Tetrahedron Vol 41 No 16 pp 3313 to 3319 1985
Printed in Great Britain

0040-4020/85 $3 00 + 00

ON THE MECHANISM OF THE FORMATION OF S(-)-(1,1'-BINAPHTHALENE)-2,2'-DIOL VIA COPPER(II)AMINE COMPLEXES

J. BRUSSEE*, J.L.G GROENENDIJK, J M te KOPPELE and A C A JANSEN

Dept of Pharmacochemistry, Subfaculty of Pharmacy, University of
Leiden, P.O Box 9502, 2300 RA Leiden, the Netherlands

(*Received in UK* 15 *March* 1985)

Abstract. The oxidative dimerization of 2-naphthol is studied by means with several copper(II)amine complexes as oxidants. Using primary amines a chemical yield of 95%-98% is obtained. Using (+)amphetamine as complexing amine a 94%-96% optically pure product is obtained It is established that this stereoselectivity is a result of selective precipitation of the copper(II)-(+)amphetamine-(-)binaphthol complex with a simultaneous racemization of the (+)binaphthol

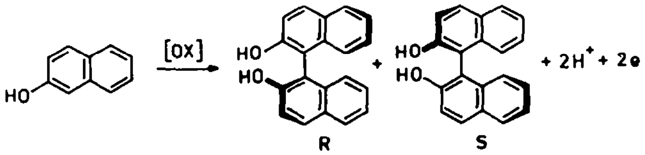
INTRODUCTION

1,1'-Binaphthalene-2,2'-diol, hereafter called binaphthol, is a compound used in a broad field of research In particular optically pure binaphthol has been used for various applications a) enantioselective reduction of ketones (1,2,3) b) stereoselective polymerisation of heterocyclic monomers (4) c) induction of axial dissymmetry into 1,1'-binaphthyl bond via an intramolecular Ullmann reaction (5) d) synthesis of chiral macrotricyclic ligands (6) and macrocycles (7) e) as a resolving agent (8) f) in chromatographic resolutions (9)

In most of these studies the optically pure binaphthol used is obtained from racemic binaphthol by resolution of the cinchonine salt of its phosphate ester (8) Racemic binaphthol is synthesized by an oxidative dimerization of 2-naphthol with $FeCl_3$ as an oxidant (10)

Optically active binaphthyls can be synthesized directly via three stereoselective routes a) an intramolecular Ullmann coupling (5) b) a nucleophilic aromatic substitution (11,12) c) an oxidative dimerization of 2-naphthol with copper(II)amine complexes as oxidants (13)

The last method interested us as this reaction distinguishes itself from the other laborious ones by its simplicity, Furthermore our interest was stimulated as the oxidizing copper(II)amine complexes are described to mimic the action of copper(II) containing enzymes, e g tyrosinase, known to catalyze biosynthetic phenol coupling (13,14)



Feringa and Wynberg reported for this reaction varying chemical yields of binaphthol (10-63%) with variable modest optical activities (up to 8%), both depending on the choice of amine (13). In order to get insight into the oxidative coupling reaction our investigations initially concentrated on the factors determining the chemical yield Subsequently, the research was extended to stereochemical aspects of the reaction It was concluded that the highly efficient stereoselective formation of S-(-)binaphthol was not the result of the oxidative reaction itself, but of a selective crystallization and racemization during the reaction

EXPERIMENTAL PROCEDURES AND APPARATUS

A Synthetic procedure

Where no special remarks are made, the syntheses of binaphthol were performed according to the following procedure

At room temperature the stated amount of amine was dissolved in 20 ml methanol, 6 mmol of a copper (II)salt dissolved in 10 ml methanol was added and the solution stirred magnetically After 30 minutes the stated amount of 2-naphthol in 10 ml methanol was added and the total volume brought up to 60 ml with methanol After 20 hours the brown precipitate (a binaphthol-copper(II)-amine complex) was destroyed with 40 ml 4N HCl. When all the precipitate was dissolved, 100 ml of water was added and the binaphthol crystallized from the solution and was isolated by filtration and dried in vacuo The whole procedure, even the filtration, was performed under N_2 atmosphere The presence of oxygen give rise to impurities and, as is clear from the paragraph 'Ethanolamines', can have influence on the yield of the reaction.

