Forschung, Wissenschaft

Asymmetric catalysis in oxidation reactions
The consequences of interactions between enantiomers*

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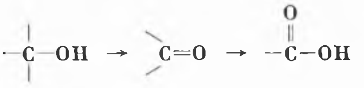
Summary

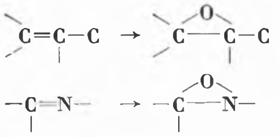
Asymmetric catalysis in epoxidation reactions has been achieved using alkaloid salts under phase-transfer conditions. A second biologically important oxidation reaction, namely phenol coupling has been studied from the point of view of stereospecificity. The differences observed in the product ratios, between the phenol coupling of a racemic phenol and an optically pure phenol is the basis for the hypothesis: "When a chiral substance undergoes a reaction, the reaction rate and the product ratio will depend upon the excess of enantiomer present in the starting material."

Surely oxidation must rank among the half dozen most important biological as well as non-biological chemical reactions. It is somewhat surprising therefore that little progress has been made to date in devising means whereby asymmetry can be produced in a molecule undergoing oxidation.

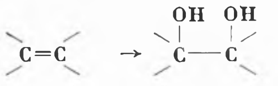

$$-\overset{|}{\underset{|}{C}}-OH \rightarrow \;>C=O \rightarrow -\overset{\overset{O}{\|}}{C}-OH \qquad (1)$$

Although the simple oxidation of an alcohol to a ketone, aldehyde or acid (process 1) obviously cannot lead to the introduction of a new asymmetric center, other oxidative processes can. We mention:

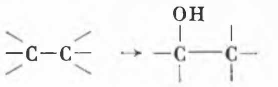
a) Epoxidation and formation of oxazirines


$$>C=C-C \rightarrow \;>\overset{O}{\widehat{C-C}}-C \qquad -C=N- \rightarrow -\overset{O}{\widehat{C-N}}- \qquad (2)$$

b) Hydroxylation


$$>C=C< \;\rightarrow\; >\overset{OH}{\overset{|}{C}}-\overset{OH}{\overset{|}{C}}< \qquad (3)$$

c) Oxygenation


$$-C-C- \;\rightarrow\; -\overset{OH}{\overset{|}{C}}-\overset{|}{C}- \qquad (4)$$

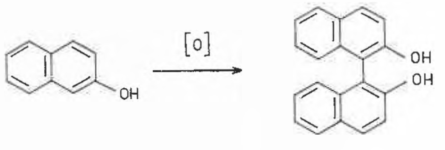
d) Sulfoxide formation


$$-S- \;\rightarrow\; -\overset{O}{\overset{\uparrow}{S}}- \qquad (5)$$

e) N-oxide formation


$$>N- \;\rightarrow\; >N\rightarrow O \qquad (6)$$

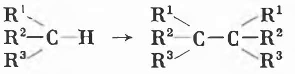
f) Phenol coupling



(7)

dl **13**

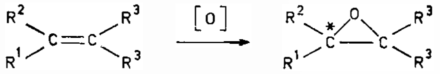
g) Other oxidative coupling reactions


$$R^1R^2R^3C-H \rightarrow R^1R^2R^3C-CR^1R^2R^3 \qquad (8)$$

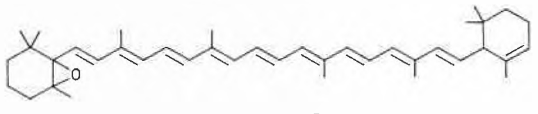
dl and meso

This lecture will confine itself to two oxidation reactions: epoxidation and phenol coupling. Successful and unsuccessful attempts to induce asymmetry by catalytic means will be discussed. The difference in reactivity between a d-isomer and the corresponding racemate will be evaluated.

Epoxidation



The epoxide function has been identified in many natural products of varying origins [1]. Terpene epoxides [2] (**1**), quinone epoxides [3] (**2**) macrolides [4] (**3**) are typical examples. More recently arene oxides [5] (**4**) have been found as metabolites of aromatic hydrocarbons.



