CHEMICAL REVIEWS



Review

# Catalytic Asymmetric Conjugate Addition and Allylic Alkylation with Grignard Reagents

Syuzanna R. Harutyunyan, Tim den Hartog, Koen Geurts, Adriaan J. Minnaard, and Ben L. Feringa

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## 1. Introduction

Catalytic asymmetric C−C bond-forming reactions using organometallic reagents are among the most important of organic transformations.[1] Frequently, these transformations are key steps in the synthesis of complex biologically active molecules.[1] The conjugate addition (CA) and allylic alkylation (AA) with organometallic compounds are especially versatile in asymmetric C−C bond-forming reactions.[2] These transformations are complementary to the catalytic asymmetric allylic alkylation[3,4] and the Michael addition,[5] both based on soft carbon nucleophiles (Scheme 1A). For both CA and AA, the organic moiety of the organometallic reagent reacts with the $sp^2$ carbon of an electron-deficient substrate, converting it to an $sp^3$ carbon (Scheme 1B). In the case of CA, subsequent quenching of the enolate leads to the final product, whereas for the related AA an appropriate leaving group is expelled to form the chiral product. The organometallic compounds used most frequently for these transformations are organozinc, Grignard, organoaluminium, organolithium and cuprate reagents.[4,6–9]

Over the last three decades considerable effort has been directed toward the development of efficient catalytic systems for the asymmetric CA and AA reactions using organometallic reagents. Complexes derived from Cu salts and chiral ligands have provided the broadest scope in the catalyzed enantioselective CA and AA of organometallic reagents. Organozinc reagents have been the most successful of the organometallic reagents in this respect.[6] Major contributions and progress in the field of asymmetric CA and AA based on organozinc reagents have been summarized in several reviews.[7–9]

Organomagnesium compounds were among the first organometallic compounds to be applied to synthetic organic chemistry and the use of Grignard reagents in Cu-catalyzed CA was first reported in 1941 by Kharash and Tawney.[10] Achieving chemo-, regio- and stereocontrol in both asymmetric conjugate addition (ACA) and asymmetric allylic alkylation (AAA), however, has proven to be challenging and has restricted the application of these transformations, in particular, to total synthesis. Typical selectivity issues pertain to 1,2- versus 1,4-addition (Scheme 2A) and $S_N2$- versus $S_N2'$-substitution (Scheme 2B).

The challenge faced in the development of stereoselective C−C bond-forming reactions is apparent when one considers that, despite three decades of intensive research in this area, only recently has efficient Cu-catalyzed enantioselective CA of Grignard reagents been achieved.[11] The earlier discovery of the highly enantioselective Cu-catalyzed CA of dialkylzinc reagents allowed for replacement of Grignard reagents in this asymmetric C−C bond-forming reaction.[6,8,9,12] Dialkylzinc reagents offer distinct advantages over Grignard reagents in their low reactivity in noncatalyzed reactions and their high tolerance to functional groups both on the substrate and on the organozinc reagent itself.[6,12] Nevertheless, there are several advantages to the use of common mono-alkylMg halide reagents, most importantly their widespread availability and the ability to transfer all of the alkyl groups of the organometallic compound. The synthetic potential of these asymmetric transformations has driven intensive research in this area, and over the past few years major breakthroughs have been realized in the enantioselective CA and AA of Grignard reagents.[11,13]

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Tim den Hartog was born in 1982, and he studied at the University of Amsterdam, The Netherlands, to obtain his degree in Organic Chemistry in 2005. He is currently performing his graduate studies in the Feringa Group at the University of Groningen in the field of asymmetric catalysis. His research focuses primarily on asymmetric conjugate addition.

Koen Geurts was born in 1975, and he studied at the University of Groningen, The Netherlands, and obtained his degree in Organic Chemistry in 2002. He is currently finishing his graduate studies in the Feringa Group at the University of Groningen in the field of asymmetric catalysis. His thesis focuses primarily on asymmetric allylic alkylation. He has recently accepted a position as a chemical development engineer within SABIC Europe.

