Asymmetric amplification due to difference in phase behavior of Cu-diphosphine based chiral complexes

Large asymmetric amplification was observed in copper catalyzed asymmetric addition of Grignard reagents to enones. Here we show that this phenomenon is not reaction or catalyst specific but can be observed for metal complexes of a variety of chiral diphosphine ligands, extensively used in asymmetric catalysis. We show that complexation of metal salts with a series of scalemic diphosphine ligands leads to extreme differences in solubility between the enantiopure and the racemic complexes. This allows separation of enantiopure ligands from nearly racemic mixtures and relaxes the requirement for enantiopure ligands for maximum enantioselectivity in catalysis.

This chapter is an adaptation of the published papers:


6.1 Introduction

Over the last decades, many catalytic asymmetric reactions have been developed using transition metal complexes or organocatalysis. The common trend in such reactions, is that the observed enantiomeric excess (ee) of the product is linearly related to the ee of the catalyst, which means that an enantiopure catalyst is a requirement to achieve high levels of enantioselectivity. Over the years, however, a number of asymmetric reactions have been discovered, that deviate from this trend and show a non-linear relationship between \( ee_{\text{prod}} \) and \( ee_{\text{cat}} \) leading to asymmetric amplification or depletion. Asymmetric amplification is a beneficial situation which allows the use of a non-enantiopure chiral catalyst to achieve maximum enantioselectivity. This phenomenon is usually specific for a given combination of chiral catalyst and reaction.

Recently we have reported that a Cu-complex of \( L_1 \), commonly used to catalyze 1,4-addition reactions of Grignard reagents to \( \alpha,\beta \)-unsaturated carbonyl compounds and therefore to prevent 1,2-addition reactions, is in fact an excellent catalyst for the formation of tertiary alcohols with high enantioselectivities. This study also comprised an investigation on non-linear behaviour of the enantioselectivity using the 1,2-addition of Grignard reagent to enone 1. Using standard reaction conditions, product 2 was obtained with excellent yield and enantioselectivity (Scheme 1).

\[
\text{Scheme 1} - \text{Cu(I) catalyzed 1,2 addition of Grignard reagents to enones.}
\]

During the mechanistic investigation of this new catalytic system, dramatic asymmetric amplification was observed in the 1,2-addition of Grignard reagents 4 to enone 3 in tBuOMe (Scheme 2).
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Scheme 2: Asymmetric amplification in 1,2-addition of a Grignard reagent to enone 3, catalysed by supernatants of scalemic L1-Cu complexes.

In addition to the asymmetric amplification, it was found an increase in the product ee along with the conversion of the substrate 3 (Scheme 2, Table 1).\textsuperscript{19}

Table 1: The relation between conversion and ee in the addition of isobutylmagnesium bromide 4 to enone 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time(min)</th>
<th>Conversion(%)$^a$</th>
<th>ee (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>5</td>
<td>44</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>25</td>
<td>69</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>74</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>95</td>
<td>84</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>180</td>
<td>99</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>270</td>
<td>99,9</td>
<td>83</td>
</tr>
</tbody>
</table>

$^a$Conversions were determined by GC-MS, $^b$Regio- and enantioselectivities were determined by chiral HPLC.

The aim of the project in this chapter was to study the origin of the strong asymmetric amplification observed in the copper catalysed 1,2-addition of Grignard to enones.

6.1.1 Non linearity in asymmetric synthesis

Asymmetric synthesis is an established field which is widely used in research laboratories and industry.\textsuperscript{20,21} In a stoichiometric or catalytic amount, a chiral auxiliary is needed to obtain a chiral product. In most cases, a linear correlation exists between the ee of the catalyst and the ee of the product obtained (Figure 3). If a reagent or catalyst system contains a non enantiopure chiral auxiliary, with an enantiomeric excess $ee_{aux}$, an enantiomerically enriched product with an enantiomeric excess of $ee_{prod}$ can be obtained.
The calculation of the enantiomeric excess of the product ($\text{ee}_{\text{max}}$), for an enantiopure auxiliary, can easily be performed if one assumes that the enantiomers of the auxiliary (in the reagent or the catalyst) act independently. The proportionality between $\text{ee}_{\text{aux}}$ and $\text{ee}_{\text{prod}}$ in Equation (1) allows the $\text{ee}_{\text{max}}$ value to be calculated ($\text{ee}$ values between 0 and 1).

$$\text{ee}_{\text{prod}}(\%) = \frac{\text{ee}_{\text{max}} \times \text{ee}_{\text{aux}}}{100} \quad (\text{eq } 1)$$

Nonlinear behavior in asymmetric catalysis is typically reported as product enantioselectivity ($\text{ee}_{\text{prod}}$) vs ($\text{ee}_{\text{cat}}$) (Figure 1).

Asymmetric amplification is the term used to describe a positive deviation from the linearity of $\text{ee}_{\text{aux}}$ vs $\text{ee}_{\text{prod}}$, and asymmetric depletion describes the case where a negative deviation from linearity is observed.

Such nonlinear effects (NLEs) can be traced to earlier observations of unusual physical and chemical properties, sometimes exhibited by mixtures of enantiomers in solution and attributed to the formation of diastereomeric species or higher order agglomerates. Wynberg and Feringa recognized that this non-ideal behavior may also have implications when a chemical reaction occurs in a non-enantiopure mixture. This was first quantified by Kagan and coworkers, both with theoretical studies and with the first experimental description of such nonlinear effects in asymmetric catalytic reactions.
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Many examples of this nonlinear behavior have since been observed, and the use of non enantiopure catalyst mixtures is rapidly becoming a common mechanistic tool based on Kagan’s work.

Kagan tried to explain the nonlinear effect present in asymmetric catalysis using some mathematical models. The mechanistic aspects of NLEs have been described by using simplified mathematical models of various catalytic systems. The majority of known examples of NLEs include complexes bearing two chiral ligands. However, models where more than two ligands are involved have also been proposed, for example the MLn model and the reservoir model. For systems with two ligands, one can envisage mainly ML2 or (ML): complexes, where M and L stand for metal and ligand, respectively. When the ligand is not enantiopure, such systems result in the formation of at least two kinds of diastereomeric species, which are either homochiral or heterochiral (Scheme 3).

For the ML2 system (Scheme 3), assuming a dynamic equilibrium between the three complexes, MLrLr, MLsLs (homochiral), and MLrLs (meso structure for simplicity), fast exchange of the enantiomeric ligands (Lr and Ls) at the metal center occurs.

According to this model, the homochiral and meso species generate the enantiomeric and the racemic products, respectively. The homochiral and meso complexes are characterized by their relative reactivity \((g=k'/k)\) and their relative concentrations \([b=z/(x+y)]\) (eq. 2). A simple kinetic treatment gives Equation 2, in which \(ee_{prod}\) is expressed as a function of \(ee_{aux}\).

\[
ee_{prod} = ee_{max}ee_{aux} \frac{1+\beta}{1+\gamma\beta} \tag{eq. 2}
\]
The entities $g$, $\beta$, and $ee_{\text{max}}$ take fixed values for a given system. $\beta$ can be derived from the equilibrium constant $K$ between the homochiral and heterochiral complexes.\textsuperscript{27} The calculation leading to Equation (2) assumes that the initial ligand (with $ee_{\text{aux}}$) is fully transferred into the set of ML\textsubscript{2} complexes, or that the external ligand retained the initial value of $ee_{\text{aux}}$. A plot of $ee_{\text{prod}}$ as a function of $ee_{\text{aux}}$ affords three types of correlations: 1) a (+)-NLE for $g<1$ (more reactive homochiral complex), 2) a (-)-NLE for $g>1$ (more reactive meso complex), and 3) Equation (2) reduces to $ee_{\text{prod}}=ee_{\text{max}}ee_{\text{aux}}$ (linear correlation), if $\beta=0$ or $g=1$. Equation (2) applies even when the proportions of $x$, $y$, and $z$ are fixed through an irreversible formation of diastereomeric complexes.\textsuperscript{15} The strength of the NLE will be higher when diastereomers are irreversibly formed than when they are reversibly formed.\textsuperscript{9} The discussion can be extended to the similar model (ML)\textsubscript{2}.\textsuperscript{28,29} The reservoir model\textsuperscript{27} (Scheme 4) describes the case when several metal complexes are generated during the catalyst preparation, one being the catalytically active species.

One can envision several models, such as the couples monomer/dimer, dimer/trimer, dimer/tetramer etc., for the reservoir effect. A non-enantiopure ligand simultaneously generates the catalytically active monoligated complex ML and, for example, the inactive stable mesodimer (ML\textsubscript{R}) (ML\textsubscript{S}) or meso complex ML\textsubscript{RLSL}. Here, the meso species serves as a trap for the racemic part of the non-enantiopure ligand, thus enabling the enantioenriched ligand to take part in the catalytic cycle as the monoligated complex (ML).
6.2 Results and discussions

6.2.1 Asymmetric amplification in the 1,2-addition of a Grignard reagent to enone, catalysed by scalemic L1-Cu complexes

We started our investigations on the asymmetric amplification, using scalemic Cu-complexes of L1 (ee’s of 0%, 20%, 50%, 70%, 100%) prepared in situ, in the 1,2-addition of the Grignard reagent 4 to enone 3. The copper-complexes were prepared either by mixing the enantioenriched chiral ligand with the corresponding amount of copper salt, 1:1 ratio (Scheme 5), or by mixing both enantiomers of already prepared enantiopure Cu-complex in tBuOMe (0.015 M), at room temperature, for 30 min.

Scheme 5 - Preparation of scalemic copper complexes of L1.

An interesting observation during the preparation of the Cu-complexes of L1, via either of these two methods, was that a significant amount of precipitate formed already within 30 min of stirring while in the first 5 min everything was soluble. An exception was the solution of the Cu-complex of enantiopure L1, which even after prolonged stirring stayed clear (Figure 2).

