / 70
4	1 mol% [**1**(CuMeCN)$_2$](BPh$_4$)$_2$, 2 h, DCM, O$_2$	70 / 70
5	1 mol% [**1**(CuBr)$_2$], 24 h, HFIP, O$_2$	75 / 46[d]
6	2 eq. **1**(PF$_6$)$_2$, 3 weeks, DCM	53 / 53
7	10 eq. ^{t}BuOO^{t}Bu, 36 h, MeCN, *hν*	12 / 4[c,d]
8	10 mol% FeCl$_3$, 1.5 eq. ^{t}BuOO^{t}Bu, 24 h, DCM	20 / 14 + 6[e]
9	10 mol% FeCl$_3$, 1.5 eq. ^{t}BuOO^{t}Bu, 24 h, HFIP, 55 °C	57 / 44 + 13[e]
10	0.5 eq. [**1**(CuBr)$_2$], O$_2$, DCM, 1 h; 2) Ar, phenols, 1 h	55 / 55
11	1 mol% [**1**(CuBr)$_2$], 2 h, 2 eq. NEt$_3$, O$_2$	56 / 56
12	1 mol% [**1**(CuBr)$_2$], 2 h, 2 eq. tetramethylguanidine, O$_2$	57 / 57

[a] If not stated otherwise, complete conversion of phenol B was achieved under the applied conditions. [b] Cross-coupling selectivity was determined via ^{1}H NMR by integrating an internal standard, the cross-coupling product and the homo-coupling product (see SI). The average of two experiments is given. [c] Formation of side-products. [d] Incomplete conversion of the starting material. [e] Biphenol product.

The higher cross-coupling selectivity obtained with this solvent, which is widely applied in phenol cross-coupling reactions, is due to three effects: 1) According to the large difference in solvation of the coupling partners, the two crucial parameters (***N*** ("global nucleophilicity") and the oxidation potential) are differently affected, favoring the radical-anion coupling mechanism.[22,57,58] 2) Displacement of the phenol with lower oxidation potential from the metal atom.[31] 3) Decrease of the reaction rate for radical formation, leading to a higher preference for a radical-anion coupling mechanism by inhibition of the radical-radical coupling pathway.[26,59] With 1 mol% of [**1**$(CuBr)_2$] in DCM, complete conversion of the starting materials required less than 2 h (entry 4, Table 3). By contrast, only ~60% of the phenol had reacted after a reaction time of 24 h in HFIP (entry 5, Table 3). We explain this result by a competitive inhibition of the catalyst due to the coordination of HFIP to the catalyst. Indeed, we were able to obtain crystals of [**1**$(Cu(C_6H_2F_6O_2)_2)_2$] (Figure 2) suitable for X-ray diffraction after the oxygenation of a solution of [**1**$(CuCl)_2$] in HFIP, showing the coordination of deprotonated HFIP to the copper atoms. In addition to the higher costs of HFIP, the dramatic decrease in the reaction rate led us to resign the use of HFIP and exploring a novel concept which is not restricted to this solvent. The observed decrease in the reaction rate seems to be a general problem of HFIP as indicated by high catalyst loadings and temperatures, as well as long reaction times in the cross-coupling of phenols in previous works (see Scheme 2).[20,30,31]

Subsequently, we tested the redox-active ligand $\mathbf{1}^{2+}$, which is also potent of phenol coupling [60] in a PCET reaction. A quantitative reaction of $\mathbf{1}^{2+}$ with both phenols led to a value of 53% for the cross-coupling selectivity in DCM solution (entry 6, Table 3), close to the cross-coupling selectivity of 58% for the benchmark catalyst (entry 1, Table 3). These results clearly show that the cross-coupling selectivity in this case is not caused by the preferred coordination of one of the phenols to the copper atom.

