PH.D.THESIS

# Creating Optical Activity

## Total Spontaneous Resolution and Viedma Ripening

Per Martin Björemark

**DEPARTMENT OF CHEMISTRY AND MOLECULAR BIOLOGY**

GÖTEBORGS UNIVERSITET

**Per Martin Björemark** graduated from University of Gothenburg in 2010 with a Master of Science in Chemistry. After that he began his dissertation work in organometallic chemistry with professor Mikael Håkansson. His PhD projects focused on the creation of optical activity.

ISBN 978-91-629-0326-8 (PRINT)
ISBN 978-91-629-0327-5 (PDF)

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University of Gothenburg

Department of Chemistry and Molecular Biology
University of Gothenburg
2017

Doctoral Thesis

Submitted for fulfilment of the requirements for the degree of
Doctor of Philosophy in Natural Science Specializing in Chemistry

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Cover picture:
Viedma ripening in progress


ISBN: 978-91-629-0326-8 (printed)
ISBN: 978-91-629-0327-5 (electronic)

http://hdl.handle.net/2077/53817

Department of Chemistry and Molecular Biology
SE-412 96 Göteborg
Sweden

Printed by BrandFactory AB
Kållered, 2017

*Listen, old man; take my advice.*
*Give me the cobalt in a thrice.*
*Though hell and devil say me nay,*
*I shall resolve cobalt today.*

Paul Karrer-1911
*Rotating and Resolving:*
*A Tragicomic Popular Play*

# Abstract

The creation of optical activity has been considered as something impossible even though reports of such creation via total spontaneous resolution since the 1940´s have been published. More recently Viedma ripening have been developed that also produce enantiopure bulk product. Both methods are examples of absolute asymmetric synthesis i.e. the synthesis of optically active product from non-optically active starting materials, catalysts or auxiliaries.

In this work twenty-four new compounds have been synthesized, isolated and characterized with X-ray diffraction. Out of these have eleven been found to crystallize as conglomerates as chiral enantiopure crystals which are optically active. The discovered conglomerates have been analyzed with solid state techniques as circular dichroism (CD) and vibrational circular dichroism(VCD).

For the moderately labile $[Ru(PS)_2Cl_2]$, $[Ru(dmso)_2(NS)Cl_2$ and $[Ru(dmso)_2(SS)Cl_2]$ have the chirality been fixated by oxidizing the ligand in solution to the corresponding sulfoxide. For the highly labile $[Co(bpy)_3](PF_6)_2$ the chirality has been fixated by oxidizing the metal from cobalt(II), solvent free in the solid state, to the inert cobalt (III) with bromine vapor or solid iodine. The optical activity of the inert complexes has been analyzed with solution techniques such as CD, HPLC and ORD.

The optical activity of the complexes $[Mo(CO)_4PS]$ and $[W(CO)_4PS]$ have been analyzed with solid state VCD with less than tenth of a milligram sample and high-quality spectra have been obtained in 20 minutes.

Total spontaneous resolution has been achieved with the compounds $[Ru(PS)_2Cl_2]$, $[Ru(dmso)_2(NS)Cl_2$, $[Ru(dmso)_2(SS)Cl_2]$ and $[Ag(PS)_2](BF_4)$ in good yield and high *ee*.

Viedma ripening has been demonstrated for the complexes $[Ag(PS)_2](BF_4)$, $[Mo(CO)_4PS]$, $[W(CO)_4PS]$ and $[Cu(mtp)_2(NO_3)_2]$. Viedma ripening has been found to be viable for the production of large quantities of optically pure metal complex.


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**Keywords:** Optical activity, absolute asymmetric synthesis, total spontaneous resolution, Viedma ripening, grinding, chirality, conglomerate, coordination compound, coordination polymer, single crystal X-ray diffraction, solvent free oxidation, enantioselective sulfide oxidation, solid state VCD.

ISBN: 978-91-629-0326-8 (printed), 978-91-629-0327-5 (electronic)

# List of publications

This thesis is based on the following publications and manuscripts, which are referred to in the text by the Roman numerals I-VII. Paper II-V is reprinted with kind permission from the publisher.

**I Copper (I) halide complexes with prochiral sulfide ligands**
Theonitsa Kokoli, Per Martin Björemark and Mikael Håkansson
*Manuscript (submitted to Inorganica Chimica Acta)*

**II Toward absolute asymmetric synthesis of coordination polymers with bidentate sulfide ligands**
Theonitsa Kokoli, Susanne Olsson, Per Martin Björemark, Staffan Persson, and Mikael Håkansson
*Journal of Organometallic Chemistry*, **2013** (724), 17-22

**III Absolute asymmetric synthesis: Protected substrate oxidation**
Theonitsa Kokoli, Susanne Olsson, Per Martin Björemark, Jonas Sundberg, Anders Lennartson, Christine J. McKenzie, and Mikael Håkansson.
*Chemistry-a European Journal*, **2015** (21), 13, 5211-5219

**IV Absolute Asymmetric Synthesis of a Tetrahedral Silver Complex**
Per Martin Björemark, Susanne Olsson, Theonitsa Kokoli, and Mikael Håkansson
*Chemistry-a European Journal*, **2015** (21), 24, 8750-8753

**V Absolute Asymmetric Synthesis: Viedma Ripening of $Co(bpy)_3^{(2+)}$ and Solvent-Free Oxidation to $Co(bpy)_3^{(3+)}$**
Per Martin Björemark, Johan Jönsson, and Mikael Håkansson
*Chemistry-a European Journal*, **2015** (21), 30 10630-10633.

**VI Viedma Ripening of Group VI Metal Carbonyl Complexes**
Per Martin Björemark and Mikael Håkansson
*Manuscript (submitted to New Journal of Chemistry)*

**VII Grinding Achiral Crystals to Enantiopurity**
Per Martin Björemark, Jonas Sundberg, Vibe B. Jacobsen, Christine J. McKenzie, and Mikael Håkansson
*Manuscript (submitted to Angewandte Chemie International Edition)*

# Publications not included in this thesis

1 **Antiplasmodial and cytotoxic activities of the constituents of Turraea *robusta* and Turraea *nilotica***
Beatrice Irungu, Nicholas Adipo, Jennifer Orwa, Francis Kimani, Mathias Heydenreich, Jacob Midiwo, Per Martin Björemark, Mikael Håkansson, Abiy Yenesew, and Maté Erdélyi
*Journal of Ethnopharmacology*, **2015**, (174), 419-425

2 **Synthesis and Structure of a Novel Substituted Benzothiazolyl-N-phenyl-2-pyridinecarbothioamide; Kinetics of Formation and Electrochemistry of Two of its Palladium Pincer Complexes**
Mark Lawrence, Yvette Jackson, Willem Mulder, Per Martin Björemark, and Mikael Håkansson
*Australian Journal of Chemistry*, **2015** (68), 5, 731-741

3 **Accessing Iron Amides from a New Phase of Mesityliron**
Jonas Sundberg, Mads Vad, John McGrady, Per Martin Björemark, Christine J. McKenzie, and Mikael Håkansson
*Journal of Organometallic Chemistry*, **2015**, (786), 40-47

# Abbreviations

| | |
|---|---|
| 1D | one-dimensional |
| 2D | two-dimensional |
| AAS | absolute asymmetric synthesis |
| BINAP | 2,2´-bis(diphenylphosphino)-1,1´binaphtyl |
| bpy | 2,2´-bipyridine |
| CD | (electronic) circular dichroism |
| CSD | Cambridge structural database |
| CPL | circularly polarized light |
| CP | circularly polarized |
| DCM | dichloromethane |
| dmso | dimethylsuloxide |
| DMDO | dimethyldioxyrane |
| DNA | deoxyribo nuckeic acid |
| HPLC | high performance liquid chromatography |
| IR | infrared radiation |
| IUPAC | International union of pure and applied chemistry |
| *ee* | enantiomeric excess |
| *de* | diastereomeric excess |
| mCPBA | *meta*-chloroperoxybensoic acid |
| mes | mesityl, 2,4,6-trimethylphenyl |
| mtp | 2-(methylthio)pyridine |
| ORD | optical rotary dispersion |
| PS | (2-(methylthio)ethyl)diphenylphosphine |
| Sally | allyl(methyl)sulfide |
| SR | spontaneous resolution |
| T-4 | tetrahedral |
| THF | tetrahydrofuran |
| TSR | total spontaneous resolution |
| Sprop | phenyl(propargyl)sulfide |
| SS | 1,2-bis(methylthio)ethane, 2,5-dithiahexane |
| VCD | vibrational circular dichroism |

# Metal complexes

**Paper I**
**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** $[Cu_4Cl_4\ (CH_3SC_2H_5)]_n$
**5** $[CuBr(CH_3SC_2H_5)]_n$
**6** $[Cu_4I_4\ (CH_3SC_2H_5)]_n$

**Paper II**
**7** $Cu_2Br_2(Sprop)_4$
**8** $Cu_2Cl_2(Sprop)_n$
**9** $[CuCl(Sally)]_n$
**10** $[Cu_4(Mes)_4(Sally)_2]$
**11** $[Cu_4(Mes)_4(SS)]_n$

**Paper III**
**12** $[Ru(PS)_2Cl_2]$
**13** $[Ru(PS_O)_2Cl_2]$
**14** $[Ru(dmso)_2(NS)Cl_2]$
**15** $[Ru(dmso)_2(NS_O)Cl_2]$
**16** $[Ru(dmso)_2(SS)Cl_2]$
**17** $[Ru(dmso)_2(SS_O)Cl_2]$

**Paper IV**
**18** $[Ag(PS)_2](BF)_4$

**Paper V**
**19** $[Co(bpy)_3](PF_6)_2$

**Paper VI**
**20** $[Cr(CO)_4PS]$
**21** $[Cr(CO)_2(PS)_2]$
**22** $[Mo(CO)_4PS]$
**23** $[W(CO)_4PS]$

**Paper VII**
**24** *trans*-$[Cu(mtp)_2(NO_3)_2]$ achiral
**25** *cis*-$[Cu(mtp)_2(NO_3)_2]$ conglomerate

# Contents

# 1

# Introduction

Optical activity has been a phenomenon that have caught the interest of scientists since François Arago discovered in 1811 that when a beam of plane polarized light passes through a crystal of quartz, the plane of polarization is rotated.[1] This might seem as a trivial discovery but when Jean-Baptiste Biot in 1815 did the same experiments on sugar solutions and was able to determine their concentration via the optical rotation, the road was laid for a new path in science.[2] In 1832, Biot investigated the optical properties of the naturally occurring tartaric acid and found that this compound is also optically active.

In 1848 the next important progress was made with Louis Pasteur's discovery that optically active crystals from a non-optically active solution of ammonium sodium tartrate could be of one out of two forms (figure 1). These crystals were mirror images of one another and the two kinds had unique facets. Pasteur was able to manually sort the crystals in two piles of such mirror images[3] with the aid of a microscope. He determined that solutions of crystals from the two piles had optical rotation of equal magnitude for the same concentration but for one of the mirror images the rotation was negative. This discovery was so controversial at the time that he personally had to visit Biot in Paris and perform the crystallization with subsequent separation in front of him to make him believe the results. A more recent evaluation of Pasteur's experiments on ammonium sodium tartrate has also been made[4] and a conclusion that the crystals drawn in figure 1 can be regarded as "perfect" crystals. Far from all crystals look that typical, however it is clear that some common faces among all crystals of the same enantiomer can be identified.

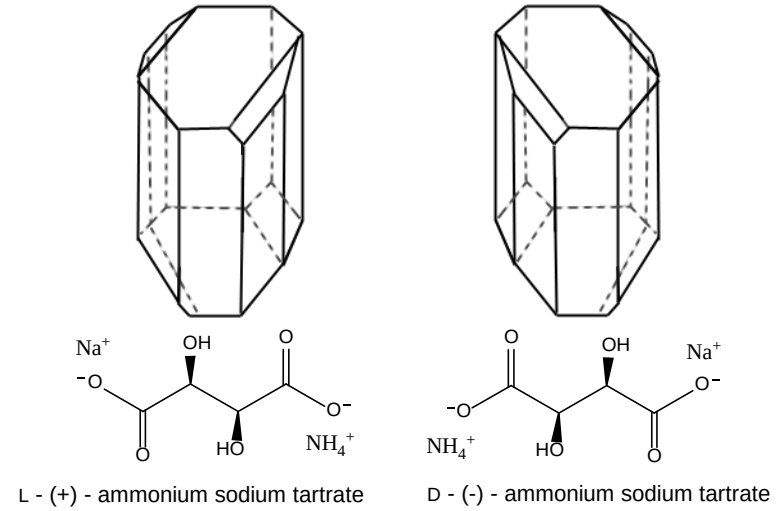



**Figure 1:** The two enantiomorphs of ammonium sodium tartrate as drawn by Pasteur.[3a-c]

It is now a known fact that the rotation of polarized light is due to that the molecules, which the light has passed through, are unsymmetrical and lack a symmetry plane. This means that two different mirror images of the same compound are non-superimposable over each other and thus different. The compound is then said to be chiral and the two mirror images are enantiomers of the same compound. All this was unknown to Pasteur.

As with the case of quartz, the compound itself does not has to be chiral to show optical activity, non-chiral species such as metal salts or organic compounds can crystallize in a chiral fashion and single crystals thus are optically active due to the orientation of the molecules in the crystal. One compound for which this phenomenon has been widely explored is sodium chlorate[5] but any non-chiral species can crystallize as a conglomerate and form such chiral crystals.[6]

For organic chemists however, chirality equals the mirror images of a carbon atom bonded to four different side chains and even if Pasteur did not understand it, this was the cause of the optical activity of his tartrate as well. Since Pasteur's discoveries it has been clear that not only the tetrahedral carbon atom can be the reason for optical activity, in fact, organic molecules and metal complexes can show many different modes of chirality.

In the beginning of the 20th century, Alfred Werner (1866-1919) did his pioneering work on metal complexes,[7] he characterized and proposed the structure for octahedral cobalt compounds. The structure and geometry he proposed later proved to be the correct one. Many of these octahedral compounds are chiral and he succeeded to resolve some of them and separate the enantiomers. His method was to use other enantiopure compounds and

synthesize diastereomers that he could separate by crystallization. Now, other methods are available that does not acquire any optically active influences.[8]

In a lecture held by Pasteur in 1860,[9] he stated that from a chemical reaction it was impossible to get optically active product if the starting materials were non-optically active. This was a misconception that lived on for more than one hundred years. Now it is well established that optical activity can be created[10] and this is absolute asymmetric synthesis (AAS). Two ways of achieving such absolute asymmetric synthesis are total spontaneous resolution (TSR) and Viedma ripening which both enables easy, cheap and up scalable routes to enantiopure material.

# 2

# Background

In the background of this thesis, the concept of chirality, crystallization, absolute asymmetric synthesis, and vibrational circular dichroism VCD) will be presented. The proposed mechanisms for total spontaneous resolution (TSR) and Viedma ripening will also be discussed.

## 2.1 Chirality

All chemistry related terms are defined by the International Union of Pure and Applied Chemistry (IUPAC), so is the term chirality:[11]

> "The geometric property of a rigid object (or spatial arrangement of points or atoms) of being non-superposable on its mirror image … if the object is superposable on its mirror image the object is described as being achiral."

This means that the term chiral is not just applicable to molecules, but to all objects around us. Chemical compounds however can be optically active and ordinary objects do not have this ability. The term chiral was introduced by Lord Kelvin in 1893 and the word derives from the greek word *cheir,* meaning hand. Many everyday objects are chiral and can exist as one out of two enantiomers; the shell of snails, screws, the overhand and granny knots and the propeller all are examples of such chiral objects (see figure 2).

The consequences of chirality in these objects are that snails of opposite enantiomers have difficulties mating,[12] that one has to use the correct rotation when driving down a screw and that the wrong enantiomer of a propeller will put the boat in reverse. That a left-hand glove fits poorly to the right hand and vice versa is also due to the fact that our two hands are non-superimposable over each other, hence the meaning of the word *chirality*.

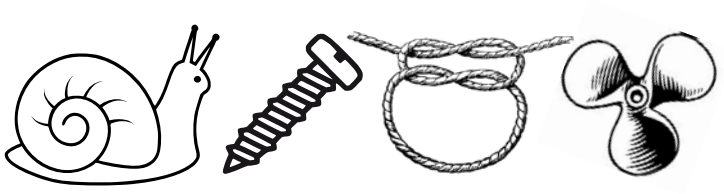


**Figure 2:** Examples of chiral everyday objects.

For the chemist, chiral objects present another problem than being stuck with two right hand gloves in the freezing winter. Chemists are challenged by the task of getting enantiopure product; in the normal case when synthesizing chiral compounds, the product is racemic and therefor consist of the two enantiomers equal amount. They can be difficult to separate on a large scale since they have the same physical properties such as melting point, boiling point and solubility. The only two ways the enantiomers of the same compound differ from each other are that they behave differently in chiral environments and that they are optically active. One consequence of interacting in chiral environments is that enantiomers of chiral drugs react differently in the human body. The receptors that they bind to are made up by amino acids and sugars. These building blocks are chiral and in the human body we can only find one of the enantiomers, in most cases D-sugars and L-amino acids. Interaction with a receptor sends a signal or prevents a signal being sent through the nervous system. This is why the taste of mint from menthol can be four times as intense depending on which enantiomer you eat and the smell of carvone either can be mint or caraway.

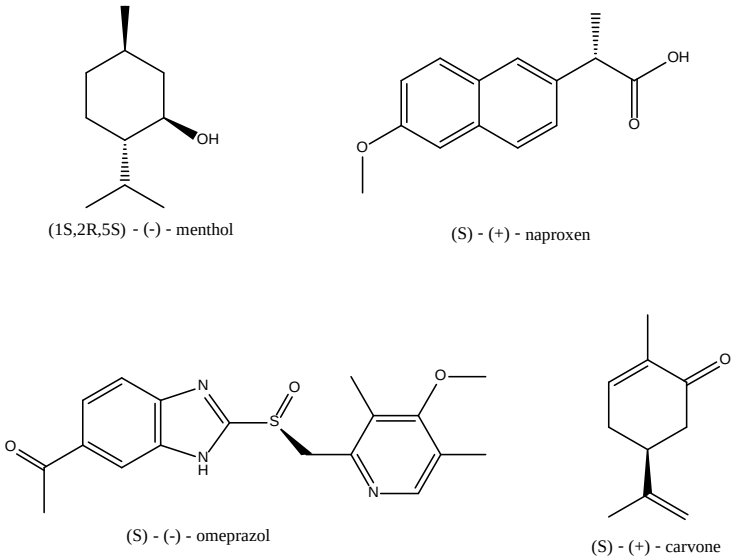



**Figure 3:** The structure of menthol, carvone, omeprazol and naproxen.

The reason for such homochirality on earth is of course unknown but several theories have been proposed as an explanation. Total spontaneous resolution and Viedma ripening are interesting in this aspect.[13] Spontaneous symmetry breaking experiments resembling the conditions on pre-biotic earth have been performed.[14] Energetically polarized beta particles and positrons as external souses of chirality have been observed to affect the chirality in crystallizations.[15] These sources were available on pre-biotic earth. There are several reports on non-stochastic homochiral formation in crystallization experiments[16]. That is, most batches contain only one of the enantiomers. In some cases, one of the enantiomers was impossible to crystallize once the other had formed. This reassembles what happened on pre-biotic earth. Statistical fluctuation is also one parameter that could have been involved in the development towards homochirality on earth; no racemic solutions consist exactly of 50% of each enantiomer. This fluctuation can be enough enantioenrichment to induce symmetry breaking in some systems and result in homochiral batch product.[17]

For the pharmaceutical industry, the fact of our homochiral bodies, can be very important. In some cases, as with the active substance omeprazole found in Losec and Nexium, one enantiomer is active and the other has no action in the body at all. For other drugs like naproxen both enantiomers are active and while one is a potent drug, the other is a poison. The enantiomers of a chiral drug have to be tested separately for its action in the human body. Enantioselective synthesis, separation of enantiomers and analysis of the enantiomeric excess (*ee*) needs therefor constant more research. One enantioselective method is absolute asymmetric synthesis (AAS) for which the work of this thesis has been dedicated.

