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## Enantioselective copper catalyzed allylic alkylation using Grignard reagents; Applications in synthesis

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# Chapter 1

## **The niche of copper in transition metal catalyzed asymmetric allylic substitution**

*The rapidly developing field of transition metal based asymmetric catalysis offers a powerful but elegant way of obtaining chiral compounds in enantiomerically pure form. The highly versatile allylic substitution reaction can be catalyzed in an enantioselective way by chiral catalysts based on several transition metals. Each metal offers distinct possibilities concerning the type of substrate or nucleophile employed. This chapter aims to provide an overview of what is possible with these transition metal catalysts in enantioselective allylic substitution, including highlights and the current state-of-the-art. Specifically, focus will be directed towards the use of copper based asymmetric catalyst systems and why this metal has filled an important niche in the field.*



## 1.1 Introduction to asymmetric catalysis

The synthesis of urea from inorganic compounds by Friedrich Wöhler in 1828<sup>1</sup> is seen by many as the birth of synthetic organic chemistry. Before this milestone, a “*vis vitalis*” was thought to be necessary to produce organic compounds, which were deemed too complicated in structure to produce them through any other means than life itself. Although this theory of vitalism was not abandoned immediately by the scientific community, including Wöhler himself, his synthesis was the start of a new era, in which chemists slowly learned how to harness the potential of synthetic organic chemistry by preparing more and more complex organic compounds.

It is easy to understand the mystification of organic chemistry by the early 19<sup>th</sup>-century chemists. The complexity found in naturally occurring organic compounds, also called natural products, can still baffle the modern organic chemist, even with our current knowledge of molecular structure. One of the aspects of this complexity is chirality. Chirality is a property which renders something non-superimposable on its mirror image.<sup>2</sup> In organic chemistry this signifies that these two mirror-images of a chiral compound, *enantiomers*, have the same connections of atoms within the molecule and the same relative spatial orientation of these atoms, but opposite absolute spatial orientation. It is best understood, when compared to objects in every-day life, including our hands, feet and ears (Figure 1.1). Our left hand is not the same as our right hand and similarly the D- and L-forms of our  $\alpha$ -amino acids are not the same compounds.

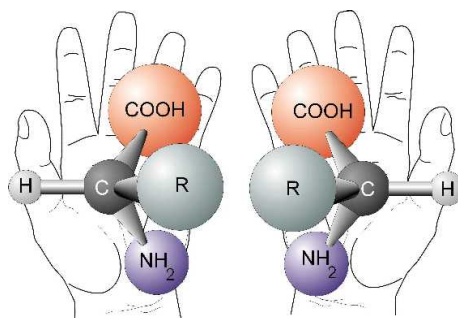


Figure 1.1: The two enantiomers of  $\alpha$ -amino acids are non-superimposable, as is the case with a right and a left hand.<sup>3</sup>

The two enantiomers of chiral compounds have the same physical properties. The main difference lies in their interaction with other chiral substances or physical forces, *e.g.* circular polarized light. To extend the analogy, we can compare it to a right hand fitting quite well in a right handed glove and not so well in a left handed one. This is an important difference, since our surroundings are often chiral at the molecular level. Life itself makes use of many chiral building blocks. DNA is chiral, for example, and all our proteins and enzymes are primarily built up from L-amino acids.

This means that our body can react in different ways to the two mirror images of chiral compounds. For instance, limonene is an organic chiral compound of which the natural D-enantiomer has a pleasant citrus-like smell. The mirror image, L-limonene, on the other hand has a harsh turpentine odor. The artificial sweetener aspartame is more than a hundred times sweeter than sucrose; its mirror image has a bitter taste, instead.

Examples with more serious consequences can be found in the pharmaceutical industry. Thalidomide was a drug marketed in the 50s and 60s for the prevention of morning sickness of pregnant women. One of the enantiomers was discovered to be teratogenic, but only after it had already caused serious birth defects in over 10.000 children. Nowadays, governments have set strict regulations regarding the enantiomeric purity of chiral pharmaceutical compounds, which are to be brought on the market. As a consequence, this has sparked a considerable interest in finding ways to obtain chiral compounds in enantiomerically pure form.

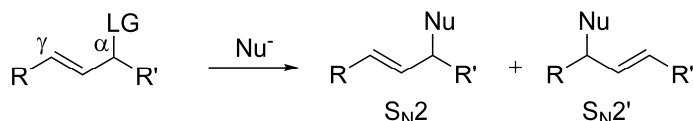
In principle, there are three basic ways of obtaining enantiopure compounds.<sup>4</sup> They can be isolated from natural sources, which produce only one enantiomer; this is called the chiral pool. An obvious drawback is that if only one enantiomer is produced, the other cannot be obtained in this way. The second way is to take a 50:50 mixture of enantiomers, a so-called racemate, and separate the two from each other. This is called resolution of a racemate and a disadvantage here is that in this case half of the compound is worthless, because it is the wrong enantiomer, unless it is recycled through racemization. The third option, asymmetric synthesis, is to prepare selectively one enantiomer of a chiral compound from an achiral starting material. To be able to do this, another source of chirality is needed, usually

in an equal or larger amount than the starting material. A notable exception to that is asymmetric catalysis, which is the subject of this thesis.

## 1.2 Transition metal catalyzed asymmetric allylic substitution

A catalyst is by definition a substance, which accelerates a reaction without being changed overall in the process itself. A small amount of an asymmetric catalyst would therefore enable the asymmetric synthesis of a larger amount of an enantiomerically pure chiral compound, which makes the process more “atom economical”.<sup>5</sup> This powerful but elegant method has become a widespread research field in the past decades and three of its pioneers were awarded the Nobel prize in chemistry at the start of the new millennium.<sup>6</sup>

The subject of this thesis is copper catalyzed asymmetric allylic substitution reactions. Allylic substitution is a powerful carbon-carbon or carbon-heteroatom bond forming reaction, in which an electrophile containing an allylic leaving group reacts with a nucleophile. Two pathways are possible in allylic substitution (Scheme 1.1): the  $S_N2$  pathway, which features direct substitution of the leaving group at the  $\alpha$ -position, or the  $S_{N2}'$  pathway, where the nucleophile attacks the  $\gamma$ -position causing a migration of the double bond.

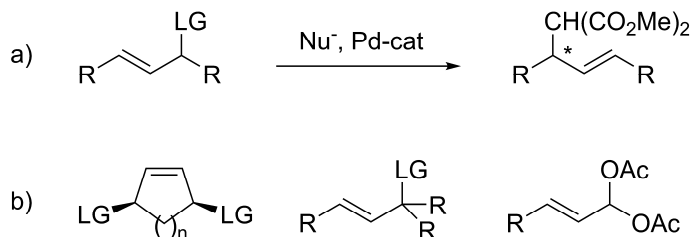


Scheme 1.1: The two possible pathways in allylic substitution lead to the  $S_N2$ -product through  $\alpha$ -substitution and the  $S_{N2}'$ -product through  $\gamma$ -substitution; LG = leaving group.

A range of different substrate classes, *e.g.* chiral racemic ( $R' \neq H$ ) and prochiral ( $R' = H$ ), and a range of nucleophiles, including stabilized carbanions (Michael donors), organometallic reagents and heteroatom nucleophiles, has been applied in catalyzed asymmetric allylic substitution reactions. The possibilities depend largely on the transition metal catalyst used in the allylic substitution reaction and a short overview of the literature presenting the key aspects will follow in this section.