Adriaan J. Minnaard received his Ph.D. degree from Wageningen Agricultural University, The Netherlands, in 1997 with Prof. Dr. Ae. de Groot and Dr. J. B. P. A. Wijnberg. He has been a scientist at DSM-Research in Geleen, The Netherlands, from 1997 to 1999. Subsequently, he joined the University of Groningen in 1999 as an Assistant Professor in the department of Prof. Ben L. Feringa. In 2005, he was appointed Associate Professor, and in 2006, he was a guest researcher in the group of Prof. H. Waldmann at the Max Planck Institute for Molecular Physiology in Dortmund, Germany. Currently, he is leading the department of Bio-Organic Chemistry. His work focuses on asymmetric catalysis and natural product synthesis.

It is perhaps appropriate, then, to begin with a brief update of developments in the Cu-mediated ACA and AAA reactions based on chiral auxiliaries and chiral substrates. There are several reasons for this. First of all, the majority of the successful approaches have focused on the use of chiral auxiliaries and chiral substrates, and the insight provided through these transformations has laid the foundation for the Cu-catalyzed ACA and AAA of Grignard reagents. Second, the outcome of the CA or AA of Grignard reagents is often highly sensitive to every parameter in the reaction protocol (i.e., stoichiometry, solvent, counterion and various reaction conditions, including the use of chiral or achiral additives and Lewis acids); therefore, key insight into the control of these parameters has been provided through studies of the CA and AA of Grignard reagents promoted by addition of stoichiometric amounts of copper salts. Third, the ECA and EAA are frequently employed in the construction of multiple stereogenic centers making it highly sensitive to the (chiral) nature of the substrate. Furthermore, the nature of the electron-withdrawing group present in the substrate (ketone, ester, amide, etc.) has a profound influence on the chemo-, regio- and stereoselectivity of the CA and AA. Finally, the studies on diastereoselective CA and AA provided important information as to potential approaches for tuning the stereochemical outcome of the 1,4-addition or the $S_N2'$-substitution using a catalyst as the exclusive source of chirality.

This review will focus on asymmetric CA and AA reactions employing Grignard reagents. Several comprehensive reviews[2,9] covering early approaches are available, and hence this review will consider progress in the diastereoselective CA of Grignard reagents from 1992 to the present. Special attention will be given to acyclic substrates. A comprehensive review on catalyzed enantioselective CA (covering 1,4- and 1,6-additions) reported since 1988 will follow. In addition, a discussion of mechanistic aspects of Cu-promoted CA will be given. Furthermore, advances in the field of diastereoselective and enantioselective AA using

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Grignard reagents since 1995 will be reviewed. Finally, the practicality of these new asymmetric transformations will be illustrated with examples of application in complex molecule synthesis using Grignard reagents in catalytic enantioselective CA or AA reactions.

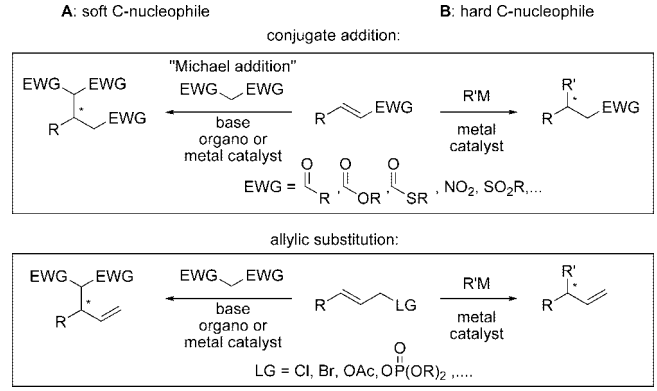
## 2. Asymmetric Conjugate Addition (ACA) with Grignard Reagents[14]

Asymmetric conjugate addition has received a tremendous level of attention over the past three decades. A comprehensive review on the use of organolithium and Grignard reagents using stoichiometric chiral ligands or employing chiral auxiliaries, reagents and/or substrates was published in 1992 by Rossiter and Swingle.[9] Despite the extensive application of ACA reactions in synthesis one drawback of these approaches is the use of stoichiometric amounts of chiral auxiliaries.

