HOMOCHIRAL CRYSTALS FOR SELECTIVE SYNTHESIS

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DOCTORAL THESIS

Submitted for partial fulfillment of the requirements for the degree of Doctor of Philosophy in Natural Science, Specializing in Chemistry

Homochiral Crystals for Selective Synthesis

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Cover Picture: Crystals used in the experiments in this thesis.

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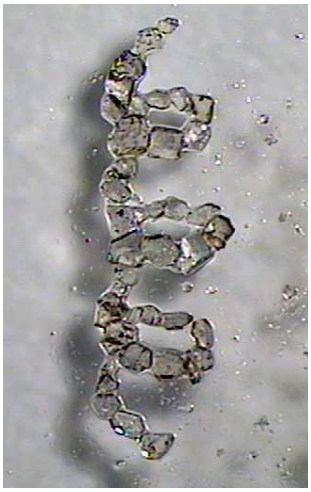

From the greatest scientists

like Pasteur, Werner and Thomson

to the more unknown,

without them this thesis would not exist.

This is my contribution to science.

Theonitsa

Abstract

Six new coordination compounds were prepared from monodentate sulfide ligands and copper(I) halides and their crystal structures were determined by single-crystal X-ray diffraction. The aim was to prepare coordination polymers that crystallize as conglomerates in order to use them in total spontaneous resolution. The anionic and neutral ligands were varied in order to examine how they would affect the crystallization. All six complexes formed racemic crystals, and five of them were polymeric.

Bidentate sulfide ligands were used to increase the possibility of obtaining a coordination polymer. Five new complexes were prepared and structurally characterized by single crystal X-ray diffraction. Three of the complexes formed coordination polymers but none of them crystallized as a conglomerate.

Tetrahedral metal complexes have been resolved by total spontaneous resolution for the first time. A cationic silver(I) complex with a bidentate sulfide ligand was prepared and it crystallized as a conglomerate. Enantioenriched crystal batches were obtained with enantiomeric excesses up to 90 %.

Three chiral Ru(II) complexes with bidentate sulfide ligands were prepared and all three crystallized as conglomerates. They were used in absolute asymmetric synthesis and oxidized enantioselectively. The oxidations resulted in a selectivity of > 98% without the use of a chiral catalyst. One of the Ru(II) complexes isomerizes when exposed to light. Four new phases, containing one or both isomers, co-crystallized from the same solution.

Keywords: Absolute asymmetric synthesis, total spontaneous resolution, optical activity, coordination compounds, coordination polymers, photoisomerization, enantioselective sulfide oxidation, single crystal X-ray crystallography, co-crystallization of diastereomers

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Manuscripts

This thesis is based on the following manuscripts:

I. **Towards absolute asymmetric synthesis of coordination polymers with prochiral substrates**
Theonitsa Kokoli and Mikael Håkansson
Submitted to CrystEngComm

II. **Towards absolute asymmetric synthesis of coordination polymers with bidentate sulfide ligands**
Theonitsa Kokoli, Susanne Olsson, Per Martin Björemark, Staffan Persson, and Mikael Håkansson
Submitted to J. Organomet. Chem.

III. **Total Spontaneous Resolution of Tetrahedral Complexes**
Theonitsa Kokoli and Mikael Håkansson
Submitted to Angew. Chem. Int. Ed.

IV. **Absolute Asymmetric Synthesis: Protected Substrate Oxidation**
Theonitsa Kokoli, Susanne Olsson, Per Martin Björemark, Jonas Sundberg, Anders Lennartson, Christine J. McKenzie, and Mikael Håkansson
Submitted to Angew. Chem. Int. Ed.

V. **Concomitant Polymorphism and Co-crystallization of Diastereomers**
Theonitsa Kokoli and Mikael Håkansson
Submitted to Chem. Eur. J.

Abbreviations

AAS	Absolute asymmetric synthesis
Ar	Aromatic
CD	Circular dichroism
CuMes	Mesitylcopper
DMDO	Dimethyldioxirane
DMSO	Dimethyl sulfoxide
ee	Enantiomeric excess
ESI-MS	Electrospray ionization mass spectrometry
NMR	Nuclear magnetic resonance
HPLC	High pressure liquid chromatography
*i*Pr	Isopropyl
IR	Infrared
Ln	Ligand
Me	Methyl
Mes	Mesityl
NS	(2-(methylthio)methyl)pyridine
Ph	Phenyl
PS	(2-(methylthio)ethyl)diphenylphosphine
PSO	(2-(methylsulfinyl)ethyl)diphenylphosphine
Sally	Allyl methyl sulfide
Sprop	Phenyl propargyl sulfide
SPY-5	Square pyramidal
SRR’	Unsymmetrical sulfide
SS	2,5-dithiahexane
T-4	Tetrahedral
TB-5	Trigonal bipyramidal
*t*Bu	*tert*-Butyl
THF	Tetrahydrofuran
TSR	Total spontaneous resolution

Crystals

1	$[Cu_4I_4(CH_3SC_6H_5)_4]$
2	$[Cu_3Br_3(CH_3SC_6H_5)_2]_n$
3	$[Cu_3Cl_3(CH_3SC_6H_5)_2]_n$
4	$[Cu_4I_4(CH_3SC_2H_5)_3]_n$
5	$[CuBr(CH_3SC_2H_5)]_n$
6	$[Cu_4Cl_4(CH_3SC_2H_5)_3]_n$
7	$[CuCl(Sprop)]_n$
8	$[Cu_2Br_2(Sprop)_4]$
9	$[CuCl(Sally)]_n$
10	$[Cu_4(Mes)_4(Sally)_2]$
11	$[Cu_4(Mes)_4(SS)]_n$
12	$[Ag(PS)_2]BF_4$
13	$[RuCl_2(PS)_2]\cdot DMSO$
14	$[RuCl_2(dmso)_2(NS)]$
15	$[RuCl_2(dmso)_2(SS)]$
16	$[RuCl_2(PSO)_2]\cdot DMSO$
17	$[RuCl_2(PS)_2]\cdot CH_2Cl_2$
18	2{(*cis,cis,trans*)-$[RuCl_2(PS)_2]$}(*trans,cis,cis*)-$[RuCl_2(PS)_2]$
19	2{*(S,S)-(trans,cis,cis)*-$[RuCl_2(PS)_2]$}*(R,R)-(trans,cis,cis)*-$[RuCl_2(PS)_2]$
20	*(trans,cis,cis)*-$[RuCl_2(PS)_2]$

Contents

1. Introduction

1.1 Coordination compounds

1.1.1 General

Coordination compounds, also known as metal complexes, consist of a metal ion that binds to ligands. Alfred Werner is considered as the founder of this branch of chemistry and therefore inorganic complexes are often called Werner complexes or classical complexes. The most common geometry in these types of compounds is octahedral and the ligands can be monodentate, bidentate or polydentate.[1] In octahedral complexes they are arranged as in figure 1. The bonds in these complexes are called coordinate bonds when both electrons come from the ligand.[2, 3]

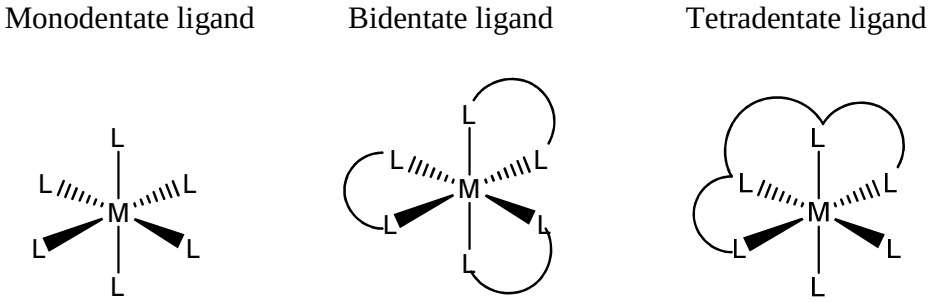


Figure 1 Ligands in octahedral complexes

A central part in coordination chemistry is the five d-orbitals (figure 2). They affect many of the properties of the metal complexes and hence the chemistry that they can undergo.

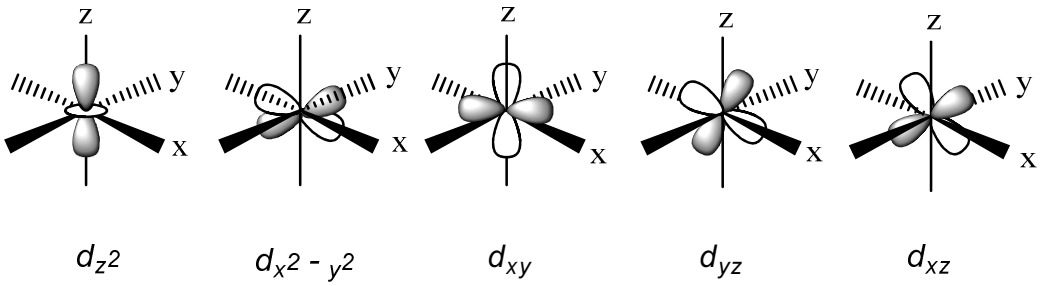


Figure 2 The five d-orbitals

When ligands bind to a metal ion then the orbitals are affected. Depending on the geometry of the complex, the orbitals will split into different energy levels. This can be illustrated in a crystal field splitting diagram. For tetrahedral and octahedral coordination compounds the orbitals are arranged as in figures 3 and 4, respectively.

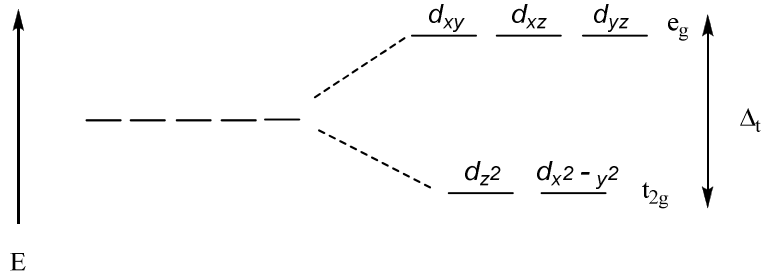


Figure 3 Crystal field splitting diagram for tetrahedral complexes

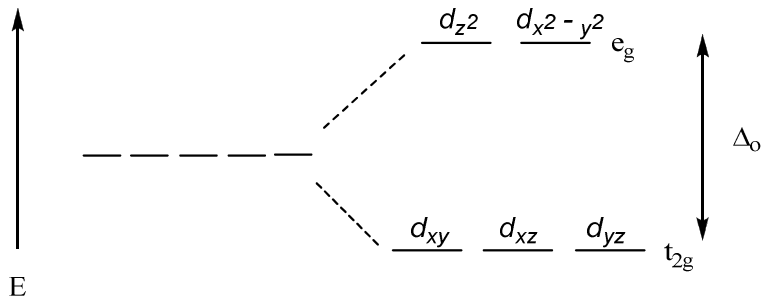


Figure 4 Crystal field splitting diagram for octahedral complexes

The orbitals in the t_{2g}-level are more stable than the orbitals in the e_g-level. The ligand-field splitting parameter (Δ) is the energy difference between e_g

and t_{2g} orbitals.[2] There are mainly three factors that affect Δ, d^n configuration of the metal, whether the metal is a third, fourth or fifth row element and if the ligand is high or low field. There is a difference between the tetrahedral geometry and the octahedral regarding Δ. In the tetrahedral geometry it is about 2/3 compared to the octahedral geometry.[3]

