Chapter 5
Catalytic Asymmetric Carbon-Carbon Bond Formation via Allylic Alkylations with Organolithium Compounds

In this chapter a copper-based chiral catalytic system is reported that allows carbon-carbon bond formation via allylic alkylation with organolithium reagents with extremely high enantioselectivities and a range of substrates tolerating several functional groups. Most critical factors in achieving successful asymmetric catalysis with organolithium reagents were the solvent used and the structure of the active chiral catalyst. The active form of the catalyst has been identified through spectroscopic studies as a diphosphine copper monoalkyl species.*

* Parts of this chapter have been published: Pérez, M.; Fañanás-Mastral, M.; Bos, P. H.; Rudolph, A.; Harutyunyan, S. R.; Feringa, B. L. Nature Chem. 2011, 3, 377.
5.1 Introduction
As presented in previous chapters, carbon-carbon bond formation is the basis for the biogenesis of nature’s essential molecules. Consequently, it lies at the heart of the chemical sciences. Chiral catalyst have been developed for asymmetric C-C bond formation to yield single enantiomers from several organometallic reagents.1, 2 Remarkably, for extremely reactive organolithium compounds, which are among the most broadly used reagents in chemical synthesis, a general catalytic method for enantioselective C-C bond formation has proven elusive,3, 4 until now.5

5.1.1 Organolithium compounds in asymmetric C-C bond formation
Since their discovery by Wilhelm Schlenk in 1917,6 and his vivid description of their properties, alkyllithium reagents have beguiled the chemical community. Methyllithium was reported to be extremely reactive, burning in air with ‘a brilliant red flame with a shower of golden sparks’.7 Initially, alkyllithium compounds were not considered useful because of their instability. It is remarkable how dramatically this situation has changed over the intervening decades. Organolithium reagents have arguably become some of the most versatile and widely used reagents4, 8 in the daily repertoire of chemical synthesis, and are indispensable in the preparation of a myriad of industrial products from pharmaceuticals to polymers.3, 9

In recent decades, asymmetric catalysis has undergone substantial developments and a broad range of C-C and C-X bond formations with high enantioselectivities are currently known.1, 10, 11 In particular, less reactive organozinc,12-14 organoaluminium15-17 and Grignard18, 19 reagents have been shown to be highly effective in asymmetric carbon-carbon bond formation.20 In stark contrast, the only glimmer of hope for enantioselective reactions with organolithium reagents was in the stoichiometric use of chiral ligands (see 5.1.1.1).3, 21, 22 Tantalizingly, catalytic asymmetric reactions of organolithium reagents using high catalyst loading with a specific substrate23 (see 5.1.1.2), catalytic asymmetric deprotonations24, 25 (see 5.1.1.3) and additions to imines (see 5.1.1.4) have been reported.26-30
5.1.1.1 Stoichiometric enantioselective reactions of organolithium reagents

Corey \textit{et al.} described the use of super-stoichiometric amounts of Gilman reagent and chiral ligand to obtain conjugate addition products with up to 95\% enantiomeric excess (Scheme 1).\textsuperscript{21} Chiral ligand (\(R,S\))-\textbf{L1} was deprotonated using one equivalent of the alkyl lithium reagent, complexed with copper(I) iodide, and treated with additional organolithium reagent to generate the chiral cuprate reagent. Subsequent conjugate addition of this reagent to 2-cyclohexenone \textbf{1} gave the alkylated products in moderate to good yields (52-90\% yield) and enantiomeric excess (72-95\% ee). However, in order to obtain these results a 1:1.6-3.5 ratio of substrate to ligand was necessary. Furthermore, it was found that small amounts of alkoxide impurities in the organolithium reagent were deleterious to the enantioselectivity in this transformation.

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme1.png}
\end{center}

\textbf{Scheme 1} Stoichiometric addition of a chiral Gilman reagent.\textsuperscript{21}

As an example of the addition of organolithium reagents to imines, the group of Denmark studied the asymmetric addition of methyl lithium to imines using stoichiometric amounts of bisoxazoline ligands (Scheme 2).\textsuperscript{22} In a majority of the examples reported, the chiral amines were isolated with modest to good enantiomeric excess (44-94\% ee). However, stoichiometric amounts of chiral ligand were necessary in order to obtain satisfactory results.

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme2.png}
\end{center}

\textbf{Scheme 2} Stoichiometric asymmetric addition of MeLi to imines.\textsuperscript{22}
5.1.1.2 **Substrate specific asymmetric conjugate addition reaction of methyllithium**

In 1993, Tanaka *et al.* reported the ‘catalytic’ asymmetric conjugate addition of methyllithium to cyclic enone 5 in order to synthesize (R)-(-)-muscone with high enantiomeric excess (Scheme 3). This transformation was achieved successfully by the use of 0.36 eq of *endo-*(+)-MPATH (*endo-L3*) and 0.33 eq of copper(I) iodide. After addition of 0.33 eq of the substrate the reaction mixture was stirred for one hour. The catalytic system was regenerated by addition of MeLi and another batch of substrate was added. This sequence is repeated three times to afford the desired product in 85% yield with 99% ee. Although substoichiometric amounts of chiral catalyst are used with regard to the final product, it is actually a sequence of three times a stoichiometric conjugate addition reaction.

![Scheme 3](image)

**Scheme 3** Catalytic asymmetric conjugate addition of MeLi to 5.

5.1.1.3 **Catalytic asymmetric deprotonation**

One of the most widely used ligands employed in the asymmetric deprotonation reaction is (-)-sparteine. In most cases, this chiral diamine (L4) is used in stoichiometric asymmetric synthesis. Furthermore, only the (-)-enantiomer is commercially available. Reports on the use of substoichiometric amounts of (-)-sparteine are rare and often less successful than their stoichiometric counterparts. Good results were obtained in the catalytic deprotonation of N-Boc pyrrolidine 7 using (-)-sparteine in substoichiometric amounts (0.06-0.2 eq) (Scheme 4). In order to obtain high yield and enantioselectivity a ligand exchange process is necessary to enable the chiral ligand to be recycled. Addition of stoichiometric amounts of achiral diamine 9 produces a new organolithium/diamine complex and at the same time regenerates the active s-BuLi/(−)-sparteine complex, which can reenter the catalytic cycle. The sterically hindered s-BuLi/9 complex failed to deprotonate 7, making it a suitable candidate for ligand exchange (excess of s-BuLi/9 afforded rac-8 in 5% isolated yield). Subsequent trapping with an electrophile, such as Me3SiCl, benzophenone or Bu3SnCl provided pyrrolidine 8 in moderate yields (54-76%) and enantiomeric excess (62-88% ee).
The Boc-group is essential as it coordinates with the organolithium reagent, limiting the procedure to these substrates.

Scheme 4  Catalytic asymmetric deprotonation followed by electrophilic trapping.32

A similar approach was utilized by O’Brien et al. (Scheme 5).25 In their study of the catalytic asymmetric synthesis of the neuronkinin-1 receptor antagonist 12, substoichiometric amounts of (-)-sparteine could be used for the asymmetric deprotonation of pyrrolidine followed by electrophilic trapping with benzaldehyde. In order to use substoichiometric amounts of (-)-sparteine, addition of 1.3 eq of lithiated dimethylaminoethanol (LiDMAE) proved to be necessary. When stoichiometric amounts of (-)-sparteine were used in combination with LiDMAE, the enantiomeric excess improved significantly from 76% ee to 96% ee.

Scheme 5  Catalytic asymmetric synthesis of neuronkinin-1 receptor antagonist 12.25
In the final example discussed in this section, the dynamic resolution of N-Boc-2-lithiopiperidine 13 was used in the total synthesis of various 2-piperidine-based natural products (Scheme 6). In this catalytic dynamic resolution, chiral ligands coordinate to the metal of a chiral organolithium reagent, causing it to undergo carbanion inversion at a selected temperature and populate one stereoisomer through equilibration. After the mixture is cooled to freeze the equilibrium, reaction with an electrophile provides the enantioenriched product. Several dilithio ligands were screened for the dynamic resolution of N-Boc-piperidine 13, and (S,S)-L5 and its diastereomer (S,R)-L5 proved to be the ligands of choice in this reaction, providing access to both enantiomers of the product with excellent enantiomeric excess (up to >98%). With these enantioenriched substituted piperidines in hand, six piperidine-based natural products were synthesized.

Although the results obtained for the catalytic asymmetric deprotonation using organolithium reagents are excellent, it should be noted that in all of these examples the alkyl group of the lithium reagent is not transferred to the substrate.

5.1.1.4 Asymmetric addition of organolithium reagents to imines

The first example of a catalytic asymmetric 1,2-addition of organolithium reagents to aryl imines was reported in 1991 by Tomioka et al. (Scheme 7). Using substoichiometric amounts of chiral ligand L6 (0.05-0.5 eq) the 1,2-addition products were obtained in excellent yields with moderate enantiomeric excess (25-64% ee). Denmark et al. could improve the enantiomeric excess of this reaction in some cases (up to 82% ee) by switching to catalytic amounts of bisoxazoline-type ligands (i.e. (S,S)-L2, see section 5.1.1.1) or by using (sub)stoichiometric amounts of (-)-sparteine (0.2-1 eq).
Catalytic Asymmetric Carbon-Carbon Bond Formation via Allylic Alkylations with Organolithium Compounds

Scheme 7 Catalytic asymmetric addition of organolithium reagents to imines.\(^{26}\)

In addition, Alexakis and Amiot published the catalytic asymmetric 1,2-addition to isoquinoline \(18\).\(^{28}\) Employing substoichiometric amounts of (-)-sparteine (0.2 eq) in the addition of methyllithium to isoquinoline in toluene at -78 °C followed by trapping the intermediate with methyl chloroformate provided a mixture of products with moderate enantiomeric excess (Scheme 8). Trapping of the lithiated intermediate with methyl chloroformate proved to be necessary in order to isolate the unstable amine.