Figure 2 - Solutions of scalemic Cu-complexes of L1.
Similar results, obtained using both methods, provide evidence that the whole process is under thermodynamic control. Subsequently, we studied the asymmetric amplification in two different ways. In the first run, the separated supernatant was used to catalyse the 1,2-addition. In the second run, the entire supernatant + precipitate of the complex was used. A large asymmetric amplification was observed in both runs (Table 2).

**Table 2: Asymmetric amplification in the 1,2-addition of a Grignard reagent to enone 3, catalysed by scalemic L1–Cu complexes**

<table>
<thead>
<tr>
<th>Scalemic Cu-L1</th>
<th>Supernatant/Precipitate</th>
<th>Supernatant</th>
</tr>
</thead>
<tbody>
<tr>
<td>ee (%)</td>
<td>loading (%)</td>
<td>3 (ee %)</td>
</tr>
<tr>
<td>20</td>
<td>25</td>
<td>80</td>
</tr>
<tr>
<td>40</td>
<td>12</td>
<td>90</td>
</tr>
<tr>
<td>60</td>
<td>8</td>
<td>90</td>
</tr>
<tr>
<td>80</td>
<td>5</td>
<td>90</td>
</tr>
<tr>
<td>100</td>
<td>5</td>
<td>--</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ee (%)</th>
<th>loading (%)</th>
<th>3 (ee %)</th>
<th>3 (conv %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>25</td>
<td>80</td>
<td>75</td>
</tr>
<tr>
<td>40</td>
<td>12</td>
<td>90</td>
<td>82</td>
</tr>
<tr>
<td>60</td>
<td>8</td>
<td>90</td>
<td>93</td>
</tr>
<tr>
<td>80</td>
<td>5</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>100</td>
<td>5</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

*Total of 5 mol% active catalyst present in the solution (using only supernatant). Reaction time 24 h. In case of using scalemic mixtures, the reaction time is 48 h. The enantioselectivity of the reaction is determined by chiral HPLC. The enantioselectivity and conversion of the reactions catalysed by the supernatants of the scalemic complexes were similar to the results obtained with the enantiopure catalyst (Table 2).

The enantioselectivity and conversion of the reactions catalysed by the supernatants of the scalemic complexes were similar to the results obtained with the enantiopure catalyst (Table 2). Slightly lower ee’s were obtained and longer reaction times were required (48 h) when the supernatant + precipitate mixtures were used to catalyse the reaction. This difference can be attributed to the presence of significant amounts of the precipitate (in particular for the Cu-complex with 20% ee) complicating efficient stirring. To gain more insight into this phenomenon, the copper complexes were prepared in tBuOMe (0.015 M) in two ways: (1) by mixing the enantioenriched chiral ligand L1 with the corresponding amount of copper salt, for 30 min; (2) by mixing both enantiomers of a priori prepared enantiopure Cu-complex at room temperature, for 30 min (Scheme 5).
Centrifugation of these solutions resulted in a precipitate and supernatant (an exception was the solution with 100% ee, which did not have any precipitate). The precipitate that starts forming after 20 min was not analyzed further due to low solubility. Nevertheless, based on the measured weight of the complexes from the solutions and precipitates and the fact that the ee of all the solutions exceeds 90%, it is certain that the precipitate in all of the samples is approximately racemic (ee <10%). Specific optical rotations and CD spectra obtained from the supernatants closely matched those from the enantiopure catalyst (Table 3, Figure 3).

**Table 3: Specific optical rotation values for the supernatants of scalemic CuBr rev-JosiPhos-L1 in tBuOMe**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Supernatant</th>
<th>[α]$^\text{D}_{20}$</th>
<th>c (g/mL)</th>
<th>Precipitate</th>
<th>[α]$^\text{D}_{20}$</th>
<th>c (g/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20 % ee</td>
<td>-6</td>
<td>1.0*10$^{-3}$</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>40 % ee</td>
<td>-7</td>
<td>2.9*10$^{-3}$</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>60 % ee</td>
<td>-7</td>
<td>5.0*10$^{-3}$</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>80% ee</td>
<td>-7</td>
<td>7.0*10$^{-3}$</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>100% ee</td>
<td>-8</td>
<td>7.1*10$^{-3}$</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*The optical rotation was measured in tBuOMe; b) Precipitate was not soluble in any organic solvent.

**Figure 3** - a) CD spectra of tBuOMe supernatants in CH$_2$Cl$_2$; b) UV spectra of supernatants in CH$_2$Cl$_2$.

Metal complexes of chiral diphosphine ligands are extensively used as chiral catalysts in asymmetric synthesis.$^{15,16,31-34}$ Therefore we decided to investigate the generality of this phenomenon among metal complexes of various structurally different ferrocenyl diphosphine ligands commonly used in asymmetric catalysis (Figure 4).
Cu-complexes of enantioenriched $L_2$ were prepared in $t$BuOMe (0.015 M) as described for $L_1$. Also in this case, a racemic precipitate was formed in $t$BuOMe, together with a virtually enantiopure solution (Table 4, Figure 5). The only difference with the previous example was that the precipitate was soluble in CH$_2$Cl$_2$. Similar results were obtained when copper complexes of $L_2$ with ee values of 20%, 50%, 70% and 100% were prepared in CH$_2$Cl$_2$ (no precipitate formed) followed by solvent removal and addition of $t$BuOMe to the solid residues of the scalemic complexes. Samples were analysed after 24 h of stirring. The higher solubility of the $t$BuOMe precipitate in CH$_2$Cl$_2$ enabled us to demonstrate its racemic composition by using CD and optical rotation in CH$_2$Cl$_2$.

**Table 4**: Specific optical rotation values for the supernatants and precipitate of scalemic CuBr JosiPhos-$L_2$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Supernatant$^a$</th>
<th>$[\alpha]_{D}^{20\alpha}$</th>
<th>$c$ (g/mL)</th>
<th>Precipitate$^{bc}$</th>
<th>$[\alpha]_{D}^{20\alpha}$</th>
<th>$c$ (g/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20% ee</td>
<td>-185</td>
<td>$1.0 \times 10^{-3}$</td>
<td>20% ee</td>
<td>-13</td>
<td>$1.8 \times 10^{-3}$</td>
</tr>
<tr>
<td>2</td>
<td>20% ee</td>
<td>-135</td>
<td>$2.8 \times 10^{-3}$</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>50% ee</td>
<td>-191</td>
<td>$1.25 \times 10^{-3}$</td>
<td>50% ee</td>
<td>-11</td>
<td>$1.3 \times 10^{-3}$</td>
</tr>
<tr>
<td>4</td>
<td>70% ee</td>
<td>-192</td>
<td>$2.13 \times 10^{-3}$</td>
<td>70% ee</td>
<td>-14</td>
<td>$1.35 \times 10^{-3}$</td>
</tr>
<tr>
<td>5</td>
<td>100% ee</td>
<td>-198</td>
<td>$4.0 \times 10^{-3}$</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$The optical rotation was measured in $t$BuOMe; $^b$The optical rotation was measured in CH$_2$Cl$_2$; $^c$The precipitate was washed with $t$BuOMe (2x5ml) and dried before preparing CH$_2$Cl$_2$ solution. $^d$Sample with 20% ee needs to be centrifuged 2-3 times. $^e$The value $[\alpha]_{D}^{20\alpha}$ in CH$_2$Cl$_2$ was -341 c (g/mL)=2.6 $\times 10^{-3}$.
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Figure 5 - a) CD spectra of supernatants measured in tBuOMe; b) CD spectra of tBuOMe precipitates measured in CH2Cl2; c) UV spectra of supernatants in tBuOMe; d) UV spectra of precipitates in CH2Cl2.

In the case of the scalemic mixture 20% ee, the mixture needs to be centrifuged 2-3 times, to remove all the racemic complex present in solution (Table 4, entries 1 and 2). In the case of the structurally quite different ligand L3, which forms a seven-membered instead of a five-membered metallacycle upon complexation with the Cu ion, we also found the racemic complex to have a lower solubility than the enantiopure complex (2.2 mg mL\(^{-1}\) and 5.3 mg mL\(^{-1}\), respectively). Thus, precipitation from the scalemic mixture leads to a supernatant solution containing a complex with an ee > 90%, (Table 5, Figure 6).

Table 5: Specific optical rotation values for the supernatants and precipitates of scalemic CuBr TaniaPhos-L3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Supernatant(^a)</th>
<th>[(\alpha)](_D^{20}) c (g/mL)</th>
<th>Precipitate(^b,c)</th>
<th>[(\alpha)](_D^{20}) c (g/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20% ee</td>
<td>+125 2.6(\times)10(^{-3})</td>
<td>20% ee</td>
<td>+9 2.5(\times)10(^{-3})</td>
</tr>
<tr>
<td>2</td>
<td>50% ee</td>
<td>+128 3.8(\times)10(^{-3})</td>
<td>50% ee</td>
<td>+2 2.4(\times)10(^{-3})</td>
</tr>
<tr>
<td>3</td>
<td>70% ee</td>
<td>+122 3.4(\times)10(^{-3})</td>
<td>70% ee</td>
<td>+44 2.6(\times)10(^{-3})</td>
</tr>
<tr>
<td>4</td>
<td>100% ee</td>
<td>+155 2.6(\times)10(^{-3})</td>
<td>-</td>
<td>- (-)</td>
</tr>
</tbody>
</table>

\(^a\)The optical rotation was measured in tBuOMe; \(^b\)The optical rotation was measured in CH2Cl2; \(^c\)The precipitate was washed with tBuOMe (2x5 ml) and dried before preparing CH2Cl2 solution; \(^d\)The value [\(\alpha\)]\(_D^{20}\) in CH2Cl2 was +166 c (g/mL)= 5.5 \(\times\)10\(^{-3}\).
Chapter 6

Figure 6 - a) CD spectra of supernatants in tBuOMe; b) CD spectra of precipitates measured in CH2Cl2; c) UV spectra of supernatants in tBuOMe; d) UV spectra of precipitates in CH2Cl2.