α-CAROTENE MONOEPOXIDE
Karrer (1945)
1

In living systems the epoxide function may possibly be involved in oxygen transport and storage and in detoxification [5] and it may act as a highly reactive "double-bond" (built-in leaving group [5]). Until now optically active epoxides have been prepared in 2—4% optical yields using molar quantities of optically active peracids [6]. Resolution of epoxides succeeds only if

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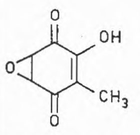
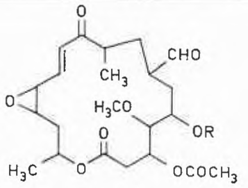


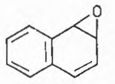
TERREIC ACID
Florey (1949)

2



MAGNAMYCIN
Woodward (1957)

3



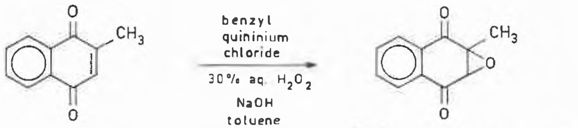
ARENE OXIDES
Witkop, Jerina (1967)

4

an appropriate functional group in addition to the epoxide function is present in the molecule [7]. All other ways of preparing optically active epoxides proceed from optically active precursors [8].

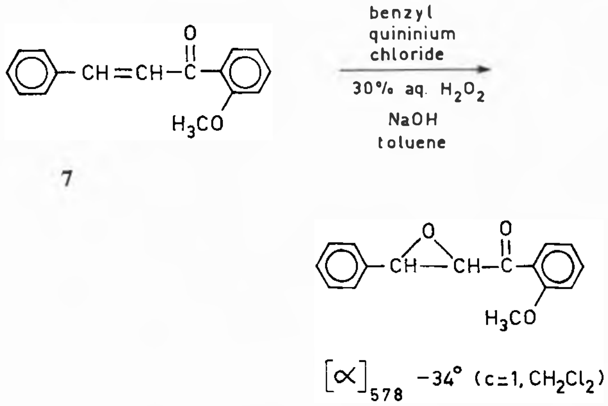
We have now found that the base catalyzed hydrogenperoxide or t-butyl hydroperoxide epoxidation of electron-poor olefins—the Weitz-Scheffer reaction [9] is subject to catalytic asymmetric induction. As with previously studied asymmetric syntheses using chiral bases as catalyst we also turned to alkaloids [10]. Our initial success using quinine in the Michael reaction [11] made this alkaloid the obvious choice in the base-catalyzed epoxidation reaction. When optical yields remained poor and the results erratic we turned to phase-transfer conditions [12] using simple N-alkyl salts of quinine and quinidine as chiral phase-transfer reagents.

Two epoxidations were studied in considerable detail, namely the conversion of the well-known [13] naphthoquinone **5** into its epoxide **6** and the epoxidation of a series of chalcones [9] (for example **7** to **8**). None of the products were known in optically active form prior to this work.



[α]$_{436}$ −12° (c = 1, acetone)

5 **6**



7

[α]$_{578}$ −34° (c=1, CH_2Cl_2)

e.e. 25% (NMR)

8

Experimental conditions were rather simple as the following typical experiment indicates:

A solution of 20.4 g of chalcone **7** in 125 ml of toluene was vigorously stirred for 24 hrs at room temperature with a solution of 7.5 g NaOH in 90 ml of 30% aq. H_2O_2 and 750 mg of the quinine salt, by which time the yellow colour of **7** had disappeared completely. Work-up of the reaction mixture and elution of the crude product on silicagel/CH_2Cl_2 (in order to remove the catalyst) gave 21.8 g (99%) of the optically active epoxide **8** as a white solid, $|\alpha|^{21°}_{578}$ −34° (c = 1, CH_2Cl_2).

