Towards the synthesis of chiral dinuclear gold(I) complexes to act as catalysts in asymmetric hydrogenation of α,β-unsaturated carboxylic acids

Anita Hoang
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Supervisor: Dr. Ebbe Nordlander
Examiner: Prof. Ola Wendt
Lund University
Institution of Chemistry
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1. Abstract
Dinuclear gold(I) complexes bearing the Walphos ligands (R)-1-\{(RP)-2-[2-(Diphenylphosphino)phenyl]ferrocenyl\}ethylbis[3,5-bis-(trifluoromethyl)phenyl]phosphine (W001) and (R)-1-\{(R_P)-2-[2-[Bis(4-methoxy-3,5-dimethylphenyl)phosphino]phenyl]ferrocenyl\}ethylbis[3,5-bis(trifluoromethyl)phenyl]phosphine (W005) have been synthesized and tested as catalysts for asymmetric hydrogenation of (E)-2-methyl-butenoic acid (tiglic acid) and (E)-2-methyl-2-pentenoic acid. Good conversion rates (> 70 %) and selectivities (> 80 %) were observed. Attempts to optimize the catalysis experiment showed indication that the gold catalyst is solvent sensitive. It was also observed that the reproducibility was poor for both the gold catalysts.

2. Introduction
2.1 Gold in catalysis research
For a long time gold has been underrated in catalysis research due to the assumption that gold is chemically inert and lacks catalytic activity. However, in the last decades gold has been “rediscovered” and the interest in gold has gained popularity in this research field,\(^1\) since new findings by Ito\(^2\) and Hashmi\(^3\) have shown that gold actually possesses high catalytic activity and provides good enantioselectivity. It has been proven that tetrachloroauric acid on active charcoal is a highly efficient catalyst for hydrochlorination of ethyne\(^4\) and some researchers have also reported the use of gold as a Lewis acid catalyst\(^{5, 6}\).

Even though gold has proven to be a highly efficient catalytic metal, there are still only few articles that have reported the use of chiral gold complexes in asymmetric synthesis. Pradal et al\(^7\) have reported the use of gold complexes as a chiral catalyst in various asymmetric syntheses in a review article. Surprisingly, only one asymmetric hydrogenation has been reported. The result presented by Corma et al\(^8\) demonstrated that chiral dinuclear phosphine-gold(I) complexes are good catalysts for asymmetric hydrogenation. They also reported that substrates with bulky substituents tend to give higher enantiomeric excess \((e.e)\). These new findings have inspired our further investigations of gold complexes as chiral catalyst in asymmetric hydrogenation.

2.2 Asymmetric synthesis\(^9, 10\)
All living organisms are chiral, and so are humans even though we look quite symmetrical in a mirror. We can distinguish the smell of orange from the smell of lemon already at young age. This is quite remarkable, since the only difference between the molecule that gives rise to the
smell of orange from the analogous molecule for lemon is that they are optical isomers (in this case, mirror images) of the same molecule, limonene. \((R)-(+)\)-Limonene smells rounded and orangey and \((S)-(−)\)-Limonene is sharp and lemony. This is also true for the molecules that are the origins of the smell of spearmint and the smell of caraway seeds, which arise from \((S)\)- and \((R)\)-carvone respectively (Figure 1).

Enantiomers are only chemically identical in an achiral environment, but placed in a chiral environment like the human body, their three-dimensional structure will give the molecules their own identity, which is the reason that we can distinguish the enantiomers. This concept will be of great importance in enantioselective synthesis.

The distinction between enantiomers is clearly of great importance. In drug manufacturing, making the correct enantiomer can be a matter of life and death. For example, Parkinson’s disease is treated with the non-proteinogenic amino acid dopa that is a chiral molecule. Only \((S)\)-dopa is effective in restoring nerve function while \((R)\)-dopa is quite toxic and ineffective (Figure 2).