Scheme 8 Catalytic asymmetric addition of \(n\)-BuLi to isoquinoline using (-)-sparteine.\(^{28}\)

5.1.2 Properties of organolithium compounds

As already mentioned, organolithium reagents are amongst the most versatile and most widely used reagents in synthetic organic chemistry.\(^4\) \(^8\) Commercially available organolithium reagents are used from small scale synthetic applications up to large scale industrial processes and are generally cheaper than organometallic reagents based on zinc, aluminium or magnesium (Table 1). Furthermore, organolithium reagents are easily and reliably accessible and have the additional advantage that they can be applied directly as opposed to heteroarylaluminium reagents, for example, which are synthesized from the corresponding aryllithium.\(^{33}\)
Due to their strongly polarized carbon-lithium bond, organolithium reagents are used as highly reactive nucleophiles and as strong bases. An important feature of organolithium reagents is their structure-reactivity relationship. An excellent overview of the current knowledge in this field was reported by Strohmann et al. In general, organolithium reagents are often depicted schematically as monomeric species with one lithium atom and a carbanionic group, such as MeLi or \( n \)-BuLi. In reality, the structure of these compounds is much more complicated. Without the addition of Lewis bases, organolithium reagents tend to form oligomeric structures. Depending on the nature of the organolithium reagent predominantly hexamers and tetramers are observed. A higher order aggregation state results in a decrease in the reactivity of the organolithium reagent and similarly, a decrease in the degree of aggregation increases the reactivity. Therefore, control over the aggregation state is important to find the right balance between reactivity and selectivity. An overview of aggregation states found for various organolithium reagents is displayed in Table 2 and in general the reactivity of the aggregates is as follows: Monomeric > Dimeric > Tetrameric > Hexameric.

<table>
<thead>
<tr>
<th>Organolithium reagent</th>
<th>Methods used</th>
<th>Solvent</th>
<th>Aggregation state</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl lithium</td>
<td>X-ray crystallography and NMR</td>
<td>THF, Et₂O</td>
<td>Tetrameric</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TMEDA</td>
<td>Tetrameric</td>
</tr>
<tr>
<td>( n )-Butyl lithium</td>
<td>IR, NMR and X-ray crystallography</td>
<td>Hydrocarbons</td>
<td>Hexameric</td>
</tr>
<tr>
<td></td>
<td></td>
<td>THF</td>
<td>Tetrameric</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TMEDA</td>
<td>Dimeric</td>
</tr>
<tr>
<td>( i )-Butyl lithium</td>
<td>X-ray crystallography</td>
<td>Hydrocarbons</td>
<td>Tetrameric</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Et₂O</td>
<td>Dimeric</td>
</tr>
<tr>
<td>( i )-Propyl lithium</td>
<td>X-ray crystallography</td>
<td>Hydrocarbons</td>
<td>Hexameric</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TMEDA</td>
<td>Dimeric</td>
</tr>
</tbody>
</table>
5.1.3 Copper-catalyzed asymmetric allylic alkylation

Together with the asymmetric conjugate addition, asymmetric allylic alkylation are among the most powerful carbon-carbon bond forming reactions (see Chapter 1). The allylic alkylation can proceed via two distinct pathways (Scheme 9). Depending on the catalytic system and the nucleophile, different ratios of $S_{N2}$ versus $S_{N2'}$ product are obtained. The palladium-catalyzed allylic substitution proceeds either via substitution with a ‘soft’ nucleophile, such as malonate, directly on allyl ligand of 22a or, in the case of ‘hard’ nucleophiles, is proposed to proceed via a transmetallation to palladium (22b) followed by reductive elimination. For the palladium-catalyzed allylic substitution different nucleophiles give a different ratio of $S_{N2}$ (23) versus $S_{N2'}$ (24) product. The copper-catalyzed version generally yields the chiral branched $S_{N2'}$ product 24 via transmetallation of the nucleophile to copper and formation of σ-alkyl intermediate followed by reductive elimination. Another advantage of copper-catalyzed allylic substitutions is that it generally is more tolerant to ‘hard’ organometallic nucleophiles.

Scheme 9 Allylic substitution. LG = leaving group.

During the past two decades significant progress was achieved in this field and numerous catalytic systems were developed suitable for a range of substrates bearing different leaving groups and with different organometallic nucleophiles. A brief overview of the copper-catalyzed allylic alkylation (AAA) with organometallic reagents is presented in Table 3.
Table 3  Overview of copper-catalyzed AAA with organometallic reagents.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Leaving group</th>
<th>Nucleophile</th>
<th>L</th>
<th>Research group</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OAc</td>
<td>RMgX</td>
<td>L7</td>
<td>Bäckvall and Van Koten et al.(^*)</td>
<td>1995</td>
</tr>
<tr>
<td>2</td>
<td>Cl</td>
<td>R(_2)Zn</td>
<td>L8</td>
<td>Knochel et al.(^*)</td>
<td>1999</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>R(_2)Zn</td>
<td>L9</td>
<td>Feringa et al.(^*)</td>
<td>2001</td>
</tr>
<tr>
<td>4</td>
<td>Cl</td>
<td>RMgX</td>
<td>L10</td>
<td>Alexakis et al.(^*)</td>
<td>2001</td>
</tr>
<tr>
<td>5</td>
<td>OPO(OEt)(_2)</td>
<td>R(_2)Zn</td>
<td>L11</td>
<td>Hoveyda et al.(^*), 43</td>
<td>2001</td>
</tr>
<tr>
<td>6</td>
<td>O-(2-pyridyl)</td>
<td>RMgX</td>
<td>L12</td>
<td>Okamoto et al.(^*)</td>
<td>2004</td>
</tr>
<tr>
<td>7</td>
<td>OPO(OEt)(_2)</td>
<td>R(_2)Zn</td>
<td>L13</td>
<td>Hoveyda et al.(^*)</td>
<td>2004</td>
</tr>
<tr>
<td>8</td>
<td>Br</td>
<td>RMgX</td>
<td>L14</td>
<td>Feringa et al.(^*), 46, 47</td>
<td>2006</td>
</tr>
<tr>
<td>9</td>
<td>OPO(OEt)(_2)</td>
<td>R(_3)Al</td>
<td>L15</td>
<td>Hoveyda et al.(^*)</td>
<td>2008</td>
</tr>
</tbody>
</table>

\(^*\) Leaving group = LG. \(^*\) Nucleophile = Nu.
5.2 Goal

The aim of this research project was to develop a general method for the highly enantioselective catalytic asymmetric allylic alkylation using extremely reactive organolithium reagents. This method should give high enantioselectivity and be able to tolerate several functional groups. Despite the great efforts, described in the introduction of this chapter, such a general method for the direct use of alkylolithium reagents for catalytic and highly enantioselective C-C bond formation had not been developed.3, 49 The main challenge of this research is to merge highly enantioselective C-C bond formation with the synthetic power and high reactivity of organolithium reagents.

5.3 Results and Discussion

5.3.1 Strategy and challenges

Several factors complicate the control of stereochemistry in this organometallic-based transformation and cause unpredictable behavior; these include the high reactivity of organolithium reagents leading to uncatalyzed reactions and the presence of aggregates35 common to organolithium reagents (see 5.1.2). It should be emphasized that, next to the desired asymmetric allylic substitution (SN2’), at least four competing pathways can occur (Scheme 10). If the leaving group exchanges with lithium, a homo-coupling reaction can occur both in a SN2’ (27) as well as in a SN2 (28) fashion. Allylic substitution would give the desired product 30 together with the linear product 29. If the substrate contains a carbonyl moiety, 1,2-addition may occur (31). Finally, if the substrate bears a alkyl- or aryl-halide, halogen-lithium exchange would lead to the formation of 32, which can give a range of other undesired side products.
5.3.2 Optimization of solvent

In order to minimize the formation of side products by finding the right balance between the reactivity of the organolithium reagent and selectivity for the desired product, we initially focused on both the co-solvent used for dilution and addition of the organolithium reagent as well as the solvent in which the catalyst and the substrate were dissolved. Initial experiments indicated that the use of dichloromethane as the solvent was absolutely essential in order to obtain the desired product with excellent regioselectivity and enantiomeric excess (see Table 5).

Using cinnamyl bromide $33a$ as the substrate, the influence of different solvents used for the dilution of $n$-butyllithium was investigated (Table 4). Initially, $n$-butyllithium $34c$ (commercially available as a 1.6 M solution in $n$-hexane) was diluted with $n$-hexane and added over 2 h to a solution of the catalyst and cinnamyl bromide $33a$ in dichloromethane at -80 °C. This afforded the desired product $35ac$ with a regioselectivity of 88:12 and with excellent enantiomeric excess (99% ee) (Table 4, entry 1). Dilution of the organolithium reagent with diethyl ether dramatically lowered both the regioselectivity (27:73) and the enantioselectivity (28% ee) (Table 4, entry 2). This can be rationalized by the change in aggregation state of the organolithium reagent, which increases the reactivity leading to a
lower selectivity for the desired product. Using the sterically more bulky ether t-BuOMe as the co-solvent restored both the regio- as well as the enantioselectivity to acceptable levels (Table 4, entry 3). Finally, next to n-hexane, toluene proved to be an excellent co-solvent as well giving good regioselectivity and excellent enantiomeric excess (Table 4, entry 4).

**Table 4** Dependence of regio- and enantioselectivity on co-solvent used for dilution of n-BuLi.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Co-solvent</th>
<th>35ac:36ac(^b)</th>
<th>ee(^c) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-hexane</td>
<td>88:12</td>
<td>99 (S)</td>
</tr>
<tr>
<td>2</td>
<td>diethyl ether</td>
<td>27:73</td>
<td>28 (S)</td>
</tr>
<tr>
<td>3</td>
<td>t-BuOMe</td>
<td>75:25</td>
<td>90 (S)</td>
</tr>
<tr>
<td>4</td>
<td>toluene</td>
<td>81:19</td>
<td>97 (S)</td>
</tr>
</tbody>
</table>

\(^a\) Conditions: n-BuLi (1.5 eq diluted to 0.3 M with the co-solvent) was added over 2 h to a mixture of 33a (0.2 mmol, 0.1 M), CuBr·Me₂S (5 mol\%) and \((R,R)\)-L\(\text{14}\) (6 mol\%) in 2 mL of CH₂Cl₂ at -80 °C and stirred overnight. \(^b\) The ratio of S\(\text{N}2':\text{SN}2\) products was determined by gas chromatography and \(^1\)H-NMR analysis. \(^c\) The enantiomeric excess was determined by chiral gas chromatography analysis (see Experimental Section). \(^d\) The absolute configuration was determined by comparison with literature data based on the sign of the optical rotation.

After optimization of the co-solvent used for dilution of the organolithium reagent, the influence of the solvent on the regio- and enantioselectivity was examined for the addition of methyllithium to cinnamyl bromide 33a (Table 5). In cases where methyllithium is used as the organolithium reagent, the use of n-hexane as co-solvent, which works the best for all the other organolithium reagents, gave solubility problems and gelation. These problems could be avoided using toluene for the dilution and addition of methyllithium. If the reaction is carried out in dichloromethane excellent regio- and enantioselectivity were obtained (Table 5, entry 1). Surprisingly, switching to a 1:1 mixture of n-hexane and dichloromethane showed an inversion of the regioselectivity and low enantiomeric excess (Table 5, entry 2). The use of toluene as a solvent resulted in a 50:50 mixture of regioisomers and very low enantiomeric selectivity (Table 5, entry 3).

