chemistry proceedings

MDPI

Proceedings Paper

Aerobic and Biomimetic Activation of C-H Bonds of Phenols Catalysed by Copper-Amine Complexes †

Mebrouka Dekhici [1,2], Didier Villemin [1,*], Nawel Cheik [2,3] and Nathalie Bar [1]

[1] Laboratoire de Chimie Moléculaire et Thioorganique, UMR CNRS 6507, INC3M, FR 3038, ENSICAEN et Université de Caen Normandie, 14050 Caen, France
[2] Université de Bechar, Faculté des Sciences et Technologies, BP 417, 08000 Bechar, Algeria
[3] Laboratoire de Catalyse Et Synthèse en Chimie Organique, Faculté des Sciences, Université de Tlemcen, BP 119, 13000 Tlemcen, Algeria
* Correspondence: didier.villemin@ensicaen.fr
† Presented at the 25th International Electronic Conference on Synthetic Organic Chemistry, 15–30 November 2021; Available online: https://ecsoc-25.sciforum.net/.

Abstract: Various copper complexes were prepared (CuCl(phen), CuCl(bipy), CuCl(neocu), CuCl(BPA), [CuCl(OH)(TMEDA)]$_2$) and tested in aerobic room temperature oxidation of p-cresol. The complexe [CuCl(OH)(TMEDA)]$_2$ was found to be the more efficient and was used in o,o and p,p coupling of various phenols and in the formation of quinones under aerobic conditions. The dimerization of substituted naphthols was also investigated. This C-H activation with formation of one C-C bond and one harmless molecule of water with air as oxidant at room temperature represents a biomimetic model of enzyme Laccase.

Keywords: green chemistry; aerobic oxidation; C-H activation; Cu complexe; phenols

Citation: Dekhici, M.; Villemin, D.; Cheik, N.; Bar, N. Aerobic and Biomimetic Activation of C-H Bonds of Phenols Catalysed by Copper-Amine Complexes. *Chem. Proc.* **2021**, *3*, x. https://doi.org/10.3390/xxxxx

Academic Editor: Julio A. Seijas

Published: 15 November 2021

1. Introduction

Many secondary metabolites produced by plants result from the oxidative coupling of phenols as demonstrated by the schools of Barton and Battersby [1].

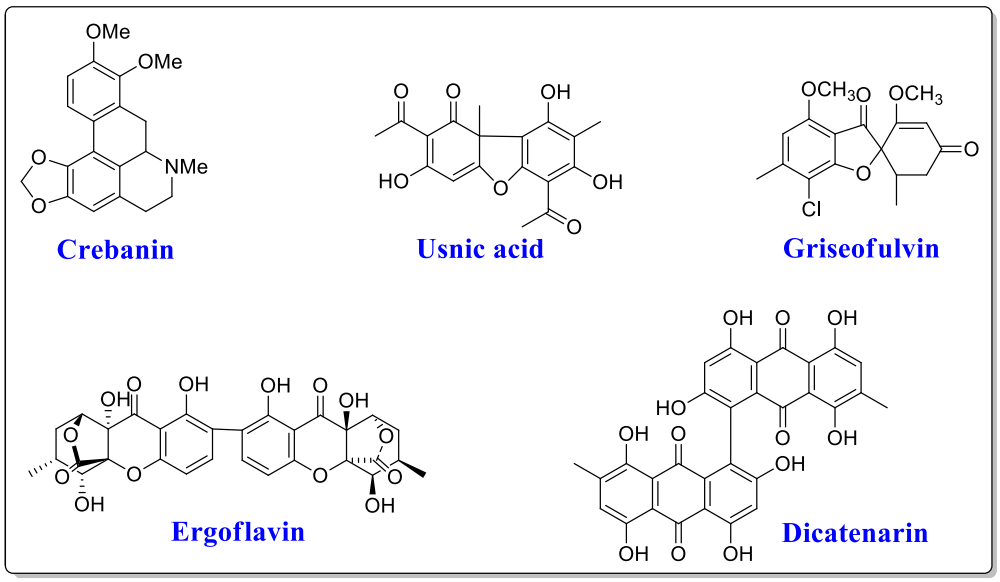
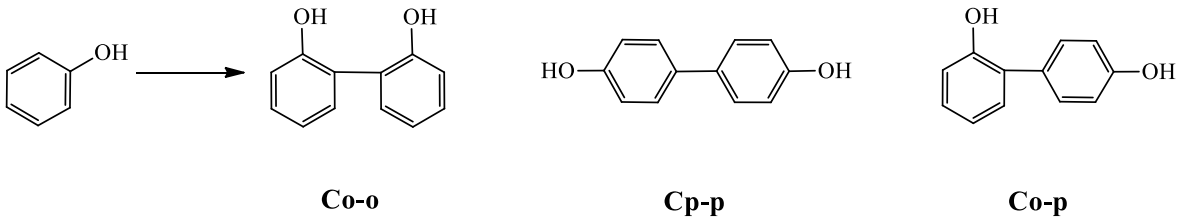