There are several methods to obtain enantiomerically pure compounds. Nearly all methods rely on the principle that enantiomers have different properties in a chiral environment. A pro-chiral molecule that reacts with an achiral reagent or catalyst that results in the formation of both enantiomers will have equal transition energies for the two isomers because the transition states are themselves enantiomeric. Figure 3a below shows enantiomeric transition states leading to a racemic mixture.
When placing a pro-chiral molecule in a chiral environment, the transition energy leading to a scalemic mixture will be different in energy because the transition states are diastereoisomeric. Figure 3b above shows diastereoisomeric transition states that lead to a scalemic mixture.

To achieve diastereisomeric transition states, the pro-chiral substrate must interact with a chiral molecule (reagent or catalyst) in such a way that it controls the formation of the new stereogenic center. This can be achieved by having a chiral catalyst present. Figure 4 below shows a schematic representation of an asymmetric reaction cycle.

2.3 Gold(I) complexes

The general structure of Au(I) complexes are linear and of the type $L \cdot Au \cdot X$, where $L$ is a π-donor ligand such as PR₃, R₂S, CO etc. and $X$ is a halogen or pseudohalogen. Gold is considered to be a soft metal with preference for soft ligands containing P, As and S donor atoms. A reliable method to obtain stable linear complexes is by using a tertiary phosphine to reduce Au(III) in ethanol (Figure 5).

$$R_3P + HAuCl_4 \rightarrow R_3P \cdot Au \cdot Cl$$

Figure 5 General reaction scheme to synthesize gold(I) complexes
2.4 Chiral ligand
Chiral catalysts are mainly transition metal complexes with chiral ligands. The role of the chiral ligand is of great importance since the ligand is responsible for the transmission of the chiral information to the substrate\[^{[12]}\]. Common ligands used in this kind of catalyst are chelating phosphines. The chirality can be achieved through ligands that possess a chiral center, and/or atropisomers, such as BINAP and Walphos ligands, that possess axial chirality. The Walphos ligands also exhibit chirality through the ligand backbone.

Walphos ligands are a novel class of ferrocenyl-aryl-based diphosphine ligands that have been shown to be efficient ligands in asymmetric synthesis\[^{[13]}\]. Nordlander et al\[^{[14]}\] have also reported that ligands of the Walphos family also possess inherent catalytic activity. This proves that Walphos ligands can be catalysts/catalyst precursors themselves and therefore give strong chiral induction (Figure 6).

![Image of Walphos ligands](image)

Figure 6 (a) The Walphos ligand W001, (R)-1-([RP]-2-[2-{Diphenylphosphino}phenyl]ferrocenyl)ethylbis[3,5-bis-(trifluoromethyl)phenyl]phosphine (b) Ligand W005 (R)-1-([RP]-2-[2-{Bis(4-methoxy-3,5-dimethylphenyl)phosphino}phenyl]ferrocenyl)ethylbis[3,5-bis(trifluoromethyl)phenyl]phosphine

Herein is presented the syntheses of dinuclear gold(I) complexes complexed with the chiral ligands W001 and W005 of the Walphos family (Figure 6). The chiral gold catalysts are used for the asymmetric hydrogenation of \(\alpha,\beta\)-unsaturated compounds.

3. Result and Discussion

3.1 Synthesis\[^{[15]}\]
\([\text{Au}_2\text{Cl}_2(\text{W001})]\) (1) and \([\text{Au}_2\text{Cl}_2(\text{W005})]\) (2) were synthesized by adding a solution of tetrachloroauric acid in ethanol to a solution of W001 or W005 in dichloromethane in a 1:1 ratio. The ferrocene-based diphosphine ligand reduces Au(III) to Au(I) at room temperature and under an atmosphere of nitrogen. In each reaction, two complexes were formed. Purification by preparative TLC yielded 1 (56%) and 2 (36%), respectively, as orange solids (Figures 7 and 8) and in each reaction a minor product in both reactions (for each reaction?) that was not fully characterized.
In each case, the main product is a dinuclear gold complex that consists of the diphosphine ligand coordinated by each of its phosphine moieties to a separate Au-Cl moiety. The $^{31}$P NMR spectrum of 1 showed peaks at $\delta$ 24.12 and 39.67 ppm corresponding to the two phosphorus atoms. The $^{31}$P NMR spectrum of 2 showed also two peaks $\delta$ 22.09 and 38.04 ppm, in agreement with the proposed structure. Further confirmation of the structure of 1 and 2 were obtained from mass spectrometry data. An ion corresponding to [Au$_2$Cl(W005)]$^+$ was observed at $m/z = 1475$ (100 %) and an ion corresponding to [Au$_2$Cl(W001)]$^+$ was observed at $m/z = 1359$ (25 %). The $^1$H NMR spectra for complex 1 and 2 are very hard to interpret because of the size and the complexity of the molecule. But important structural information can be deduced by comparing the spectrum of the complex and the spectrum of the free ligand$^{[13]}$. The cyclopentadiene protons (ferrocene) give rise to signals between $\delta$ 3.28 – 4.11 ppm and the phenyl protons give rise to signals between $\delta$ 6.91 – 7.98 ppm for the free ligand. Signals near these regions can be observed for complex 1 and 2 as well which indicates the existence of the ferrocene moieties and the phenyl protons in complex 1 and 2.