B Optical rotation

Binaphthol was dissolved in THF, concentration 0.5g/100 ml, and the $[\alpha]_D^{20}$ was compared to the literature value of -35.5° (15) to calculate the optical purity

C. Quantitative analysis of the yields

When the chemical yield of the reaction has to be estimated exactly, procedure A was followed up to the addition of 100 ml of water. Instead of the addition of water to the homogeneous solution this solution was extracted thrice with 60 ml of diethylether. The combined ether layers were washed three times with 40 ml of water and dried over Na_2SO_4 The ether was evaporated in vacuo and the residue was acetylated with a mixture of 3 ml pyridine and 2 ml acetic anhydride After two hours 50 ml 2N HCl was added and the mixture extracted with diethylether (3x60 ml) The combined etheral layers were washed with water (3x10 ml) and dried over Na_2SO_4 After evaporation of the ether in vacuo the residue was dissolved in a mixture of hexane/n-propanol (96 4) containing a standard amount of biphenyl added as a internal standard, and the mixture was analyzed quantitatively via HPLC.

D. Apparatus

Polarimeter. Perkin-Elmer 141. HPLC LDC Constamatic I combined with a UV III detector and an HP 3390 A integrator Column. LiChrosorb-Si-60-10. Eluent Hexane/n-propanol 96 4

RESULTS AND DISCUSSION

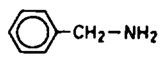
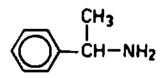
A. Chemical yield

A1. The influence of the structure of the amine and the stoichiometry of the reaction

As we were interested in the properties of amines required to form a copper(II) complex effective as an oxidant, several basic amines were tested Stoichiometric research was combined with these experiments by adding variable amounts of amine to 6 mmol copper(II)nitrate and 6 mmol 2-naphthol Table I shows the tested amines and their pK_a values and Figure 1 shows the chemical yield of binaphthol as a function of the amine/copper(II) ratio

All primary amines show similar behaviour over the full range of amine/copper(II) ratios A distinct plateau value is reached at a 4 1 amine/copper(II) ratio. This 4.1 ratio corresponds with the ratio necessary to form an optimal square-planar copper(II) amine complex (16). However, this does not mean that this ratio is the same in the actual oxidizing complex because 2-naphthol (pK_a=9.5) will protonate and replace some of the amine in the complex This supposition is corroborated by experiments using sodium 2-naphtholate, where the plateau value was reached at

Table I.

STRUCTURE	NAME	pKa
$H_3C-CH_2-NH_2$	ETHYLAMINE	10 8
	BENZYLAMINE	9 3
	α-METHYL-BENZYLAMINE	9 8
$(CH_3-CH_2)_2NH$	DIETHYLAMINE	10.5
$(CH_3-CH_2)_3N$	TRIETHYLAMINE	11 0

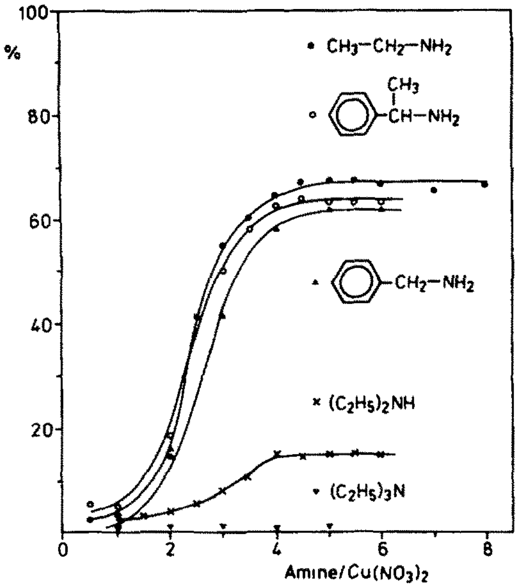


Fig 1 Percentage yield on binaphthol as a function of the amine/copper(II) ratio The copper(II)/2-naphthol ratio was fixed at 1.1.