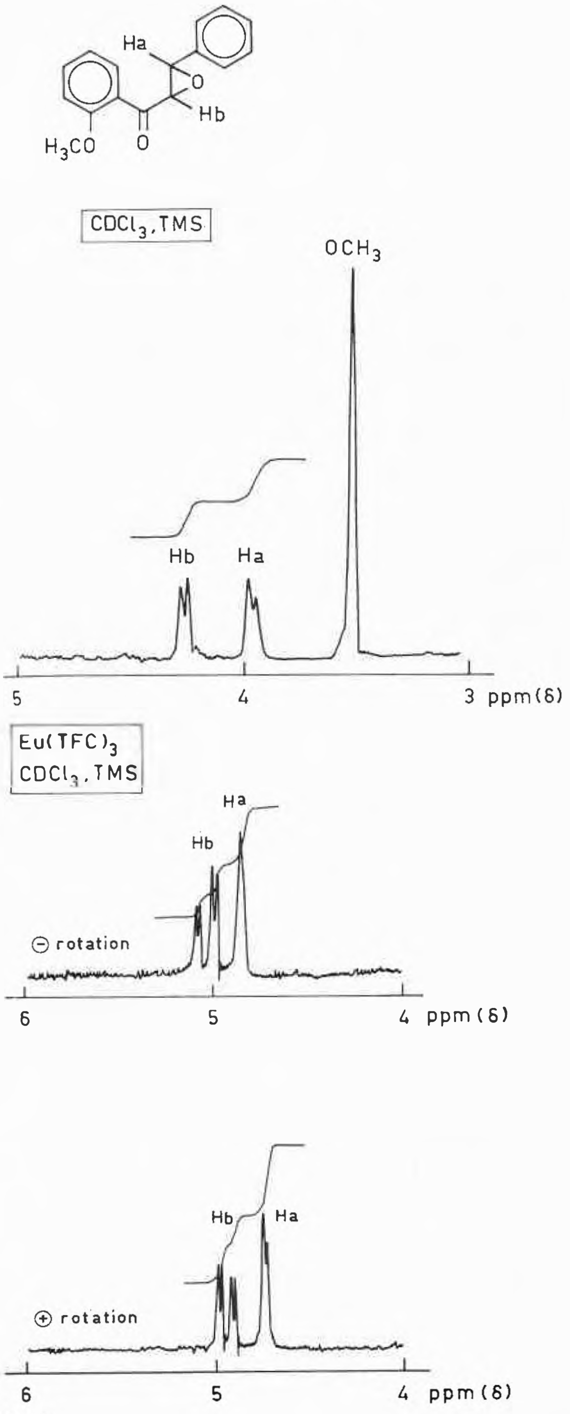
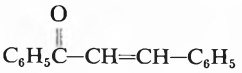
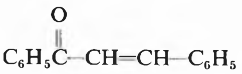
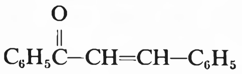
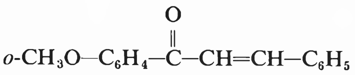
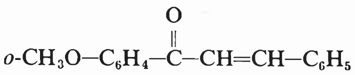
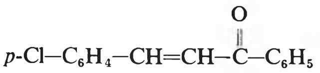
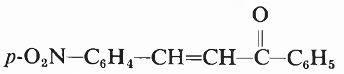
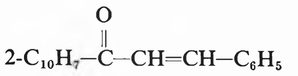
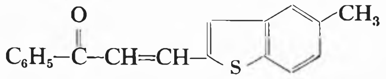