### 1.2.1 Palladium catalyzed asymmetric allylic substitution

Among the transition metals used for catalyzing asymmetric allylic substitution, palladium is by far the most extensively studied and the subject has been thoroughly reviewed.<sup>7</sup> Traditionally, these reactions are performed using stabilized carbanions as nucleophiles, such as malonate esters, and symmetrically 1,3-disubstituted allylic electrophiles, *i.e.* bearing the same substituents on the  $\alpha$ - or  $\gamma$ -position (Scheme 1.2, a). This is because Pd-catalyzed allylic substitution is a regioselective as opposed to a regiospecific reaction. Regioselectivity means that one of the two possible products (if  $R \neq R'$  in Scheme 1.1) is formed preferentially, while regiospecificity is the preference for one of the two pathways ( $S_N2$  vs.  $S_N2'$ ) regardless of the substituents.

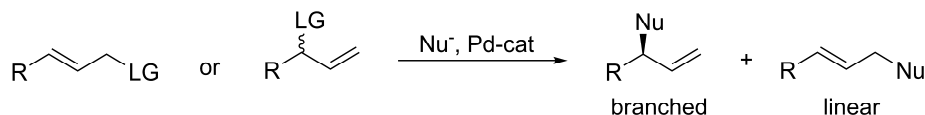


Scheme 1.2: a) The benchmark reaction in Pd-catalyzed asymmetric allylic substitution and b) Examples of other substrates applied successfully; LG = leaving group.

Generally, Pd-catalysis is regioselective for the least substituted position, making many prochiral substrates unsuitable for the reaction. Exceptions to this are, for example, cyclic *meso*-compounds bearing two enantiotopic leaving groups, 1,1,3-trisubstituted allylic substrates and allylic *gem*-diacetates (Scheme 1.2, b).<sup>7</sup> In these cases, substitution at the least hindered position will still lead to a chiral product. Excellent regio- and enantioselectivity has been achieved in many examples of the palladium catalyzed allylic substitution with several classes of chiral ligand and the reaction has been applied in the total syntheses of several natural products.<sup>8</sup>

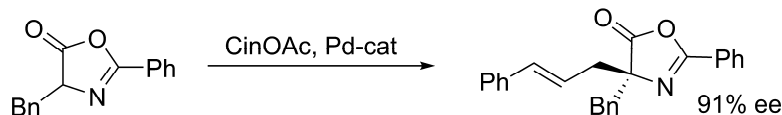
Only recently, have catalysts been developed, which can induce a regioselective formation of a branched product from monosubstituted allylic substrates.<sup>9-12</sup> It is straightforward to induce this formation in intramolecular

reactions, where formation of a five- or six-membered ring is strongly preferred over larger rings.<sup>7</sup> However, preferred formation of a branched product over the linear product is more problematic in an intermolecular substitution reaction (Scheme 1.3). Nevertheless, it has been achieved in high selectivity with a few catalysts. Trost and co-workers have been able to perform these reactions with oxygen nucleophiles using their diphosphine ligand systems.<sup>9</sup> The selective formation of branched products with stabilized carbanions as nucleophiles was first accomplished by the groups of Hayashi<sup>10</sup> and Pfaltz<sup>11</sup> and following this, other catalytic systems have been reported that can achieve high selectivities (up to b/l = >99:1 and 98% ee) in this difficult transformation.<sup>12</sup>



Scheme 1.3: Pd-catalyzed allylic substitution of monosubstituted allylic substrates; the linear product is usually the major product.

Significant progress in the field of Pd-catalyzed allylic substitution has been made in the application of a range of nucleophiles. As discussed above, the conventional nucleophile is a stabilized carbanion, such as a malonate ester. However, a carbanion with two different electron-withdrawing groups, which is a prochiral nucleophile, can be applied, also.<sup>7,8</sup> In this case the regioselective formation of a linear product still leads to a chiral compound and even simple non-substituted allyl electrophiles can be applied in an enantioselective reaction. A good example is the enantioselective formation of  $\alpha$ -amino acid derivatives through Pd-catalyzed allylic alkylation (Scheme 1.4).<sup>13</sup>

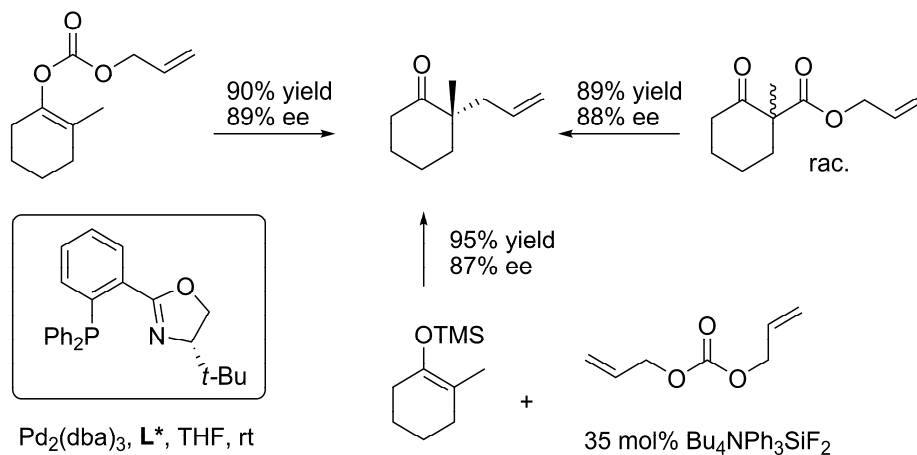


Scheme 1.4: Enantioselective synthesis of an amino acid derivative through Pd-catalyzed allylic substitution with a prochiral nucleophile; CinOAc = cinnamyl acetate.

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An important class, from a synthetic perspective, of prochiral nucleophiles is the enolate of a ketone. In contrast to the nucleophiles employed traditionally, these carbanions are not stabilized by an additional electron-withdrawing group and their use in Pd-catalyzed allylic alkylation has been reported only recently.<sup>14</sup> Initially, ketones were used, which have just one  $\alpha$ -carbon with acidic protons (e.g. 2-methyl-1-tetralone)<sup>15</sup> or two, which were chemically equivalent (cyclohexanone).<sup>16</sup>

The development of the enantioselective Tsuji allylation, which is a decarboxylative allylation, by Stoltz and co-workers has enabled the application of ketones with inequivalent  $\alpha$ -carbons, both of which bear acidic protons.<sup>17</sup> The reaction can be performed with allyl enol carbonates, silyl enol ethers and allyl  $\beta$ -ketoesters. In general, application of the same conditions to these different substrates provided products with the same enantioselectivity (Scheme 1.5).<sup>18</sup> This seems to indicate that for the three substrate classes a part of the mechanism, and in particular the stereoselective step, is essentially the same. Enantioselectivities of up to 99% ee have been achieved in some examples and the reaction has been applied in the total syntheses of a number of natural products.<sup>19</sup>

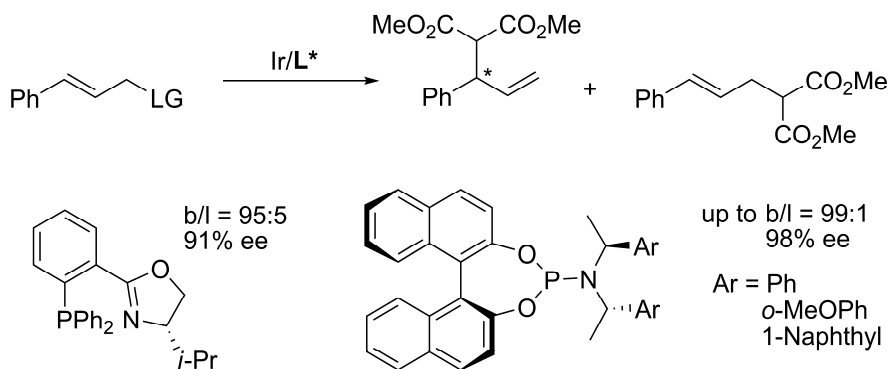


Scheme 1.5: Enantioselective Tsuji allylation can be performed on three different classes of substrate with essentially the same result; dba = dibenzylideneacetone.