The minor product was also of orange color and the $^{31}$P NMR showed four peaks $\delta$ 31.69 (d, $J = 13.0$ Hz), 28.95 (s), 25.29 (d, $J = 14.2$ Hz), 23.68 (d, $J = 13.6$ Hz). The mass spectrum of the minor product showed a peak at $m/z = 2396$ (100 %) might consistent with the dimer of complex 2 with the lost of a fragment that have a molecular mass of 178 $m/z$. The minor product was not of interest in this investigation and was therefore not further investigated.

Unfortunately no crystals for X-ray diffraction were obtained for 1 and 2. The proposed structures are based only on the results of $^{31}$P NMR and $^1$H NMR spectroscopy and mass spectrometric analysis and on the knowledge that gold(I) complexes have linear structures in general.

![Figure 7 Schematic presentation of the reaction route to complex 1](image-url)
3.2 Catalytic experiment\cite{8}

There are only a few reported asymmetric hydrogenations with a chiral gold complex as catalyst.\cite{7,8} In order to investigate the catalytic activity of the prepared gold(I) complexes, asymmetric hydrogenation of tiglic acid (3) and (E)-2-methyl-2-pentenoic acid (4) (Figure 9) in the presence of gold complexes 1 and 2 was examined. The results are presented in Table 1 below.

It was found that gold catalyzes the hydrogenation of tiglic acid in ethanol under mild conditions. Good conversion was achieved when the reaction was performed at room temperature and a hydrogen pressure of 15 bar was used. It was found that within 2 hours, 72 % of substrate 3 and 44 % of substrate 4 had converted to 2-methylbutanoic acid (3a) and 2-methylpentanoic acid (4a), respectively, when gold complex 2 was used as the catalyst. When the reaction was repeated again, it was found that only 32 % substrate 3 had converted to 3a. Catalyst 2 gave higher catalytic activity than catalyst 1. It was found that 83 % of substrate 4 had converted to 4a, which is also the best result in this investigation. However, bad conversion was achieved when complex 1 was used in the hydrogenation of substrate 3.

The drawback is that the reproducibility was poor. This behavior of dinuclear gold complexes has not been reported before. Further investigations must be carried out before any reasonable explanation can be given.
Table 1 Summarized results of the catalysis experiments

