Phosphoramidites as ligands for copper in catalytic asymmetric C-C bond formation reactions with organozinc reagents
Arnold, Alexander Erich

Publication date: 2002

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Chapter 8

The allylic alkylation

8.1 The allylic alkylation

Transition metal catalyzed allylic alkylation has become a highly versatile synthetic methodology in contemporary organic chemistry. The allylic alkylation is an attractive route for the formation of carbon-carbon bonds because the allylated products can be transformed into organic molecules possessing a variety of functional groups. This transformation is fascinating since the reaction of a carbon nucleophile and substrate 8.1 with a leaving group (LG) in the allylic position can give two different products, the $\text{SN}_2$- or $\alpha$-product 8.2 and the $\text{SN}_2'$- or $\gamma$-product 8.3 (Scheme 8.1). These two products are formed by: 1) displacement of the leaving group of 8.1 involving an allylic shift of the double bond affording 8.2, and 2) direct displacement of the leaving group of 8.1 in an $\text{SN}_2$ fashion affording 8.3 (Scheme 8.1).

$$\begin{align*}
\text{LG} + \text{Nu} & \rightarrow \text{SN}_2'\text{-product} + \text{SN}_2\text{-product} \\
\text{Nu} + R\gamma\alpha \text{LG} & \rightarrow R\gamma\alpha \text{Nu} + \text{LG}^{-}
\end{align*}$$

Scheme 8.1 Regioselectivity of the allylic alkylation reaction.

Because of this regioselectivity issue the development of methods that give rise to a controlled C-C bond formation at the $\gamma$-position has attracted much interest. In addition to the formation of a new C-C bond in the allylic alkylation a new stereogenic center is created (if Nu≠R, Nu≠vinyl and R≠H).

For the allylic alkylation with carbon nucleophiles one can use a variety of organometallic reagents. Note that although stabilized carbon nucleophiles like enolates or malonates are widely used as nucleophiles in the (Pd- or Ni-catalyzed) allylic substitution reaction. These reactions are neither the subject of this introduction nor of this thesis.

The difference between soft and hard carbon nucleophiles has already been explained in section 2.1.3. The use of soft or hard carbon nucleophiles in the allylic alkylation reaction has a similar effect regarding the regioselectivity as for the 1,4-addition discussed in chapter 2. For example: The reaction of BuMgCl (a hard carbon nucleophile) and cinnamyl chloride 8.4 in THF at $-70^\circ C$ afforded only the $\text{SN}_2$ product 8.6. In contrast, when Bu2CuLi (a soft
carbon nucleophile) was used in the reaction with $8.4$, the $S_N2'$ product $8.5$, was obtained as major product (Scheme 8.2). Over the past 20 years, organocopper reagents leading to the $S_N2'$-coupling product have been intensively studied.\(^3\)

```
\[ \begin{align*}
\text{8.4} & \xrightarrow{\text{BuM, BuMgCl, Bu}_2\text{CuLi}} \text{BuMgCl} + \text{Bu}_2\text{CuLi} \\
\text{8.5} & \text{SN2'} \\
\text{8.6} & \text{SN2}
\end{align*} \]
```

Scheme 8.2 The use of soft and hard nucleophiles in the allylic alkylation.

### 8.2 The catalytic allylic alkylation

Again it was Kharasch who carried out the initial experiments (see section 2.1.3).\(^4\) Based on the early results efforts have been made to combine Cu\(^5\) and Zn\(^6\) catalysts with organometallic reagents based on Mg\(^5,7\), Zn\(^8\), Al\(^9\), or Ti\(^10\). In most cases catalytic allylic alkylation with Grignard reagents gave only moderate regioselectivities because of a background $S_N2$-substitution (Scheme 8.2). The use of sterically hindered allylic esters\(^5c\) or copper complexes\(^11\) instead of copper salts was shown to enhance the regioselectivity and a similar effect was reached by the slow addition of the substrates to the catalyst solution.\(^12\) Organozinc or organotitanium reagents, in contrast, do not react with allylic halides in the absence of copper salts.

Note that the reaction of $8.4$ with organozinc or Grignard reagents in the presence of a catalytic amount of a Ni-complex afforded only the $S_N2'$ product.\(^8\) This reaction is called the cross-coupling of allyl electrophiles and is a subject not discussed in this thesis.\(^13\)

### 8.3 Enantioselective copper catalyzed allylic alkylation

In this chapter a review about the enantioselective copper catalyzed allylic alkylation is given that appeared during the course of our studies. Furthermore a catalytic cycle is proposed based on some preliminary studies.