### 1.2.2 Iridium catalyzed asymmetric allylic substitution

As explained in the previous section, it is difficult to obtain branched chiral products from monosubstituted allylic substrates when using Pd-catalysts. For this reason, other transition metals have been explored as potential catalysts, also. Some of these metals were found to have a preference for the branched product. One of the most widely studied transition metals, that provides high enantioselectivity in addition to regioselectivity in these transformations, is iridium.<sup>20</sup>

The first asymmetric iridium catalyzed allylic substitution reaction was reported by the group of Helmchen in 1997.<sup>21</sup> The reaction involved the substitution of cinnamyl acetate with a malonate ester using a chiral phosphinooxazoline ligand and provided the branched product selectively in high enantiomeric excess (Scheme 1.6). However, the substrate scope was limited and aliphatic substrates did not give the same excellent results as aromatic substrates.



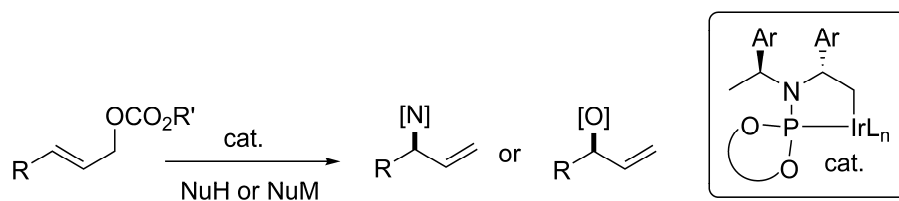
Scheme 1.6: Iridium catalyzed asymmetric allylic substitution of cinnamyl substrate with dimethyl sodiomalonate.

Following this first report, several groups have investigated the optimization of Ir-catalyzed asymmetric allylic substitution and a number of important discoveries have been reported.<sup>20</sup> For example, allylic carbonates provide better results than acetates and phosphoramidites are excellent chiral ligands.<sup>22</sup> Both the racemic branched isomer and the linear achiral

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isomer of the substrate are viable starting materials and several types of stabilized carbanion can be employed as nucleophile.

Another important aspect of iridium catalyzed asymmetric allylic substitution is the possibility of using heteroatom nucleophiles. Among others aliphatic amines, anilines, amides and hydroxylamines (N-nucleophiles) and aliphatic alcohols, phenols, oxims and silanols (O-nucleophiles) have been applied successfully with high regio- and enantioselectivity (Scheme 1.7).<sup>23</sup> Substantial effort has been directed to elucidate the mechanism of the reaction. The information obtained has led to the discovery of an iridacycle as an actual catalytic species (Scheme 1.7), the development of improved reaction conditions, more selective ligands and more convenient precatalyst systems.<sup>24</sup>



Scheme 1.7: Allylic amines and allylic ethers can be obtained using N-nucleophiles [N] and O-nucleophiles [O], respectively; the catalytic species is in many cases an iridacycle.

It should be noted that organometallic reagents have been applied in this reaction, also. The group of Alexakis reported an iridium catalyzed allylic substitution using aryl zinc reagents.<sup>25</sup> The enantioselectivities are moderate to excellent (up to 99%) and although the regioselectivity was not good (up to 73:27 b/l, ca. 50:50 typically), the asymmetric allylic substitution of monosubstituted allylic substrates with aromatic organometallic nucleophiles was unprecedented.

### 1.2.3 Asymmetric allylic alkylation with stabilized nucleophiles catalyzed by other transition metals

The first metal, other than Ir or Pd, discovered to give high regioselectivity for the branched product (up to 96:4) in an asymmetric allylic substitution was tungsten.<sup>26</sup> The reaction was performed on prochiral

linear allylic phosphates with dimethyl sodiomalonate as the nucleophile and a catalyst prepared from  $[\text{W}(\text{CO})_3(\text{MeCN})_3]$  and the phosphino-oxazoline ligand shown in Scheme 1.6. However, the report was not followed by many further studies on the use of tungsten-based catalysts in this reaction.

In 1998, Trost et al. reported studies on W and Mo-based catalysts in which they found that molybdenum was the more viable candidate.<sup>27</sup> A Mo-based catalyst bearing a dipyrindyl ligand catalyzed the regioselective asymmetric allylic substitution in equally high regio- and enantioselectivity as the tungsten equivalent (98:2, 99% ee). However, the Mo-catalyst was far more active than the W-catalysts. Several reports of Mo-catalyzed asymmetric allylic alkylation have followed,<sup>28</sup> including mechanistic studies that established a double retention pathway for the reaction.<sup>29</sup> Only stabilized carbanions have been applied as nucleophiles with Mo-based catalysts.

Recently, ruthenium based catalysts were reported to catalyze asymmetric allylic substitution reactions.<sup>30</sup> Reaction (a) in Scheme 1.2 could be performed with high enantioselectivity using malonate esters and with an amine with moderate enantioselectivity.<sup>31</sup> A reaction similar to the Tsuji allylation provided branched products through a Carroll-type rearrangement with excellent regioselectivity and moderate enantioselectivity.<sup>32</sup> Aromatic and aliphatic alcohols have been applied as nucleophiles with moderate to excellent selectivities using prochiral linear monosubstituted allylic substrates.<sup>33</sup>

#### 1.2.4 The application of organometallic reagents in the transition metal catalyzed asymmetric allylic alkylation

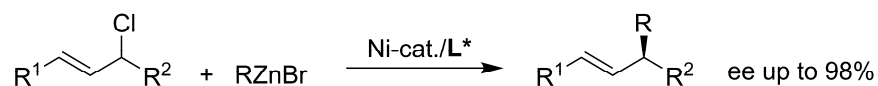
All of the transition metals discussed previously catalyze asymmetric allylic substitution reactions using either heteroatom nucleophiles, stabilized carbanions or, in a few cases, unstabilized enolate nucleophiles. The direct introduction of an alkyl or aryl group through the use of an organometallic reagent is generally not possible in an efficient regio- and enantioselective manner (the Ir-catalyzed substitution with arylzinc reagents reported by the group of Alexakis<sup>25</sup> being a notable exception, *vide supra*).

In the case of Pd-catalyzed allylic alkylation, it is known that the reaction pathway for allylic substitution with soft stabilized carbanion

nucleophiles is different than with hard organometallic reagents.<sup>7</sup> This is possibly the reason why highly enantioselective Pd-catalyzed allylic substitution with organometallic reagents has not been accomplished.<sup>34</sup> A few other transition metals have been reported to catalyze asymmetric allylic alkylation using organometallic reagents, of which copper has been the most widely studied. The progress in the field of copper catalysis will be discussed in more detail in section 1.3. Here two other metals, which have been applied successfully, nickel and rhodium, will be highlighted.

At a very early stage, nickel was discovered to enable asymmetric allylic alkylation of some allylic ethers and esters using Grignard reagents.<sup>35</sup> High enantioselectivity was attained occasionally in cyclic and acyclic substrates, where regioselectivity was not an issue,<sup>36</sup> and regio- and enantioselective substitution on cyclic allylic acetals has been reported, as well.<sup>37</sup> However, the use of monosubstituted allylic electrophiles led to low regioselectivity.

Recently, Fu and co-workers reported a Ni-catalyzed asymmetric cross-coupling of secondary allylic chlorides and aliphatic zinc bromides (Scheme 1.8).<sup>38</sup> Both symmetrically substituted ( $R^1 = R^2$ ) and asymmetrically substituted allyl electrophiles can be applied and the products can be obtained with good to excellent enantiomeric excess. Sufficient steric difference between  $R^1$  and  $R^2$  would lead to excellent regioselectivity even if mixtures of regioisomeric substrates were used.

