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Biomimetic Asymmetric Oxidative Coupling of Phenols

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This paper describes the first examples of asymmetric induction in the oxidative coupling of phenols using chiral oxidants. When chiral cupric–amine complexes were used as oxidants, low asymmetric induction was achieved in the coupling of naphthols. The formation of optically active *d*-dehydrogriseofulvin and *l*-Licarin A using the cupric–*l*-α-phenylethylamine complex perhaps mimics the action of copper-containing enzymes known to catalyze phenol coupling.

INTRODUCTION

Few problems in asymmetric synthesis are more challenging than that of finding ways to transfer chirality efficiently from chiral reagents to achiral substrates (*1*). Among asymmetric syntheses, oxidation reactions are relatively unexplored, comparative to reductions, additions, and rearrangements (*2*). Many types of oxidations could be involved in asymmetric biosynthetic processes, and recently large asymmetric inductions in catalytic epoxidation using alkaloids (Wynberg *et al.*) (*2*, *3*) and vanadium and molybdenum complexes [Sharpless *et al.* (*4*) and Yamada *et al.* (*5*)] have been reported.

It has long been recognized that oxidative coupling of phenols serves as a key-step in the biosynthesis of many classes of natural products (*6–8*). Although in a few cases aryloxyradicals have been detected, neither the mechanism nor the reactive species during enzymic phenol coupling has been elucidated (*9*, *10*).

One of the major unsolved problems concerning the mechanism of enzymic phenol oxidation is the stereospecificity of these reactions. Many enzymic phenol coupling products are chiral (*6–8*). The elements of chirality are often partly or totally introduced during the coupling reaction (*6*).

The presence of asymmetric centers in the substrate and the introduction of new chiral elements during the coupling or the creation of chirality during the coupling step starting with achiral substrates give rise to a complex of stereochemical factors. There are some reports that stereochemical control during the coupling step can be exerted by the asymmetric centers present in the substrate (*6*, *11*). In alkaloid syntheses, especially in the conversions of 1-benzyl-isoquinolines into morphine alkaloids (*11*), the stereospecificity during the coupling reaction arises from the fact that with a given configuration at the asymmetric center, one of the diastereomeric coupling modes is strongly favored. Bobbitt and co-workers (*12*), in a study of the intermolecular oxidative coupling in the isoquinoline series, reported the stereoselective and

[1] Dedicated to my esteemed teacher, Professor William S. Johnson.

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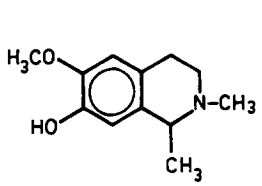
stereospecific electrochemical dimerization of tetrahydroisoquinoline (**1**). We recently reported (*13*) the stereospecific coupling of tetrahydronaphthalene (**2**) using $K_3Fe(CN)_6$, in which coupling the stereospecificity is caused by the presence of an asymmetric centre in the substrate.



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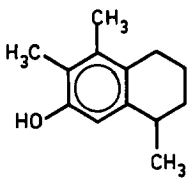

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The *in vivo* asymmetric phenol oxidation, in which the enzyme is the chiral agent, is probably common to several biosynthetic coupling pathways (*6*). Several purified enzymes as well as cell-free extracts of higher plants have been found to catalyze the coupling of phenols (*6*, *9*). Most of these studies have been carried out with the horseraddish peroxidase–hydrogen peroxide system (*6*, *7*). The results of these oxidations with different substrates, especially the oxidations in which new centers of chirality are generated and which could be of interest from an enzyme-stereospecificity point of view, are summarized by Scott (*7*). In none of the examples has any optical activity been observed in the products (*7*). One explanation for these observations is that the coupling occurs outside the active site of the enzyme. The peroxidases and oxidases catalyze the production of free radicals, which are involved in the oxidative coupling.

For phenol oxidations only few reports exist of *in vitro* stereochemical control by external chiral agents. An interesting observation was made by Nozawa and Hatano (*14*) who investigated the copper (II)–poly-L-lysine complex as a model for enzyme-catalytic behavior in the oxidation of 3,4-dihydroxyphenylalanine (DOPA). They observed a preference of D-DOPA oxidation using this complex. Morrison and Bayse (*15*) observed in the horseradish-peroxidase (HRP)-catalyzed oxidation of tyrosine that the D-tyrosine was more readily oxidized than the L-tyrosine. In contrast to this result, lactoperoxidase (LP) catalyzed the oxidation of L-tyrosine more readily than that of the D-isomer. These examples appear to be the first reports of stereoselectivity in phenol oxidations. Furthermore, prior to these observations no peroxidase stereospecificity has been reported (*15*).