Asymmetric $S_N2'$-substitutions of allylic substrates with a chiral leaving group have only been reported for stoichiometric organocuprates.\(^14\) Investigations into catalytic asymmetric allylic alkylation started in 1995 in a collaboration between Van Koten and Bäckvall.\(^15\) The reaction of an allylic acetate and a Grignard reagent in the presence of a chiral copper catalyst afforded only the $S_N2'$ product with an enantiomeric excess of 42\% (Scheme 8.3).
The allylic alkylation

\[ \text{allylic alkylation} \]

\[ \text{ether, } 0^\circ \text{C} \]

\[ \text{n-BuMgI 15 mol\%} \]

\[ \text{8.10} \]

\[ \text{Cu} \]

\[ \text{8.10} \]

\[ \text{trimer} \]

\[ \text{8.8} \]

\[ \text{(100\%) 42\%ee} \]

\[ \text{8.9} \]

\[ \text{(0\%)} \]

Scheme 8.3 The first copper catalyzed enantioselective allylic alkylation with Grignard reagents.

The reaction was carried out with 8.7 and butyl magnesium iodide in the presence of a chiral arenethiolatocopper (I) complex 8.10. This complex was also successfully used in the copper catalyzed 1,4-addition of Grignard reagents (section 2.2). In ether at 0°C the regioselective formation of 8.8 was observed with an ee of 42%, when both n-BuMgI and substrate 8.7 were added separately over 2 h to the catalyst solution (Scheme 8.3). A more detailed investigation with different arenethiolatocopper (I) complexes variations, substrates, Grignard reagents and copper salts was subsequently carried out later without significant improvements.

In 1999, a new asymmetric allylic alkylation was reported by Knochel using allylic chlorides and dialkylzinc reagents in the presence of a novel copper/ferrocenyl amine catalyst (Scheme 8.4).

\[ \text{RC l THF, } -90^\circ \text{C, 18h} \]

\[ \text{10 mol\%} \]

\[ \text{8.16} \]

\[ \text{1 mol\% CuBr*Me2S} \]

\[ \text{Zn} \]

\[ \text{THF, } -90^\circ \text{C, 18h} \]

\[ \text{72\%} \]

\[ \text{8.12} \]

\[ \text{(97\%)} \]

\[ \text{87\%ee} \]

\[ \text{8.14} \]

\[ \text{(3\%)} \]

\[ \text{8.13} \]

\[ \text{(98\%)} \]

\[ \text{76\%ee} \]

\[ \text{8.15} \]

\[ \text{(2\%)} \]

Scheme 8.4 Enantioselective allylic alkylation with diorganozinc reagents.

The reaction of cinnamyl chloride 8.4 and dineopentylzinc in the presence of 1 mol\% CuBr*Me2S and 10 mol\% 8.16 afforded the alkylation products 8.12/8.14 in a ratio of 97:3 and the major product 8.12 was obtained in 87% ee. In the same reaction with substrate 8.11 a ratio of 98:2 for 8.13/8.15 could be achieved with an ee of 76% for 8.13. The reaction is very sensitive to variations in the reaction temperatures. When the reaction was performed at −20°C 8.12 with 50% ee was obtained whereas at room temperature only 25% ee was found. A reason for the use of 10 equivalents of ligand with respect to the copper salt was not reported. A further improvement of ligand 8.16 (3,5-di-tert-butylphenyl instead of 2-
naphthyl) and the simultaneous addition of diorganozinc and allylic chloride over 3 h could increase the ee up to 96% for 8.12. Furthermore, it was observed that the use of sterically demanding diorganozinc compounds was important for obtaining good asymmetric induction. Using diethylzinc in the same reaction 44% ee was found for the corresponding Sn2 product.

Inspired by the ferrocenyl amine ligand reported by Knochel, a new ferrocenyl ligand was introduced by Bäckvall in 2001. In addition, new reaction conditions were introduced including toluene as solvent and a reaction temperature of 25°C. Furthermore a substoichiometric amount of ligand (35 mol%) was necessary to afford the corresponding alkylation products in good yields and with moderate enantiomeric excesses.

The reaction of substrate 8.7 and n-BuMgI in the presence of 35 mol% ligand 8.18 and 10 mol% CuI afforded 8.8/8.9 in a ratio of 98:2 and the major product 8.8 with 64% ee (Scheme 8.5). Using 8.17 in this reaction a ratio of 95:5 for 8.5/8.6 was achieved and an ee of 38% was determined for the main product 8.5. In all cases the Grignard reagent was added slowly to a solution of catalyst and allylic acetate. The ligand 8.18 is stable under argon but suffers from oxidation to the disulfide in the presence of minor amounts of oxygen.