Figure 1. Some natural products formed by oxidative coupling of phenols.

Phenols are oxidized by air (aerobic oxidation) or hydrogen peroxide in the presence of oxidases which are enzymes containing copper [2], iron or vanadium in their catalytic site. The reactions consist in the oxidation of aromatic CH bond with the formation of C-C and/or C-O bonds (aromatic CH and phenol) along side hydroxylation and subsequent oxidation to quinone.



Scheme 1. Different o-o, p-p and o-p couplings of phenol.

Pummerer was a pioneer in the study of the oxidation of phenols under stoichiometrically conditions by iron III complexes ($FeCl_3$, $K_4Fe(CN)_6$). Barton who have used these reactions in biomimetic syntheses of many natural products [1,3,4], has suggested that these reactions were explained by monoelectronic transfers leading to a phenoxyl radical whose mesomeric forms could then react to conduct to dimers.

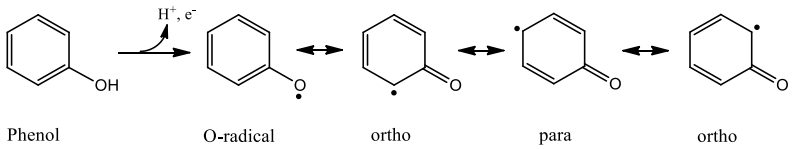
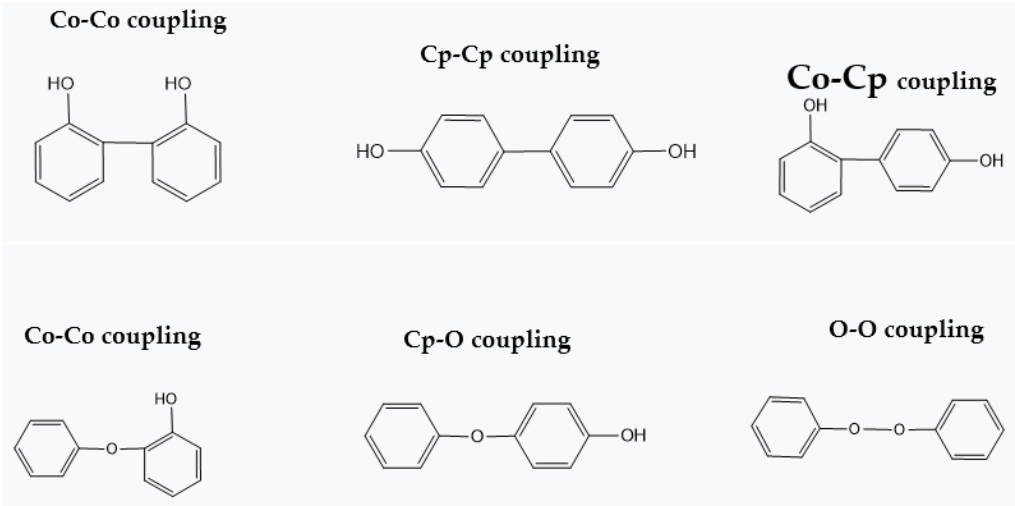


Figure 2. Phenoxy radical and its mesomeric forms.