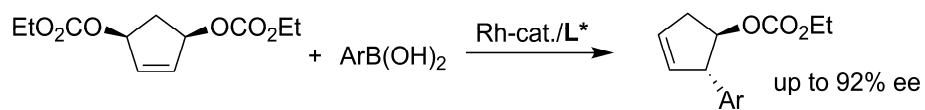


Scheme 1.8: Ni-catalyzed asymmetric allylic alkylation using aliphatic zinc bromides.

Rhodium, on the other hand, has not been explored extensively as a potential catalyst for asymmetric allylic substitution. The metal was instead reported to conserve the enantiomeric excess of non-racemic substrates<sup>39</sup> and possibly therefore assumed to be unsuitable for an enantioselective version of the reaction. Nevertheless, Hayashi et al. reported an asymmetric allylic alkylation catalyzed by rhodium, which provided excellent regio- and enantioselectivity with malonate ester as the nucleophile.<sup>40</sup>

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Interestingly, this transition metal can be used as a catalyst in the asymmetric allylic substitution with boron reagents. The reaction has been performed using arylboroxines on *cis*-allylic diols<sup>41</sup> and using arylboronic acids on a cyclic allylic *meso*-dicarbonate.<sup>42</sup> In particular the latter example led to products in excellent enantiomeric excess (Scheme 1.9).



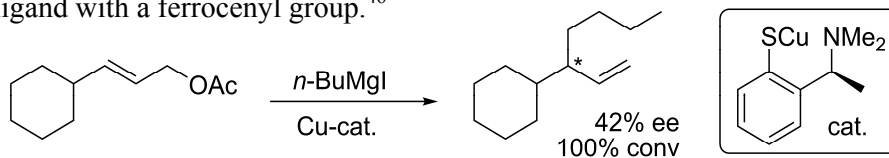
Scheme 1.9: Rh-catalyzed allylic substitution with aryl boronic acid nucleophiles.

### 1.3 Copper catalyzed asymmetric allylic alkylation

Within the spectrum of transition metals able to catalyze asymmetric allylic substitution reactions, copper holds a special position. The metal owes this position to two important properties: the general regioselectivity for the branched product in an allylic substitution reaction with a monosubstituted allylic substrate and its compatibility with organometallic reagents, which enables the direct introduction of alkyl groups.<sup>43</sup> These characteristics make copper complementary to the other transition metals catalysts for asymmetric allylic substitution reactions. In addition copper is not as expensive and less toxic than many of those metals.

The area of copper-catalyzed asymmetric allylic alkylation, although not as widely studied as the Pd-catalyzed reaction, has been a focus of interest in asymmetric catalysis for some time and has been reviewed extensively.<sup>44</sup> This section will provide a comprehensive overview of the catalyst systems and the organometallic reagents that have been applied. It will present the groundbreaking work of several groups including ours, which preceded the investigation described in this thesis and discuss the results that have been reported in the course of the realization of this thesis. The section will not review any applications in synthesis, because those will be discussed in the introductions of following chapters.

The first report in 1995 of a copper catalyzed enantioselective allylic alkylation resulted from a collaboration between the groups of Bäckvall and van Koten.<sup>45</sup> A Grignard reagent was used with allylic acetates as the electrophilic substrates. The best result at that time was an enantiomeric excess of 42% for the branched S<sub>N</sub>2' product found exclusively using an arenethiolato copper complex as catalyst (Scheme 1.10). Screening of experimental parameters and ligands effected an increase in enantioselectivity to 64%, after replacing the phenyl ring of the original ligand with a ferrocenyl group.<sup>46</sup>

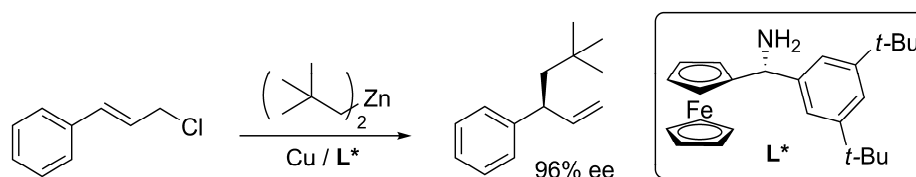


Scheme 1.10: The first copper catalyzed asymmetric allylic alkylation, reported in 1995.

### 1.3.1 Zinc reagents in Cu-catalyzed asymmetric allylic alkylation

Following the first report of Bäckvall and van Koten, Knochel and co-workers reported a copper catalyzed asymmetric allylic alkylation using dialkylzinc reagents instead.<sup>47</sup> Dialkylzinc compounds are generally less reactive than Grignard reagents, which facilitates the prevention of uncatalyzed side reactions. In addition, they exhibit a high functional group tolerance, which enables the use of functionalized organometallic nucleophiles.<sup>48</sup>

The group of Knochel reported the application of chiral ferrocenyl based amine ligands. This enabled a highly selective allylic alkylation of allylic chlorides with the bulky dineopentylzinc reagent (b/l = 98:2, 96% ee, Scheme 1.11). Sterically less hindered zinc reagents provided significantly lower enantioselectivities (*e.g.* 44% ee for Et<sub>2</sub>Zn).



Scheme 1.11: Copper catalyzed asymmetric allylic alkylation using a dineopentylzinc.

This promising result sparked an interest in the application of zinc reagents in the enantioselective copper catalyzed allylic alkylation. Several groups developed new catalytic systems to apply in the reaction with diorganozinc compounds. The benchmark reaction by which these catalyst systems can be compared is the allylic substitution on a cinnamyl substrate using diethylzinc as the nucleophilic reagent (Figure 1.2).

Hoveyda and co-workers applied their modular peptide-based ligand system on this benchmark reaction using cinnamyl phosphate as the substrate and attained excellent regio- and enantioselectivity (b/l = >98:2, 95% ee).<sup>49</sup> A range of substrates and diorganozinc reagents could be applied with similar and even better results (up to 98% ee).<sup>50</sup> Furthermore, chiral quaternary carbon centers could be formed in excellent selectivity when using  $\gamma$ -disubstituted allylic phosphates.

The niche of copper in transition metal catalyzed asymmetric allylic substitution