1.1.2 Inert and labile complexes

Coordination compounds can be classified as inert or labile. In labile complexes ligand dissociation occurs more easily. Definite classification into the two categories is difficult but an arbitrary classification can be made according to the following definition by Henry Taube: ¨If no delay is noted in the substitution reaction under ordinary conditions (i.e., room temperature, *ca* 0.1 *M* solutions) the system will be described as labile.¨[4] The majority of complexes that are substitutionally inert have either octahedral or square planar geometry.[1] A complex is labile if the difference in free energy between the reactant and the activated complex is small. The lability in octahedral complexes can be predicted with some reliability. If the central metal atom in a complex has *d* electrons in the e_g-level or less than three *d* electrons, it will often be labile. A common electron configuration for inert complexes with octahedral geometry is d^6. A large value for Δ results in a low spin complex and vice versa. For example, complexes with d^6 configuration can be either high spin or low spin, depending on the value of Δ (figure 5).[2, 3, 5]

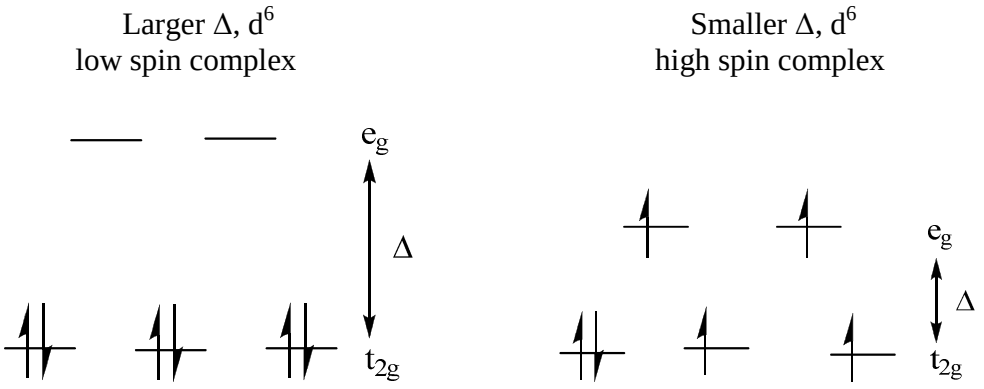


Figure 5 Electron configurations for octahedral complexes

Labile complexes racemize rapidly in solution if they are chiral, in contrast to inert complexes. Coordination compounds with tetrahedral geometry are in general labile. There are cases in which a tetrahedral complex is inert but those cases are exceptions. This is in complete contrast to organic chemistry and tetrahedral carbon compounds.[1, 6]

1.1.3 Isomerization

There are different types of isomerism in coordination compounds. Some types apply for several geometries while others are specific for one geometry. *Cis/trans*-isomerism is common in octahedral complexes but doesn't exist in tetrahedral complexes. Another type of isomerism that exists for octahedral complexes is facial (*fac*) and meridional (*mer*) isomerism (figure 6).

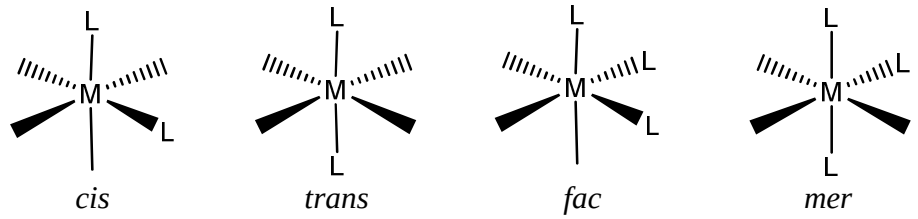


Figure 6 *Cis-trans* isomerism and *fac-mer* isomerism

Isomers can have different properties and can then be distinguished by chemical or physical methods. Isomerization can occur due to exposure to light or heat, i.e. photoisomerization and thermal isomerization, respectively. Both types of isomerization can be reversible or irreversible. Just as in organic chemistry there is also stereoisomerism in coordination compounds. The subclassification is the same, enantiomers and diastereomers.[1, 7, 8]

1.2 X-ray crystallography

1.2.1 Principles of the method

X-ray crystallography is an important method for the analysis of coordination compounds. It is used for crystal structure determination. From the crystal structure one can determine connectivity in the molecule, bond lengths, bond angles and the crystal packing.

Many analytical methods are based on the absorption or emission of electromagnetic radiation by matter. For this absorption to occur the energy in the radiation has to match energy levels in the compound. Different wavelengths of the radiation affect matter in different ways. X-rays have short wavelength, ~1Å, and are high in energy. The electrons in the atoms have the ability to scatter X-ray beams and one can take advantage of this in X-ray crystallography. For the analysis single crystals are required. In a crystal atoms or molecules are arranged in very regular patterns, lattices, which are repeated infinitely. The smallest repeating unit in the crystal is called the unit cell and there are several possibilities for a unit cell (figure 7). By exposing the crystal to X-rays, the electrons scatter the X-ray beams and a diffraction pattern is obtained. From it the crystal structure of the compound can be deduced.[9, 10]

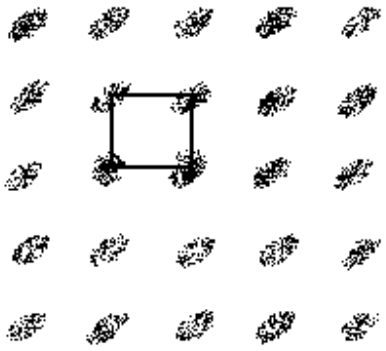


Figure 7 Crystal lattice and a unit cell

1.2.2 Different types of crystals

For a single compound there may exist several crystal structures. This is called polymorphism, although strictly speaking there are no clear definitions of what polymorphism is.[11, 12] Different polymorphs have different physical properties such as density, melting point and solubility.[13] There are several reasons for polymorphism and different kinds of polymorphism. Which polymorph that is obtained might depend on the solvent, temperature or impurities.[14-16] In packing polymorphism the difference lies in crystal packing and in conformational polymorphism there are different conformers. Hydrates and solvates are not really considered as polymorphs since there is a

difference in constitution but nevertheless they are called pseudopolymorphs. If chirality aspects are considered, then a compound can crystallize as a racemate, conglomerate or solid solution. In a racemic crystal both enantiomers are present in equal amounts. In conglomerates the crystals are enantiopure but the whole crystal batch may still be racemic if there is an even distribution of both types of crystals. In solid solution there can be an uneven distribution of the two enantiomers (figure 8).[17]

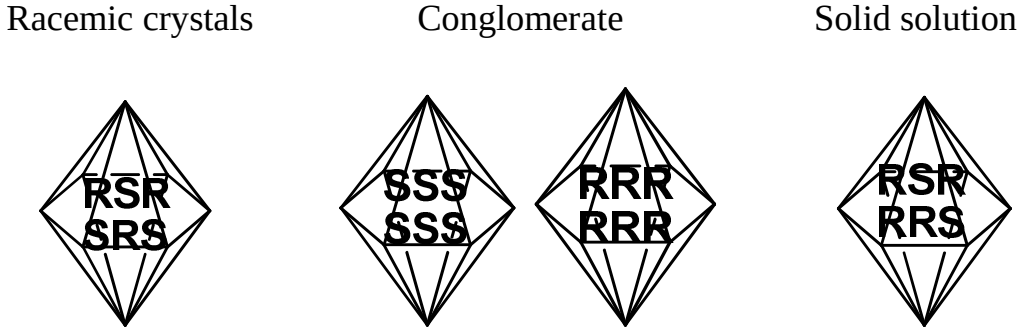


Figure 8 Chirality aspects in crystals

The symmetry operations in molecules can be gathered into 32 point groups. The total number of combinations for the symmetry elements in crystals is 230 and they are called space groups.[10] Racemic solutions normally crystallize as racemic crystals. It is quite rare for a compound to crystallize as a conglomerate, it is estimated that only 5-10 % of all organic and organometallic compounds crystallize as conglomerates.[18] Compounds that crystallize as conglomerates belong to one of the 65 Sohncke groups. Among these space groups 22 of them are chiral, i.e. 11 enantiomorphic pairs. The rest are not chiral even though a compound crystallizing in such a group will crystallize as a conglomerate. Lately another term has been introduced for the Sohncke space groups, namely chirodescriptive. One reason is that the term Sohncke space group is not self-explanatory.[19] Enantiopure compounds crystallize as conglomerates by necessity, but racemic or achiral compounds may crystallize either in an achiral or a Sohncke space group.[17] If an achiral compound crystallizes as a conglomerate, the chirality originates from the packing.[17, 20]

1.3 Chirality

1.3.1 Chirality in coordination compounds

When chirality was first discovered it was thought that it only was a property of organic compounds. Several attempts made by Alfred Werner to prove that chirality could originate from coordinate compounds could be discarded by Jørgensen.[21] Alfred Werner finally managed to prove that this restriction did not exist by the resolution of hexol (figure 9). Hexol was the first optically active non-carbon containing compound to be resolved.[22, 23]

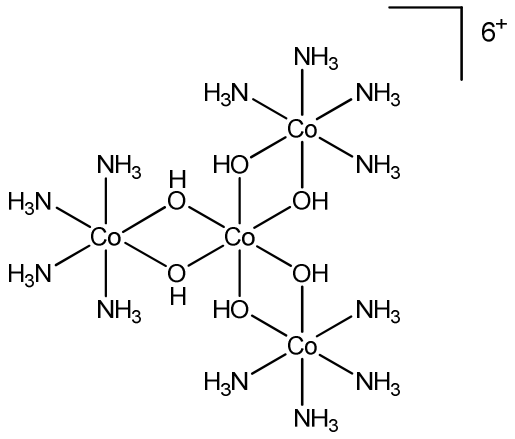
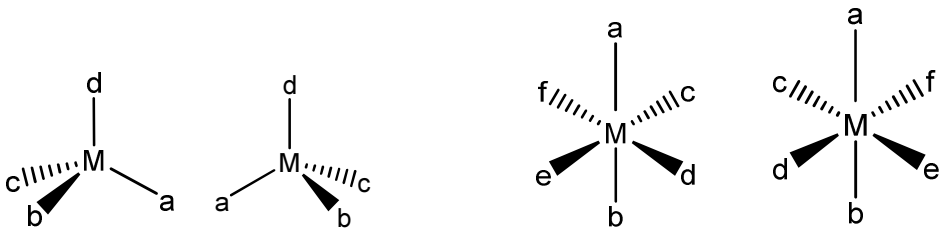


Figure 9 The cation of hexol

The different geometries in coordination compounds result in a rich stereochemistry. There are three reference systems for the designation of chirality in metal complexes. The first is the steering wheel reference system which is also used in organic chemistry. In tetrahedral complexes the two enantiomers are named *R* and *S*, respectively. In all other cases the two enantiomers are named *C* (for clockwise) and *A* (for anti clockwise) (figure 10).