The chirality of chemical compounds can be divided into different categories depending on the type of compound. For organic chemists, the central chirality occurring when a carbon atom bonds four different substituents is well known. The same type of chirality is also valid for other compounds containing tetravalent atoms with four different bonded groups, such as the sulfur, nitrogen and the phosphorous atoms. In chiral compounds including one of those heteroatoms, the fourth substituent can be a lone electron pair. Sulfur containing compounds where the sulfur atom binds two different substituents are thus prochiral and upon binding to one of the lone pars, the product becomes chiral. One convenient way to synthesize chiral sulfur compounds is oxidation to the corresponding sulfoxide as in figure 4. The two enantiomers in all such chiral tetrahedral compounds are denoted *R*- and *S*- depending of the order of the substituents according to the Cahn-Ingold –Prelog rules stated in 1956.[18] These rules are explained in detail in most organic chemistry textbooks.

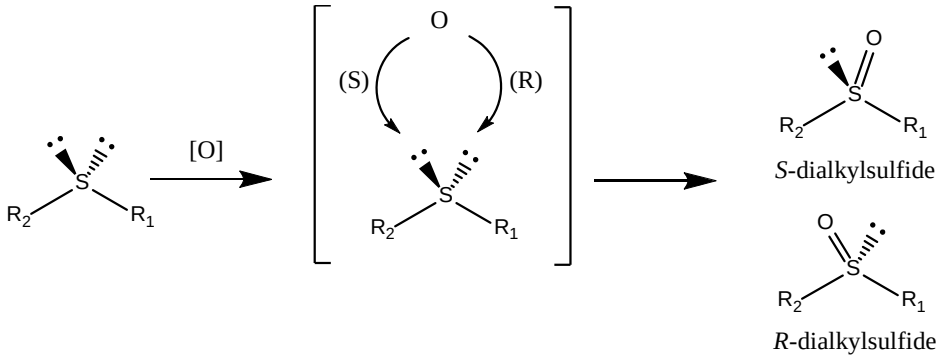



**Figure 4:** The oxidation of a prochiral sulfide to the corresponding sulfoxide.

Sulfoxides are an important class of compounds because many are registered drugs like omeprazol. Enantioupure sulfoxides are also used as chiral auxiliaries for example as in the stereoselective synthesis of $[Ru(bpy)_3]Cl_2$[19] where the sulfoxide is used in one step of the synthesis to direct the chirality and then later removed. Sulfoxides can also be used as catalysts.[20]

In addition to the central chirality, organic compounds can be chiral in other ways than incorporating an chirogenic tetravalent atom. The axial chirality of allenes[21] and binap type compounds[22] as well as the helical chirality of helicenes[23] (figure 5). Organic polymers can also adopt a chiral superstructure as the well-known helix in DNA.[24]

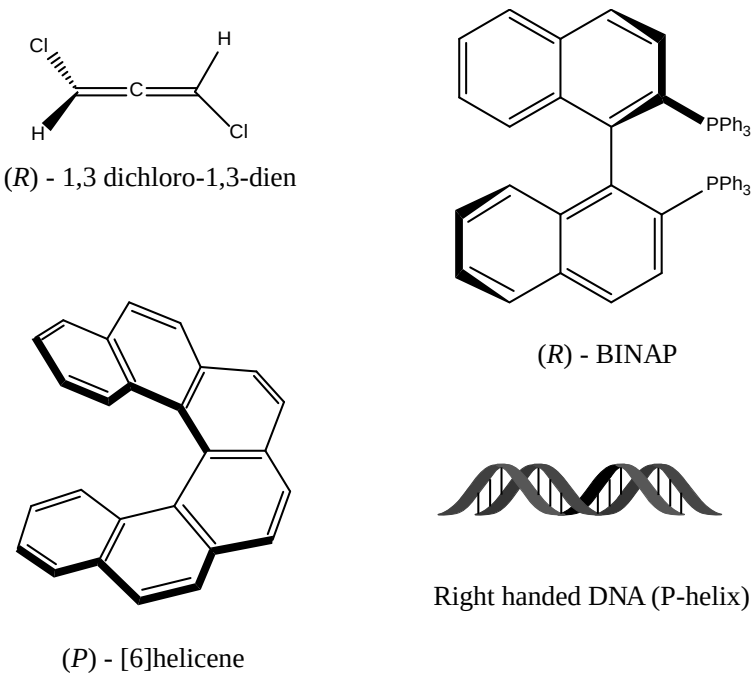



**Figure 5:** The structure of a chiral allene, binap, helicene and of a double helix polymer.

Organic compounds are often stereochemically inert and once the carbon atom becomes chirogenic, the chirality of the compound is fixed and the *ee* of the batch is unchanged over time; most organic molecules do not enantiomerize in solution.

Metal complexes can show different modes of chirality than carbon and sulfur compounds due to their diversity in coordination geometry. Oppose to organic molecules, metal complexes are often labile and solutions of such are often racemic. A tetrahedral metal center is chiral analog with the carbon atom and named accordingly (see figure 6). However, such compounds can be cumbersome to synthesize due to the frequent exchange of ligands between metal centers, still some examples exist in the literature.[25]

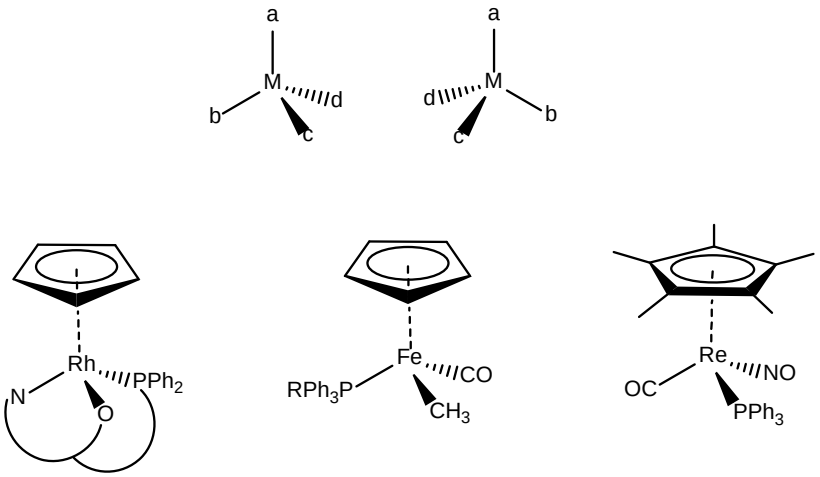



**Figure 6:** Previously reported tetrahedral M(abcd)-complexes.

A tetrahedral (T-4) metal complex with two identical, bidentate, unsymmetrical ligands is chiral. For these spiro-type compounds, the two enantiomers are denoted $\overline{\Delta}$ and $\overline{\Lambda}$. The relative orientation of the two ligands determine the chirality of the complex (see figure 7), and the oriented skew-line system is used to differentiate the enantiomers.[26]

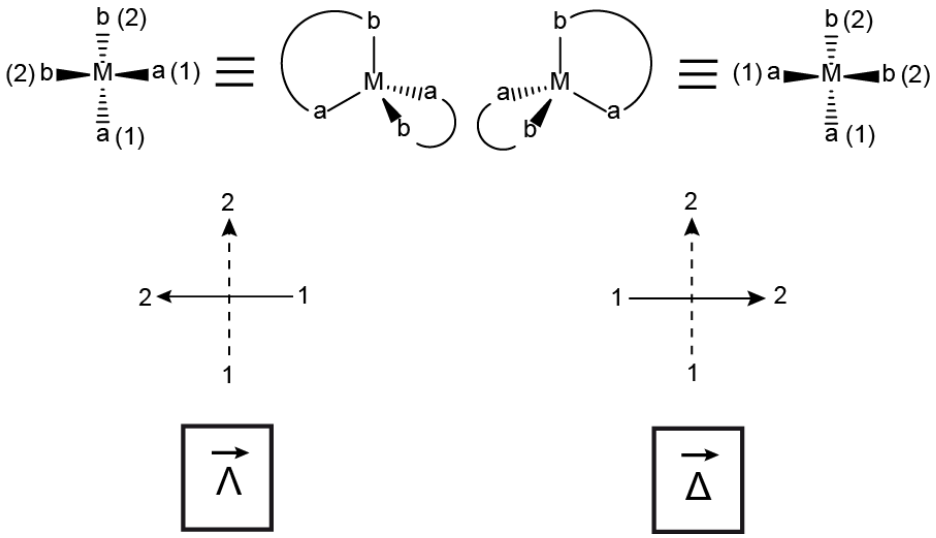



**Figure 7:** Principles of the nomenclature for $M(ab)_2$ type chiral complexes. N.B. the arrow over the symbols

The compound is oriented so that the central atom is in the middle with one of the chelate rings of in front of it and the other one behind. The two identical asymmetric rings are numbered according to the Cahn-Ingold-Prelog sequence rules and the molecule is oriented so that the ring furthest away has the highest prioritized atom downwards. If now the closest ring is oriented with falling priority from left **to right,** the chirality is $\overline{\Delta}$ . If it is oriented from right **to left,** it is denoted $\overline{\Lambda}$ .

Octahedral metal complexes can be chiral in several ways depending of the hapticity of the ligands, for example, using six different monodentate ligands offers 15 pairs of enantiomers. As with complexes of type M(abcd), the synthesis of such compounds can be tricky and even relatively inert complexes can interconvert in solution resulting in many different isomers after equilibrium has been reached. Using three pairs of monodentate ligands being *cis*- to each other opens up the possibility for the helical chirality where the enantiomers can be compared to propellers of opposite rotation (figure 8).

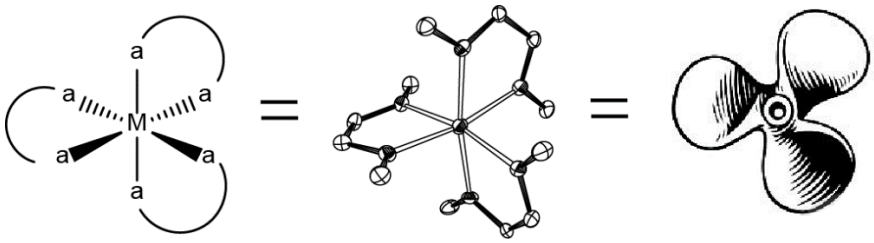



**Figure 8:** "All"-*cis* octahedral metal complexes compared to a propeller.

Still, for complexes with different monodentate ligands, a selective synthesis of the desired chiral complex can be hard to achieve and complexes of the type $M(a_2b_2c_2)$ will in most cases not be the final product, the possibility of achiral *trans*- complexes is also always imminent. One way to get around the *trans*-problem totally is to construct octahedral complexes with only bidentate ligands which forces the metal atom to form all *cis*-complexes (figure 8). For these types of complexes all three ligands can be symmetrical and of the same kind, the complex is still chiral (see figure 9). The enantiomers of such complexes are denoted Δ and Λ respectively depending on which way the propeller spins.

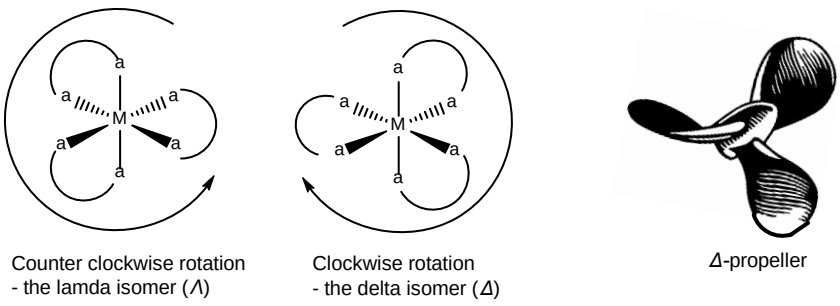



**Figure 9:** The nomenclature of octahedral helical $M(aa)_3$-type complexes.

Since metal complexes can have coordination numbers other than four and six, the possibility of other types of chirality exists. Recently, five[27]-, seven[28]-, eight[29]- and nine[30]- coordinate chiral metal complexes have been synthesized and resolved.

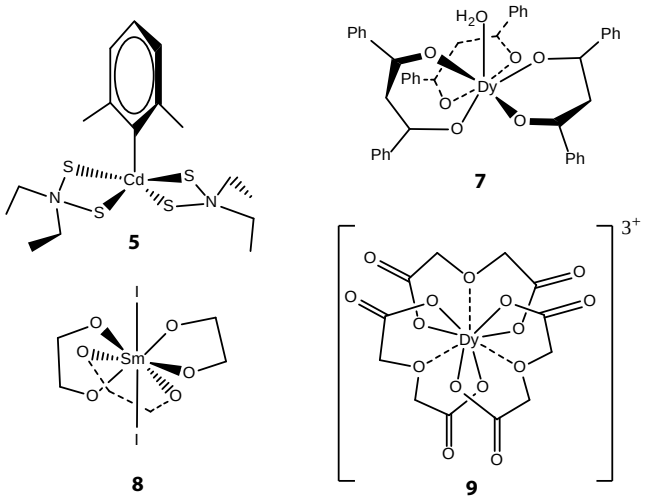



**Figure 10:** Chiral five-, seven-, eight- and nine -coordinate chiral complexes.

The binding of a chiral compound to a metal center as ligand is also a route to chiral metal complexes. If one uses enantiopure compounds as ligands in the synthesis, the chirality can be predetermined,[31] and the product homochiral.

Another type of chirality is also available for metal complexes with any coordination number, upon binding a prochiral ligand, the metal complex becomes chiral. This ligand can contain a coordinating heteroatom like sulfur, nitrogen or phosphorous. Combining the chirality of the metal complex with the prochirality of the ligands can produce diastereomers that makes the chirality issue and nomenclature more complex.

The previously discussed types of chirality depend upon the orientation of the ligands or substituents relative to each other and chirality in those examples is a feature of the compound. The compound is then chiral in the solid state, liquid state, gas phase and in solution. A totally other type of chirality occurs when the crystallization induces chirality and the spatial arrangement of the molecules or ions within the crystal is chiral, often a spiral. If all spirals in one crystal are of the same turn, the crystal itself is homochiral and single crystals of such compounds are thus optically active. Once such an enantiopure crystal is dissolved, the optical activity is gone. Classical examples of this rare phenomenon are the crystals of quartz[1, 32] or sodium chlorate[5] but other compounds are known to undergo such spontaneous resolution.

## 2.2 Crystallization

A material is said to be crystalline when a small unit is repeated in the same way through the whole solid material, which then is called a crystal or a single crystal. Because of this repeating unit, the structure of a single crystal is highly ordered which is the property that is used in single crystal X-ray diffraction. In this analysis method, an X-ray beam entering a crystal will diffract and create a diffraction pattern which in turn can be used to calculate the positions of the atoms in the crystal (see figure 11). Since the intensity of the reflections correlates to the electron density, the different atoms in the crystal can be identified and their bond lengths and bond angles determined. X-ray diffraction is still the only way for direct determination of the absolute configuration.

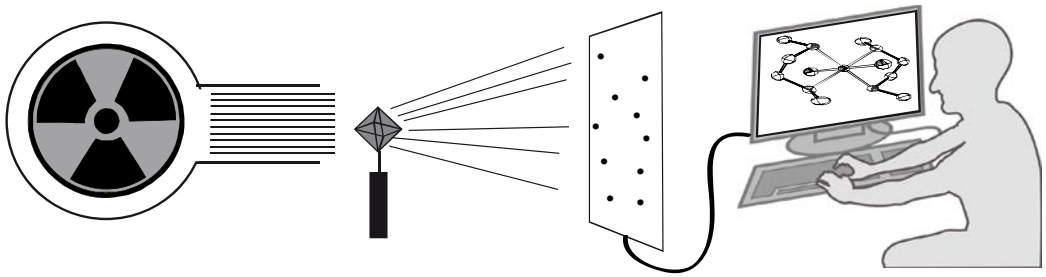


**Figure 11:** Schematic drawing of the basic principles behind X-ray diffraction.

The smallest repeating unit in the crystal is the unit cell and the crystal phase is defined by its unit cell parameters, the three distances (a,b,c) and the three angles (α, β,γ). Almost all phases have different unit cell parameters but isomorphs with similar cell parameters do exist. The same compound can crystallize in several different phases and such polymorphism is quite common, one such example is $[RuCl_2(dmso)_4]$ used as starting material for the compounds in paper III. Each unit cell can hold several molecules of the crystallized compound. The smallest repeating unit inside the unit cell is called the asymmetric unit and this can be parts of a molecule, a whole molecule or many molecules. The repetition of the asymmetric unit in the unit cell is described by the symmetry of the crystal. Crystals can belong to one out of seven crystal systems, determined by the unit cell symmetry. Each crystal system allows for different kinds of symmetry and in total, a compound can crystallize in one out of the 230 existing space groups (figure 12). Out of all these space groups there are only 65 that lacks mirror or inversion symmetry and thus only contain rotation or screw axes.

| Crystal system | Unit cell restrictions | Crystal structures (rel %) | Sohncke space group (%) |
|---|---|---|---|
| Triclinic | no restrictions | 26 | 3.7 |
| Monoclinic | α=γ=90° | 52 | 12 |
| Orthorhombic | α=β=γ=90° | 17 | 45 |
| Tetragonal | a=b; α=β=γ=90° | 2.2 | 30 |
| Rhombohedral | a=b=c; α=β=γ(≠90°) | 1.1 | 54 |
| Hexagonal | a=b; α=β=90°; γ=120° | 1.2 | 15 |
| Cubic | a=b=c; α=β=γ=90° | 0.6 | 22 |

**Figure 12:** The different crystal systems combined with data from CSD.[37]

These space groups were defined and described by Leonard Sohncke in 1879[33] and are the only ones that enantiopure compounds can crystallize in. Those 65 space groups are named after him and usually called Sohncke space groups. In an attempt to give them a more explanatory name the term chiro-descriptive space groups[33a] has been introduced. Achiral molecules and a racemic mixture of chiral molecules can also crystallize in a Sohncke space group but then in a chiral, enantiopure fashion. Most single crystals from those 65 space groups are enantiopure even though twinning by inversion (sometimes referred to as racemic twinning) is possible, yielding either racemic or enantioenriched crystals. Such twinning is a rare phenomenon[34] and if racemic crystals are solved in Sohncke space groups, maybe the wrong space groups have been chosen for the refinement.[34a, 35] To determine that a crystal solved in a Sohncke space group is enantiopure the "Flack parameter" could be used. This parameter was developed by Leonard Flack in 1983[36] as the *x*-parameter. In his equation (1) the real crystal structure is compared to a hypothetic crystal twinned by inversion. If the Flack parameter of a crystal is 0 (with a low standard deviation) the crystal structure describes the correct enantiomer, if it is 1, it describes the wrong one. For all other numbers than 1 and 0 the flack parameter has no interpretation than that the absolute configuration for the crystallized compound cannot be determined with certainty. Either the crystal is not enantiopure or a better data set is needed.

$$|F(h,x)| = (1-x)|F(h)|^2 + x|F(-h)|^2 \quad (1)$$

To clarify or put it in another way, there are three distinct ways that chiral molecules can organize themselves when crystallizing (figure 13). Either the two enantiomers crystallize in the same crystal or they crystallize in separate crystals. If they crystallize in the same crystal this can be ordered as in racemic crystals or the distribution of the enantiomers can be uneven throughout the crystal as in a pseudoracemate (solid solution). Domains of a pseudoracemic crystal can therefore be optically active. Such domains are difficult to identify and separate from each other. In both cases, all single crystals are racemic in and

thus not optically active. If the enantiomers end up in different crystals, the single crystals are optically active. Spontaneous resolution has then been achieved and the compound has crystallized as a conglomerate in a Sohncke space group. For achiral molecules, the same three ways of crystallizing are possible but no molecular enantiomers can of course be identified. Chiral crystals or chiral, enantiopure domains in a crystal can form by the arrangement of the molecules within the crystal. Homochiral crystals from achiral compounds are only optically active in the solid state.