Based on these results, dichloromethane was chosen as the solvent of choice for the asymmetric allylic alkylation and the organolithium reagents were diluted with n-hexane (toluene in case of MeLi) and added slowly (2-5 h) to the reaction mixture.
Table 5  Optimization of solvent.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>35aa:36aa\textsuperscript{b}</th>
<th>ee\textsuperscript{c} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH\textsubscript{2}Cl\textsubscript{2} 90:10</td>
<td>99 (S)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>n-hexane/CH\textsubscript{2}Cl\textsubscript{2}\textsuperscript{e} 15:85</td>
<td>33 (S)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>toluene\textsuperscript{c}</td>
<td>50:50</td>
<td>10 (S)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Conditions: MeLi (1.5 eq diluted to 0.3 M with toluene) was added over 2 h to a mixture of 33a (0.2 mmol, 0.1 M), CuBr·Me\textsubscript{2}S (5 mol\%) and (R,R\textsubscript{F}c)-L\textsubscript{14} (6 mol\%) in 2 mL of solvent at -80 °C and stirred overnight. \textsuperscript{b} The ratio of S\textsubscript{N}2':S\textsubscript{N}2 products was determined by gas chromatography and \textsuperscript{1}H-NMR analysis. \textsuperscript{c} The enantiomeric excess was determined by chiral gas chromatography analysis (see Experimental Section). \textsuperscript{d} The absolute configuration was determined by comparison with literature data based on the sign of the optical rotation. \textsuperscript{e} A 1:1 mixture of solvents was used. \textsuperscript{f} 5 vol\% of dichloromethane was added to improve solubility.

5.3.3 Optimization of the chiral ligand

After optimization of the solvent system a range of chiral ligands were screened in the copper-catalyzed asymmetric allylic alkylation of cinnamyl bromide 33a with \textit{n-}butyllithium 34c. Starting with ferrocenyl-type chiral diphosphines, we found that the enantioselectivity increased dramatically by changing the chiral ligand from (R,R\textsubscript{F}c)-Josiphos L\textsubscript{16} to reversed (S,R\textsubscript{F}c)-L\textsubscript{17} (Table 6, entries 1-2). However, in both cases the achiral linear product 36 resulting from a S\textsubscript{N}2 substitution reaction was predominantly found. A major increase in regioselectivity towards the branched product 35 was achieved using Binap-type ligands (R)-L\textsubscript{18}, (R)-L\textsubscript{19} and (R)-L\textsubscript{20}, and phosphoramidites (S,R,R\textsubscript{F}c)-L\textsubscript{21} and (S,S,S)-L\textsubscript{22} (Table 6, entries 3-8). Enantioselectivities up to 94\% ee were obtained using these ligands. Interestingly, high values of regio- and enantioselectivities were obtained not only when using cinnamyl bromide 33a, but also with cinnamyl chloride 33b in combination with phosphoramidite ligands (Table 6, entry 9). To our surprise, NHC-based ligand (R,R)-L\textsubscript{23} gave full selectivity for the linear achiral product (36) (Table 6, entry 10). The highest enantioselectivities for cinnamyl bromide 33a were reached in the S\textsubscript{N}2\textsuperscript{allylic alkylation with the copper catalyst based on (R,R\textsubscript{F}c)-Taniaphos L\textsubscript{14} (Table 6, entry 11). An intriguing observation is that both monodentate (phosphoramidites L\textsubscript{21} and L\textsubscript{22}) and bidentate (L\textsubscript{17}, L\textsubscript{18}, L\textsubscript{19}, L\textsubscript{20} and L\textsubscript{14}) chiral ligands are effective in controlling the stereoselectivity in the carbon-carbon bond formation with \textit{n-}butyllithium.
Table 6  Screening of chiral ligands for the asymmetric allylic alkylation.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Ligand</th>
<th>S(<em>{\text{N}2'}):S(</em>{\text{N}2})</th>
<th>ee(^\circ) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>L(_{16})</td>
<td>23:77</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>L(_{17})</td>
<td>17:83</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>L(_{18})</td>
<td>61:39</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>L(_{19})</td>
<td>74:26</td>
<td>91</td>
</tr>
<tr>
<td>5(^d)</td>
<td>Br</td>
<td>L(_{19})</td>
<td>71:29</td>
<td>92</td>
</tr>
<tr>
<td>6(^d)</td>
<td>Br</td>
<td>L(_{20})</td>
<td>87:13</td>
<td>94</td>
</tr>
<tr>
<td>7(^e)</td>
<td>Br</td>
<td>L(_{21})</td>
<td>73:27</td>
<td>62</td>
</tr>
<tr>
<td>8</td>
<td>Br</td>
<td>L(_{22})</td>
<td>87:13</td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td>Cl</td>
<td>L(_{22})</td>
<td>91:9</td>
<td>95</td>
</tr>
<tr>
<td>10</td>
<td>Br</td>
<td>L(_{23})</td>
<td>0:100</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>Br</td>
<td>L(_{14})</td>
<td>88:12</td>
<td>99</td>
</tr>
</tbody>
</table>

\(^a\) Conditions: \(n\)-BuLi (1.5 eq diluted to 0.3 M with CH\(_2\)Cl\(_2\)) was added over 2 h to a mixture of 33 (0.2 mmol, 0.1 M), CuBr·Me\(_2\)S (5 mol%) and the chiral ligand L (6 mol%) in 2 mL of CH\(_2\)Cl\(_2\) at -80 °C and stirred overnight. \(^b\) The ratio of S\(_{\text{N}2'}\):S\(_{\text{N}2}\) products was determined by gas chromatography and \(^1\)H-NMR analysis. \(^c\) The enantiomeric excess was determined by chiral gas chromatography analysis (see Experimental Section). \(^d\) In this case 7.5 mol% of ligand was used. \(^e\) In this case 10 mol% of ligand was used.
5.3.4 Optimization of the copper salt

After optimization of the chiral ligand and solvent system, the influence of the copper salt was examined (Table 7).

Table 7  Influence of the copper salt.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Cu]</th>
<th>35ac:36ac\textsuperscript{b}</th>
<th>ee\textsuperscript{c,d} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuBr·Me2S</td>
<td>88:12</td>
<td>99 (S)</td>
</tr>
<tr>
<td>2</td>
<td>CuCl</td>
<td>83:17</td>
<td>98 (S)</td>
</tr>
<tr>
<td>3</td>
<td>CuI</td>
<td>85:15</td>
<td>99 (S)</td>
</tr>
<tr>
<td>4</td>
<td>CuTC</td>
<td>81:19</td>
<td>97 (S)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Conditions: n-BuLi (1.5 eq diluted to 0.3 M with CH₂Cl₂) was added over 1 h to a mixture of 33a (0.2 mmol, 0.1 M), [Cu] (5 mol%) and (R,R,Fc)L14 (6 mol%) in 2 mL of CH₂Cl₂ at -80 °C and stirred overnight. \textsuperscript{b} The ratio of S\textsubscript{N2}':S\textsubscript{N2} products was determined by gas chromatography and \textsuperscript{1}H-NMR analysis. \textsuperscript{c} The enantiomeric excess was determined by chiral gas chromatography analysis (see Experimental Section). \textsuperscript{d} The absolute configuration was determined by comparison with literature data based on the sign of the optical rotation. \textsuperscript{e} CuTC = copper(I) thiophene-2-carboxylate.

The catalytic system based on CuBr·Me₂S gave excellent regio- and enantioselectivity (Table 7, entry 1). Changing the counterion of the copper salt did not improve upon these results and although the enantiomeric excess remained very high, a slightly lower regioselectivity was found in all cases (Table 7, entries 2-4).

5.3.5 Scope of the asymmetric allylic alkylation with organolithium reagents

Using our optimized reaction protocol, involving the slow addition of 1.5 eq of methylolithium (diluted with toluene) over 2 h to a solution of substrate 33a and 5 mol% of catalyst in dichloromethane at -80 °C, provided the corresponding chiral product 35aa in 90% isolated yield, and a 90:10 ratio of regioisomers and 99% ee (Table 8, entry 1). The optimized CuBr·Me₂S/Taniaphos L14 catalytic system proved to be remarkably effective for a range of allylic substrates and alkylolithium reagents with, in nearly all cases, excellent enantioselectivities (Table 8). Using longer alkyl moieties in the lithium reagent (in these cases 1.2 eq diluted with n-hexane) gave the desired products with over 98% ee without exception (Table 8, entries 1-4). Importantly, allyl chloride 33b is equally efficient in this transformation when chiral phosphoramidite ligand (S,S,S)-L22 is used (Table 8, entry 5).
With this protocol, it is not only primary organolithium reagents that can be used; secondary ones are well tolerated when phosphoramidite \((S,R,R)\)-L21 is used in combination with CuBr·Me₂S. In stark contrast with other organometallic reagents, we could achieve regioselectivities of more than 90% and enantioselectivities up to 91% ee in the allylic alkylation of cinnamyl chloride \(33b\) with \(i\)-PrLi and \(s\)-BuLi (Table 8, entries 6-7). This entry is the highest value reported to date for the transfer of an \(i\)-propyl moiety from organometallic reagents to this allylic substrate.\(^{50-52}\) In addition, no examples have been reported for the direct enantioselective addition of \(s\)-butyllithium.

This reaction system also tolerates more sterically demanding substrates; in particular, high enantiomeric excess (96-99% ee) is achieved with allyl bromide \(33c\) bearing a 1-naphthyl substituent, using a copper catalyst based on ligand L14 (Table 8, entries 8-9). Remarkably, the catalytic system can even tolerate the presence of halides in the aromatic moiety of the allylic substrates (Table 8, entries 10-16). There was no evidence of the common lithium-halogen exchange in the case of \(p\)-bromo-cinnamyl bromide \(33e\) (Table 8, entry 16), demonstrating the extremely high activity of the chiral catalyst, which can dominate the reactivity of the organolithium compound towards competing reactions.

