Enantioselective copper catalyzed allylic alkylation using Grignard reagents; Applications in synthesis
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Chapter 2
Enantioselective Cu-catalyzed allylic alkylation with Grignard reagents using ferrocenyl diphosphine ligands

In this chapter the development of a new method for copper catalyzed enantioselective allylic alkylation with Grignard reagents is described. The new catalyst system is based on ferrocenyl diphosphine ligands, the application of which was demonstrated previously in enantioselective conjugate addition. The ligand which gives the best results is Taniaphos (up to 98% ee). The use of this ligand results in a catalyst, which is complementary to previously reported systems for copper catalyzed allylic alkylation with Grignard reagents in that it gives the best results obtained thus far with methyl Grignard reagents. The scope of the reaction is explored and a range of aromatic and aliphatic substrates have been applied with excellent results.*

* This chapter has been published in part: López, F.; van Zijl, A. W.; Minnaard, A. J.; Feringa, B. L. Chem. Commun. 2006, 409-411.
2.1 Introduction

Enantioselective copper catalyzed allylic alkylation (Figure 2.1) is a powerful C-C bond forming reaction.\(^1\) It allows the formation of stereogenic centers with simple alkyl substituents, which are ubiquitous in natural products. As discussed previously in chapter 1, several catalyst systems have been reported in recent years; however, most of them suffer serious drawbacks including low selectivity or limited substrate scope. The exceptions, which include the systems reported by the groups of Hoveyda\(^2,3\) and Alexakis,\(^4\) have enabled the application of enantioselective copper catalyzed allylic alkylation with high selectivity and an appreciable substrate scope.

Hoveyda and coworkers have in fact developed two different catalytic asymmetric systems, both applicable to the allylic alkylation using dialkylzinc reagents: one system based on modular peptidic Schiff base ligands (Figure 2.1a)\(^2\) and one based on chiral N-heterocyclic carbene ligands (Figure 2.1b).\(^3\) Both systems can catalyze the allylic alkylation efficiently, providing a large range of chiral products with high selectivity.

![Figure 2.1: Asymmetric Cu-catalyzed allylic alkylation and the best chiral ligands so far: a) modular peptidic Schiff base ligand (Hoveyda); b) Ag-dimer of a NHC-ligand (Hoveyda); c) phosphoramidite ligand (Alexakis). Mes = mesitylene.](image-url)
The group of Alexakis, in contrast, has reported a catalyst system, which is effective in the enantioselective allylic alkylation using Grignard reagents. A phosphoramidite ligand was used, which comprised a binaphthol-backbone and a bis(1-(o-methoxyphenyl)ethyl)amine moiety (Figure 2.1c). High selectivities were attained with several aromatic substrates and one aliphatic substrate. The use of a methyl Grignard reagent proved to be problematic, though, especially with respect to the regioselectivity of the reaction. This was unfortunate, since the methyl group is the most common aliphatic moiety in natural products.

Grignard reagents are, in general, cheaper and easier to handle than dialkylzinc reagents and this makes their use in enantioselective reactions attractive. The fact that the introduction of a methyl group remained problematic, was an incentive to develop a new catalyst system, which could make efficient use of methyl Grignard reagent in the enantioselective copper catalyzed allylic alkylation. The new catalyst system should have a high substrate and reagent scope, excellent regio- and enantioselectivity and it should be convenient to use for synthetic chemists. An additional advantage would be a catalyst based on a readily available ligand, which in the aforementioned systems from the Hoveyda and Alexakis groups has to be synthesized in several steps.

### 2.1.1 Ferrocenyl diphosphine ligands and Grignard reagents in Cu-catalyzed conjugate addition reactions

A commercially and hence readily available ligand class (Figure 2.2) was applied recently in the copper catalyzed enantioselective conjugate addition using Grignard reagents. Prior to this, achieving high chemo-, regio- and enantioselectivity in the enantioselective conjugate addition of Grignard reagents presented a considerable challenge. This was in contrast to major successes in the use of dialkylzinc reagents. Application of Grignard reagents to Cu-catalyzed conjugate addition reactions suffered from several drawbacks. Amongst these were low regio- and enantioselectivity and in cases where the enantioselectivity was appreciably high (up to 92% ee) there was usually a restricted scope in the Grignard reagents or substrates that could be employed and a large amount of catalyst (substoichiometric chiral ligand) had to be used.
In 2004 Feringa and coworkers reported for the first time that ferrocenyl diphosphine ligands (Figure 2.2) could be employed in catalyst systems that provide for the conjugate addition of several Grignard reagents to cyclic $\alpha,\beta$-unsaturated carbonyl substrates efficiently.\(^{9}\) Unprecedented enantiomeric excesses of up to 96\% and high regioselectivities were achieved with the Taniaphos ligand $L1$ (Scheme 2.1).

\[
\text{Cu-salt} / L1 \\
\begin{array}{c}
\text{RMgX} \\
\text{Et}_2\text{O}, 0 \degree \text{C}
\end{array} \\
\rightarrow \\
\begin{array}{c}
\text{R} \\
\end{array}
\]

\[
\text{Cu-salt} / L2 \\
\begin{array}{c}
\text{RMgX} \\
t-\text{BuOMe}, -75 \degree \text{C}
\end{array} \\
\rightarrow \\
\begin{array}{c}
\text{R'} \\
\end{array}
\]

$R = \text{linear alkyl (Me, Et, n-Pr)}$  \hspace{1cm} $R' = \text{alkyl, aryl}$  \hspace{1cm} $R'' = \text{Me, OMe, SEt}$

Scheme 2.1: Cu-catalyzed enantioselective conjugate addition reactions to cyclic and acyclic substrates using Grignard reagents.

This first report was followed by several further studies demonstrating the use of these catalyst systems in the asymmetric conjugate addition to different classes of acyclic $\alpha,\beta$-unsaturated carbonyl substrates. Although a lower reaction temperature was necessary in the conjugate addition to these...
Enantioselective Cu-catalyzed allylic alkylation with Grignard reagents using ferrocenyl diphosphine ligands

acyclic substrates (Scheme 2.1), the selectivities were again excellent when using the ligand Josiphos L2 (Figure 2.1). Several distinct substrate classes, including \( \alpha,\beta \)-unsaturated ketones,\textsuperscript{10} oxoesters\textsuperscript{11} and thioesters,\textsuperscript{12} and a range of Grignard reagents could be applied with excellent results.

Insight into the mechanism was gained through spectroscopic, kinetic, electrochemical and catalysis data. A structure for the catalytically active species was proposed, together with a catalytic cycle for the reaction.\textsuperscript{13} It was found that the CuX/ligand complex forms a solvent dependent monomer/dimer equilibrium in solution. However, the dimers are broken up after addition of the Grignard reagent to form a mononuclear species associated closely with the alkylmagnesium halide (Scheme 2.2). This mononuclear species is the active catalyst and it was proposed that the rate limiting step in the catalytic cycle is the reductive elimination of a Cu(III)-\( \sigma \) adduct, in which a halogen bridges with the magnesium enolate.