This Barton hypothesis leads to an explanation, although in fact it seems that the radicals (or radical-ions) or equivalent organometallic species are involved in a restricted space (solvent cage, dimer) to observe these dimerisations and not classical free radicals.

The most studied oxidases in the oxidation of phenols are the Laccase and Tyrosinase, enzymes containing copper atoms in their active site. Oxidations by copper complexes are well documented.

2. Discussion

First, we have prepared copper complexes and an iron (III) complex containing nitrogen ligands, which are hard ligands according to the Pearson definition, therefore not very oxidizable and stabilizing the high degree of oxidation of the metal.

3. Choice of a Catalyst

The complexes displaying bipyridine, phenanthroline, neocuproine, and propan-1,3-diamine ligands were obtained by simple complexation of cupric chloride. On the other side, the $[CuCl(OH)TMEDA]_2$ described by Koga, was prepared from cuprous chloride, as the polyethylenimine cuprous chloride complex (PEI).

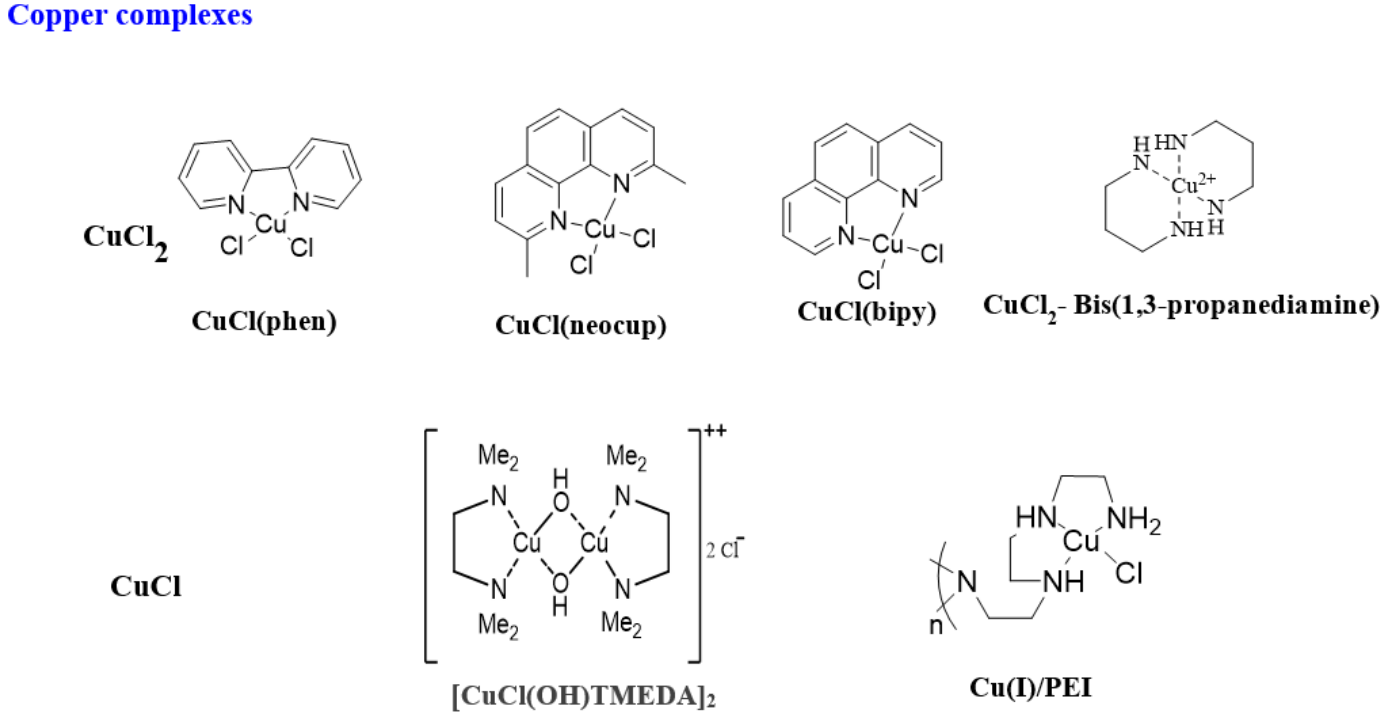
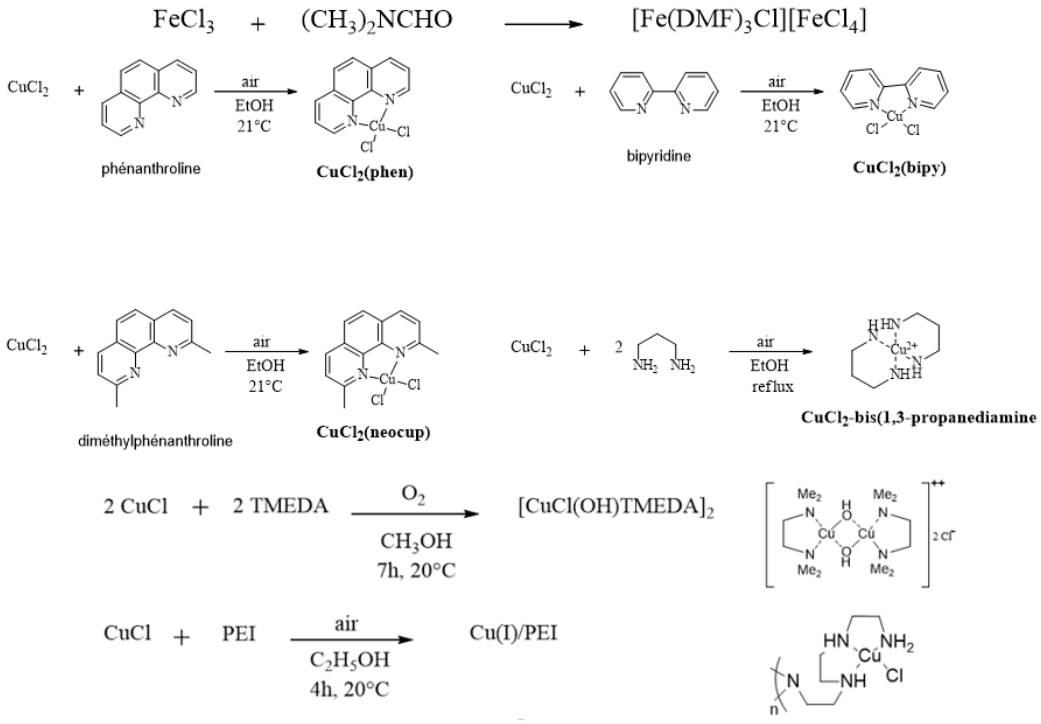
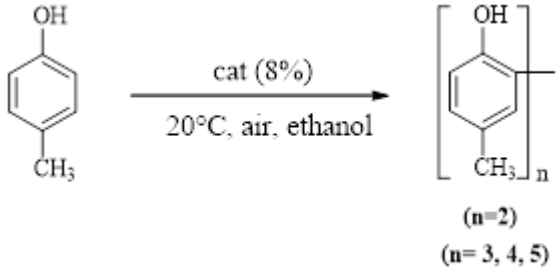