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Substrate</th>
<th>Temp.</th>
<th>Reaction time</th>
<th>Pressure</th>
<th>Solvent</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>R.t</td>
<td>2 h</td>
<td>15 bar</td>
<td>EtOH</td>
<td>72 %</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>3</td>
<td>R.t</td>
<td>2 h</td>
<td>15 bar</td>
<td>DCM</td>
<td>24 %</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>3</td>
<td>R.t</td>
<td>24 h</td>
<td>15 bar</td>
<td>EtOH/Tol 1:1</td>
<td>2.7 %</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>3</td>
<td>R.t</td>
<td>2 h</td>
<td>5 bar</td>
<td>EtOH/Tol 1:1</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>3</td>
<td>50 °C</td>
<td>2 h</td>
<td>25 bar</td>
<td>EtOH/Tol 9:1</td>
<td>7.4 %</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>3</td>
<td>R.t</td>
<td>2 h</td>
<td>15 bar</td>
<td>EtOH</td>
<td>32 %</td>
</tr>
<tr>
<td>7</td>
<td>Blanc</td>
<td>3</td>
<td>R.t</td>
<td>2 h</td>
<td>15 bar</td>
<td>EtOH</td>
<td>Traces</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>3</td>
<td>R.t</td>
<td>1 h</td>
<td>15 bar</td>
<td>EtOH</td>
<td>11 %</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>3</td>
<td>R.t</td>
<td>4 h</td>
<td>15 bar</td>
<td>EtOH</td>
<td>19 %</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>4</td>
<td>R.t</td>
<td>2 h</td>
<td>15 bar</td>
<td>EtOH</td>
<td>44 %</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>3</td>
<td>R.t</td>
<td>2 h</td>
<td>15 bar</td>
<td>EtOH</td>
<td>14 %</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>4</td>
<td>R.t</td>
<td>2 h</td>
<td>15 bar</td>
<td>EtOH</td>
<td>83 %</td>
</tr>
<tr>
<td>13</td>
<td>1</td>
<td>4</td>
<td>R.t</td>
<td>2 h</td>
<td>25 bar</td>
<td>EtOH</td>
<td>26 %</td>
</tr>
</tbody>
</table>

The crude catalysis mixtures were analyzed by $^1$H NMR spectroscopy directly after a catalysis experiment to evaluate the conversion factor$^{[16]}$. Figure 10 shows the $^1$H NMR of the crude product consisting of a mixture of 3 and 3a and Figure 11 shows the $^1$H NMR of a mixture of 4 and 4a; these spectra were used to determine the conversion factors for entry 1 and entry 11, respectively.
3.3 Determination of the enantiomeric excess\textsuperscript{[16, 17]}

The converted carboxylic acids 3 and 4 were separated from the gold complexes 1 and 2 after the catalytic experiment. The enantiomeric excess of the product was determined by converting the reduced carboxylic acid to a diastereomeric derivative by reacting 3\textsubscript{a} and 4\textsubscript{a} with S-mandelate (Figure 12). The diastereomeric mixture was then analyzed by \textsuperscript{1}H NMR spectrometry as described by Tyrell et al\textsuperscript{[17]}. The results are summarized in table 2 below.

\begin{align*}
3\textsubscript{a}: R &= \text{Methyl} \\
4\textsubscript{a}: R &= \text{Ethyl}
\end{align*}

\begin{align*}
5: R &= \text{Methyl} \\
6: R &= \text{Ethyl}
\end{align*}

Figure 12 Schematic presentation of synthetic route to the diastereomeric derivative of the products
The $^1$H NMR of Entry 1 was not good enough to evaluate the enantiomeric excess. This is due to apparent low selectivity in the reaction, $^1$H NMR showed that the sample contained several products that could not be completely identified. Figure 13 and 14 show the $^1$H NMR spectra of diastereomer 5 and 6, respectively. The downfield triplet corresponds to the $S,S$ diastereomer and the upfield triplet corresponds to the $R,S$ diastereomer.

There is an indication that the enantioselectivity depends on the carbon length of the substrate. Hydrogenation of carboxylic acid 3 gave good enantioselectivity but when the substrate had one more carbon (carboxylic acid 4) the enantioselectivity changed drastically to 80 %. This proves that a chiral gold complex can provide good enantioselectivity.

### Table 2 Enantiomeric excess results

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Substrate</th>
<th>Conversion</th>
<th>Enantiomeric excess</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>74 %</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>4</td>
<td>44 %</td>
<td>53 %</td>
<td>S</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>4</td>
<td>83 %</td>
<td>80 %</td>
<td>S</td>
</tr>
</tbody>
</table>