Recently Alexakis reported an enantioselective copper catalyzed allylic alkylation using cinnamyl chloride and Grignard reagents in the presence of copper/phosphite complex achieving enantioselectivities up to 73%.20

The reaction of substrate 8.11 and EtMgBr in the presence of 1 mol% ligand 8.23 and 1 mol% CuCN afforded 8.19/8.21 in a ratio of 94:6 and the major product 8.19 with 73% ee (Scheme 8.6).
The reaction of 8.11 and ethyl magnesium bromide in the presence of 1 mol% 8.23 and 1 mol% CuCN in CH₂Cl₂ at –78°C afforded the corresponding alkylation products 8.19/8.21 in a ratio of 94:6 with an ee of 73% for the major product 8.19 (Scheme 8.6). In the case of cinnamyl chloride 8.4 exactly the same selectivities were obtained for 8.20. The Grignard reagent was added slowly over 40 min to the reaction mixture thereby increasing the enantioselectivity from 63% to 73% but lowering the ratio between 8.20/8.22 from 100:0 to 94:6. Furthermore, different Grignard reagents were screened. For n-BuMgBr an ee of 52% was found for the corresponding SN2’ product, whereas only 21% ee could be achieved using an aryl Grignard reagent.

Hoveyda has reported the use of modular pyridinyl peptide ligands in the enantioselective copper catalyzed allylic alkylation.21 The reaction of allylic phosphates with diethylzinc in the presence of a CuCN/pyridinyl catalysts gave good enantioselectivities and excellent SN2'/SN2 ratios (Scheme 8.7).

The reaction of 8.24 and diethylzinc in the presence of 10 mol% CuCN and 10 mol% 8.27 afforded almost exclusively SN2’-product 8.20 with 66% ee. However, the use of substituted aryl allylic phosphates gave ee’s of up to 87% (in the case of o-NO₂Ph). The introduction of substituted allylic phosphates like 8.25 as substrate for this reaction gave the corresponding product 8.26 in a highly regioselective manner with an ee of 78%. Also in this case substrates with aryl substituents resulted in higher enantioselectivities of up to 90% (for p-TsOPh). The value of this reaction was illustrated in the asymmetric synthesis of (R)-sporochnol (Scheme 8.8).
The reaction of 8.29 and an unsaturated zinc reagent\textsuperscript{22} in the presence of a CuCN/8.27 catalyst afforded the corresponding tosyl-protected compound 8.30, which was converted in the presence of base to 8.30 in 82% yield over two steps and with an enantiomeric excess of 82% (Scheme 8.8).

### 8.4 Mechanism of the copper catalyzed allylic alkylation

Very early proposals exist concerning the catalytic cycle for the copper (I) catalyzed allylic alkylation. One of the first was published by Goering.\textsuperscript{5b} The cuprate species A at the top of the catalytic cycle is generated as shown in Scheme 8.9. The main features of this scheme are the same as those proposed earlier for stoichiometric alkylation with alkylcuprates.\textsuperscript{23} Olefin-cuprate \( \pi \) complexation to give B is followed by oxidative addition with complete allylic rearrangement leads to the \( \sigma \)-allyl copper (III) complex C.\textsuperscript{24} The overall regiochemistry of the allylic alkylation is determined by the relative rates at which C undergoes reductive elimination (\( k_\text{re} \)) (regiospecific \( \gamma \)-coupling) to give G and isomerization (\( k_i \)) to the \( \pi \)-allyl complex D (which results in loss of regiochemistry). When \( Z = \text{CN} \), reductive elimination results in formation of stable CuCN together with \( \gamma \)-product G. When the \( k_\text{re}/k_i \) ratio for C is large regiospecific \( \gamma \)-coupling is observed. If \( Z = \text{R'} \) (alkyl) reductive elimination gives relatively unstable R''-Cu together with product. In this case allylic rearrangement of C by the \( \sigma\rightarrow\pi \) mechanism becomes important and loss of regiospecificity is observed. This mechanism was confirmed by Bäckvall.\textsuperscript{5,12}
Studies on substituent effects in the competitive cuprate reaction suggested that the rate-determining step might involve a two-electron transfer from copper to the allylic substrate.\textsuperscript{25} Furthermore, scant information is available for the transition state. The stereoselectivity of the $S_{\text{N}2}'$ reaction of $\delta$-substituted allylic halides suggests that the transition state for the delivery of an R group from copper reagent ($R_2\text{Cu}^-$) has a four-centered character (Scheme 8.10, M). This conjecture was supported by theoretical comparison of the transition state geometries of olefin carbolithiation and acetylene carbocupration.\textsuperscript{26}

Scheme 8.9 Catalytic cycle proposed by Goering.\textsuperscript{5b}

Scheme 8.10 Suggested four-centered transition state of the allylic alkylation (cuprates).
8.5 New proposed mechanism for the enantioselective copper catalyzed allylic alkylation of dialkylzincs to cinnamyl bromide.