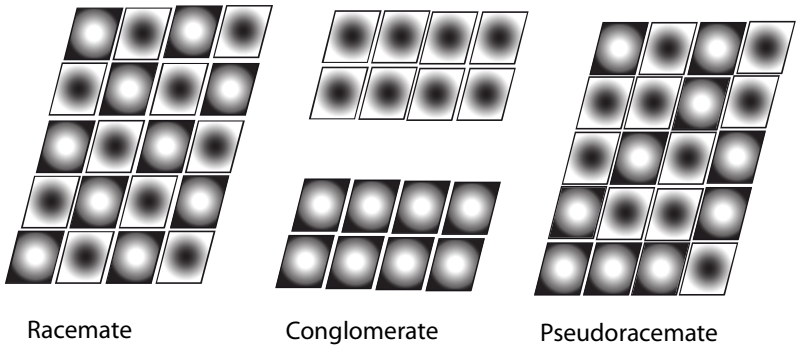



**Figure 13:** Graphical representation of the three ways of crystallizing.

In the Cambridge structural database (CSD), where all published crystal structures can be deposited there are currently over 860 000 entries.[37] Approximately 140 000 of these are found to crystallize in a Sohncke space group. The main part originates from enantiopure material being crystallized. It has been estimated from CSD-data that the chance of a racemate of a chiral organic compound for crystallizing in a Sohncke space group is 5-10 %.[6, 38] For achiral structures or for metal complexes, no such examination has been performed. Since determining the correct chance demands reading and analyzing over 100 000 references, estimation is the only possible option. In conclusion, there is a small chance that a non-optically active solution crystallizes into optically active crystals and in most cases the crystals are racemic or achiral.

The advantages of utilizing the art of crystallization in chemical synthesis can be the cheap upscaling, purified product and the high yields; crystallization is as easy to do on the kilogram scale as it is done on ordinary laboratory scale and usually no additional risks occur when increasing the scale. Since the mother liquor often can be reused, high yields are expected. The highly ordered structure of the crystalline state does not allow impurities in the crystal lattice and the solids are therefore purer after recrystallization than before. Even the *ee* can increase with crystallization.

## 2.3 Vibrational Circular Dichroism

Vibrational Circular Dichroism (VCD) spectroscopy is an advanced form of infrared (IR) absorption spectroscopy, in which information about the chirality of a sample is obtained; VCD is together with electronic Circular Dichroism (CD) and Optical Rotary Dispersion (ORD) used to analyze optically active compounds. In VCD, the enantiomers of a chiral compound absorb left and right circularly polarized (CP) infrared radiation differently[39] (see figure 15). The result obtained in a VCD measurement is thus an ordinary infrared radiation (IR) absorbance spectrum and a delta absorbance spectrum for the left and right CP-IR. Best results are obtained if the strongest absorbing peaks have an IR absorbance under 1 au, otherwise the noise can be too high and disturbances occur. If weak absorbing and very strong bonds (peaks) are present for the same sample, the VCD-signals for some regions can be very week and hard to observe. Very strong and very weak VCD-signals have then to be recorded at different concentrations and in different measurements. Maybe this is not a problem with organic molecules as much as with metal complexes with several ligands of the same type.

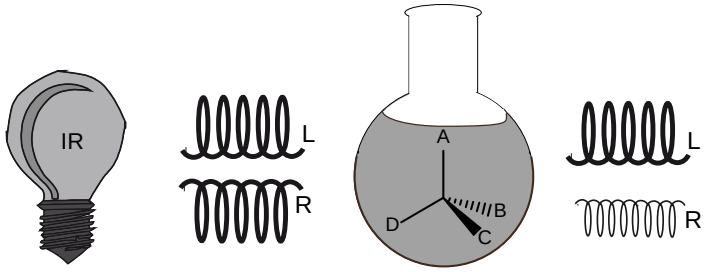



**Figure 15:** The principle of vibrational circular dichroism.

Compared to the spectra obtained in electronic CD, VCD spectra are more detailed because of the many bands in the mid-IR "fingerprint" region. A model compound for VCD is the natural product α-Pinene, as its two enantiomers are commercially available, it is an oil at room temperature and the absorbance of the different regions is of the same magnitude (see Figure 16). Since the discovery of VCD over four decades ago,[40] the technique has been applied mostly too small stereochemically inert organic molecules in solution or as neat oil.[39] In the solid state, ground samples have been suspended in oil such as nujol[41] and flourolube[42] or pressed in a KBr disc.[43] Solution casted films[44] have also been used in solid VCD analysis and even a single crystal has been used as it was.[45] Compared to CD, the sensitivity of VCD is lower and more sample is often needed to get high quality spectra, for VCD often several milligrams is needed compared to CD where it is sufficient with one-hundredth of that amount. In CD analysis, Pressed KBr-discs with a single crystal are frequently used which usually are enough sample to yield spectra with high quality, which is not the case for VCD.

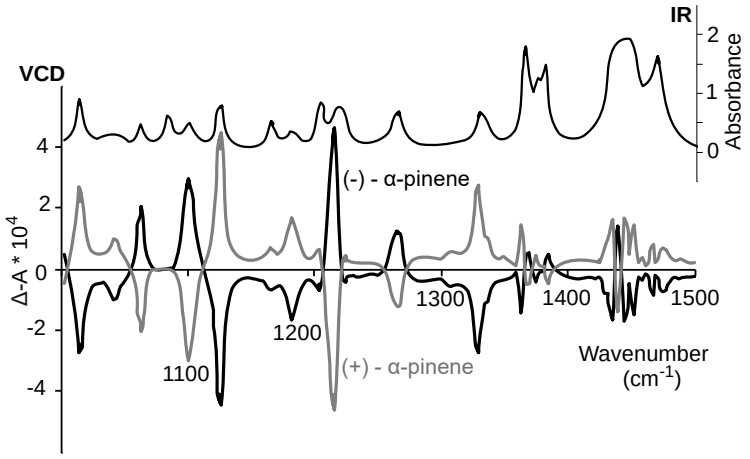



**Figure 16:** VCD and IR spectra of α-pinene.

## 2.4 Absolute Asymmetric Synthesis

The creation of optical activity from non-optically active starting materials, catalysts or reagents is absolute asymmetric aynthesis[10] and the term was first introduced by the German chemist Bredig in 1923.[46] Experiments with AAS as a goal had been performed even earlier[47] and LeBel introduces the idea that circularly polarized light (CPL) could induce optical activity in the products in a reaction as early as 1874.[48] Since then there have been many examples on the phenomenon AAS and it is now totally clear that optical activity can be created without the influence of other homochirality of any kind.

In organic synthesis of a chiral compound where a nucleophile attacks a substrate, it is as likely that the nucleophile attacks the prochiral substrate from one side yielding one of the enantiomers as it is that it attacks from the second side yielding the other (see figure 17). To be able to get other than racemic product, one has to block the attack on one of the sides. This blocking can be done with enantiopure substrates, enantiopure catalysts aiding the reaction or with enantiopure reactants. Most reactions yielding other than racemic product involves some kind of optically active part that influences the outcome. Those optically active compounds can be quite expensive if they do not come from natural sources and in that case the product is often limited to only one of the enantiomers.

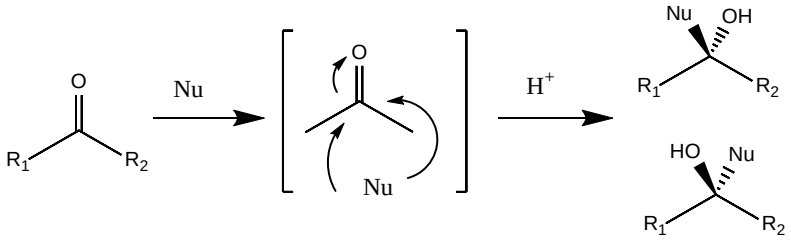



**Figure 17:** Nucleophilic attack of a substrate.

Separation of the enantiomers from a racemic mixture can however be done with chromatography on a column with enantiopure packing material. Such separations can be quite expensive and take time as several different columns and eluents have to be evaluated. To separate large quantities of material via chromatography is something that can be time consuming, if it is possible at all. With AAS on the other hand, production of the desired enantiopure material without separations or expensive starting materials can be done easily.

Bredig argued in his time for the influence of asymmetrical external physical forces in AAS, such as magnetical-, electrical- and photochemical forces for the induction of AAS. His own experiments with CPL, were however found to be fruitless.[49] Later AAS experiments with electrical- and magnetical forces has been performed but proven not to be reproducible. The use of CPL for the induction of AAS has been successful a handful of times in the earlier years yielding products of low *ee*.[10] However, recent discoveries that

CPL can be used for the synthesis of chiral liquid crystal films have been reported during the last 20 years.[50] This self-assembly can be performed with either handedness of the light and yield highly optically active propeller like structures.[51] One can debate if using external forces like CPL in synthesis really is an example of true AAS or not due to the use of "enantiopure" light, but as it follows the definition it could be regarded as one such example.

In 1941, Havinga reports on "*spontaneous generation of optically active material starting from an inactive system*".[52] He succeeded to get optically active batches of methyl-ethyl-allyl-anilinium iodide from a racemic mixture via crystallization. Since the solution showed no optical activity prior to and after the crystallization this is clearly regarded as AAS. The optical rotation of the crystal batch was measured in a solvent where the racemization was slow or did not occur at all. Spontaneous resolution in a racemizing solution, yielding enantioenriched crystal batch in a racemic mother liquor can be called total spontaneous resolution (TSR).[38a] In TSR, to exclude inoculation effects, the formation of a specific enantiomer over the other should be by random and the distribution of (+) and (-) samples stochastic.

In 1969, Penzien and Schmidt[53] managed to perform spontaneous resolution on 4,4´-dimethyl-chalcon and subsequently expose single crystals to bromine vapor, yielding optically active product in low *ee*´s (see figure 18). As bromination products in solution did not show any optical activity and the solid state reaction product with bromine vapor did, they claim to have achieved AAS. Penzien and Schmidt reported to have seen inoculation effects and this fact was later used to prove that bulk polycrystalline samples upon exposure to bromine vapor are optically active and that AAS through TSR has occurred.[54] Further experiments showed that *ee*´s up to 25 % of either handedness can be produced via TSR in the crystallization of this α,β-unsaturated diketone.[54-55]

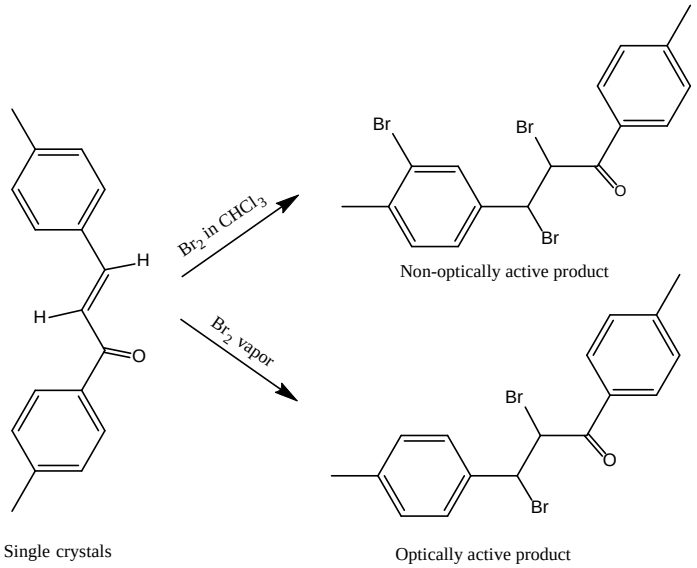



**Figure 18:** The bromimination of 4,4´-dimethyl-chalcon reported by Havinga.

The phenomenon of TSR is rare[56] but since Havingas discovery in 1941, several reports of such optical activity creation have been made (see figure 19). Pincock *et al* reported in 1971[57] optical activity in bulk samples of 1,1 binaphtyl, crystallized from an enantiomerizing melt. Okada *et al* reported in 1983 of AAS with a oxazolobenzodiazepone, that probably enantiomerizes via a quaternary iminium ion.[58] Crystallizations made by Okada yielded high *ee* bulk product of either enantiomer. The first example of AAS with an organometallic compound was reported in 2003 by Vestergren *et al*[59]. Bulk samples of the *para*-tolyl Grignard reagent reacted with an aldehyde was found to result in optically active product with modest *ee*. However, the crystallization of the Grignard reagent, which is the TSR step, was reported to give near optically pure batch. Recently this group has reported examples of organometallic reagents in TSR with near quantitative yield and optically pure product.[60]

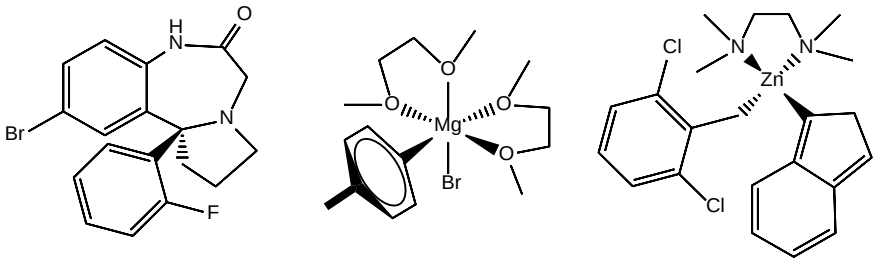



**Figure 19:** The structure of compounds for which TSR has been reported.

To further increase the chance to obtain optically active product in crystallization experiments, Kondepudi *et al* showed in 1990 that constant stirring during the crystallization can achieve higher *ee*´s of the bulk and a more frequent success rate.[61] In the crystallization of sodium chlorate, the *ee* of the bulk without stirring is zero and with stirring the product is more or less enantiopure. For the α,β-unsaturated diketone experimented on by Penzien and Schmidt in the sixties, low *ee*´s can be detected without stirring but optically pure bulk product with stirring.[55]

In 1995, Soai *et al* discovered the asymmetric autocatalytic synthesis of pyrimidine-5-carbaldehyde from Zn(*i*Pr)$_2$ with an *ee* of 99,5% that is not considered as AAS.[17b] The Soai reaction is catalyzed by the product and starts from samples with a small *ee*, which is added to the reaction mixture. Almost any homochiral influence have proven to direct the product into the desired enantiomer. However, more importantly, the autocatalysis has been proven to work on the statistical fluctuations[17a, 62] of the initial reactions, this makes it a true example of AAS.

Ostwald ripening[63] (that big crystals grow over time on the expense of smaller) can also be AAS. If conglomerate crystals of a compound that enantiomerizes in solution undergo Ostwald ripening, the process has proven to yield optically active bulk product.[64] In 2005, Cristobal Viedma showed that grinding a racemic mixture of conglomerate crystals with glass balls in a racemizing solution, can result in that the whole batch of crystals becomes enantiopure.[65] Ostwald ripening with chiral crystals and Viedma ripening are examples of AAS.

To conclude, synthesis with CPL and other homochiral forces might not be AAS but have produced optically active products from optically inactive starting materials. Total spontaneous resolution, Soai´s autocatalytic synthesis, Ostwald- and Viedma ripening are all examples of absolute asymmetric synthesis that have produced optically pure product.

## 2.5 On the mechanisms of TSR and Viedma ripening

The mechanism of the symmetry breaking in TSR and Viedma ripening is still under debate and not yet fully understood. A summary of the theories will herein be given. It is not only the true mechanism that is unclear, not even the term total spontaneous resolution is something that there is consensus about. The phenomenon total spontaneous resolution is also called *total resolution, total transformation of racemic compound in to a single enantiomer,*[66] *total resolution by dynamic preferential crystallization*, *total resolution by crystallization*, *dynamic crystallization,*[67] *crystallization-induced asymmetric transformation* and *"second order" asymmetric transformation.*[68] To name the term as total *spontaneous resolution* (TSR) is herein made of reasons for synergy with the term *spontaneous resolution* i.e. the formation of conglomerates and the fact that the term TSR after all is well established[38a, 66-69] in the scientific society.

Viedma ripening is also described as *attrition enhanced deracemization*[67, 70] and named *"induced Ostwald ripening"* or *dissolution-growth by abrasion-grinding in a closed system* by Cristobal Viedma in the original article.[65] Others have called the phenomenon *Viedma deracemization.*[71] The term "Viedma ripening", which is also commonly used[70c] will be used throughout this text.

### Total spontaneous resolution as classically described

To purify chemicals through crystallization is an old technique and such crystallizations near equilibrium (slow cooling or evaporation) can produce samples of high purity due to the fact that the impurities does not fit as good into the crystal lattice as the crystallizing compound.

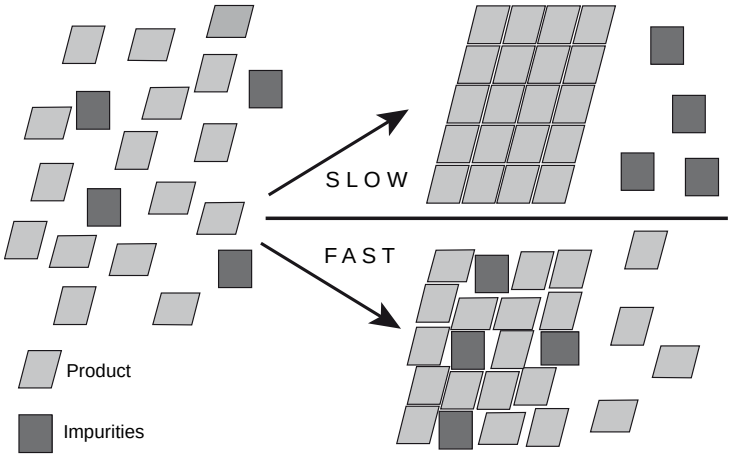



**Figure 20:** A 2D-schematic drawing of fast and slow crystallization,

Enantiomers on the other hand crystallize together if the crystals are racemic. If a compound crystallizes as a conglomerate it is possible to preferentially crystallize one of the enantiomers and this way get a separation.[72] The yield in such separations of racemic mixtures is however limited to maximum 50% as half of the mass consists of the unwanted enantiomer. Usually the yield is even lower because the crystallization is stopped in advance due to purity reasons; high *ee* in the mother liquor makes the other enantiomer crystallize and the crystal batch will not be optically pure. Optical purification via crystallization of enantioenriched compounds should be easier as conglomerate formation should have a higher success rate in enantioenriched systems. Such purifications have been performed in industry on the kilogram scale and one example is the synthesis of esomeprazol.[73]

Total spontaneous resolution has for a long time been believed to follow the "Adam" mechanism.[52a, 68] That is, primary nucleation is a rare event and once a primary nucleus is formed to a "Adam" or mother crystal, all future crystals are formed by secondary nucleation and thus have the same handedness. Faster racemization of the mother liquor than the rate of crystallization is a factor that would make a compound suitable for TSR. Suppressing the primary nucleation would enhance the *ee* further and optically pure batches of either handedness can thus be obtained (see figure 21). Forming crystals of one of the enantiomers over the other should be at random and without seeding the sign of the optical rotation cannot be predetermined.

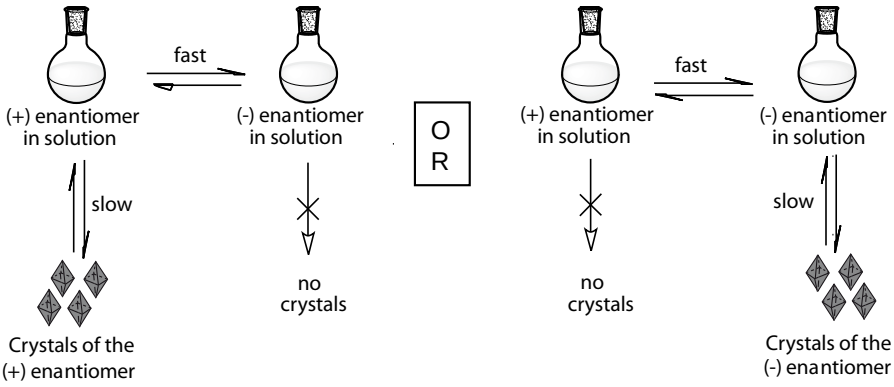



**Figure 21:** Schematic representation of TSR following the "Adam" mechanism. Via TSR can enantiopure samples of both enantiomers be synthesized in 100% yield and *ee*.