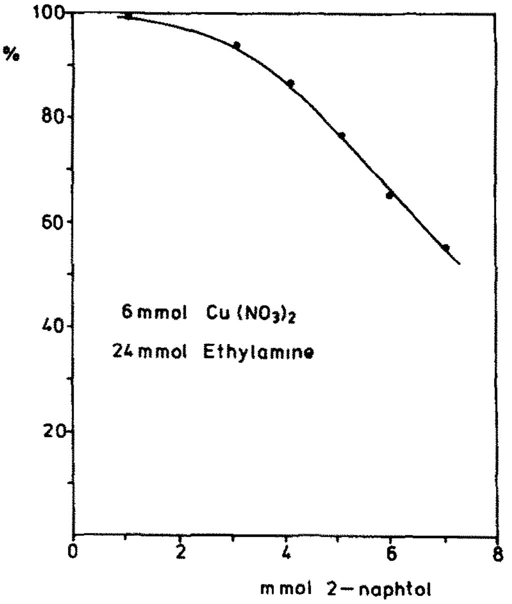


Fig 2. Percentage yield on binaphthol as a function of the amount of 2-naphthol.

a 3 1 amine/copper(II) ratio In the sequence primary, secondary and tertiary amine the plateau level drops from 67% tot 40% and 0% respectively These differences cannot be attributed to pK_a differences, hence the structure of the amine seems to be the decisive factor.

Both the observed maximal yield of 67% obtained with primary amines and the observation that the dark brown precipitate, obtained at the end of the reaction, contains copper(II) (cf 14b), give rise to the supposition that copper(II) is withdrawn from the reaction. In that case equimolar amounts of copper(II) and 2-naphthol will not be the optimal condition to dimerize 2-naphthol quantitatively, as can be seen from the following equation

$$3\ Cu(II) + 3\ 2\text{-naphthol} \rightarrow 2\ Cu(I) + 1\ \text{binaphthol-}Cu(II) + 1\ 2\text{-naphthol}$$

weight 67% weight 33%

So for quantitative dimerization the ratio between copper(II) and 2-naphthol has to be at least 3;2. Figure 2 shows the results of an experiment in which the amount of 2-naphthol was varied, using fixed amounts of copper(II)nitrate (6 mmol) and ethylamine (24 mmol) An increasing copper/2-naphthol ratio did enhance the binaphthol yield up to 98% To be sure of an optimal situation a ratio of 2.1 can be chosen.

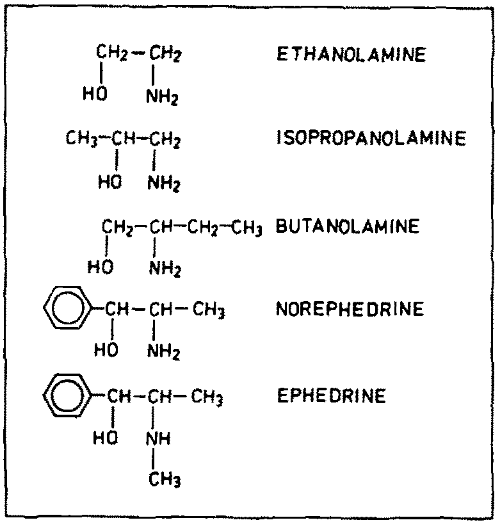
Based on the findings so far, we suggest the following conditions to get an optimal yield a strict nitrogen atmosphere, a primary amine as a ligand and a copper(II)/amine/2-naphthol ratio of 2·8.1 With this procedure a reproducible yield of at least 95% is obtained.