Taking these data into account it is problematical how a chiral redox catalyst could achieve asymmetric induction in phenol coupling reactions *in vitro*. Nevertheless because of the paucity of experimental evidence in this intriguing area, we set out to try to achieve asymmetric induction in phenol coupling reactions.

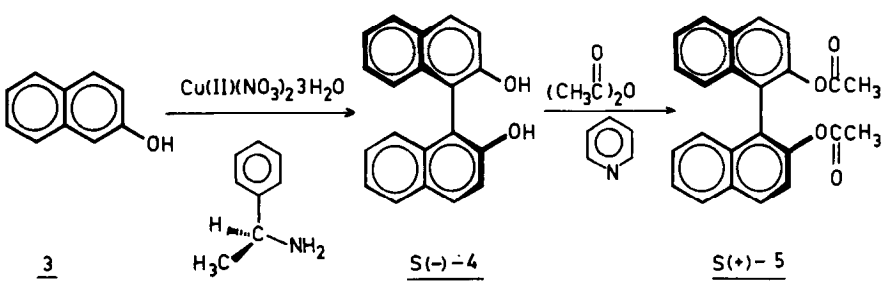
Attempts to achieve this goal were mainly based on the use of chiral metal complexes.[3] A successful route via optically active cupric–amine complexes will be described.

[3] Several attempts to achieve asymmetric induction in phenol coupling using chiral modifications of the manganic tris(acetylacetonate) complexes (*16*) or chiral modifications of the ferric-DMF complexes which Tobinaga *et al.* (*17*) reported, failed.

RESULTS AND DISCUSSION

The cupric–amine complexes described previously (*18*) could be attractive oxidants for asymmetric phenol coupling reactions, both because they are easily prepared and because the structure can be varied readily. There are indications that complexation of the phenolic compounds occurs, which is likely a fundamental requirement for asymmetric inductions. 2-Naphthol (**3**) was chosen as a substrate in our initial studies for the following reasons: (a) it is easy to oxidize; (b) all oxidation products have been characterized; (c) often high yields of 2,2′-dihydroxy-1,1-dinaphthyl (**4**) are formed; (d) the enantiomers have been separated and characterized, and the absolute configurations are known; and (e) the enantiomeric dimers have a relatively high optical stability.

The optically active cupric–*l*-α-phenylethylamine complexes [Cu(II)–*l*-α-P.E.A.] (Scheme 1) were prepared by stirring cupric acetate or cupric nitrate and the amine in a 1 to 4 molar ratio in methanol at room temperature for 15 min under a nitrogen atmosphere. The oxidation of 2-naphthol (**3**) was performed by stirring a mixture of the cupric–*l*-α-P.E.A. complex and **3** in equimolar quantities at room temperature for 20 hr under a nitrogen atmosphere (*18*).



SCHEME 1. Oxidation of 2-naphthol (**3**).

Optically active **4** was obtained in 63% chemical yield. The optically active 2,2′-dihydroxy-1,1′-dinaphthyl (**4**) obtained via asymmetric oxidation had the rotation: $[\alpha]_{578}^{22}$ − 0.98 ± 0.10° (*c* 0.9, THF). An optical purity of 2.5% is calculated for this material based on $[\alpha]_{578}^{22}$ − 38.0 ± 0.5° (*c* 1.0, THF) for optically pure S(−)-**4** (*21*). The diacetate **5**, $[\alpha]_{578}^{22}$ + 0.40 ± 0.05° [*c* 2.1, $(C_2H_5)_2O$] with an optical purity of 2.8% was obtained via esterification of **4**. Optically pure diacetate S(+)-**5**, $[\alpha]_{578}^{22}$ + 13.8 ±0.2° [*c* 0.76, $(C_2H_5)_2O$], was obtained from optically pure S(−)-**4**.

Only nonfractionating procedures were used to obtain the product to avoid any change in the enantiomeric ratio in going from crude reaction products to pure compounds.

All spectral data (except for chiroptical data) of the optically active dimer **4** and diacetate **5** were identical to those of the racemic compounds (*18*, *19*) and those of optically pure **4** and **5**, compounds which were prepared independently (*20*, *21*). The optical purity of the S(−)-**4** obtained via resolution (*20*, *21*) is probably >95% on basis of the specific rotation: $[\alpha]_{456}^{22}$ −52.0 ± 0.7° (*c* 0.99, THF) (mp, 204.3–204.9°C); lit (*21*), $[\alpha]_{546}^{25}$ −51.5 ± 0.7° (*c* 1.0, THF) (mp, 207–208°C).