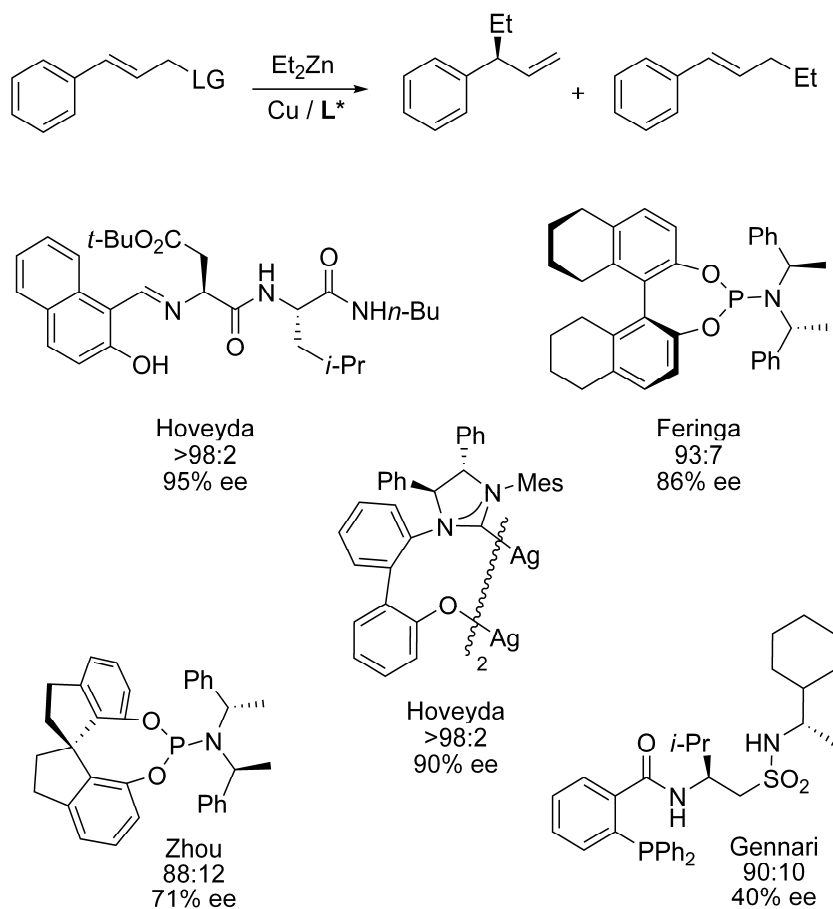


Figure 1.2: The benchmark copper catalyzed asymmetric allylic alkylation, which uses a cinnamyl derivative and diethylzinc as the organometallic reagent and the ligands developed by several groups with the regioselectivity and enantiomeric excess; LG = leaving group; Mes = mesityl.

Phosphoramidites were studied as ligands for the enantioselective copper catalyzed allylic alkylation in our laboratories.<sup>51</sup> The reaction proceeded with high selectivity when cinnamyl bromide was used as the substrate (b/l = 93:7, 86% ee). A range of dialkylzinc reagents and *p*-substituted cinnamyl bromides could be applied with similar results. The use

of non-cinnamyl substrates led to a significant decrease in selectivity, though. Zhou and co-workers applied phosphoramidite ligands with a spirocyclic backbone as opposed to the BINOL-based backbone in the Feringa ligand.<sup>52</sup> The selectivities attained with these ligands were slightly lower.

Another modular ligand library was developed by the group of Gennari and applied in the copper catalyzed allylic alkylation of cinnamyl phosphate.<sup>53</sup> High selectivity was not attained with this substrate (up to 40% ee). However, they were able to apply this catalyst system in the desymmetrizing allylic alkylation of cyclic *meso*-compounds with much better results.<sup>54</sup> The same group reported the use of phosphoramidite ligands with these *meso*-substrates (see section 3.1.1).<sup>54a,55</sup>

In addition to their modular ligand library, the group of Hoveyda recently reported a new catalyst system for asymmetric allylic alkylation based on NHC-ligands (Figure 1.2 shows the dimeric Ag(I) complex of the ligand).<sup>56</sup> They achieved excellent regio- and enantioselectivities using allylic phosphates as substrates. This catalyst system enabled the application of a wide range of substrates and diorganozinc reagents with similar and higher selectivity (up to b/l = >98:2 and 98% ee). It is important to note that they reported the only example so far of the use of an aromatic organometallic nucleophile, in this case diarylzinc reagents, in enantioselective copper catalyzed allylic alkylation and enantioselectivities of up to 92% were achieved with a ligand similar to that shown in Figure 1.2.<sup>56a</sup>

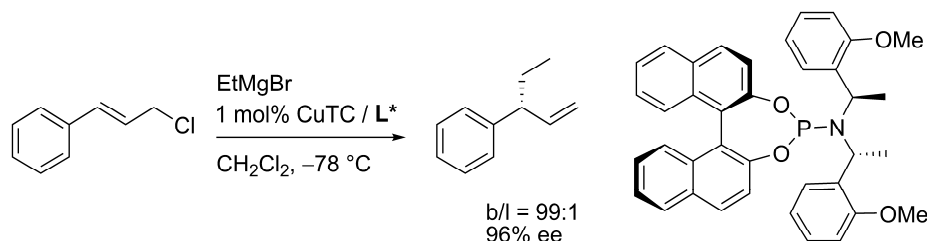
One further example of the use of dialkylzinc reagents in Cu-AAA is that reported by Woodward and co-workers.<sup>57</sup> Enantioselectivities of up to 90% were attained using chiral amines as ligands and allylic chlorides derived from Baylis-Hillman products. This reaction is described in more detail in section 3.1.1.

### 1.3.2 Grignard reagents in Cu-catalyzed asymmetric allylic alkylation

Initially, the efforts to develop efficient catalyst systems for enantioselective copper catalyzed allylic alkylation focused primarily on the use of diorganozinc compounds. The Grignard reagents, applied originally by the group of Bäckvall, were not left out of consideration, though. Grignard reagents are more reactive than their zinc counterparts and less tolerant to functional groups. However, they are readily obtained, easy to

handle and cheap compared to dialkylzinc reagents and exhibit a better “atom economy”,<sup>5</sup> since they contain one alkyl group only.

The group of Alexakis focused on Grignard reagents. Their initial reports featured both phosphite and phosphoramidite ligands and moderate to high selectivities (up to 86% ee and generally b/l = >90:10) were attained with a range of allylic chlorides and several Grignard reagents.<sup>58</sup> They arrived at a breakthrough, when they introduced a new phosphoramidite ligand in 2004, which enabled the copper catalyzed allylic alkylation using Grignard reagents with excellent regio- and enantioselectivity (Scheme 1.12).<sup>59</sup>



Scheme 1.12: Highly selective copper catalyzed allylic alkylation with Grignard reagent using a phosphoramidite ligand; TC = 2-thiophenecarboxylate.

The method was subsequently extended to different substrate classes, including, for example,  $\beta$ -substituted allylic chlorides.<sup>60</sup> A major draw-back of the catalyst system was the inefficient introduction of a methyl group using methyl Grignard reagents, particularly with regard to the regioselectivity. However, increase in catalyst loading and slow addition of the Grignard reagent (4 h) improved the selectivity of the reaction substantially, allowing, for example, the methylation of cinnamyl chloride with 96% ee and a regioselectivity of 89:11.<sup>61</sup>

Two groups reported the use of NHC-ligands in copper catalyzed asymmetric allylic alkylation with Grignard reagents (Figure 1.3). Okamoto et al. reached an enantioselectivity of 70% and excellent regioselectivity using a chiral imidazolium carbene.<sup>62</sup> More recently, Hong and co-workers applied a bisisoquinoline based carbene in copper catalyzed allylic alkylation and attained selectivities up to b/l = 88:12 and 77% ee.<sup>63</sup>

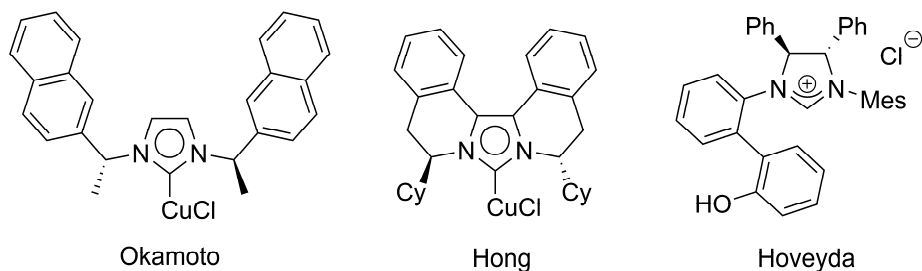


Figure 1.3: Chiral *N*-heterocyclic carbenes have been used in the catalytic asymmetric allylic alkylation, often, although not exclusively, with copper.

The contribution of our group to the field of copper catalyzed asymmetric allylic alkylation using Grignard reagents will be extensively discussed in the following chapters of this thesis.