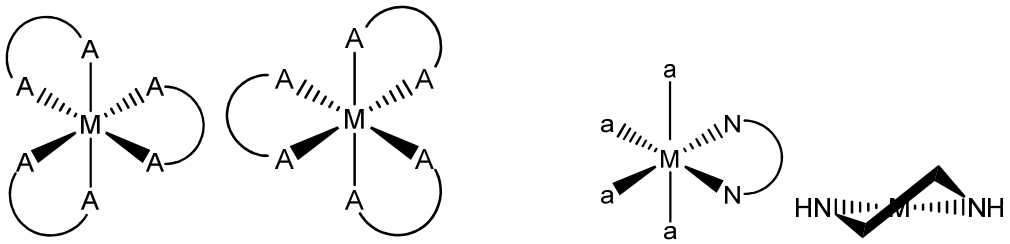


S *R* *C* *A*

[Mabcd] [Mabcdef]

Figure 10 The steering wheel reference system in tetrahedral and octahedral complexes

Bidentate ligands can form chelate rings when they bind to a metal atom. In order to describe the chirality in the complexes, the skew line reference system is used. This is the second reference system. The two enantiomers are designated as Λ and Δ if the whole molecule is considered or λ/δ if only the chelate ring is under consideration (figure 11).



Λ Δ λ/δ λ

Figure 11 Δ/Λ and λ/δ chirality

The oriented line reference system is the third reference system (figure 12). It is suitable for some tetrahedral complexes.[1, 24]

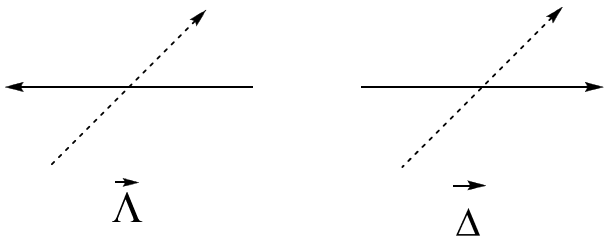


Figure 12 Oriented line reference system

Single atoms in the ligand can also be the source of chirality. This can happen if the ligating atom becomes stereogenic upon complexation or if the ligand is chiral to start with. In both these cases the result is a chiral complex (figure 13).[1]

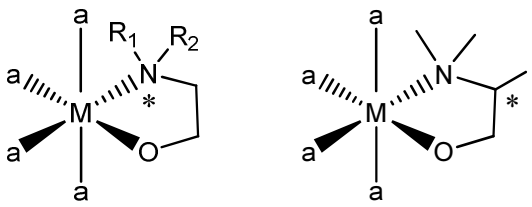
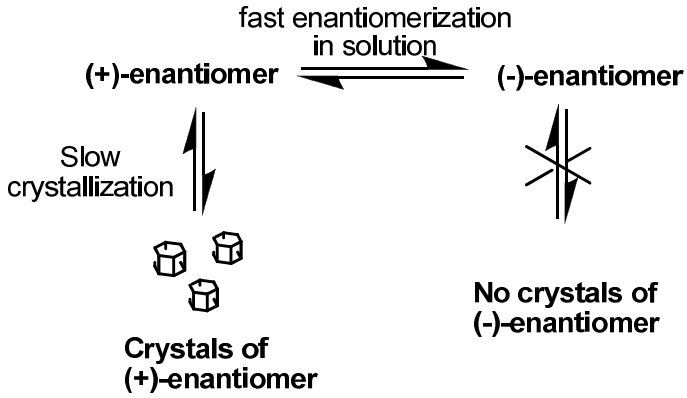


Figure 13 Chirogenic nitrogen or carbon atom

1.3.2 Absolute asymmetric synthesis and total spontaneous resolution

Asymmetric synthesis is the preparation of enantiopure compounds, but it usually requires a preexisting optical activity. Absolute asymmetric synthesis (AAS) on the other hand creates optical activity from achiral or racemic precursors. This is in contradiction with a common view that says that optical activity cannot be created in a closed system. The definition of AAS has changed throughout the years. Bredig was the first who introduced the term in 1923 and in that definition asymmetric forces were important in order to achieve absolute asymmetric synthesis.[25] Today's definition simply states: in absolute asymmetric synthesis optical activity is created from achiral or racemic starting materials.[26] Two major approaches exist for absolute asymmetric synthesis, either the use of circularly polarized light or by the crystallization of a compound in enantiopure crystals. Attempts have also been made with chiral physical forces but without success.[26]

If a compound crystallizes as enantiopure crystals then there is the possibility of total spontaneous resolution (TSR), where all the crystals obtained in a batch have the same handedness. The compound has to be labile so that fast enantiomerization can occur in solution. Slow crystallization is also necessary so that only one nucleus will form as a result of primary nucleation. From this nucleus the rest of the nuclei will form through secondary nucleation (scheme 1).[1, 27-30]



Scheme 1 Total spontaneous resolution

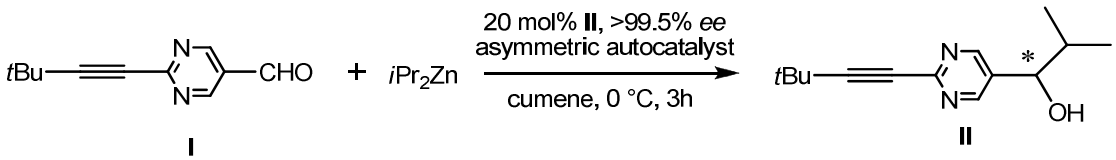
Kondepudi *et al* showed in 1990 that stirring during the crystallization of $NaClO_3$ resulted in homochiral crystal batches. During the crystallization one nucleus is formed from primary nucleation and the rest are formed from secondary nucleation. This resulted in homochiral crystal batches.[20] McBride *et al* showed this mechanism in a video recording.[31]

The first time enantiopure crystals were used in a stereoselective reaction was in 1969. Penzien & Schmidt reacted enantiopure crystals of 4,4'-dimethylchalcone with bromine gas or bromine liquid. The reaction with gas resulted in 6-25% *ee* but in the reaction with liquid bromine there was no optical activity.[32, 33] In 1971 Pincock *et al* resolved 1,1'-binaphthyl by heating crystals to 105-150 °C.[34] Vestergren *et al* reported in 2003 absolute asymmetric synthesis reaction with Grignard reagents and aldehydes. The *ee* in those reactions were up to 22%.[35] In 2005 helical aluminum homochiral complexes did react with organometallic reagents and the resulting alcohols were obtained with a maximum *ee* of 16%.[36] In 2009 a reaction between a labile indenylzinc complex and *N*-chlorosuccinimide resulted in a maximum *ee* of 89% for the product 1-chlorindene.[37]

1.3.3 Homochirality in nature

An interesting aspect of chirality is the homochirality in biomolecules: for example the sugar molecules deoxyribose and ribose in DNA and RNA, respectively, and amino acids in proteins. There are theories on how this phenomenon arose and evolved.[26, 38, 39] In a publication from 1953, Frank suggested a mechanism where a compound is both the chiral catalyst and the

product in a stereoselective reaction. Soai *et al* have been working with asymmetric autocatalysis and in 1995 they published a paper where the *ee* in a reaction increased from 2% to 88%. In 1999 they optimized the reaction and gained a yield of 99% and an *ee* of 99.5% (scheme 2).[40-42]



Scheme 2 Asymmetric autocatalysis

Viedma showed that grinding undissolved $NaClO_3$ in a saturated solution resulted in an enantiopure sample. If there was no enantiomeric excess in the sample either of the enantiomers could be formed. But by adding one enantiomer with an enantiomeric excess of 5% to the samples, one could control which enantiomer that would form.[43]

1.4 Sulfoxides

1.4.1 Chiral sulfoxides

Counting the two free electron pairs on the sulfur atom, sulfides possess a tetrahedral geometry. This feature makes unsymmetrical sulfides prochiral, since upon oxidation they become chiral sulfoxides. Chiral sulfoxides have gained a lot of interest over the years in stereocontrolled reactions and this is mainly because of their high optical stability, efficiency in carrying chiral information and accessibility of both enantiomers. Since sulfoxides are ambidentate and can bind with the sulfur atom and/or the oxygen atom they are able to bind to both hard and soft metals. Due to their low rate low of racemization, a common application is as chiral auxiliaries. Sulfoxides normally require harsh conditions for racemization to occur. They are also interesting in biological systems as drugs, with the most famous being omeprazole. Of the two enantiomers it is the S-enantiomer that is the active form and it is called esomeprazole (figure 14).[1, 44-47]

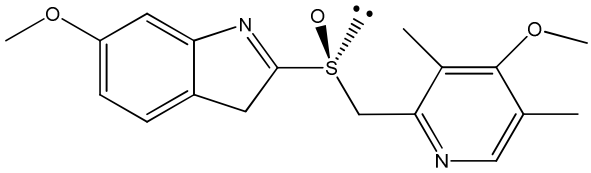


Figure 14 Esomeprazole

Chiral sulfoxides are also frequently occurring in natural products. One of the most familiar is alliin that exists in garlic (figure 15).[48]

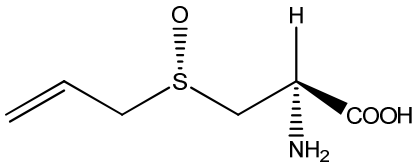


Figure 15 Alliin

1.4.2 Stereoselective sulfide oxidation

Enantiopure sulfoxides can either be prepared by the oxidation of a prochiral sulfide or by nucleophilic substitution of chiral sulfur derivatives, if resolution methods are excluded. Among different methods for enantioselective sulfoxidation the most commonly used is catalytic enantioselective oxidation. In those reactions the catalyst is usually a coordination compound with chiral ligands. Titanium catalysts are among the most frequently used.[49-51]

By adding 1 equiv of H_2O to Sharpless epoxidation reagent, Kagan's group could oxidize prochiral sulfides into chiral sulfoxides in good enantiomeric excess in 1984.[52] Modena *et al* managed in 1984, independently of Kagan, to obtain high selectivity in the oxidation of prochiral sulfides, as well. As in the case of Kagan, they used a modified Sharpless system but without the addition of water and with a larger amount of diethyltartrate.[44], [53] Despite some limitations in modified Sharpless catalysts, they are still considered as one of the most effective sulfoxidation systems.[51] A few changes were introduced into the modified Sharpless system in the preparation of esomeprazole. The system was reported in 2000 by von Unge *et al* and the enantioselectivity was >94 % *ee*. The changes in the system were that the catalyst was prepared in

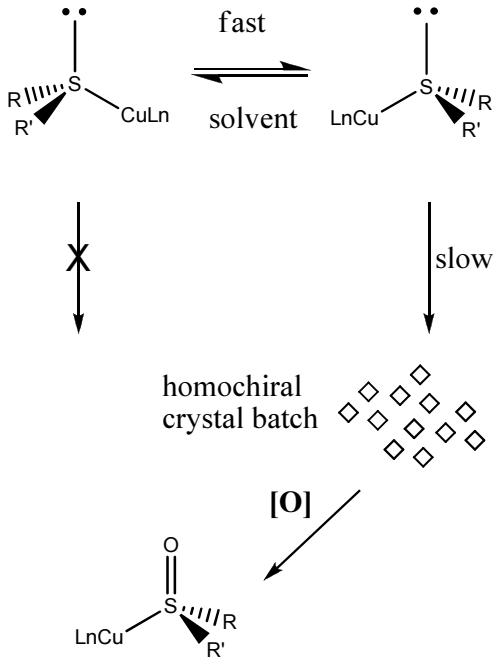
the presence of the unsymmetrical sulfide, the dissolved titanium complex was equilibrated at an elevated temperature and/or for a longer period of time and finally there was also the addition of an amine.[54]

A different approach that does not use a modified Sharpless system is demonstrated by Schenk *et al*. In this case the sulfide was attached to a chiral ruthenium complex, oxidized and afterwards removed.[55] Chavarot *et al* used a ruthenium(II) complex as well as a catalyst. The catalyst was chiral at the metal and the oxidations resulted in a maximun *ee* of 18%.[50]

2. Coordination polymers with prochiral sulfides

The origin of homochirality in nature is still a matter of discussion. Examples of AAS are thus interesting from that aspect since they can provide an insight into how optical activity is created. One method is to use TSR where homochiral crystal batches can be obtained from achiral or racemic compounds. There are two requirements for that to occur, the compound has to be stereochemically labile and it has to crystallize as a conglomerate. We know how to prepare a labile complex but we cannot predict how a complex will crystallize. One way to address this problem is by the crystallization of very similar compounds. In this way it is possible to obtain knowledge on how small variations in the molecule will affect the crystal packing.[28, 39, 56-59]

The aim with this project was to prepare chiral coordination polymers with sulfides as ligands. When sulfides are oxidized, sulfoxides are obtained and they are generally inert. If prochiral sulfides are used then it is possible to trap the chirality. Copper(I) halides were used as Lewis acids for two reasons, their lability and because they are soft Lewis acids (scheme 3).