For the Cu-complex of ferrocenyl ligand L4, we found the effect to be the opposite: the precipitate had a much higher enantiopurity than the corresponding supernatant which contained the nearly racemic complex (Table 6, Figure 7).

**Table 6: Specific optical rotation values for the supernatants and precipitates of scalemic CuBr WalPhos-L4***

<table>
<thead>
<tr>
<th>Entry</th>
<th>Supernatant&lt;sup&gt;a&lt;/sup&gt;</th>
<th>[α]_D&lt;sup&gt;b&lt;/sup&gt;</th>
<th>c (g/mL)</th>
<th>Precipitate&lt;sup&gt;b&lt;/sup&gt;</th>
<th>[α]_D&lt;sup&gt;b&lt;/sup&gt;</th>
<th>c (g/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20 % ee</td>
<td>-6</td>
<td>1.56*10^-5</td>
<td>20% ee</td>
<td>-35</td>
<td>5*10^-3</td>
</tr>
<tr>
<td>2</td>
<td>50 % ee</td>
<td>-17</td>
<td>1.52*10^-5</td>
<td>50% ee</td>
<td>-72</td>
<td>5.3*10^-3</td>
</tr>
<tr>
<td>3</td>
<td>70% ee</td>
<td>-8</td>
<td>1.48*10^-5</td>
<td>70% ee</td>
<td>.96</td>
<td>4.1*10^-3</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>-</td>
<td>100% ee</td>
<td>-99</td>
<td>2.0*10^-3</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>The optical rotation was measured in tBuOMe; <sup>b</sup>The optical rotation was measured in CH2Cl2.
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Differently from the other complexes, that are true racemates, CuBr Walshos L4 behaves as conglomerate. Only 5-10% of the compounds are conglomerates. The conglomerate (or racemic conglomerate) consists of a physical mixture of pure crystals of one enantiomer and its counterpart. In the crystal structure, molecules have a greater affinity for the same enantiomer than for the counterpart and the two enantiomers crystallize separately. The true racemate (or racemic compound) is formed by a single crystalline phase in which the two enantiomers are ordered in a 1:1 ratio.

In this case, molecules have a greater affinity for the counterpart than for the same enantiomer. One of the difference between the compounds that are true racemates and conglomerates is the melting point. In the case of true racemates, the melting point of the racemic compound is around 20 °C higher than the corresponding enantiopure. On the other side for the conglomerates, the racemic compound has a lower melting point than his corresponding enantiopure compound.
We were curious whether this phenomenon is somewhat specific to ferrocenyl ligands and therefore performed similar experiments with binaphthyl phosphine ligand L5 (BINAP). For this complex we had to use a solvent mixture (tBuOMe–CH₂Cl₂) due to the poor solubility of the enantiopure complex in pure tBuOMe. In this case, while the difference in solubility between racemic and enantiopure samples was less extreme (10 mg mL⁻¹ and 40 mg mL⁻¹, respectively), significant enantioenrichment was still observed (Table 7).

Table 7: Specific optical rotation values for the supernatants and precipitates of scalemic CuBr-BINAP-L5

<table>
<thead>
<tr>
<th>Entry</th>
<th>Supernatantᵃ</th>
<th>[α]D₂⁰ (g/mL)</th>
<th>Precipitateᵇ</th>
<th>[α]D₂⁰ (g/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20% ee</td>
<td>-75</td>
<td>20% ee</td>
<td>-4</td>
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<tr>
<td>2</td>
<td>50% ee</td>
<td>-154</td>
<td>50% ee</td>
<td>-4</td>
</tr>
<tr>
<td>3</td>
<td>70% ee</td>
<td>-189</td>
<td>70% ee</td>
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</tr>
<tr>
<td>4</td>
<td>100% ee</td>
<td>-195</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

ᵃThe optical rotation was measured in CH₂Cl₂;ᵇThe optical rotation was measured in a mixture of CH₃CN/MeOH (5:1).

The next question to assess was whether metal complexation is required for this phenomenon to occur, and whether it is unique to copper. Scalemic JosiPhos-L1 (with 0%, 20%, 50% and 70% ee) was stirred for 24 h in tBuOMe as well as in CH₂Cl₂, both at room temperature and at 0 °C. No precipitate was formed, clearly indicating that it is the metal complexation that changes the solid-solution phase behaviour of these chiral diphosphine ligands in the provided solvents.

6.2.2 Generality of the phenomenon: other metals

At this point the next question to answer was: is this phenomenon specific for copper? Is it possible to use other metals?

We prepared scalemic mixtures of the Pd and Rh complexes with L2 and L3. In the case of palladium a mixture of tBuOMe–CH₂Cl₂ was used as solvent, and in the case of rhodium 5% of methanol needed to be added initially to have completely homogenous solutions. We found that the phenomenon also persists in these cases. For simplicity due to fact that in case of rhodium a mixture of tBuOMe–CH₂Cl₂ and MeOH needed to be used, because of the poor solubility of the complex. We only studied further the Pd-L2 and Pd-L3 complexes.
Similar to the results obtained for the Cu-complex of BINAP, the difference in solubility between the racemic (2.5 mg mL\(^{-1}\)) and enantiopure (12 mg mL\(^{-1}\)) Pd complex of \(\text{L2}\) was less extreme, resulting in a lower \(\text{ee}\) value at the eutectic (Table 8, Figure 8).

**Table 8**: Specific optical rotation values for the supernatants and precipitate of scalemic \(\text{PdCl}_2\)-JosiPhos-\(\text{L2}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Supernatant(^a)</th>
<th>([\alpha]_{20}^\text{BuOMe})</th>
<th>(c) (g/mL)</th>
<th>Precipitate(^b)</th>
<th>([\alpha]_{20}^\text{BuOMe})</th>
<th>(c) (g/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20% ee</td>
<td>-115</td>
<td>2.1\times10^{-3}</td>
<td>20% ee</td>
<td>-35</td>
<td>2.3\times10^{-3}</td>
</tr>
<tr>
<td>2</td>
<td>50% ee</td>
<td>-122</td>
<td>3.0\times10^{-3}</td>
<td>50% ee</td>
<td>-13</td>
<td>1.5\times10^{-3}</td>
</tr>
<tr>
<td>3</td>
<td>70% ee</td>
<td>-129</td>
<td>4.8\times10^{-3}</td>
<td>70% ee</td>
<td>-5</td>
<td>0.9\times10^{-3}</td>
</tr>
<tr>
<td>4</td>
<td>100% ee</td>
<td>-211</td>
<td>4.8\times10^{-3}</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^a\)The optical rotation was measured in \(\text{tBuOMe}\); \(^b\)The optical rotation was measured in CH\(_2\)Cl\(_2\); The precipitate was washed with \(\text{tBuOMe}\) (2x5 mL) and dried before preparing CH\(_2\)Cl\(_2\) solution.

**Figure 8** - a) CD spectra of supernatants measured \(\text{tBuOMe}\); b) CD spectra of \(\text{tBuOMe}\) precipitates measured in CH\(_2\)Cl\(_2\).

For the Pd complex of \(\text{L3}\), the solubilities of the racemic and enantiopure samples were 0.3 mg mL\(^{-1}\) and 14.4 mg mL\(^{-1}\) respectively, and the \(\text{ee}\)'s of all the supernatants were >80% (Table 9).
Table 9: Specific optical rotation values for supernatants and precipitate of scalemic PdCl2-TaniaPhos-L3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Supernatant$^a$</th>
<th>$[α]_{D}^{20}$</th>
<th>c (g/mL)</th>
<th>Precipitate$^b$</th>
<th>$[α]_{D}^{20}$</th>
<th>c (g/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20% ee</td>
<td>-117</td>
<td>1.7*10^{-3}</td>
<td>20% ee</td>
<td>18</td>
<td>0.68*10^{-3}</td>
</tr>
<tr>
<td>2</td>
<td>50% ee</td>
<td>-125</td>
<td>2.1*10^{-3}</td>
<td>50% ee</td>
<td>44</td>
<td>0.58*10^{-3}</td>
</tr>
<tr>
<td>3</td>
<td>70% ee</td>
<td>-144</td>
<td>2.4*10^{-3}</td>
<td>70% ee</td>
<td>42</td>
<td>0.42*10^{-3}</td>
</tr>
<tr>
<td>4$^b$</td>
<td>100% ee</td>
<td>-148</td>
<td>3.9*10^{-3}</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$ The optical rotation was measured in tBuOMe. $^b$ The optical rotation was measured in CH2Cl2. $^c$ The precipitate was washed with tBuOMe (2x5 mL) and dried before preparing CH2Cl2 solution.

6.2.3 Solution and solid state of the corresponding copper complexes

The dramatic difference in solubility of the chiral copper complex of rev-JosiPhos-L1 is the primary factor for the previously observed asymmetric amplification. This difference in solubility was showed to be valid for all the other phosphine ligands (L2, L3, L4, and L5). To understand the structural differences between the racemic and the enantiopure complexes, we first studied the species formed in solution. The initial hypothesis was that dinuclear and mononuclear species can have different solubilities, and depending on whether the ligand is racemic or enantiopure, either of the two species is formed. To confirm this hypothesis we first studied solutions (in CH2Cl2 and tBuOMe) and solid samples of both racemic and enantiopure complexes using high resolution ESI-MS and DART-MS spectrometry. Unfortunately, molecular ions corresponding to dimeric and monomeric species were found for all samples, so this was inconclusive. No significant differences were observed in the $^1$H, $^{31}$P, and $^{13}$C-NMR spectra for the copper complexes of the racemic and enantiopure ligands. To reveal the composition of the copper complexes in the solid phase, crystals of racemic and enantiopure copper complexes of all three ligands were grown and subjected to X-ray crystallography. The crystal structures of the Cu-complexes of rev-JosiPhos L1 show a dimeric structure for both the racemate, and the single enantiomer, albeit with a different symmetry (Figure 9a and 9b).
Asymmetric amplification due to difference in phase behavior of Cu-diphosphine based chiral complexes

Due to the extremely low solubility of the racemic Cu complex of rev-JosiPhos, crystals were obtained by doping one enantiomer in CH₂Cl₂ solution into poly(ethylene oxide) hydrogel followed by addition, as an antisolvent, a solution of the opposite enantiomer in toluene. The structure of rac-CuBr-rev-JosiPhos L1 is located on an inversion center: the centrosymmetric dimer is the “meso” form. In both cases the unit cell consists of one moiety of a dinuclear copper complex, bridged by two Br atoms. Analysis of the crystal structures of the racemate and single enantiomer of Cu/JosiPhos revealed monomeric structures (Figure 10a). Similarly the racemate and the single enantiomer of Cu/TaniaPhos showed monomeric structures (Figure 10b).