Kondeopudi *et al* have shown that primary nucleation can be suppressed and secondary nucleation can be increased on applying simple stirring during crystallization.[55, 61] The initial research was done on sodium chlorate[61] but the stirring technique has produced crystal batches of organic compounds with high *ee*.[55] This process is said to be autocatalytic since all evolving nuclei comes from the first and other secondary nuclei. The concentration is kept at such a level that further primary nucleation is virtually zero. The products in most crystallizations were optically pure and crystals of both handedness in the same batch was a rare event; most batches were enantiopure.

**Viedma ripening as described by Christobal Viedma**

In 1896, Wilhelm Ostwald described the spontaneous process that occurs when having a batch of crystals in a saturated solution.[63] Under these conditions, smaller particles will dissolve and the molecules or ions will crystallize onto the larger crystals (see figure 22). This will continue until the thermodynamic ground state has been reached, which is fewer larger crystals of equal size. The Ostwald ripening is due to the Gibbs-Thompson effect that states that smaller particles have a higher solubility than larger ones and the fact that larger particles grow faster than smaller ones.[74] The timeframe of this process can be from months to hundreds of years. For the author of this thesis, sodium chloride crystals in aqueous solution has not changed its appearance in twenty years but for other researchers and with sodium chlorate crystals the process can be much faster and Ostwald ripening have been achieved in months.[64]

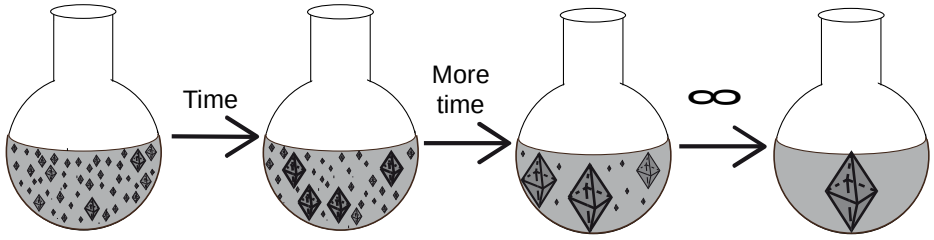



**Figure 22:** Schematic drawing of Ostwald ripening.

Compounds that form conglomerate crystals and racemizes in solution can also undergo Ostwald ripening and the result can then be one enantiopure crystal of either handedness.[64] If no racemization occurs in solution the most stable state would be two enantiopure crystals and enantiomeric separation would have been performed.

In 2005, Cristobal Viedma published his findings from experiments with sodium chlorate in physical review letters as "*Chiral Symmetry Breaking During Crystallization: Complete Chiral Purity Induced by Nonlinear Autocatalysis and Recycling*".[65] He claimed to be the first to reach optical purity when starting from a racemic mixture of crystals and achieved this by wet grinding of conglomerate crystals; stirring a suspension of a sodium chlorate crystals with small glass balls resulted in that the solids reached optical purity within 24 hours. Starting from a slight *ee* (5%) made it possible to reach optical purity faster and like seeding, the handedness of the product could be determined in advance. Increasing the amount of glass beads reduced the time needed to reach homochirality, as did an increase the stirring speed. Other factors that later has been found to affect the reaction rate is the size of the glass beads, the rate of enantiomerization and the concentration; small glass beads, high concentration and fast racemization speeds up the Viedma ripening process.[75]

In a typical Viedma ripening, a racemic mixture of enantiopure conglomerate crystals is ground into smaller pieces in a mortar and transferred to a reaction vessel i.e. a round bottom flask (see figure 23). A magnetic stirrer bar is added together with mother liquor from the crystallization or a suitable solvent. For inert compounds like amino acids, a racemization catalyst is also needed during the grinding. The mixture is stirred until the solids are enantiopure and no further increase in the optical activity can be detected.

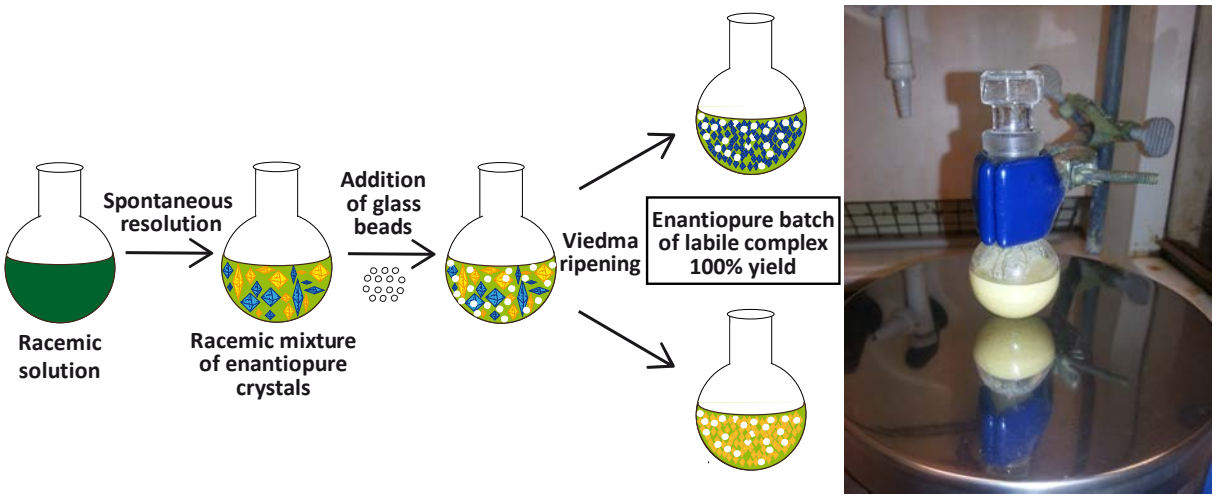



**Figure 23:** Schematic drawing of Viedma ripening and a photograph of the experiments in paper V

It was clear that the model of an initial single enantiopure crystal produced by primary nucleation could not be applied as an explanation of the Viedma ripening and another theory was therefore initiated by Viedma himself[13a, 76] and further investigated Blackmond *et al.*[77] Their opinion is that the Viedma ripening can be explained by the feedback that occurs between the thermodynamics and kinetics of dissolution-growth near equilibrium.[13a] The grinding produces micro crystallites or crystal fragments of the same handedness as the mother crystal, this way micro crystallites or chiral clusters of both enantiomers are created and this could be seen as a form of secondary nucleation. According to the Gibbs- Thompson effect the solubility in the crystalline phase is according to particle size and smaller crystal fragments will dissolve more easily than larger ones, creating a slight concentration gradient in the reaction vessel between larger and smaller particles. The smaller crystallites are therefore dissolved and feeds the larger ones which grow. The clusters of an achiral compound like $NaClO_4$ has to be bigger than the unit cell to be chiral i.e. for $NaClO_4$, four formal units whereas for chiral compounds clusters of any size are chiral. Clusters smaller than this critical size can therefor feed larger growing crystals of any handedness. According to some authors, the existence of such achiral building blocks can be one factor that is behind the success of Viedma ripening.[13a, 76-78]

In Viedma ripening, according to this theory of autocatalysis near equilibrium, the less abundant enantiomer is the one for which crystals dissolve more easily, this process is thermodynamically driven. The growth of crystals is determined kinetically and crystals of the more abundant enantiomer grows faster. These two factors together with the existence of a back reaction (racemization in solution) lead to the increase of *ee* over time in the grinding process until the solids are optically pure.

**The chiral cluster mechanism and meta-stability in boiling saturated solutions.**

While the previously proposed mechanisms and explanations of TSR and Viedma ripening relied on being near equilibrium, a second opinion has aroused that focus on a far from equilibrium scenario.[79] The theory was based on results from experiments on crystallizations of sodium chlorate from boiling water solutions which had a great temperature gradient through the reactor. Four aliquots, without any visible formed crystals, were taken simultaneously from the cluster forming region near the top of the reactor. In most samplings, the four aliquots gave rise to crystals of the same handedness. This was believed to indicate that the symmetry breaking occurs before the crystal growth at the metastable stage for such saturated solutions. At this stage, the concentration of subcritical clusters is at maximum and Ribó *et al* suggests that subcritical nuclei of the same chirality form by cluster to cluster interactions.[71, 80] When the conditions are met for crystal growth, the system is already homochiral and the symmetry thus broken. If such chiral clusters are the ground for symmetry breaking, the authors states that the mechanism of one single "Adam" crystal, Ostwald ripening or secondary nucleation are irrelevant for the breaking of the symmetry as "*the system is already seeded by a sea of clusters*".[80]

Viedma have also looked into the symmetry breaking in such boiling solutions[81] and agrees that it can occur at the metastable stage but also says that it can originate in achiral or chiral cluster formation. The achiral clusters can then feed the larger. That the temperature gradient leads to a far from equilibrium scenario in such crystallizations is a clear fact.

That chiral clusters and a far from equilibrium scenario can be the explanation for Viedma ripening and TSR has been proposed.[82] The theory is supported by extensive data simulations. On the other hand, other calculations and theories have shown that the other proposed mechanisms can be true.[77a, 77b, 83] Still no consensus exists for how the symmetry is broken during crystallization and Viedma ripening.[13b]

# 3

# Aim

It has been considered impossible to create optical activity. Despite this, examples of total spontaneous resolution and more recently Viedma ripening have been demonstrated. Metal complexes should be especially suitable for these purposes because they enantiomerize easily and often form good quality crystals.

The aim of this thesis is to find new metal complexes that can be evaluated in terms of total spontaneous resolution and Viedma ripening. This allows the mechanism for such phenomena to be studied.

The use of vibrational circular dichroism of metal complexes in solution has been limited because such solutions are often racemic. Finding a way to record high quality VCD-spectra of single crystals would be useful.

Since metal complexes often racemize rapidly in solution, ways of reducing the rate of enantiomerization must be devised so that inert solutions can be obtained for future applications.

# 4

# Results

The presentation of the results of this thesis can be divided into three subtopics; the search for conglomerates, total spontaneous resolution and Viedma ripening. In the first section, a review of some of the compounds synthesized, leading to the discovery of new conglomerates will be made. The forthcoming sections will be focused on conglomerates for which TSR and Viedma ripening have been a successful route to optically pure material.

## 4.1 The search for interesting conglomerates (papers I-II)

Every project in this thesis starts with the will of finding new interesting conglomerates. To be interesting, the compounds should have some kind of application, preferably in organic synthesis. Since one of the requirements for TSR and Viedma ripening is a racemizing solution, conglomerates of metal complexes should be suitable. Prochiral ligands that upon chemical reactions will bind its chirality and prevent enantiomerization is also beneficial. Unsymmetrical sulfides will upon oxidation produce chiral sulfoxides. As most reactions producing chiral compounds this one usually yields a 50/50 mixture of enantiomers because there is an equal chance that the oxidation will take place at either of the available lone electron pairs. If one of the pairs is coordinated to a metal the oxidation is directed towards the other. In a conglomerate, all sulfides in one single crystal will have the same configuration and there is a good chance that an oxidation of the sulfur atom will yield a enantioenriched product, see figure 24. If Viedma ripening or TSR is successful with the sulfide complex, enantiopure sulfoxide would be available on the kilogram scale. A search

for conglomerates of metal complexes with prochiral sulfide ligands should be a good starting point and if found, any conglomerates could be a candidate for TSR and Viedma ripening.

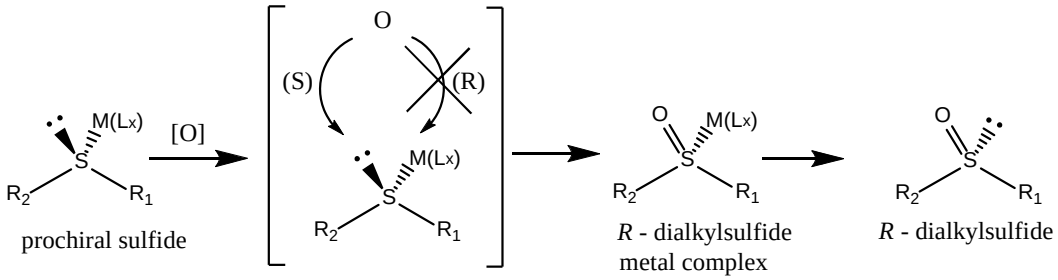


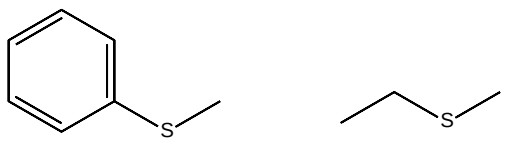

**Figure 24:** Oxidation of a prochiral sulfide protected by complexation. Oxidizing the other enantiomer would yield *S*-dialkylsulfide.

Since the sulfide is characterized as a soft ligand it would make strong coordination bonds to a soft metal ion; $Cu^{+}$, $Ag^{+}$, $Au^{+}$, $Hg^{+}$, $Hg^{2+}$ and $Cd^{+}$ should be excellent metal ions for sulfide coordination. For environmental and economic reasons were copper the choice for the following projects.

Monomeric copper(I) species could present another problem, they might lose the ligands outside of the mother liquor. The crystals will then fall apart and are thus not suitable for oxidations in the solid state. In this case would polymeric structures be preferred. Halide ions are known to bridge between metal centers and in this way form coordination polymers. The recipe for success could therefore be soft, unsymmetrical, sulfides as ligands with copper(I)chloride, copper(I)bromide and copper(I)iodide. Will the new complexes form polymers and will the crystals be stable enough?

**Monodentate prochiral sulfur ligand complexes (paper I)**

For the first experiments, a set of two different monodentate ligands were chosen (see figure 25), thioanisole and ethyl(methyl)sulfide. These unsymmetrical and thus prochiral sulfids were combined with different copper(I) salts in a set of crystallization experiments. This way new compounds (**1-6**) were synthesized, crystallized, isolated and analyzed with single crystal X-ray diffraction.




methyl(phenyl)sulfide (thioanisole)

ethyl(methyl)sulfide

**Figure 25:** The prochiral sulfide ligands bonded to Cu(I) in paper I.

It was found that five out of six found compounds form polymers. Using the thioanisole ligand, discrete tetrameric aggregates were found for $[Cu_4I_4(CH_3SC_6H_5)_4]$ (**1**) and chains with different stoichiometry were found for $[Cu_3Br_3(CH_3SC_6H_5)_2]_n$ (**2**) and $[Cu_3Cl_3(CH_3SC_6H_5)_2]_n$ (**3,** figure 26). Coordinating ethyl(methyl)sulfide to CuCl, CuBr and CuI formed two different kinds of coordination polymers. In $[Cu_4Cl_4\ (CH_3SC_2H_5)]n$ (**4**) and $[CuBr(CH_3SC_2H_5)]_n$ (**5**) Cu(1) aggregates are incorporated macrocyclic 28-membered rings that span layers. For $[Cu_4I_4(CH_3SC_2H_5)]_n$ (**6**), face-capped copper-based tetrahedral aggregates form chains.

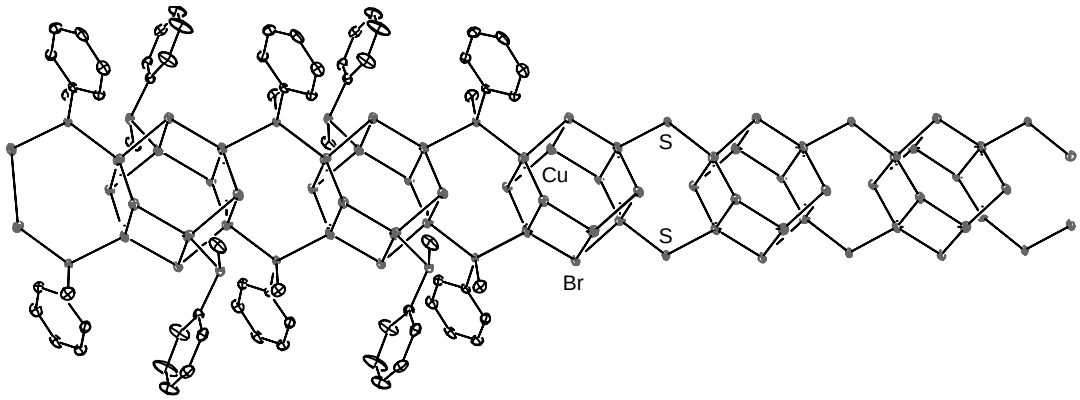



**Figure 26:** Drawing of compound **3** showing the shape of the 1D-polymer

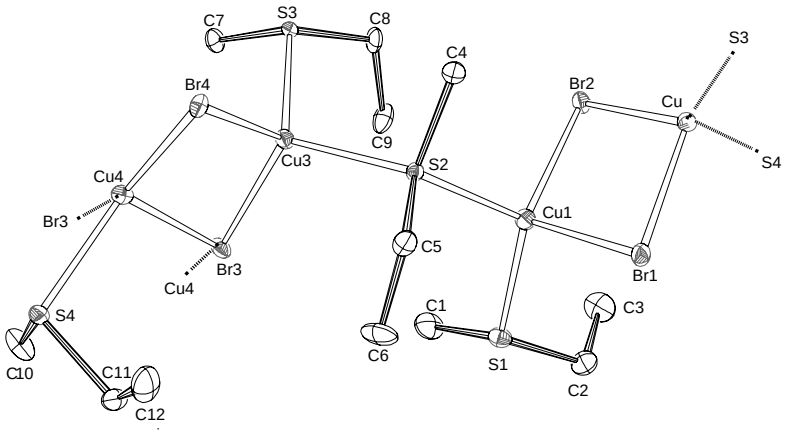


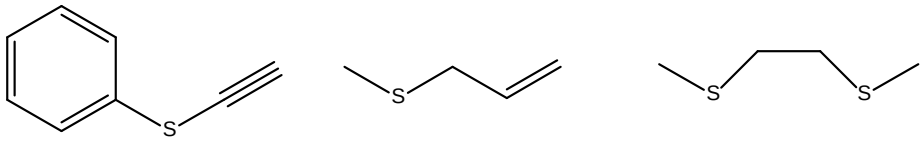

**Figure 27:** Ortep drawing of compound **5** showing the asymmetric unit. Hydrogen atoms are removed for clarity and ellipsoids are drawn at the 50% probability level.

For all synthesized compounds, the sulfur ligand was found to be terminal which means that it is possible to oxidize its remaining electron pair. One concern with using sulfur ligands was that this ligand also can bridge between metal centers and we were pleased to find that all synthesized complexes had terminal sulfur ligands. In some of the complexes sulfur also bridged between metal centers. Many interesting polymeric structures were found in this type of system but even though coordination polymers are indeed formed, it seems that the stability of the crystals are too low. Outside the mother liquor the crystals become opaque quickly, most likely due to the loss of the sulfur ligands with consequently

breakdown of the crystal lattice. Unfortunately, no conglomerates were found with these two ligands. Maybe bidentate ligands would be a better choice due to the higher stability of such complexes.

## Complexes with bidentate prochiral sulfur ligands (paper II)

Since monodentate ligands that were chosen for the experiments presented in paper 1 seemed to form more sensitive complexes and no conglomerates were found, three bidentate ligands were used in the synthesis of total of five new copper(I) coordination polymers (compound **7-11**) that were prepared, crystallized, isolated and analyzed with single crystal X-ray diffraction. When combining one of the ligands phenyl(propargyl) sulfide (Sprop), allyl(methyl)sulfide (Sally), or 1,2-bis(methylthio)ethane (2,5-dithiahexane, SS), see figure 29, with copper(I)chloride, copper(I)bromide and mesityl copper, discrete dimers and discrete tetramers were synthesized. Polymers such as layers and chains were also identified.




phenyl(propargyl)sulfide (Sprop) | allyl(methyl)sulfide (Sally) | 1,2-dithiahexane (SS)

**Figure 28:** The bidentate prochiral ligands bonded to Cu(I)Cl in the complexes in paper II.

Discrete dimers are formed for $[Cu_2Br_2(Sprop)_4]$ (**7,** figure 29) where the bromides bridge two copper atoms. Each copper atom is coordinating two Sprop-ligands and the alkyne groups do not coordinate to the metal.