Fig. 1

Table 1: Conversion of alkenes into epoxides

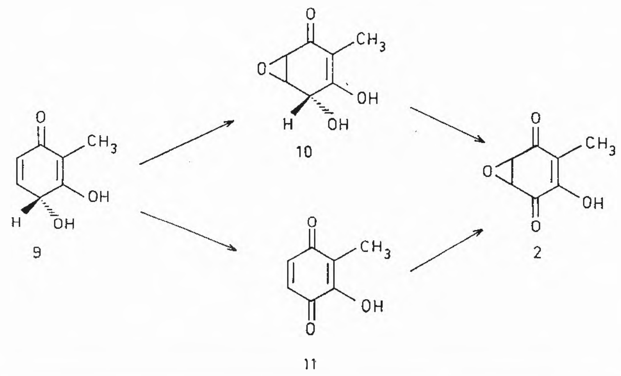
Alkene	Conditions	$\|\alpha\|^{21^\circ}_{578}$ of epoxide *
5	QS**, H_2O_2	0° (−12°, 436 mμ)
5	QS**, $t\text{-}C_4H_9OOH$ (−5 °C)	0° (−8°, 436 mμ)
 $C_6H_5\overset{\overset{O}{\|}}{C}{-}CH{=}CH{-}C_6H_5$	QS**, H_2O_2	−51°
 $C_6H_5\overset{\overset{O}{\|}}{C}{-}CH{=}CH{-}C_6H_5$	QS**, $t\text{-}C_4H_9OOH$	+24°
 $C_6H_5\overset{\overset{O}{\|}}{C}{-}CH{=}CH{-}C_6H_5$	Quinidine-$C_6H_5CH_2Cl$ salt, H_2O_2	+49°
 $o\text{-}CH_3O{-}C_6H_4{-}\overset{\overset{O}{\|}}{C}{-}CH{=}CH{-}C_6H_5$ (**7**)	Quinidine-$C_6H_5CH_2Cl$ salt, H_2O_2	+29°
 $o\text{-}CH_3O{-}C_6H_4{-}\overset{\overset{O}{\|}}{C}{-}CH{=}CH{-}C_6H_5$ (**7**)	QS**, H_2O_2	−34°
 $p\text{-}Cl{-}C_6H_4{-}CH{=}CH{-}\overset{\overset{O}{\|}}{C}{-}C_6H_5$	QS**, H_2O_2	−62°
 $p\text{-}O_2N{-}C_6H_4{-}CH{=}CH{-}\overset{\overset{O}{\|}}{C}{-}C_6H_5$	QS**, H_2O_2	−33°
 $2\text{-}C_{10}H_7{-}\overset{\overset{O}{\|}}{C}{-}CH{=}CH{-}C_6H_5$	QS**, H_2O_2	−31°
	QS**, H_2O_2	−56°
$C_6H_5{-}CH{=}C(CH_3)NO_2$	QS**, H_2O_2	− 3°

* Estimated on epoxide freed from catalyst. In some cases starting alkene was still present. (E) chalcones were used and gave the corresponding epoxides.

** QS: salt of quinine, see [11].

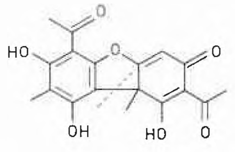
Table 1 shows the results obtained to date. Enantiomeric excess could be determined in a few cases, characteristically when the aromatic ring contained at least one methoxy group. Thus chalcone epoxide **8** was obtained in 25% enantiomeric excess as determined on the crude reaction mixture. See fig. 1 for NMR spectra.

It is interesting to compare the role of the catalyst, benzyl quininium chloride, to the role of a biological catalyst in epoxidation reactions. Read [14] has shown that the epoxide oxygen in terreic acid (**2**) derives from atmospheric oxygen. Since terreic acid (**2**), as isolated from natural sources is optically active [3] two paths to the optical activity in terreic acid can be visualized. In one of these a precursor to terreic acid (for example **9**) is epoxidized, to **10**, and oxidized as shown in sequence **9** to **10** to **2** (terreic acid). However, direct chiral transfer of molecular oxygen to quinone **11** cannot be ruled out. If the latter route obtains, the quinine salt experiment using phase-transfer conditions may be a reasonable model of the bio-synthetic pathway.

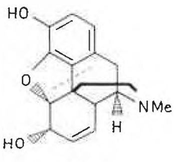


Phenol coupling

Once again natural products abound which owe their existence—in part—to a reaction known as the phenol coupling reaction [15, 16]. Some examples are shown below.