For the enantioselective copper catalyzed allylic alkylation of dialkylzinc reagents to cinnamyl bromide the following mechanism is proposed (Scheme 8.11, see also chapter 9).

The copper complex is formed \textit{in situ} by mixing a copper salt and a chiral ligand. The addition of dialkylzinc and allylic substrate affords \( \pi \)-complex I, already proposed in Scheme 8.9. The next step is the oxidative addition with complete allylic rearrangement which leads to the \textit{chiral} \( \sigma \)-allyl-copper(III)complex J. This step is still analogous to that proposed in Scheme 8.9. This copper(III)complex J is in fast equilibrium with the copper complexes K and L. Copper complex K is \textit{achiral} whereas L is chiral. At this point it is the relationship between the reaction rates \( k_1 \), \( k_2 \) and \( k_3 \) which determine the regio and enantioselectivity of this reaction. If \( k_3 \) is larger than \( k_1 \) and \( k_2 \) then it is the \( S_N2' \) product which is formed in excess and the \( S_N2' \) product is the minor one. On the other hand if \( k_1 \) and \( k_2 > k_3 \) than the \( S_N2' \) product is the major product. In this case the enantioselectivity is
determined by the relationship between $k_1$ and $k_2$. Both chiral copper complexes $L$ and $J$ are in equilibrium perhaps with the participation of a $\pi$-allyl complex. If $k_1$ is larger than $k_2$ than the (S)-$\text{SN}_2'$ product is formed in excess. If $k_2$ is larger than $k_1$ it is the (R)-$\text{SN}_2'$ which is formed in excess. Experimental data (see, section 9.4.9) support this mechanism (Scheme 8.12).

The reactions with diethylzinc and allylic bromides 8.26 and racemic 8.27 afforded the same product 8.28 as major product with a ratio of $\text{SN}_2'$- and $\text{SN}_2$-products of 91:1 after full conversion. In both cases an enantiomeric excess of 82% could be measured for 8.28. The important difference of the allylic bromides is that 8.26 is achiral whereas 8.27 is chiral. If the oxidative addition with complete allylic rearrangement takes place with compound 8.27 then achiral copper complex $K$ is formed. To achieve the same results for substrate 8.26 there has to be an equilibrium between $K$ and $L$ or $J$. The equilibrium needs to be faster than the reaction rate $k_3$ because otherwise a different regioselectivity has to be expected in the allylic alkylation with 8.27. Therefore the alkyl transfer should be the rate-determining step. These experiments support the notion that $k_1$, $k_2$ and $k_3$ determine the regio- and enantioselectivity of the copper catalyzed allylic alkylation.

**8.6 Summary and concluding remarks**

The copper catalyzed allylic alkylation is a further example of a C-C bond formation reaction, which arose out of the additions of cuprates to activated double bonds (see 1,4-addition, chapter 2). Analogous to conjugate addition, an intensive investigation towards the catalytic allylic alkylation enabled the development of an asymmetric version. This development started in 1995 and since 1999 seven articles have been published with slightly different systems for the enantioselective copper catalyzed allylic alkylation.\(^{16,17,18,19,27,21}\)

High regioselectivities could be achieved with all catalytic systems and the enantioselectivities range between 40% and 90% for different substrates and organometallic reagents. A general system for different substrates has not been developed yet. The mechanism proposed for the copper catalyzed allylic alkylation in the 90s by Goering is still
in agreement with these new experimental data. Very little effort has been made so far to study the intermediates or the kinetics of this reaction. In section 8.5 a mechanistic proposal for the asymmetric copper catalyzed allylic alkylation is presented based on experiments which are presented in chapter 9. Unfortunately, no conclusive evidence for the postulated intermediates can be given at the presence.

The enantioselective copper catalyzed allylic alkylation is gaining more and more attention. In the future, it is excepted that ligands inducing higher regio- and enantioselectivities for a broad range of allylic substrates will be reported. A closer look at the mechanism (intermediates and kinetics) will hopefully follow.

8.7 References


The allylic alkylation