A2. Ethanolamines as ligands.

In the literature (13) it is reported that by means of butanolamine and ephedrine as ligands a negligible binaphthol yield is obtained These compounds are representatives of the important class of ethanolamines. Ethanolamines are known to be bidentate (17), i e to coordinate with the amine nitrogen as well as with the hydroxy oxygen Because of this intramolecular ligand binding, the copper(II)ethanolamine complex can be considered to be very stable (13). Oxidation of the 2-naphthol by the complex would imply the formation of copper(I) and thus an unfavourable change in complex geometry (18). For this reason copper(II) in these complexes is not expected to act as an oxidant in this kind of reactions. However, because of the biological importance of ethanolamines we extended the number of tested ethanolamines to five (Table II)

In a nitrogen atmosphere none of the tested copper(II)ethanolamine complexes did oxidize 2-naphthol to an appreciable extent, supporting the explanation described above. By accident, however, we noticed that in the presence of oxygen a fairly high yield of binaphthol (up to 72%) was obtained. This points to oxidation by dioxygen in complex with copper(II) and amine, as has been described in the literature (14,19,20,21). With regard to this phenomenon special attention has been paid to isopropanolamine (IPA) Figure 3 shows the results of experiments in which the amount of isopropanolamine has been varied. The copper(II)/2-naphthol ratio in these experiments was kept on 1:1

Table II.



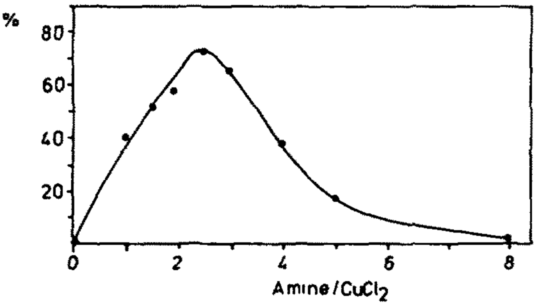


Fig. 3 Percentage yield on binaphthol as a function of the IPA/copper(II) ratio. The copper(II)/2-naphthol ratio was fixed at 1:1.

The appearance of a maximum yield at an IPA/copper(II)chloride ratio of 2.5:1 is striking. A similar relationship was found with coppernitrate, implying the ratio to be independent on the counter ion. Considering the equal pK_a values of 2-naphthol and IPA, 2-naphthol will be at least partly deprotonated without simultaneously being taken up as a ligand in a copper(II) complex. This in contrast to the mechanism described for copper(II)amine complexes The extra consumption of IPA may be responsible for the fact that the maximum in Figure 3 is situated at an ethanolamine/copper(II) ratio higher than 2:1.

Experiments with norephedrine as a complexing ethanolamine showed similar behaviour.

For the mechanism of the oxidation reaction it is proposed that the approach of a naphtholate anion to the complex will take place at the site opposite to the coordinated oxygen. The naphtholate anion now supplies an electron to dioxygen via copper(II) and is oxidized. By means of oxygen as an oxidant in this way (22) an unfavourable change in complex geometry is avoided as copper(II) is not reduced to copper(I). Figure 4 shows the proposed square-planar complex structure under oxygen atmosphere As can be seen from Figure 3, an increase of the IPA/copper(II) ratio diminishes the binaphthol yield finally to zero. We assume that at a high isopropanolamine concentration all six copper(II) coordination sites are occupied by isopropanolamine. In that situation the copper(II) cannot coordinate with oxygen and the naphthol anion and no oxidation is possible.

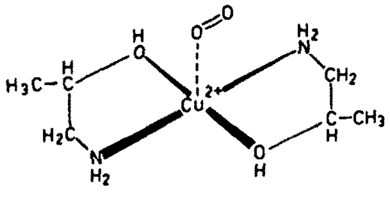


Fig. 4. A square-planar complex structure of isopropanolamine and copper(II) in presence of oxygen.