When we compared the crystal structures of the racemates and the single enantiomers, we made the interesting observation that racemic CuBr-rev-JosiPhos L1 and CuBr-JosiPhos L2 have a higher density and a higher packing index than the single enantiomers (Table 10). For data on crystal packing see experimental part.

Figure 9 - X-ray crystal structures of the copper bromide complexes of rev-JosiPhos L1: a) rac-CuBr-rev-JosiPhos; b) enant-CuBr-rev-JosiPhos (the asymmetric unit consists of a dinuclear copper complex, with a molecule of water present in the cell)17a.

Figure 10 - X-ray crystal structures of the copper bromide complexes of JosiPhos L2 and TaniaPhos L3: a) rac-CuBr-JosiPhos L2; b) rac-CuBr-TaniaPhos L3.
According to the principle of "close packing" this is a sign for higher stability of the crystal. Enantiopure CuBr-rev-JosiPhos L1 is characterized by strong intermolecular O-H...Br hydrogen bonds forming a one-dimensional chain in the crystal structure. Racemic CuBr-rev-JosiPhos L1 has no such strong intermolecular interactions, nevertheless its density is higher than that of the single enantiomer. The exception is CuBr-TaniaPhos L3, for which the densities of the racemic and enantiopure crystals were similar. This could be due to the co-crystallized solvent (CH₂Cl₂) in the racemic crystals. Combined MS-spectrometry, NMR spectroscopy and X-ray spectroscopy confirmed that both mononuclear and dinuclear species can be present in solution and the solid state for both the racemic and the enantiopure complexes of all ligands studied.

It is a common phenomenon that the stability of racemates is higher than that of single enantiomers; however, the resulting difference in solubility is usually not sufficient to provide enantiopure supernatants through preferential crystallization of the racemate from the scalemic solution. One the other hand, the introduction of intermolecular interactions, e.g. H-bonding or ionic interactions, can amplify the solubility difference.

### 6.2.4 Mechanistic considerations

It is a general trend that crystals of racemates are more stable than those of their single enantiomers but extreme differences in their stability, allowing efficient separation, are rare.

---

**Table 10: Crystal packing characteristics**

<table>
<thead>
<tr>
<th>CuBr-Ligand</th>
<th>CCDC number</th>
<th>Space group</th>
<th>Dₙ [g/cm³]</th>
<th>K.P.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>rac-CuBr-rev-JosiPhos L₁</td>
<td>CCDC 908802</td>
<td>C2/c (no. 15)</td>
<td>1.545</td>
<td>69.8%</td>
</tr>
<tr>
<td>enant-CuBr-rev-JosiPhos L₁</td>
<td>CCDC 610500⁷</td>
<td>C222₁ (no. 20)</td>
<td>1.475</td>
<td>67.0%</td>
</tr>
<tr>
<td>rac-CuBr-rev-JosiPhos L₂</td>
<td>CCDC 908803</td>
<td>P1 (no. 2)</td>
<td>1.540</td>
<td>69.7%</td>
</tr>
<tr>
<td>enant-CuBr-rev-JosiPhos L₂</td>
<td>CCDC 261573</td>
<td>P2₁ (no. 4)</td>
<td>1.529</td>
<td>69.3%</td>
</tr>
<tr>
<td>rac-CuBr-TaniaPhos L₃</td>
<td>CCDC 908804⁶</td>
<td>P2₁/c (no. 14)</td>
<td>1.539</td>
<td>68.0%</td>
</tr>
<tr>
<td>enant-CuBr-TaniaPhos L₃</td>
<td>CCDC 909403</td>
<td>P2₁2₁2₁ (no. 19)</td>
<td>1.539</td>
<td>68.5%</td>
</tr>
</tbody>
</table>

⁷ monohydrate; ⁶ CH₂Cl₂ solvate.
Asymmetric amplification due to difference in phase behavior of Cu-diphosphine based chiral complexes

The introduction of intermolecular interactions, e.g. H-bonding or ionic interactions, can amplify the solubility difference which is probably the reason behind a number of asymmetric amplifications, based on a dual phase behavior, reported for reactions utilizing chiral derivatives of amino acids, diaminocyclohexane, bisoxazoline and phosphoric acid as catalysts. (Figure 11).

Figure 11 - Catalyst used in the asymmetric amplification reactions: a) Aldol reaction, b),c) Addition of diethylzinc to aldehydes, d) Biginelli reaction.

In 1969, Morowitz showed that scalemic (e.g. non-racemic) mixtures of phenylalanine and leucine can be resolved by solid-solution equilibration. In 2006, complex solid-solution phase behaviour of amino acids (in particular proline) was shown to be responsible for non-linear effects in asymmetric catalysis and it was hypothesised that this feature played an important role in the evolution of biomolecular homochirality. The groups of Blackmond and Hayashi observed a large asymmetric amplification in the proline-catalyzed aldol reaction of acetone with 2-chlorobenzaldehyde (Scheme 6). The asymmetric amplification originates from the fact that racemic proline is much less soluble than enantiopure proline.

Scheme 6 - Proline catalyzed aldol reaction.
Recently, asymmetric amplification based on a difference in phase behaviour was reported for reactions utilising chiral derivatives of diaminocyclohexane, bisoxazoline, and phosphoric acid as catalysts. The group of Gong and coworkers showed an asymmetric amplification in the reaction of para-nitrobenzaldehyde, thiourea, and ethyl acetoacetate catalyzed by the phosphoric acid (Scheme 7). The (+)-NLE effect resulted from the enhancement of the solution ee values by formation of less soluble supramolecular structures of the racemic phosphoric acid through hydrogen bonds formed with a water molecule. In contrast, the authors observed an absolutely linear effect for the same reaction under almost identical reaction conditions except that chloroform was used as the reaction medium instead of toluene. In their kinetic study’s authors showed that the optically pure phosphoric acid afforded a much faster reaction in toluene, but in chloroform, the optically pure and the racemic catalysts exhibited comparable catalytic activities.

Furthermore, when the authors compared the solubility of racemic and optically pure phosphoric acid in toluene and in chloroform, found that both the racemic and optically pure samples of phosphoric acid were soluble and formed a clear solution. However, with stirring of the toluene solution a large amount of solid precipitated from the solution containing the racemic phosphoric acid (Figure 12). Interestingly, they observed that the optically pure sample maintained a clear solution even with prolonged stirring. In contrast, authors found that both racemic and optically pure samples were very soluble in chloroform and remained as clear solutions after being stirred for 36 hours.

Scheme 7 - Asymmetric amplification in the Biginelli reaction catalyzed by phosphoric acid.
Asymmetric amplification due to difference in phase behavior of Cu-diphosphine based chiral complexes

Figure 12 - The toluene solutions of the pure enantiomer (left tube) and the racemic mixture (right tube) of the 13 upon stirring at room temperature. The white object at the bottom is the stir bar (figure source Gong et al.)

The phenomenon, that the solubility of single enantiomers differs from that of the racemate, is inherent to a compound in a given solvent and independent of the reaction at hand, making it applicable to any type of reaction using this compound. It is known that crystals of racemates are generally more stable than that of the single enantiomers but extreme differences in their stability, allowing efficient separation, are rare. Strong intermolecular interactions – often hydrogen bonding – enhances the difference in stability of the crystals. Therefore, the examples of extreme solid-solution phase behaviour described in the literature, as discussed above, may be attributed to intermolecular hydrogen bonding. Examples are BINAP, JosiPhos and particularly the industrially important XiliPhos, TaniaPhos and WalPhos-type ligands. Although crystalline solids, these ligands lack the possibility of intermolecular hydrogen bonding or ionic interactions, and large differences in solubility between racemate and single enantiomer have not been reported.
In our system there is no possibility for these kinds of intermolecular interactions when free ligands are considered. Hence the formation of metal complexes acts as a surrogate for such interactions leading to the formation of mononuclear and/or dinuclear homochiral and heterochiral species (Scheme 8a). It is reasonable to assume that this leads to the large difference in solubility of the dinuclear homo- and hetero-chiral species which results in an enantiopure supernatant. However, it is not necessarily the case that the precipitate is the dinuclear complex as in some cases the mononuclear complexes have been obtained as racemic and enantiopure solids. Hence, the observed solid-solution behaviour can be accounted for with large differences in solubility between (Scheme 8b): 1) mononuclear enantiopure and racemic complexes; 2) mononuclear enantiopure and dinuclear heterochiral complexes; 3) dinuclear homochiral and heterochiral complexes; 4) dinuclear homochiral and racemic complexes.

None of these cases can be excluded. What is certain is that metal complexation causes higher geometric rigidity of the complex, compared to the free ligands, which in turn enhances the differences in packing of racemic and enantiopure complexes.
6.2.5 Access to copper free enantiopure and racemic ferrocenyl diphosphine ligand

Next, we investigated whether it is possible to access the enantiopure free ligand \( \text{L1} \) from the corresponding scalemic copper complexes. For this purpose, a 20\% ee solution of the Cu-complex of \( \text{L1} \), in tBuOMe, was prepared and stirred for 12 h, followed by centrifugation and separation of the precipitate and supernatant (Figure 13). Both supernatant and precipitate were treated with ethylenediamine (en), in CH\(_2\)Cl\(_2\), at 0\(^\circ\)C. After 1 h, the formation of the free ligand and CuBr-(en) was complete. Upon purification using column chromatography, the enantiopure and racemic ligands of the corresponding complexes were obtained. The specific optical rotation of \( \text{L1} \) obtained from the supernatant is presented in Table 11 (entries 1 and 2).