To rationalize the observed high cross-coupling selectivity and to exclude a radical-radical coupling pathway, we tested the cross-coupling selectivity for a free radical-radical coupling pathway by generating radicals from irradiation of di-*tert*-butyl peroxide with a Xenon lamp in MeCN. A hydrogen-atom-transfer (**HAT**) process leads to free phenoxyl radicals, which couple spontaneously to the dimer. The cross-coupling chemo-selectivity of this radical-radical coupling process is very low, leading to only 12% of **8** (entry 7, Table 3). The preference for homo-coupling can easily be explained by the favored oxidation of phenol A due to its lower oxidation potential.[20] Another route to generate phenoxyl radicals is the use of $FeCl_3$ as catalyst with di-*tert*-butyl peroxide as oxidation agent.[20] Herein, with 10 mol% of $FeCl_3$ and 1.5 eq. of di-*tert*-butyl peroxide (entry 8, Table 3) a low cross-coupling chemo-selectivity of 20% was obtained. According to the literature,[20] a solvent change to HFIP leads to a radical-anion coupling mechanism. Interestingly, a cross-coupling selectivity of 57% was obtained under similar conditions (entry 9, Table 3). This observation highlights the necessity of HFIP in cross-coupling reactions, accompanied with the search for alternative pathways. Furthermore, the very similar value of ca. 55% in the cross-coupling selectivity obtained with several catalysts/oxidizing agents applied in this work, e.g. with [**2**CuBr], might argue for a similar coupling mechanism, namely a radical-anion one. On the other hand, it has to be a special version of a radical-anion coupling mechanism due to the absence of the solvent HFIP.

The cyclovoltammogram (**CV**) recorded for both phenols in DCM shows no oxidation wave in the potential window permitted by the solvent, indicating that proton transfer is a crucial process in the reaction sequence. Further CV studies demonstrate that both phenols can be easily oxidized after their deprotonation (see SI). Deprotonation of the phenols (Scheme 6) leads to very strong nucleophiles, making the use of HFIP redundant. In the second step phenol A is oxidized. The oxidation potential of deprotonated phenol A (0.52 V vs. Ag/AgCl in DCM) is significantly lower than that of deprotonated phenol B (0.63 V), as estimated by CV measurements after addition of the strong base tetramethylguanidine (see SI). Therefore, more of deprotonated A than of deprotonated B is oxidized. In the third step, the nucleophilic attack from phenolate B followed by an oxidation leads to the cross-coupled product A-B.

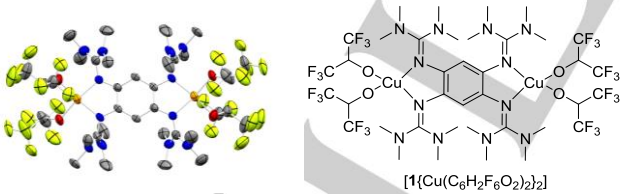
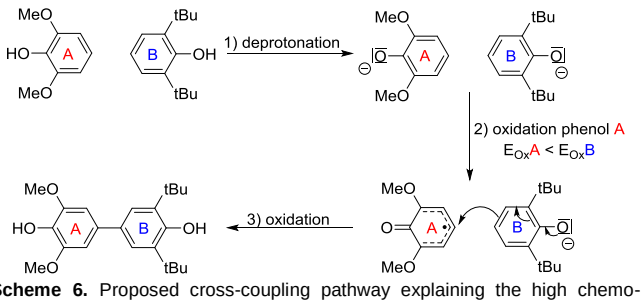


Figure 2. Visualization of the structure of the complex [**1**$\{Cu(C_6H_2F_6O_2)_2\}_2$] in crystals obtained from a HFIP/Et_2O solution (Cu atoms in orange, N atoms in blue, C atoms in grey, O atoms in red and F atoms in yellow). Thermal ellipsoids are drawn at the 50% probability level. Hydrogen atoms and solvent molecules are omitted for clarity.