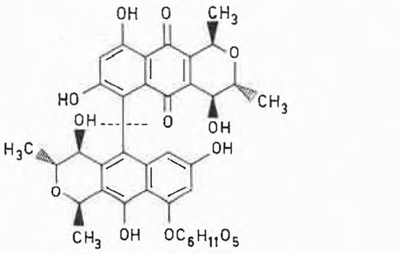


usnic acid Barton et.al.,1956

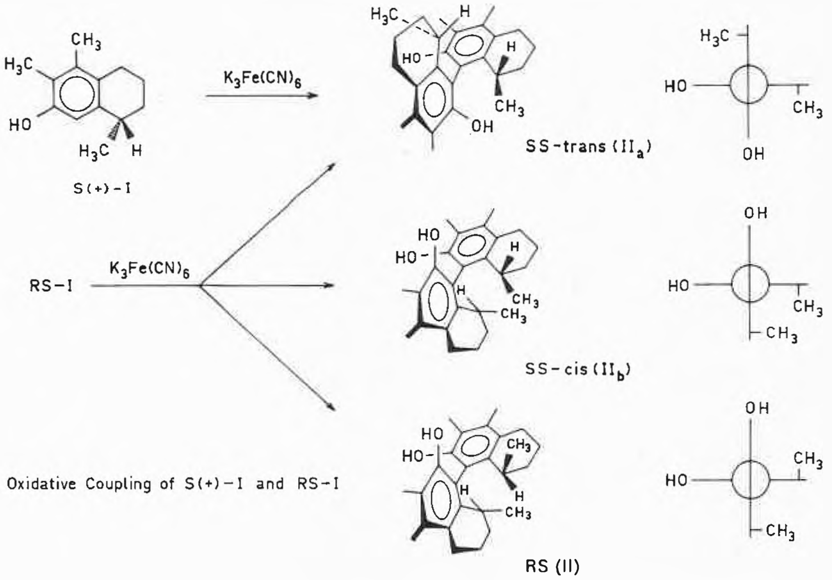


morphine

Robinson et.al.,1931
Barton et.al.,1957



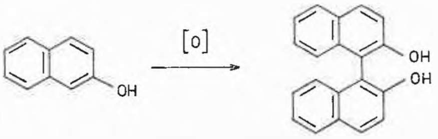
protoaphin-fb Todd et. al.,1952



Oxidative Coupling of S(+)-I and RS-I

These natural products are all optically active. In no case has it been determined with any certainty at what stage the optical activity has been induced into the molecule. Let us focus on just one aspect of the phenol coupling reaction, namely the carbon-carbon bond formation at ortho- or para-positions of a phenol (or naphthol) with the subsequent formation of a diaryl. In many cases the diaryl formed will be capable of existing in d- and l-forms due to the hindered rotation about the center bond.

Once again our initial attempts to affect the formation of the bisnaphthol **13** using a chiral catalyst had scant success. These results parallel to a certain extent the



failure of A.I. Scott [15] to obtain optically active phenol coupling products using a peroxidase enzyme system. Since lignin formed in part by phenol coupling reactions is optically inactive, the suggestion has been made that the phenol coupling reaction itself is a non-enzymic reaction. The optical activity in compounds such as **14**, the aphid pigments, must then depend upon the asymmetry already present in the monomer phenol. With this concept in mind, racemic and optically active tetrahydronaphthol **15** was synthesized [17].

Both racemic **15** and optically pure S(+) — **15** were subjected to the phenol coupling reaction under identical condition. (The results are listed in table 2)

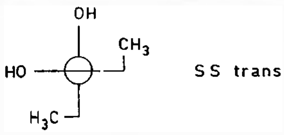
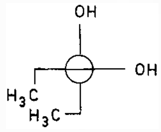
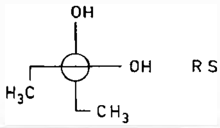
We observe the following: All three possible dl products are formed when racemic phenol **15** is used as starting material. The reaction shows stereospecificity in that racemate SS-trans is formed in preponderance [17].

Most notable however is the oxidation of optically pure S(+) — **15**. In this case only one dimer, namely SS-*trans* was isolated. No trace of the (only possible) other dimer SS-*cis* could be found even in the crude reaction mixture.