Enantioselective, and in particular catalyzed asymmetric, 1,4-addition of organometallic reagents presented a major challenge primarily for two reasons. First, although appreciable enantiomeric excess (ee) could be obtained with a wide variety of chiral catalysts, the stereocontrol reached remained too low to see general application in synthetic chemistry. Second, the catalyzed enantioselective reaction must compete with the noncatalyzed addition of the highly reactive organomagnesium or organolithium reagents to either a carbonyl group (i.e., 1,2-addition, Scheme 2A) or to a conjugated alkene, providing a racemic 1,4-addition product.

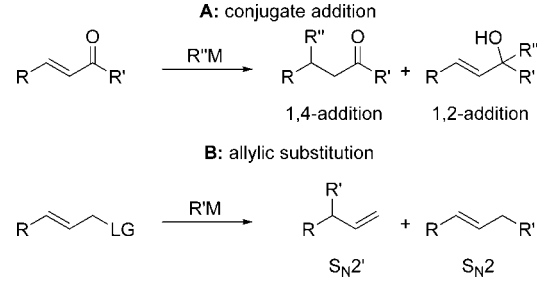
In the following section recent advances in diastereoselective conjugate addition (DCA) are discussed, followed by a review of developments in the emerging field of enantioselective conjugate addition (ECA) reactions, i.e. addition of organometallic reagents catalyzed by chiral Cu-complexes.

**Scheme 1. Allylic Substitution and Conjugate Addition of Carbon Nucleophiles[a]**




[a] EWG: electron-withdrawing group; LG: leaving group; M: metal.

**Scheme 2. Typical Competing Reactions for ACA (A) and AAA (B)**




### 2.1. Diastereoselective Conjugate Additions (DCA)

As its name suggests, DCA reactions intend to yield a single diastereoisomer of the product and can be effected through one of two approaches. The first approach uses a chiral auxiliary to favor addition to one of the diastereotopic $\pi$-faces of the substrate (section 2.1.1). The second approach is to embed the stereochemical information in the substrate to direct addition toward formation of a single diastereoisomer (section 2.1.2).

As discussed in depth by Rossiter and Swingle,[9] methods employing chiral auxiliaries have been available for over two decades, and hence one of the most important challenges to meet in the field of CA is the development of a catalytic asymmetric version of the DCA (i.e., ECA). Nevertheless, a considerable number of new synthetic methods for the DCA reaction have been reported recently, and several important insights have been made into the parameters governing stereocontrol in the conjugate addition reaction with challenging acyclic substrates that are especially relevant to the study of the catalyzed ACA of Grignard reagents.

#### 2.1.1. DCA Employing Chiral Auxiliaries

Chiral auxiliaries are ideally simple to attach and remove, recoverable and applicable to a wide range of substrates.[15]