The results obtained using ferrocenyl diphosphine ligands together with Grignard reagents and the wealth of information regarding the active species

Scheme 2.2: Catalytic cycle proposed for the enantioselective copper catalyzed conjugate addition using Grignard reagents.
and catalytic cycle, prompted the application of these ligands to the enantioselective copper catalyzed allylic alkylation. Although there are expected to be several differences in the mechanism of the two reactions, there are many similarities, also (Scheme 2.3). An alkyl substituent has to be transferred from the organometallic reagent to a carbon of an olefinic double bond, thereby shifting this double bond. In the case of a conjugate addition, the formation of an enolate allows this double bond shift. In the case of an allylic substitution reaction, a leaving group has to be expelled. In both cases another regiochemical outcome of the reaction is possible; 1,2-addition is competing with the conjugate addition reactions and SN2-substitution with SN2’-substitution in allylic alkylation. In general, although success of a catalyst system in one of these two reactions is no guarantee for success in the other, many catalysts can be used in both reactions, albeit with adapted conditions.

Scheme 2.3: Related copper catalyzed reactions: a) conjugate addition; b) allylic alkylation.
2.1.2 The absolute and relative configuration of Taniaphos

Taniaphos L1, amongst others, has become an important ligand in enantioselective copper catalyzed allylic alkylation. It is pertinent to discuss the structure of the compound. This is necessary, due to confusion regarding its configuration, which arose due to an erroneous representation in the first report of its synthesis and use in asymmetric catalysis in 1999.14

![Scheme 2.4: Original synthesis of Taniaphos where CBS-reduction and di-lithiation were key transformations. Note the erroneous representation of the configuration of Taniaphos.](image)

Knochel and coworkers reported the synthesis of the compound through an asymmetric CBS-reduction of o-bromophenyl(ferrocenyl)ketone, followed by substitution, di-lithiation and reaction with ClPPh₂ (Scheme 2.4). The stereochemical outcome of the CBS-reduction was known and the diastereoselectivity of the o-lithiation on the ferrocene was predicted based on the work by Ugi and coworkers. This led to the assumption that they had synthesised the (R,Sp)-stereoisomer of Taniaphos, as shown in Scheme 2.4.

In 2007 Fukuzawa et al. reported the synthesis of a ligand, assumed to be the diastereomer of Taniaphos with the configuration (R,Rp). Later however they reported that the configuration was in fact the same as for Taniaphos. The X-ray structure of the ligand in the original report by Knochel and coworkers showed that the configuration of Taniaphos was (R,Rp) also, nevertheless, the stereochemistry of (+)-Taniaphos was assigned incorrectly. In reaction to Fukuzawa’s remarks, Knochel published a corrigendum to correct the stereochemical assignment (Figure 2.3).19
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Figure 2.3: The originally reported stereochemistry versus the corrected stereochemistry of the diphosphine ligand (+)-Taniaphos.

The misassignment is of interest as initial lithiation of the arylbromide causes the amine moiety to complex the aryllithium, thus diminishing its potential for directing the o-lithiation. In my opinion, the high selectivity for lithiation on the opposite position could be attributed to cluster formation of the lithium species, which could turn the aryllithium moiety into a directing group in the o-lithiation.

Figure 2.4: X-ray crystal structures of CuCl (left) and CuBr (right) complexes with the ferrocenyl diphosphine ligand Taniaphos.

The correct stereochemistry of Taniaphos is visible also in the X-ray crystal structures of complexes of CuCl and CuBr with Taniaphos prepared in our laboratories (Figure 2.4). Remarkable is the close proximity of the
benzylic hydrogen (H41 and H23, respectively) to the metal center and the 
elongation of the benzylic C–H bond in both complexes: the interatomic 
distances (Å) for C–H are 1.1763(-) and 1.39(8) and for Cu–H they are 
2.17(-) and 1.91(8) in the CuCl and CuBr complexes, respectively. The 
Cu–H–C bond angles are 137(-) and 138(5), respectively. This could 
indicate an agostic interaction between the copper atom and the benzylic 
C–H bond of the ligand, since the bond lengths and angles in these 
complexes are within the generally expected values for agostic interactions 
reported by Brookhart et al.21

In summary, in all publications between 1999 and 2008 where 
Taniaphos is represented as the (R,Sp)-stereoisomer, the (+)-(R,Rp)- 
stereoisomer was used, instead (Figure 2.3). This includes some of the work 
presented in this thesis, which was published previously22,23 and the 
publications from this group, where Taniaphos was used in conjugate 
additions.9,10 In addition, in a recent report, which described the use of 
Taniaphos in the synthesis of chiral allylic esters, (−)-(R,S)-Taniaphos 
should be (+)-(R,Rp)-Taniaphos.24

Scheme 2.5: Stereochemical outcome in copper catalyzed 1,4-addition and allylic 
alkylation using ligands a) (R,Rp)-Taniaphos or b) (R,Sp)-Josiphos.
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The misassignment of Taniaphos is relevant, also, because it can have important implications in models to predict enantioselectivity, such as that presented by Harutyunyan et al.\textsuperscript{13} The conjugate addition of EtMgBr to cyclohexenone and other cyclic substrates affords opposite enantiomers of the product using the ligands ($R,R_p$)-Taniaphos $L_1$ and ($R,S_p$)-Josiphos $L_2$ (Scheme 2.5).\textsuperscript{9} However, conjugate addition to the acyclic enone 3-nonen-2-one results in the same enantiomer using the ligands $L_1$ and $L_2$.\textsuperscript{10}

In the copper catalyzed allylic alkylation with Grignard reagents (\textit{vide infra}) the same enantiomer is obtained with both ligands also. Clearly, the development of a general enantiodiscrimination model for these ferrocenyl diphosphine ligands in copper catalyzed reactions with Grignard reagents is not a trivial matter.
2.2 Results and Discussion

2.2.1 Asymmetric allylic alkylations with Josiphos ligands

As the best results in the conjugate addition to acyclic substrates were obtained with the ligand Josiphos L2 (Figure 2.2, vide supra), the first attempts towards allylic alkylation were performed with this ligand. Cinnamyl bromide 1a was chosen as the primary substrate and three solvents, that had shown good results in conjugate addition reactions with Grignard reagents, were tested (Table 2.1).

Table 2.1: Solvent dependence of the reaction with Josiphos L2 and cinnamyl bromide.\(^a\)

<table>
<thead>
<tr>
<th>entry</th>
<th>RMGBr</th>
<th>solvent</th>
<th>product</th>
<th>(2:3) (^b)</th>
<th>ee (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeMgBr</td>
<td>(t)-BuOMe</td>
<td>2a</td>
<td>85 : 15</td>
<td>85%</td>
</tr>
<tr>
<td>2</td>
<td>MeMgBr</td>
<td>(Et_2O)</td>
<td>2a</td>
<td>78 : 22</td>
<td>76%</td>
</tr>
<tr>
<td>3</td>
<td>MeMgBr</td>
<td>(CH_2Cl_2)</td>
<td>2a</td>
<td>49 : 51</td>
<td>73%</td>
</tr>
<tr>
<td>4(^c)</td>
<td>MeMgBr</td>
<td>(t)-BuOMe</td>
<td>2a</td>
<td>50 : 50</td>
<td>82%</td>
</tr>
<tr>
<td>5</td>
<td>EtMgBr</td>
<td>(t)-BuOMe</td>
<td>2b</td>
<td>38 : 62</td>
<td>56%</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: 1a (added after all other reagents, 1.0 equiv), RMGBr (2.5 equiv), CuBr·SMe\(_2\) (5 mol%), L2 (6 mol%), \(-75\) °C, 12 h, > 98% conversion (GC); \(^b\) Determined by GC-analysis; \(^c\) Reverse addition: RMGBr added after all other reagents.