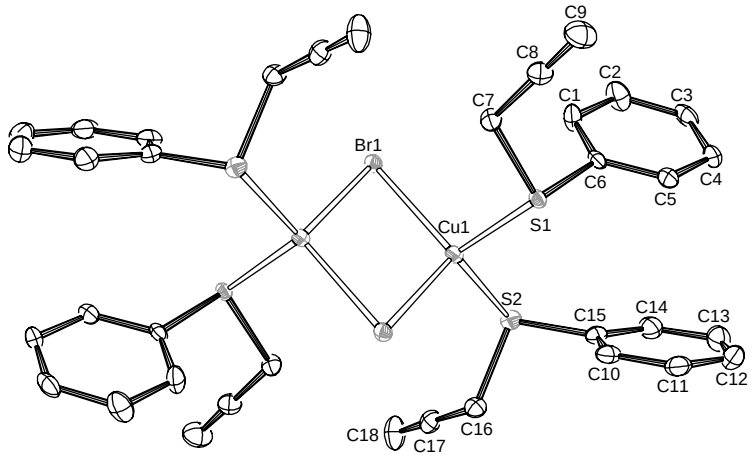



**Figure 29:** Ortep drawing of **7**. Hydrogen atoms are removed for clarity and ellipsoids are drawn at the 50% probability level.

Corresponding dimers like **7** forms for $[Cu_2Cl_2(Sprop)]_n$ (**8**) as well but as CuCl is more prone to be apart in π-coordination the alkyne is coordinating to another copper atom then the sulfur and extending the network in 2 dimensions into layers.

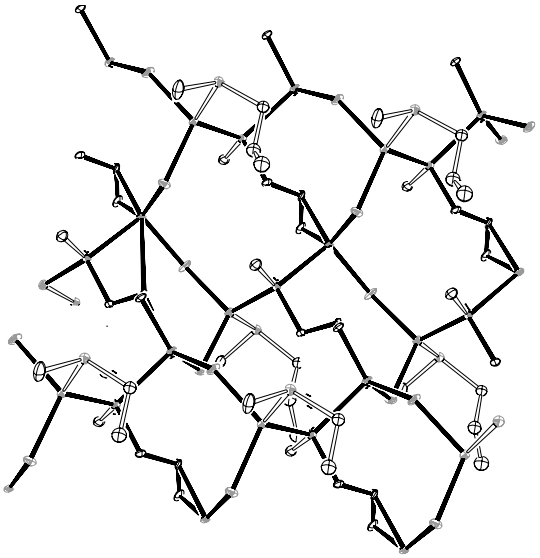


**Figure 30:** Drawing of **9,** showing the network expanding in 2 dimensions.

The Sally-ligand offers also a possibility for π-bonding which is demonstrated in $[CuCl(Sally)]_n$ (**9**, figure ) where layers are being formed via the π-coordination of the allyl groups.

Mesityl copper is a useful compound because a) its high solubility in organic solvents, b) its usefulness in the synthesis of organo-copper and cuprate complexes and c) for safety reasons. The solubility for mesityl copper is good in solvents like THF and toluene and even though it reacts readily with air and moisture, it is not pyrophoric and explosive. Mesityl copper is known to form aggregates in solution[84] (pentamers when crystallized from toluene and tetramers from THF). To see whether the sally ligand was powerful enough to break these aggregates, $[Cu_4(Mes)_4(Sally)_2]$ (**10,** figure 31) was prepared. Compound **10** forms chiral, discrete tetramers. Unfortunately, it forms racemic crystals. The SS ligand was not found to break the aggregates either but linked the tetramers into racemic chains as for $[Cu_4(Mes)_4(SS)]_n$ (**11,** figure 32).

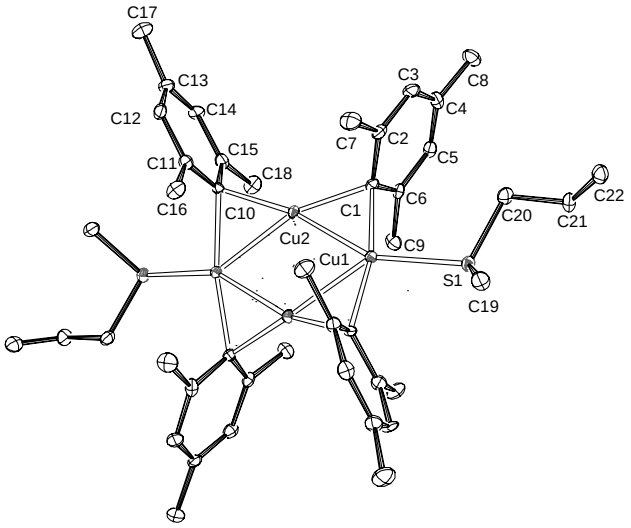



**Figure 31:** Ortep drawing of **10**. Hydrogen atoms are removed for clarity and ellipsoids are drawn at the 50% probability level.

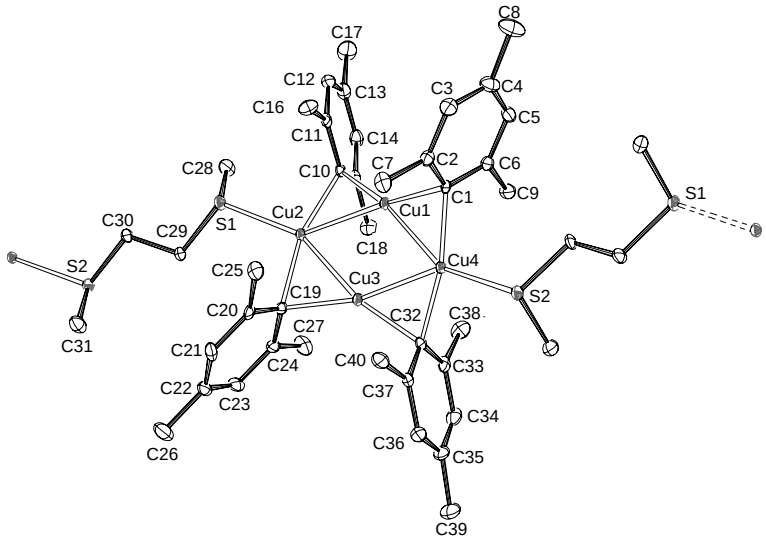



**Figure 32:** Ortep drawing of **11**. Hydrogen atoms are removed for clarity and ellipsoids are drawn at the 50% probability level.

For the three ligands used, three out of five synthesized complexes form coordination polymers and in all of them the sulfur atom is terminal and available for oxidation. Chiral compounds have been synthesized but none of the compounds **7**-**11** was found to form chiral crystals.

It seems that sulfur ligands and a copper(I) metal center might not be the best choice for forming conglomerates after all. If this statement really is true is too early to say and maybe a differentiation of the ligand or anion would be beneficial for conglomerate formation. The crystals of complexes formed with monomeric with bidentate ligands were too unstable to be handled outside the mother liquor. If the crystals are going to be used in further synthesis another approach has to be made and another strategy for conglomerate formation has to be initialized.

## 4.2 Total spontaneous resolution of metal complexes (papers III and IV)

Using other unsymmetrical, bidentate sulfides as ligands and other metal centers, several new conglomerates were found and three new octahedral ruthenium complexes were found that undergo TSR upon crystallization. Both TSR and viedma ripening were demonstrated with a discovered tetrahedral silver complex.

### The protected substrate oxidation, paper III

Tetrakis(dimethylsulfoxide)dichlororuthenium(II), $[RuCl_2(dmso)_4]$, is a well-known compound and was chosen as starting material for the synthesis of three new conglomerates. The starting material is easy to crystallize and is readily soluble in many organic solvents as methanol, ethanol and dimethylsuloxide (DMSO). As to now this compound can crystallize in five different phases where four of them have the chloride ions *cis*[85] and only one of them is a *trans*-complex.[85c, 86] None of these crystals are chiral and therefor do not crystallize in a Sohncke space group. A rearrangement into a dimer with three bridging chlorides and loss of DMSO is also a known phase.[87]

The goal of this project was to synthesize compounds that were conglomerates and could undergo TSR or Viedma ripening. The complex should be designed so that at least one of the ligands should be prochiral and contain a sulfur atom that could be oxidized to the corresponding sulfoxide. Since the cause of helical chirality is to have all ligands *cis*, a selection of bidentate ligands were synthesized and used in complex formation so that at least two of the six positions should be coordinated to the same ligand and adopt the *cis* conformation.

Since binding a bidentate prochiral sulfur ligand to an octahedral metal center produces three chirogenic centers, four pairs of enantiomers (ΛSR and ΔSR, ΛRS and ΔSR, ΛRR and ΔSS, ΛSS and ΔRR) are possible products. On top of this comes the possibility to yield the enantiomers of the *trans*-complex. Bearing this in mind, it seemed as a hard task to synthesized one compound selectively, especially when the enantioselective oxidation of the sulfur atoms was one of the goals. This goal could only be achieved with the enantiomers, ΛRR and ΔSS, ΛSS and ΔRR; the oxidized free sulfide for the other enantiomers will be a non-chiral *meso* compound. Despite these concerns, a trial and error search for new conglomerates with bidentate sulfur ligands (see figure 33) were performed. In this search, many new compounds were synthesized, crystallized and their structure determined with single crystal X-ray diffraction.

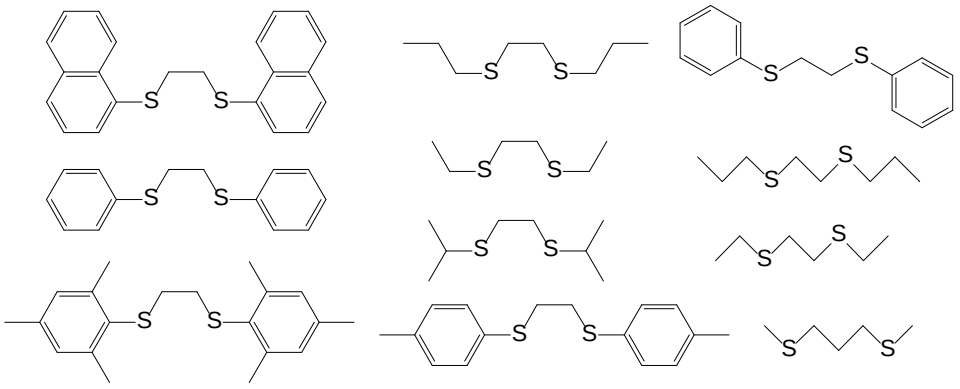


**Figure 33:** The bidentate prochiral compounds tried as ligands in the search for new conglomerates.

Using the ligand 1,2-bis(1-naftylthio)ethane a mixture of products were found in the reaction vessel. In one of the products the ruthenium coordinated one bidentate ligand and in the other, it coordinated two (see figure 34). The product was a mixture of those two compounds in different ratios depending on the amount of bidentate sulfide used. The same results were achieved using 1,2-bis(*p*-tolylthio)ethane as a ligand.

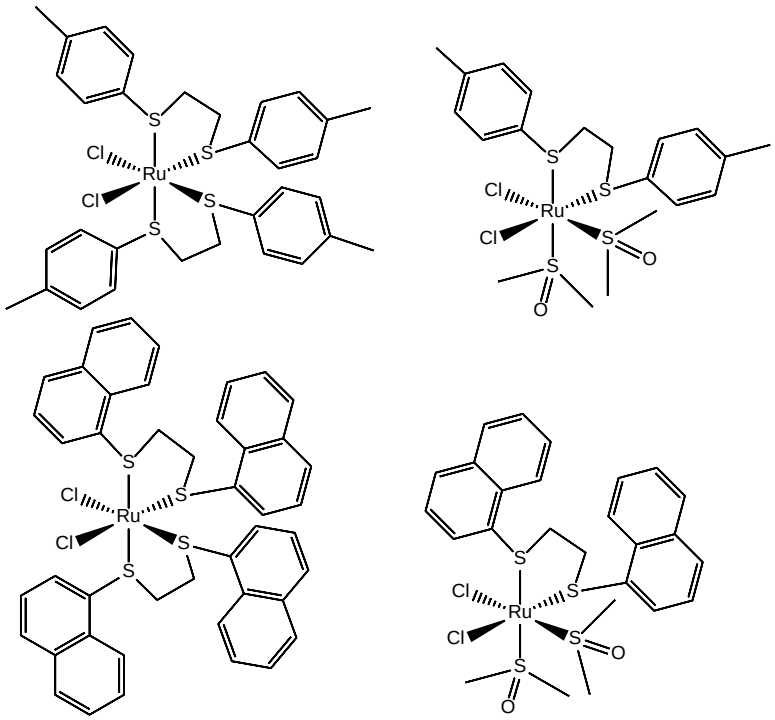


**Figure34:** The structure of some of the compounds from the work leading to paper III. All crystallized as racemic crystals.

For other ligands such as 2,6-dithiaheptane, the complex with two ligands crystallized first, even though only one equivalent of ligand was added. A mixture of the starting material and the product [$RuCl_2$(2,6-dithioheptane)$_2$] was thus obtained.

In the synthesis of the red complex [$RuCl_2$(1,2-bis(phenylthio)ethane)] only one product crystalized., unfortunately the crystals were not chiral and a further search with other types of ligands had to be performed.

Three other bidentate ligands were found to be involved in conglomerate formation. One ligand is the commercially available (2-(methylthio)pyridine (the NS-ligand), one was synthesized from diphenylphosphine and (2-chloroethyl)(methyl)sulfide 2-(methylthio)ethyl diphenylphosphane, (the PS-ligand) and the third was a symmetrical sulfur ligand that was synthesized from 1,2 ethanedithiol and iodomethane 1,2-bis(methylthio)ethane (the SS-ligand), see figure 35.

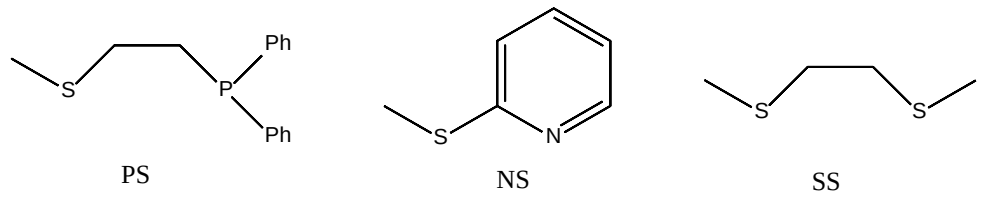



**Figure 35:** Ligands involved in conglomerate formation when exchanging dmso in [$RuCl_2(dmso)_4$].

Using these ligands, three new conglomerates were discovered. All three complexes are "all *cis*". In the complex $RuCl_2(PS)_2$ (**12**), two PS-ligands are coordinated to the metal center and no DMSO-molecules at all. In $RuCl_2(dmso)_2$(NS) (**14**) and $RuCl_2(dmso)_2$(SS) (**16,** figure 37) one bidentate ligand coordinates to ruthenium which coordinates two DMSO by the sulfur atom. In **14**, the sulfur atom is *trans* to chloride and the pyridine is *trans* to DMSO. For complex **16** the two sulfur atoms in the SS-ligand are not chemically equivalent. One is *trans* to a chloride and one is *trans* to dmso. This might play a crucial role in the oxidation step.

Attempts to enantioselectively oxidize the sulfur atom(s) in single crystals of the three synthesized conglomerates were successful (see figure 36) and confirmed with CD, high performance liquid chromatography (HPLC) and single crystal X-ray diffraction. Since solutions of the three complexes racemize slowly, the oxidations, which proceed very quick, could be performed in solution. Full racemization was achieved in days. For the PS-complex **12** and the NS-complex **14**, the oxidation was done in dichloromethane with dimethyldioxyrane (DMDO).[88] For the SS-complex **16**, *meta*-chloroperoxybensoic acid (mCPBA), that is commercially available, gave satisfying results and was therefore used. Total spontaneous resolution has been demonstrated with all three conglomerates and they all yielded enantioenriched bulk product. Viedma ripening were not successful with these complexes, but we were pleased to find that TSR worked fine for all three of them. For the SS-complex **16** however, the results were most promising and all further work was concentrated on the oxidation of this complex.

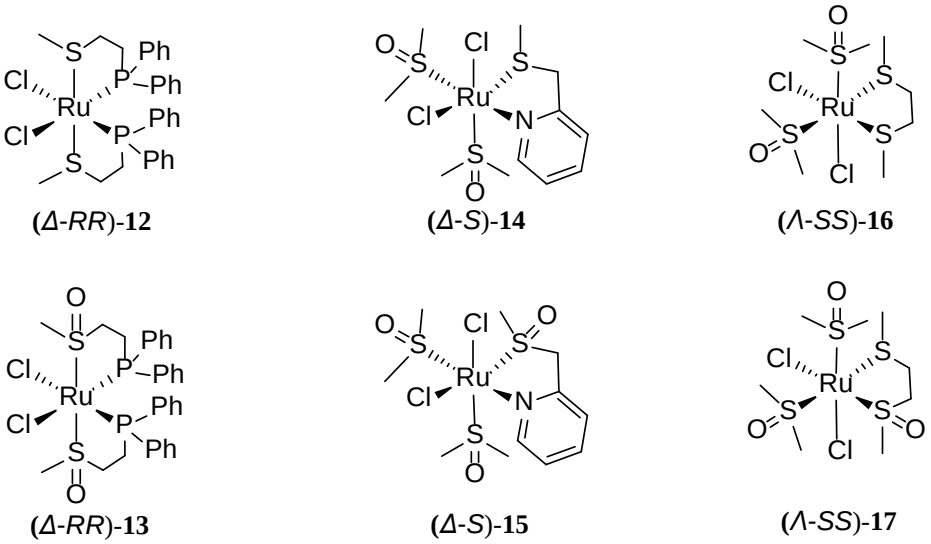



**Figure 36:** The three discovered conglomerates and the corresponding oxidized products.

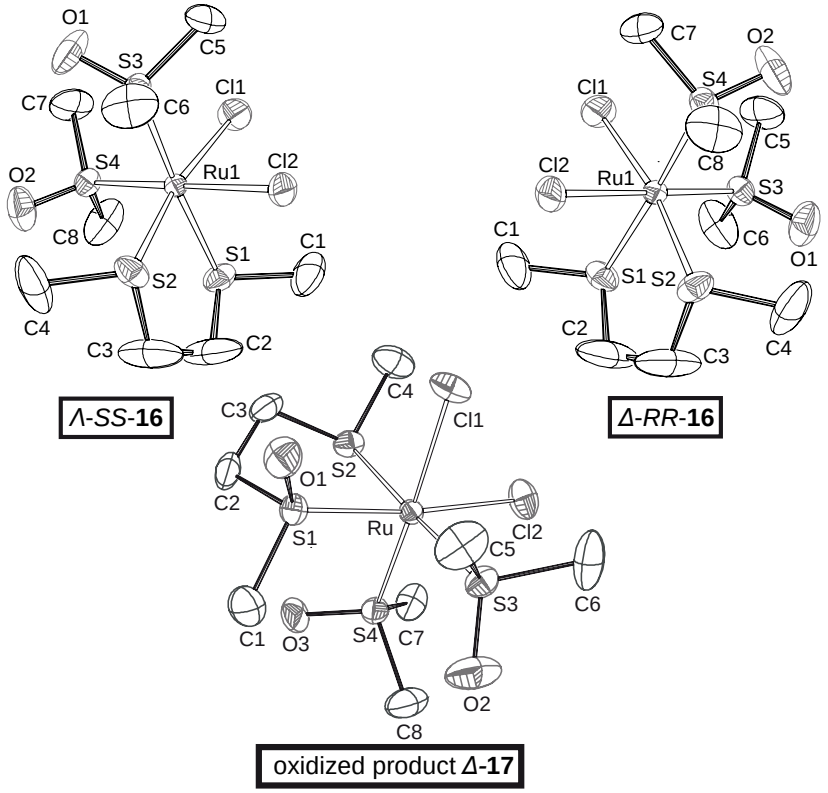



**Figure 37:** Ortep drawings of *Λ-SS*-**16**, *Δ-RR*- **16** and **17**. Hydrogen atoms are removed for clarity and ellipsoids are drawn at the 50% probability level.

The reason why Viedma ripening did not work for any of the complexes cannot be determined with certainty but one reason could have been due to the slow enantiomerization of the complexes. One other reasonable explanation can be the possibility for other stereoisomers in solution. Since the Viedma ripening was not successful at all and TSR worked, no further attempts to find the reasons for why the Viedma ripening failed were made.