The enantiomeric excess of optically pure **5** obtained via the asymmetric oxidation of

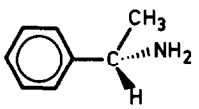
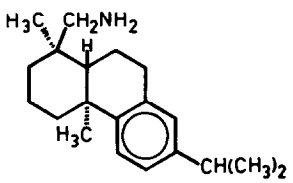
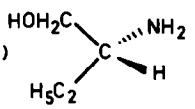
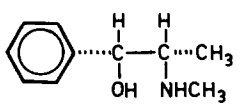
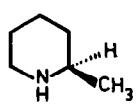
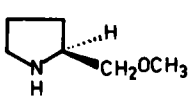
3 could not be established by means of 1H-nmr using the chiral shift reagent europium–tris(*d*-trifluoracylcamphor) (*22*). Although the CD Cotton effects of optically active **4** and **5** obtained via asymmetric oxidation were not quantitatively useful owing to a too low enantiomeric excess, curves with the same characteristics as those found for **4** and **5** obtained via resolution were established. The absolute configuration of 2,2′-dihydroxy-1,1′-dinaphthyl (**4**) was established by Yamada *et al.* (*23*). The (−)-enantiomer of **4** obtained from the asymmetric oxidation with Cu(II)–*l*-α-P.E.A. has the S-configuration, and the same configuration can be assigned to the (+)-diacetate **5**.

When racemic **4** was allowed to react under the conditions used for the asymmetric oxidation experiment, 90% of the optically inactive dimer could be recovered, showing that a kinetic resolution or a "second-order asymmetric transformation" ("optical activation") cannot be the cause of the optical activity observed.

No change in the rotation of the coupled product was observed when the oxidation reaction was run in methanol to which varying amounts of *l*-α-P.E.A. had been added.

TABLE 1

ASYMMETRIC OXIDATION OF **3** WITH CHIRAL Cu(II)–AMINE COMPLEXES

	chiral amine	yield of S(+)-5 (%)	$[\alpha]_{578}^{22}$ $(C_2H_5)_2O$	optical purity(%)
(−)		62	+0.40° (c 2.1)	2.8
(+)		18	+0.20° (c 1.1)	1.4
(−)		—	—	
(−)		—	—	
(−)		10	+0.70 (c 1.25)	4.7
(−)		36	+1.10 (c 1.62)	7.9

This indicates that no significant chiral solvent effect was present during the oxidative coupling of **3**.

In Table 1 are summarized the results of the oxidations of 2-naphthol (**3**) using the cupric-amine complexes of different optically active amines. The Cu(II)–(+)-dehydroabietylamine complex compared to the Cu(II)–*l*-α-P.E.A. complex as an oxidant yielded the dimer **4**, having a lower optical purity. Probably this result is due to the fact that the asymmetric center in the (+)-dehydroabietylamine is situated in a β-position to the NH_2 group. A higher asymmetric induction was observed in the Cu(II)-*l*-α-methylpipecoline oxidation of **3**. This effect may be due to a more rigid chiral complex. The Cu(II)–*l*-ephedrine and Cu(II)–*l*-2-aminobutanol complexes did not oxidize **3**. Probably complexation of 2-naphthol is blocked due to the excessive chelating ability of the ligands.

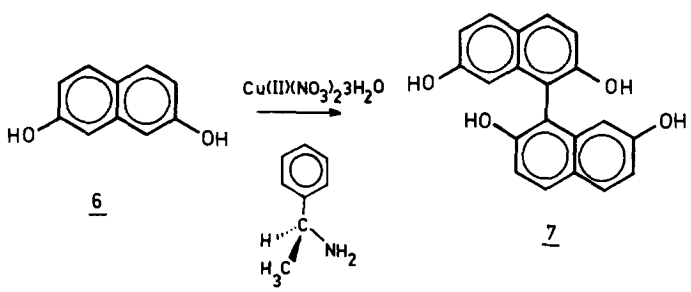
The Cu(II)–*l*-2-methoxymethyl-pyrrolidine complex as an oxidant yielded **4** with an optical purity of 7.9%. The higher induction may be attributed to a stronger discrimination between the diastereomeric transition states due to the fact that Cu(II) can interact with amine and ether functionalities and with the 2-naphthol molecule. A more rigid complex can account for the stronger influence of the chirality of the ligand.

l-2-Methoxymethyl-pyrrolidine $\{[\alpha]_D^{20} + 3°$ (*c* 2, $C_6H_6)\}$ was synthesized according to the procedure described (*24*).

