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OXIDATIVE PHENOL COUPLING WITH CUPRIC-AMINE COMPLEXES

Ben Feringa and Hans Wynberg*
Department of Organic Chemistry,
The University, Zernikelaan, Groningen, The Netherlands

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The oxidative coupling of phenolic compounds as a mode of formation of a diversity of biological important structures has been investigated for a long time[1]. Phenol oxidations with modified metal complexes have received considerable attention during the last years[2].

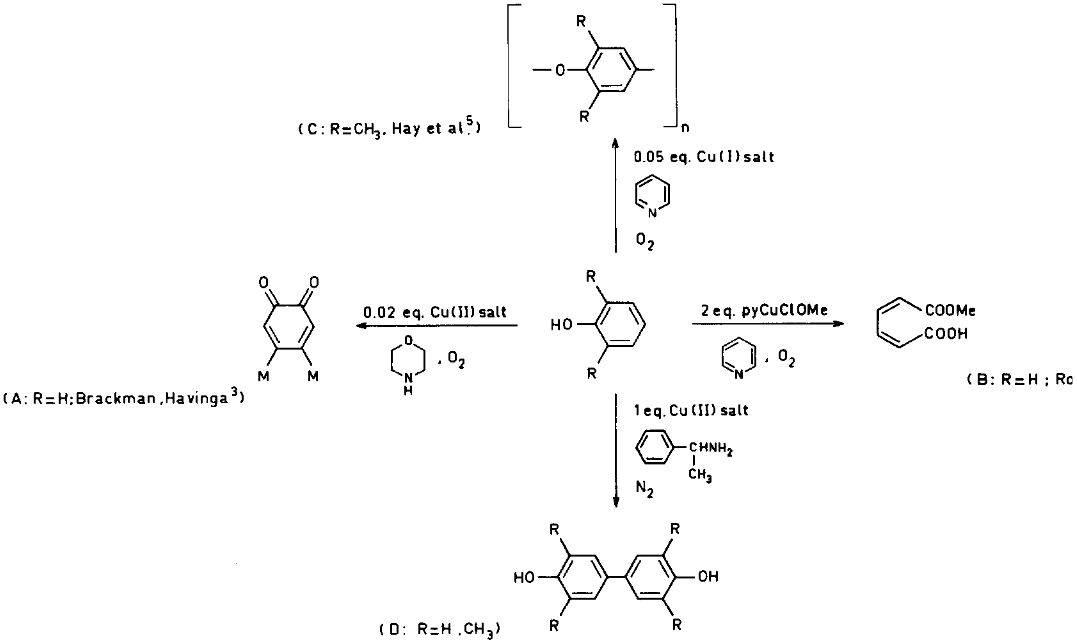
Although the role of copper ions in enzymic (laccase, tyrosinase) phenol oxidations has been recognized[1,2], relatively little attention has been paid to the use of copper complexes in phenol oxidations, either as a synthetic method or in a biomemitic type synthesis of natural products. Oxidations of phenols using copper complexes under aerobic conditions yield quinones, polyethers or carbon-carbon bond cleaved products. Thus Brackman and Havinga, in a study of the mode of action of tyrosinase, reported the use of catalytic amounts of a cupric-morpholine complex in the oxidation of phenol giving *o*-benzoquinone as a primary product followed by substitution and oxidation to *di*-morpholino-substituted *o*-benzoquinone (Scheme I, A)[3].

Rogič and coworkers recently showed that oxidation of phenol using an excess of the pyridine-cupric complex PyCuClOMe as oxidant gave *cis*-,*cis*-muconic acid *via* an intermediate *o*-benzoquinone. When an oxygen substituent is already present in the *ortho* position of phenol - as in the case of catechol or *o*-benzoquinone - oxidation to *cis*-,*cis*-muconic acid occurs also under anaerobic conditions (Scheme I, B)[4].

Furthermore, the formation of polyethers from the cupric-pyridine complex catalyzed oxidation of 2,6-dimethylphenol, in which *o*-quinone formation is blocked, under aerobic conditions is a well-described process (Scheme I, C)[5].

Exclusion of oxygen in the oxidation of phenol 1 could lead to the elimination of pathways A and B, possibly giving coupled phenolic products (Scheme I, D)[6].

We now wish to report this supposition to be correct. Using cupric-amine complexes under anaerobic conditions in molar quantities, we have observed the intra- and intermolecular coupling of phenols as a general reaction.