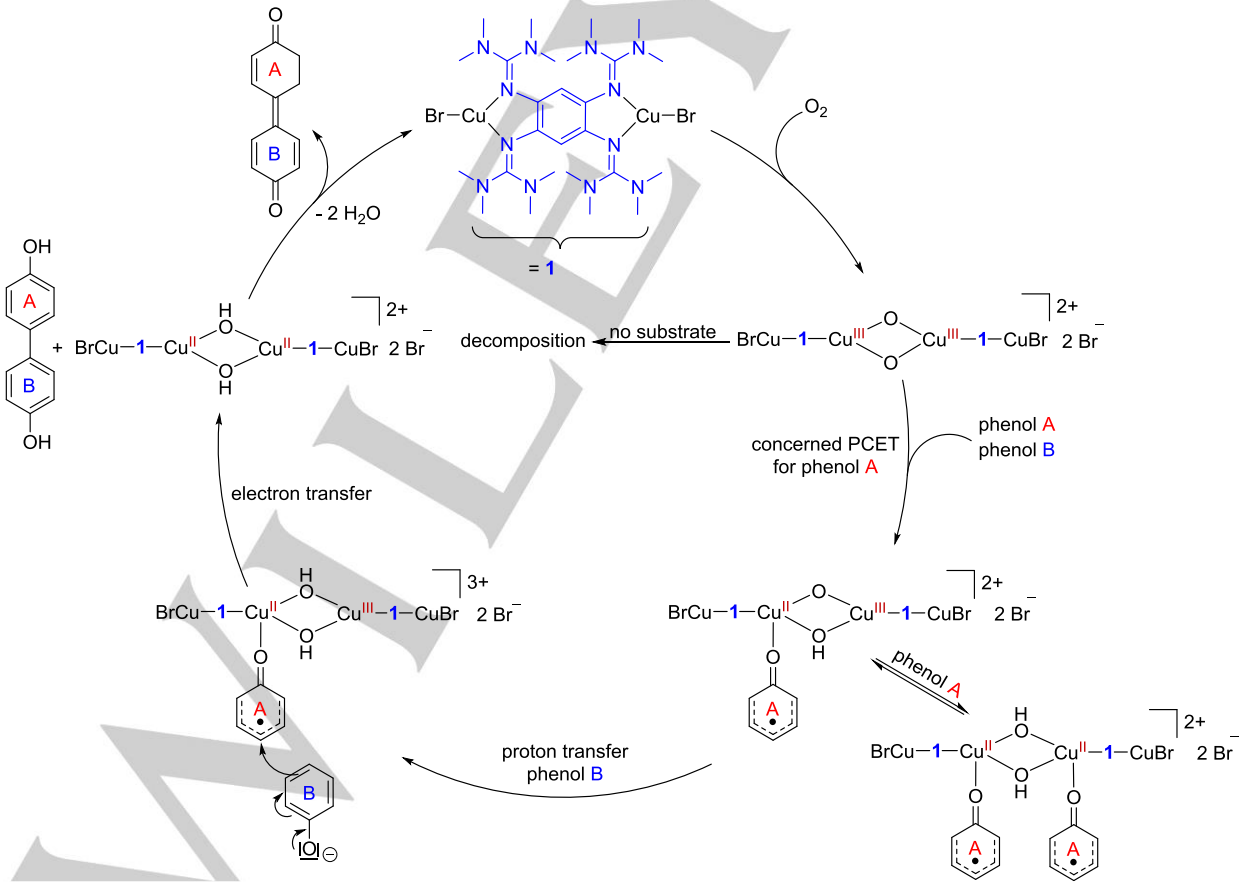
Scheme 6. Proposed cross-coupling pathway explaining the high chemo-selectivity of the cross-coupling reactions.

We also tested if the dioxygen complex of the catalyst is the active species or if a more stable product between dioxygen and the copper complex is relevant for the chemo-selectivity of the phenol cross-coupling (entry 10, Table 3). For this purpose, we passed O_2 at r.t. into a solution of [**1**$(CuBr)_2$] in DCM for 1 h, and subsequently degassed the solution with three pump-thaw cycles. After the addition of 1 eq. of both phenols, the reaction mixture was quenched with degassed $NaHSO_4$ solution and a cross-coupling selectivity of 55% (entry 10, table 3) for the

cross-coupling reaction determined by ^{1}H NMR spectroscopy. The lower selectivity compared with a direct conversion of the phenols with [**1**(CuBr)$_2$] and O_2 (entry 3, Table 3) indeed indicates a short-lived species responsible for the high cross-coupling selectivity, in line with the observed formation of unstable copper-dioxygen species. The conversion of the phenols after degassing the solution can be explained by the formation of stoichiometric amounts of the oxidized ligand, **1**$^{2+}$, from decomposition of the initially formed dioxygen complex, and its reaction with the phenols (as reported already earlier).[60]