A3. The influence of the anion of the copper(II) salt.

In order to determine the influence of difference in anion by the reaction under nitrogen atmosphere, experiments were carried out with copper(II)nitrate, chloride, sulfate and acetate The copper(II)-2-naphthol/amine ratio was fixed at 2 1 8 according to the standardization established in paragraph A1 No significant differences in binaphthol yield (95%) were found using the various Cu(II) salts However, an important advantage was noticed when copper(II)chloride was used With ethylamine and amphetamine as a cómplexing amine a homogeneous solution of the complex in methanol was obtained, this in contrast to the precipitate formed when using the other copper(II) salts So a further standardization was fixed the use of copper(II)chloride instead of the previously used nitrate With this new standardization again a relation was determined between the amine/ copper(II) ratio and the binaphthol yield Ethylamine and amphetamine were used as primary amines (Fig 5)

As was expected, the plateau reached a level of nearly 100% With copper(II)nitrate this level started at a 4 1 ratio amine/copper(II) (see Fig 2) But with copper(II)chloride the level is reached at an amine/copper(II) ratio of 2 1 This difference between nitrate and chloride is understandable considering the greater ability of chloride to coordinate as a ligand compared to nitrate It is likely that a copper(II)chloride/ amine complex in a 1 2 2 ratio is formed This is in accordance with the literature (15,16) describing the same difference between chloride and nitrate in the formation of square-planar copper(II) complexes In order to produce a very high chemical yield the standardized copper(II)/amine/2-naphthol ratio of 2 8 1 was maintained

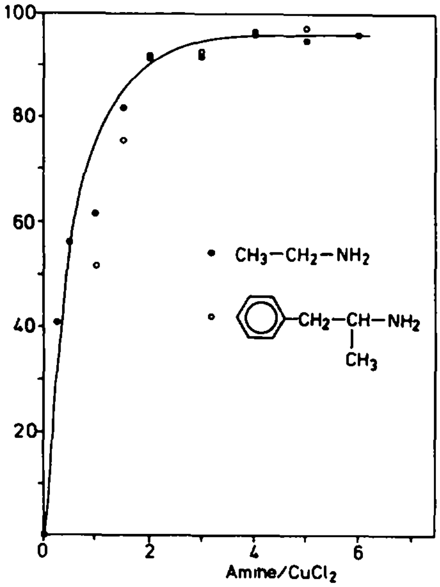


Fig 5 Percentage yield on binaphthol as a function of the amine/copper(II) ratio The amounts of copper(II) and 2-naphthol were fixed at 6 and 3 mmol respectively

Summarizing what has been found so far it can be stated that a simple, reproducible, highly efficient synthesis of pure racemic binaphthol is possible when the following conditions are used

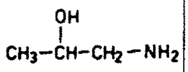
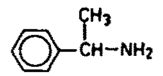
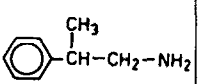
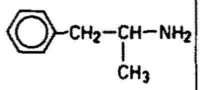
- a nitrogen atmosphere during the whole procedure
- a primary amine as a ligand
- copper(II)chloride as oxidant
- a copper(II)/amine/2-naphthol ratio of 2 8 1

B Stereoselectivity

Feringa and Wynberg (13) reported optical purities up to 8% for the dimerization of 2-naphthol, using chiral copper(II)amine complexes as oxidizing agents In our department several chiral amines were tested The amines, chemical yield and optical purity are listed in Table III

