Total syntheses of (–)-Borrelidin and (–)-Doliculide and the development of the catalytic asymmetric addition of Grignard reagents to ketones
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2012

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Madduri Venkata, A. V. R. (2012). Total syntheses of (–)-Borrelidin and (–)-Doliculide and the development of the catalytic asymmetric addition of Grignard reagents to ketones Groningen: University of Groningen

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Chapter 6

Asymmetric Amplification in the Copper-Catalyzed 1,2-Addition of Grignard Reagents to Carbonyl Compounds

In this chapter the asymmetric amplification in the copper-catalyzed 1,2-addition of Grignard reagents to carbonyl compounds is described. This phenomenon is explained by the solid-solution equilibrium of copper ligand complex of the catalyst.

Parts of this chapter will be submitted for publication: Caprioli, F.; Madduri, A. V.; Minnaard, A. J., Harutyunyan, S. R. 2012.
6.1 Introduction

Methodology for the synthesis of enantiopure compounds includes chiral resolution, chiral-auxiliary-induced enantioselective transformations, and asymmetric catalytic reactions. Typically, the enantiopurity of the resulting product is linearly dependent on the enantiopurity of the resolving agent, auxiliary, or catalyst. Therefore, most of the catalytic enantioselective transformations can be described by the following equation (Equation 1) where the actual enantiomeric excess of the product, maximum enantiomeric excess of the product and the enantiomeric excess of a catalyst are $ee_{prod}$, $ee_{max}$ and $ee_{aux}$ respectively ($ee$ values between 0 and 1).

$$ee_{prod} (\%) = ee_{max} \times ee_{aux} \times 100$$

Equation 1:

Research in asymmetric catalysis over the last 25 years, however, has shown that many reactions can’t be described by this equation. These deviations were for the first time mathematically rationalized by Kagan, who also introduced the concept of non-linearity. Kagan analyzed various phenomena leading to a deviation from the usual linear relationship between enantiopurity of the metal complex (presence of ligand on metal) and the resulting product. A positive nonlinear effect (\(+\)-NLE), also called asymmetric amplification, is a convex deviation from the linear relationship between the enantiopurity of the chiral ligand $ee_{aux}$ and that of the product $ee_{prod}$. On the other hand, the concave deviation is termed a negative nonlinear effect (\(-\)-NLE), or asymmetric depletion (Figure 1).
Asymmetric amplification

positive nonlinear effect: asymmetric amplification

negative nonlinear effect: asymmetric amplification

Figure 1: Graph depicting the possible relations between the ee of the product versus the ee of the catalyst or auxiliary

The asymmetric amplification (+NLE) will be useful in cost effective asymmetric synthesis when compared to those using enantiomerically pure catalysts. It also provides information about mechanism of the reaction. Furthermore, it is an important phenomenon in autocatalysis.\textsuperscript{2,3}

The first reported example of a (+)-NLE, came from the Sharpless epoxidation of geraniol (1) with nonracemic (R,R\textsuperscript{+})-diethyl tartrate (DET) (Scheme 1).\textsuperscript{4} The phenomenon of asymmetric amplification in this reaction was studied by Kagan and coworkers, who observed that ee values of the epoxide were higher than those calculated using equation 1, based on the ee values of the nonracemic DET.\textsuperscript{5} To explain this phenomenon it was suggested that the heterochiral dimer was more stable, that means preferentially formed, and catalytically less active than the corresponding homochiral species.

Scheme 1: Asymmetric amplification (+)-NLE observed in the Sharpless epoxidation of Geraniol

An example of asymmetric depletion (-)-NLE was found as well, again by Kagan and coworkers, in the sulfide (thio-ether) oxidation with a water-modified Sharpless
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reagent in the presence of nonracemic \((R,R)\)-(+)\-DET. Here, the ee values of the product were found to be lower than calculated for a linear correlation. To explain the observed \((-)\)-NLE, the heterochiral dimer was proposed to be catalytically more reactive than the homochiral species. Mechanistic studies suggest that the NLEs observed in catalytic asymmetric reactions are originated from the diastereomeric associations of chiral ligands outside and/or inside the catalytic cycles.

Mechanistic studies suggest that the NLEs observed in catalytic asymmetric reactions are originated from the diastereomeric associations of chiral ligands outside and/or inside the catalytic cycles.