The catalyst was formed in situ from 5 mol% CuBr·SMe\(_2\) and 6 mol% of L2. The asymmetric allylic alkylations were performed with 2.5 equivalents of methyl Grignard at \(-75\) °C with 1a added after all other reagents. Full conversion was reached in 12 h in all cases and it was found that \(t\)-BuOMe
gave the best regio- and enantioselectivity: the branched and linear products, 2 and 3, respectively, were obtained in a ratio of 85 : 15 and the enantiomeric excess for 2 was 85% (Table 2.1, entry 1). Both Et₂O and CH₂Cl₂ gave lower regio- and enantioselectivity (Table 2.1, entries 2 and 3). The order of addition of the reagents was found to be critical. Addition of the Grignard reagent after the substrate lowered the regioselectivity substantially (Table 2.1, entry 4). With ethyl Grignard reagent the results were less promising than with MeMgBr (Table 2.1, entry 5).

Table 2.2: Variation of the copper salt with Josiphos L₂ and cinnamyl bromide.

<table>
<thead>
<tr>
<th>entry</th>
<th>RMgBr</th>
<th>[Cu]</th>
<th>product</th>
<th>2 : 3</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeMgBr</td>
<td>CuBr·SMe₂</td>
<td>2a</td>
<td>85 : 15</td>
<td>85%</td>
</tr>
<tr>
<td>2</td>
<td>MeMgBr</td>
<td>CuCN</td>
<td>2a</td>
<td>85 : 15</td>
<td>86%</td>
</tr>
<tr>
<td>3</td>
<td>MeMgBr</td>
<td>CuCl</td>
<td>2a</td>
<td>85 : 15</td>
<td>84%</td>
</tr>
<tr>
<td>4</td>
<td>MeMgBr</td>
<td>[Cu(MeCN)₄]PF₆</td>
<td>2a</td>
<td>84 : 16</td>
<td>84%</td>
</tr>
<tr>
<td>5</td>
<td>MeMgBr</td>
<td>CuTC</td>
<td>2a</td>
<td>60 : 40</td>
<td>84%</td>
</tr>
<tr>
<td>6 ⁶</td>
<td>EtMgBr</td>
<td>CuCN</td>
<td>2b</td>
<td>50 : 50</td>
<td>n.d.</td>
</tr>
<tr>
<td>7 ⁶</td>
<td>EtMgBr</td>
<td>[Cu(MeCN)₄]PF₆</td>
<td>2b</td>
<td>25 : 75</td>
<td>38%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>entry</th>
<th>RMgBr</th>
<th>[Cu]</th>
<th>product</th>
<th>2 : 3</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeMgBr</td>
<td>CuBr·SMe₂</td>
<td>2a</td>
<td>85 : 15</td>
<td>85%</td>
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<tr>
<td>2</td>
<td>MeMgBr</td>
<td>CuCN</td>
<td>2a</td>
<td>85 : 15</td>
<td>86%</td>
</tr>
<tr>
<td>3</td>
<td>MeMgBr</td>
<td>CuCl</td>
<td>2a</td>
<td>85 : 15</td>
<td>84%</td>
</tr>
<tr>
<td>4</td>
<td>MeMgBr</td>
<td>[Cu(MeCN)₄]PF₆</td>
<td>2a</td>
<td>84 : 16</td>
<td>84%</td>
</tr>
<tr>
<td>5</td>
<td>MeMgBr</td>
<td>CuTC</td>
<td>2a</td>
<td>60 : 40</td>
<td>84%</td>
</tr>
<tr>
<td>6 ⁶</td>
<td>EtMgBr</td>
<td>CuCN</td>
<td>2b</td>
<td>50 : 50</td>
<td>n.d.</td>
</tr>
<tr>
<td>7 ⁶</td>
<td>EtMgBr</td>
<td>[Cu(MeCN)₄]PF₆</td>
<td>2b</td>
<td>25 : 75</td>
<td>38%</td>
</tr>
</tbody>
</table>

Table 2.2: Variation of the copper salt with Josiphos L₂ and cinnamyl bromide.

<table>
<thead>
<tr>
<th>entry</th>
<th>RMgBr</th>
<th>[Cu]</th>
<th>product</th>
<th>2 : 3</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeMgBr</td>
<td>CuBr·SMe₂</td>
<td>2a</td>
<td>85 : 15</td>
<td>85%</td>
</tr>
<tr>
<td>2</td>
<td>MeMgBr</td>
<td>CuCN</td>
<td>2a</td>
<td>85 : 15</td>
<td>86%</td>
</tr>
<tr>
<td>3</td>
<td>MeMgBr</td>
<td>CuCl</td>
<td>2a</td>
<td>85 : 15</td>
<td>84%</td>
</tr>
<tr>
<td>4</td>
<td>MeMgBr</td>
<td>[Cu(MeCN)₄]PF₆</td>
<td>2a</td>
<td>84 : 16</td>
<td>84%</td>
</tr>
<tr>
<td>5</td>
<td>MeMgBr</td>
<td>CuTC</td>
<td>2a</td>
<td>60 : 40</td>
<td>84%</td>
</tr>
<tr>
<td>6 ⁶</td>
<td>EtMgBr</td>
<td>CuCN</td>
<td>2b</td>
<td>50 : 50</td>
<td>n.d.</td>
</tr>
<tr>
<td>7 ⁶</td>
<td>EtMgBr</td>
<td>[Cu(MeCN)₄]PF₆</td>
<td>2b</td>
<td>25 : 75</td>
<td>38%</td>
</tr>
</tbody>
</table>

Subsequently, the dependence on the copper source was explored (Table 2.2). The counterion can influence the nature of the catalytically active species. However, copper salts other than CuBr·SMe₂ could be used in the allylic alkylation of 1a with MeMgBr without significant effect on the
selectivity with the exception of CuTC, which provided lower regioselectivity (Table 2.2, entries 2-5 vs entry 1). The use of other copper salts in the allylic alkylation with EtMgBr led to a very low conversion in t-BuOMe and diminished selectivity in CH2Cl2 (Table 2.2, entries 6 and 7).

In contrast to conjugate addition reactions, allylic alkylation involves the loss of a leaving group. This leaving group is important in the reaction as it changes the activity and nature of the electrophile and can also have a pronounced effect on the active catalyst species after the cleavage. For these reasons, different leaving groups were explored (Table 2.3).

The use of less active electrophiles, such as cinnamyl chloride 1b or cinnamyl acetate 1c, in the allylic alkylation with MeMgBr slowed down the reaction substantially and gave only the linear product 3 (Table 2.3, entries 2 and 3). Both cinnamyl diethyl phosphate 1d and cinnamyl methyl carbonate 1e were very slow to react in t-BuOMe, also, and gave low regioselectivity in dichloromethane (Table 2.3, entries 4-7).