Scheme 3 Total spontaneous resolution and subsequent oxidation

Six new complexes **1**-**6** were prepared in order to obtain coordination polymers that crystallize as conglomerates. The chosen sulfides were thioanisole and ethyl methyl sulfide (figure 16).

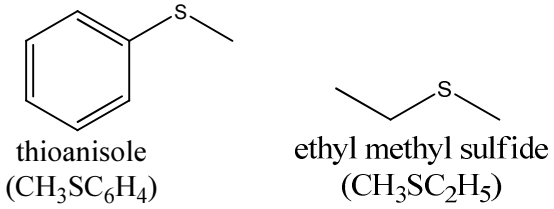


Figure 16 The ligands used in the complexes

Thioanisole was chosen because it is commonly used in oxidation reactions.[44] Ethyl methyl sulfide is an interesting ligand because asymmetric catalytic oxidation of dialkyl sulfides is usually difficult.[55] The sulfides can act both as terminal and as bridging ligands.[60] If they act as terminal ligands then the sulfur atom will be chirogenic. Complexes **1**-**3** have thioanisole as ligand and **4**-**6** have ethyl methyl sulfide as ligand. Table 1 shows a compilation of the aggregation and coordination mode in the complexes.

Table 1 Aggregation and coordination mode in **1**-**6**

Complex	Aggregate	CuX:L	L[a]
(**1**)$[Cu_4I_4(CH_3SC_6H_5)_4]$	Tetramer	1:1	4:0
(**2**)$[Cu_3Br_3(CH_3SC_6H_5)_2]_n$	Chain	3:2	1:1
(**3**)$[Cu_3Cl_3(CH_3SC_6H_5)_2]_n$	Chain	3:2	1:1
(**4**)$[Cu_4I_4(CH_3SC_2H_5)_3]_n$	Chain	4:3	2:1
(**5**)$[CuBr(CH_3SC_2H_5)]_n$	Layer	1:1	1:3
(**6**)$[Cu_4Cl_4(CH_3SC_2H_5)_3]_n$	Layer	4:3	0:3

[a]terminal:bridging sulfide ligands

In **2**-**6** polymers did indeed form while **1** formed discrete molecules. Unfortunately none of the complexes crystallized as a conglomerate. In complexes **1**-**5** the sulfides act both as bridging and/or terminal ligands. In **6** there are only bridging ligands. The molecular structure of $[Cu_4I_4(CH_3SC_6H_5)_4]$ (**1**) is shown in figure 17. The complex forms tetrameric aggregates and it can also be considered as a very distorted cubane.[61] All the ligands have the same configuration, which makes the complex chiral.

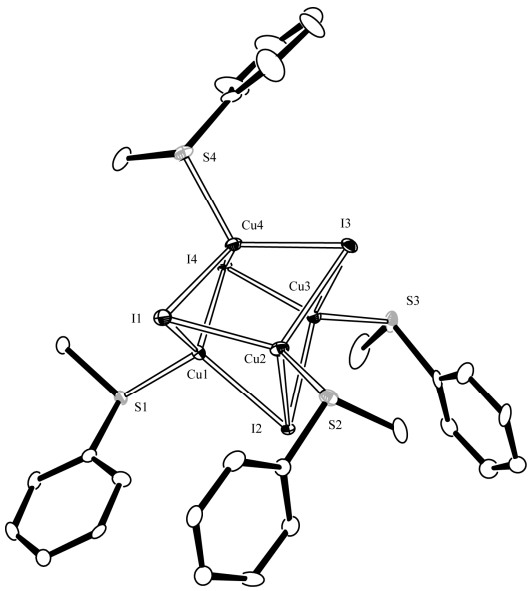
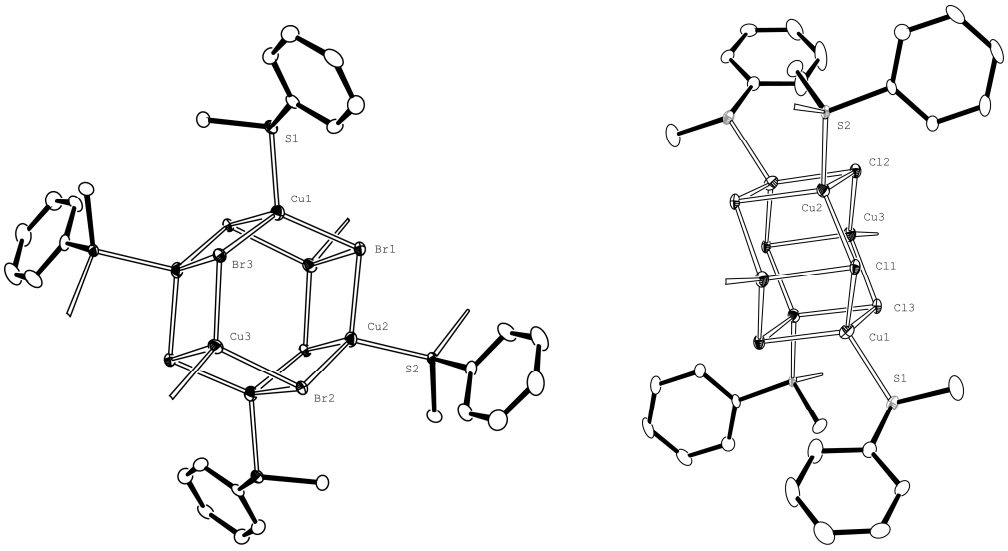


Figure 17 Molecular structure of **1**

Changing the anion in **1** results in several changes in the structures for $[Cu_3Br_3(CH_3SC_6H_5)_2]_n$ (**2**) and $[Cu_3Cl_3(CH_3SC_6H_5)_2]_n$ (**3**). The complexes form isostructural chains linked together by bridging ligands (figures 18 and 19). Since there are terminal ligands as well there are two kinds of sulfur atoms in the structure. One type is chirogenic and the other is not. The chirogenic sulfur atoms in the structure have different configurations in a 1:1 ratio. Another feature in **2** and **3** is that the aggregates in the chains have the shape of hexagonal drums.



2 **3**

Figure 18 Part of the chains in **2** and **3**

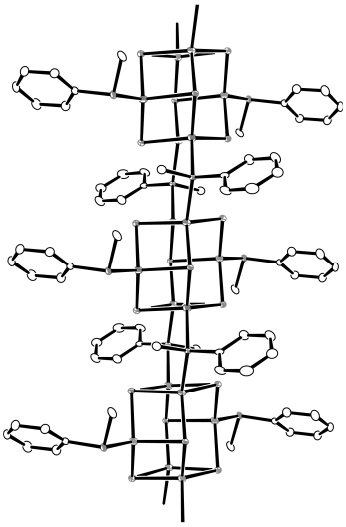


Figure 19 Chain formation in **2** and **3**

The polymer $[Cu_4I_4(CH_3SC_2H_5)_3]_n$ (**4**) forms tetrahedral aggregates quite similar to **1** but in **4** they are linked together with bridging ligands resulting in chains, (figure 20). The sulfur atoms in the terminal ligands have opposite configurations.

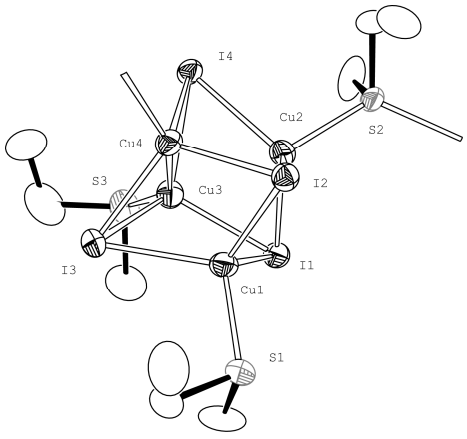


Figure 20 The asymmetric unit in **4**

The complex $[CuBr(CH_3SC_2H_5)]_n$ (**5**) forms layers with two types of aggregates, a tetranuclear ladder and a dinuclear rhombus. These two aggregates form 28-membered rings, (figure 21).

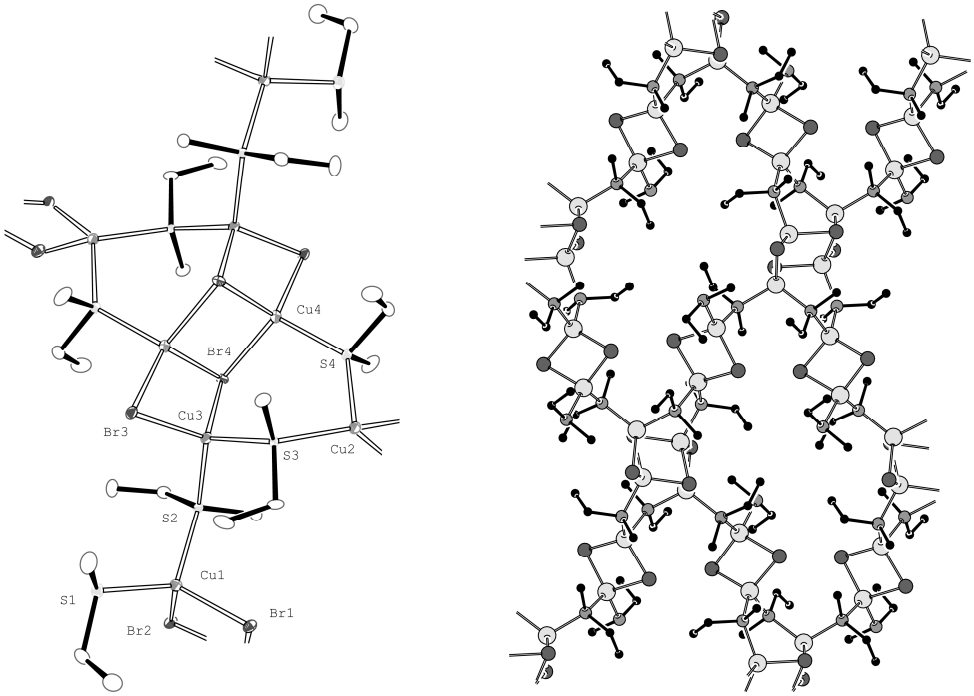


Figure 21 Asymmetric unit and part of a layer in **5**

The complex $[Cu_4Cl_4(CH_3SC_2H_5)_3]_n$ (**6**) also forms layers that consist of 28-membered rings but the rings consist of octanuclear aggregates instead, (figure 22).