Scheme 2: Kagan’s ML\(_2\) model to explain the origin of NLE’s

For a better understanding of nonlinearity, Kagan and coworkers developed mathematical models involving two chiral ligands. For a catalytic system with a metal and two ligands, one can envisage mainly ML\(_2\) or (ML\(_2\)) 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. For example, Scheme 2 presents the situation for the ML\(_2\) system, assuming a dynamic equilibrium between the three complexes, ML\(_2\)L\(_R\), ML\(_2\)L\(_S\) (homochiral), and ML\(_2\)L\(_R\)L\(_S\) (heterochiral), and a fast exchange of the ligands L\(_R\) and L\(_S\) at the metal center. According to this model, the homochiral and heterochiral or meso species can generate enantiomerically pure and racemic products. The exact ratio will be dependent on the catalytic activity of the homo- and heterochiral species. ee\(_\text{prod}\) is expressed as a function of ee\(_\text{aux}\). The entities g, \(\beta\), and ee\(_\text{max}\) have fixed values for a given system, \(\beta\) can be derived from the equilibrium constant K between the homochiral and heterochiral complexes. The calculation leading to Equation 2 assumes that the initial ligand with ee\(_\text{aux}\) is fully transferred into the set of ML\(_2\) complexes, or that the external ligand retained the initial value of ee\(_\text{aux}\). A plot (shown earlier in Figure 1)
Asymmetric amplification

of ee$_{aux}$ as a function of ee$_{aux}$ affords three types of correlations: 1) (+)-NLE for $g<1$ (more reactive homochiral complex), 2) (−)-NLE for $g>1$ (more reactive meso complex) and 3) linear correlation if $b = 0$ or $g = 1$. The strength of the NLE will be higher when diastereomers are formed irreversibly rather than reversibly.

This concept can be extended to the similar model (ML)$_2$.

Another interesting model, called the reservoir model, explains a case where several metal complexes are generated during the catalyst preparation, one being the catalytically active species. These models are described in detail by Kagan and coworkers in their seminal review.

Application of these mathematic models, in particular the ML$_2$ system, has been well studied for the observed (+)-NLE in the Sharpless epoxidation. It was shown that the heterochiral dimer was more stable and less active than the homochiral species. Thus, the heterochiral dimer removes part of the racemic DET from the catalytic cycle, thereby allowing the remaining enantiomer enriched (R,R)-(−)-DET to take part in the catalytic cycle, hence leading to a (+)-NLE. Involvement of less reactive dimeric meso complex and more reactive dimeric chiral catalyst in ML$_2$ model can explain the NLE, and is consistent with the Sharpless mechanism implicating two molecules of DET in the active catalyst.

Another example of a (+)-NLE in a ML$_2$ system was reported by Maruoka and co-workers, who prepared a Ti$^{IV}$-binolate catalyst for the asymmetric alkylation of 3-phenylpropanal (3) with allyltributyltin (4) (Scheme 3). The structure of 6 (homochiral) and 7 (heterochiral) was established by mass spectrometry. Since it was not certain that these structures would remain intact during the course of the reaction, the authors took advantage of the presence of a nonlinear effect to study the structure of the catalyst in the catalytic cycle. A strong (+)-NLE was observed when 6 was prepared from partially resolved (S)-BINOL.
Another interesting case was observed by Kagan coworkers in the addition of diethylzinc to aromatic aldehydes, in the presence of trans-1,2-diaminocyclohexane-bistriflamide L1 (Figure 2).\textsuperscript{11} The asymmetric amplification originates from the insolubility of the virtually racemic catalyst precursor L1, with a concomitant large increase in ee for the minor soluble part. This was further confirmed by determination of the eutectic composition from the values of the melting points of racemic and enantiopure L1.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Asymmetric amplification observed in the addition of diethylzinc to aromatic aldehydes in the presence of trans-1,2-diaminocyclohexane bistriflamide L1}
\end{figure}
Asymmetric amplification

Inanaga and co-workers observed remarkably high levels of asymmetric amplification in the Yb([R]-BNP])_2-catalyzed (BNP = binaphthyl-2,2'-diyl phosphate) hetero-Diels-Alder reaction. To gain insight into the mechanism that led to the observed (+)-NLE, the authors carried out the reactions shown in Figure 3. The ytterbium complex was prepared from the ligand with 50% ee (R:S 75:25), and the isolated complex was treated with 2,6-lutidine in dichloromethane. Separation of the DCM soluble part, complex 8, from the insoluble part, complex 9, by centrifugation (8:9 41:59), followed by LiAlH₄ reduction of each part, afforded the corresponding BINOLs with 98% and 7% ee, respectively. In addition, complex 8 did catalyze the reaction in 90% ee and 98% yield, whereas complex 9 hardly promoted the reaction under the same reaction conditions (<1% yield). These results clearly indicate that the active catalyst A is composed entirely of the enantiopure ligand, whereas the inactive B is made from almost a 1:1 mixture of enantiomers.
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Figure 3: a) The asymmetric amplification observed in the hetero-Diels-Alder reaction with catalyst L*. b) Correlation between the THF-soluble complex and the ee of the ligand.