Table 2.3: The effect of different leaving groups on the allylic alkylation with Josiphos L2.*

<table>
<thead>
<tr>
<th>entry</th>
<th>RMgBr</th>
<th>product</th>
<th>conversion</th>
<th>2 : 3b</th>
<th>ee b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeMgBr (2.5 eq.)</td>
<td>2a</td>
<td>&gt;98%</td>
<td>85 : 15</td>
<td>85%</td>
</tr>
<tr>
<td>2</td>
<td>MeMgBr (2.5 eq.)</td>
<td>2a</td>
<td>29%</td>
<td>0 : 100</td>
<td>-</td>
</tr>
<tr>
<td>3c</td>
<td>MeMgBr (2.5 eq.)</td>
<td>2a</td>
<td>22%</td>
<td>0 : 100</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>MeMgBr (2.5 eq.)</td>
<td>2a</td>
<td>&lt;10%</td>
<td>81 : 19</td>
<td>58%</td>
</tr>
<tr>
<td>5d,e</td>
<td>MeMgBr (1.5 eq.)</td>
<td>2a</td>
<td>75%</td>
<td>36 : 64</td>
<td>58%</td>
</tr>
</tbody>
</table>
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| 6<sup>e</sup> | 1e | MeMgBr | (1.5 eq.) | 2a | no reaction |
| 7<sup>d,e</sup> | 1e | MeMgBr | (1.5 eq.) | 2a | 25% | 8 : 92 | 57% |
| 8 | 1b | EtMgBr | (1.15 eq.) | 2b | 70% | 9 : 91 | 0% |
| 9<sup>d</sup> | 1b | EtMgBr | (1.15 eq.) | 2b | >98% | 57 : 43 | 36% |
| 10<sup>d,e</sup> | 1b | EtMgBr | (1.15 eq.) | 2b | 96% | 74 : 26 | 40% |
| 11<sup>d</sup> | 1d | EtMgBr | (1.5 eq.) | 2b | >98% | 13 : 87 | 20% |

<sup>a</sup> Reaction conditions: I (added as the last reagent, 1.0 equiv), RMgBr (2.5 equiv), CuBr·SMe₂ (5 mol%), L₂ (6 mol%), t-BuOMe, −75 °C, 12 h; b Determined by GC-analysis; c Reaction temperature: −75 °C → −30 °C; d CH₂Cl₂ as solvent; e Copper source: [Cu(MeCN)₄]PF₆.

In the case of ethylmagnesium bromide, although the regioselectivity could be improved by using cinnamyl chloride in CH₂Cl₂ with [Cu(MeCN)₄]PF₆, the enantioselectivity remained low (Table 2.3, entries 8-10). With cinnamyl diethyl phosphate (Table 2.3, entry 11) lower selectivities were attained than with cinnamyl bromide 1a using EtMgBr (<sup>vide supra</sup>, Table 2.1, entry 5).

Although the use of Josiphos L₂ as a ligand in the allylic alkylation with MeMgBr provided acceptable regio- and enantioselectivity (85 : 15, 86% ee), the use of EtMgBr resulted in mediocre selectivities at best. In the conjugate addition with Grignard reagents, the use of the ligand reverse-Josiphos L₃ (Figure 2.5) occasionally affords better results than L₂ (e.g. with aromatic and sterically demanding oxoesters).<sup>11</sup> Cinnamyl bromide 1a is an aromatic substrate and consequently, ligand L₃ was tested in the allylic alkylation (Table 2.4).

Figure 2.5: (R,S<sub>₅</sub>)-reverse-Josiphos L₃, (R,R<sub>₉</sub>)-Taniaphos L₁ and a few Taniaphos derivatives L₁b-d.
The use of ligand L3 with EtMgBr as the Grignard reagent in t-BuOMe did not improve the regio- or enantioselectivity (Table 2.4, entry 1). However, when the reaction was performed in CH₂Cl₂ with [Cu(MeCN)₄]PF₆ as the copper source, the branched product 2b was obtained with the highest enantiomeric excess so far, albeit with low regioselectivity (Table 2.4, entry 2). Finally, the use of cinnamyl chloride 1b and L3 as a ligand gave higher regioselectivities but lower enantioselectivities (Table 2.4, entries 3 and 4).

![Table 2.4](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>RMgBr</th>
<th>product</th>
<th>2 : 3b</th>
<th>ee b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>t-BuOMe</td>
<td>EtMgBr</td>
<td>2b</td>
<td>30 : 70</td>
<td>40%</td>
</tr>
<tr>
<td>2c</td>
<td>CH₂Cl₂</td>
<td>EtMgBr</td>
<td>2b</td>
<td>16 : 84</td>
<td>75%</td>
</tr>
<tr>
<td>3d</td>
<td>CH₂Cl₂</td>
<td>EtMgBr</td>
<td>2b</td>
<td>45 : 55</td>
<td>33%</td>
</tr>
<tr>
<td>4c,d</td>
<td>CH₂Cl₂</td>
<td>EtMgBr</td>
<td>2b</td>
<td>65 : 35</td>
<td>40%</td>
</tr>
<tr>
<td>5e</td>
<td>t-BuOMe</td>
<td>MeMgBr</td>
<td>2a</td>
<td>66 : 34</td>
<td>80%</td>
</tr>
<tr>
<td>6</td>
<td>CH₂Cl₂</td>
<td>MeMgBr</td>
<td>2a</td>
<td>20 : 80</td>
<td>40%</td>
</tr>
</tbody>
</table>

a Reaction conditions: 1a (added as the last reagent, 1.0 equiv), RMgBr (1.15 equiv), CuBr·SMe₂ (5 mol%), L3 (6 mol%), −75 °C, 12 h, conversion > 98%; b Determined by GC-analysis; c Copper source: [Cu(MeCN)₄]PF₆; d Substrate 1b was used; e RMgBr (2.5 equiv).

The reaction with reverse-Josiphos L3 as a ligand and MeMgBr as the Grignard reagent proceeded with higher enantioselectivity in t-BuOMe than in dichloromethane (Table 2.4, entries 5 and 6). The use of L2 as a ligand generally provided higher selectivities than the use of L3, however.
2.2.2 Asymmetric allylic alkylations with Taniaphos

As discussed in section 2.1, another ferrocenyldiphosphine ligand, which had performed well in conjugate addition reactions, is Taniaphos L1 (Figure 2.5). This ligand was applied in the allylic alkylation with EtMgBr as the Grignard reagent, as well (Table 2.5). When t-BuOMe was used as the solvent, the ligand Taniaphos L1 afforded similar results to those obtained with the ligands L2 and L3 (Table 2.5, entry 1). A dramatic improvement was observed when the solvent was changed for dichloromethane, though. Under these conditions, the branched product was obtained in good regioselectivity and excellent enantioselectivity (82 : 18, 96% ee, Table 2.5, entry 2). An equally remarkable improvement was observed, when MeMgBr was used as the Grignard reagent; the branched product 2a was obtained in excellent regioselectivity and enantiomeric excess (98 : 2, 97% ee, Table 2.5, entry 3).