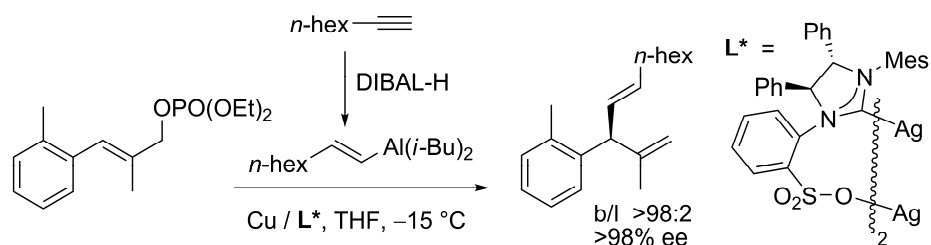
Although not a copper catalyzed allylic alkylation, the allylic alkylation with Grignard reagents reported by the group of Hoveyda is certainly worth mentioning.<sup>64</sup> The substitution of  $\gamma$ -chloro- $\alpha,\beta$ -unsaturated esters is catalyzed with high selectivity (up to b/l = 93:7 and 98% ee) through Lewis base activation by a chiral carbene alone (Figure 1.3).

### 1.3.3 Other reagents in Cu-catalyzed asymmetric allylic alkylation

In addition to dialkylzinc compounds and Grignard reagents, trimethylaluminum has been applied in copper catalyzed allylic alkylation.<sup>65</sup> The reaction is a key step in the total synthesis of baconipyron C and is discussed in more detail in section 3.1.3.

Aluminum reagents have been employed in a copper catalyzed asymmetric allylic alkenylation by the group of Hoveyda, also.<sup>66</sup> The catalyst system featured one of the NHC-ligands and the alkenylaluminum reagents were formed *in situ* from alkynes and DIBAL-H (Scheme 1.13). The allyl phosphate substrates were alkenylated exclusively and transfer of the *iso*-butyl group did not occur. A range of substrates and alkynes could be applied in high to excellent regio- and enantioselectivity (up to >98% ee and full regioselectivity). The *E*-isomer of the product was formed in all cases except when *tert*-butyl propargyl ether was used as the alkyne, in which case the *Z*-isomer was formed exclusively.

*The niche of copper in transition metal catalyzed asymmetric allylic substitution*



Scheme 1.13: An example of enantioselective copper catalyzed allylic alkenylation using aluminum reagents formed in situ from DIBAL-H and an alkyne.

Very recently, an enantioselective copper catalyzed allylic substitution was reported, which employed a diboron reagent as nucleophile.<sup>67</sup> The reaction enables the synthesis of allylboronates in high optical purity and is, to the best of my knowledge, the only example of a copper catalyzed asymmetric allylic substitution, which does not make use of an organometallic nucleophile.

## 1.4 Aim and Outline of this Thesis

The aim of the research presented in this thesis was the development of a new catalyst system for copper catalyzed asymmetric allylic substitution. The system should enable highly regio- and enantioselective reactions with a broad substrate and reagent scope. In particular, the focus is on reactions that remained challenging with the catalyst systems available so far (described in this chapter); for instance, the introduction of a methyl substituent through allylic alkylation using Grignard reagents.

In addition, the versatility of the copper catalyzed asymmetric allylic alkylation was to be highlighted. The intention was to demonstrate several routes by which the products of the reaction can be applied in a synthetically useful manner.

Chapter 2 describes the development of a new method, which uses a copper catalyst system based on the ferrocenyl diphosphine ligand Taniaphos. Allylic bromides and Grignard reagents are employed providing excellent regio- and enantioselectivity. In particular, the high selectivity using methylmagnesium bromide makes the system complementary to the existing methods.

In chapter 3 the application of the new catalyst system to functionalized substrates is described. The versatility of the terminal olefinic double bond is highlighted through several derivatization reactions of the products obtained in the asymmetric allylic alkylation of these substrates. Multiple chiral bifunctional building blocks, which had shown their merit in total synthesis already, were synthesized in this manner.

Chapter 4 describes the development of a new protocol for the asymmetric synthesis of vicinal dialkyl arrays. The method is based on copper catalyzed allylic alkylation, cross-metathesis and copper catalyzed asymmetric conjugate addition. Two pheromones of two species of ants were prepared using this route, demonstrating the applicability of the protocol in the total synthesis of natural products.

The total syntheses of the pheromones required a cross-metathesis reaction of a terminal olefin with a thioacrylate. This reaction had not been reported previously and chapter 5 describes a new and efficient route to

obtain *S*-ethyl thioacrylate and its application in cross-metathesis with a range of olefins.

Chapter 6 describes the application of copper catalyzed allylic alkylation to the preparation of chiral heterocyclic compounds. The products of Cu-AAA are subjected to a range of cyclization reactions providing valuable heterocyclic building blocks in high optical purity.

## 1.5 Conclusions and Perspectives

In summary, the highly versatile asymmetric allylic substitution reaction is an important tool for synthetic organic chemists. The reaction can be catalyzed by several transition metals, of which palladium has proven the most widely applicable so far. Most of these transition metal catalysts can be applied with stabilized carbanions and heteroatomic nucleophiles, albeit not with organometallic reagents.

Copper holds a special position among these transition metals; one might even say an important niche. It is the only metal so far that can both be applied to prochiral linear allylic substrates, with a general regioselectivity for the branched product, and be used efficiently with a wide range of organometallic reagents. These qualities allow for the synthesis of versatile chiral compounds containing a terminal olefin, which is a useful functional group for further transformations, and a new stereogenic center with a simple alkyl substituent.

Over the last decade, several efficient catalyst systems for copper catalyzed asymmetric allylic alkylation have been developed. Particularly effective for the application of dialkylzinc reagents are the systems based on the modular peptide ligands and the NHC-ligands, both originating from Hoveyda's group. In the case of Grignard reagents, the most effective systems are based on phosphoramidites, as reported by Alexakis' group, or the diphosphine ligand Taniaphos, which is further described in the following chapters of this thesis.

Considering the impressive results reported in the field already, it seems that the area is no longer in its infancy, but has reached adolescence. The focus of current research has shifted from development of more selective

## Chapter 1

procedures to broadening the scope of these procedures and applications in synthesis. Nevertheless, before the area can reach maturity, *i.e.* the reaction becomes a standard tool in industrial as well as laboratory chemistry, major hurdles remain to be overcome.

In many cases, catalyst loadings remain too high; 1 mol% is still considered high by industrial standards. In addition, the reaction temperature is often too low: the reactions with Grignard reagents are all performed at around  $-78\text{ }^{\circ}\text{C}$ . Some of the reactions reported by Hoveyda's group can be performed at  $-15\text{ }^{\circ}\text{C}$ , however, his use of dialkylzinc compounds is not as atom economical as the use of Grignard reagents. A solution could be the use of monoalkylzinc compounds ( $\text{RZnX}$ ). The low reactivity of these compounds should allow their use at higher temperatures, however, it seems to have precluded the development of an efficient catalyst system thus far.<sup>68</sup>

In addition, little is known about the mechanism of the reaction. In general, hypothetical models extrapolated from the knowledge of copper catalyzed conjugate addition are used. Definitive information on the catalytic species and cycles is still unavailable. More insight into the mechanism would help substantially in the amelioration of the reaction, as has been seen in other catalyzed processes.