**Figure 13** $^1$H NMR spectrum of a diastereomeric mixture of 5 that was used to evaluate the enantiomeric excess

**Figure 14** $^1$H NMR spectrum of a mixture of diastereomers of 5 that was used to evaluate the enantiomeric excess
3.4 Optimization of the catalysis
Optimization of the catalysis turned out to be a difficult task since the catalysis is highly solvent sensitive. Catalysis performed in different solvent systems can be seen in Table 1 above. It turned out that ethanol was the best solvent among those that have been tested. An interesting note is that the catalyst was the least soluble in ethanol. After every catalysis experiment, it was found that only a small amount of the catalyst had dissolved in the ethanol. A hypothesis is that ethanol is important in the mechanism that is presented in Figure 15 below and proposed by Corma et al. A previous study on the solvent effect in enantioselective hydrogenation of α,β-unsaturated carboxylic acids have also reported that ethanol was a good solvent in hydrogenation of α,β-unsaturated carboxylic acids.\[18\]

Change of temperature and pressure did not improve the catalysis. In entry 4 in Table 1, one can see that increasing the pressure and temperature, (25 bar and 50 °C) gave low conversion. This was also the case when the temperature was constant but the pressure was raised to 25 bar (entry 12).

Because of this behavior, the catalysis was monitored by TLC analysis to investigate whether new compounds form or if the gold complex is decomposing. The result could not explain the strange behavior. Within the first 15 min of the catalysis, it can be seen that two new spots have appeared but disappear after one hour. The spot of the gold complex was weak when the new spots were formed. When the new spots disappeared, the gold(I) complex became more concentrated. It was not possible to analyze the newly formed compounds.

3.5 Hydrogenation in the absence of a catalyst/catalyst precursor
Catalysis without the gold complexes present was carried out to rule out that no contaminations are responsible for the above-mentioned results. Substrate 3 was dissolved in degassed ethanol in the absence of any potential catalyst and pressurized with 15 bar of hydrogen. After stirring at room temperature for 2 hours, no hydrogenated products were detected. This indicates strongly that the presence of the gold complex does play a key role in the hydrogenation of α,β-unsaturated carboxylic acids.

3.6 A tentative mechanism\[8\]
Corma et al. used similar dinuclear gold complexes in their investigation in which they presented a tentative mechanism for the hydrogenation reaction. The dinuclear gold complexes in this investigation should operate in a similar mechanism as suggested by Corma et al. Oxidative addition of H₂, which is the generally accepted mechanism for Rh- and Ir- complexes, is less favored in the case of Au. Corma et al therefore suggested that the electron rich Au-complex
bearing heteroatoms (Cl) promote the heterolytic splitting of hydrogen as the activation step. Then the catalysis cycle starts with hydride ion transfer to the gold, replacing the chloride ion to give a hydride-gold complex. The substrate forms a π-complex with the hydride-gold complex. Hydride ion transfer from gold to the substrate occurs simultaneously as the π-complex forms. Separation of the catalyst-product complex occurs upon proton transfer to the converted substrate, followed by insertion of ethoxide to the gold center. Regeneration of the catalyst occurs when hydrogen is added in the last step (Figure 15).

![Diagram](image)

**Figure 15** A tentative mechanism suggested by Corma *et al.*

### 4. Conclusion

In conclusion, two chiral gold(I) complexes with chiral diphosphine ligands have been synthesized. On the basis of previous results, a structure of the gold(I) complexes has been proposed. The chiral gold catalysts/catalyst precursors were shown to exhibit good catalytic activities and selectivities albeit bad reproducibility. Gold complexes as chiral catalysts has high potential and further studies should be carried out.

### 5. Experimental part

**General:** All reactions were performed under inert atmosphere (nitrogen) and manipulations of the products were performed in air. All solvents used in syntheses and catalysis experiments were distilled and dried before use. The ligand (R)-1-{(RP)-2-[2-(Diphenylphosphino)phenyl]ferrocenyl}ethylbis[3,5-bis-(trifluoromethyl)phenyl]phosphine (W001) and (R)-1-{(R)-2-[2-[Bis(4-methoxy-3,5-dimethylphenyl)phosphino]phenyl]ferrocenyl}ethylbis[3,5-bis(trifluoromethyl)phenyl]phosphine (W005) were purchased from Sigma-Aldrich and used as received. $^1$H and $^{31}$P NMR spectra were recorded on a Varian Unity
300 MHz spectrometer and a Varian Inova 500 MHz spectrometer. Thin-layer chromatography was performed on commercially available 20 x 20 cm glass plates, covered with Merck Kieselgel 60 to 0.25 mm thickness.