As can be seen, stereoselective induction was very poor with most amines The superior optical purity produced by using S-(+)-α-methyl-phenylethylamine (S-(+)amphetamine) as a ligand was surprising Very similar amines (see Table III) showed far less stereoselective induction The fact that with amphetamine an unprecedented optically pure binaphthol could be obtained (23) stimulated us to optimise this reaction A problem which had to be faced was the irreproducibility of the optical purity of the endproduct, (-)binaphthol, under apparently identical reaction conditions As was described in 'Experimental procedures', the syntheses were carried out at room temperature and no influence of temperature on chemical yield was observed However, in view of the irreproducibility of the optical purity obtained, we decided to set up experiments in order to determine the relation between the optical purity and chemical yield at one hand and temperature on the other The standardization fixed with respect to the chemical yield was applied, so all reactions were carried out using a copper(II)chloride/S-(+)amphetamine/2-naphthol ratio of 2 8 1 Each procedure, including the isolation of binaphthol by crystallization, was carried out at one chosen temperature Figure 6 shows the results of these experiments The chemical yield was independent of temperature (95-98%) However, within a very small temperature range (10 to 20°C) the optical

Table III.

STRUCTURE	NAME	CHEMICAL YIELD	ENANTIOMERIC EXCESS
 $CH_3-CH(OH)-CH_2-NH_2$	ISOPROPANOLAMINE	1%	0%
	α-METHYL-BENZYLAMINE	97%	8%
	β-METHYL-PHENYLETHYLAMINE	97%	8%
	α-METHYL-PHENYLETHYLAMINE (AMPHETAMINE)	98%	96%

purity increased from 5% e.e. up to 96% e e. These results solve the problem of the irreproducibility of the experiments before the variation in 'room temperature' between ca 15 and 25°C explains the variation in the optical purity obtained.

The determined relation between temperature and the stereoselectivity of the reaction is remarkable as in general a reverse relationship is found So these data give rise to the supposition that not the oxidative coupling reaction itself induces stereoselectivity but, depending on solubilities and in this way on temperature, stereoselective crystallization of the (-)binaphthol-copper(II)chloride-(+)amphetamine complex (brown precipitate) should be responsible for the stereoselectivity of the process. A simultaneous racemization of the remaining (+)binaphthol in solution (wether or not complexed) would explain the found combination of a high optical purity and a high chemical yield. These suppositions were checked experimentally as follows At a temperature of 25°C under nitrogen atmosphere (+)amphetamine and copper(II)chloride dissolved in methanol were added successively to a methanolic solution of <u>racemic</u> binaphthol. After 20 hours the precipitated complex was filtered off. Binaphthol was isolated both from the precipitate and from the filtrate and analyzed. The data are shown in the scheme.

It can be seen that the originally racemic binaphthol is transformed into an enantiomeric mixture of 89% (-)binaphthol and 11% (+)binaphthol. This experiment was repeated at 0°C. The precipitate (94%) and the binaphthol in solution (6%) didn't show any optical activity.

These results confirm the supposition that it is not the oxidative dimerization responsible for the stereoselectivity of the process but the stereoselective crystallization of the complex.

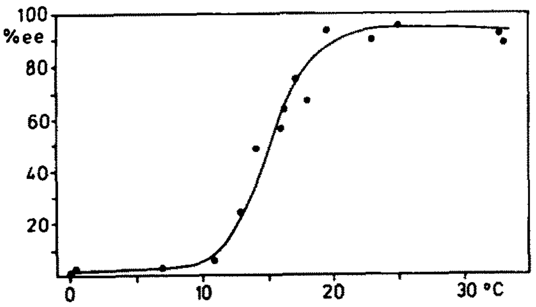
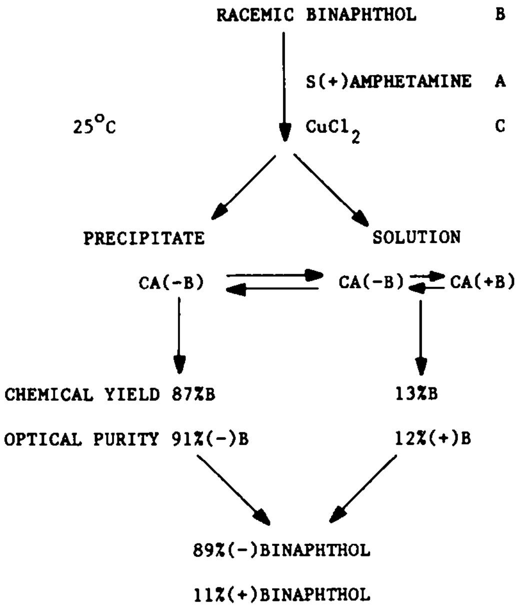