That TSR have been successful in the crystallization experiments of the SS-complex **16**, have been shown with HPLC and CD, the *ee* for the whole batch can be determined by using normal-phase HPLC on a Daicel OD column (see figure 38). Good yields with up to 97% *ee* have been obtained. The optical activity of the mother liquor was analyzed so that not merely preferential crystallization has taken place and it was found that CD-signal of the mother liquor was virtually zero.

| Enantiomeric excess (%) | Major enantiomer | Isolated mass (mg) |
|---|---|---|
| 97 | Λ | 36 |
| 90 | Δ | 15 |
| 90 | Δ | 20 |
| 78 | Δ | 71 |
| 74 | Δ | 15 |
| 65 | Δ | 137 |
| 64 | Λ | 42 |
| 60 | Δ | 238 |
| 50 | Λ | 217 |
| 44 | Δ | 20 |
| 40 | Δ | 2.5 |
| 29 | Λ | 20 |
| 20 | Δ | 109 |
| 12 | Δ | 16 |
| 10 | Λ | 14 |
| 0 | - | 89 |
| 0 | - | 45 |

**Figure 38:** All crystallizations performed of **16** where the *ee* has been determined.

Oxidations of **16** were found to take place enantioselective and regioselective. The sulfur atom *trans* to the chloride ion was singly oxidized no matter how much oxidant that was used and the sulfur atom *trans* to dmso was left unchanged. In the oxidation reaction, a mysterious biproduct appeared. It was optically active and the amount was varying with the solvent used. After an intensive study, we finally managed to crystallize this byproduct and found out that it originated in the enantiomerization of the sulfur atom that was not oxidized. So, the oxidation of Δ*RR*-**16** gave the oxidized products Δ*RR*-**17** and it´s diastereomer (Δ*RS*) and the oxidation of *ΛSS*-**16** gave the oxidized products *ΛSS*-**17** and the diastereomer (*ΛSR*). Evaluation of different solvents to be used in the oxidation showed that when using chloroform, it was possible to get high yields and high stereoselectivity (figure 39). The diastereomers could be separated on an achiral semi-preparative HPLC-column and crystals of the oxidized product was obtained after such separation.

| Solvent | *ee* (%) | *de* (%) |
|---|---|---|
| DCM | >97 | 42 |
| Chloroform | >97 | 70 |
| THF | 90 | 44 |
| Methanol | 85 | 0 |
| toluene | 74 | 98 |
| acetone | 47 | 18 |

**Figure 39:** Oxidations of **16** with mCPBA in different solvents.

Analysis of the CD spectrum prior to and after the addition of the oxidant showed that the spectra changed quite intensively du to addition of *m*CPBA (see figure 40). However single crystals of the enantiomers of **16** and **17** were quite similar (see Figure 41). The CD-spectrum of the diastereomers *ΛSR and* Δ*RS* on the other hand differed a lot from the spectrum of **17** (see figure 42).

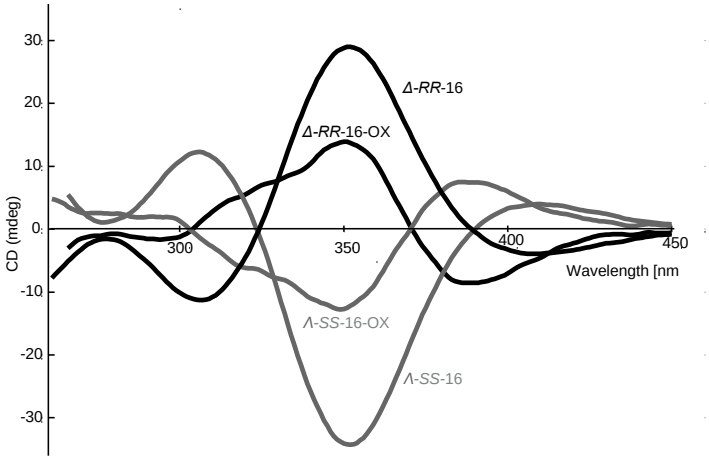



**Figure 40:** CD-spectrum of **16** overlapped with the CD-spectrum for the crude oxidation product.

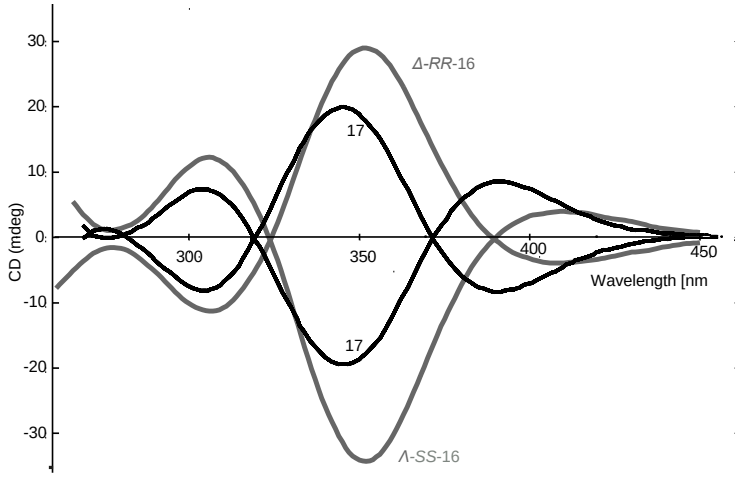



**Figure 41:** CD-spectrum of **16** overlapped with the CD spectrum of **17**.

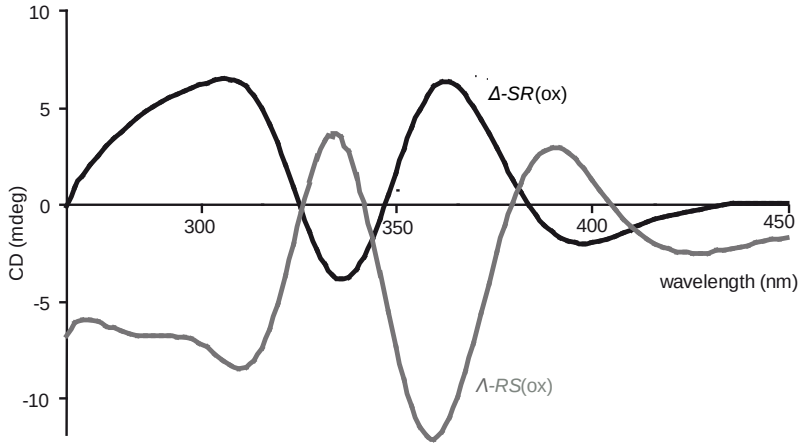



**Figure 42:** Single crystal CD-spectrum of the minor oxidation product.

To conclude, three new conglomerates with bidentate sulfide ligands have been synthesized, isolated and analyzed with CD, HPLC and X-ray diffraction spectroscopy. For all three complexes TSR have been achieved and enantioselective oxidation have been performed to yield the corresponding sulfoxide complex in high yield and *ee*.

## The absolute asymmetric synthesis of a tetrahedral silver complex – paper IV

Tetrahedral (T-4) stereochemistry is a central concept within organic chemistry whereas for inorganic chemistry the tetrahedral stereogenic metal center is almost unexplored.[26a, 89] One reason for this can be the lability of such complexes which makes them enantiomerize, isomerize and exchange ligands rapidly in solution. Analyzing the possibilities of T-4 geometry for metal complexes, several choices to construct them are possible.

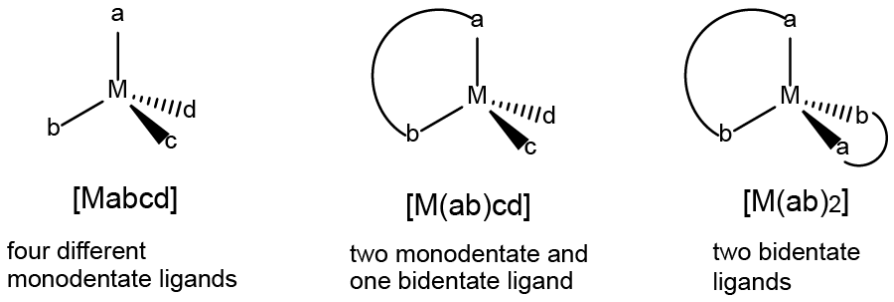



**Figure 44:** Chiral tetrahedral metal complexes.

The first type of complex, [Mabcd], would really be presenting the chemist a challenge, not in the planning as much as in the synthesis. The exchange of ligands between metal centers in this type of complexes is really fast and the chance to end up with several products is imminent. There is no way to predict which complexes that will crystallize and to know what´s in the solution is even harder. Synthesizing a complex such as [M(ab)cd] could be easier especially if one of the ligands is the anion and thus usually bonds harder to the metal center. The lability still presents the possibility of several products and this might not after

all be a good choice. When synthesizing a complex of type [M(ab)(cd)] there is a good chance that no byproducts will form, especially if a non-coordinating anion such as the tetrafluoroborate ion is chosen. Even greater chance of homogeneous product would a complex like [M(ab)$_2$] present. Analyzing the options for synthesizing a complex suitable for resolving the different enantiomers in a T-4 metal complex, the choice fell on a type M(ab)$_2$ complex. That a and b are different is the key to why this complex is chiral and its chirality could be determined according to the oriented skew-line system.[26a] The metal was chosen so that a tetrahedral geometry would be preferred and the ligands so that they would bond strong to the metal. For silver, soft ligands (i.e. containing phosphorous and sulfur atoms) would be good match. The lability of the complex would make it enantiomerize fast and thus be perfect for synthesizing enantiopure batches via TSR and Viedma ripening. The only thing that now was needed was a conglomerate of such complex previously described.

Using a prochiral ligand could present another problem with synthesizing one single product, several diastereomers could be present. Using the PS-ligand (2-(methylthio)ethyl)-diphenylphosphine in combination with silver tetrafluoroborate could in theory produce several stereoisomers (Λ-*R,R*; Δ-*R,R*; Λ-*S*-*S*; Δ-*S,S*; Λ-*R,S* and Δ-*R,S*) but despite this problem, a selective synthesis towards the enantiomeric par, Δ-*R,R* and Λ-*S,S* was found for the complex [Ag(PS)$_2$]BF$_4$ (**18**) . This complex crystallizes as a conglomerate in the chiral space groups $P3_121$ and $P3_221$. The crystal structure for both enantiomers was solved.

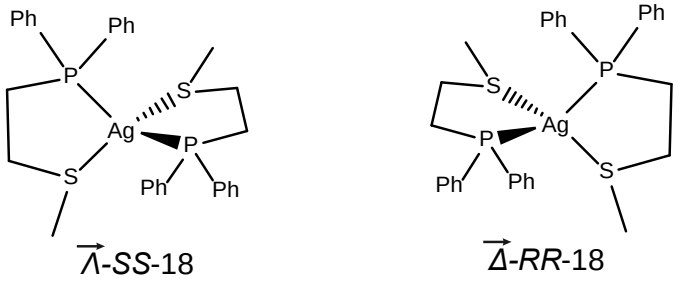



**Figure 45:** The structure of **18**.

The complex **18** adopts a distorted tetrahedral coordination geometry and the two sulfur atoms for the Λ- enantiomer is exhibits the configuration S and for the Δ-enantiomer both are R. Since this complex enantiomerizes immediately after the crystals are dissolved, solutions of this complex lack optical activity. For the analysis of optical activity, solid state CD[90] had to be used. This method can be used for analyzing the *ee* of bulk samples[28, 69] and that AAS was successful via TSR was shown when the CD-signal of a bulk sample was compared with the CD-signal of an enantiopure single crystal (see figure 46) with low Flack parameter[36]. Samples of equal mass were compared and found to have the same magnitude. For the TSR-experiment, a (racemic) solution of **18** in dichloromethane (DCM) was allowed to evaporate slowly. In this way nine crystallizations were made and crystal batches with an average *ee* of 89% were obtained.

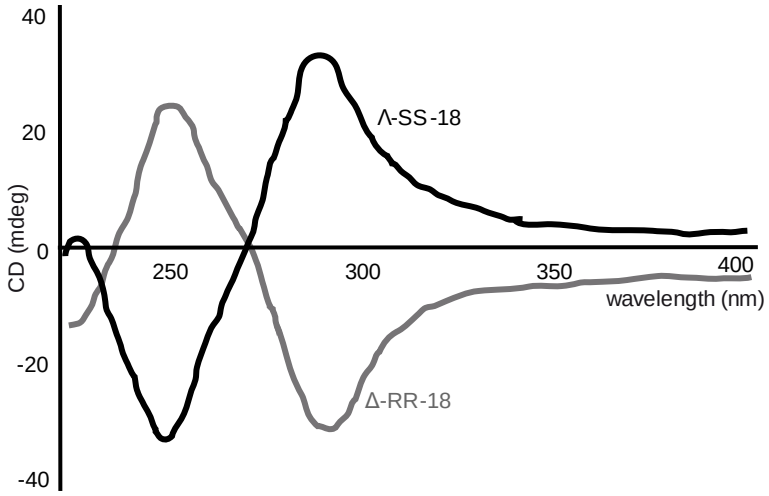



**Figure 46:** Single crystal solid state CD-spectrum of **18.**

Viedma ripening of this complex was successful by grinding a suspension **18**-crystals in toluene with glass balls. The solubility of **18** in toluene was suspected to be very low and was determined to be less than 0,1 mg /ml. The reason for not using DCM was the high solubility of **18** in this solvent (around 1 g/mL), even solutions with a fraction of DCM would have a high content of **18**. Another reason not to mix DCM and toluene and use as medium in the grinding experiments would be that their boiling points and vapor pressures are quite different. A guarantee that the mother liquor contains the same percentage DCM (and concentration) throughout the grinding process cannot be given. A combination of Viedma ripening and crystallization would then occur or at least be possible. Enantiopure sample after Viedma ripening was found to correlate to a difference in magnitude of the CD-signals at 247 and 286 at 33 mdeg for 0.1 mg sample in 100 mg KBr. Several grinding experiments resulted in this magnitude difference (see figure 47). Viedma ripened powder of opposite enantiomers mixed in equal amount, produced after additional grinding, microcrystalline powder with CD-intensity of 33mdeg. Addition of the opposite enantiomer to this powder, temporarily lowered the *ee* but after grinding the signal was approximately 33 mdeg again. The CD intensity can depend on the particle size and the difference in particle size for the Viedma ripened microcrystalline powder and the by hand ground single crystals made the CD-signals for the two different samples incomparable. The mixing experiments is a proof that Viedma ripening has been successful for **18**.

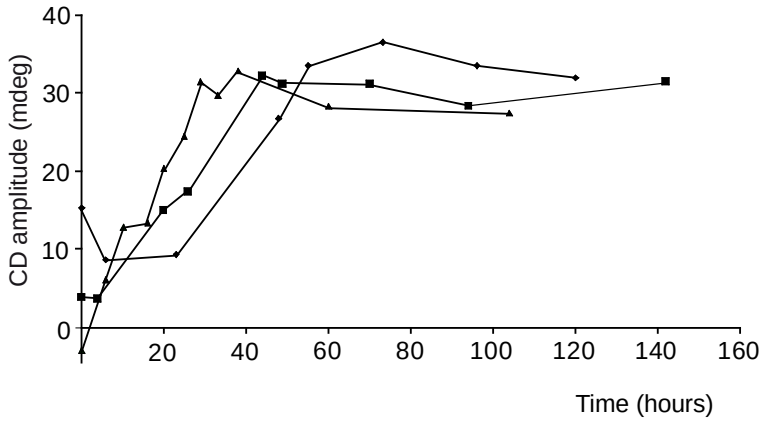



**Figure 47:** Three different Viedma ripening experiments of **18** followed by solid state CD (KBr)

The degree of oversaturation for this system was measured. Evaporating solutions of **18** in DCM was found to have a concentration of 2 mg/ml before crystals started to form. This is double the solubility at equilibrium. Evaporating solutions were also found to display a temperature gradient. Together this might indicate that the crystallizations of **18** were not close to equilibrium.

In conclusion, a T-4 complex have been resolved and enantiopure crystal batches have been obtained via Viedma ripening. Absolute asymmetric synthesis has also been demonstrated with total spontaneous resolution with an average *ee* of 89% over nine crystallizations. The crystal structures of this complex have been solved for both enantiomers.

## 4.3 Viedma ripening of metal complexes (papers IV-VII)

For a handful of compounds where TSR does not give any optically active product, the Viedma ripening has been a route to enantiopure batch product. The only exception from this has been $[Ag(PS)_2](BF_4)$ (**18**) from previous section, that yields optically active product with the two different methods independently.

### Viedma ripening and solvent-free oxidation -paper V

As many projects, this one began with an idea and a search in the Cambridge Structural database (CSD). The idea was that 2,2´-bipyridine (bpy) ligands should be involved in the formation of ridgid chiral complexes. A hope we had was that the database contained conglomerates of some metal-bipyridine complexes. The parameters of the search in the CSD was; Sohncke space group, any metal center, three bipyridine ligands, and one kind of anion in each search. For the hexaflourophosphate anion the results of the search can be seen in figure 48, many known conglomerates, but there were some missing, neither $[Fe(bpy)_3](PF_6)_2$ nor $[Co(bpy)_3](PF_6)_2$ had any hits for conglomerates in the database.

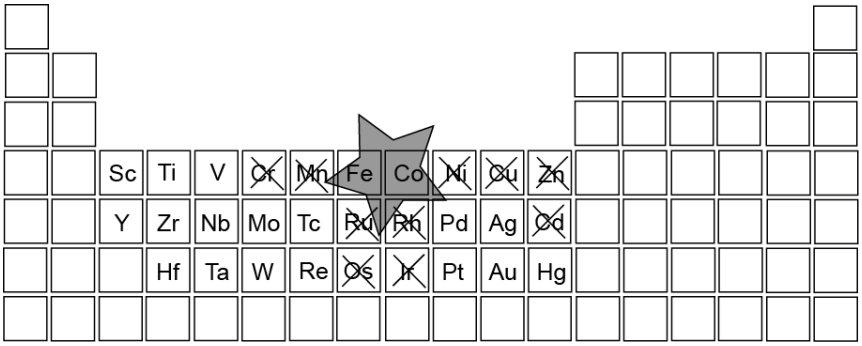



**Figure 48:** The periodic table with previously known conglomerates marked.

Both $[Fe(bpy)_3](PF_6)_2$ and $[Co(bpy)_3](PF_6)_2$ were evaluated in terms of synthesis analysis and utilization. After this assessment the choice fell on $[Co(bpy)_3](PF_6)_2$ to be a substrate in the search for a new conglomerate.

The crystal field theory states that an octahedral complex have two energy levels for the d-orbitals, the lower $t_{2g}$ level with maximum six electrons and the higher $e_g$ level with maximum four electrons.[91] The theory further states that the lower level will be filled first and after that the higher level will be filled. A complex with three or six electrons in only the $t_{2g}$ level will be more inert than a complex than one with 1,2,4 or 5 electrons. A complex with electrons in both levels is also labile. For example, is manganese(II) inert with 2 electrons in the $t_{2g}$ and chromium (III) inert with only three.

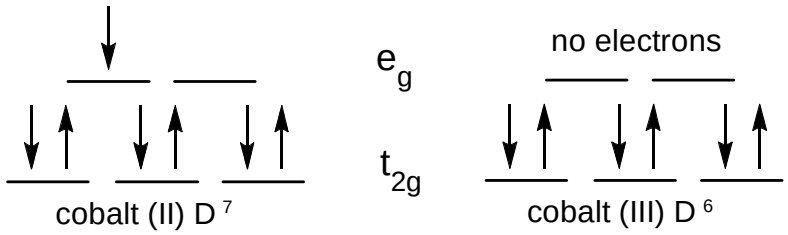



**Figure 49:** Electron configuration of cobalt(II) and cobalt(III) metal complexes.

Since cobalt(II) forms $d^7$ systems, it is likely to center labile complexes ($t_{2g}$ six electrons, $e_g$ one electron). Oxidation to cobalt(III) that is $d^6$ ($t_{2g}$ six electrons) should prevent enantiomerization of the complex in solution (figure 49). This should be a convenient way to fixate the homochirality created in the Viedma ripening or TSR step. The fact that the final product does not racemize makes the optical purity easier to analyze with polarimetry and circular dichroism.