Figure 3. Stuctures of some copper complexes.

Finally for the tested soft we have prepared the complex of iron (III) $(Fe(DMF)_3Cl)FeCl_4$.



We have tested these complexes in the aerobic oxidation of paracresol in ethanol under both catalytic and aerobic (air oxidation) conditions. Ethanol was chosen as a green solvent, although it can also oxidize in this reaction. The reaction was carried out at room temperature in air by simple stirring in the absence of light. As the oxidations take place very slowly, we analyzed the products formed after 120 h. A white reaction (without catalyst) have shown that no oxidative coupling of cresol occurs in the absence of a catalyst.



Oxidative conditions:

Phenol/Cu (100/8)

Phenol/Fe (100/8) room temperature (20 °C), EtOH, 120 h.

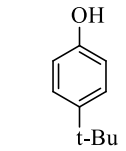
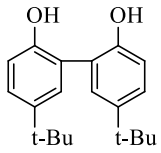
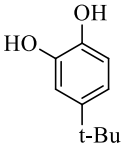
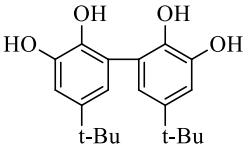
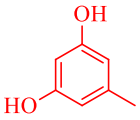
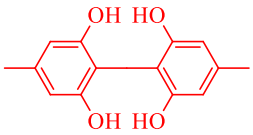
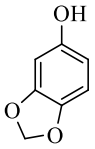
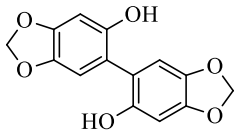
Complexe	
CuCl(OH).TMEDA	**Yield (%)**
Cu(I)/PEI	31
CuCl(phen)	17
CuCl(neocup)	39
CuCl(bipy)	9
$CuCl_2$- Bis(1,3- prdia)	41
$[Fe(DMF)_3Cl][FeCl_4]$	63

Along with the coupling products (polycresols), traces of oxidation products are found which have not been identified. The results are reported in Table 1. Polycresols were identified by NMR and mass spectroscopy.

The iron complex appears to be active as a catalyst, but since it is not very stable and has led to unclear products, further studies have been abandoned. The Koga complex, $[CuCl(OH)TMEDA]_2$ dimer seems to be the most efficient, so we have selected it with the CuCl complex (PEI) for the continuation of our work.

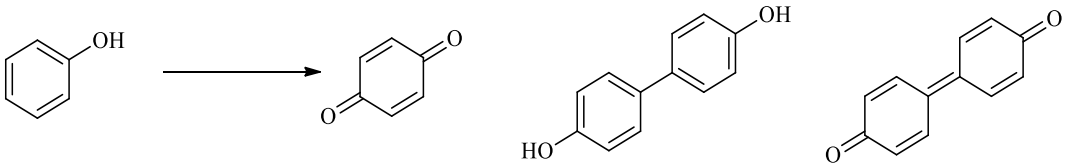
Polycresols were analyzed by HPLC / mass spectroscopy and a distribution with n = 2 to 5 was found. Besides the coupling products resulting from the formation of a C-C bond, there are oxidation products leading to quinones.

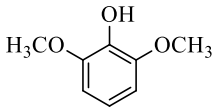
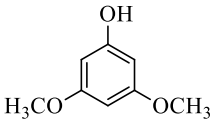
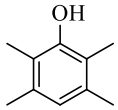
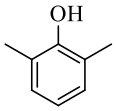
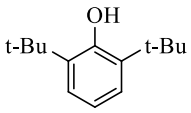
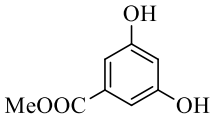
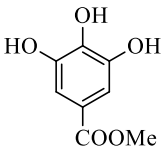
The ortho-ortho coupling has been studied with phenols whose para position is substituted or heavily hindered. The products obtained by aerobic oxidation in ethanol in the presence of $[CuCl(OH)\ TMEDA]_2$ as a catalyst are reported in Table A.

Reagent	Product	Yield(%)
		63
		67
		**80**
		48

Phenol/Cu = 100/8, ethanol, 21°C, 96 h.

The para-para coupling was investigated under the same experimental conditions with the phenols whose ortho positions are substituted. It is noteworthy that the electron donor groups (OR or R) promote the oxidation reaction while the electron withdrawing groups (COOR, NO_2) have a negative effect.

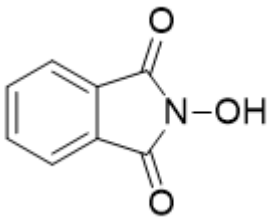


Reagent	Yield (%) Quinone	Yield(%)Bisphenol	Yield (%) Diphenoquinone
	0	0	53
	**16**	**75**	**0**
	0	15	41
	0	0	**87**
	0	0	**99**
	0	0	0
	0	0	0

Phenol / Cu (100 / 8), 21°C, EtOH, 96 h.

4. Oxidation in the Presence of NHPI

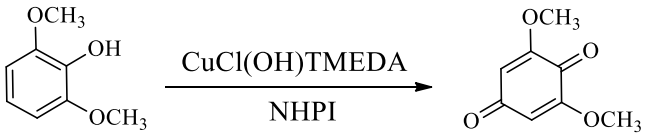
N-hydroxyphthalamide (NHPI) has been used in oxidation reaction as a source of N-oxyl radical which promotes some monoelectronic oxidation.