High stereospecificity in a phenol coupling reaction, using electrodes, has been observed once previously [17]. The presence of the *cis*-dimer—in the reaction on the racemate—and its complete absence in the coupling of optically pure S(+) — **15** needs additional coment.

Table 2:

product distribution

		R,S monomer	S monomer
	S S trans	66.0 %	> 97.5%
	S S cis	7.9%	—
	R S	26.1 %	—

The consequences of the non-bonded interactions of enantiomers

A considerable body of evidence exists which supports the inherently self-evident notion that the physical properties of one pure enantiomer are different from those of the racemate. Naturally deviation from ideal behavior will increase in the sequence: gas → dilute solution → concentrated solution → liquid crystal → solid phase.

A recent paper by Jacques [18] discusses the well-documented difference in the solid phases of conglomerates, racemic crystals and crystals consisting of one enantiomer only.

Horeau [19] has carefully reviewed the data pertaining to the physical properties of solutions of one enantiomer as compared to solutions of the racemate. One of the clearest experiments proving beyond a doubt that differences exist in non-bonded interactions between molecules of like configurations and molecules of opposite configuration is the experiment of Uskoković [20]. The latter showed that clear differences in the chemical shifts of the proton NMR spectra can be observed between a solution of d-dihydroquinine and dl-dihydroquinine in *achiral* solvents [21].

When we turn our attention from the difference in physical properties to differences in chemical reactivity, the situation is not nearly as clear.

Most authors assumed ideal behavior when discussing the reaction of a racemate with that same reaction on the optically active substrate. This assumption (ideal behavior) though not explicitly stated is the basis for the following statements in two important text books on stereochemistry [22]. In discussing the $LiAlH_4$ reduction of 2-methylcyclopentanone to the epimeric 2-methylcyclopentanols Morrison and Mosher [22] conclude: "If instead of starting with the racemic RS-2-methyl-cyclopentanone, pure S-2-methylcyclopentanone had been reduced with lithium aluminium hydride, the epimeric carbinols would have been formed in the *same* ratio. Thus it is seen that for the determination of percent stereoselectivity it is *unnecessary* to work with optically active material ..."

In discussing the epimerization of (–)-menthone Eliel [22] concludes: "Since (±) menthone is a mixture of equal parts of (–) menthone and (+) menthone and (±) isomenthone is a mixture of equal parts of (+) isomenthone and (–) isomenthone the equilibrium of (+) menthone and (+) isomenthone is the *same* as that of their pure isomers".

Neither on the basis of symmetry nor on the basis of a free energy argument can these statements cited above be completely correct except under conditions of ideal behavior. Consider the following reactions:

$$\left.\begin{array}{l}50\%\ \text{d-antipode}\\ 50\%\ \text{l-antipode}\end{array}\right\}\xrightarrow{\text{reagents}}\text{products}$$

$$100\%\ \text{d-antipode}\ \xrightarrow{\text{reagents}}\text{products}$$

These two reactions are neither identical nor enantiomeric, hence they are different. Thus the $\Delta G^{\ddagger}$ of these two reactions must be different resulting in different reaction rates and different product ratios.

This lead us to the following general statement: *"When a chiral substance undergoes a reaction, the reaction rate and the product ratio will depend—inter alia— upon the excess of enantiomer present in the starting material."*

The difference we have found in the phenol coupling reaction of racemic and optically active **15** may be considered on this basis. If we consider that *all* reactions in which the behavior of one d-isomer is compared with the behavior *of that d-isomer* in the presence of a chiral substance (its antipode, the l-isomer) is essentially comparable with solvent effects, the discussion becomes somewhat simplified. Since it is well known that solvents can play a dominant role in a large number of reactions it should not be surprising that even "minute" changes such as we are discussing now, should have an observable effect. It is surprising however that such an effect has not been discovered previously although the thermodynamic and kinetic basis for such an effect has been somewhat obscured by the assumption of ideality. Let us separate two "effects" when discussing the reactions of a chiral substance namely an enantiomeric recognition effect (ER effect) and an enantiomeric interaction effect (EI effect). The first effect plays a role in all reactions in which enantiomers react with one another.