Addition of aryllithium compounds, in particular phenyllithium, provided more than 99% ee when phosphoramidite ligand \((S,R,R)\)-L21 was used for the allylic alkylation of \(p\)-chloro-cinnamyl bromide \(33d\). However, the regioselectivity in this case needs to be improved (Table 8, entry 15).\(^{53}\)

With aliphatic substrate \(33f\), the Taniaphos L14 based catalyst was found to be the best, providing 95% ee (Table 8, entry 17). A major challenge and potential limitation of using alkyllithium compounds in organic synthesis is related to functional group tolerance, because of the high basicity and nucleophilicity of organolithium species. Allylic substrates with various functional groups were therefore examined. Importantly, the catalytic system tolerates the benzyloxy and N-Boc-protected amine groups, with only a slight decrease in enantioselectivity, and provides important chiral building blocks for natural product synthesis (Table 8, entries 18-22).

It is well known that esters and alcohols are highly reactive to alkyllithium reagents, and the ultimate test of our catalytic system was therefore the allylic alkylation with \(n\)-BuLi and MeLi of highly sensitive ester-substituted allylic substrate \(33i\) bearing a heteroatom directly at the \(\gamma\)-position of the allyl bromide and substrate \(33j\), with an unprotected alcohol group (Table 8, entries 23-25). To our delight, the ester-protected allylic alcohol from the asymmetric \(S_{\alpha}2'\) reaction with \(n\)-BuLi was obtained as the exclusive product in 82% isolated yield and 98% ee, with only a small decrease in selectivity when MeLi was used (Table 8, entries 23-24). In addition, high regioselectivity and an enantiomeric excess of 90% were obtained with hydroxymethyl-substituted allyl bromide \(33j\) bearing an unprotected hydroxyl group using 2.2 eq of \(n\)-butyllithium without formation of any side products (Table 8, entry 25).
Table 8: Scope of the asymmetric allylic substitution with organolithium reagents.

<table>
<thead>
<tr>
<th>Entry</th>
<th>33, R</th>
<th>X</th>
<th>34, R'</th>
<th>L</th>
<th>35:36&lt;sup&gt;a&lt;/sup&gt; Yield (%)</th>
<th>35, ee&lt;sup&gt;a&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33a, Ph</td>
<td>Br</td>
<td>34a, Me</td>
<td>L14</td>
<td>90:10 90%</td>
<td>35aa, 99 (S)</td>
</tr>
<tr>
<td>2</td>
<td>33a, Ph</td>
<td>Br</td>
<td>34b, Et</td>
<td>L14</td>
<td>84:16 80%</td>
<td>35ab, 98 (S)</td>
</tr>
<tr>
<td>3</td>
<td>33a, Ph</td>
<td>Br</td>
<td>34c, n-Bu</td>
<td>L14</td>
<td>90:10 88%</td>
<td>35ac, 99 (S)</td>
</tr>
<tr>
<td>4</td>
<td>33a, Ph</td>
<td>Br</td>
<td>34d, n-Hex</td>
<td>L14</td>
<td>90:10 92%</td>
<td>35ad, &gt;99 (S)</td>
</tr>
<tr>
<td>5</td>
<td>33b, Ph</td>
<td>Cl</td>
<td>34e, n-Bu</td>
<td>L22</td>
<td>91:9 90%</td>
<td>35be, 95 (S)</td>
</tr>
<tr>
<td>6</td>
<td>33b, Ph</td>
<td>Cl</td>
<td>34e, i-Pr</td>
<td>L21</td>
<td>90:10 77%</td>
<td>35be, 91 (S)</td>
</tr>
<tr>
<td>7&lt;sup&gt;+&lt;/sup&gt;</td>
<td>33b, Ph</td>
<td>Cl</td>
<td>34f, s-Bu</td>
<td>L21</td>
<td>97:3 80%</td>
<td>35bf, 82 (+)</td>
</tr>
<tr>
<td>8</td>
<td>33c, 1-Naphthyl</td>
<td>Br</td>
<td>34a, Me</td>
<td>L14</td>
<td>80:20 96%</td>
<td>35ea, 99 (-)</td>
</tr>
<tr>
<td>9</td>
<td>33c, 1-Naphthyl</td>
<td>Br</td>
<td>34c, n-Bu</td>
<td>L14</td>
<td>81:19 97%</td>
<td>35ec, 96 (-)</td>
</tr>
<tr>
<td>10</td>
<td>33d, p-Cl-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Br</td>
<td>34a, Me</td>
<td>L14</td>
<td>85:15 90%</td>
<td>35da, &gt;99 (+)</td>
</tr>
<tr>
<td>11</td>
<td>33d, p-Cl-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Br</td>
<td>34b, Et</td>
<td>L14</td>
<td>82:18 91%</td>
<td>35db, 96 (+)</td>
</tr>
<tr>
<td>12</td>
<td>33d, p-Cl-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Br</td>
<td>34c, n-Bu</td>
<td>L14</td>
<td>86:14 91%</td>
<td>35dc, 97 (+)</td>
</tr>
<tr>
<td>13&lt;sup&gt;+&lt;/sup&gt;</td>
<td>33d, p-Cl-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Br</td>
<td>34d, n-Hex</td>
<td>L14</td>
<td>85:15 90%</td>
<td>35dd, &gt;99 (+)</td>
</tr>
<tr>
<td>14</td>
<td>33d, p-Cl-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Br</td>
<td>34d, n-Hex</td>
<td>L14</td>
<td>83:17 93%</td>
<td>35dd, &gt;99 (+)</td>
</tr>
<tr>
<td>15</td>
<td>33d, p-Cl-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Br</td>
<td>34g, Ph</td>
<td>L14</td>
<td>40:60 39%</td>
<td>35dg, 99 (S)</td>
</tr>
<tr>
<td>16</td>
<td>33e, p-Br-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Br</td>
<td>34c, n-Bu</td>
<td>L14</td>
<td>88:12 93%</td>
<td>35ec, 98 (S)</td>
</tr>
<tr>
<td>17</td>
<td>33f, n-Pent</td>
<td>Br</td>
<td>34b, Et</td>
<td>L14</td>
<td>94:6 100%</td>
<td>35fb, 95 (nd)</td>
</tr>
<tr>
<td>18</td>
<td>33g, BnOCH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Br</td>
<td>34a, Me</td>
<td>L14</td>
<td>85:15 98%</td>
<td>35ga, 90 (S)</td>
</tr>
<tr>
<td>19</td>
<td>33g, BnOCH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Br</td>
<td>34b, Et</td>
<td>L14</td>
<td>93:7 90%</td>
<td>35gb, 91 (+)</td>
</tr>
<tr>
<td>20</td>
<td>33g, BnOCH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Br</td>
<td>34c, n-Bu</td>
<td>L14</td>
<td>86:14 &gt;99%</td>
<td>35ge, 90 (S)</td>
</tr>
<tr>
<td>21</td>
<td>33g, BnOCH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Br</td>
<td>34d, n-Hex</td>
<td>L14</td>
<td>85:15 96%</td>
<td>35gd, 86 (+)</td>
</tr>
<tr>
<td>22</td>
<td>33h, TosN(Boc)CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Br</td>
<td>34b, Et</td>
<td>L14</td>
<td>84:16 72%</td>
<td>35hb, 86 (+)</td>
</tr>
<tr>
<td>23&lt;sup&gt;+&lt;/sup&gt;</td>
<td>33i, PhCO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Br</td>
<td>34c, n-Bu</td>
<td>L14</td>
<td>100:0 82%</td>
<td>35ic, 98 (+)</td>
</tr>
<tr>
<td>24</td>
<td>33i, PhCO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Br</td>
<td>34a, Me</td>
<td>L14</td>
<td>90:10 62%</td>
<td>35ia, 96 (S)</td>
</tr>
<tr>
<td>25&lt;sup&gt;+&lt;/sup&gt;</td>
<td>33j, HOC&lt;sub&gt;2&lt;/sub&gt;H</td>
<td>Br</td>
<td>34c, n-Bu</td>
<td>L14</td>
<td>96:4 99%</td>
<td>35jc, 90 (nd)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Conditions: n-BuLi (1.5 eq diluted to 0.3 M with the co-solvent) was added over 2 h to a mixture of 33a (0.2 mmol, 0.1 M), CuBr·Me<sub>2</sub>S (5 mol%) and ligand L (6 mol%) in 2 mL of CH<sub>2</sub>Cl<sub>2</sub> at -80 °C and stirred overnight. The ratio of S<sub>n</sub>2<sup>-</sup>:S<sub>n</sub>2 products was determined by gas chromatography and <sup>1</sup>H-NMR analysis. <sup>b</sup> Refers to the isolated yield of S<sub>n</sub>2<sup>-</sup>:S<sub>n</sub>2 products. <sup>c</sup> The enantiomeric excess was determined by chiral gas or high-performance liquid chromatography analysis (see Experimental Section). <sup>d</sup> The absolute configuration was determined by comparison with literature data based on the sign of the optical rotation. <sup>e</sup> Ratio of diastereomers determined as 1:1 with ee values of 82% and 81%, respectively. <sup>f</sup> Pre-formed CuBr·L<sub>14</sub> complex was used. <sup>g</sup> The S<sub>n</sub>2<sup>-</sup> product could be isolated pure in this case. <sup>h</sup> This value refers to conversion; very volatile product. <sup>i</sup> 4% of double 1,2-addition product was isolated in this case. <sup>j</sup> 2.2 eq of n-BuLi were used. nd = not determined.
5.3.6 Mechanistic studies

5.3.6.1 NMR studies

After obtaining these excellent results, the question remains which chiral copper complex is responsible for this unique activity and selectivity and what is the role of the solvent in the asymmetric allylic alkylation with organolithium reagents. As with the formation of organocuprates, we surmised that a transmetallation between the organolithium and copper bromide would occur before catalytic asymmetric C-C bond formation. The formation of the chiral transmetallated copper catalyst in dichloromethane-d$_2$ was examined by $^1$H, $^{31}$P and $^6$Li/$^7$Li NMR spectroscopy using different combinations of copper salt, solvents and quantities of methyllithium over a range of temperatures. The most striking observation is that in dichloromethane, in the presence of diethyl ether using 10 eq of MeLi and the copper bromide-Taniaphos complex 36 (Figure 2), four distinct species are observed: A, B, C, D (Figure 1, S2). The proposed chemical structures and transformations for species A, B, C and D are illustrated in Figure 2.