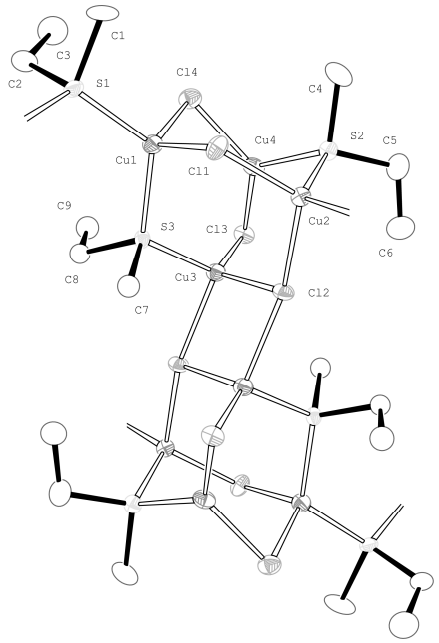
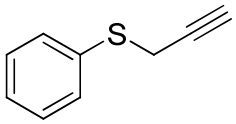
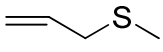


Figure 22 Part of a layer in **6**

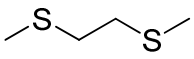
Since none of the complexes **1**-**6** crystallized as conglomerates, five new complexes **7**-**11** (table 2) were prepared. Bidentate ligands were used in order to facilitate polymer formation. The ligands are shown in figure 23.



phenyl propargyl sulfide (Sprop)



allyl methyl sulfide (Sally)



2,5-dithiahexane (SS)

Figure 23 The ligands used in complexes **7**-**11**

Three of the complexes formed polymers but unfortunately none of **7**-**11** crystallized as conglomerates.

Table 2 Aggregation and coordination mode in **7**-**11**

Complex	Aggregate	CuX:L	L[a]
(**7**)[CuCl(Sprop)]$_n$	layer	1:1	1:0
(**8**)[Cu_2Br_2(Sprop)$_4$]	dimer	1:2	1:0
(**9**)[CuCl(Sally)]$_n$	layer	1:1	1:1
(**10**)[Cu_4Mes_4(Sally)$_2$]	tetramer	2:1	2:0
(**11**)[Cu_4Mes_4(SS)]$_n$	chain	4:1	1:0

[a]terminal:bridging sulfide ligands

The complex [CuCl(Sprop)]$_n$ (**7**) (figure 24) was prepared from Sprop and CuCl. It formed layers and both functional groups bind to copper atoms. In this complex there are only terminal sulfide ligands. The two sulfur atoms have different configuration.

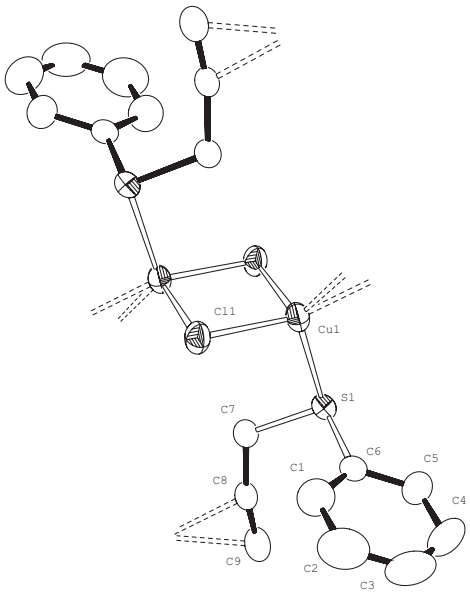


Figure 24 The asymmetric unit in **7**

Crystals of $[Cu_2Br_2(Sprop)_4]$ (**8**) was prepared by using CuBr instead but with the same ligand as **7** (figure 25). In this complex the propargyl group does not coordinate to a metal atom and all sulfide ligands are terminal. This complex is a discrete molecule and forms a dimer. All sulfur atoms are chirogenic but the molecule is not chiral because two of the sulfur atoms have R configuration and the rest have S configuration.

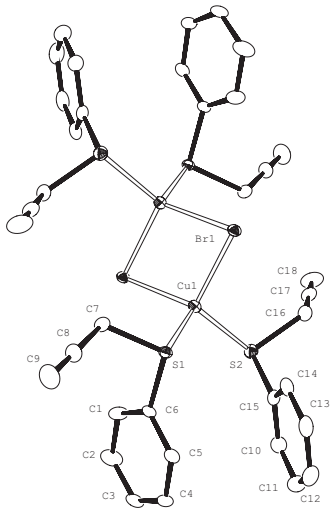


Figure 25 The dimer in **8**

Direct reaction between CuCl and Sally resulted in $[CuCl(Sally)]_n$, (**9**). The asymmetric unit is shown in figure 26. Both functionalities in Sally coordinate to copper atoms. In this complex there are both terminal and bridging sulfide ligands. However, the terminal sulfide ligands are disordered.

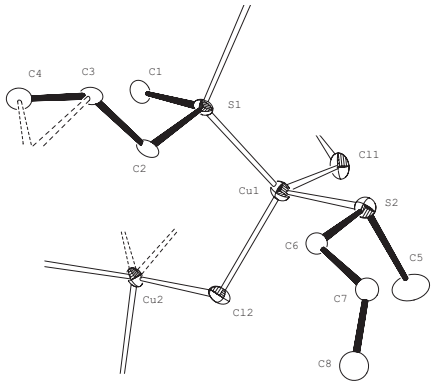


Figure 26 The asymmetric unit in **9**

In the final two structures the copper source is mesitylcopper. In the first structure Sally is used as a ligand. The complex $[Cu_4(Mes)_4(Sally)_2]$ (**10**) did not form polymers but all ligands are terminal and have the same configuration which makes the complex chiral, even though it does not crystallize as a conglomerate. The molecular structure for the complex is shown in figure 27.

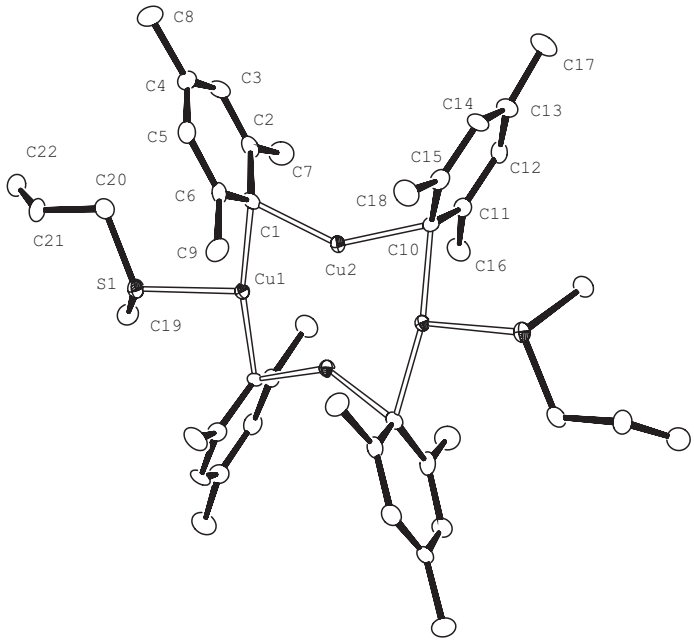


Figure 27 The molecular structure of **10**

Changing ligand from Sally to the SS ligand was indeed a good choice since the ligand managed to link the tetramers in mesitylcopper. The final compound $[Cu_4(Mes)_4(SS)]_n$ (**11**) is a coordination polymer that consists of chains (figure 28). There are only terminal ligands in this complex but the sulfur atoms have opposite configurations, which results in racemic chains.

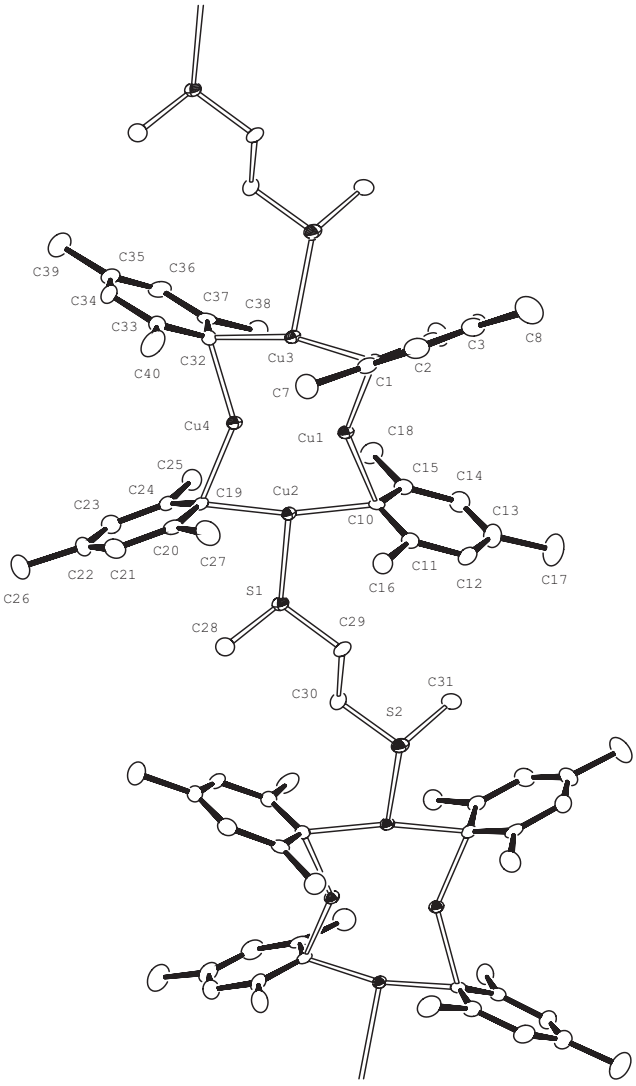


Figure 28 Part of a chain in **11**

3. Total spontaneous resolution of tetrahedral complexes

Tetrahedral stereochemistry is fundamental in organic chemistry. In sharp contrast, inorganic stereochemistry based on tetrahedral metal complexes is mainly unexplored.[1] One reason for this is the lability in most tetrahedral (T-4) metal complexes which makes isolation of T-4 stereoisomers difficult. Tetrahedral Be(II) and Zn(II) complexes have been partially resolved by formation of diastereomeric complexes with brucine and strychnine.[62, 63] For a tetrahedral complex with bidentate ligands to be chiral there are some restrictions (figure 29). The two ligating atoms in the bidentate ligand have to be different and if the other two ligands are monodentate they have to be different as well.