The use of the Cu(II)–(−)-quinine complex in chloroform solution for the oxidation of **3** yielded only small amounts of dimer **4**. No optical activity of this product could be measured.

Naphthols

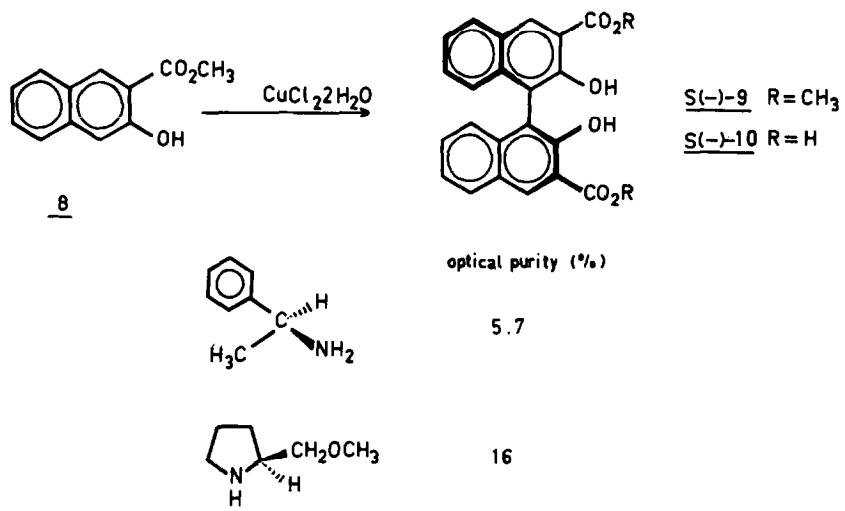
The successful oxidative coupling of a diversity of phenolic substrates using Cu(II)–amine complexes, as reported previously (*18*), offers the possibility of extending the scope of the asymmetric synthesis. 2,7-Dihydroxynaphthalene (**6**) was oxidized using the Cu(II)–*l*-α-P.E.A. complex as described for the coupling of **3** (Scheme 2). Optically



SCHEME 2. Oxidation of 2,7-dihydroxynaphthalene (**6**).

active 2,7,2′,7′-tetrahydroxy-1,1′-dinaphthyl (**7**) $\{[\alpha]_{578}^{22} + 2.5° \pm 0.2°$ (*c* 0.20, $(C_2H_5)_2O\}$ was obtained via chromatographic separation of the crude products. The enantiomeric excess and the absolute configuration of this product are unknown.

Oxidative coupling of 3-hydroxy-2-naphthoic acid methyl ester (**8**) using the Cu(II)–*l*-α-P.E.A. complex furnished the optically active dimer S(−)-**9** in 72% yield $\{[\alpha]_{578}^{22} -$ 9.1° (*c* 0.65, THF)} (Scheme 3). The product S(−)-**9** had an optical purity of 5.7%



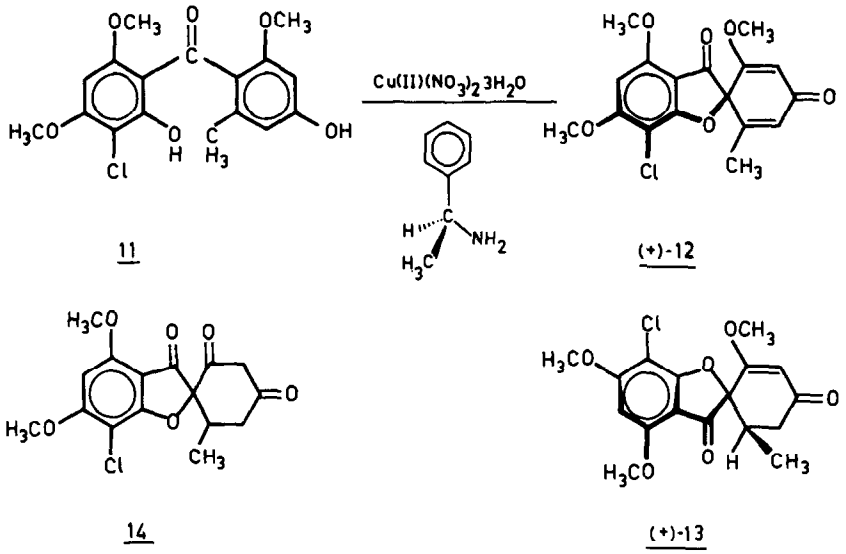
SCHEME 3. Oxidation of 3-hydroxy-2-naphthoic acid methyl ester.