![Figure 13 - Access to the enantiopure ligand.](image)

Measuring \([\alpha]_{D20}\) of the free ligand and CD (Figure 14) provided a more accurate ee determination due to the higher net value of the rotation. Furthermore, particles were not present in solution scattering the light and interfering with the results.

![Figure 14 - a) CD spectra of an enantiopure ligand and of ligand isolated from supernatant of complex with 20% ee measured in CH\(_2\)Cl\(_2\); b) UV spectra of the corresponding compounds.](image)
The same process was also applied to the other complexes (Table 11), in all the cases a more accurate value of optical rotation was obtained. This process of removing the copper from the complex, has been applied to the synthesis of new ligands were the asymmetric approach is deficient.

Table 11: Optical rotation values for the free ligands after treatment with ethylenediamine.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>$[\alpha]_{D}^{20}$</th>
<th>c (g/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L1-100% ee</td>
<td>-163</td>
<td>1.25 *10$^{-3}$</td>
</tr>
<tr>
<td>2</td>
<td>L1-20% ee</td>
<td>-158</td>
<td>2.76 *10$^{-3}$</td>
</tr>
<tr>
<td>3</td>
<td>L2-100% ee</td>
<td>-370</td>
<td>1.3 *10$^{-3}$</td>
</tr>
<tr>
<td>4</td>
<td>L2-20% ee</td>
<td>-363</td>
<td>0.95 *10$^{-3}$</td>
</tr>
<tr>
<td>5</td>
<td>L2-50% ee</td>
<td>-352</td>
<td>1.05 *10$^{-3}$</td>
</tr>
<tr>
<td>6</td>
<td>L3-100% ee</td>
<td>+267</td>
<td>2.5 *10$^{-3}$</td>
</tr>
<tr>
<td>7</td>
<td>L3-20% ee</td>
<td>+246</td>
<td>3.6 *10$^{-3}$</td>
</tr>
<tr>
<td>8</td>
<td>L4-100% ee</td>
<td>-13</td>
<td>2.08 *10$^{-3}$</td>
</tr>
<tr>
<td>9</td>
<td>L4-20% ee</td>
<td>-11</td>
<td>0.71 *10$^{-3}$</td>
</tr>
</tbody>
</table>

*a Optical rotation values measured in CH$_2$Cl$_2$. b Optical rotation value of the enantiopure commercially available ligand.

6.3 Conclusions

We have found that complexation of a transition metal with chiral diphosphine ligands induces an extreme difference in the solubility between the racemates and the single enantiomers, an effect which is absent in the case of the free ligands. This phenomenon is responsible for a large asymmetric amplification observed in the 1,2-addition of Grignard reagents to enones and furthermore allows the efficient separation of racemic and enantiopure complexes from a scalemic mixture by simple filtration. The metal complexation causes higher geometric rigidity of the complex, compared to the free ligands, which in turn enhances the differences in packing of racemic and enantiopure complexes.
6.4 Experimental section

6.4.1 General Remarks

Chiral ligands rev-JosiPhos-L1, JosiPhos-L2, TaniaPhos-L3 and WalPhos-L4 were donated by Solvias (Basel). BINAP-L5, CuBr·SMe2 and (C6H5CH2CN)2PdCl2 were purchased from Aldrich or Acros, and used without further purification. tBuOMe was purchased as anhydrous grade, stored on 4 Å MS and used without further purification. Solvents used were either technical grade (pentane) or distilled from the indicated drying agents (dichloromethane: P2O5). CD2Cl2 and CDCl3 were used for NMR. 1H NMR, 13C{1H} NMR, and 31P{1H} NMR spectra were obtained with Varian VXR600 (600 and 150 MHz, respectively), 500 (500 and 125 MHz, respectively), 400 (400 and 100.59 MHz respectively) spectrometers equipped with a 5 mm z-gradient broadband probe. 1H, 31P and 13C chemical shifts (δ) are reported in parts per million (ppm) and were measured relative to the residual solvent peak (CD2Cl2 δ = 5.30 ppm for hydrogen atoms, δ = 53.5 ppm for carbon atoms, CDCl3, δ = 7.26 ppm for hydrogen atoms, δ = 77.0 ppm for carbon atoms). 31P chemical shifts are referenced to the standard PPh3 (-9 ppm). Coupling constants (J) are reported in Hertz (Hz). Due to 31P coupling, resonances for certain carbon atoms in the phosphines listed below were observed as doublets. UV spectral data were obtained using a JASCO V630 DUAL BEAM spectrophotometer; CD spectra were obtained using a JASCO CD Spectropolarimeter J815. Progress of the reaction and conversion were determined by GC-MS (GC, HP6890: MS HP5973) with HP1 or HP5 columns (Agilent Technologies, Palo Alto, CA). Enantiomeric excesses (ee values) for 3 were determined by HPLC analysis using a Shimadzu LC 10ADVP HPLC equipped with a Shimadzu SPD-M10AVP diode array detector and chiral columns as indicated. Sample injections were made using an HP 6890 Series Auto sample Injector. Exact mass spectra were recorded on a LTQ Orbitrap XL (ESI+) or on a DART Xevo G2 QTof. Optical rotations were measured in tBuOMe and CH2Cl2 on a Perkin Elmer 241 MC polarimeter with a 10 cm cell (concentration c given in g/mL). To calculate the error bars for optical rotation, each rotation measurement was done several times and the standard deviation for each sample is typically a few degrees. The uncertainties in the concentration of the samples were addressed by preparing the same sample 5 times. The standard deviation was found to be 5%. Overall the uncertainties of the optical rotation values are dominated by the uncertainties in the concentration of the corresponding samples. Therefore the error budget for the specific optical rotation values have a typical error of 5%. All the reactions were performed under nitrogen atmosphere using standard Schlenk techniques. Reaction vessels were flame-dried prior to use. Flash chromatography was performed using Merck 60 Å 230-400 mesh silica gel. All organic extracts were dried over MgSO4, filtered, and concentrated under reduced pressure using a rotary evaporator.
6.4.2 1,2-addition of Grignard reagents

Standard procedure for asymmetric catalytic 1,2-addition of Grignard reagents to enones.\(^{18}\)

A Schlenk flask equipped with septum and stirring bar was charged with CuBr-SMe\(_2\) (0.015 mmol, 5 mol %) and ligand \(L1\) (0.018 mmol, 6 mol%). Dry \(t\)BuOMe (3 mL) was added and the solution was stirred under nitrogen for 30 min. Then, the corresponding enone 3 (0.3 mmol in 1 mL \(t\)BuOMe) was added and the resulting solution was cooled to \(-78\) °C. In a separate Schlenk, the corresponding Grignard reagent 4 (0.36 mmol, 1.2 eq.) was diluted with \(t\)BuOMe (combined volume of 1 mL) under nitrogen and added dropwise to the reaction mixture over 3 h using a syringe pump. Once the addition was complete, the reaction mixture was monitored by TLC and GC-MS. The reaction was quenched by the addition of MeOH (1 mL) and saturated aqueous NH\(_4\)Cl (2 mL) and the mixture was warmed to rt, diluted with Et\(_2\)O and the layers were separated. The aqueous layer was extracted with Et\(_2\)O (3 x 5 mL) and the combined organic layers were dried with anhydrous Na\(_2\)SO\(_4\), filtered and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography on silica gel using mixtures of \(n\)-pentane and Et\(_2\)O as the eluent. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, \(n\)-heptane \(i\)-PrOH 99 : 1, 40 °C, detection at 240 nm, retention times (min): 22.6 and 23.7.

Procedure for 1,2-addition of Grignard reagents to enones catalysed by a CuBr complex of scalemic rev-JosiPhos-L1:

Catalysts of varying enantiopurities (100, 80, 60, 40, 20 or 0% ee) were obtained by mixing the requisite ratios of equimolar stock solutions of the CuBr complexes of both enantiomers of rev-JosiPhos-\(L1\) in CH\(_2\)Cl\(_2\).

After stirring for 1 h, the solvent was removed in vacuo followed by addition of \(t\)BuOMe and stirring at rt for 5 h. The resulting suspension was centrifuged to provide a precipitate and a supernatant (Cu-complex of rev-JosiPhos-L1 with 20% ee needs to be centrifuged twice). The supernatant was separated, evaporated, and the resulting residue was used to catalyze the 1,2-addition reaction of Grignard reagent 4 to enone 3. We found that the enantioselectivity of the reactions catalyzed by 5 mol% of the supernatant of complexes with 80, 60, 40 and 20% ee was very similar to the results obtained with the enantiopure catalyst (5 mol% rev-JosiPhos-\(L1\), 5 mol% of CuBr-SMe\(_2\) in 3 mL of \(t\)BuOMe).

When the supernatant/precipitate mixture was used in entirety as catalyst for the 1,2-addition, the reaction was found to proceed with somewhat lower ee but longer reaction time (48 h) and vigorous stirring was required due to the presence of a significant amount of the precipitate.
6.5.3 General procedure for preparing the CuBr complexes

Procedure for preparing CuBr complex of enantiopure ligand

A solution of corresponding enantiopure ligand (0.006 mmol) and CuBr·SMe₂ (0.006 mmol) in t-BuOMe or CH₂Cl₂ (1.3 mL) in a Schlenk tube was stirred at rt for 1 h. The solvent was removed under vacuum and the resulting orange crude residue was washed with cold pentane to afford enantiopure CuBr-complex as an orange powder.