Phenol coupling reactions, aldol condensations, in fact all dimerization and polymerization reactions involving chiral substrates will show an ER effect. Differences in product ratios due to an ER effect are well-documented and even predictable [23].

The EI effect however has not been documented previously [24]. It is—as stated above—concerned with the influence on the reaction of one enantiomer when this substance reacts in two different surroundings. Surrounding A is that provided by its own molecules; surrounding B is that provided by a mixture of the two antipodes. The EI effect is therefore important not only in dimerization or polymerization reactions but in all reactions with a chiral substrate.

It is well to note some consequences of the EI effect.

1. The effect will be highly concentration dependent. Nonbonding interactions—e.i. the structure of the liquid phase—will play a crucial role, as will complex formation during a reaction. In the reaction with a racemate, diastereomeric complexes may be formed, which is not possible when a pure enantiomer undergoes a reaction under achiral conditions.
2. The preferential structuring which may occur in concentrated solution of racemic solutes may have played a critical role in the origin of optical activity in living systems. It is fascinating to read that Young [25] has observed optical activity in racemic (!) liquid crystals. These local inhomogeneities might well have been the original loci for polymer formation resulting in self-replicating biopolymers [26].

I believe that further careful work on this EI effect may pay dividends not only in the understanding of asymmetric synthesis but in the important twilight area of non-bonded interactions.

Acknowledgement

My enthusiastic coworkers, Ben Feringa, Renne Helder, Kurt Hermann, Kees Hummelen, Remi Laane are mainly responsible for the fact that I could present this work. I thank them for their creative and stimulating contributions.

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The latter author was the first to determine the stereospecificity in an (electrolytic) oxidative phenol coupling reaction.
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The notation of the configuration needs a brief comment. The starting phenol **15** has one chiral center, namely the carbon atom in the saturated ring bearing the methyl group. The configuration at this carbon atom (either R or S) will not change during the coupling reaction. Thus, in the dimer, we find either an SS, RR, or RS configuration for those two chiral centers. Normally dimerization of a dl-monomer leads to a dl- and meso-compound. In this case however additional dissymmetry is obtained due to restricted rotation about the aryl-aryl single bond. Instead of using R- and S- for the configuration of these bisnaphthols we have used the words *trans-* and *cis-* to emphasize the relationship of the two methyl groups to one another. However the dimer formed in the largest amount (SS-trans-IIa) has the configuration SSS^1 when S^1 denotes the biaryl configuration. It is obvious that when RS-I (RS-**15**) is dimerized both enantiomers (of all three diastereomers) are formed. In the drawings just one enantiomer is shown. Thus in the coupling of RS-**15**, S,S,S^1 + R,R,R^1 (dimer IIa), SSR^1 + $R.R,S^1$ (dimer IIb) and RSR^1 + SRS^1 (dimer IIc) are formed in the ratio 66 : 8 : 26. In the coupling of optically pure S(+)-I (**15**) the dimer SSS^1 (SS-trans-IIa) is formed exclusively.
The fact that the ratio of racemic dimers (8 : 1 : 3) differs from random distribution (1 : 1 : 1) is not surprising. It should be noted however that Bobbitt [16] obtained only one racemic dimer upon coupling of his racemic phenol monomer containing a tetrahydroisoquinoline structure. Since the general mechansim of the coupling reaction must be the same for the formation of all the three racemic dimers, the difference in yield directly reflects steric differences in the reaction of an R-isomer with either another R-isomer or the S-isomer. Enantiomeric recognition is the term used for this phenomenon.

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21 This paper will not discuss the large body of evidence which exists, proving a *chiral* substance can "recognize" the difference between the two antipodes in a racemate, cf.
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24 For a full discussion as well as additional experimental evidence for the existence of the EI effect see H. Wynberg and B. Feringa, submitted to Tetrahedron. We will restrict this discussion to the influence of the chiral *reactants* upon one another, fully aware that the number, kind and ratio of *products* may further influence the course of the reaction. Chiral products again change the chiral surroundings of the reactants.
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