![Figure 1: $^{31}$P-NMR spectroscopic study of Taniaphos-CuBr complex 36.](image)

In the absence of diethyl ether, Taniaphos-CuMe (complex A, Figure 2) is found exclusively at -80 °C (Figure 1, S5). To prove the structure of this chiral monomethyl copper species it was independently prepared using copper complex 36 with either MeLi in the absence of diethyl ether or using Me$_3$Mg or with MeMgBr followed by removal of MgBr$_2$ by coordination to dioxane, confirming the proposed structure. To establish the
relevance of species A in the catalytic asymmetric allylic substitution, it was used in the stoichiometric alkylation of cinnamyl bromide 33a resulting in greater than 98% enantiomeric excess. In this case lithium is not a part of the active catalyst. This is in contrast to the catalytic system used for the asymmetric conjugate addition of Grignard reagents, in which magnesium is present in the catalytically active species.54

Figure 2 Chemical structures and transformations proposed for species A, B, C and D.

Addition of diethyl ether to species A leads to the dissolution of the excess dry MeLi and formation of a mixture of B and C. A temperature-dependent dynamic equilibrium was observed between species B and C+D. Species B is the major species between -80 and -110 °C (Figure 1, S3), but at a temperature higher than -80 °C, species C and D are dominant (Figure 1, S4). It is important to note that species D was observed in the 1H-NMR in this case, as it does not contain phosphorus. The same equilibrated mixture of species B and C can also be obtained independently by mixing Me₂CuLi and Taniaphos L14 in dichloromethane-d₂. Additional control experiments confirmed the detrimental effect of diethyl ether on the enantioselectivity, due to the formation of multiple copper species. Also the observed absence of influence of the copper salt used (vide supra) in the catalytic process is in accordance with the presence of the unique catalytic complex A. The integration of the 1H-NMR spectra indicates that only one methyl group is bound to copper.
in case of species A. In case of species B two methyl groups with different shifts are detected. At the same time for species C no peak for Me–Cu is observed. Species D is only observed in the $^1$H-NMR, indicating that no chiral ligand is bound and it only appears when species B and C are present. Species C and D were identified by independent preparation followed by NMR spectroscopy. When species A was prepared exclusively no Li peak was observed with $^6$Li/$^7$Li-NMR spectroscopy also confirming our hypothesis that lithium is not present in the active catalytic species. However, depending on the bulkiness of the phosphine ligands and the alkyl group and, more significantly, the nature of the solvent, dimeric species cannot be excluded. Because complexes of a dimeric structure in which the alkyl groups bridge two copper centers have not been reported in literature, the structure displayed in Figure 2 is proposed for species A.54

5.3.6.2 Monitoring the reaction in time

Upon investigation of the scope of the organolithium reagents, we observed that employing MeLi•LiBr (instead of MeLi) under the optimized conditions, very poor results in both the regio- and enantioselectivity were obtained. It is known that lithium salts can have a profound effect on the outcome of the allylic alkylation.57 For this reason the regio- and enantioselectivity of the asymmetric allylic alkylation of cinnamyl bromide 33a with $n$-butyllithium 34c were followed in time to investigate if the build-up of LiBr during the reaction has an influence on the regio- and enantioselectivity (Table 9). In the initial stages of the reaction a slightly lower regio- and enantioselectivity is observed, but overall these changes are negligible. Formation of the active catalytic species could explain the slightly lower regioselectivity and also accounts for the initial delay in the reaction speed. What is important to note is that the regio- and enantioselectivity do not suffer from the build-up of lithium bromide during the course of the reaction.
Chapter 5

Table 9  Study of the regio- and enantioselectivity during the addition of n-BuLi in time.$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction time (min)</th>
<th>Conversionb (%)</th>
<th>35ac:36ac$^c$</th>
<th>ee$^d$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>11</td>
<td>81:19</td>
<td>95.8</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>53</td>
<td>86:14</td>
<td>97.1</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
<td>98</td>
<td>84:16</td>
<td>97.3</td>
</tr>
<tr>
<td>7</td>
<td>160</td>
<td>full</td>
<td>84:16</td>
<td>97.2</td>
</tr>
</tbody>
</table>

$^a$ Conditions: n-BuLi (1.2 eq diluted to 0.3 M with CH$_2$Cl$_2$) was added over 2 h to a mixture of 33a (0.2 mmol, 0.1 M), CuBr•Me$_2$S (5 mol%) and (R,R)$_1$4 (6 mol%) in 2 mL of CH$_2$Cl$_2$ at -80 $^\circ$C and quenched directly after the addition completed. $^b$ The conversion of substrate 33a was determined by gas chromatography using n-dodecane as an internal standard. $^c$ The ratio of SN$_2'$:SN$_2$ products was determined by gas chromatography. $^d$ The enantiomeric excess was determined by chiral gas chromatography analysis (see Experimental Section).

5.4 Conclusions

In conclusion, for the first time since the discovery of organolithium compounds, it has been demonstrated that near absolute levels of enantioselectivity can be achieved in catalytic asymmetric carbon-carbon bond formation through allylic alkylation with these organometallic reagents. This is possible as a result of our ability to tune a dynamic system towards a unique and highly reactive catalyst featuring a chiral monoalkyl copper phosphine complex. The choice of solvent proved to be essential in order to obtain good results for the addition of organolithium reagents. By using dichloromethane as the solvent, the formation of highly reactive lithium aggregation states, and as a result non copper-catalyzed background reactions, could be prevented. Now that the elusive alkylolithium reagents have finally been tamed for catalytic asymmetric carbon-carbon bond formation, the stage is set for the discovery of a myriad of new catalytic applications for organolithium reagents, for the practical synthesis of highly valuable chiral products. So far, organolithium reagents have already been applied to the catalytic asymmetric ring opening of oxabicyclic alkenes (Chapter 6),$^{58}$ the formation of tertiary and quaternary centers using copper/phosphoramidite-catalyzed asymmetric allylic alkylation of allylic halides,$^{59}$ and the allylic alkylation of allylic ethers using organolithium reagents.$^{60}$
5.5 Experimental Section

General Experimental

Chromatography: Merck silica gel type 9385 230-400 mesh, TLC: Merck silica gel 60, 0.25 mm. Components were visualized by UV and cerium/molybdenum or potassium permanganate staining. Progress and conversion of the reaction were determined by GC-MS (GC, HP6890: MS HP5973) with an HP1 or HP5 column (Agilent Technologies, Palo Alto, CA). Mass spectra were recorded on an AEI-MS-902 mass spectrometer (EI+) or a LTQ Orbitrap XL (ESI+). $^1$H- and $^{13}$C-NMR were recorded on a Varian AMX400 (400 and 100.59 MHz, respectively) or a Varian VXR300 (300 and 75 MHz, respectively) using CDCl$_3$ as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard (CHCl$_3$: $\delta$ 7.26 for $^1$H, $\delta$ 77.0 for $^{13}$C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. Optical rotations were measured on a Schmildt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (c given in g/100 mL). Enantiomeric excesses were determined by HPLC analysis using a Shimadzu LC-10AD VP HPLC equipped with a Shimadzu SPD-M10A VP diode array detector or by capillary GC analysis (HP 6890, CP-Chiralsil-Dex-CB column (25 m x 0.25 mm) or Chiralix B-PM (30 m x 0.25 mm x 0.25 μm)) using a flame ionization detector.

All reactions were carried out under a nitrogen atmosphere using oven dried glassware and using standard Schlenk techniques. Dichloromethane was dried and distilled over calcium hydride; toluene, THF and n-hexane were dried and distilled over sodium. Cinnamyl bromide (33a), cinnamyl chloride (33b) and all copper-salts (CuI, CuCN, CuTC, and CuBr•SMe$_2$) were purchased from Aldrich, and used without further purification. Allyl bromides 33c-j were prepared following literature procedures (33c$^{50}$, 33d$^{10}$, 33e$^{61}$, 33f$^{62}$, 33g$^{63}$, 33h$^{64}$, 33i$^{65}$, 33j$^{66}$). Organolithium reagents 34 were purchased from Aldrich (MeLi (34a) (1.6 M in Et$_2$O), EtLi (34b) (0.5 M in benzene/cyclohexane 9:1), n-HexLi (34d) (2.3 M in n-hexane), i-PrLi (34e) (0.7 M in n-pentane), PhLi (34g) (1.8 M in dibutyl ether), or from Acros (n-iBuLi (34c) (1.6 M in n-hexane) and sec-BuLi (34f) (1.3 M in cyclohexane/hexane 92:8). Ligands L16-20 and L14 were purchased from Aldrich. Phosphoramidite ligands L21$^{67}$ and L22$^{68}$ were prepared as reported in the literature. NHC-ligand L23 was kindly provided by Aditiya Gottumukkala.

Racemic products were synthesized by reaction of the allyl halides 33 and the corresponding organolithium reagent 34 at -78°C in dichloromethane in the presence of CuI (10 mol%) and PPh$_3$ (20 mol%). All reactions in this chapter were carried out by the Lithium team: Manolo Pérez, Martín Fañanás-Mastral, Alena Rudolph and Pieter Bos. Spectroscopic studies of the mechanism were carried out by Syuzanna Harutyunyan.
General procedure for the copper-catalyzed allylic alkylation of allyl halides 33 with organolithium reagents 34

A Schlenk tube equipped with septum and stirring bar was charged with CuBr•SMε2 (0.01 mmol, 2.06 mg, 5 mol%) and the appropriate ligand (0.012 mmol, 6 mol%). Dry dichloromethane (2 mL) was added and the solution was stirred under nitrogen at room temperature for 15 min. Then, allyl halide 33 (0.2 mmol) was added and the resulting solution was cooled to -80 °C. In a separate Schlenk, the corresponding organolithium reagent 34 (0.24 mmol, 1.2 eq) was diluted with hexane (combined volume of 1 mL) under nitrogen and added dropwise to the reaction mixture over 2 h (over 5 h when using phosphoramidite ligands) using a syringe pump. Once the addition was complete, the mixture was stirred for another two hours at -80°C. The reaction was quenched with a saturated aqueous NH₄Cl solution (2 mL) and the mixture was warmed to room temperature, diluted with dichloromethane and the layers were separated. The aqueous layer was extracted with dichloromethane (3 x 5 mL) and the combined organic layers were dried with anhydrous Na₂SO₄, filtered and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography on silica gel using different mixtures of n-pentane/diethyl ether as the eluent.

Note: Gas chromatography analysis was carried out to determine the b:l ratio on a sample obtained after aqueous extraction with dichloromethane, which has been passed through a short plug of silica gel to remove transition metal residues.

Note 2: In some cases it was necessary to carry out a hydroboration/oxidation or an ozonolysis/reduction protocol to determine the enantiomeric excess of the products (vide infra).