The groups of Blackmond and Hayashi observed a large asymmetric amplification in the proline-catalyzed aldol reaction of acetone (11) with 2-chlorobenzaldehyde (10) (Scheme 4).\(^{13-15}\) The asymmetric amplification originates from the fact that racemic proline is much less soluble than enantiopure proline. Blackmond and coworkers demonstrated that there is a comprehensive explanation of the equilibrium solid-solution phase behavior of amino acids in order to explain the origin of this asymmetric amplification.

Scheme 4: Proline catalyzed aldol reaction

Recently, Liu-Zhu Gong and coworkers showed an unprecedented asymmetric amplification in the reaction of para-nitrobenzaldehyde (13), thiourea (14), and ethyl acetoacetate (15) catalyzed by the phosphoric acid L2 (Figure 4a).\(^{16}\) 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 (Figure 4b). In their kinetic studies authors showed that the optically pure
phosphoric acid afforded a much faster reaction in toluene (Figure 4c), but in chloroform, the optically pure and the racemic catalysts exhibited comparable catalytic activities (Figure 4d).

Furthermore, when the authors compared the solubility of racemic and optically pure phosphoric acid L2 in toluene and in chloroform, found that both the racemic and optically pure samples of phosphoric acid L2 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 4e). 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.
Figure 4: Asymmetric amplification in the Biginelli reaction catalyzed by phosphoric acid L2. Left figure (a) (+)-NLE observed in toluene (b) ee dependence observed in chloroform (c) Speed of the reaction catalyzed by racemic and enantiopure L2 ligand toluene-d8 (d) Speed of the reaction catalyzed by racemic and enantiopure L2 in CDCl3. e) The toluene solutions of the pure enantiomer (left tube) and the racemic mixture (right tube) of the L2 upon with stirring at room temperature. The white object at the bottom is the stir bar (figure source Gong et al.)

A few more examples are known that show asymmetric amplification with precipitate formation of the heterochiral complexes, and these have been reviewed as well.1,17-21

Here we report a strong asymmetric amplification in the copper catalyzed asymmetric 1,2-addition of Grignard reagents to α,β-unsaturated ketones, a reaction previously discussed in Chapter 4. Furthermore, isopropanol was found to have a pronounced positive effect on the enantioselectivity of the copper catalyzed asymmetric 1,2-addition of Grignard reagents to α,β-unsaturated aldehydes.

6.2 Results and discussion

As mentioned in the introduction, asymmetric amplification phenomena are common in the catalytic asymmetric addition of organometallic reagents to carbonyl compounds. Consequently we investigated dependence of enantioselectivity of the product on enantiopurity of the catalyst, in the copper catalyzed 1,2-addition of Grignard reagents to α,β-unsaturated ketones, (discussed in chapter 3). We performed the addition of (2-ethylbutyl)magnesiumbromide 18 to enone 17
Asymmetric amplification with catalysts of varying enantiomeric excess (Table 1). We observed a non-linear dependency of the ee of product versus the ee of the catalyst used. As shown in Table 1 the ee of the product remains uninfluenced by the enantiopurity of the ligand used for catalysis. In practical terms, this implies that a catalyst of merely 20% ee is sufficient to bring about the same level of asymmetric induction as the enantiomerically pure catalyst.

Table 1: The relation between the ee of the catalyst and the ee of the product in the addition of ethylbutylmagnesium bromide to 17.

<table>
<thead>
<tr>
<th>Entry</th>
<th>L3 ee (%)a</th>
<th>catalyst loading (mol%)</th>
<th>Yield of 19 (%)</th>
<th>ee of 19 (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>5</td>
<td>94</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>6.25</td>
<td>93</td>
<td>94</td>
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<td>3</td>
<td>60</td>
<td>8.33</td>
<td>92</td>
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<td>4</td>
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<td>12.5</td>
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<td>5</td>
<td>20</td>
<td>25</td>
<td>92</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>rac</td>
<td>10</td>
<td>51</td>
<td>2</td>
</tr>
</tbody>
</table>

aTotal of 5 mol% active catalyst present in the solution. bThe enantioselectivity of the reaction is determined by chiral HPLC.