## References:

- <sup>1</sup> Wöhler, F. *Ann. Phys. Chem.* **1828**, *88*, 253-256.
- <sup>2</sup> Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds* **1994**, Wiley, New York.
- <sup>3</sup> Artwork from: <http://web99.arc.nasa.gov/~astrochm/aachiral.html>
- <sup>4</sup> Sheldon, R. A. *Chirotechnology* **1993**, Dekker, New York.
- <sup>5</sup> a) Trost, B. M. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259-281; b) Trost, B. M. *Science* **1991**, *254*, 1471-1477.
- <sup>6</sup> [http://nobelprize.org/nobel\\_prizes/chemistry/laureates/2001/index.html](http://nobelprize.org/nobel_prizes/chemistry/laureates/2001/index.html)
- <sup>7</sup> a) Ma, S.; Lu, Z. *Angew. Chem. Int. Ed.* **2008**, *47*, 258-297; b) Pfaltz, A.; Lautens, M. in *Comprehensive Asymmetric Catalysis* Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Heidelberg, **1999**; Vol. 2, Chapter 24; c) Helmchen, G. *J. Organomet. Chem.* **1999**, *576*, 203-214; d) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395-422.
- <sup>8</sup> a) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813-5837; b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921-2943.
- <sup>9</sup> See for example: a) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **2000**, *122*, 3785-3786; b) Trost, B. M.; Tsui, H.-C.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 3534-3535; c) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 9074-9075.
- <sup>10</sup> a) Hayashi, T. *Acc. Chem. Res.* **2000**, *33*, 354-362 and references therein; b) Hayashi, T.; Kawatsura, M.; Uozumi, Y. *Chem. Commun.* **1997**, 561-562.
- <sup>11</sup> a) Hilgraf, R.; Pfaltz, A. *Adv. Synth. Cat.* **2005**, *347*, 61-77 and references therein; b) Prétôt, R.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 323-325.
- <sup>12</sup> a) Zheng, W.-H.; Sun, N.; Hou, X.-L. *Org. Lett.* **2005**, *7*, 5151-5154; b) Pàmies, O.; Diéguez, M.; Claver, C. *J. Am. Chem. Soc.* **2005**, *127*, 3646-3647; c) You, S.-L.; Zhu, X.-Z.; Luo, Y.-M.; Hou, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2001**, *123*, 7471-7472.
- <sup>13</sup> Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727-10737.
- <sup>14</sup> For a review of the method in an achiral fashion see: Kazmaier, U. *Curr. Org. Chem.* **2003**, *7*, 317-328.
- <sup>15</sup> a) Trost, B. M.; Schroeder, G. M. *Chem. Eur. J.* **2005**, *11*, 174-184; b) You, S.-L.; Hou, X.-L.; Dai, L.-X.; Zhu, X.-Z. *Org. Lett.* **2001**, *3*, 149-151; c) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759-6760.
- <sup>16</sup> Braun, M.; Laicher, F.; Meier, T. *Angew. Chem. Int. Ed.* **2000**, *39*, 3494-3497.
- <sup>17</sup> Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044-15045.

- <sup>18</sup> For comprehensive reviews see: a) Mohr, J. T.; Stoltz, B. M. *Chem. Asian J.* **2007**, *2*, 1476-1491; b) You, S.-L.; Dai, L.-X. *Angew. Chem. Int. Ed.* **2006**, *45*, 5246-5248.
- <sup>19</sup> a) Enquist, J. A., Jr.; Stoltz, B. M. *Nature* **2008**, *453*, 1228-1231; b) White, D. E.; Stewart, I. C.; Grubbs, R. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 810-811; see also references cited in ref 18.
- <sup>20</sup> For reviews see: a) Helmchen, G.; Dahnz, A.; Dübon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 675-691; b) Takeuchi, R.; Kezuka, S. *Synthesis* **2006**, 3349-3366; c) Miyabe, H.; Takemoto, Y. *Synlett* **2005**, 1641-1655.
- <sup>21</sup> Janssen, J. P.; Helmchen, G. *Tetrahedron Lett.* **1997**, *38*, 8025-8026.
- <sup>22</sup> a) Polet, D.; Alexakis, A.; Tissot-Croset, K.; Corminboeuf, C.; Ditrach, K. *Chem. Eur. J.* **2006**, *12*, 3596-3609; b) Alexakis, A.; Polet, D. *Org. Lett.* **2004**, *6*, 3529-3532; c) Bartels, B.; García-Yebra, C.; Helmchen, G. *Eur. J. Org. Chem.* **2003**, 1097-1103.
- <sup>23</sup> See, for example: a) Singh, O. V.; Han, H. *J. Am. Chem. Soc.* **2007**, *129*, 774-775; b) Lyothier, I.; Defieber, C.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 6204-6207; c) Shu, C.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2004**, *43*, 4794-4797; d) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164-15165.
- <sup>24</sup> a) Marković, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 11680-11681; b) Polet, D.; Alexakis, A. *Org. Lett.* **2005**, *7*, 1621-1624; c) Kiener, C. A.; Shu, C.; Incarvito, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 14272-14273; d) Bartels, B.; García-Yebra, C.; Rominger, F.; Helmchen, G. *Eur. J. Inorg. Chem.* **2002**, 2569-2586.
- <sup>25</sup> Alexakis, A.; El Hajjaji, S.; Polet, D.; Rathgeb, X. *Org. Lett.* **2007**, *9*, 3393-3395.
- <sup>26</sup> Lloyd-Jones, G. C.; Pfaltz, A. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 462-464.
- <sup>27</sup> Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104-1105.
- <sup>28</sup> For a review, see: Belda, O.; Moberg, C. *Acc. Chem. Res.* **2004**, *37*, 159-167.
- <sup>29</sup> a) Hughes, D. L.; Lloyd-Jones, G. C.; Krska, S. W.; Gouriou, L.; Bonnet, V. D.; Jack, K.; Sun, Y.; Mathre, D. J.; Reamer, R. A. *Proc. Nat. Acad. Sci. USA* **2004**, *101*, 5379-5384; b) Lloyd-Jones, G. C.; Krska, S. W.; Hughes, D. L.; Gouriou, L.; Bonnet, V. D.; Jack, K.; Sun, Y.; Reamer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 702-703.
- <sup>30</sup> For reviews, see: a) Bruneau, C.; Renaud, J.-L.; Demerseman, B. *Pure Appl. Chem.* **2008**, *80*, 861-871; b) Bruneau, C.; Renaud, J.-L.; Demerseman, B. *Chem. Eur. J.* **2006**, *12*, 5178-5187.
- <sup>31</sup> Matsushima, Y.; Onitsuka, K.; Kondo, T.; Mitsudo, T.; Takahashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 10405-10406.
- <sup>32</sup> Constant, S.; Tortoioli, S.; Müller, J.; Lacour, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 2082-2085.