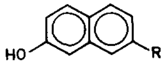


Scheme I: Oxidations of phenol and 2,6-dimethylphenol with copper complexes.
M= morpholine
py= pyridine

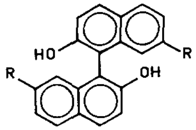
The green or blue coloured stock solutions of the cupric-amine complexes were prepare stirring $Cu(OAc)_2H_2O$ or $Cu(NO_3)_23H_2O$ and amines in a 1 to 3 ratio in either methanol, etha water or alcohol-water mixtures at room temperature under nitrogen for 15 minutes.

A typical oxidative coupling using these complexes was carried out in the following m To a solution of the complex formed from 0.72 g (3.0 mmol) $Cu(NO_3)_2.3H_2O$ and 1.09 g (9.0 m dl-α-phenylethylamine[7] (α-P.E.A.) in 30 ml of CH_3OH, 0.43 g (3.0 mmol) of 2-naphthol (2) d solved in 10 ml CH_3OH was added and the mixture was stirred at room temperature under nitr for 20 hours. The dark-brown product - probably the copper-dinaphthol-amine complex - was composed with dil. hydrochloric acid and gave after a normal work-up 1,1'-dinaphthol (3) i 62% yield (m.p. 216-218°C). A similar oxidation of 2 in water as a solvent at 100°C using cupric complex of pyridine gave 3 in 70% yield[9].

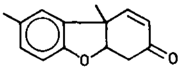
The oxidations of the following phenols using the cupric-α-P.E.A. complex were also investigated.



2, R=H
5, R=OH



3, R=H
6, R=OH



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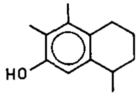

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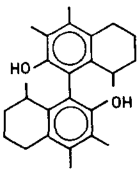

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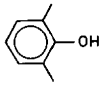

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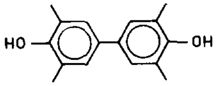

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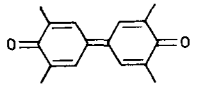

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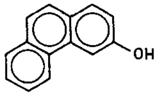

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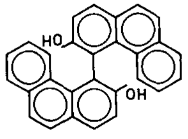

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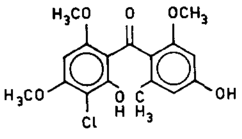

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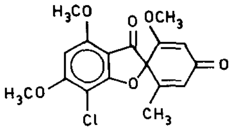

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The oxidation of *p*-cresol gave "Pummerer's ketone" (4) in 15% yield. The dimer (6) of 2,7-dihydroxynaphthalene (5) could be isolated in 25% yield and dimerization of 3,4,8-trimethyltetrahydronaphthol (7)[10] gave 8 in 46% yield.

Oxidation of 2,6-dimethylphenol (1) with the cupric-α-P.E.A. complex under nitrogen gave dimers 9 and 10 as a 7 to 1 mixture in 20% yield. Only traces of polymers were present (Scheme I, C and D). The coupling of 3-hydroxyphenanthrene (11)[11] occurred at the hindered 4-position and the racemic 4,4'-biphenanthrol (12) was obtained in 20% yield[12]. A biogenetic type synthesis of dehydrogriseofulvin[1,13] could also be achieved. Oxidation of griseophenone 13 with the cupric-dl-α-P.E.A. complex in methanol, water (1:9) gave the C-O coupled product 14 in 40% yield, identical with an independently prepared sample of the compound[13].

On the basis of the present results it is clear that a diversity of phenol oxidation reactions can be performed with a cupric-amine complex. Considerable control can be exercised over the nature of the products by considering the structure of the starting phenol and the presence or absence of oxygen.

It is not too far fetched to suggest that this multi-parameter dependence in copper-amine oxidations is reminiscent of the known lack of specificity of many phenol oxidases[1].

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6) Endres and coworkers have shown that it is possible to get 3,3',5,5'-tetramethyldiphenoquinone as a major product from the oxidation of 2,6-dimethylphenol with molar quantities of cupric pyridine complex under nitrogen (ref. 5).
7) Using d-α-phenylethylamine, low but reliable asymmetric induction has been achieved and will be the subject of a separate communication. B. Feringa and H. Wynberg, manuscript in preparation.
8) Identical with the product of a $FeCl_3$ oxidation of 2. The remaining 38% consists mainly of starting material.
9) Reaction time, 3 minutes.
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