It was found that various copper salts as well as EtMgCl as the Grignard reagent could be applied with the same high regio- and enantioselectivity (Table 2.5, entries 4-7). The use of different substrates, such as cinnamyl chloride 1b or cinnamyl diethyl phosphate 1d, gave slower reactions with lower selectivities, however (Table 2.4, entries 8 and 9). Subsequently, three other Taniaphos derivatives (L1b-d, Figure 2.5) were applied under the same conditions. These reactions gave similar results albeit with slightly lower selectivities (Table 2.5, entries 10-12).

Table 2.5: Asymmetric allylic alkylations with Taniaphos derivatives as ligands.

<table>
<thead>
<tr>
<th>entry</th>
<th>[Cu]</th>
<th>L1</th>
<th>RMgBr</th>
<th>product</th>
<th>2 : 3&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>CuBr·SMe&lt;sub&gt;2&lt;/sub&gt;</td>
<td>L1</td>
<td>EtMgBr</td>
<td>2b</td>
<td>31 : 69</td>
<td>32%</td>
</tr>
<tr>
<td>2</td>
<td>CuBr·SMe&lt;sub&gt;2&lt;/sub&gt;</td>
<td>L1</td>
<td>EtMgBr</td>
<td>2b</td>
<td>82 : 18</td>
<td>96%</td>
</tr>
</tbody>
</table>
Enantioselective Cu-catalyzed allylic alkylation with Grignard reagents using ferrocenyl diphosphine ligands

<p>| | | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>CuBr·SMe₂</td>
<td>L₁</td>
<td>MeMgBr</td>
<td>2a</td>
<td>98 : 2</td>
<td>97%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>CuTC</td>
<td>L₁</td>
<td>EtMgBr</td>
<td>2b</td>
<td>82 : 18</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>CuCl</td>
<td>L₁</td>
<td>EtMgBr</td>
<td>2b</td>
<td>82 : 18</td>
<td>95%</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Cu(MeCN)₄PF₆</td>
<td>L₁</td>
<td>EtMgBr</td>
<td>2b</td>
<td>83 : 17</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>CuBr·SMe₂</td>
<td>L₁</td>
<td>EtMgCl</td>
<td>2b</td>
<td>80 : 20</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>CuBr·SMe₂</td>
<td>L₁</td>
<td>EtMgBr</td>
<td>2b</td>
<td>80 : 20</td>
<td>88%</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>CuBr·SMe₂</td>
<td>L₁</td>
<td>EtMgBr</td>
<td>2b</td>
<td>73 : 27</td>
<td>38%</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>CuBr·SMe₂</td>
<td>L₁b</td>
<td>EtMgBr</td>
<td>2b</td>
<td>71 : 29</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>CuBr·SMe₂</td>
<td>L₁c</td>
<td>EtMgBr</td>
<td>2b</td>
<td>78 : 22</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>CuBr·SMe₂</td>
<td>L₁d</td>
<td>EtMgBr</td>
<td>2b</td>
<td>78 : 22</td>
<td>88%</td>
<td></td>
</tr>
</tbody>
</table>

*a Reaction conditions: 1a (added as the last reagent, 1.0 equiv), RMgBr (1.15 equiv), [Cu] (5 mol%), L₁ (6 mol%), CH₂Cl₂, −75 °C, 12 h, >98% conversion; b Determined by GC-analysis; c t-BuOMe as solvent; d Substrate 1b was used, 45% conversion; e Substrate 1d was used, <10% conversion. TC = 2-thiophenecarboxylate.

Having thus obtained excellent selectivities with Taniaphos as a ligand in the allylic alkylation of cinnamyl bromide with MeMgBr and EtMgBr, an exploration of the scope of the reaction was undertaken (Table 2.6). The reactions were performed, as specified previously, in dichloromethane at −75 °C and with 1.15 equiv of the Grignard reagent. The catalyst loading, however, was lowered to 1.0 mol% CuBr·SMe₂ and 1.1 mol% L₁, which did not have an adverse effect on the selectivity of the reaction with either MeMgBr or EtMgBr and the products 2a and 2b could be isolated in good yield, high regioselectivity and excellent enantiomeric excess (Table 2.6, entries 1 and 2).

Other aliphatic Grignard reagents were found to be applicable in the asymmetric allylic alkylation (Table 2.6, entries 3-5). Reactions with n-butylmagnesium bromide and 3-buten-1-ylmagnesium bromide as the Grignard reagents yielded the products 2c and 2d in excellent regio- and enantioselectivity. The use of the sterically more demanding Grignard reagent i-BuMgBr led to an incomplete reaction with very low selectivity,
though. In enantioselective conjugate additions the catalyst systems described in this chapter were found to perform better with linear aliphatic Grignard reagents than with branched ones, also.9,10

Table 2.6: Exploration of the scope of the allylic alkylation with Taniaphos L1.a

<table>
<thead>
<tr>
<th>entry</th>
<th>R’</th>
<th>product</th>
<th>yieldb</th>
<th>2 : 3c</th>
<th>ee³</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td><img src="image1.png" alt="Image" /></td>
<td>91%</td>
<td>97 : 3</td>
<td>98% (S)</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td><img src="image2.png" alt="Image" /></td>
<td>92%</td>
<td>81 : 19</td>
<td>95% (S)</td>
</tr>
<tr>
<td>3</td>
<td>n-Bu</td>
<td><img src="image3.png" alt="Image" /></td>
<td>92%</td>
<td>87 : 13</td>
<td>94% (S)</td>
</tr>
<tr>
<td>4</td>
<td>i-C₃H₇</td>
<td><img src="image4.png" alt="Image" /></td>
<td>93%</td>
<td>91 : 9</td>
<td>95% (S)</td>
</tr>
<tr>
<td>5d,e</td>
<td>i-Bu</td>
<td><img src="image5.png" alt="Image" /></td>
<td>89%f</td>
<td>42 : 58</td>
<td>6%</td>
</tr>
</tbody>
</table>
### Enantioselective Cu-catalyzed allylic alkylation with Grignard reagents using ferrocenyldiphosphine ligands

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Yield</th>
<th>Regioselectivity</th>
<th>Enantiomeric Excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>1f Me</td>
<td>95%</td>
<td>99 : 1</td>
<td>97%</td>
</tr>
<tr>
<td>7</td>
<td>1f Et</td>
<td>80%</td>
<td>82 : 18</td>
<td>96%</td>
</tr>
<tr>
<td>8</td>
<td>1g Me</td>
<td>94%</td>
<td>98 : 2</td>
<td>97%</td>
</tr>
<tr>
<td>9</td>
<td>1h Me</td>
<td>87%</td>
<td>100 : 0</td>
<td>96% (S)</td>
</tr>
<tr>
<td>10</td>
<td>1h Et</td>
<td>86%</td>
<td>87 : 13</td>
<td>90%</td>
</tr>
<tr>
<td>11</td>
<td>1i Me</td>
<td>99%</td>
<td>100 : 0</td>
<td>92%</td>
</tr>
<tr>
<td>12</td>
<td>1i Et</td>
<td>99%</td>
<td>100 : 0</td>
<td>93%</td>
</tr>
<tr>
<td>13</td>
<td>1j Et</td>
<td>20%</td>
<td>25 : 75</td>
<td>22%</td>
</tr>
</tbody>
</table>

**Reaction conditions:**
- 1a (added as the last reagent, 1.0 equiv), RMgBr (1.15 equiv), CuBr·SMe2 (1.0 mol%), L1 (1.1 mol%), CH2Cl2, −75 °C, 12 h, >98% conversion.
- Isolated yield of combined 2 and 3.
- Determined by GC-analysis.
- 5 mol% catalyst.
- R'MgBr (2.5 equiv).
- Conversion (GC).
- Reaction performed at −50 °C.