Procedure for preparing CuBr complex of racemic ligand

Method A

Equimolar solutions of both enantiomers of CuBr complex of the corresponding ligand-L (+) were prepared by mixing CuBr·SMe₂ (0.006 mmol) with enantiopure ligand-L (-) (0.006 mmol) in 1.3 mL of a solvent (CH₂Cl₂ or tBuOMe) in a Schlenk tube and stirring at rt for 1h. Corresponding solutions were mixed together, stirred for additional hour to form the racemic complex. The precipitate was formed within that period. The solvent was removed under vacuum and the resulting crude residue was washed with cold pentane and dried to afford racemic CuBr complex.

Method B

To a solution of one enantiomer L (+) (0.006 mmol) in 2.6 ml of CH₂Cl₂ the second enantiomer of the ligand L (-) (0.006 mmol) was added, followed by addition of CuBr·SMe₂ (0.0125 mmol). The resulting solution was stirred at rt for 1 h. The precipitate formed within that period. The solvent was removed under vacuum and the resulting orange crude residue was washed with cold pentane to afford racemic CuBr-complex.

Method C

To circumvent this problem we applied different approach. We prepared enantioenriched complexes (70, 50 and 20% ee) in CH₂Cl₂ using method B. After stirring for 2 h (no precipitation was observed) CH₂Cl₂ was evaporated to dryness. tBuOMe was added (0.025 M) followed by stirring at rt for 48 h. Centrifugation of these solutions resulted in a precipitate and a supernatant. CD spectra obtained from the supernatants closely matched those from the enantiopure catalyst.
6.4.4 CuBr-rev Josiphos L1

The complex was obtained as orange powder.

\((S,R)\text{-revJosiPhos-L1 CuBr enantiopure complex} \)

\(^1\text{H-NMR (500 MHz, CD}_2\text{Cl}_2\) \(\delta 7.66 (m, 2H, ArH), 7.51 - 7.40 (m, 5H, ArH), 7.29 (t, \(J = 7.2\ \text{Hz}, 2H, ArH)), 4.34 (d, \(J = 9.5\ \text{Hz}, 2H, FcH)), 4.9 (s, 1H, FcH), 4.11 (s, 5H, FcH), 3.60 (m, 1H, CH), 2.63-0.86 (m, 25H, CyH and CH}_3\). \(^3\text{P NMR (162 MHz, CD}_2\text{Cl}_2\) \(\delta -19.29 (m)\). \(^{13}\text{C-NMR (126 MHz, CD}_2\text{Cl}_2\) \(\delta 16.0 (s, CH}_3\), 22.2 (s, 1C), 22.9 (s, 1C), 25.2 (d, \(J = 18.5\ \text{Hz}, 2CH)_2\), 25.9 (d, \(J = 6.6\ \text{Hz}, 1CH, 1CH_2\), 26.3 (bs, 1CH_2), 27.1 (d, 1CH_2), 29.2 (d, 1CH_2), 29.6 (d, \(J = 4.1\ \text{Hz, 1CH}_2\), 30.7 (d, 2CH_2), 32.9 (d, 1CH), 34.3 (m,1CH_2), 38.1(d, \(J = 29.1\ \text{Hz, 1CH}_2\), 67.2 (s, 1CH), 68.1 (s, 1CH), 69.1 (s, 5CH), 72.8 (s, 1CH), 73.7(d, \(J = 29.1\ \text{Hz, 1C}_1\), 91.4 (d, 1C), 127.5 (d, \(J = 8.3\ \text{Hz, 2CH}_2\), 127.9 (d, \(J = 7.9\ \text{Hz, 2CH}_2\), 129.1 (d, 1CH), 130.1 (s, 1CH), 132.6 (d, \(J = 16.0\ \text{Hz, 2CH}_2\), 133.5 (d, \(J = 15.5\ \text{Hz, 2CH}_2\). ESI-MS (CHCl_3): 1472 [M+ (C_72H_88P_4Fe_2Cu_2Br_2)], 1393 [M+ - Br (C_36H_44P_4Fe_2Cu_2Br)], 736 [M+ - C_36H_44P_2FeCuBr]. All isotopic patterns are in agreement with those calculated. Mp (decomposition) 198-200°C.

CuBr complex \((S,R)-(R,S)\text{ rev-JosiPhos-L1 racemate} \)

No NMR measurements were performed due to the very low solubility of the racemate in any organic solvent. ESI-MS (CHCl_3): 1472 [M+ (C_72H_88P_4Fe_2Cu_2Br_2)], 1393 [M+ - Br (C_36H_44P_4Fe_2Cu_2Br)], 736 [M+ - C_36H_44P_2FeCuBr]. All isotopic patterns are in agreement with those calculated. Mp (decomposition) 250-255°C.

Isolation of rev-JosiPhos –L1 from supernatant of Cu-complex with 20% ee

The supernatant of CuBr complex of rev-Josiphos-L1 obtained in tBuOMe was evaporated and solubilized in CHCl_3 (0.005 M) followed by addition of 20 equiv of ethylenediamine at 0 °C. The resulting solution was stirred for 1 h at the same temperature. The reaction progress was followed by TLC (pentane /ethyl acetate). Purification by column chromatography (pentane /ethyl acetate) afforded the free ligand in 76% yield.

Supernatant of complex with 20% ee \([\alpha]_D^{20} = -6 \quad (c = 9.3 \times 10^{-3} \text{ g/mL in tBuOMe})\)

CuBr-rev-JosiPhos-L1 with 100% ee \([\alpha]_D^{20} = -8 \quad (c = 7.1 \times 10^{-3} \text{ g/mL in tBuOMe})\)

Free ligand from sample with 20% ee \([\alpha]_D^{20} = -158 \quad (c = 1.25 \times 10^{-3} \text{ g/mL in CHCl_3})\)

rev-JosiPhos-L1 with 100% ee \([\alpha]_D^{20} = -163 \quad (c = 2.76 \times 10^{-3} \text{ g/mL in CHCl_3})\)
Asymmetric amplification due to difference in phase behavior of Cu-diphosphine based chiral complexes

6.4.5 CuBr complex of JosiPhos-L2

(R,S) - JosiPhos-L2 CuBr enantiopure complex 

1H-NMR (500 MHz, CD2Cl2) δ 8.07 – 7.91 (m, 2H, ArH), 7.55 – 7.46 (m, 3H, ArH), 7.24-7.21 (m, 5H), 4.57 (m, 1H, FcH), 4.33-4.26 (m, 1H, FcH), 3.81 (s, 5H, ArH), 3.52-3.41 (m, 1H, CH), 2.22-0.95 (m, 25H, CyH and CH3).

31P-NMR (CD2Cl2 at rt) δ, 5.74 (d, J = 193.1 Hz), -26.61 (d, J = 194.6 Hz),

13C-NMR (126 MHz, CD2Cl2) δ 15.9 (s, CH3), 26.4 (d, J = 20.1 Hz, 2CH), 27.2 (dd, J = 10.3 Hz, 2CH), 32.0 (t, 2CH), 32.5 (d, J = 8.6 Hz, 1CH), 30.7 (d, J = 7.9 Hz, 1CH), 29.5 (d, J = 6.5 Hz, 1CH), 29.2 (d, J = 6.5 Hz, 1CH), 28.2 (d, J = 13.7 Hz, 1CH), 29.2 (d, J = 6.5 Hz, 1CH), 29.5 (d, J = 7.6 Hz, 1CH), 30.7 (m, 2CH), 32.0 (t, 2CH), 32.5(d, J = 8.6 Hz, 1CH), 70.3 (d, J = 4.3 Hz, 1CH), 70.8 (s, 5CH), 71.3 (d, J = 8.3 Hz, 1CH), 73.7 (d, J = 28.5 Hz, 1C), 94.6 (d, J = 23.4 Hz, 1C), 128.7 (d, J = 8.3 Hz, 2CH), 129.0 (d, J = 10.3 Hz, 2CH), 129.3 (s, 1CH), 131.07 (s, 1CH), 132.8 (d, J = 14.1 Hz, 2CH), 135.5 (s, J = 17.8 Hz, 2CH), 136.2 (m, 2C). ESI-MS (CH2Cl2): 1472 [M+ (C72H88P4Fe2Cu2Br2)], 1393 [M+ - Br (C36H44P2FeCuBr)], 736 [M+ - C36H44P2FeCuBr (C36H44P2FeCuBr)], 698 [M+ - Br + CH3CN (C35H56P2FeCu)]. ESI-MS (tBuOMe): 1472 [M+ (C72H88P4Fe2Cu2Br2)], 1393 [M+ - Br (C36H44P4Fe2Cu2Br)], 736 [M+ - C36H44P2FeCuBr (C36H44P4FeCuBr)]. All isotopic patterns are in agreement with those of calculated. Mp (decomposition) 176-180 °C.

CuBr complex (S,R)-(R,S)-JosiPhos-L2 racemate 

1H-NMR (500 MHz, CD2Cl2) δ 8.04 – 7.95 (m, 2H ArH), 7.57 – 7.16 (m, 3H ArH), 7.57-7.19 (m, 5H), 4.57 (m, 1H, FcH), 4.47 (t, 1H, FcH), 3.82 (s, 5H, FcH), 3.54-3.45 (m, 1H, CH), 2.20-0.73 (m, 25H, CyH and CH3).