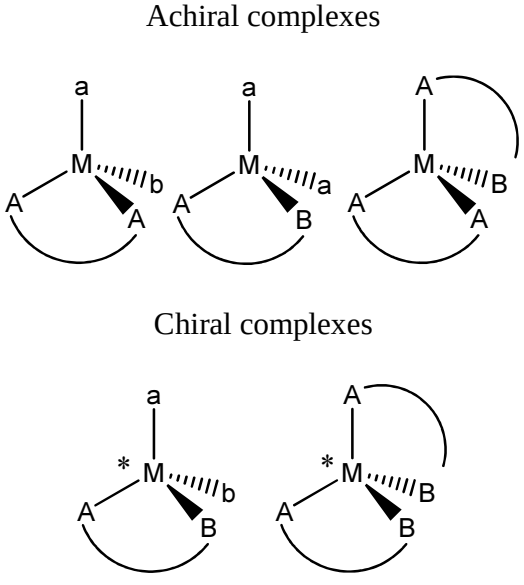
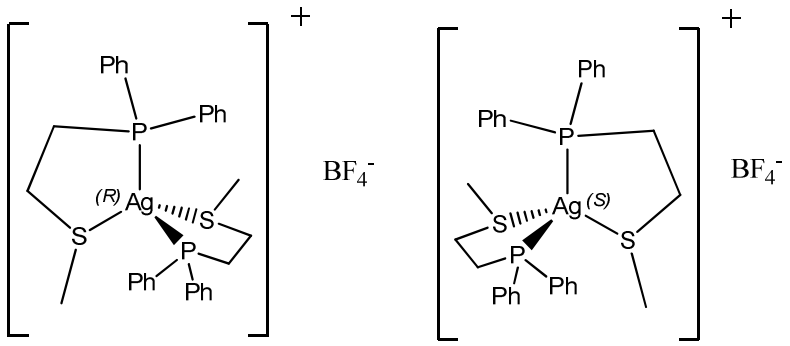


Figure 29 Chirality in tetrahedral complexes with bidentate ligands

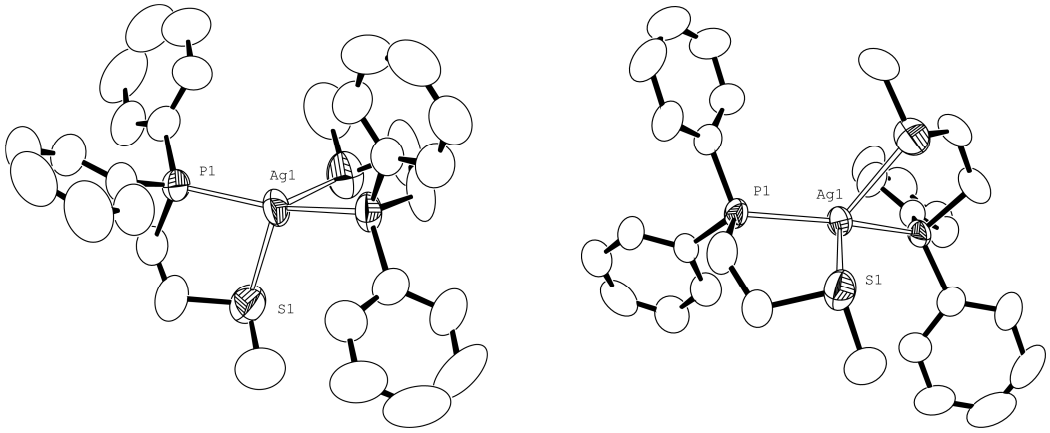
The bidentate ligand (2-(methylthio)ethyl)diphenylphosphine (PS) was used together with $AgBF_4$ in the preparation of $[Ag(PS)_2]BF_4$ (**12**), shown in figure 30. Complex **12** has a distorted tetrahedral geometry and crystallizes as a conglomerate.



(Λ,S,S) –**12** *(Δ,R,R)* –**12**

Figure 30 The two enantiomers of **12**

The two enantiomers crystallize in the chiral space groups $P3_121$, (*Λ*,*S*,*S*)–**12**), and $P3_221$, (*Δ*,*R*,*R*)–**12**), respectively. Oxidations have been performed in order to obtain the enantiopure sulfoxide but so far only racemic product has been obtained. The molecular structures of the cation of the two enantiomers are shown in figure 31.



(Λ, *S*, *S*) – **12** (Δ, *R*,*R*) – **12**

Figure 31 Molecular structure of the cation of the two enantiomers of **12**

This complex is labile and undergoes total spontaneous resolution upon slow crystallization from acetonitrile, with an obtained *ee* of approximately 90 %. Since the two ligating atoms in **12** are different and the complex has distorted tetrahedral geometry, the chirality in the complex can be described by the oriented-lines reference system (figure 32).[1] [64]

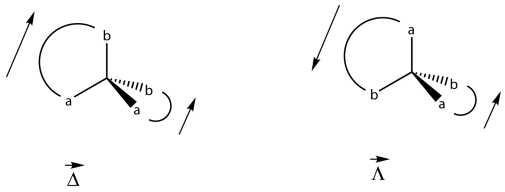


Figure 32 Oriented-lines reference system in **12**

For the determination of the *ee,* solid state CD spectroscopy was used. A single crystal was used as reference. By measuring it and performing an X-ray crystallography analysis it was possible to determine its mass and enantiomeric purity. By doing so it was also possible to determine the configuration of the two enantiomers in the CD spectra. The CD spectra for the enantiomers are illustrated in figure 33.

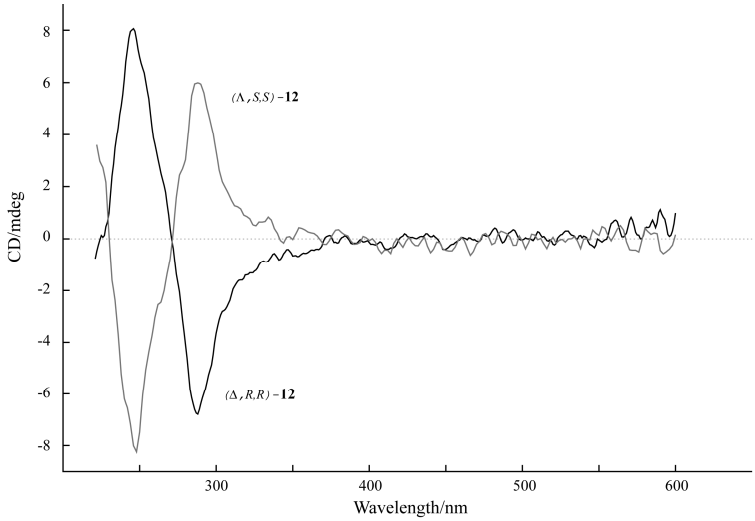
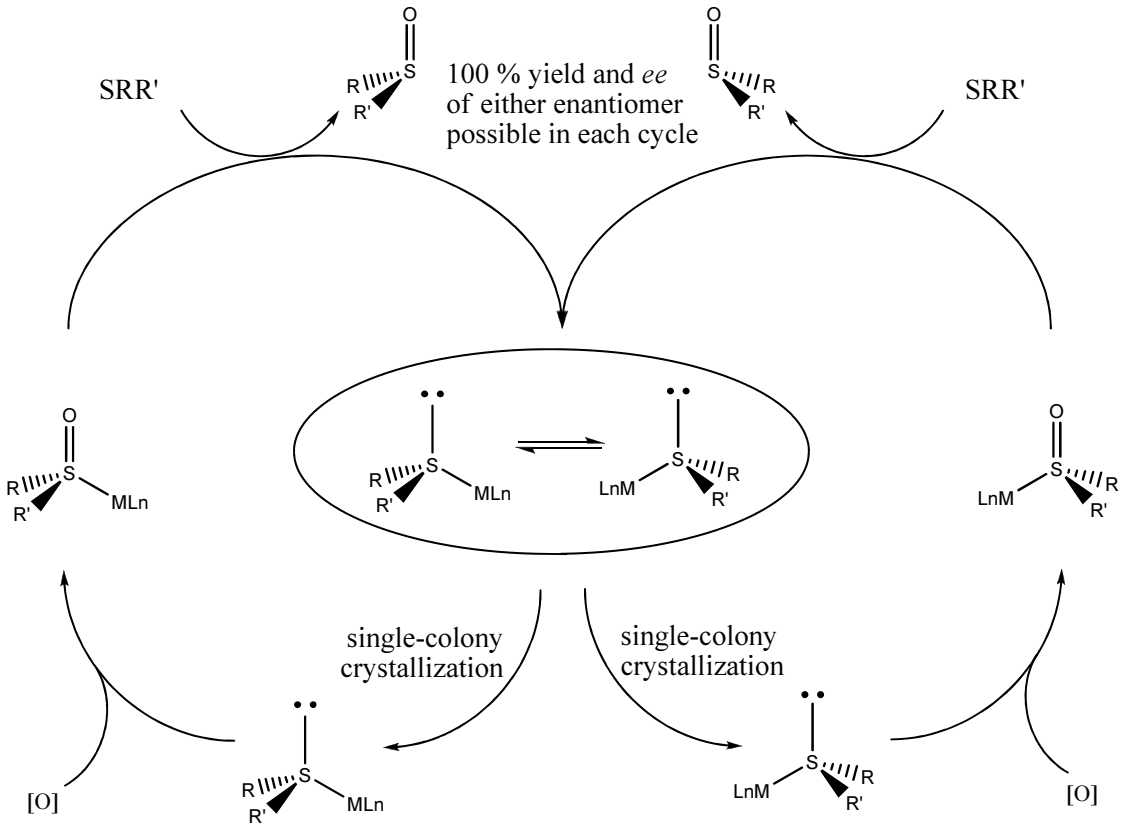


Figure 33 Superimposed solid state CD-spectra of (Λ,*S*,*S*)-**12** and (Δ,*R*,*R*)-**12**

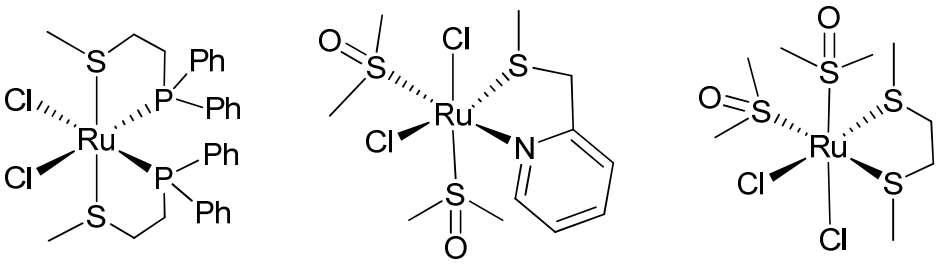
4. Absolute asymmetric synthesis: protected substrate oxidation

Oxidation of unsymmetrical sulfides results in chiral sulfoxides. A direct oxidation usually results in a racemic product and in order to obtain enantiopure sulfoxides there has to be some modifications in the oxidation methods. One common method is to use a chiral catalyst. Here a different method is introduced (scheme 4). The unsymmetrical sulfide is used as a ligand in a complex and upon complexation the sulfur atom will be chirogenic. If the complex crystallizes as a conglomerate and undergoes TSR then homochiral crystal batches of the sulfide complex can be obtained. The enantiopure compound can then be oxidized and if the oxidation proceeds faster than the racemization of the complex, it is possible to obtain an enantiopure sulfoxide complex. Sulfoxides are generally inert and the liberation of the sulfoxide should not result in a decrease of *ee*. Since optical activity is created from achiral and/or racemic precursors this method illustrates an example of AAS. As can been seen from scheme 4 the procedure is recyclable and both enantiomers can be obtained equally easily.



Scheme 4 Recyclable, stereoselective sulfide protection and oxidation

With AAS as the intention, three new complexes $[RuCl_2(PS)_2]\cdot DMSO$, $[RuCl_2(dmso)_2(NS)]$ and $[RuCl_2(dmso)_2(SS)]$ (**13-15**) were prepared (figure 34). They all crystallized as conglomerates and were therefore good candidates for AAS.



13 **14** **15**

Figure 34 Complexes **13-15**

All three complexes exhibit Λ/Δ chirality in addition to the chirogenic sulfur atoms. Complex **13** and **15** have two chirogenic sulfur atoms. The molecular structures for one of the enantiomers in **13-15** are shown in figures 35-37.