A wide range of different substrates could be applied in the reaction. In the case of other aromatic allyl bromides, substitution at the p-position or the use of 1-naphthyl allyl bromide 1h did not have an adverse effect on the selectivity (Table 2.6, entries 6-10). The products 2f-j were all obtained in good yield and excellent regioselectivity and enantiomeric excess.
Gratifyingly, the allylic alkylation of the aliphatic allyl bromide 1i with MeMgBr and EtMgBr proceeded in high selectivity, when performed with 5 mol% catalyst. A catalyst loading of 1 mol% resulted in a small but significant decrease of both the regioselectivity and the enantiomeric excess. The substrate 1j, which has R = t-Bu, was unreactive under these conditions. Although at an elevated reaction temperature of ~50 °C the products were observed, the conversion was still low and both regio- and enantioselectivity were poor.
2.3 Conclusions

In summary, a new catalyst system was developed for copper catalyzed asymmetric allylic alkylation. The catalyst system, which can be formed \textit{in situ} from CuBr·SMe\textsubscript{2} and Taniaphos L1, performs excellently with allylic bromides as substrates in dichloromethane at −75 °C. A diverse range of linear aliphatic Grignard reagents can be applied with equally high yields, regioselectivities and enantiomeric excesses. In particular, the use of MeMgBr leads to very high selectivities and this is an important achievement, since the majority of alkyl substituents at stereogenic centers in natural products are methyl groups. It should not be forgotten that the introduction of a methyl group through asymmetric allylic alkylation, either using methyl Grignard reagents or dimethylzinc, has been challenging so far\textsuperscript{1,6}

A series of aromatic allylic bromides are suitable substrates for the reaction and particularly noteworthy are the results obtained with \textit{n}-heptenyl bromide, since most catalysts previously reported do not give the same high selectivities in the asymmetric allylic alkylation of acyclic aliphatic electrophiles. However, using the ligand Taniaphos excellent enantioselectivity and full regioselectivity was achieved with this aliphatic substrate.
2.4 Experimental Part

General Remarks: $^1$H NMR spectra were recorded at 300 or 400 MHz with CDCl$_3$ as solvent. $^{13}$C NMR spectra were obtained at 75.4 or 100.59 MHz in CDCl$_3$. Chemical shifts were determined relative to the residual solvent peaks (CHCl$_3$, $\delta$ = 7.26 ppm for hydrogen atoms, $\delta$ = 77.0 for carbon atoms). The following abbreviations are used to indicate signal multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Progress and conversion of the reaction was determined by GC-MS with HP1 or HP5 columns. Enantiomeric excesses and regioselectivities were determined by capillary GC analysis using a flame ionization detector (in comparison with racemic products). Optical rotations were measured at ambient temperature in CHCl$_3$ on a Schmidt + Haensdch polarimeter (Polartronic MH8) with a 10 cm cell ($c$ given in g/100 mL). Absolute configurations of the products were determined by comparison with compounds previously published. Thin-layer chromatography (TLC) was performed on commercial Kieselgel 60F$^{254}$ silica gel plates, and components were visualized with KMnO$_4$ reagent. Flash chromatography was performed on silica gel. Drying of solutions was performed with MgSO$_4$ or Na$_2$SO$_4$. Concentrations were performed using a rotary evaporator.

Ligands L$_1$, L$_2$ and L$_3$ were generously donated by Solvias, purchased from commercial sources or prepared according to literature procedures. Taniaphos derivatives L$_{1b-d}$ were prepared according to literature procedures. Copper sources were purchased from commercial sources, and used without further purification. CuTC refers to copper thiophene-2-carboxylate. The substrates 1a-c were purchased from commercial sources. The substrates 1d, 1e, 1f-h, 1i and 1j were prepared according to literature procedures. Grignard reagents were purchased from commercial sources (EtMgBr, MeMgBr) or prepared from the corresponding alkyl bromides and magnesium turnings in Et$_2$O following standard procedures. Grignard reagents were titrated using s-BuOH and catalytic amounts of 1,10-phenanthroline. t-BuOME was purchased as anhydrous grade, stored over 4Å mol sieves and used without further purification. Et$_2$O was distilled from Na/benzophenone. CH$_2$Cl$_2$ was
distilled from CaH₂. All reactions were conducted under an argon atmosphere using standard Schlenk techniques.

Racemic products 2 and regioisomers 3 were obtained by reaction of the bromides 1 with the corresponding Grignard reagent (5.0 equiv) at −25 °C in CH₂Cl₂ in the presence of CuCN (100 mol %). In some cases, the racemic products were also obtained by using racemic-L1 ligand, following the general procedure described below. Spectroscopic and analytical data of products 2b-d, 2g, 2j were obtained from their mixtures with the corresponding compounds 3, due to inseparability by flash chromatography.

**General Procedure for the Enantioselective Cu-catalyzed Allylic Alkylation with Grignard Reagents:** In a Schlenk tube equipped with septum and stirring bar, CuBr·SMe₂ (15.0 μmol, 3.08 mg) and ligand L1 (18 μmol, 12.4 mg) were dissolved in CH₂Cl₂ (3.0 mL) and stirred under argon at room temperature for 10 min. The mixture was cooled to −75 °C and the corresponding Grignard reagent (solution in Et₂O, 1.73 mmol) was added dropwise. Allylic bromide 1 (1.50 mmol) was then added dropwise as a solution in CH₂Cl₂ over 15 min via a syringe pump. Once the addition was complete the resulting mixture was further stirred at −75 °C for 4-12 h. The reaction was quenched by addition of MeOH (0.5 mL) and the mixture was allowed to reach rt. Then, aqueous NH₄Cl solution (1M, 2 mL) was added to the mixture. The organic phase was separated, and the resulting aqueous layer was extracted with Et₂O (0.5 mL, 3x). The combined organic phases were dried and concentrated to a yellow oil, which was purified by flash chromatography to yield the corresponding products as a mixture of S_N2' (2) and S_N2 (3) regioisomers. Note: GC analysis was carried out on a sample obtained after aqueous extraction with Et₂O, which has been passed through a short plug of silica gel to remove transition metal residues.