31P-NMR (CD2Cl2 at rt) δ, 5.06 (d, J = 193.1 Hz), -26.79 (d, J = 194.6 Hz),

13C-NMR (126 MHz, CD2Cl2) δ 15.6 (s, CH3), 26.4 (d, J = 20.1 Hz, 2CH), 27.2 (dd, J=21.3, 11.9 Hz, 1CH, 1CH), 27.8 (d, J = 7.9 Hz, 1CH), 28.2 (d, J = 13.7 Hz, 1CH), 29.2 (d, J = 6.5 Hz, 1CH), 29.5 (d, J = 7.6 Hz, 1CH), 30.7 (m, 2CH), 32.0 (t, 2CH), 32.5(d, J = 8.6 Hz, 1CH), 70.3 (d, J = 4.3 Hz, 1CH), 70.8 (s, 5CH), 71.3 (d, J = 8.3 Hz, 1CH), 73.7 (d, J = 28.5 Hz, 1C), 94.6 (d, J = 23.4 Hz, 1C), 128.7 (d, J = 8.3 Hz, 2CH), 129.0 (d, J = 10.3 Hz, 2CH), 129.3 (s, 1CH), 131.07 (s, 1CH), 132.8 (d, J = 14.1 Hz, 2CH), 135.5 (s, J = 17.8 Hz, 2CH), 136.2 (m, 2C). ESI-MS (CH2Cl2): 1393 [M+ - Br (C36H44P4FeCuBr)], 698 [M+ - Br + CH3CN (C35H56P4FeCu)]. All isotopic patterns are in agreement with those of calculated. Mp (decomposition) 215-220 °C.
Determination of the solubility for racemic and enantiopure Cu-complexes of JosiPhos-L2 in tBuOMe at rt.

6.4.6 CuBr complex of racemic JosiPhos-L2

A saturated solution of racemic complex of Josiphos-L2 was prepared in tBuOMe (15 mL). The resulting heterogeneous mixture was stirred for 24 h at rt followed by centrifugation. The supernatant (15 mL) was evaporated and 1 ml of CD2Cl2 was added to the residue. The 1H and 31P-NMR analysis of the solution did not show any traces of the copper complex.

6.4.7 CuBr complex of enantiopure JosiPhos-L2

A saturated solution of the enantiopure complex of JosiPhos-L2 was prepared in tBuOMe. The resulting heterogeneous solution was stirred for 24 h at rt followed by centrifugation. Two samples of 50 µL and 100 µL of supernatant solution were transferred in an Eppendorf, evaporated and dried under vacuum overnight, followed by weight determination. 100 µL sample → 7.1 mg; 50 µL sample → 3.4 mg. Therefore the solubility of enantiopure the complex is 70 mg/mL and for the racemic complex less than 1 mg/15 mL (0.07 mg/mL).

6.4.8 CuBr complex of TaniaPhos-L3

(R,R)- TaniaPhos-L3 CuBr enantiopure complex 1H-NMR (600 MHz, CD2Cl2) δ 8.21 (t, 2H, ArH), 8.05 (bs, 2H, ArH), 7.59 – 7.40 (m, 6H, ArH), 7.33 (d, 2H, ArH), 7.23 (t, 1H, ArH), 7.06 (m, 3H, ArH), 6.99-6.96 (m, 1H, ArH), 6.90 (t, 2H, ArH), 6.65 (t, 1H, ArH), 6.39-6.34 (dt, 4H, ArH), 5.68 (d, 1H, CH), 4.95 (s, 1H, FcH), 4.61 (t, 1H, FcH), 4.13 (s, 1H, FcH), 4.05 (s, 5H, FcH), 1.96 (s, 6H, 2CH3). 31P-NMR (162 MHz, CD2Cl2) δ -26.4 – -29.4(m). ESI-MS (CH2Cl2): 843 [M+ (C44H41P2FeNCuBr)], 764 [M+ - Br + CH3CN (C44H41P2FeNCuBr)]. ESI-MS (tBuOMe): 843 [M+ (C44H41P2FeNCuBr)]. All isotopic patterns are in agreement with those of calculated. Mp (decomposition) 187-200 °C.

(R,R)-(S,S) - TaniaPhos-L3 CuBr racemic complex 1H-NMR (600 MHz, CD2Cl2) δ 8.21 (bs, 2H, ArH), 8.04 (bs, 2H, ArH), 7.59 – 7.40 (m, 6H, ArH), 7.33 (bs, 2H, ArH), 7.23 (t, 1H, ArH), 7.06 (m, 3H, ArH), 6.99-6.96 (bs, 1H, ArH), 6.90 (t, 2H ArH), 6.64 (bs, 1H, ArH), 6.39-6.34 (d, 4H, ArH), 5.69 (bs, 1H, CH), 4.94 (s, 1H, FcH), 4.61 (s, 1H, FcH), 4.13 (s, 1H, FcH), 4.05 (s, 5H,FcH), 1.95 (s, 6H, 2CH3). 31P-NMR (162 MHz, CD2Cl2) δ -26.3 – -29.7 (m). ESI-MS (CH2Cl2): 1579 [M+Br- (C46H40P4Fe4NCu4Br4)], 791 [M+Br+ CH3CN (C46H39P4Fe4NCu4CH3CN)], 753 [M+-Br-(C46H39P4Fe4NCu)]. All isotopic patterns are in agreement with those of calculated. Mp (decomposition) 206-243 °C.
Asymmetric amplification due to difference in phase behavior of Cu-diphosphine based chiral complexes

6.4.9 CuBr complex of WalPhos-L4

(R,S)-WalPhos-L4 CuBr enantiopure complex ¹H-NMR (500 MHz, CD₂Cl₂) δ 7.98 (bs, 1H, ArH), 7.76 (t, 2H, ArH), 7.47 (t, 2H, ArH), 7.44–7.35 (m, 7H, ArH), 7.22 (t, 1H, ArH), 6.87 (t, 1H, ArH), 4.23 (s, 5H, FcH), 4.11 (s, 1H, FcH), 3.98 (s, 1H, FcH), 3.14 (s, 1H, FcH), 2.65 (t, 1H, CH), 2.11 (bs, 2H, CyH), 1.92–0.85 (m, 23H, CyH and CH₃). ³¹P-NMR (162 MHz, CD₂Cl₂) δ 14.5 (d, J = 135.0 Hz), 19.1 (d, J = 139.9 Hz). ESI-MS (CH₂Cl₂): 1545 [M⁺-Br (C₈₄H₉₆P₄Fe₂Cu₂Br)], 812 [M⁺- (C₄₂H₄₈P₂FeCuBr)], 733 [M⁺-Br-(C₄₂H₄₈P₂FeCuBr)]. All isotopic patterns are in agreement with those of calculated. Mp (decomposition) 245-252 °C.

(R,R)-(S,S) –WalPhos-L4 CuBr racemic complex ¹H-NMR (500 MHz, CD₂Cl₂) δ 8.02 (bs, 1H, ArH), 7.75 (t, 2H, ArH), 7.47 (t, 1H, ArH), 7.22 (t, 1H, ArH), 7.44–7.35 (m, 7H, ArH), 7.22 (t, 1H, ArH), 6.87 (t, 1H, ArH), 4.22 (s, 5H, FcH), 4.10 (s, 1H, FcH), 3.97 (s, 1H, FcH), 3.13 (s, 1H, FcH), 2.65 (t, 1H, CH), 2.10 (t, 2H, CyH), 1.92 – 0.85 (m, 23H, CyH and CH₃). ³¹P NMR (202 MHz, CD₂Cl₂) δ -8.9 (d, J = 141.2 Hz), -24.6 (d, J = 138.5 Hz). ESI-MS (CH₃Cl): 1545 [M⁺-Br (C₈₄H₉₆P₄Fe₂Cu₂Br)], 733 [M⁺-Br-(C₄₂H₄₈P₂FeCuBr)]. All isotopic patterns are in agreement with those of calculated. Mp (decomposition) 212-218 °C.

6.4.10 CuBr complex of BINAP

(R)-(R)-Binap CuBr enantiopure complex ¹H-NMR (400 MHz, CD₂Cl₂) δ 8.14 (bs, 4H), 7.49 (t, 4H), 7.29 (m, 13H), 7.07 (t, 2H), 6.84 (d, 2H), 6.67 (t, 2H), 6.51 (t, 4H). ³¹P NMR (162 MHz, CD₂Cl₂) δ -5.45. ESI-MS (CH₃Cl): 1454.1863 [M⁺-Br (C₈₈H₆₆P₄Cu₂Br)], 767.039 [M⁺-Br (C₄₄H₃₃P₂CuBr)].

(R)-(S)-Binap CuBr racemic complex ¹H-NMR (400 MHz, CD₂Cl₂) δ 8.09 (bs, 4H), 7.39 (t, 4H), 7.30 (m, 13H), 7.12 (t, 2H), 6.99 (d, 2H), 6.69 (t, 2H), 6.53 (t, 4H). ³¹P NMR (162 MHz, CD₂Cl₂) δ -3.98. ESI-MS (CH₃Cl): 1454.1850 [M⁺-Br (C₈₈H₆₆P₄Cu₂Br)], 767.041 [M⁺-Br (C₄₄H₃₃P₂CuBr)].

6.4.11 General procedure for preparing the PdCl₂ complexes

Procedure for preparing PdCl₂ enantiopure complex

A solution of (+)-L ligand (0.006 mmol) and (C₆H₅CH₂CN)₂PdCl₂ (0.006 mmol) in CH₂Cl₂ (2 mL) in a Schlenk tube was stirred at rt for 24 h. The solvent was removed under vacuum and the residue was washed with cold pentane to afford the Pd-complex as a red powder.
Procedure for preparing PdCl₂ racemic complex

PdCl₂ (±) -L racemate was prepared by mixing the enantiomers (+) -L (0.006 mmol), (-) -L (0.006 mmol) and (C₆H₅CH₂CN)₂PdCl₂ (0.012 mmol) in 5 mL of CH₂Cl₂ in a Schlenk tube and stirring at rt for 24 h. The solvent was removed under vacuum and the residue was washed with cold pentane to afford the Pd-complex as a red powder.