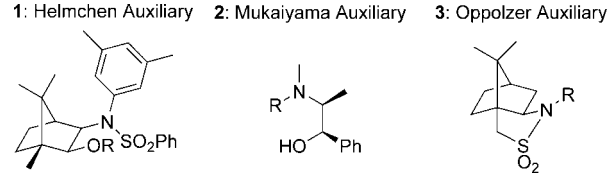



**Figure 1.** Chiral auxiliaries used for DCA. R = substrate.

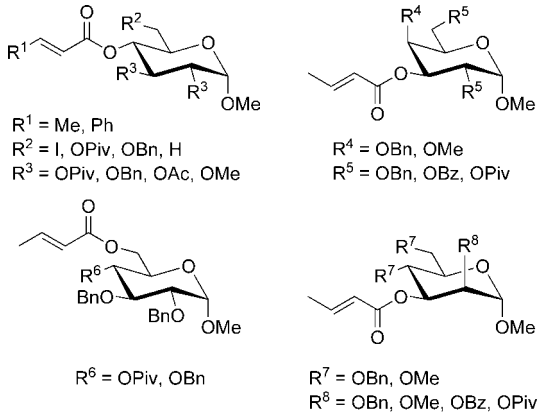



**Figure 2.** Chiral sugar derived auxiliary−substrate combinations.

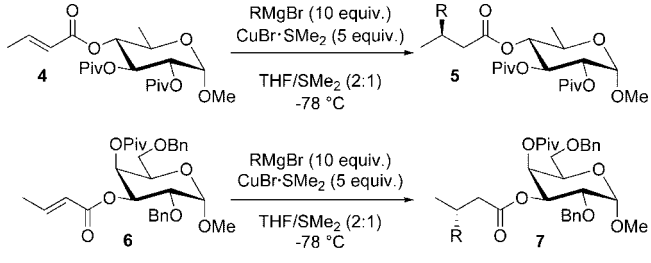
Esters and amides have been the functionalities of choice for attachment of chiral auxiliaries in DCA.[9] The camphor-based ester **1**,[16] ephedrine-derived amide **2**[17] and camphor-derived enoyl sultam **3**[18] meet many of these requirements (Figure 1).

Auxiliary **1**, developed by Helmchen and Wegner,[16] allows for addition of a wide variety of cuprates derived from Grignard or lithium reagents (alkyl, vinyl and phenyl) to linear alkyl α,β-unsaturated esters in high yield (70−99%) and diastereoselectivity (96−99%). However, CA reactions to cinnamyl substrates using this auxiliary have not been reported to date.

In general Cu is not necessary to control the reactivity of Grignard and lithium reagents toward the formation of the 1,4-regioisomer in the DCA to α,β-unsaturated amides. Mukaiyama and Iwasawa[17] have developed the ephedrine-derived auxiliary **2** toward the DCA of alkyl and aromatic Grignard reagents to linear alkyl and aromatic α,β-unsaturated amides in moderate yield (40−60% after the deprotection step) but with high diastereoselectivity (79−99%). The Oppolzer sultam **3**[18] has led, in some cases, to addition products with lower diastereoselectivity. The advantage of using this auxiliary is the ability to conveniently isolate the diastereomerically pure products by recrystallization. Furthermore, the yield of diastereomerically pure product is enhanced (50−70% after deprotection) compared to the yields obtained using the ephedrine-derived auxiliary.

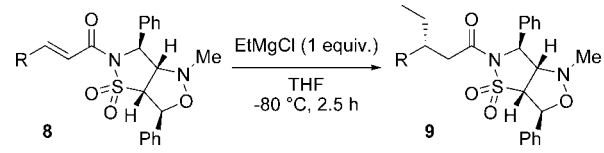
Several new methods[19] for the DCA of Grignard reagents to chiral auxiliary-based α,β-unsaturated esters have been developed in recent years, with the majority being based on chiral sugars.[19a–d] The use of sugar-based auxiliaries was examined by Tadano and co-workers.[19c,d] It was concluded, based on a systematic investigation of multiple protection patterns (Figure 2), that crotonic esters **4** and **6** (Scheme 3)