based on the specific rotation $[\alpha]_D^{25}$ + 15.9° (*c* 1.0, THF) which was reported for R(+)-**9**. The latter compound was obtained from R(+)-diacid **10** {$[\alpha]_D^{25}$ +190° (*c* 1.0, THF)}, which is probably optically pure (*25*). The absolute configuration assignment (Scheme 3) is based on the work of Yamada *et al.* (*23*). The higher optical purity of **9** compared to that of **4**, both obtained via Cu(II)–*l*-α-P.E.A. oxidations, can be explained via a better complexation of the 3-hydroxy-2-naphthoic acid methyl ester to the chiral complex during the oxidation step.

When **8** was oxidized with the cupric complex prepared from $CuCl_2 \cdot 2H_2O$ and *l*-2-methoxymethyl-pyrrolidine, the dimer S(−)-**9** was formed in 21% yield. A specific rotation $[\alpha]_{578}^{22}$ −26° (*c* 0.44, THF) was found in this case, corresponding to an optical purity of 16%. After one crystallization from hexane, toluene, S(−)-**9** with $[\alpha]_{578}^{22}$ −58.8 (*c* 0.21, THF) was obtained (optical purity, 36%). The higher optical activity is caused by enantiomeric enrichment due to preferential crystallization. The relatively high asymmetric induction compared to the Cu(II)–*l*-α-P.E.A. oxidation of 2-naphthol is probably due to both the possibility for forming a more rigid chiral cupric complex as Cu(II) interacts with both amine and ether functionalities and furthermore the interactions with the hydroxy and ester groups in the substrate.

(+)-Dehydrogriseofulvin: (**12**)

We previously described the synthesis of (±)-dehydrogriseofulvin using the Cu(II)–*d,l*-α-phenylethylamine complex as an oxidant (*18*). Griseophenone A (**11**), which was the substrate in this oxidation, has been converted into dehydrogriseofulvin (**12**), using oxygen and laccase, or hydrogen peroxide peroxidase as oxidants (*5*). Brown (*9*) has stated that important questions are raised concerning the relevance of these reactions to the biosynthesis of griseofulvin. Neither of the enzymic processes is stereospecific; each gives rise to racemic dehydrogriseofulvin. However, the intact organisms *Pennicilium griseofulvum* and *P. patulum*, sources of griseofulvin, produce optically active material. It may thus be argued that the sequence involving homolytic coupling cannot constitute the biosynthetic pathway to griseofulvin in the molds *P. griseofulvum* and *P. patulum*.



SCHEME 4. Oxidation of griseophenone A (**11**).

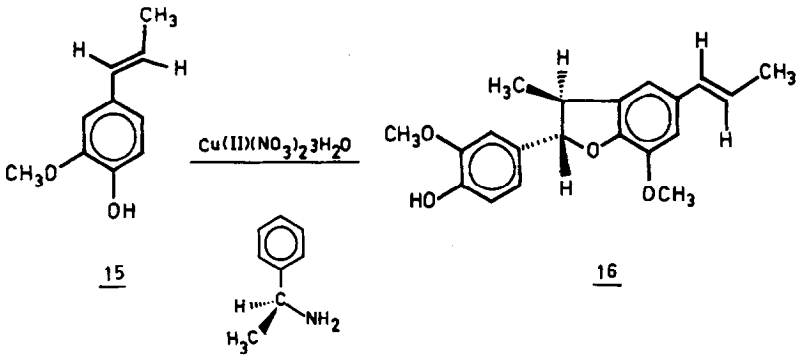
When griseophenone A (**11**) was oxidized with the Cu(II)–*l*-α-P.E.A. complex in a methanol/water mixture, optically active dehydrogriseofulvin (**12**) with $[\alpha]_{578}$ +0.4° (acetone) was isolated. (Scheme 4). Optically active griseofulvin {**13**, $[\alpha]_D^{24}$ +339° (*c* 1.03 $CHCl_3$)} has been obtained from natural sources (*P. griseofulvum*) and via resolution of (±)-griseofulvic acid (**14**) (*26*). (–)-Dehydrogriseofulvin {$[\alpha]_D$ –31.6° (acetone)} was obtained from the (+)-enantiomer of the natural product **13** (*26*). An optical purity of 1.3 ± 0.2% can be calculated for synthetic **12**, assuming that the natural product is enantiomerically pure and that no racemization in the dehydrogenation step has occurred. The (+)-dehydrogriseofulvin (+)-**12**) is related to (–)-griseofulvin [(–)-**13**], which compound is shown to be biological inactive, in contrast to the (+)-antipode of **13**. As optically active dehydrogriseofulvin is the product of the oxidation of griseophenone A using Cu(II)–*l*-α-P.E.A., it is quite possible that **11** is involved in the biosynthetic pathway. The fact that on using isolated enzymes no asymmetric synthesis was observed does not necessarily mean that the intermediacy of **11** is excluded. A modified action of laccase or peroxidase *in vivo* or a multienzyme complex as suggested by Rhodes (*27*) is still possible.