The amplification observed in our case was found to be the result of a difference in the solubility of the enantiopure and the racemic copper complex in iBuOMe, which was used as the solvent. While preparing stock solutions of L3-CuBr of different enantiopurity (ee’s of 100, 80, 60, 40, 20, 0%) by mixing solutions of CuBr•SMe2 with different ratios of (R)-L3 and (S)-L3 in iBuOMe, a precipitate was formed (Figure 5).
Figure 5: Catalyst solutions of CuBr-L3 prepared using various ratios of L3 and ent-L3 with equimolar amounts of CuBr•SMe₂. The precipitate consists of racemic complex and the mother liquor consists of the complex with 99% ee (determined by optical rotation).

It turned out that the racemic catalyst complex precipitated quantitatively in each case. Consequently, the supernatant of each sample, after centrifugation, had an identical specific rotation, corresponding to the enantiopure catalyst complex (100% ee for all the stock solutions).

This phenomenon is easily explained by the difference in solubility of the diastereomers formed during the catalyst preparation. The previously observed homochiral dimeric complex 20 stays in the mother liquor and is reactive in the 1,2-addition reactions whereas the heterochiral dimeric complex 21 precipitates from the solution (Figure 6).
Asymmetric amplification has not been reported for enantioselective reactions using ferrocenyl diphosphine-based catalysts. Since this phenomenon is inherent to the catalyst in \( t \)-BuOMe and independent of the reaction itself, it may be applied to any reaction-type using this copper complex in \( t \)-BuOMe.

### 6.2.1 Increasing enantioselectivity with progress of the reaction

In addition to the asymmetric amplification, we found another interesting feature in this copper-catalyzed 1,2-addition to enones, namely an increase in the product ee during the reaction. To understand this, we studied the kinetics of the reaction and the progress of the enantioselectivity during 1,2-addition of \( i \)BuMgBr (23) to \( \alpha,\beta \)-unsaturated ketone 22 (Scheme 6).

![Scheme 6: Catalytic asymmetric 1,2-addition of Grignard reagents to \( \alpha,\beta \)-unsaturated ketones](image)
Chapter 6

Table 2: The relation between conversion and ee in the addition of isobutylmagnesium bromide 23 to enone 22.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time(min)</th>
<th>Conversion(%)</th>
<th>ee(%)</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>

Conversions were determined by GC-MS. Regio- and enantioselectivities were determined by chiral HPLC.

The reaction was followed in time by measuring the ee and product formation (Table 2). From this Table, it is clear that an increase of ee with conversion is observed. The mechanism of this amplification is not clear but we speculate that the magnesium alkoxide of the product, formed during the course of the reaction, might be involved in the structure of the most active and selective catalyst.

6.2.2 1,2-Addition of Grignard reagents to \( \alpha,\beta \)-unsaturated aldehydes; the effect of additives

To expand the scope of this new copper(I) catalyzed 1,2-addition of organometallic reagents, also the addition of Grignard reagents to \( \alpha,\beta \)-unsaturated aldehydes was studied, both with \( \alpha \)-methyl and \( \alpha \)-bromo substituents (25, Scheme 6). For aldehydes, a considerably faster non-catalyzed background reaction compared to ketones is expected. Despite this, the Cu(I)-catalyzed 1,2-addition was still found to be competitive, and led to secondary alcohol 26a and b with significant enantioselectivities.

\[
\begin{align*}
\text{Ph} & \quad \text{H} \\
\text{O} & \quad \text{X} \\
\text{25} & \quad \text{Me}_2\text{E}^- \\
\text{23} & \quad \text{5 mol\% Cu-I} \\
& \quad \text{tBuOH, -73°C} \\
\end{align*}
\]

\( X = \text{Me}, \text{Br} \)

26a: \( X = \text{Me}, 52\% \) yield, 92\% ee

Reaction performed by using 15 mol\% \( \text{tBuOH}, 94\% \) yield, 94\% ee

26b: \( X = \text{Br}, 53\% \) yield, 62\% ee

Reaction performed by using 15 mol\% \( \text{tBuOH}, 55\% \) yield, 82\% ee
Asymmetric amplification