NHPI: 

The use of NHPI is well documented [5]. We have studied the oxidation of 2,6-dimethoxyphenol in the presence of NHPI under different conditions affording 2,6-dimethoxyquinone, and the best result was achieved in the non-protic solvent, acetonitrile. In general, NHPI inhibits C-C couplings in favor of oxidation to quinone.

The highly oxidizable pyrogallol phenol in the presence of $[CuCl(OH)TMEDA]_2$ have been converted into Purpurogallin, which is also the oxidase product of pyrogallol. The

reaction is very clean and constitutes a good synthesis of purpurogallin under green conditions.

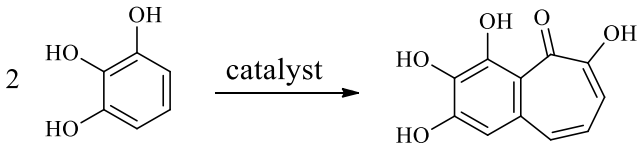


Phenol/Cu/NHPI = 100/8/10, 21°C, 96 h.

Solvent	Temperature (°C)	Yield (%)
EtOH	21	16
EtOH	70	27
CH_3CN	21	32
CH_3CN	**70**	**92**

5. Purpurogallin

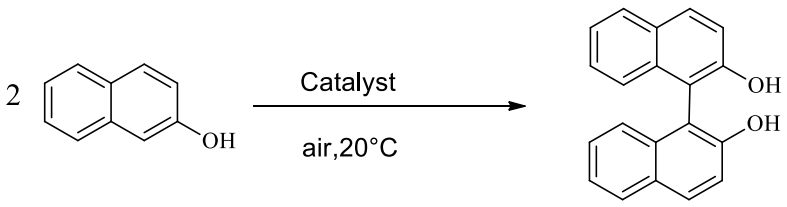
Oxidation at room temperature with the formation of carbon dioxide and water as a by-product. This reaction also shows that [CuCl(OH)TMEDA]$_2$ is a model for oxidase [6].



Catalyst	Solvent	T (°C)	Yield (%)
CuCl(OH)TMEDA [a]	EtOH	20	43
Cu(I)/PEI [b]	EtOH	20	0
CuCl(OH)TMEDA / NHPI [c]	CH_3CN	70	0

6. Binaphthols

The oxidation of 2-naphthol under aerobic conditions [7] in the presence of [CuCl(OH)TMEDA]$_2$ furnishes binaphthol. here we have extended our studies to substituted 2-naphthols

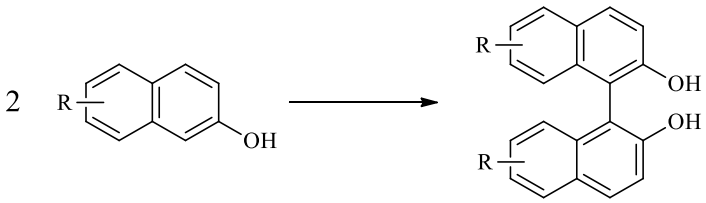


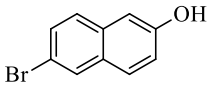
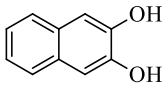
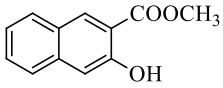
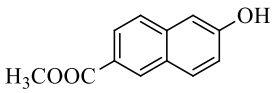
Catalyst	Solvent	T (°C)	Yield (%)
CuCl(OH)TMEDA [a]	**EtOH**	**21**	**86**
CuCl(OH)TMEDA / NHPI [b]	CH_3CN	70	43
Cu(I)/PEI [c]	EtOH	21	77
$CuCl_2$(phen) [a]	EtOH	21	29

$CuCl_2$(neocup) [a]	EtOH	21	31

Conditions: [a] naphthol/Catalysor (100/8), 96 h. [b] naphthol /Cu/NHPI (100/8/10), 96 h. [c] naphthol/Cu (100/3.75) (1.5 mL), 96 h.