While the synthesis of $[Co(bpy)_3](PF_6)_2$ (**19,** figure 50) is straight forward, the formation of conglomerate crystals is not. For the formation of the complex, a cobalt(II) salt is refluxed with three equivalents of bipyridine in absolute ethanol for one hour and the product precipitated after the addition of $NH_4PF_6$ in water. For the crystallization, many conditions were tried out but the one that yielded conglomerate crystals was to layer a saturated acetone solution with threefold amounts of absolute ethanol.

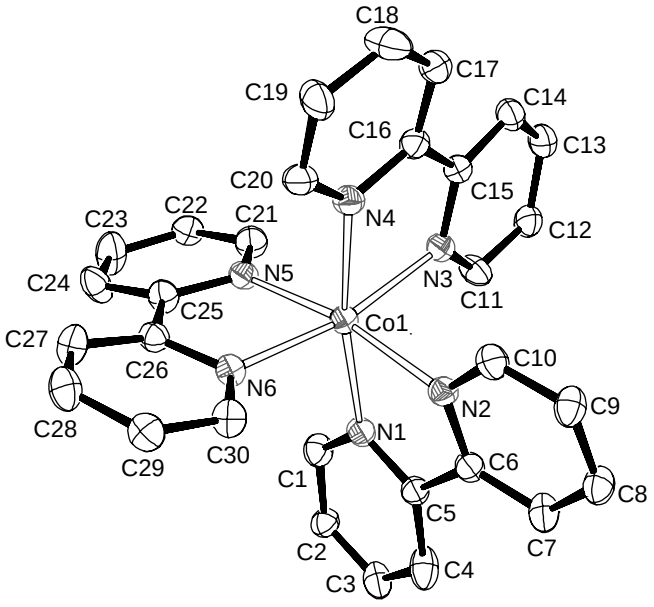



**Figure 50:** Ortep drawing of Λ-**19**. Hydrogen atoms and the $PF_6^-$ anions are removed for clarity and ellipsoids are drawn at the 50% probability level.

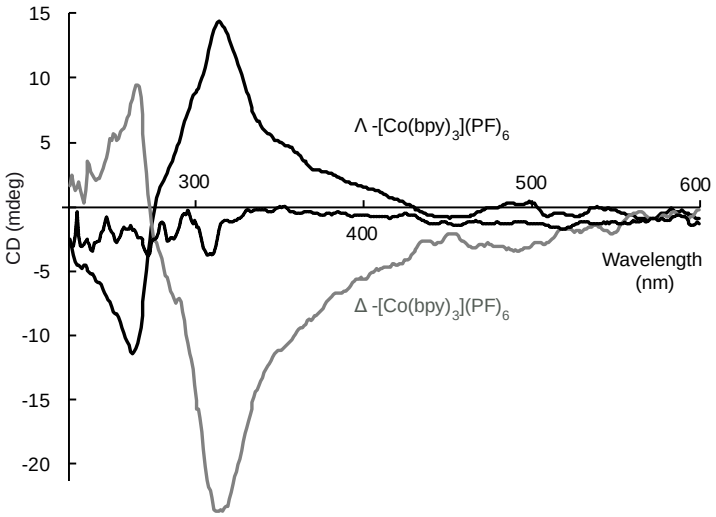



**Figure 51:** Single crystal solid state CD spectrum of **19** compared to a CD-spectrum of the entire batch. The Δ-crystal was slightly bigger and shows therefore a stronger signal.

Less ethanol or slow evaporation yields the acetone solvate or the racemic crystals. TSR was not successful for the crystallization of the chiral crystals this way, maybe this was due to that layering was involved in the formation of the chiral crystals. However, Viedma ripening could be performed with high *ee* (see figure 52) as long as the mother liquors´ composition was at least three to one for ethanol and acetone respectively. If the amount of ethanol was too high, the solubility decreases which results in slower deracemization, if the acetone concentration is too high, the racemic phase forms while grinding.

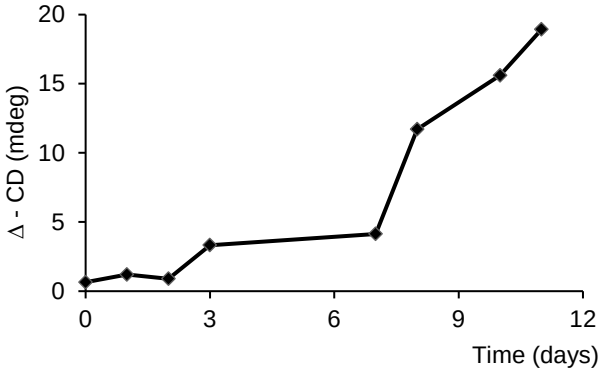



**Figure 52:** The Viedma ripening of **19** followed by solid state CD (KBr) of the cobalt(II) complex.

Determination of the actual *ee* presented a delicate problem, comparison of the CD-signal with the one from a single enantiopure crystal as been done in previous projects was not an option due to the difference in particle size for the Viedma ripened material and the by hand ground single crystal in the KBr-disc. Solution methods as HPLC, ORD, and CD

could not be used due to the quick enantiomerization of the complex. However, if an enantiospecific, solid state reaction that could fixate the chirality could be found, solution methods could be used to measure the enantiomeric excess. The oxidation to cobalt(III) could be such a reaction and initial trials with iodine confirmed this theory. Since the excess of iodine was hard to get rid of and in some cases increased the absorbance of the sample during measurement of the specific rotation leaving, the results non-reproducible, another oxidant had to be found.

Bromine vapor was examined and found to give an enantiospecific and clean solid state oxidation to $[Co(bpy)_3]^{3+}$. After the reaction, the microcrystalline oxidized material was exposed to air and the excess bromine evaporated readily. Comparison of the specific rotation of the samples with literature values[92] showed that the Viedma ripening had been achieved (figure 53) and that enantiopure samples of $[Co(bpy)_3]^{2+}$ and $[Co(bpy)_3]^{3+}$ of either handedness easily can be synthesized.

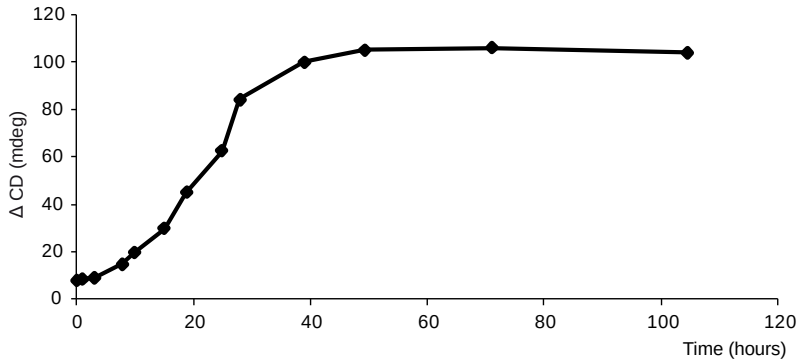



**Figure 53:** The Viedma ripening of **19** followed by CD in solution of the oxidized Co(III) complex ($CH_3CN$).

In conclusion it was found that homochiral batches with either enantiomer of $[Co(bpy)_3](PF_6)_2$ prepared by Viedma ripening can be readily oxidized enantiospecific to cobalt(III). Solvent-free oxidations with solid iodine or bromine vapor as oxidant to form enantiopure, non-racemizing product in quantitative yield have been performed. This combination of Viedma ripening and the labile/inert Co(II)/Co(III) couple constitutes a convenient method of absolute asymmetric synthesis. Solutions of $[Co(bpy)_3]^{3+}$ does not racemize and the optical rotation and CD-signals are unchanged for several months.

**The chiral metal carbonyl complexes and solid state VCD – paper VI**

In the analysis of chiral compounds, circular dichroism-spectroscopy has proven to be a sensitive method that can be performed in the solid stat.[90] The amount needed for obtaining a high-quality spectrum in solution or in a KBr-disc should preferably be less than one tenth of a milligram. For CD-analysis one single crystal is often a sufficient amount of sample. Vibrational circular dichroism (VCD) on the other hand is not as sensitive and is often run in solution or neat liquid[39] Labile compounds that racemize in solution, such as many metal complexes, cannot be analyzed with CD or VCD in solution. For optically active, labile compounds VCD has therefore not been widely used and since VCD it is less sensitive than CD, several milligrams are often needed to get high quality spectra, which often rules out analysis of single crystals.

It is well known that metal carbonyls give rise to strong signals in infrared (IR) spectroscopy.[93] The CO peak(s) of metal carbonyls can typically be found around 1800 - 2000 $cm^{-1}$. Since there are no other signals at that frequency and due to their strength, metal carbonyls should be ideal for VCD-spectroscopy. A search for conglomerates of metal carbonyls began with a goal to test the theory and see if solid state VCD spectra of metal carbonyls were possible to record in the solid state.

A search in the CSD resulted in a hit for a conglomerate of $[Mo(CO)_4PS]$ crystallizing in spacegroup $P2_12_12_1$ published in an article from 1968.[94] Since this was before the Flack parameter[36] was described and no chiral analysis had been done on the crystals this could be a good place to start this project. With the starting materials $[M(CO)_6]$ (M=Cr, Mo, and W) commercially available and a small amount of the PS-ligand left from other projects, the synthesis and subsequent crystallization could begin. In the synthesis of $[Cr(CO)_4PS]$ (**20**) the yield was low and the product consisted of two different complexes together with the chromium hexacarbonyl used as starting material; the conglomerate $Cr(CO)_4PS$ (**20**, figure 54) and the racemic crystals of $[Cr(CO)_2(PS)_2]$(**21**, figure 55). Changed reaction parameters as solvent, reaction temperature or reaction time did not affect the results much and no selective synthesis towards the conglomerate compound was found.

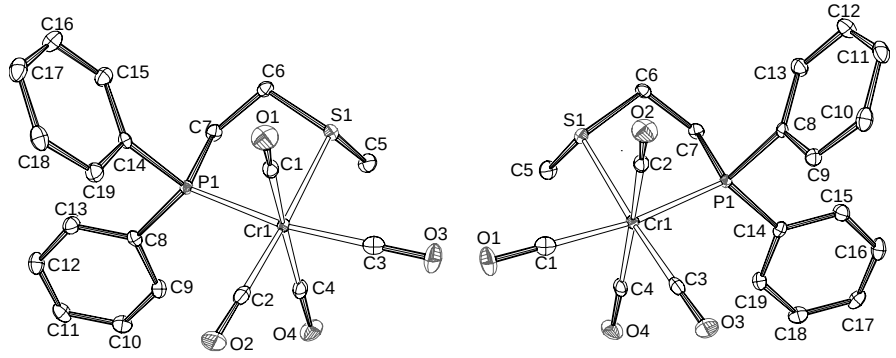



**Figure 54:** Ortep drawing of *S*-**20 and** *R*-**20** Hydrogen atoms are removed for clarity and ellipsoids are drawn at the 50% probability level.

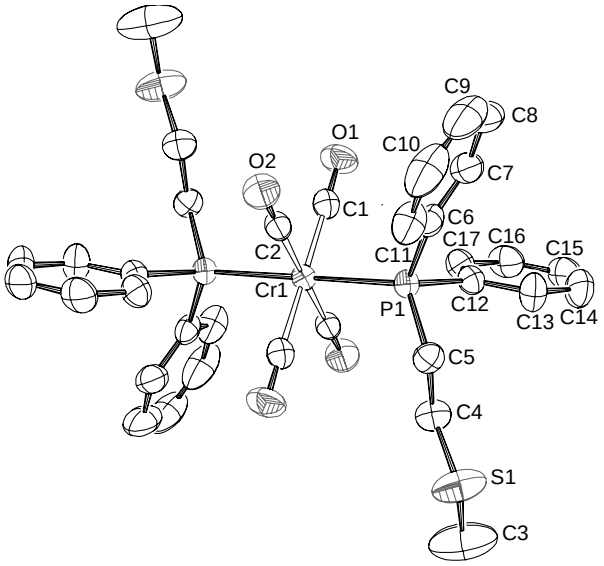



**Figure 55:** Ortep drawing of **21**. Hydrogen atoms are removed for clarity and ellipsoids are drawn at the 50% probability level.

For molybdenum and tungsten on the other hand, a selective synthesis with only one PS-ligand per metal center was found. X-ray diffraction revealed that these complexes were isomorphic with (**21**) and thus also conglomerates. The Flack parameter for the single crystals of [$Mo(CO)_4PS$] (**22**, figure 56) and [$W(CO)_4PS$] (**23**, figure 57) indicated that all crystals (>10) analyzed with X-ray diffraction were enantiopure. The chirality in the complexes **20**, **22** and **23** comes from the binding of the prochirogenic sulfur atom of PS and the enantiomers are therefore denoted *R* or *S*.

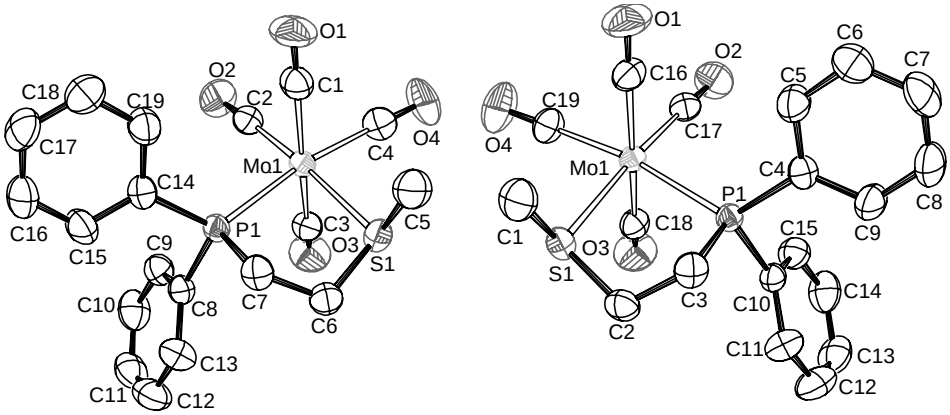



**Figure 56:** Ortep drawing of *S*-**22** and *R*-**22**. Hydrogen atoms are removed for clarity and ellipsoids are drawn at the 50% probability level.

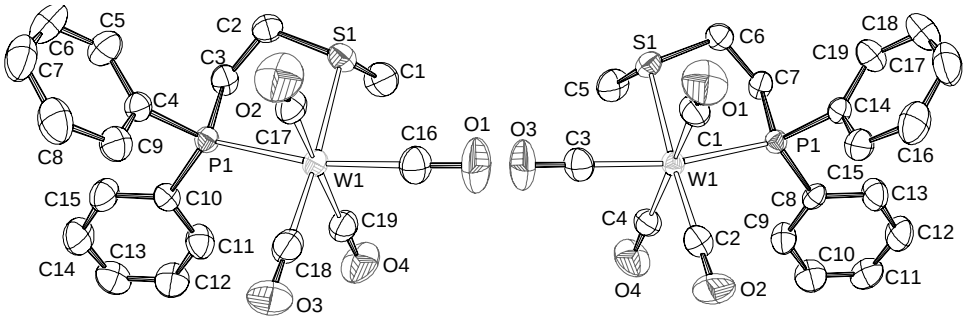



**Figure 57:** Ortep drawing of *S*-**23** and *R*-**23**. Hydrogen atoms are removed for clarity and ellipsoids are drawn at the 50% probability level.

CD-spectroscopy of **22** and **23** showed no signals for measurements of single crystals in solution even at low temperatures. Solid state CD-spectroscopy of single crystals in KBr-discs however was found to show a Cotton effect for enantiomers of both complexes (figure 58 and 59). The conclusion that the enantiomerization in solution is very fast for **22** and for **23** was made and experiments with VCD in the solid state could now start.

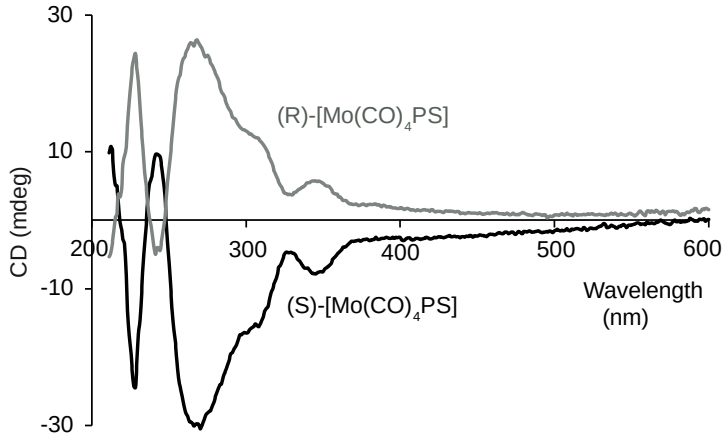



**Figure 58:** Single crystal solid state CD of *S*-**22** and *R*-**22**.

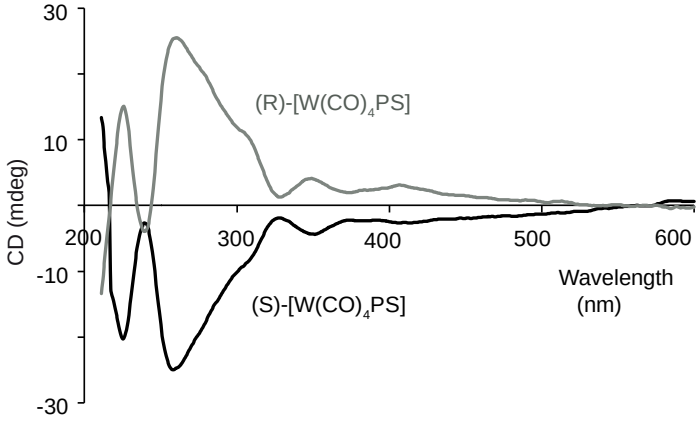



**Figure 59:** Single crystal solid state CD of *S*-**23** and *R*-**23**.

Solid state VCD was found to work very well on these complexes, and as expected the VCD-signals were strong in the carbonyl region round 1800 $cm^{-1}$. High quality spectra in this region can be obtained with as little sample as one tenth of a milligram in only 2 hours (figure 60 and 61). After only 20 minutes of measurement the spectra are usually good enough and without errors. This means that the amount of sample is comparable with CD-spectroscopy and the same KBr-disc have been used on both instruments.