5.1 Synthesis of gold(I)complex 1
Using a Schlenk-line system, degassed CH₂Cl₂ (2.5 ml) was added to dissolve W001 (49.8 mg, 53.5 µmol) in a Schlenk – tube. A solution of HAuCl₄ (20.6 mg, 50.0 µmol) in degassed EtOH (2.5 ml) was added dropwise under 5 min to the ligand solution. The reaction was stirred at room temperature and monitored by TLC (CH₂Cl₂/MeOH 99:1 and 5 drops of Et₃N) After 12 h the reaction solution was concentrated in vacuo to yield the crude product as a brown solid. Purification by preparative TLC yielded 1 as an orange solid (40.7 mg, 56 %); ³¹P NMR (CDCl₃) δ = 39.67 (s), 24.12 (s) ppm; MS (ESI) m/z (%) 1359 (M⁺-Cl, 30) and the minor product as an orange solid (low yield); ³¹P NMR (202 MHz, CDCl₃) δ =31.67 (s), 28.99 (s), 25.30 (d, J = 11.9 Hz), 23.69 (d, J = 11.6 Hz); MS (ESI) m/z (%) 2396 (M⁺-Cl, 35)

5.2 Synthesis of gold(I)complex 2
Using a Schlenk-line system, degassed CH₂Cl₂ (2.5 ml) was added to dissolve W005 (64.6 mg, 61.7 µmol) in a Schlenk – tube. A solution of HAuCl₄ (25.5 mg, 61.9 µmol) in degassed EtOH (2.5 ml) was added dropwise under 5 min to the schlenk – tube. The reaction was stirred at room temperature and monitored by TLC (CH₂Cl₂/MeOH 99:1 and 5 drops of Et₃N) After 12 h the reaction solution was concentrated in vacuo to yield the crude product as a brown solid. Purification by preparative TLC yielded 2 as an orange solid (34.2 mg, 36 %). ³¹P NMR (CDCl₃) δ = 37.99 (s), 22.06 (s) ppm; MS (ESI) m/z (%) 1475 (M⁺-Cl, 30).

5.3 Catalysis
The catalyst (5 mg) and substrate (100 molar excess) were dissolved in degassed EtOH (6 ml) in a small laboratory autoclave (45 ml). The autoclave was sealed and purged three times with 20 bar H₂(g) before being pressurized with 15 bar H₂(g) and stirred at room temperature for 2 h. The autoclave was thereafter opened and the reaction solution was concentrated in vacuo. The NMR sample was collected immediately to calculate the conversion factor. The residue was redissolved in diethyl ether (10 ml). The carboxylic acid was extracted with NaHCO₃(aq) (4 x 10 ml) and washed with Et₂O (2 x 5 ml). The water phase was thereafter acidified with H₂SO₄ (conc) until pH 1. The protonated carboxylic acid was thereafter re-extracted with Et₂O (4 x 10 ml) and washed with water (2 x 5 ml) and dried over MgSO₄. The residual solution was concentrated in vacuo to obtain the carboxylic acid. No further purification was carried out. The
organic phase containing the cluster was washed with water (2 x 5 ml) and dried over MgSO₄. The organic solution was concentrated in vacuo to yield the catalyst as an orange solid.

5.4 Enantiomeric excess experiment
Using a Schlenk-line system, degassed CH₂Cl₂ (3.5 ml) was added to dissolve the converted carboxylic acid (32.0 mg, 0.27 mmol) and cooled down to -10 °C using dry ice in a mix of acetone/water. DMAP (17.5 mg, 0.14 mmol) was added to the reaction solution followed by S-mandelate (46.4 mg, 0.28 mmol) and DCC (58.3 mg, 0.28 mmol) under -10 °C. The reaction solution was stirred over night and stopped after 12 h. The precipitated urea was filtered off and the filtrate was concentrated in vacuo to yield the diastereoisomer as white solid. The enantiomeric excess was calculated based on the ¹H NMR analysis.
6. References