Scheme 6: CuBr•SMe\textsubscript{2}/L\textsubscript{3} catalyzed 1,2-addition of iBuMgBr to α,β-unsaturated aldehydes

To improve the initially observed ee’s, the effect of additives in the reaction was studied. A very interesting observation was made when 15 mol\% of isopropanol (iPrOH) was added; it increased the ee of the reaction from 60\% to 84\% and 62\% to 82\% for compound 26a and 26b, respectively (Scheme 6). When iPrOH was replaced with tertiary butanol (tBuOH), the reaction was found to be much slower, and a decrease in the enantioselectivity of the product was observed. However, iPrOH had no influence on ee’s in case of enones. Addition of 3-buten-2-ol or 2-methyl-3-buten-2-ol (alkenols mimicking the structure of the product) has no significant influence either. Furthermore, the influence of externally added magnesium alcoholates, Mg(O\textsubscript{t}Bu)\textsubscript{2} or Mg(OEt)\textsubscript{2} was studied. The reaction did not take place, perhaps due to the insolubility of magnesium alcoholates in tBuOMe.

This exact effect of the added iPrOH on increasing the ee for the 1,2-addition to enals remains unexplained. Analogous to our previous speculation (Section 6.2.1) we postulate that the magnesium isopropanoxide formed during the reaction is involved in the structure of the active catalyst. Further studies of this reaction should focus on the performing the reaction with magnesium alcoholates of the product.

6.3 Summary and concluding remarks

In this chapter we have reported an asymmetric amplification that has been observed in the copper-L\textsubscript{3} catalyzed 1,2-addition of Grignard reagents to ketones. This asymmetric amplification has been explained by the formation of a soluble homochiral and an insoluble heterochiral dimer. Asymmetric amplification phenomena are beneficial in terms of the price and availability of highly enantiopure expensive chiral ligands because it allows the use of enantiomerically impure chiral ligands.

Furthermore, the interesting phenomenon of increasing enantioselectivity with conversion in the case of α-substituted α,β-unsaturated ketones was observed. Together with the increase of enantioselectivity upon addition of isopropanol in the case of α-substituted α,β-unsaturated aldehydes as substrates, this makes a mechanistic study to understand and use these observations highly warranted.
6.4 Experimental section

General Experimental Procedures:

See the Chapter 5.

Procedure A: addition to \( \alpha \)-substituted \( \alpha, \beta \)-unsaturated aldehydes

A Schlenk flask equipped with septum and stirring bar was charged with CuBr•SMe\(_2\) (0.015 mmol, 3.08 mg, 5 mol%) and ligand L3 (0.018 mmol, 6 mol%). Dry tBuOMe (3 mL) was added and the solution was stirred under nitrogen at room temperature for 15 min. Then, the corresponding aldehyde (0.3 mmol in 1 mL tBuOMe) was added and the resulting solution was cooled to –78 °C. In a separate Schlenk, the corresponding Grignard reagent (0.36 mmol, 1.2 eq) was diluted with tBuOMe (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.

Procedure B: addition to \( \alpha \)-substituted \( \alpha, \beta \)-unsaturated aldehydes using isopropanol

A Schlenk flask equipped with septum and stirring bar was charged with CuBr•SMe\(_2\) (0.015 mmol, 3.08 mg, 5 mol%) and ligand L3 (0.018 mmol, 6 mol%). Dry tBuOMe (3 mL) was added and the solution was stirred under nitrogen at room temperature for 15 min. Then, corresponding aldehyde (0.3 mmol in 1 mL tBuOMe) and (iPrOH 0.045 mmol, 15 mol%) was added and the resulting solution was cooled to –78 °C. In a separate Schlenk, the corresponding Grignard reagent (0.54 mmol, 1.8 eq) was diluted with tBuOMe (combined volume of 1 mL) under nitrogen and added dropwise to the reaction mixture over 4 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.