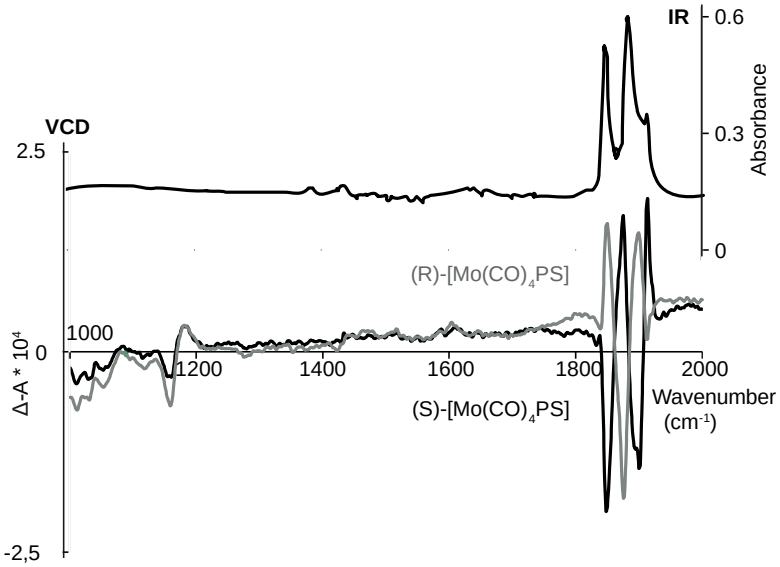



**Figure 60:** Single crystal solid state VCD of *S*-**22** and *R*-**22**. (0,1mg sample, 100mg KBr)[95]

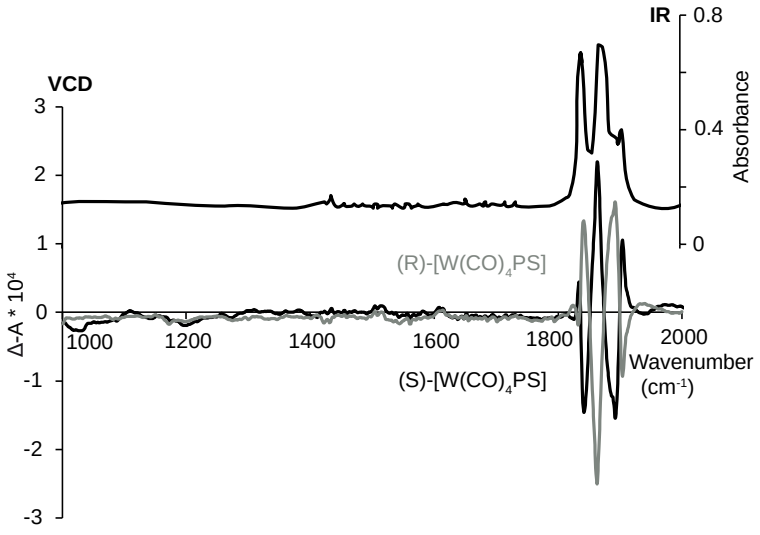



**Figure 61:** Single crystal solid state VCD of *S*-**23** and *R*-**23**. (0,1mg sample, 100mg KBr)[95]

Usually VCD-signals are recorded along the whole IR-region from 1000 to 3000 $cm^{-1}$. The carbonyl region is only a fraction of the whole spectrum and the low sensitivity of the VCD-spectrometer demanded more enantiopure sample if measurements for rest of the spectral

range should be made. Unfortunately, all experiments aiming at total spontaneous resolution were fruitless and all trials resulted in racemic batch product for either of the complexes **22** and **23**. Even seeding with an enantiopure crystal was not a successful route to enantiopure product. Viedma ripening however was found to work excellently for these complexes (figure 62) and enantiopure samples of any of the enantiomers for **22** and **23** have been synthesized. The enantiopure powder was used in VCD-spectroscopy in the region 1000-1500 $cm^{-1}$ (see figure 63). For these measurements, several milligrams had to be used. For the CO-region with this amount of sample, the noise was to large due to high absorbance and no signals could be seen.

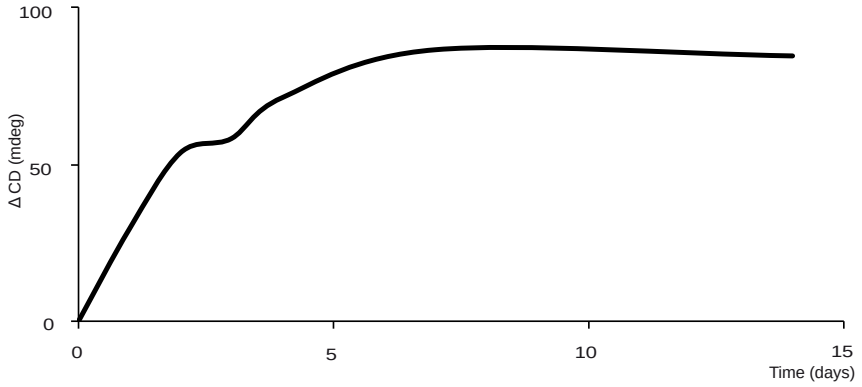



**Figure 62:** The Viedma ripening of **23** followed by solid state CD.

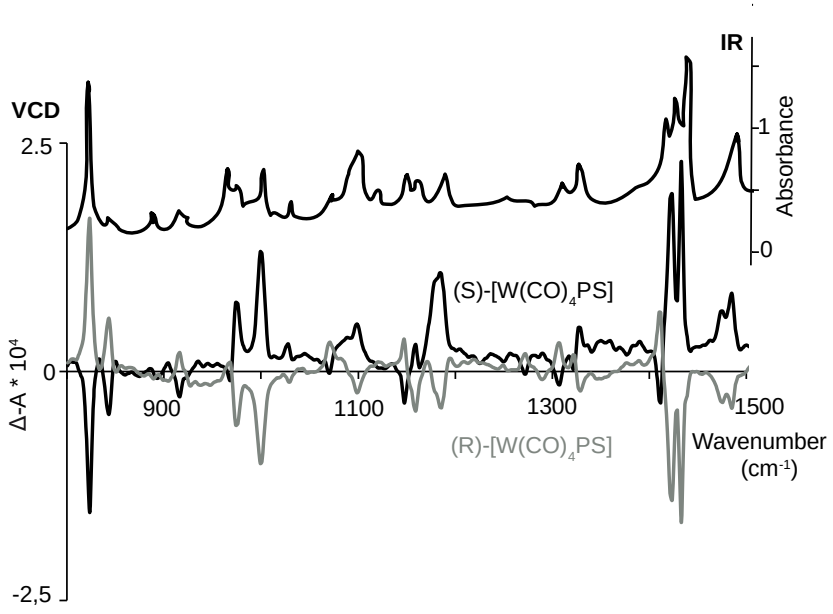



**Figure 63:** Solid state VCD spectrum of **23** (2 mg sample/ 100mg KBr)[95] .

In conclusion, the crystal structures of the compounds $[Cr(CO)_4PS]$, $[Cr(CO)_4(PS)_2]$ $[Mo(CO)_4PS]$ and $[W(CO)_4PS]$ have been reported. These compounds crystallize as conglomerates in the orthorhombic space group $P2_12_12_1$ and racemize very fast in solution.

From racemic mixtures have enantiopure batches of both enantiomers of **22** and **23** been obtained via Viedma ripening. VCD-spectra in the carbonyl region with samples as small as a tenth of a milligram have been recorded in the solid state for single crystals in as short time as 20 minutes.

### Grinding achiral $[Cu(NO_3)_2(mtp)_2]$ crystals to enantiopurity – paper VII

The crystallization of $Cu(NO_3)_2 \bullet 3H_2O$ in neat 2-(methylthio)pyridine (mtp) can yield a handful of different compounds. However, if the concentration of the copper salt in the ligand is high and the reaction temperature is kept high during synthesis (boiling mtp, 197°C) this can be a way to synthesize the achiral phase of *trans*-$[Cu(NO_3)_2\ (mtp)_2]$ (**24**) selectively. These crystals are easy to distinguish from the conglomerate phase *cis*-$[Cu(NO_3)_2(mtp)_2]$ (**25)** with the aid of a microscope by shape. The achiral crystals are thinner and rectangular in shape whereas the chiral crystals are rhombic prisms and often darker green because of its thickness. If the achiral crystals of **24** are allowed to stand for several months in the mother liquor they will transform to the conglomerate phase of **25**. Synthesis with less saturated solutions can yield a whole set of different compounds where in some of them, the copper(II) has been reduced to copper(I). This is also the occasion if alcohols are being used as a solvent in the synthesis, the solutions and the precipitates become colorless.

The achiral **24** (figure 64) and the enantiopure **25** (figure 65) have both been characterized with single crystal X-ray diffraction.

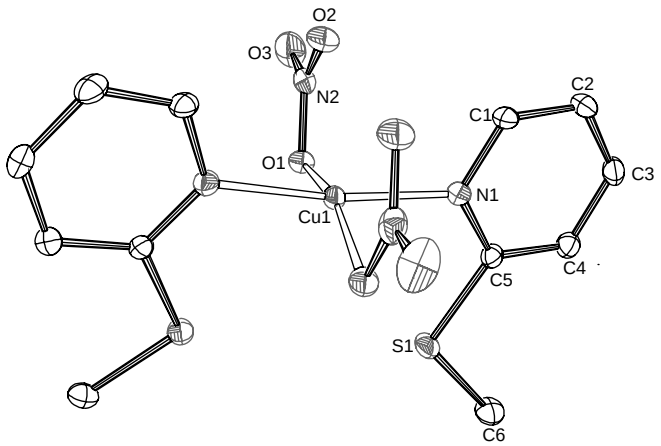



**Figure 64:** Ortep drawing of the achiral **24**. Hydrogen atoms are removed for clarity and ellipsoids are drawn at the 50% probability level.

Binding a prochiral sulfide such as mtp to a metal center usually yields a chirogenic sulfur atom, this is not the case with **24** and **25**. The explanation for this is that the sulfur atom is too far away from the metal and is therefore not properly bonded to it. The ligand acts merely as a monodentate pyridine ligand in the copper complexes **24** and **25**. The chirality

of the complexes derives instead from the bidentate bonding of the nitrate anions making the complex distorted octahedral and thus can the chirality be described as Δ or Λ.

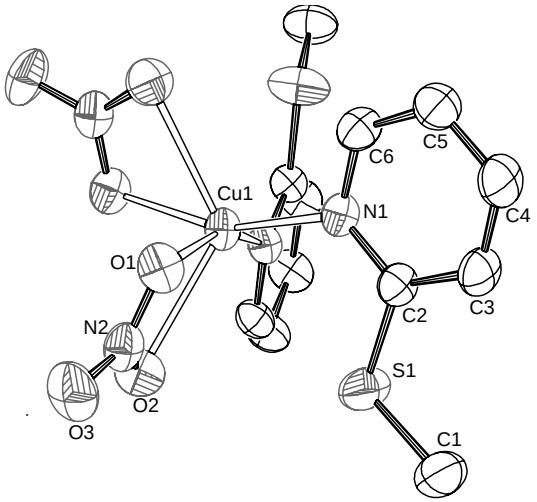



**Figure 65:** Ortep drawing of Λ-**25**. Hydrogen atoms are removed for clarity and ellipsoids are drawn at the 50% probability level.

The crystals and other solid material of the copper complexes **24** and **25** are badly smelling and decompose in air with loss of the ligands. Single crystals will decompose within days and ground powder within hours outside the mother liquid (neat mtp). Solid state CD of **25** therefore has to be performed quickly and extensive grinding or ball milling is out of the question because the signal will start to disappear before the KBr-disk is mounted on the CD-instrument. However fast and intensive grinding by hand followed by immediate pressing of the disc, reveals that **25** displays a Cotton effect.

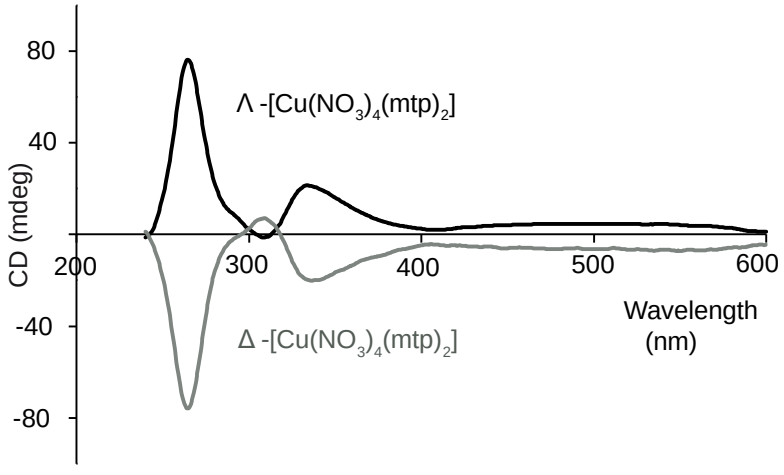



**Figure 66:** Solid state single crystal CD spectra of Λ-**25** and Δ-**25**. (0,1 mg sample in 100 mg KBr).

Keeping the analyzation time below one hour made it possible to record solid state VCD-spectrum in KBr of Λ-**25** and Δ-**25**. After that time the signals in some of the analyzed samples started to decrease.

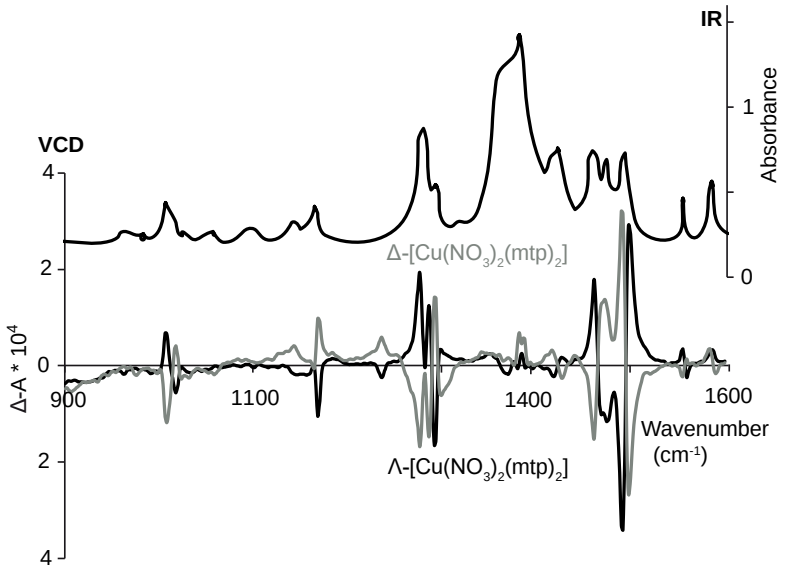



**Figure 67:** Solid state VCD spectra of Λ-**25** and Δ-**25**. (0,7mg sample, 100mg KBr)[95].

Viedma ripening has been successful for this complex starting from the conglomerate phase (**25**), a mix of the two phases and as well as starting from the achiral phase (**24**). For the latter experiments several crystal batches were inspected under a microscope and manually sorted so that the starting point for the deracemization were 100% crystals of the achiral phase. Single crystals selected by random were X-rayed and no chiral crystals were found. The low solubility of the complex in the ligand at room temperature resulted in a longer reaction time than for other complexes and complete deracemization was obtained within two-three weeks. The times were approximately the same for all performed Viedma ripening experiments.

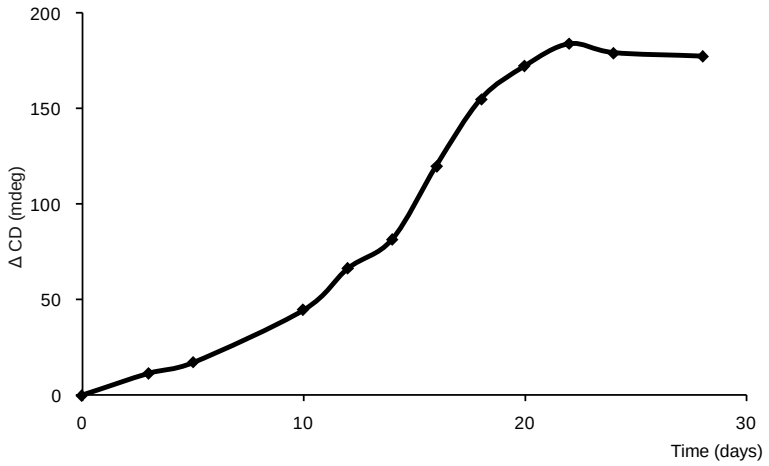



**Figure 68:** The Viedma ripening of **25** followed by solid state CD.

In conclusion, two new phases of $[Cu(mtp)_2(NO_3)_2]$ have been synthesized and characterized with single crystal X-ray diffraction, IR, CD and VCD. Enantiopure batches have been obtained for **25** via Viedma ripening starting from the achiral **24**.

# 5

# Conclusions

In total, twenty-four new metal complexes have been synthesized, isolated and characterized with single crystal X-ray diffraction. Eleven of them are conglomerates.

Total spontaneous resolution has been demonstrated for several metal complexes in good yield and high *ee*.

Viedma ripening has produced enantiopure batches of four metal complexes.

Solid state VCD has been used to record high-quality spectra of metal carbonyls in short time with a small amount of sample.

The enantiomerization rate of metal complexes has been reduced significantly with stereoselective oxidative reactions.

Evidence indicating that the mechanisms for Viedma ripening and total spontaneous resolution could be similar has been presented.

# 6

# Future outlook

Since the mechanism of Viedma ripening in not fully understood, it would be interesting to develop experimental methods to examine it. Mechanistic knowledge might help everybody in the planning of new Viedma ripening experiments.

Enantiopure catalysts used in asymmetric catalysis are expensive and in some aspects hard to come by. Producing them via Viedma ripening would therefore be a valuable utilization of the technique. One interesting idea would be to synthesize non-optically active precursors to such (metal) catalysts used today. They should be crystallized as conglomerates and after Viedma ripening or TSR, transformed enantiospecific to the optically active catalyst.

The formation of conglomerates is one thing that is not fully investigated. With high precision, predict whether a compound will crystallize as a conglomerate or not cannot be done today. More research of the factors behind conglomerate formation is needed. A long-term project would therefore be to crystallize themes of compounds and draw conclusions from the results. Crystallizing the same compound in many different conditions until the conglomerate phase is discovered is also one thing that would be interesting to examine.

# Acknowledgement

Professor **Mikael Håkansson**, min handledare, förtjänar ett stort tack för allt tålamod och stöd samt för att du tagit emot mig som doktorand, din hjälp har varit ovärderlig. Dina (ibland vilda) idéer har lett mig till stordåd.

I also would like to thank **Christine McKenzie** for your help with this work. Thanks to you my trips to Denmark have been light and productive.

**Dr Andres Lennartson**, tack för ditt stöd, hjälp och våra diskussioner som rört det mesta här i livet. Den laborativa och teoretiska expertis du gladeligen delat med dig av de senaste 12 åren har varit mycket värdefull.

**Dr Susanne Olsson**, tack för att kontoret varit en plats med högt i tak och tack för alla diskussioner som oftast lett projekten till nya nivåer.

**Dr Jonas Sundberg**, från det att vi lärt känna varandra under masterstiden och framåt har dina synpunkter varit upplysande, du behärskar det mesta från bloggvärden till vetenskaplig metod och teori.

**Dr Johan Eriksson** tackas för stöd i labbet och gott sällskap.

Mina examensarbetare: **M.Sc. Staffan Persson, M.Sc. Johan Jönsson, M.Sc. Elham Rastighasrodashti och M.Sc Mikael Bjurström.** Jag har uppskattat all hjälp och samarbete i labbet. Tack också för trevligt sällskap.

Jag vill också tacka mina medförfattare till samtliga publikationer för gott samarbete,

Alla mina samtida doktorander vid institutionen för kemi och senare KMB såsom **Dr Tina Seifert, Dr David Bliman, Dr Marielle Pettersson, Dr Mario Janjetovic, Emma Danelius och Alexei Cravenko**, förtjänar ett särskilt tack för givande diskussioner, fester och trevligt sällskap.

Övriga som vistats på plan 8 (och 9) såsom examensarbetare, postdocs, lektorer, professorer mm tackas för en bra doktorandtid.

My african coworkers, you know who you are. Thank you for our discussions.

Mina danska vänner **David** och **Christina**, tusen tack för labtid, diskussioner om kristallisation, kemi i allmänhet och allt annat som förgyllt mina veckor i Odense.

**Dr Marcus Malo** förtjänar ett stort tack för alla stunder på slaskens matinrättning, alla skratt och diskussioner.

**Fil. Lic. Tommie Lindahl** för en introduktion till allt som gäller kristallisation. Stora perfekta enkristaller kan trots allt inte bara växa ifrån övermättade lösningar av alun.

**Roland Aronsson** tackas för dina många kemiexperiment under grundskolan. Redan i årskurs 7 demonstrerade du under våra första lektioner skönheten hos kristaller. Det är nu utom tvivel fastlagt att små, korta, enkla, laborativa demonstrationer kan skapa intresse som leder till vetenskapliga framsteg i framtiden.

Med risk för att vissa får ett dubbelt tack vill jag även tacka morgonkaffeklubbens deltagare för en god start på dagen. Att vissa av oss varit morgonpigga (mer eller mindre) har lett till en tidig start med dagens nya upptäckter av världsklass och en bit på vägen med lösningen av en hel del världsproblem.

Jag vill slutligen tacka min familj, utan ert stöd hade knappast detta projekt rotts i hamn. Karin, tack för att du stått ut med min frånvaro från hemmet. Arvid Wilhelm och Alva. Förlåt för all tid spenderad någon annanstans. Tack också för allt sällskap i labbet och vid diffraktometern. Den känner sig nog ensam nu.

Mot framtida stordåd, oktober 2017

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