**Scheme 3. DCA to α,β-Unsaturated Esters Using Chiral Sugar-Derived Auxiliaries**



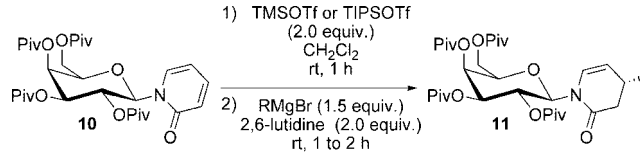

R= Et, *i*-Pr, vinyl; yield: 80-95%; de: 92-96%

**Scheme 4. DCA to α,β-Unsaturated Amides Using Chiral Bicyclic Sultam Auxiliaries**



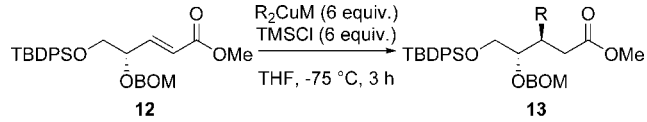

R = Me; yield: 95%; de: 98%
R = Ph; yield: 82%; de: 96%
Oppolzer Auxiliary **3**; yield: 80%; de: 89%

**Scheme 5. DCA to an Unsaturated Piperidone Using a Chiral Sugar Auxiliary**




R = Et, *n*-Pr, *i*-Pr, *n*-Bu, *n*-decyl, *c*-hexyl, Ph, homoallyl; yield: 54-88%; de: >98%
R = *t*-Bu, Bn; yield: 22-34%; de: >98%

**Scheme 6. DCA to Chiral γ-Alkoxy-α,β-unsaturated Ester 12**



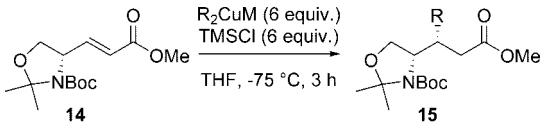

$R_2CuM$: $Me_2CuLi$, $Et_2CuMgBr$, *n*-$Bu_2CuLi$, vinyl$_2$CuMgBr, allyl$_2$CuLi;
yield: 60-93%; de: 78%-96%

provide the best results in terms of both yield and diastereoselectivity due to the distinct steric properties of the substituents at the 2- and 6-positions of the sugar moiety. With these auxiliaries, addition products were obtained with excellent yields (80−95%) and diastereoselectivity (92−96%). Furthermore, it was apparent that $R_2CuMgBr$ was a more effective reagent than $RCu\cdot BF_3$ or $R_2CuLi$ for this transformation. These results demonstrate the sensitivity of the CA reaction to small changes in the reagents employed and the chiral nature of the substrate. The effectiveness of these auxiliaries is comparable to that of the camphor-based ester auxiliary developed by Helmchen et al.[16]

Overall, efforts toward the development of the DCA of Grignard reagents to α,β-unsaturated amides have focused on the use of oxazolidinone[20] and sultam[21] auxiliaries. Although other auxiliaries[22] have been reported also, a major improvement in terms of diastereoselectivity over that obtained with the ephedrine-derived auxiliary developed by Mukaiyama and co-workers[17] or the sultam auxiliary introduced by Oppolzer and co-workers[18] has not been achieved to date. Building on the work of Oppolzer and co-workers,[18] Chiacchio and co-workers[21a] have reported a series of bicyclic sultams which provided the addition products **9** with increased diastereoselectivity (Scheme 4) and allowed for deprotection of the sultam group in higher yield (∼85% vs 56%).

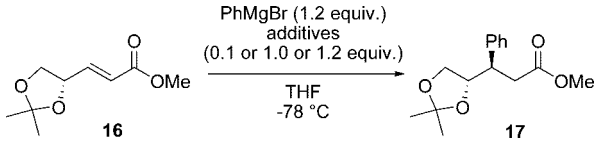
Kunz and co-workers[23] investigated the DCA of a variety of Grignard reagents on TIPS triflate activated unsaturated piperidones **10** attached to a chiral sugar auxiliary in the preparation of 4-substituted piperidines. This strategy afforded excellent diastereoselectivity (>98%, Scheme 5). Replacement of Grignard reagents with nonbulky Gilman cuprates afforded comparable results. However, 4-piperidones gave addition products with low diastereoselectivity. This observation again illustrates the sensitivity of the CA reaction to changes in the structure of the substrate.