Proposed mechanism of the phenol cross-coupling

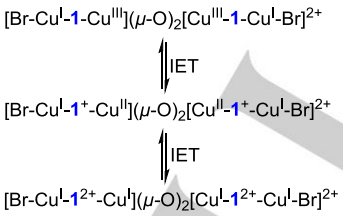
The accumulated experimental data leave no doubt that the initial step of the catalytic cycle is the fast reaction of the complex [**1**(CuBr)$_2$] with dioxygen. Presumably an extremely reactive **Cu$_2$O$_2$** complex is formed, in line with previous studies of *C-C* coupling of phenols with copper catalysts.[33] Experiments in which radical scavengers were added in the phenol coupling reactions are inconsistent with the involvement of free radicals in the catalytic cycle. Moreover, the high selectivity in the cross-coupling reaction cannot be explained with a free radical-radical coupling mechanism, as shown by the direct usage of the radical initiator di-*tert*-butyl peroxide or with the catalyst $FeCl_3$ in DCM. Therefore, the phenoxyl radical formed upon phenol deprotonation and oxidation has to be bound to the copper catalyst. Consequently, we suggest a PCET process from the phenol to the **Cu$_2$O$_2$** complex forming a phenoxyl radical (similar to the conclusions of Itoh *et al.* for **Cu$_2$O$_2$** complexes);[33] however, it has to be bound to one of the Cu atoms. Together with the proposed radical-anion coupling scenario sketched in Scheme 6, a reaction mechanism can be formulated that is consistent with all observations (Scheme 7). To further elaborate on the higher cross-coupling selectivity obtained with copper complexes with ligand **1** compared with ligand **2**, we added 2 eq. of a base, triethylamine (entry 11, Table 3) or tetramethylguanidine (entry 12, Table 3) to the phenols in DCM, followed by the addition of 1 mol% of [**1**(CuBr)$_2$] and dioxygen. In both cases, the differences in the cross-coupling selectivity of both ligands vanished upon base addition. According to the pK_a values, triethylamine (pK_a = 10.74 in H_2O)[61] can only deprotonate 2,6-dimethoxyphenol (pK_a = 9.98 in H_2O),[62] whereas tetramethylguanidine (pK_a = 13.6 in H_2O)[63] is also able to deprotonate the less acidic 2,6-di-*tert*-butylphenol (pK_a = 11.7 in H_2O),[62] in line with the CV studies with base addition (see SI). The obvious inference is that the mode of deprotonation of 2,6-dimethoxyphenol plays a decisive role for the selectivity of cross-coupling with [**1**(CuBr)$_2$]. Thus, we suggest a concerted PCET process for complexes with ligand **1**, preferentially leading to (bound) phenoxyl radicals of 2,6-dimethoxyphenol (A). Reaction with another molecule of phenol A results in the



Scheme 7. Proposed catalytic cycle for the cross-coupling of the two phenols A and B with [**1**(CuBr)$_2$] as catalyst following a radical-anion coupling pathway.

deprotonation of phenol A, coupled with a fast oxidation (E_{Ox}(A) < E_{Ox}(B)) or a concerned PCET, eventually yielding a copper complex with two bound phenoxyl radicals. However, due to their different spatial orientation, these bound phenoxyl radicals cannot couple to the dimer. On the other hand, deprotonation of phenol B (slow oxidation to the corresponding radical) in the vicinity to the copper complex with bound phenoxyl radical A initiates cross-coupling to the product A-B via a radical-anion coupling mechanism (Scheme 7). Consequently, addition of a base (tetramethylguanidine or triethylamine) leads to a decrease of the cross-coupling selectivity due to the generation of stoichiometric amounts of deprotonated phenol A, being now available as reaction partner and yielding the homo-coupling product. Usually, the preferred oxidation of phenol A is the prime obstacle for the cross-coupling of non-complementary phenols. Herein, we suggest this to be the reason for the high cross-coupling selectivity. According to our proposed mechanism, complementary phenols should lead to lower cross-coupling selectivity. This will be discussed in the next section (see ross-coupling reaction to diquinone **13** (entry 6, Table 4)).

As illustrated in Scheme 8, intramolecular electron transfer (**IET**) can lead to several oxidation states of the metal atoms in the **Cu_2O_2** complex formed from [**1**$(CuBr)_2$] and O_2. Due to the instability of this complex, we were unfortunately not able to specify its electronic structure (oxidation states of the copper atoms or the redox-active ligand). In principle, the formation of oligomeric species, connected through bridging dioxygen, is also possible. However, the already quite high charge of +2 of the monomeric units opposes an oligomerization. Furthermore, the complex [**1**$(CuMeCN)_2$]$(BPh_4)_2$ should be a better precursor to such oligomers. Since [**1**$(CuMeCN)_2$]$(BPh_4)_2$ displays a lower activity than [**1**$(CuBr)_2$], the formation of oligomeric appears to be not relevant for the catalytic cycle. In addition, the initially formed **Cu_2O_2** complex, which is only present in catalytic amounts, reacts more likely with a phenol which is available in high excess, than with a second copper complex.