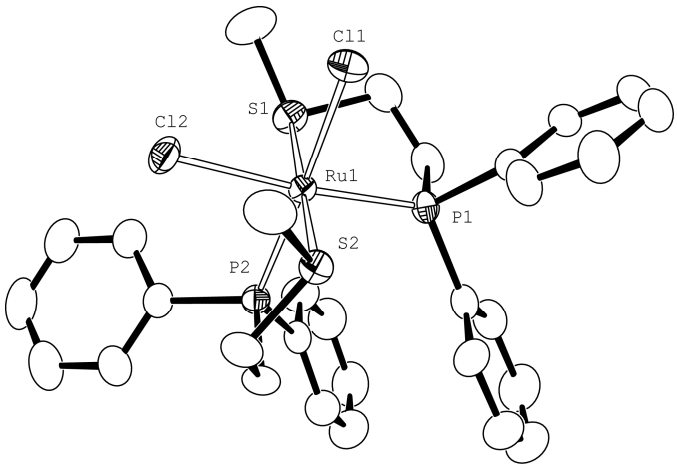


Figure 35 Molecular structure for the enantiomer (*Λ*,*S*,*S*)-**13**

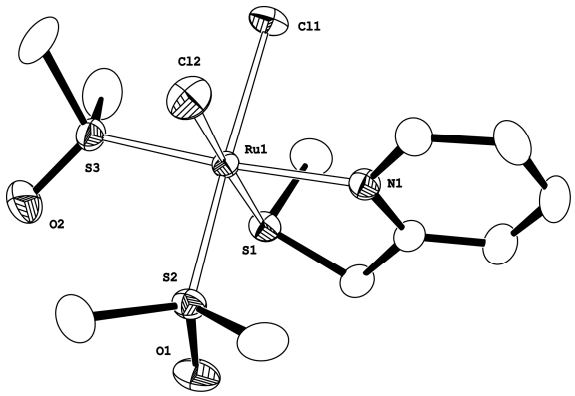


Figure 36 Molecular structure for the enantiomer (Δ,*S*)-**14**

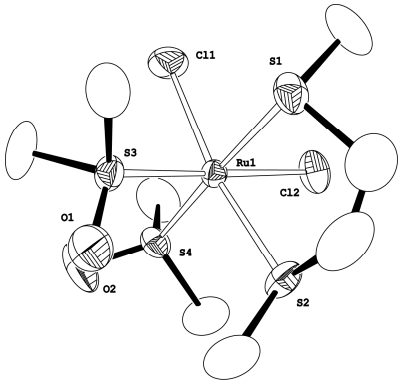


Figure 37 Molecular structure for the enantiomer *(Δ,R,R)*-**15**

The complexes were prepared from $[RuCl_2(dmso)_4]$ and the aim was to oxidize them enantioselectively. The first step was to obtain enantiopure crystal batches and although crystal batches with an enantiomeric excess were obtained in all three cases, the best results were achieved with complex **15**. With TSR crystal batches with up to 90% *ee* were obtained. For the oxidations dimethyldioxirane (DMDO) was chosen as oxidizing agent. The oxidized product for **13** could be characterized by single crystal X-ray crystallography. The structure of the oxidized compound, $[RuCl_2(PSO)_2]\cdot DMSO$ (**16**) is shown in figure 38.

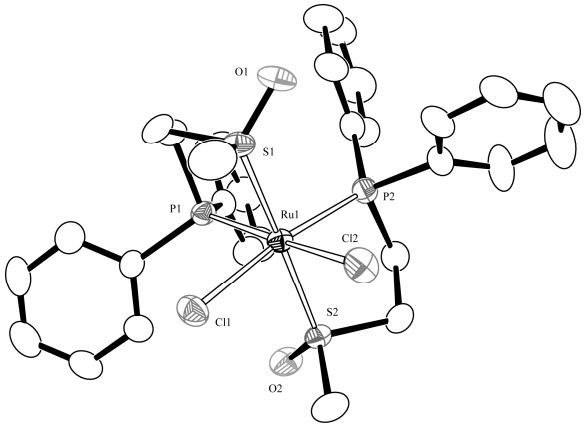


Figure 38 Molecular structure for the enantiomers *(Δ,R,R)*-**16**

Compound **16** crystallize as a conglomerate and is isomorphous with **13**. Single crystals of **13** could be oxidized enantioselectively. The oxidations were performed in CH_2Cl_2 and monitored with both CD spectroscopy and reversed phase HPLC. A single crystal oxidation is shown in figure 39. As a reference a single crystal of **16** was used.

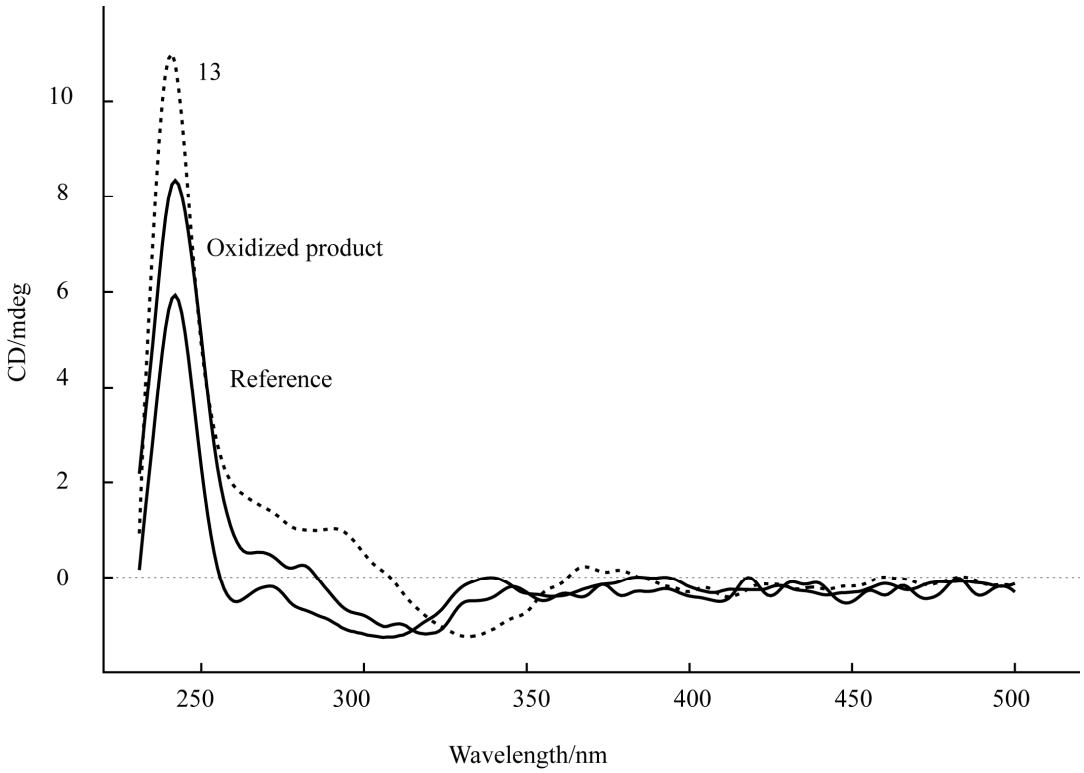


Figure 39 CD spectra for an oxidation of **13**, with **16** used as a reference

The selectivity of the oxidations is shown in figure 40 monitored by reversed phase HPLC. The spectrum shows that the oxidation product is obtained with >98 % *ee* for both enantiomers.

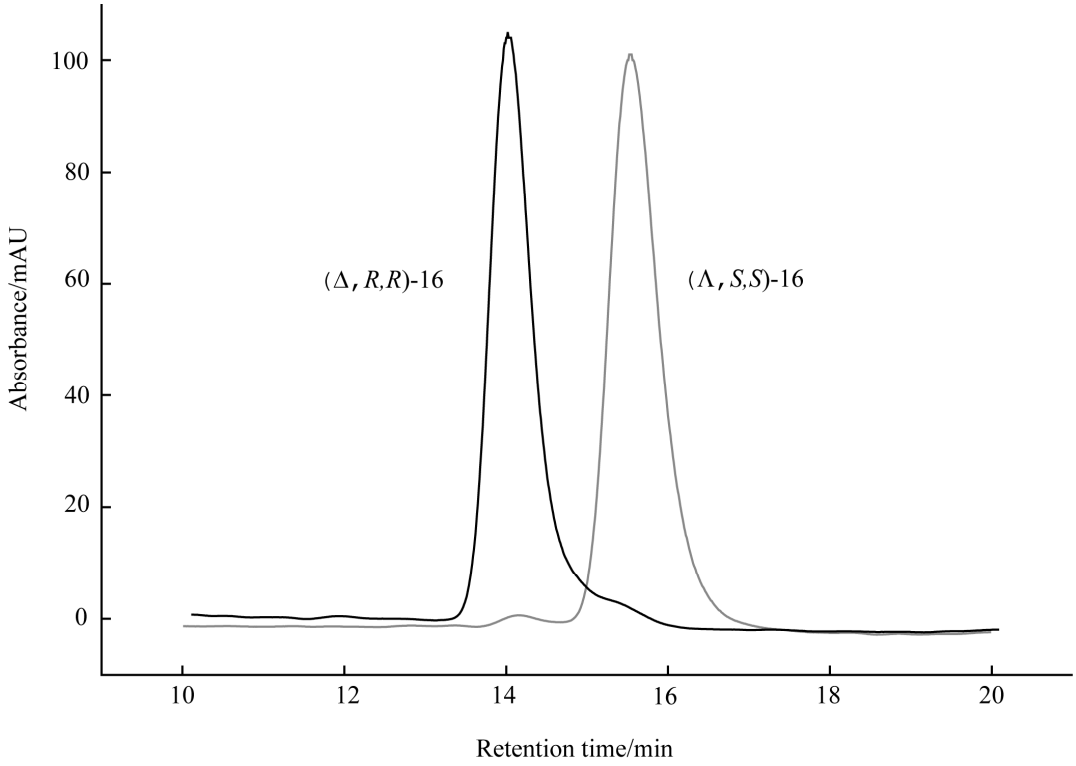


Figure 40 HPLC diagram for the two enantiomers of **16**

The absolute configuration of the oxidized product was determined with single crystal X-ray diffraction analysis. By using the same crystal in X-ray diffraction analysis and in CD spectroscopy it was possible to identify the two enantiomers in CD spectroscopy. In a similar way the two enantiomers could be identified in HPLC. After an oxidation the residue was split into two parts. One part was for HPLC analysis and the other part for CD spectroscopy. Since **16** is obtained in nearly 100% *ee* during the oxidations the mechanism is thought to proceed via direct oxidation of the free electron pair on the sulfur atom. A possibility would otherwise be that an oxo-ruthenium intermediate would form which would result in breakage and reassembly of the sulfur-metal bond.[65] This could lead to loss of selectivity.

5. Concomitant polymorphism and co-crystallization of diastereomers

$[RuCl_2(PS)_2]$ can exist as five possible diastereomers if chirality aspects are not considered (figure 41). In **13** the *cis,cis,trans*-isomer with co-crystallized DMSO, is found.