The examples are summarized in Table. The binaphthols obtained here are on a racemic form. Moreover, binaphthols are very important in asymmetric synthesis.

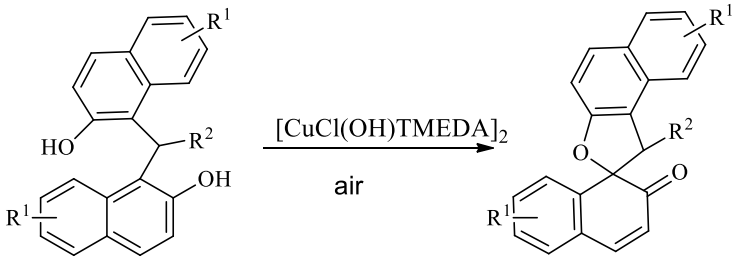


Reagent	[CuCl(OH)TMEDA]$_2$[a]		[CuCl(OH)TMEDA]$_2$/NHPI][b]		Cu (I)/PEI[c]	
	t (h)	Rdt (%)	t (h)	Rdt (%)	t (h)	Rdt (%)
	96	80	96	43	96	0
	96	67	96	0	96	traces
	24	85	96	31	96	10
	24	**99**	96	**49**	96	traces

Conditions: [a] naphthol/Cu (100/8), 21 °C, EtOH, [b] naphthol /Cu/NHPI (100/8/10), 70°C, CH_3CN, [c] naphthol /Cu (100/3.75), (1.5 mL), EtOH, 21 °C.

7. Case of Alkylidenenaphthol

We have shown that methylenedinaphthol aerobically oxidizes at room temperature by spiraling, creating a C-C bond and de-aromatization of one of the aromatic rings [8].



naphtol/Cu (100/8), 21°C, 48 h.

References

1. Taylor, W.I.; Battersby, A.R.; Barton, D.H.R.; Cohen, T. *Festschrift Arthur Stoll*; Birkhauser: Basel, Switzerland, 1957; pp. 117–143.
2. Allen, S.E.; Walvoord, R.R.; Padilla-Salinas, R.; Kozlowski, M.C. Aerobic Copper-Catalyzed Organic Reactions. *Chem. Rev*. **2013**, *113*, 6234–6458, doi :10.1021/cr300527g.
3. Scott, A.I.; Taylor, W.I.; Battersby, A.R. *Oxidative Coupling of Phenols*; Dekker: New York, NY, USA, 1967; pp. 1–387.
4. DonaldGordon, P.D.M.; Hamilton, A., CHAPTER II—Mechanisms of Phenolic Oxidative Coupling Reactions. *Org. Chem.* **1973**, *5*, 97–134, doi :10.1016/B978-0-12-697250-4.50007-1.
5. Terent'ev, A.O.; Krylov, I.B.; Lipatnikov, A.D. Oxidative coupling of N-hydroxyphthalimide with toluene. *Russ. J. Gen. Chem.* **2014**, *84*, 2084–2087, doi : 10.1134/S1070363214110061.
6. Dib, S.; Villemin, D.; Hamhami, A.; Mostefa-Kara, B.; Bar, N.; Dekhici, M.; Cheikh, N. On the green catalytic synthesis of Purpurogallin. *Rev. Roum. Chim*. **2020**, *65*, 1153–1157, doi: 10.33224/rrch.2020.65.12.1.
7. Jaffrès, P.-A.; Bar, N.; Villemin, D. Phosphonation of 1,1′-binaphtalene-2,2′-diol (BINOL): Synthesis of (R) and (S) 2,2′-dihydroxy-1,1′-binaphtalene-6,6′-diyldiphosphonic acid. *J. Chem. Soc. Perkin I* **1998**, *1*, 2083–2089, doi: 10.1039/A801522H.
8. Dekhici, M.; Plihon, S.; Bar, N.; Villemin, D.; Elsiblani, H.; Cheikh, N. Aerobic Copper Catalytic Oxidation of Methylene and Arylidenebisnaphthols: A Green and Efficient Synthesis of Spironaphthalenones. *ChemistrySelect* **2019**, *4*, 705–708, doi: 10.1002/slct.201803153.