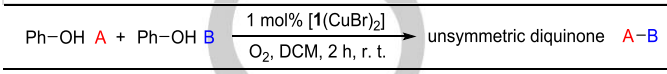
Scheme 8. Three out of a number of possible electronic structures with different copper oxidation states in a **Cu_2O_2** complex with the redox-active ligand **1**.

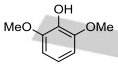
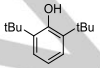
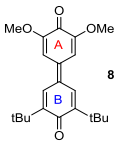
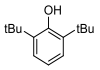
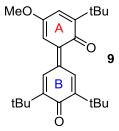
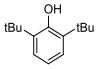
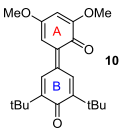
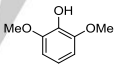
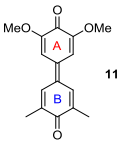
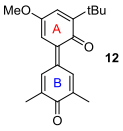
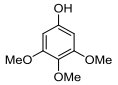
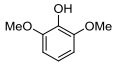
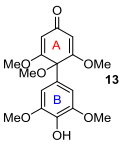
Cross-coupling reactions

Finally, we studied the cross-coupling reaction of further non-complementary phenols (entry 1-5, Table 4, ΔN = −0.35 to −0.52, see SI for detailed values of N and E_{Ox}) to test the scope of the new catalytic reaction. In addition to the already known diquinone **8** [64] we were able to synthesize the new compounds **9**-**12** with a high chemo-selectivity, at ambient conditions, quite fast (2 h) with only 1 mol% catalyst (Table 4) and without the need of HFIP as solvent. Furthermore, we tested a complementary pair of phenols (**13**[20], entry 6, table 4, ΔN = 0.49), which showed the lowest chemo-selectivity in our study as suggested in our mechanistic discussion (see previous section).

For **10**, a subsequent Diels-Alder dimerization to **14** was observed in the presence of traces of acids, e. g. in $CDCl_3$ (Figure 6). The yield of the diquinones **11** and **12** was lower than the cross-coupling selectivity of the *C-C* coupled products.

Table 4. Scope of the cross-coupling reaction to the diquinones **8**–**13**.



#	phenol A	phenol B	product	selectivity[a] / yield (%)
1			 **8**	70 / 70
2			 **9**	80 / 80
3			 **10**	68 / 68
4			 **11**	79 / 45
5			 **12**	74 / 41
6			 **13**	47 / 47

[a] Cross-coupling selectivity was determined via ^{1}H NMR by integrating an internal standard, the cross-coupling product and the homo-coupling product (see SI). The average of two experiments is given.

According to the ^{1}H NMR and ^{13}C NMR spectra of the reaction solution, we suggest the formation of a further *C-O* coupling product, leading to additional NMR signals that occurred alongside the signals due to the known *C-C* coupling products (diquinone, biphenol).[65] This product only appeared if 2,6-dimethylphenol is used and therefore its formation might require

the relatively low steric demand of this phenol. However, we were unfortunately not able to identify this by-product.
For the applied conditions, the reactions are restricted to electron-rich phenols. Halogenated phenols, which have a higher oxidation potential, show no conversion. We suggest this to be a consequence of the electron-rich ligands, that provide the copper atoms with extra electron-density. On the one hand, this leads to a fast dioxygen activation and most importantly to a very efficient phenol deprotonation, accelerating the reactions (as shown by the comparison of catalysts for the homo-coupling reactions). On the other hand, it reduces the oxidation power of the formed **Cu_2O_2** complex due to higher electron density at the copper atoms (Scheme 8).

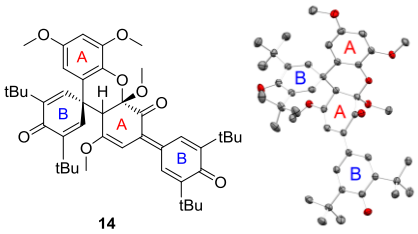


Figure 6. a) Lewis structure of **14**. b) Illustration of the structure of **14** in crystals obtained from $CDCl_3$ solution. Thermal ellipsoids are drawn at the 50% probability level. C atoms in grey, O atoms in red, hydrogen atoms are omitted for clarity.