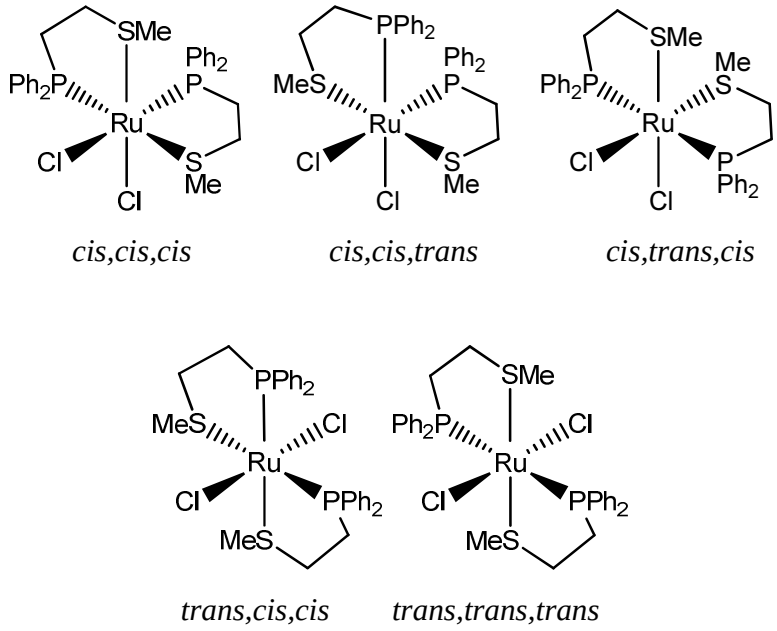


Figure 41 The five possible isomers of $[RuCl_2(PS)_2]$

$[RuCl_2(PS)_2]$ undergoes photoisomerization from *cis,cis,trans* to *trans,cis,cis.* In a dichloromethane solution of **13** layered with hexane, four new types of crystals are formed when the solution is exposed to light. The first type of

crystals that are formed is the *cis,cis,trans*-isomer crystallizing as a racemate, $[RuCl_2(PS)_2]\cdot CH_2Cl_2$, (**17**), (figure 42) and they became visible after one day.

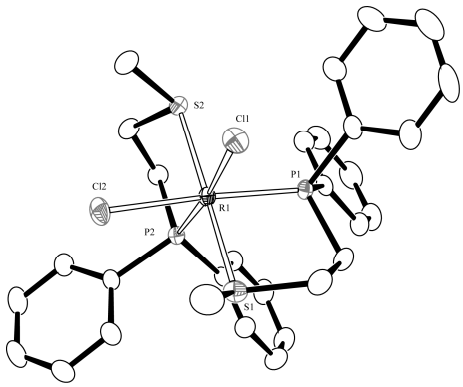


Figure 42 Molecular structure of **17**

Upon subsequent exposure to light the *trans,cis,cis*-isomer is starting to crystallize in the solution. Within a few days pale orange crystals of 2{(*cis,cis,trans*)-$[RuCl_2(PS)_2]$}(*trans,cis,cis*)-$[RuCl_2(PS)_2]$ (**18**), that contain the diastereomers, cis,cis,trans and trans,cis,cis, start to grow (figure 43).

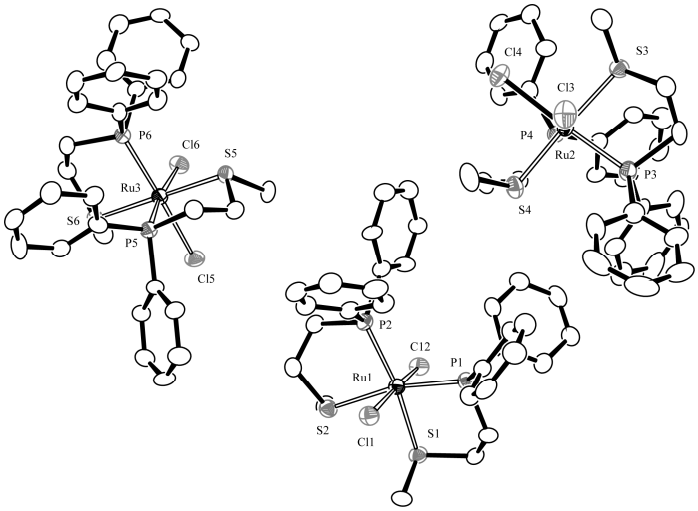


Figure 43 The asymmetric unit in **18**. Co-crystallization of the two diastereomers, cis,cis,trans and trans,cis,cis

After a week crystals of the *trans,cis,cis*-isomer, 2{*(S,S)-(trans,cis,cis)*-$[RuCl_2(PS)_2]$}*(R,R)-(trans,cis,cis)*-$[RuCl_2(PS)_2]$ (**19**), are obtained. This

isomer crystallizes in a chirodescriptive group but since there are three molecules in the asymmetric unit and both enantiomers are present in a 2:1 ratio, the *ee* in a crystal is 33%. The asymmetric unit of **19** is presented in figure 44.

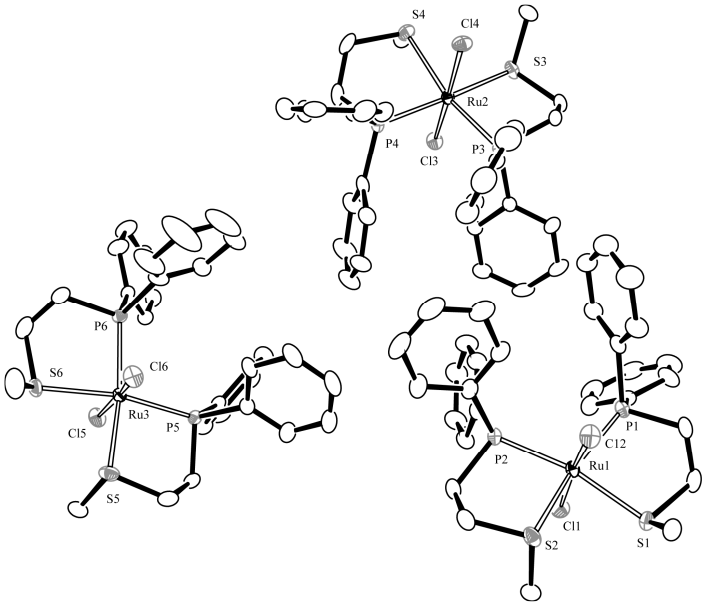


Figure 44 There are three molecules in the asymmetric unit in **19**. The complex crystallizes in a chirodescriptive space group and both enantiomers are present in a 2:1 ratio

Finally a racemic form of the *trans,cis,cis*-isomer, $[RuCl_2(PS)_2]$, (**20**), was obtained as well (figure 45).

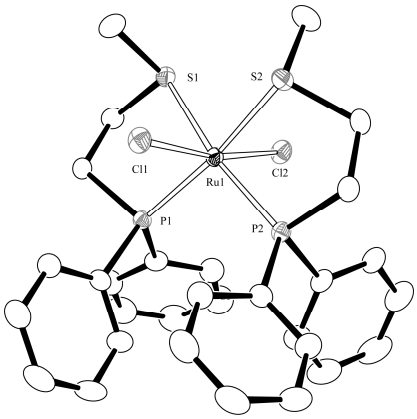
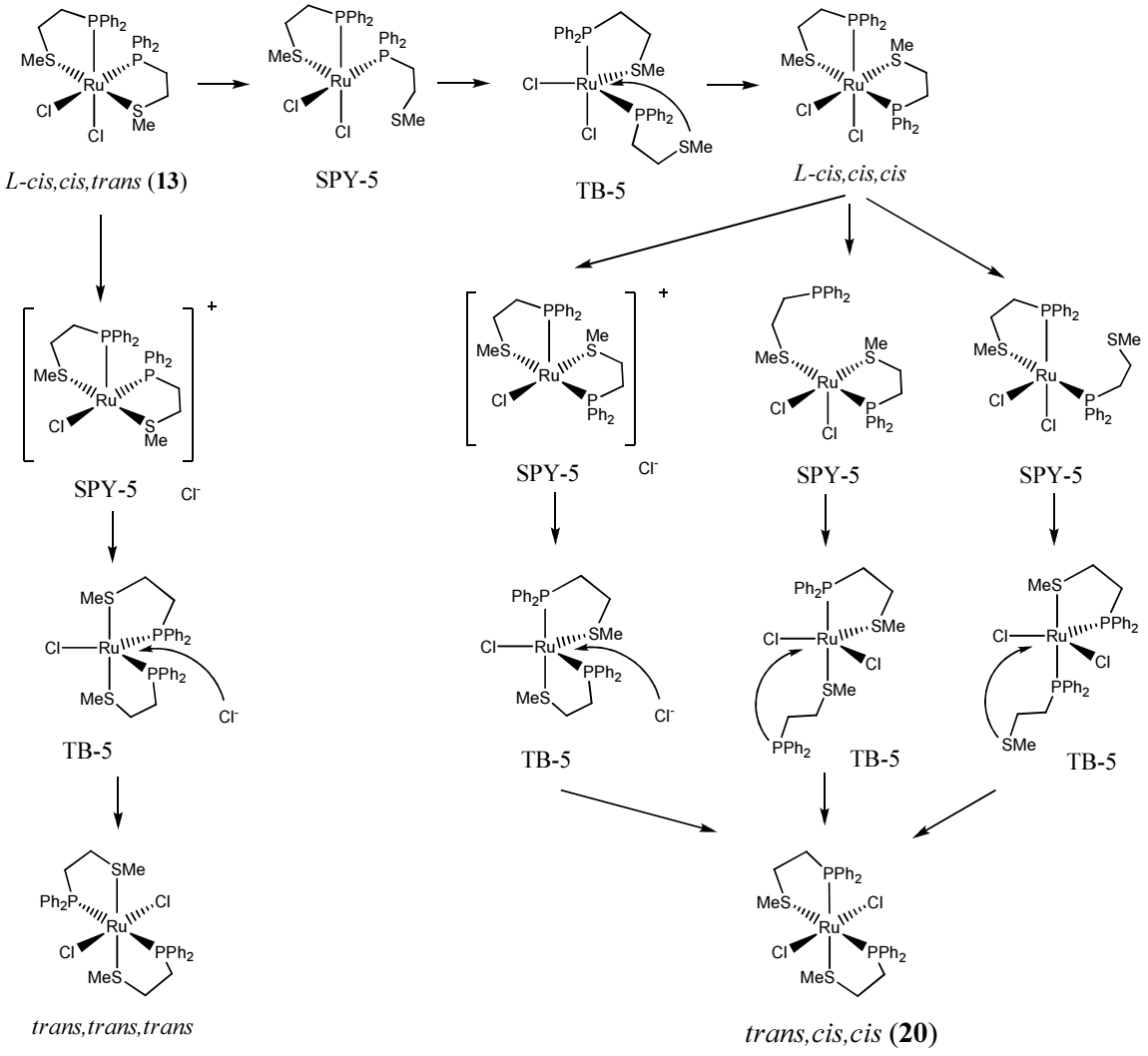


Figure 45 Molecular structure of **20**. The *trans,cis,cis* isomer crystallizing as a racemate

The photoisomerization was monitored with ^{1}H-NMR. Two NMR samples were prepared with **13** dissolved in $CDCl_3$. One sample was kept in the dark while the other was exposed to light. In the sample that was exposed to light the *trans,cis,cis*-isomer started to form within a day and **13** had completely isomerized in two weeks. In order to determine if the photoisomerization was reversible the NMR sample which had been exposed to light was kept in the dark for approximately a month. A new NMR spectrum showed that there had not been any changes during this period of time. A suggestion for the isomerization mechanism is presented in scheme 5.



Scheme 5 Suggested mechanism for the isomerization

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