- <sup>33</sup> a) Onitsuka, K.; Okuda, H.; Sasai, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 1454-1457; b) Mbaye, M. D.; Renaud, J.-L.; Demerseman, B.; Bruneau, C. *Chem. Commun.* **2004**, 1870-1871.
- <sup>34</sup> One example of Pd-catalyzed enantioselective allylic alkylation with an organometallic reagent has been reported: Fotiadu, F.; Cros, P.; Faure, B.; Buono, G. *Tetrahedron Lett.* **1990**, *31*, 77-80.
- <sup>35</sup> Consiglio, G.; Morandini, F.; Piccolo, O. *J. Chem. Soc., Chem. Commun.* **1983**, 112-114.
- <sup>36</sup> a) Nomura, N.; RajanBabu, T. V. *Tetrahedron Lett.* **1997**, *38*, 1713-1716; b) Indolese, A. F.; Consiglio, G. *Organometallics* **1994**, *13*, 2230-2234 and references therein; c) Hiyama, T.; Wakasa, N. *Tetrahedron Lett.* **1985**, *26*, 3259-3262.
- <sup>37</sup> Gomez-Bengoa, E.; Heron, N. M.; Didiuk, M. T.; Luchaco, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 7649-7650.
- <sup>38</sup> Son, S.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 2756-2757.
- <sup>39</sup> Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581-5582.
- <sup>40</sup> Hayashi, T.; Okada, A.; Suzuka, T.; Kawatsura, M. *Org. Lett.* **2003**, *5*, 1713-1715.
- <sup>41</sup> Miura, T.; Takahashi, Y.; Murakami, M. *Chem. Commun.* **2007**, 595-597.
- <sup>42</sup> Menard, F.; Chapman, T. M.; Dockendorff, C.; Lautens, M. *Org. Lett.* **2006**, *8*, 4569-4572.
- <sup>43</sup> For reviews on the general reactivity of copper-based reagents and catalysts in allylic alkylation, see: a) Breit, B.; Demel, P. in *Modern Organocopper Chemistry* Krause, N. (Ed.), Wiley-VCH, Weinheim, **2002**. Chapter 6; b) Karlström, A. S. E.; Bäckvall, J.-E. in *Modern Organocopper Chemistry* Krause, N. (Ed.), Wiley-VCH, Weinheim, **2002**. Chapter 8; c) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901-1930.
- <sup>44</sup> a) Geurts, K.; Fletcher, S. P.; van Zijl, A. W.; Minnaard, A. J.; Feringa, B. L. *Pure Appl. Chem.* **2008**, *80*, 1025-1037; b) Falcicola, C. A.; Alexakis, A. *Eur. J. Org. Chem.* **2008**, 3765-3780; c) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824-2852; d) Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 4435-4439; e) Alexakis, A.; Malan, C.; Lea, L.; Tissot-Croset, K.; Polet, D.; Falcicola, C. *Chimia* **2006**, *60*, 124-130.
- <sup>45</sup> van Klaveren, M.; Persson, E. S. M.; del Villar, A.; Grove, D. M.; Bäckvall, J.-E.; van Koten, G. *Tetrahedron Lett.* **1995**, *36*, 3059-3062.
- <sup>46</sup> a) Cotton, H. K.; Norinder, J.; Bäckvall, J.-E. *Tetrahedron* **2006**, *62*, 5632-5640; b) Karlström, A. S. E.; Huerta, F. F.; Meuzelaar, G. J.; Bäckvall, J.-E. *Synlett* **2001**, 923-926; c) Meuzelaar, G. J.; Karlström, A. S. E.; van Klaveren, M.; Persson, E. S. M.; del Villar, A.; van Koten, G.; Bäckvall, J.-E. *Tetrahedron* **2000**, *56*, 2895-2903.

- <sup>47</sup> a) Dübner, F.; Knochel, P. *Tetrahedron Lett.* **2000**, *41*, 9233-9237; b) Dübner, F.; Knochel, P. *Angew. Chem. Int. Ed.* **1999**, *38*, 379-381.
- <sup>48</sup> a) von Wangelin, A. J.; Frederiksen, M. U. in *Transition Metals for Organic Synthesis* 2nd Ed.; Vol. 1; Beller, M.; Bolm, C. (Eds.); Wiley-VCH, Weinheim, **2004**. Chapter 3.7; b) Knochel, P.; Almerna Perea, J. J.; Jones, P. *Tetrahedron* **1998**, *54*, 8275-8319.
- <sup>49</sup> a) Kacprzynski, M. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 10676-10681; b) Luchaco-Cullis, C. A.; Mizutani, H.; Murphy, K. E.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2001**, *40*, 1456-1460.
- <sup>50</sup> a) Murphy, K. E.; Hoveyda, A. H. *Org. Lett.* **2005**, *7*, 1255-1258; b) Hoveyda, A. H.; Hird, A. W.; Kacprzynski, M. A. *Chem. Commun.* **2004**, 1779-1785; c) Murphy, K. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4690-4691.
- <sup>51</sup> a) van Zijl, A. W.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. *Adv. Synth. Catal.* **2004**, *346*, 413-420; b) Malda, H.; van Zijl, A. W.; Arnold, L. A.; Feringa, B. L. *Org. Lett.* **2001**, *3*, 1169-1171.
- <sup>52</sup> Shi, W.-J.; Wang, L.-X.; Fu, Y.; Zhu, S.-F.; Zhou, Q.-L. *Tetrahedron: Asymm.* **2003**, *14*, 3867-3872.
- <sup>53</sup> Onger, S.; Piarulli, U.; Roux, M.; Monti, C.; Gennari, C. *Helv. Chim. Acta* **2002**, *85*, 3388-3399.
- <sup>54</sup> a) Piarulli, U.; Daubos, P.; Claverie, C.; Monti, C.; Gennari, C. *Eur. J. Org. Chem.* **2005**, 895-906; b) Piarulli, U.; Daubos, P.; Claverie, C.; Roux, M.; Gennari, C. *Angew. Chem. Int. Ed.* **2003**, *42*, 234-236.
- <sup>55</sup> Piarulli, U.; Claverie, C.; Daubos, P.; Gennari, C.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 4493-4496.
- <sup>56</sup> a) Kacprzynski, M. A.; May, T. L.; Kazane, S. A.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2007**, *46*, 4554-4558; b) Van Veldhuizen, J. J.; Campbell, J. E.; Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 6877-6882; c) Larsen, A. O.; Leu, W.; Nieto Oberhuber, C.; Campbell, J. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 11130-11131.
- <sup>57</sup> a) Goldsmith, P. J.; Teat, S. J.; Woodward, S. *Angew. Chem. Int. Ed.* **2005**, *44*, 2235-2237; b) Börner, C.; Gimeno, J.; Gladiali, S.; Goldsmith, P. J.; Ramazzotti, D.; Woodward, S. *Chem. Commun.* **2000**, 2433-2434.
- <sup>58</sup> a) Alexakis, A.; Croset, K. *Org. Lett.* **2002**, *4*, 4147-4149; b) Alexakis, A. *Pure Appl. Chem.* **2002**, *74*, 37-42; c) Alexakis, A.; Malan, C.; Lea, L.; Benhaim, C.; Fournioux, X. *Synlett* **2001**, 927-930; d) Alexakis, A.; Croset, K. *Org. Lett.* **2003**, *5*, 4239 correction 58a.
- <sup>59</sup> a) Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 2426-2428; b) Tissot-Croset, K.; Polet, D.; Gille, S.; Hawner, C.; Alexakis, A. *Synthesis* **2004**, 2586-2590.

<sup>60</sup> a) Falciola, C. A.; Tissot-Croset, K.; Reyneri, H.; Alexakis, A. *Adv. Synth. Catal.* **2008**, *350*, 1090-1100; b) Falciola, C. A.; Alexakis, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 2619-2622; c) Falciola, C. A.; Tissot-Croset, K.; Alexakis, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 5995-5998.

<sup>61</sup> Tissot-Croset, K.; Alexakis, A. *Tetrahedron Lett.* **2004**, *45*, 7375-7378.

<sup>62</sup> a) Okamoto, S.; Tominaga, S.; Saino, N.; Kase, K.; Shimoda, K. *J. Organomet. Chem.* **2005**, *690*, 6001-6007; b) Tominaga, S.; Oi, Y.; Kato, T.; An, D. K.; Okamoto, S. *Tetrahedron Lett.* **2004**, *45*, 5585-5588.

<sup>63</sup> Seo, H.; Hirsch-Weil, D.; Abboud, K. A.; Hong, S. *J. Org. Chem.* **2008**, *73*, 1983-1986.

<sup>64</sup> Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 15604-15605.

<sup>65</sup> Gillingham, D. G.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2007**, *46*, 3860-3864.

<sup>66</sup> Lee, Y.; Akiyama, K.; Gillingham, D. G.; Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 446-447.

<sup>67</sup> a) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *Pure Appl. Chem.* **2008**, *80*, 1039-1045; b) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856-14857.

<sup>68</sup> The use of RZnX nucleophiles in a highly regio- and stereospecific Cu-catalyzed allylic substitution at room temperature has been reported recently: Nakata, K.; Kiyotsuka, Y.; Kitazume, T.; Kobayashi, Y. *Org. Lett.* **2008**, *10*, 1345-1348.