6.4.12 JosiPhos-L₂ PdCl₂ complex

(S,R)-JosiPhos-L₂ PdCl₂ enantiopure complex ¹H-NMR (500 MHz, CD₂Cl₂) δ 8.28 (dd, J = 12.9, 3.8 Hz, 2H, ArH), 7.63 (s, 3H, ArH), 7.57 – 7.42 (m, 3H, ArH), 7.38 (d, J = 5.3 Hz, 2H, ArH), 4.64 (s, 1H, FcH), 4.41 (s, 1H, FcH), 4.20 (s, 1H, FcH), 3.73 (s, 5H, FcH), 3.30 (m, 1H, ), 2.50 – 0.72 (m, 25H, CyH, and CH₃). ³¹P-NMR (202 MHz, CD₂Cl₂) δ 71.3 (d, J = 5.0 Hz), 12.4 (d, J = 5.0 Hz). ESI-MS (CH₂Cl₂): 1505 [M⁺-Cl(C₇₂H₈₈P₄Fe₂Pd₂Cl)], 735 [M⁺-C₇₂H₈₈P₄Fe₂Pd₂Cl₂-(C₃₆H₄₄P₂FePdCl)]. All isotopic patterns are in agreement with those calculated. Mp 156-167 °C.

(S,R)-(R,S) JosiPhos-L₂ PdCl₂ racemic complex ¹H-NMR (500 MHz, CD₂Cl₂) δ 8.28 (dd, J = 12.9, 3.8 Hz, 2H, ArH), 7.63 (s, 3H, ArH), 7.57 – 7.42 (m, 3H, ArH), 7.38 (d, J = 5.3 Hz, 2H, ArH), 4.64 (s, 1H, FcH), 4.41 (s, 1H, FcH), 4.20 (s, 1H, FcH), 3.73 (s, 5H, FcH), 3.30 (m, 1H, ), 2.50 – 0.72 (m, 25H, CyH, and CH₃). ³¹P-NMR (202 MHz, CD₂Cl₂) δ 77.1 (d, J = 5.0 Hz), 18.2 (d, J = 5.0 Hz). ESI-MS (CH₂Cl₂): 1505 [M⁺-Cl(C₇₂H₈₈P₄Fe₂Pd₂Cl)], 735 [M⁺-C₇₂H₈₈P₄Fe₂Pd₂Cl₂-(C₃₆H₄₄P₂FePdCl)]. All isotopic patterns are in agreement with those calculated. Mp 190-202 °C.

Precipitation studies

Solution 1 (S,R)-JosiPhos-L₂ PdCl₂ - A solution of (S,R)-JosiPhos-L₂ (0.034 mmol) and (C₆H₅CH₂CN)₂PdCl₂ (0.034 mmol) in tBuOMe (2.2 mL) and CH₂Cl₂ (500 μL) in a Schlenk tube was stirred at rt for 24 h.

Solution 2 (R,S)-JosiPhos-L₂ PdCl₂ - A solution of (R,S)-JosiPhos-L₂ (0.012 mmol) and (C₆H₅CH₂CN)₂PdCl₂ (0.012 mmol) in tBuOMe (0.8 mL) and CH₂Cl₂ (100 μL) in a Schlenk tube was stirred at rt for 24 h.

CH₂Cl₂ was added due to the low solubility of both the enantiopure and racemic Pd complexes of JosiPhos-L₂ in pure tBuOMe. From these standard solutions, the corresponding enantioenriched and racemic mixtures (100, 50, 20, 0% ee) were prepared with a final volume of 1 mL. All the solutions were mixed for 12 h. Centrifugation of these solutions resulted in a precipitate and supernatant (an exception was the solution with 100% ee, which did not have any precipitate). The precipitate was washed with tBuOMe (2x5 mL) and solubilized in CH₂Cl₂.
Asymmetric amplification due to difference in phase behavior of Cu-diphosphine based chiral complexes

6.4.13 PdCl₂ complex of TaniaPhos-L3

Procedure for preparing PdCl₂ complex of enantiopure (R,R)-TaniaPhos-L3

Enantiopure and racemic PdCl₂ complexes of TaniaPhos-L3 were prepared as described earlier for the corresponding PdCl₂ complexes of JosiPhos-L2.

(R,R)-TaniaPhos-L3 PdCl₂: enantiopure complex ³¹P-NMR (202 MHz, CD₂Cl₂) δ 14.1 (s), 8.0 (s). Mp 157-160°C. ESI-MS (CH₂Cl₂): 1691 [M+Cl (C₈₆H₇₈P₄Fe₂Pd₂Cl₄)], 830 [M⁺-C₈₆H₇₈P₄Fe₂PdCl₄-(C₄₃H₃₉P₂FePdCl)]. All isotopic patterns are in agreement with those of calculated. Mp 157-160°C.

(R,R)-(S,S)-TaniaPhos-L3 PdCl₂: racemic complex ³¹P NMR (202 MHz, CD₂Cl₂) δ 14.1 (s), 8.0 (s). ESI-MS (CH₂Cl₂): 1691 [M⁺-Cl (C₈₆H₇₈P₄Fe₂Pd₂Cl₄)], 830 [M⁺-C₈₆H₇₈P₄Fe₂PdCl₄-(C₄₃H₃₉P₂FePdCl)]. All isotopic patterns are in agreement with those of calculated. Mp 195-198°C.

6.4.14 X-ray diffraction data with crystal packing characteristics

X-ray crystal structure determinations

Reflections were measured on a Bruker Kappa ApexII diffractometer with sealed tube and Triumph monochromator (0.71073 Å) at a temperature of 150(2) K. Software packages used for intensity integration were Eval15⁴⁵ (I0304, I0292) and Saint (I0297) Bruker (2001), SAINT-Plus. Bruker AXS Inc., Madison, Wisconsin, USA). Absorption correction and scaling was performed based on multiple measured reflections with SADABS and TWINABS.⁴⁶ The structures were solved by Direct Methods using the programs SHELXS-9710. Least-squares refinement was performed with SHELXL-97⁴⁷ against F² of all reflections. Non-hydrogen atoms were refined freely with anisotropic displacement parameters. Hydrogen atoms were located in difference Fourier maps and refined with a riding model. Geometry calculations and checking for higher symmetry was performed with the PLATON program.⁴⁷

rac-CuBr– rev-JosiPhos L1: CCDC 908802 (I0304a), rac-CuBr– JosiPhos: CCDC 908803 (I0292a), rac-CuBr–TaniaPhos: CCDC 908804 (I0297a) and enant. CuBr–TaniaPhos: CCDC 909403 (CP 928) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
rac-CuBr- rev-JosiPhos L1 (l0304a): C_{72}H_{88}Br_{2}Cu_{2}Fe_{2}P_{4}, Fw = 1475.90, yellow needle, 0.23 x 0.07 x 0.05 mm³, monoclinic, C2/c (no. 15), a = 25.5740(13), b = 13.1576(5), c = 21.5042(7) Å, β = 118.745(2) °, V = 6344.3(4) Å³, Z = 4, Dc = 1.545 g/cm³, = 2.51 mm⁻¹. 53920 Reflections were measured up to a resolution of (sin θ/λ)max = 0.65 Å⁻¹. 7293 Reflections were unique (Rint = 0.062), of which 5387 were observed [I>2σ(I)]. 371 Parameters were refined with no restraints. R1/wR2 [I > 2σ(I)]: 0.0333 / 0.0672. R1/wR2 [all refl.]: 0.0596 / 0.0751. S = 1.018. Residual electron density between -0.35 and 0.48 e/Å³.

rac-CuBr-JosiPhos L1 (l0292a): C_{36}H_{44}BrCuFeP_{2}, Fw = 737.95, orange block, 0.53 x 0.29 x 0.21 mm³, triclinic, P 1 (no. 2), a = 10.2840(5), b = 12.7983(6), c = 13.8363(6) Å, α = 66.466(3), β = 72.416(2), γ = 84.314(2) °, V = 1591.15(13) Å³, Z = 2, Dc = 1.540 g/cm³, μ = 2.51 mm⁻¹. The crystal consisted of several fragments and the intensity integration was performed with three orientation matrices. 32999 Reflections were measured up to a resolution of (sin θ/λ)max = 0.65 Å⁻¹. 7312 Reflections were unique (Rint = 0.022), of which 6596 were observed [I>2σ(I)]. 373 Parameters were refined with no restraints. R1/wR2 [I > 2σ(I)]: 0.0230 / 0.0577. R1/wR2 [all refl.]: 0.0271 / 0.0590. S = 1.061. Residual electron density between -0.45 and 0.39 e/Å³.

rac-CuBr-TaniaPhos L3 (l0297a): C_{43}H_{39}BrCuFePCH_{2}Cl_{2}, Fw = 915.92, yellow needle, 0.32 x 0.12 x 0.07 mm³, monoclinic, P21/c (no. 14), a = 12.7006(17), b = 15.406(2), c = 22.137(3) Å, β = 114.090(3) °, V = 3954.3(9) Å³, Z = 4, Dc = 1.539 g/cm³, = 2.16 mm⁻¹. 43034 Reflections were measured up to a resolution of (sin θ/λ)max = 0.65 Å⁻¹. 9044 Reflections were unique (Rint = 0.074), of which 5658 were observed [I>2σ(I)]. 471 Parameters were refined with no restraints. R1/wR2 [I > 2σ(I)]: 0.0476 / 0.1052. R1/wR2 [all refl.]: 0.1021 / 0.1239. S = 1.010. Residual electron density between -0.85 and 0.77 e/Å³.

Enanti-CuBr-TaniaPhos L3 (cp928): C_{43}H_{39}BrCuFeNP_{2}, M_r = 831.03, orthorhombic, P2_12_2_1, a = 11.268(3), b = 16.852(4), c = 18.885(4) Å, V = 3586.0(15) Å³, Z = 4, Dc = 1.539 g/cm³, F(000) = 1696, μ = 22.34 cm⁻¹, λ(MoKα) = 0.71073 Å, T = 100(1) K, 28199 reflections measured, Goof = 0.948, wR(F) = 0.1548 for 7340 unique reflections and 445 parameters and R(F) = 0.0623 for 4153 reflections obeying F_e ≥ 4.0 σ(F_e) criterion of observability. The asymmetric unit consists of one molecule of the title compound.
Asymmetric amplification due to difference in phase behavior of Cu-diphosphine based chiral complexes

6.5 References

Chapter 6