Synthesis and reaction conditions for the compounds 15 and 18, see Chapter 4.
Asymmetric amplification

\((+)-(R, E)-2,5\text{-dimethyl-1-phenylhex-1-en-3-ol (20a)}: \)

Using method A: Reaction was performed with ligand \text{ent-L3} and \text{iBuMgBr}. Colorless oil obtained after column chromatography (SiO\textsubscript{2}, n-pentane:Et\textsubscript{2}O 90:10), \(20a\) [92% yield, 60% ee]. \textsuperscript{1}H NMR (201 MHz, CDCl\textsubscript{3}) \(\delta 7.41 – 7.26 (m, 3H), 7.19 (d, J = 6.7, 2H), 6.50 (s, 1H), 4.37 – 4.19 (m, 1H), 1.87 (s, 3H), 1.82 – 1.62 (m, 1H), 1.59 – 1.39 (m, 3H), 0.94 (2d, J = 6.5, 6H). \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta 140.79, 137.53, 128.94, 128.09, 126.39, 125.59, 76.40, 44.34, 24.87, 23.11, 22.45, 13.11\). [\(\delta\)] \(D\) \(20\) = +21.6 (c = 0.8, CHCl\textsubscript{3}). HRMS (ESI\textsuperscript{+}, m/z): calcd for C\textsubscript{14}H\textsubscript{20}O-OH [M-OH]\textsuperscript{+}: 187.1487; found: 187.1481. Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OD-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 240 nm, retention times (min): 31.2 (minor) and 36.1 (major). The absolute configuration of this compound is assumed to be (R), analogous to the other products. \textsuperscript{2} Using method B: Reaction was performed with ligand \text{ent-L3} and \text{iBuMgBr}. Colorless oil obtained after column chromatography (SiO\textsubscript{2}, n-pentane:Et\textsubscript{2}O 90:10), \(20a\) [94% yield, 84% ee].

\((\text{-})(S, Z)-2\text{-bromo-5-methyl-1-phenylhex-1-en-3-ol (20b)}: \)

Using method A: Reaction was performed with ligand \text{L3} and \text{iBuMgBr}. Colorless oil obtained after column chromatography (SiO\textsubscript{2}, n-pentane:Et\textsubscript{2}O 90:10), \(20b\) [83% yield, 62% ee]. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta 7.61 (d, J = 6.9, 2H), 7.34 (m, 3H), 7.05 (s, 1H), 4.33 (t, J = 6.3, 1H), 1.77 (m, 1H), 1.70 – 1.59 (m, 2H), 0.98 (2d, J = 6.5, 6H). \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta 135.07, 130.96, 129.11, 128.14, 127.94, 76.01, 45.02, 24.62, 22.66, 22.47. [\(\delta\)] \(D\) \(20\) = –26.1 (c = 0.3, CHCl\textsubscript{3}). HRMS (ESI\textsuperscript{+}, m/z): calcd for C\textsubscript{13}H\textsubscript{17}BrO-OH [M-OH]: 251.0436; found: 251.0433. Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OB-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 240 nm, retention times (min): 26.3 (minor) and 27.6 (major). The absolute configuration of this compound is assumed to be (S), analogous to the other products. Using method B: Reaction was performed with ligand \text{L3} and \text{iBuMgBr}. Colorless oil obtained after column chromatography (SiO\textsubscript{2}, n-pentane:Et\textsubscript{2}O 90:10), \(20b\) [85% yield, 82% ee].

Procedure for reaction with optically impure ligand:

Catalysts of varying enantiopurities (100, 80, 60, 40, 20 or 0%) were obtained by mixing the requisite ratios of equimolar stock solutions of Cu-L3 and Cu-\text{ent-L3} in \text{tBuOMe}. Centrifugation of these solutions resulted in a precipitate, which was found to be composed of the racemate of the complexes. The weight of the precipitate, in each case, was found to be equivalent to twice the weight of the limiting enantiomer of the added complex, indicating complete precipitation. Consequently, the supernatant was found to contain, essentially enantiopure
catalyst. Specific optical rotations obtained from the supernatant matched the specific rotation of the enantiopure catalyst. Additionally, the residue obtained by evaporating the supernatant to dryness catalyzed the 1,2 addition reaction of Grignard reagent to enones, with identical enantiomeric excess as the enantiopure catalyst. Further, when the centrifugate and supernatant were added in entirety to the reaction mixture (catalyst loadings: 6.25 mol% of 80% ee, 8.33 mol% of 60% ee and 25 mol% of 20% ee), without additional catalyst; the reaction was found to proceed with the same ee and yield. This demonstrates that the precipitate (racemic) has no influence on the reaction.

Moreover preparation of catalyst solutions Cu-L3 using varying ratios of L3 and ent-L3 with equimolar amounts of CuBr•SMe2 in tBuOMe gave similar results.

6.5 References