Licarin A (**16**)

The dimerization of *trans*-isoeugenol (**15**) is a principal model for the mechanism of lignification (*6*). The latter reaction was studied by Cousin and Hérissey (*28*) using the juice of the mushroom *Russula delica* and also by Erdtman's group (*29*). The oxidative coupling of **15** using $FeCl_3$ furnished the dimer **16** in 30% yield. This coupling mode established the importance of phenylcoumarinstructures in the lignification process (*6*).

When *trans*-isoeugenol (**15**) was oxidized with the Cu(II)–*l*-α-P.E.A. complex in methanol at room temperature under the conditions previously described for the oxidation of 2-naphthol, a mixture of oxidized products was obtained (Scheme 5).

Optically active **16** could be isolated in 21% chemical yield {$[\alpha]_{436}^{22}$ –0.71° [*c* 2.75



15 16

SCHEME 5. Oxidation of *trans*-isoeugenol (**15**).

$(C_2H_5)_2O$]}. Spectral data of this compound were identical to those of racemic **16** prepared via $FeCl_3$ oxidation of **15**. Recently (–)-**16** has been isolated from the trunkwood of *Licaria aritu* Ducke, a Lauraceae species in the Amazonas area in Brazil (*30*). It is known as the neolignan Licarin A. The compound **16** {$[\Phi]_{400}$ –3950, (*c* 1.16, CH_3OH)} had an absolute configuration as pictured in Scheme 5, with a 2S,3S-2-aryl-3-methyl-2,3-dihydrobenzofuran structure (*31*). Since the absolute rotation of **16** at 436 nm was not reported (*30*), no optical purity of our product could be calculated. Nevertheless it is evident from the value of the rotation of **16** at 400 nm that the extent of asymmetric induction found by us is low.

Oxidations *in vitro* of lignan precursors gave rise to racemic products, although *in vivo* chiefly one of the enantiomers is produced via enzymic oxidation. Horseradish peroxidase–hydrogen peroxide oxidation of **15** yielded the dimer **16** as a racemate (*28*, *29*). It may be suggested, on the basis of this first, admittedly low asymmetric induction, that optically active lignols and lignans may in principle be formed in phenol coupling reactions even if the substrate is not optically active (*32*).

FINAL REMARKS

As was shown in the previous sections, low asymmetric inductions were observed in the oxidations of phenols with chiral cupric–amine complexes. Optical activity was created during the formation of C–C and C–O bonds and in the formation of asymmetric centers and biaryldissymmetry. On the basis of the present results it seems that at least to some extent interactions between the chiral cupric complex and the phenol are present. Questions are raised concerning the widely accepted radical theory of phenol coupling.

EXPERIMENTAL SECTION

Melting points (uncorrected) were determined on a Mettler F.P.-2 melting point apparatus equipped with a Mettler F.P.21 microscope. Infrared spectra were recorded on an Unicam SP200 spectrophotometer. ^{1}H-nmr spectra were recorded on Varian A-60 and Hitachi Perkin–Elmer R24B apparatus. TMS was used as an internal standard

(δ = 0 ppm). Optical rotations were measured on a Perkin–Elmer 241 polarimeter. ORD and CD spectra were recorded on a Cary 60 recording spectropolarimeter equipped with a Cary 6002 CD accessory.

Materials

All chemicals and solvents were purified where necessary by standard procedures prior to use. The optically active amines were purchased from Aldrich (*l*-α-phenylethylamine, *l*-2-amino-1-butanol, *d*-dehydroabietylamine, and *l*-ephedrine) or prepared via literature procedures (*24*) (2-methylpiperidine and *l*-2-methoxy-methylpyrrolidine). 2-Naphthol (**3**), 2,7-dihydroxynaphthalene (**6**), and *trans*-isoeugenol (**15**) were purchased from Aldrich, and 3-hydroxy-2-naphthoic acid methyl ester (**8**) was obtained from 3-hydroxy-2-naphthoic acid (Aldrich) via esterification. 2,4′-Dihydroxy-4,6,2′-trimethoxy-6′-methyl-3-chlorobenzophenone (**11**) was synthesized according to the procedure described by Taub and co-workers (*26*).