Conclusions

Herein, we report on the reactivity of copper(I) complexes with a redox-active guanidine ligand (**1**) in the oxidative *C*-*C* homo- and cross-coupling of phenols. The results are compared with experiments, in which the copper complexes of the virtually non-redox-active ligand (**2**) were used. As shown by homo-coupling reactions between 2,4-di-*tert*-butylphenol and 2,6-di-*tert*-butylphenol, a significant higher activity is observed when the redox-active ligand (**1**) is used. The catalyst [**1**(CuBr)] showed a remarkably high reactivity in all test experiments.
Oxidative cross-coupling experiments with two phenols with non-complementary relationship (usually afflicted with a low chemo-selectivity) proved the complex [**1**(CuBr)] to be not only very active, but also to enable cross-coupling reactions with high chemo-selectivity. A detailed inspection of the reaction between 2,6-di-*tert*-butylphenol and 2,6-dimethoxyphenol disclosed the advantages of catalysts with the redox-active ligand (**1**) in comparison to other catalysts with respect to the activity and chemo-selectivity. Moreover, the effect of several modifications of the reaction conditions on the activity and chemo-selectivity was examined, allowing clear-cut conclusions concerning the reaction mechanism. First of all the reaction follows a radical-anion mechanism; a radical-radical mechanism could be excluded. Moreover, the enhancement of the difference between basicity and redox-activity of the initially-formed dicopper bis-μ-oxo complex by the electron-donating ligand **1** was found to be the key point to anticipate the high chemo-selectivity in cross-coupling reactions of phenols with non-complementary relationship. This effect also explains the poor chemo-selectivity observed for cross-coupling reactions between phenols with complementary relationship, in clear difference to traditionally employed catalysts. On the basis of these conclusions, a catalytic cycle was suggested that is in full agreement with all experimental results.
Finally, we elaborated on the scope of the cross-coupling reactions with the newly developed catalyst. For 6 examples a high chemo-selectivity was proven. The advantages of the new catalytic system are: 1) Special solvents such as HFIP or the addition of sub-stoichiometric amounts of a base are not necessary. 2) Fast and efficient cross-coupling reactions of electron-rich phenols with non-complementary relationship are enabled with high chemo-selectivities and without side-products at room-temperature. 3) Dioxygen is used as green and inexpensive oxidizing reagent.
As consequence of the high electron-donation of **1**, the reactions are restricted to electron rich phenols. In ongoing work in our group, we are expanding our experiments to redox-active guanidine ligands with slightly higher redox-potential (see the bisguanidine ligands in ref. 36,38,39), to achieve the optimal balance between fast activation of dioxygen with an efficient phenol deprotonation, and the ability to oxidize less electron-rich phenols.

Experimental Section

Experimental details for the preparation of [**1**$(CuBr)_2$], [**1**$(CuMeCN)_2$]$(BPh_4)_2$, homo-coupling of 2,4-di-*tert*-butylphenol and 2,6-di-*tert*-butylphenol, cross-coupling of **8**–**13**, low-temperature UV/Vis spectroscopic studies of the catalysts [**1**$(CuBr)_2$], [**1**$(CuMeCN)_2$]$(BPh_4)_2$, [**2**CuBr] and [**2**CuMeCN]BPh_4 with dioxygen, and cyclovoltammetric studies of 2,6-di-tert-butylphenol and 2,6-dimethoxyphenol are provided in the SI.

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Keywords: cross-coupling • redox-active ligands • phenols • guanidines • catalysis

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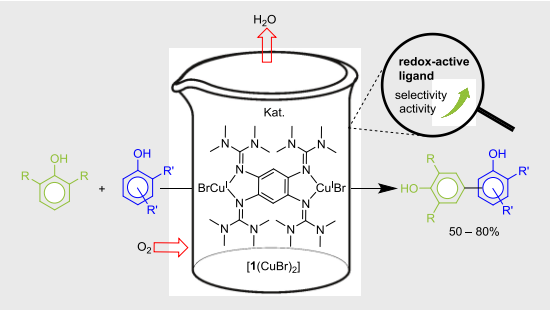
FULL PAPER

Herein we report on new copper catalysts for the *C-C* coupling of phenols using dioxygen as a green oxidation reagent. By using redox-active ligands, the activity as well as chemo-selectivity in the phenol cross-coupling is significantly improved.



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Catalytic Aerobic Phenol Homo- and Cross-Coupling with Copper Complexes Bearing Redox-Active Guanidine Ligands