(+)-1-((S)-But-3-en-2-yl)benzene (2a):³³

Reaction time: 4h. Purification by column chromatography (2 : 98 Et₂O/n-pentane) afforded a 97 : 3 mixture of 2a and 3a as a colorless oil. [91% yield, 2a: 98% ee, [α]D = +5.4 (e 1.2, CHCl₃), lit. ³³a (81% ee) [α]D = + 4.8 (neat), lit. ³³b for (R)-2a (60% ee) [α]D = −2.2 (e 0.7, CHCl₃)]. 2a: ¹H-NMR δ 7.28-7.14 (m, 5H), 6.02-5.93 (m, 1H), 5.04-4.98 (m, 2H), 3.47-3.40 (m, 1H), 1.33 (d, J =
7.0 Hz, 3H); $^{13}$C-NMR $\delta$ 145.5, 143.2, 128.3, 127.2, 126.0, 113.0, 43.1, 20.7. Enantioselectivity determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 75 °C, retention times (min): 15.6 (minor) and 15.8 (major); Retention time 3a: 23.7 min.

**(+)1-((S)-Pent-1-en-3-yl)benzene (2b):** $^{2,4,30}$

Reaction time: 4h. Purification by column chromatography (2 : 98 Et$_2$O/n-pentane) afforded a 81 : 19 mixture of 2b and 3b as a colorless oil. [92% yield, 2b: 95% ee, [\(\alpha\)]$_D$ = +47 (c 1.0, CHCl$_3$), lit.$^4$ (96% ee) [\(\alpha\)]$_D$ = + 55 (c 1.1, CHCl$_3$); lit.$^2$ for (R)-2b (95% ee) [\(\alpha\)]$_D$ = − 51 (c 0.5, CHCl$_3$)]. 2b: $^1$H-NMR $\delta$ 7.32-7.12 (m, 5H), 5.91 (m, 1H), 5.01-4.97 (m, 2H), 3.11 (q, $J$ = 7.4 Hz, 1H), 1.74-1.64 (m, 2H), 0.83 (t, $J$ = 7.31 Hz, 3H); $^{13}$C-NMR $\delta$ 144.4, 142.2, 128.4, 127.6, 126.1, 114.0, 51.7, 28.3, 12.1. MS (EI) $m/z$ 146 (M$^+$, 32), 128 (10), 117 (100), 91 (62). Enantioselectivity determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 75 °C for 30 min, then 5 °C/min to 100 °C (final temp), retention times (min): 26.0 (minor) and 26.2 (major); Retention time 3b: 38.0 min.

**(+)1-((S)-Hept-1-en-3-yl)benzene (2c):** $^{3,30,34}$

Reaction time: 4h. Purification by column chromatography (2 : 98 Et$_2$O/n-pentane) afforded a 87 : 13 mixture of 2c and 3c as a colorless oil. [92% yield, 94% ee, [\(\alpha\)]$_D$ = +47 (c 0.5, CHCl$_3$), lit.$^{30}$ (88% ee) [\(\alpha\)]$_D$ = + 44 (c 0.1, CHCl$_3$)]. 2c: $^1$H-NMR $\delta$ 7.21 (m, 5H), 5.95 (m, 1H), 5.02 (m, 2H), 3.32 (q, $J$ = 7.5 Hz, 1H), 1.70 (q, $J$ = 7.4 Hz, 2H), 1.39-1.02 (m, 4H), 0.87 (t, $J$ = 7.0 Hz, 3H); $^{13}$C-NMR $\delta$ 144.7, 142.5, 128.4, 127.6, 126.0, 113.8, 49.9, 35.1, 29.7, 22.6, 14.0. Enantioselectivity determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 80 °C for 60 min, then 10 °C/min to 140 °C (final temp), retention times (min): 53.7 (minor) and 54.2 (major); retention time 3c: 70.4 min.

**(+)1-((S)-Hepta-1,6-dien-3-yl)benzene (2d):** $^{2,4}$

Reaction time: 4h. Purification by column chromatography (2 : 98 Et$_2$O/n-pentane) afforded a 91 : 9 mixture of 2d and
Enantioselective Cu-catalyzed allylic alkylation with Grignard reagents using ferrocenyl diphosphine ligands

**3d** as a colorless oil. [93% yield, 95% ee, $[\alpha]_D = +36$ (c 1.5, CHCl$_3$)]

$\text{(92\% ee) } [\alpha]_D = +33 \text{ (c 1.0, CHCl}_3$). **2d**: $^1$H-NMR $\delta$ 7.30-7.16 (m, 5H), 5.95 (m, 1H), 5.79 (m, 1H), 5.03-4.92 (m, 4H), 3.26 (q, $J = 7.5$ Hz, 1H), 2.10-1.94 (m, 2H), 1.81-1.75 (m, 2H); $^{13}$C-NMR $\delta$ 144.1, 142.1, 138.4, 128.4, 127.6, 126.1, 114.6, 114.1, 49.1, 34.4, 31.5: MS (EI) m/z 172 (M$^+$, 13), 159 (6), 130 (33), 117 (100), 115 (41), 91 (48); HRMS Calcd. for C$_{13}$H$_{16}$ 172.1252, found 172.1255. Enantioselectivity determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 90°C for 45 min, then 5 °C/min to 140 °C (final temp), retention times (min): 30.0 (minor) and 30.3 (major); retention time **3d**: 56.0 min.

**(+)-1-(-But-3-en-2-yl)-4-chlorobenzene (2f):**

![Chemical structure of 2f](image)

Reaction time: 4h. Purification by column chromatography (2 : 98 Et$_2$O/n-pentane) afforded a 99 : 1 mixture of **2f** and **3f** as a colorless oil. [95% yield, 97% ee, $[\alpha]_D = +12$ (c 1.6, CHCl$_3$)]. **2f**: $^1$H-NMR $\delta$ 7.29 (d, $J = 8.5$ Hz, 2H), 7.07 (d, $J = 8.5$ Hz, 2H), 6.00-5.90 (m, 1H), 5.06-4.97 (m, 2H), 3.44-3.36 (m, 1H), 1.32 (d, $J = 7.0$ Hz, 3H); MS (EI) m/z 166 (M$^+$, 47), 165 (9), 151 (46), 139 (10), 131 (68), 91 (100); HRMS Calcd. for C$_{10}$H$_{11}$Cl 166.0549, found 166.0557. Enantioselectivity determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 95°C for 45 min, then 2°C/min to 140 °C (final temp), retention times (min): 25.8 (minor) and 26.1 (major); retention time **3f**: 40.8 min.