Fig. 6. The influence of temperature on the optical purity of the isolated binaphthol

FINAL REMARKS

Firstly the title of our previous paper (23) "A HIGHLY STEREOSELECTIVE SYNTHESIS OF S(-)-(1,1'-BINAPHTHALENE)-2,2'-DIOL" is not correct. The formation of S-(-)binaphthol turns out to be a stereoselective crystallization combined with racemization in solution,



a "second order asymmetric transformation" (13)

Secondly it is clear from our mechanistic research that this reaction cannot be presented any longer as a model for the biosynthetic oxidative phenol coupling as is mentioned by Feringa and Wynberg (13)

Thirdly it is established that although S-(-)binaphthol is described to be optically stable (100°C, 24hr) in dioxan-water (24), in the presence of copper(II)-amine complexes racemization occurs even at room temperature

REFERENCES

1 M Nishizawa, M Yamada and R Noyori, Tetrahedron Lett , 22, 247 (1981)
2 R Noyori, I Timono and M Nishizawa, J Am Chem Soc , 101, 5843 (1979)
3 J P Vigneron and I Jacquet, Tetrahedron, 32, 939 (1976)
4 M Sépulchre, N Spassky, C Mark and V Schuring, Makromol Chem , Rapid Comm 2, 261 (1981)
5 S Miyano, M Tobita and H Hashimoto, Bull Chem Soc Jpn , 54, 3522 (1981)
6 J M Lehn, J Simon and A Moradpour, Helv Chim Acta, 61, 2407 (1978)
7 D.J Cram and J M Cram, Acc Chem Res , 11, 8 (1978)
8 J Jacques, C Fouquey and R Viterbo, Tetrahedron Lett , 48, 4617 (1971)
9 L R. Sousa, G D Y Sogah, D Hoffman and D J Cram, J Am. Chem Soc , 100, 4569 (1978)
10 R Pummerer, E Prell and A Rieche, Chem Ber , 59, 2159 (1926)
11 I Meyers and K A Lutomsky, J Am Chem Soc , 104, 879 (1982)
12 J M Wilson and D J. Cram, J Am Chem. Soc , 104, 881 (1982)
13 B Feringa and H Wynberg, Bioorg Chem , 7, 397 (1978)
14 a) W. Brackman and E Havinga, Recl Trav Chim Pays-Bas, 74, 937 (1955) b) ibid 74, 1021 (1955) c) ibid 74, 1070 (1955) d) ibid 74, 1101 (1955) e) ibid 74, 1107 (1955)
15 S Miyano, M Tobita, M Nawa, S Sato and H Hashimoto, J Chem Soc Chem Comm , 1233 (1980)
16 G W. Watt and W.J Wells, J Inorg Nucl Chem , 38, 921 (1976)
17 G Nieuwpoort and W.L. Groeneveld, Recl Trav Chim Pays-Bas, 99, 394 (1980)
18 M A Augustin and J K Yandell, J Chem Soc Chem Comm , 370 (1978)
19 A.J. Schouten, G Challa and J Reedijk, J Mol Catal , 9, 41 (1980)
20 E I Solomon, Inorg. Chim Acta, 79, 3 (1983)
21 A Scozzafava, Inorg. Chim. Acta, 62, 15 (1982)
22 C.M Visser, Bioorg Chem , 9, 261 (1980)
23 J. Brussee and A C A Jansen, Tetrahedron Lett , 24, 3261 (1983)
24 E.B Kyba, K. Koga, L R Sousa, M G Siegel and D J Cram, J Am Chem Soc., 95, 2692 (1973)