General protocol for the hydroboration and oxidation of alkenes 35ad and 35ga

To a suspension of the alkene (1 mmol) in dry THF (3 mL) 9-BBN in THF (0.5 M, 3 mmol, 3 eq) was added and the reaction mixture was stirred at room temperature for 2 h. Then, ethanol (4.5 mL), an aqueous solution of NaOH (6.0 M, 1.2 mL) and H₂O₂ (30 % in water, 7 mL) were added at 0 °C over and the reaction mixture was stirred for 1 h. The reaction mixture was quenched with brine and the mixture extracted with ethyl acetate (3 x 10 mL). The organic layer was dried with MgSO₄, filtered and the solvent evaporated in vacuo. The
crude product was purified by flash chromatography on silica gel using different mixtures of n-pentane/diethyl ether as the eluent.

**General protocol for the ozonolysis and reduction of alkene 35hb**

![Diagram](attachment:image.png)

Ozone was bubbled for 15 min through a solution of the alkene (0.081 mmol) in a mixture of DCM (2 mL) and MeOH (2 mL) at -78°C. After stirring for 15 min (solution stays blue) the reaction mixture was purged with nitrogen. Sodium borohydride (7.68 mg, 0.203 mmol, 2.5 eq) was added and the mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was quenched by addition of a 1M aqueous HCl solution. The layers were separated and the aqueous layer was extracted with DCM twice. The combined organic layers were dried with sodium sulfate and concentrated in vacuo. The crude product was purified by column chromatography on SiO₂, n-pentane/diethyl ether (1:1) to give the product as a colorless oil that solidified upon standing.

**(+)-(S)-But-3-en-2-ylbenzene (35aa)**

Colorless oil obtained as a 90:10 mixture of 35aa and 36aa after column chromatography (SiO₂, n-pentane), [90% yield, 99% ee]. The spectroscopic data matched those reported in literature:46 [α]D²⁰ = +6.3 (c = 1.0, CHCl₃), [lit.46 (98% ee): [α]D²⁰ = +5.4 (c = 1.2, CHCl₃)]. Enantiomeric excess was determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temperature 75 °C, retention times (min.): 23.8 (minor) and 24.2 (major); retention time 36aa: 42.3 min.

**(+)-(S)-Pent-1-en-3-ylbenzene (35ab)**

Colorless oil obtained as a 84:16 mixture of 35ab and 36ab after column chromatography (SiO₂, n-pentane), [80% yield, 98% ee]. The spectroscopic data matched those reported in literature:46 [α]D²⁰ = +56.0 (c = 1.0, CHCl₃), [lit.46 (95% ee): [α]D²⁰ = +47 (c = 1.0 CHCl₃)]. Enantiomeric excess was determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25m x 0.25mm), initial temp. 75 °C for 40 min, then 10 °C/min to 140 °C (hold for 10 min, final temp), retention times (min): 39.6 (minor) and 40.4 (major); retention time 36ab: 47 min.
Chapter 5

(+)-(S)-Hept-1-en-3-ylbenzene (35ac)

Colorless oil obtained as a 90:10 mixture of 35ac and 36ac after column chromatography (SiO$_2$, n-pentane), [88% yield, 99% ee]. The spectroscopic data matched those reported in literature. [46] $\alpha$D$^{20} = +49.4$ (c = 1.0, CHCl$_3$), [lit. [46] (94% ee): $\alpha$D$^{20} = +47$ (c = 0.5, CHCl$_3$)]. Enantiomeric excess was determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 80 °C for 80 min, then 1 °C/min to 140 °C (hold for 5 min), then 10 °C/min to 180 °C (final temp), retention times (min.): 75.5 (minor) and 76.6 (major); retention time 36ac: 127.5 min.

(+)-(S)-Non-1-en-3-ylbenzene (35ad)

Colorless oil obtained as a 90:10 mixture of 35ad and 36ad after column chromatography (SiO$_2$, n-pentane), [92% yield, 99% ee]. The spectroscopic data matched those reported in literature. [69] $\alpha$D$^{20} = +29.2$ (c = 1.0, CHCl$_3$). The enantiomeric excess was determined for the terminal alcohol obtained following the hydroboration and oxidation protocol of the terminal double bond ([vide supra]). Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OJ-H column, n-heptane/i-PrOH 99:1, 40 °C, 210 nm, retention times (min.): 19.4 (major) and 20.1 (minor).

(-)-(S)-1-(But-3-en-2-yl)naphthalene (35ca)

Colorless oil obtained as a 80:20 mixture of 35ca and 36ca after column chromatography (SiO$_2$, n-pentane), [96% yield, 99% ee]. The spectroscopic data matched those reported in literature. [46] $\alpha$D$^{20} = -14.5$ (c = 1.0, CHCl$_3$), [lit. [46] (96% ee): $\alpha$D$^{20} = -29.8$ (c = 1.1, CHCl$_3$)]. Enantiomeric excess was determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temperature 120 °C for 60 min, retention times (min.): 31.2 (minor) and 31.4 (major); retention time 36ca: 49.0 min.
Catalytic Asymmetric Carbon-Carbon Bond Formation via Allylic Alkylations with Organolithium Compounds

(-)-1-(Hept-1-en-3-yl)naphthalene (35cc)

Colorless oil obtained as a 81:19 mixture of 35cc and 36cc after column chromatography (SiO₂, n-pentane), [97% yield, 96% ee]. 1H NMR (400 MHz, CDCl₃): 8.15 (d, J = 8.9 Hz, 1H), 7.80 (m, 2H), 7.60 – 7.40 (m, 4H), 6.33 – 5.99 (m, 1H), 5.15 – 5.05 (m, 2H), 4.11 (q, J = 7.3, 1H), 1.90 (q, J = 7.3, 2H), 1.40 – 1.21 (m, 1H), 0.95 – 0.85 (m, 3H). 13C NMR (100 MHz, CDCl₃): 142.9, 141.0, 133.9, 131.7, 126.8, 125.7, 125.6, 125.3, 123.9, 123.4, 114.4, 44.2, 35.0, 30.0, 22.8, 14.1. [α]D²⁰ = -7.6 (c = 0.9, CHCl₃). Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OD-H column, n-heptane/i-PrOH 98:2, 40 °C, 240 nm, retention times (min.): 18.3 (major) and 19.9 (minor). HRMS (ESI⁺, m/z): calcd for C₁₇H₂₀Na [M+Na]⁺: 247.14572; found: 247.14580.

In accordance with the results obtained in the other allylic alkylations, the absolute configuration of this compound is assumed to be (S), analogous to the other products.

(+)-(S)-1-(But-3-en-2-yl)-4-chlorobenzene (35da)

Colorless oil obtained as a 85:15 mixture of 35da and 36da after column chromatography (SiO₂, n-pentane), [90% yield, 99% ee]. The spectroscopic data matched those reported in literature.⁴⁶ [α]D²⁰ = +15 (c = 1.0, CHCl₃), [lit.⁴⁶ (97% ee): [α]D²⁰ = +12 (c = 1.6, CHCl₃)]. Enantiomeric excess was determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temperature 95 °C for 45 min, then 2 °C/min to 140 °C (final temperature), retention times (min.): 37.4 (minor) and 37.6 (major); retention time 36da: 41.0 min.

(+)-1-Chloro-4-(pent-1-en-3-yl)benzene (35db)

Colorless oil obtained as a 82:18 mixture of 35db and 36db after column chromatography (SiO₂, n-pentane), [91% yield, 96% ee]. The spectroscopic data matched those reported in literature.⁵⁰ [α]D²⁰ = +35.4 (c = 1.0, CHCl₃). Enantiomeric excess was determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25m x 0.25 mm), initial temp. 50 °C, then 10 °C/min to 120 °C (hold for 30 min), then 10 °C/min to 160 °C (final temp), retention times (min): 23.4 (minor) and 24.0 (major); retention time 36db: 38.7 min.

In accordance with the results obtained in the other allylic alkylations, the absolute configuration of this compound is assumed to be (S), analogous to the other products.
Chapter 5

(+)-1-Chloro-4-(hept-1-en-3-yl)benzene (35dc)

Colorless oil obtained as a 86:14 mixture of 35dc and 36dc after column chromatography (SiO₂, n-pentane), [91% yield, 97% ee].

\[ \text{δ (300 MHz, CDCl}_3 \text{) } \]

\[ \begin{align*}
\text{7.27 (d, } J = 8.3 \text{ Hz, 3H), 7.12 (d, } J = 8.3 \text{ Hz, 2H), 5.96 – 5.84 (m, 1H), 5.04 – 4.95 (m, 2H), 3.21 (q, } J = 7.3 \text{ Hz, 1H), 1.73 – 1.62 (m, 2H), 1.34 – 1.19 (m, 4H), 0.87 (t, } J = 7.0 \text{ Hz, 3H).} \\
\text{13C NMR (75 MHz, CDCl}_3 \text{) δ 143.3, 142.2, 129.2, 128.70, 127.3, 114.4, 49.4, 35.3, 29.9, 22.8, 14.2.}
\end{align*} \]

\[ [\alpha]_{D}^{20} = +36.6 \text{ (c = 1.0, CHCl}_3 \text{).} \]

Enantiomeric excess was determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 130 °C for 60 min, then 10 °C/min to 175 °C (hold for 5 min, final temp), retention times (min.): 24.6 (minor) and 25.1 (major); retention time 36dc 62.3 min. HRMS (ESI+, m/z): calcld for C₁₃H₁₇ClNa [M+Na]⁺: 231.09165; found: 231.09166.

(+)-1-Chloro-4-(non-1-en-3-yl)benzene (35dd)

Colorless oil obtained as a 83:17 mixture of 35dd and 36dd after column chromatography (SiO₂, n-pentane), [93% yield, 99% ee].

The spectroscopic data matched those reported in literature.\(^{70}\) \[ [\alpha]_{D}^{20} = +18.0 \text{ (c = 1.0, CHCl}_3 \text{).} \]

Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OJ-H column, 0.5 mL/min, n-heptane/i-PrOH 100:0, 40 °C, 215 nm, retention times (min): 8.8 (major) and 10.4 (minor); retention time 36dd: 11.8 min.

In accordance with the results obtained in the other allylic alkylations, the absolute configuration of this compound is assumed to be (S), analogous to the other products.

(+)-(S)-1-Bromo-4-(hept-1-en-3-yl)benzene (35ec)

Colorless oil obtained as a 88:12 mixture of 35ec and 36ec after column chromatography (SiO₂, n-pentane), [93% yield, 98% ee].