(l)-2,2′-Dihydroxy-1,1′-dinaphthyl (l-4)

To a solution of *l*-α-phenylethylamine (*l*-α-P.E.A.) (1.45 g, 12.0 mmol) in 30 ml of CH_3OH, freed from oxygen by repeated degassing and saturation with nitrogen, was added 0.72 g (3.0 mmol) of $Cu(NO_3)_2 \cdot 3H_2O$, and the mixture was stirred at 20°C for 15 min under a nitrogen atmosphere. To the resulting dark green suspension of the Cu(II)–*l*-α-P.E.A. complex, was added 0.43 g (3.0 mmol) of **3**. Stirring was continued at 20° for 20 hr, and to the brown suspension were then added 25 ml of 2 *N* HCl and 25 ml of H_2O. The mixture was extracted with diethyl ether (2 × 40 ml), and the organic layer was separated and washed with 2 *N* HCl (2 × 20 ml) and H_2O (2 × 25 ml). The organic layer was subsequently extracted with 1 *N* NaOH (2 × 25 ml). The basic aqueous solution was treated with excess 2 *N* HCl and then extracted with diethyl ether (2 × 30 ml). The ethereal extracts were washed with H_2O (3 × 25 ml) and dried over $MgSO_4$. After removal of the solvent under diminished pressure, 0.42 g of a pale yellow solid was obtained. Preparative tlc using Polyamide 11F254 (E. Merck AG, Darmstadt) and a mixture of benzene, dioxan, acetic acid (25:8:1) as an eluent furnished **4** (60%): mp 214–216°C; $[\alpha]_{578}^{22}$ −0.98 ± 0.10° (*c* 0.9, THF); ir (nujol) 3400 and 3500 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 5.3 (s, 2H), 7.1–7.6 (m, 10*H*), 7.75–7.81 (m, 4*H*); and **3** (30%) identical with the starting material.

An easier preparative separation of the products was possible via the esters. The crude product (0.42 g) was dissolved in a mixture of 3 ml of dry pyridine and 2 ml of acetic acid anhydride, and the resulting solution was stirred for 2 hr at 20°. After a normal work-up 0.55 g of a mixture of esters was obtained which were separated chromatographically (silica gel, CH_2Cl_2) in **5**, 0.34 g (62%: mp 103–105°C; $[\alpha]_{578}^{22}$ +0.40 ± 0.05° [*c* 2.1, $(C_2H_5)_2O$]; ir (nujol 1740 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1.75 (s, 6H), 7.0–8.1 (m, 12*H*); and 0.20 g (35%) of 2-acetoxynaphthalene (identical with the acetate of **3**).

The oxidations of **3** using different cupric salt *l*-α-P.E.A. ratios as well as the oxidations of **3** using different optically active amines were performed as described above. When different amines were used special care was taken to avoid any contamination of the product by amine or amine oxidation products. With *d*-

dehydroabietylamine, several washings with 2 *N* HCl and H_2O were necessary to remove all of the amine or amine salts.

*Optically pure l-***4**. Optically pure *l*-**4** was obtained via resolution of *d,l*-**4** following the procedure described by Jacques (*20*) and Cram and co-workers (*21*): mp 204.3–204.9°C; $[\alpha]_{546}^{22}$ −52.0 ± 0.7° (*c* 0.99 THF); lit. (*21*) mp 207–208°; $[\alpha]_{546}^{25}$ −51.5 ± 0.7° (*c* 1.0, THF). Spectroscopic data (except for chiroptical) identical with those of **4** obtained via *l*-α-P.E.A. oxidation.

*d,l-***4**. Racemic **4** was prepared by oxidation of **3** using $FeCl_3 \cdot H_2O$ as described by Pummerer *et al.* (*19*), mp 216–218°C, identical (except for chiroptical data) with **4** obtained via Cu(II)–*l*-α-P.E.A. oxidation of **3**.

d-2,7,2',7'-Tetrahydroxy-1,1'-dinaphthyl (*d*-**7**)

The oxidation of 2,7-dihydroxynaphthalene (**6**) was performed as described for the oxidation of **3**. Chromatographic separation of the crude product (polyamide) yielded 25% d-**7**: mp 111–113°C; $[\alpha]_{578}^{22}$ +2.5 ± 0.2° {*c* 0.20, $(C_2H_5)_2O$}; spectroscopic data (except chiroptical data) identical with those of *d,l*-**7** prepared via $FeCl_3 \cdot 6H_2O$ oxidation of **6** as described by Ioffe (*33*).