**1-Chloro-4-(pent-1-en-3-yl)benzene (2g):**

![Chemical structure of 2g](image)

Reaction time: 4h. Purification by column chromatography (2 : 98 Et$_2$O/n-pentane) afforded an 82 : 18 mixture of **2g** and **3g** as a colorless oil. [80% yield, 96% ee] **2g**: $^1$H-NMR $\delta$ 7.25 (d, $J = 8.4$ Hz, 2H), 7.09 (d, $J = 8.4$ Hz, 2H), 5.88 (m, 1H), 5.00 (m, 2H), 3.10 (dt, $J = 7.7$ and 7.3 Hz, 1H), 1.69 (m, 2H), 0.83 (t, $J = 7.3$ Hz, 3H). Enantioselectivity determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 50°C, then 10°C/min to 120 °C (final temp) for 30 min, retention times (min): 19.7 (minor) and 20.1 (major).
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(+)-Methyl 4-((but-3-en-2-yl)benzoate (2h): 

Reaction time: 4h. Purification by column chromatography (2: 98 Et₂O/n-pentane) afforded a 98: 2 mixture of 2h and 3h as a colorless oil. [94% yield, 97% ee, [α]D = +12 (c 0.9, CHCl₃)]. 2h: ¹H-NMR δ 7.91 (d, J = 8.30 Hz, 2H), 7.22 (d, J = 8.30 Hz, 2H), 5.97-5.90 (m, 1H), 5.03-4.98 (m, 2H), 3.84 (s, 3H), 1.32 (d, J = 7.0 Hz, 3H); ¹³C-NMR δ 167.0, 150.9, 142.2, 129.7, 128.0, 127.2, 113.8, 51.9, 43.1, 20.5; MS (EI) m/z 190 (M⁺, 44), 159 (33), 131 (100), 115 (25), 91 (22), 59 (8); HRMS Calcd. for C₁₂H₁₄O₂ 190.0994, found 190.0997. Enantioselectivity determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 105 °C for 70 min, then 1°C/min to 140 °C (final temp), retention times (min): 71.7 (minor) and 72.1 (major); retention time 3h: 93.8 min.

(−)-1-((S)-but-3-en-2-yl)naphthalene (2i): 

Reaction time: 4h. Purification by column chromatography (2: 98 Et₂O/n-pentane) afforded 2i (3i was not observed) as a colorless oil. [87% yield, 96% ee, [α]D = -29.8 (c 1.1, CHCl₃); lit. [α]D = -29 (c 1.0, CHCl₃); lit. [α]D = -37 (neat); lit. for (R)-2i (90% ee) +16.3 (c 0.4, CHCl₃)]. 2i: ¹H-NMR δ 8.15 (d, J = 8.3 Hz, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.54-7.41 (m, 4H), 6.23-6.15 (m, 1H), 5.17-5.13 (m, 2H), 4.36-4.29 (m, 1H), 1.54 (d, J = 7.0 Hz, 3H); ¹³C-NMR δ 142.9, 141.4, 134.0, 131.4, 128.9, 126.8, 125.7, 125.6, 125.3, 123.6, 123.5, 113.6, 37.8, 20.2; MS (EI) m/z 182 (M⁺, 50), 167 (100), 165 (31), 152 (24), 84 (27), 51 (11); HRMS Calcd. for C₁₄H₁₄ 182.1096, found 182.1107. Enantioselectivity determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 120°C for 60 min, retention times (min): 35.8 (minor) and 36.3 (major); retention time 3i: 56.3 min.

(−)-1-(Pent-1-en-3-yl)naphthalene (2j): 

Reaction time: 4h. Purification by column chromatography (2: 98 Et₂O/n-pentane) afforded a 87: 13 mixture of 2j and 3j as a colorless oil. [86% yield,
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90% ee, \([\alpha]_D = \text{-}26 \ (c 1.0, \text{CHCl}_3)\]. \(2j\): \(^1\)H-NMR \(\delta 8.12 \ (d, J = 8.1 \ \text{Hz}, 1\text{H}), 7.84 \ (d, J = 7.9 \ \text{Hz}, 1\text{H}), 7.70 \ (d, J = 7.9 \ \text{Hz}, 1\text{H}), 7.51-7.36 \ (m, 4\text{H}), 6.11-6.02 \ (m, 1\text{H}), 5.11-5.07 \ (m, 2\text{H}), 4.01 \ (q, J = 7.1 \ \text{Hz}, 1\text{H}), 1.95-1.88 \ (m, 2\text{H}), 0.95 \ (t, J = 7.4 \ \text{Hz}, 3\text{H}); \(^{13}\)C-NMR \(\delta 142.8, 141.5, 135.3, 132.9, 130.0, 127.7, 126.7, 126.6, 126.4, 125.0, 124.5, 115.7, 47.1, 29.1, 13.5; \) MS (EI) \(m/z\) 196 (M\(^+\), 26), 152 (42), 139 (11), 115 (14). Enantioselectivity determined by chiral HPLC analysis, Chiralcel OD-H (99.75% heptane/iPrOH), 40°C, retention times (min): 20.4 (major) and 23.2 (minor); retention time \(3j\): 32.1 min.

3-Methylhept-1-ene (2k): \(^{39}\)

Reaction carried out using 5.0 mol% CuBr-SMe\(_2\) and 6.0 mol% L1. \(^{40}\) Reaction time: 12 h. Purification by column chromatography (2 : 98 Et\(_2\)O/n-pentane) afforded 2k (3k was not observed) as a colorless oil. [99% conversion, \(^{41}\) 92% ee]. \(2k\): \(^1\)H-NMR \(\delta 5.67-5.58 \ (m, 1\text{H}), 4.83 \ (dd, J = 10.4 \text{ and } 7.3 \ \text{Hz}, 2\text{H}), 2.05-2.01 \ (m, 1\text{H}), 1.28-1.19 \ (m, 6\text{H}), 0.91 \ (d, J = 6.7 \ \text{Hz}, 3\text{H}), 0.82 \ (t, J = 7.0 \ \text{Hz}, 3\text{H}); \(^{13}\)C-NMR \(\delta 144.9, 112.1, 37.7, 36.3, 29.4, 22.8, 20.1, 14.0. \) Enantioselectivity determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 55°C for 20 min, retention times (min): 5.4 (minor) and 5.5 (major).

3-Ethylhept-1-ene (2l): \(^{42}\)

Reaction carried out using 5.0 mol% CuBr-SMe\(_2\) and 6.0 mol% L1. \(^{43}\) Reaction time: 12 h. Purification by column chromatography (2 : 98 Et\(_2\)O/n-pentane) afforded 2l (3l was not observed) as a colorless oil. [99% conversion, \(^{41}\) 93% ee]. \(2l\): \(^1\)H-NMR \(\delta 5.51-5.42 \ (m, 1\text{H}), 4.92-4.86 \ (m, 2\text{H}), 1.80-1.77 \ (m, 1\text{H}), 1.37-1.15 \ (m, 8\text{H}), 0.85-0.78 \ (m, 6\text{H}); \(^{13}\)C-NMR \(\delta 143.4, 113.9, 45.8, 34.4, 29.4, 27.7, 22.8, 14.1, 11.6; \) MS (EI) \(m/z\) 126 (M\(^+\), 3), 97 (18), 84 (72), 69 (81), 55 (100). Enantioselectivity determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 55°C for 20 min, retention times (min): 9.8 (minor) and 9.9 (major).
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References:


5 Tissot-Croset, K.; Alexakis, A. Tetrhedron Lett. 2004, 45, 7375-7378.


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40 With 1.0 mol% CuBr·SMe2 and 1.1 mol% L1 the product 2k was obtained with 99% conversion, a regioselectivity of 100:0 and 84% ee.
41 Conversion based on GC. The high volatility of the products 2k and 2l did not allow to completely remove the solvents after the chromatography, impeding the determination of an accurate isolated yield.
43 With 1.0 mol% CuBr·SMe2 and 1.1 mol% L1 the product 2l was obtained with 99% conversion, a regioselectivity of 97:3 and 88% ee.