The spectroscopic data matched those reported in literature.\(^{71}\) \[ [\alpha]_{D}^{20} = +30.4 \text{ (c = 1.0, CHCl}_3 \text{); [lit.] (R isomer, 68% ee): } [\alpha]_{D}^{20} = -11.4 \text{ (c = 0.28, CHCl}_3 \text{).} \]

Enantiomeric excess was determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 130 °C for 60 min, then 10 °C/min to 175 °C (hold for 5 min, final temp), retention times (min.): 39.9 (minor) and 40.7 (major); retention time 36ec: 69.3 min.
3-Ethylct-1-ene (35fb)

Colorless oil obtained as a 94:6 mixture of 35fb and 36fb after column chromatography (SiO₂, n-pentane/diethyl ether, 98:2), [99% conversion, 95% ee]. The high volatility of the products 35fb and 36fb did not allow to completely remove the solvents after the chromatography, impeding the determination of an accurate isolated yield. Enantiomeric excess was determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25m x 0.25mm) initial temp. 55 °C for 30 min (final temp), retention times (min.): 26.5 (minor) and 27.0 (major).

In accordance with the results obtained in the other allylic alkylations, the absolute configuration of this compound is assumed to be (S), analogous to the other products.

(-)-(S)-(((2-Methylbut-3-en-1-yl)oxy)methyl)benzene (35ga)

Colorless oil obtained as a 85:15 mixture of 35ga and 36ga after column chromatography (SiO₂, n-pentane), [98% yield, 89% ee]. The spectroscopic data matched those reported in literature.46 [α]D²⁰ = -3.6 (c = 1.0, CHCl₃), [lit.46 (92% ee): [α]D²⁰ = -6 (c = 1.1, CHCl₃)]. The enantiomeric excess was determined for the terminal alcohol obtained following the hydroboration and oxidation protocol of the terminal double bond (vide supra). Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OD-H column, n-heptane/i-PrOH 99:1, 40 °C, 213 nm, retention times (min.): 56.9 (major) and 62.0 (minor).

(+)-(S)-(((2-Ethylbut-3-en-1-yl)oxy)methyl)benzene (35gb)

Colorless oil obtained as a 93:7 mixture of 35gb and 36gb after column chromatography (SiO₂, n-pentane:Et₂O 98:2), [90% yield, 91% ee]. The spectroscopic data matched those reported in literature.46 [α]D²⁰ = +9.2 (c = 1.0, CHCl₃) [lit.46 (94% ee): [α]D²⁰ = +19 (c = 1.1, CHCl₃)]. Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OD-H column, 0.5 mL/min, n-heptane/i-PrOH 99.75:0.25, 40 °C, 215 nm, retention times (min): 10.2 (major) and 11.0 (minor); retention time 36gb: 15.1 min.

(+)-(S)-(((2-Vinylhexyl)oxy)methyl)benzene (35gc)

Colorless oil obtained as a 86:14 mixture of 35gc and 36gc after column chromatography (SiO₂, n-pentane:Et₂O 98:2), [quant. yield, 87% ee]. The spectroscopic data matched those reported in literature.47 [α]D²⁰ = +11.9 (c = 2.8, CHCl₃); [lit.47 (S isomer, 94% ee): [α]D²⁰ = +18.5 (c = 2.2, CHCl₃)].
Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OD-H column, 0.5 mL/min, n-heptane/i-PrOH 100:0, 40 °C, retention times (min.): 11.6 (minor) and 13.5 (major); retention time 36ge: 19.0 min.

(+)-((2-Vinylcthoxy)methyl)benzene (35gd)

Colorless oil obtained as a 85:15 mixture of 35gd and 36gd after column chromatography (SiO₂, n-pentane:Et₂O 98:2), [96% yield, 86% ee]. ¹H NMR: (400 MHz, CDCl₃) δ 7.36 – 7.25 (m, 5H), 5.66 (ddd, J = 8.4, 10.7, 16.9 Hz, 1H), 5.09 – 5.04 (m, 2H), 4.51 (s, 2H), 3.38 (d, J = 6.5 Hz, 2H), 2.38 – 2.29 (m, 1H), 1.60-1.45 (m, 1H), 1.43 – 1.24 (m, 9H), 0.89 (t, J = 6.9, 3H). ¹³C NMR: (100 MHz, CDCl₃) δ 138.6, 128.3, 127.5, 127.4, 115.4, 73.9, 72.9, 41.4, 31.8, 31.2, 29.4, 26.9, 22.6, 14.1. [α]D²⁰ = +8.2 (c = 1.0, CHCl₃). Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OD-H column, 0.5 mL/min, n-heptane/i-PrOH 100:0, 40 °C, 210 nm, retention times (min): 11.4 (minor) and 13.2 (major); retention time 36gd: 19.6 min.

In accordance with the results obtained in the other allylic alkylations, the absolute configuration of this compound is assumed to be (S), analogous to the other products.

(-)-tert-Butyl (2-ethylbut-3-en-1-yl)(tosyl)carbamate (35hb)

Colorless oil obtained as an 84:16 mixture of 35hb and 36hb after column chromatography (SiO₂, n-pentane: Et₂O 95:5), [72% yield, 86% ee]. The spectroscopic data matched those reported in literature.⁴⁷ [α]D⁰ = -0.4 (c = 1.0, CHCl₃) [lit.⁴⁷ (91% ee): [α]D⁰ = -0.4 (c = 8.5, CHCl₃)]. The enantiomeric excess was determined for the terminal alcohol obtained following the ozonolysis and reduction protocol of the terminal double bond (vide supra). Enantiomeric excess was determined by chiral HPLC analysis, Chiralpak AD column, 1.0 mL/min, n-heptane/i-PrOH 98:2, 40 °C, 227 nm, retention times (min): 37.2 (major) and 52.6 (minor). In accordance with the results obtained in the other allylic alkylations, the absolute configuration of this compound is assumed to be (S), analogous to the other products.
Catalytic Asymmetric Carbon-Carbon Bond Formation via Allylic Alkylations with Organolithium Compounds

(+)-Hept-1-en-3-yl benzoate (35ic)

Colorless oil obtained after column chromatography (SiO₂, n-pentane:Et₂O 80:1), [82% yield, 98% ee]. 

\( ^1\text{H NMR} \ (400 \text{ MHz, CDCl}_3) \delta \) 8.08 – 8.06 (m, 2H), 7.56 (tt, \( J = 7.4, 1.4 \text{ Hz, 1H} \)), 7.47 – 7.42 (m, 2H), 5.90 (ddd, \( J = 17.0, 10.5, 6.3 \text{ Hz, 1H} \)), 5.52 – 5.47 (m, 1H), 5.32 (dt, \( J = 17.3, 1.3 \text{ Hz, 1H} \)), 5.20 (dt, \( J = 10.5, 1.2 \text{ Hz, 1H} \)), 1.85 – 1.68 (m, 2H), 1.45 – 1.30 (m, 4H), 0.91 (t, \( J = 7.1 \text{ Hz, 3H} \)). 

\( ^{13}\text{C NMR} \ (101 \text{ MHz, CDCl}_3) \delta \) 165.9, 136.6, 132.8, 130.6, 129.6, 128.3, 116.5, 75.3, 34.0, 27.2, 22.5, 14.0. 

\([\alpha]_D^{20} = +31.2 \ (c = 1.0, \text{CHCl}_3)\).

HRMS (ESI+, \( m/z \)): calcld for C₁₄H₁₈O₂Na [M+Na]⁺: 241.11990; found: 241.12010.

Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OB-H column, n-heptane/i-PrOH 99.8:0.2, 40 °C, 225 nm, retention times (min.): 12.9 (major) and 15.1 (minor).

(+)-(S)-But-3-en-2-yl benzoate (35ia)

Colorless oil obtained after column chromatography (SiO₂, n-pentane:Et₂O 80:1), [62% yield, 96% ee]. The spectroscopic data matched those reported in literature.\(^{72}\) 

\([\alpha]_D^{20} = +41.4 \ (c = 1.0, \text{CHCl}_3)\). \([\text{lit.}]^{72} (98% \text{ ee}): \ [\alpha]_D^{20} = +43.7 \ (c = 0.35, \text{CHCl}_3)\).

Enantiomeric excess was determined by chiral HPLC analysis, Chiralse OB-H column, n-heptane/i-PrOH 99.7:0.3, 40 °C, 225 nm, retention times (min.): 13.1 (major) and 14.8 (minor).

2-Vinylhexan-1-ol (35jc)

Colorless oil obtained as a 96:4 mixture of 35jc and 36jc after column chromatography (SiO₂, n-pentane:Et₂O 4:1), [99% conversion, 90% ee]. 

\( ^1\text{H NMR} \ (400 \text{ MHz, CDCl}_3) \delta \) 5.58 (ddd, \( J = 17.0, 10.4, 8.7 \text{ Hz, 1H} \)), 5.20 – 5.08 (m, 2H), 3.57 (ddd, \( J = 10.5, 7.9, 5.1 \text{ Hz, 1H} \)), 3.46 – 3.34 (m, 1H), 2.36 – 2.05 (m, 1H), 1.53 – 0.99 (m, 6H), 0.88 (t, \( J = 6.9 \text{ Hz, 3H} \)). 

\( ^{13}\text{C NMR} \ (101 \text{ MHz, CDCl}_3) \delta \) 140.1, 117.3, 65.6, 47.0, 30.4, 29.2, 22.7, 14.0. The high volatility of the products 35jc and 36jc did not allow to completely remove the solvents after the chromatography, impeding the determination of an accurate isolated yield. Enantiomeric excess was determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25m x 0.25 mm) initial temp. 35 °C for 30 min, then 10 °C/min to 175 °C (final temp), retention time (min.): 4.0 (minor) and 4.1 (major); retention time 36jc: 7.0 min.

In accordance with the results obtained in the other allylic alkylations, the absolute configuration of this compound is assumed to be (S), analogous to the other products.
(+)-(S)-(4-Methylpent-1-en-3-yl)benzene (35be)

Colorless oil obtained as a 90:10 mixture of 35be and 36be after column chromatography (SiO₂, n-pentane), [77% yield, 91% ee]. The spectroscopic data matched those reported in literature.⁵⁰ [α]D²⁰ = +105.6 (c = 0.18, CHCl₃). [lit.⁵⁰ (88% ee): [α]D²⁰ = +104.2 (c = 0.15, CHCl₃)]. Enantiomeric excess was determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), isothermic 85 °C, retention times (min.): 30.6 (minor) and 32.5 (major); retention time 36be 68.6 min.