l-2,2'-Dihydroxy-1,1'-dinaphthyl-3,3'-dicarboxylic acid dimethylester (*l*-**9**)

The oxidation of 3-hydroxy-2-naphthoic acid methyl ester (**8**) was performed as described for the oxidation of **3**. Chromatographic separation of the products (silica gel; petroleum ether and ether, 4 : 1 afforded *l*-**9** in 72% yield: mp 276–278°C; $[\alpha]_{578}^{22}$ −9.1° (*c* 0.65, THF); ir (nujol) 1690 (s, C=O) and 3200 cm^{-1} (m, OH); ^{1}H-nmr ($CDCl_3$) δ 3.98 (s, 6*H*), 7.0–8.0 (m, 10*H*), 8.48 (s, 2*H*), 10.65 (s, 2*H*).

*d,l-***9** was prepared via Cu(II)–*d,l*-α-P.E.A. oxidation of **8**: mp 282–283°C; spectral data (except for chiroptical data) identical with those of *l*-**9**.

d-Dehydrogriseofulvin (*d*-**12**)

2,4-Dihydroxy-4,6,2'-trimethoxy-6'-methyl-3-chlorobenzophenone (**11**) (0.35 g, 1.0 mmol) and the cupric complex prepared from 0.67 g (3.0 mmol) of $Cu(NO_3)_2 \cdot 3H_2O$ and 1.45 g (12.0 mmol) of *l*-α-P.E.A. in a mixture of 5 ml of CH_3OH and 45 ml of H_2O were stirred under a nitrogen atmosphere for 45 hr at 20°C. To the resulting dark green suspension was added 50 ml of 2 *N* HCl and 50 ml of CH_2Cl_2. After separation of the organic layer, the aqueous layer was extracted with 50 ml of CH_2Cl_2. The combined organic solutions were washed with 2 *N* HCl (2 × 25 ml) and H_2O (4 × 20 ml) and dried over $MgSO_4$, and the solvent was removed by distillation. From the crude yellow product mixture, *d*-**12** (0.14 g, 40%) was isolated using preparative tlc (alumina, CH_2Cl_2); mp 285–287°C; $[\alpha]_{578}$ +0.4° (*c* 1.7, acetone); ir (nujol) 1725 (s, C=O and 1670 cm^{-1} (s, C=O).

*d,l-***12** was prepared according to the procedure described by Taub *et al.* (*26*). Oxidation of **11** with $K_3Fe(CN)_6$ yielded *d,l*-**12** in 45%: mp 287–289°C; lit. (*26*) 288–290°C. All spectral data (except for chiroptical data) identical to those of *d*-**12** and those of *d*, *l*-**12** and *d*-**12** as reported.

*(l)-Dehydrodiisoeugenol (l-***16**)

A solution of 1.47 g (9.0 mmol) of isoeugenol (**15**) in 10 ml of CH_3OH was added under nitrogen to the stirred solution of the cupric complex prepared from 1.86 g (9.9 mmol) of $Cu(NO_3)_2 \cdot 3H_2O$ and 38.4 g (30.0 mmol) of *l*-α-P.E.A. in 75 ml of CH_3OH. The reaction mixture was stirred at 20°C for 24 hr and slowly turned brown. 2 *N* HCl (100 ml), H_2O (50 ml), and diethyl ether (100 ml) were added. The mixture was stirred for 15 min, and the organic layer was separated. The aqueous layer was extracted with diethyl ether (2 × 75 ml). The combined ether solutions were washed with 2 *N* HCl (2 × 30 ml) and H_2O (5 × 30 ml). After drying of the solution over $MgSO_4$ and removing of the solvent by distillation, 1.25 g of a brown oil was obtained. Separation of this product mixture using preparative tlc (silica gel, CH_2Cl_2) afforded **16**, 0.30 g (0.94 mmol, 21%): mp 123–126°C; lit. (*30*) S(–)-**16** mp 114–116°C; lit. (*29*) R,S-**16** mp 133–134°C. The ir and nmr data of **16** were identical to the published data (*29*, *30*) and to those of R,S-**16** prepared via $FeCl_3$ oxidation of **15.**

*d,l-Dehydrodiisoeugenol (d,l-***16**)

d,l-Dehydroiisoeugenol (*d,l-***16**) (mp 130–132°C, lit. (*29*) mp 133–134°C) was prepared in 16% yield by an oxidation of **15** with $FeCl_3$ as described by Erdtman (*29*).

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