(+)-(4-Methylhex-1-en-3-yl)benzene (35bf)

Colorless oil obtained as a 97:3 mixture of 35bf (obtained as a 1:1 mixture of diastereomers) and 36bf after column chromatography (SiO₂, n-pentane), [80% yield, diast. 1, 81% ee; diast. 2, 82% ee]. ¹H NMR (400 MHz, CDCl₃) δ 7.31 – 7.26 (m, 2H diast. 1 + 2H diast. 2), 7.20 – 7.16 (m, 3H diast.1 + 3H diast. 2), 6.05 – 5.95 (m, 1H diast. 1 + 1H diast. 2), 5.06 – 5.02 (m, 2H diast. 1 + 2H diast. 2), 3.05 (t, J = 8.7 Hz, 1H diast. 1), 3.01 (t, J = 8.8 Hz, 1H diast. 1), 1.80 – 1.70 (m, 1H diast. 1 + 1H diast. 2), 1.69 – 1.59 (m, 1H diast. 1), 1.35 – 1.24 (m, 1H diast. 2), 1.17 – 1.05 (m, 1H diast. 1), 1.02 – 0.94 (m, 1H diast. 2), 0.93 (d, J = 6.8 Hz, 3H diast. 2), 0.91 (t, J = 7.4 Hz, 3H diast. 1), 0.83 (t, J = 7.4 Hz, 3H diast. 2). ¹³C NMR (101 MHz, CDCl₃) δ 144.4 (diast. 1), 144.2 (diast. 2), 141.4 (diast. 1), 140.7 (diast. 2), 128.3 (diast. 1), 128.3 (diast. 2), 128.0 (diast. 1), 127.9 (diast. 2), 125.9 (diast. 1), 125.9 (diast. 2), 115.1 (diast. 1), 114.8 (diast. 2), 56.8 (diast. 1), 56.4 (diast. 2), 39.0 (diast. 1), 38.9 (diast. 2), 27.1 (diast. 1), 26.8 (diast. 2), 16.8 (diast. 1), 11.3 (diast. 1), 11.2 (diast. 2). [α]D²⁰ = +64.6 (c = 1.0, CHCl₃). Enantiomeric excess was determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 80 °C for 80 min, then 1 °C/min to 140 °C (hold for 5 min), then 10 °C/min to 180 °C (final temp), retention times (min.): 67.6 (diast. 1, minor), 72.6 (diast. 2, minor) and 81.4 (diast. 2, major).

(-)-(S)-1-Chloro-4-(1-phenylallyl)benzene (35dg)

Colorless oil obtained pure from a crude 40:60 mixture of 35dg and 36dg after column chromatography (SiO₂, n-pentane/Et₂O 100:1), [39% yield, 99% ee]. The spectroscopic data matched those reported in literature.⁷³ [α]D²⁰ = -8.5 (c = 0.33, CHCl₃). [lit.⁷³ (R isomer, 71% ee): [α]D²¹ = +5.6 (c = 0.50, CHCl₃)]. Enantiomeric excess was determined by chiral GC analysis, Chiraldex B-PM (30 m x 0.25 mm x 0.25 μm), initial temp. 60 °C, 0.5 °C/min to 120 °C (hold for 30 min), then 0.5 °C/min to 160 °C, then 5 °C/min to 60 °C (final temp), retention times (min.): 169.8 (minor), 172.9 (major); retention time 36dg 221.3 min.
NMR studies

$^{31}$P chemical shifts are referenced to an external standard: 85% H$_3$PO$_4$ (0 ppm). $^6$Li NMR and $^7$Li NMR shifts are referenced to an external standard: 0.1 M LiCl in H$_2$O (0 ppm). For more detail: see Supporting Information of reference 5, Section 5.6.

Preparation of Cu-complex 36

A solution of ($R,R$)-Taniaphos (L14, 0.145 mmol) and CuBr•SMe$_2$ (0.145 mmol) in t-BuOMe (7 mL) in a Schlenk tube was stirred at room temperature for 30 min. The solvent was removed under vacuum and the resulting orange crude residue was washed with cold pentane several times to afford Cu-complex as an orange powder (120 mg, 99% yield).

NMR data for Cu-complex 36 at 25 °C

$^1$H NMR (500 MHz, CD$_2$Cl$_2$) $\delta$ 8.29 – 8.12 (m, 2H), 8.05 (m, 2H), 7.50 (d, $J = 7.7$ Hz, 6H), 7.33 (s, 2H), 7.24 (t, $J = 7.4$ Hz, 1H), 7.17 – 6.81 (m, 2H), 6.66 (t, $J = 7.3$ Hz, 2H), 6.37 (dt, $J = 17.4$ Hz, 8.5 Hz 2H), 5.64 (d, $J = 4.8$ Hz, 1H), 4.95 (s, 1H), 4.61 (s, 1H), 4.13 (s, 1H), 4.05 (s, 5H), 1.94 (s, 6H). $^{13}$C NMR (126 MHz, CD$_2$Cl$_2$) $\delta$ 148.5 (d, $J = 17.2$ Hz), 137.7 (d, $J = 31.9$ Hz), 136.7 (d, $J = 16.7$ Hz), 134.9, 134.7 (d, $J = 11.8$ Hz), 133.8 (d, $J = 14.2$ Hz), 133.0, 132.4 (d, $J = 9.3$ Hz), 132.0 (d, $J = 29.6$ Hz), 131.6 (d, $J = 32.2$ Hz), 131.5, 131.4, 131.1 (d, $J = 6.9$ Hz), 130.7, 129.6), 129.4 (d, $J = 9.8$ Hz), 128.8 (d, $J = 8.3$ Hz), 128.7 (d, $J = 10.1$ Hz), 128.3, 128.2 (d, $J = 8.0$, Hz), 127.4 (d, $J = 4.5$ Hz), 101.1 (d, $J = 22.6$ Hz), 71.8, 71.1, 70.9 (d, $J = 7.8$ Hz), 67.5 (d, $J = 20.4$ Hz), 67.5 (d, $J = 20.4$ Hz), 66.62 (d, $J = 33.0$ Hz), 45.76. Several peaks appear as doublets due to carbon-phosphorus coupling. $^{31}$P NMR (202 MHz, CD$_2$Cl$_2$) $\delta$ -18.40 (d, $J = 181.1$ Hz 1P), -20.59 (d, $J = 180.4$ Hz, 1P). Doublets are observed due to the phosphorus–phosphorus coupling.

Formation of mixture of species A, B, C, D (See Figure 1).

1) From complex 36 and MeLi:

Cu-complex 36 (0.012 mmol, 10 μg) was dissolved in 0.7 mL DCM-d$_2$ under nitrogen atmosphere directly in the NMR tube, followed by decreasing the temperature to -70 °C and rapid addition of 10 equiv MeLi (1.6M in Et$_2$O). A mixture of four species was observed. Formation of the dynamic equilibrium of the newly formed species A, B, C, D was monitored by $^1$H, $^{31}$P and $^7$Li/$^6$Li NMR spectroscopy at (-75 to -110 °C.) No changes were observed for species A. However species B became the major one between –80 to -110 °C, while at temperatures higher than -80°C, species C became the dominant one.
2) From species A:
The mixture of species A, B, C, D could be also obtained by adding diethyl ether to species A obtained as described below. Diethyl ether dissolves the excess of dry MeLi and initiates further reaction and formation of species B, C, and D. A similar temperature dependent dynamic equilibrium between species B and C was observed as described in experiment 1 above.

Formation of species A (Figure 1).

1) From complex 36 and MeLi (dry).
MeLi (10 eq) was transferred to the NMR tube and the solvent was evaporated to give dry MeLi powder. A cold solution of complex 36 (0.012 mmol, 10 mg) dissolved in 0.7 mL of DCM-d2 was added rapidly to the dry MeLi powder at -80 °C. After shaking several times complex 36 slowly transformed into species A exclusively.

2) From complex 36 and Me2Mg (in Et2O).
Cu-complex 36 (0.012 mmol, 10 mg) was dissolved in 0.7 mL DCM-d2 under nitrogen atmosphere directly in the NMR tube, followed by decreasing the temperature to -75 °C and rapid addition of Me2Mg (10 eq, 0.4 M in Et2O). Complex 36 transformed exclusively into species A.

3) From complex 36 and MeMgBr (in Et2O) and dioxane
Cu-complex 36 (0.012 mmol, 10 mg) was dissolved in 0.7 mL DCM-d2 under a nitrogen atmosphere directly in the NMR tube, followed by decreasing the temperature to -75 °C and rapid addition of MeMgBr (10 equiv, 3.0 M in Et2O). Formation of a new mixture of species was observed. Dioxane was used to prepare Me2Mg form MeMgBr due to its coordinating ability and upon addition of dioxane the mixture of new species transformed exclusively into species A.

Formation of equilibrium mixture of exclusively species B and C (Figure 1).

1) From CuBr•SMe2 and (R,R)-L14
CuBr•SMe2 (0.024 mmol, 5 mg) was added to an NMR tube followed by addition of DCM-d2. The NMR tube was cooled down to -60 °C, followed by addition of MeLi (10 equiv, 1.6 M in Et2O) and stirred for 10 min. After formation of Me2CuLi74,75, the mixture was cooled down to -75 °C and (R,R)-Taniaphos ligand L14 (0.024 mmol, 16.5 mg) was added. Only species B and C were detected.
Stoichiometric addition of species A to cinnamyl bromide 33a.
Species A was prepared from 36 (0.036 mmol, 30 mg) and MeLi (0.8 equiv) in dichloromethane (0.5 mL). The solution was cooled down to -80 °C and added within 3 min to a solution of cinnamyl bromide 33a (0.036 mmol, 7.1 mg) in dichloromethane (4 mL). The reaction was quenched after 2 h. The enantiomeric excess was 98% (determined by chiral GC analysis, vide supra).

5.6 References

(9) Majewski, M.; Snieckus, V. Organometallics: Compounds of Group 1 (Li...Cs) 8a; Thieme: Stuttgart, Germany, 2006.
(34) Source: www.sigmaaldrich.com, April 2011.
(44) Tomioka et al. reported the asymmetric allylic arylation with arylMgBr using a copper/NHC complex with up to 97% regioselectivity and up to 98% ee. Selim, K. B.; Matsumoto, Y.; Yamada, K.; Tomioka, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 8733.
(45) Tomioka et al. reported the asymmetric allylic arylation with arylMgBr using a copper/NHC complex with up to 97% regioselectivity and up to 98% ee. Selim, K. B.; Matsumoto, Y.; Yamada, K.; Tomioka, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 8733.
Catalytic Asymmetric Carbon-Carbon Bond Formation via Allylic Alkylations with Organolithium Compounds