**Scheme 7. DCA to Chiral γ-Amido-α,β-unsaturated Ester 14**



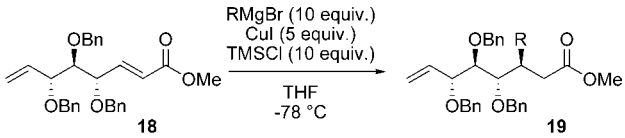

$R_2CuM$: $Me_2CuLi$, $Et_2CuMgBr$, $n$-$Bu_2CuLi$, $vinyl_2CuMgBr$, $allyl_2CuLi$, $Ph_2CuMgBr$; yield: 70-97%; de: 78%-96%

**Scheme 8. DCA of PhMgBr to Chiral γ-Alkoxy-α,β-unsaturated Ester 16**



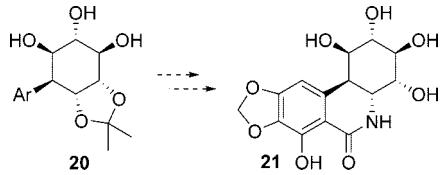

$CuBr{\cdot}SMe_2$, $SMe_2$, TMSCl; yield: 100%; de: 72%
CuCN, TMSCl; yield: 80%; de: 78%
$CuBr{\cdot}SMe_2$, LiBr, TMSCl; yield: 70%; de: 92%

**Scheme 9. DCA to Chiral γ-Alkoxy-α,β-unsaturated Ester 18**




R: Ph, $p$-$MeOC_6H_4$, $(OCH_2O)C_6H_3$, $m$-$MeO(OCH_2O)C_6H_2$; yield: 95-97%; de: >99%

**Scheme 10. Intermediate for the Synthesis of Pancratistatins**



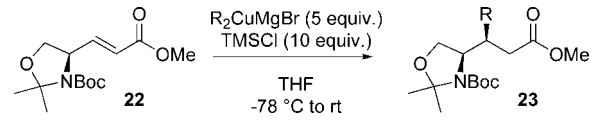

### 2.1.2. DCA to Chiral Substrates

High levels of diastereoselectivity can be achieved in the copper-mediated CA to chiral substrates, especially chiral cyclic enones, using organometallic reagents.[24] In recent years, a considerable number of chiral substrates[19e,25] have been tested for their ability to impart stereocontrol to the CA reaction. One of the most significant advances consists of the DCA of Grignard reagents to chiral acyclic γ-alkoxy- and γ-amino-α,β-unsaturated esters and ketones and the successful addition of aryl Grignard reagents. The products obtained through these Cu-catalyzed DCA reactions are key components in the stereoselective synthesis of acyclic building blocks containing multiple stereogenic centers.[26]

Hanessian and co-workers have reported the DCA of several organometallic reagents to α,β-unsaturated esters bearing a stereogenic center at the γ-position and have prepared polypropionate motifs through the DCA of Mg and Li cuprates to γ-alkoxy-α,β-unsaturated esters.[25e] Anti addition products were obtained with excellent diastereoselectivity (up to >96%, Scheme 6). The DCA of a range of Mg and Li organocuprates to protected γ-amino-α,β-unsaturated esters allows access to important amino alcohol motifs, and for this class of substrate the syn addition products were obtained with high de (up to >96%, Scheme 7).[25f]

Building on the work of Hanessian and co-workers, Han and Hruby identified suitable conditions for highly stereoselective DCA of PhMgBr to γ-alkoxy-α,β-unsaturated esters (de up to 92%, Scheme 8).[25j] Interestingly addition of LiBr to the reaction mixture led to an increase in diastereoselectivity (entry 3, 92%), which was proposed to be due to chelation of the $Li^+$ ion by the carbonyl and the γ-alkoxy groups and hence inhibition of syn addition.

**Scheme 11. DCA to Chiral γ-Amino-α,β-unsaturated Ester 22**

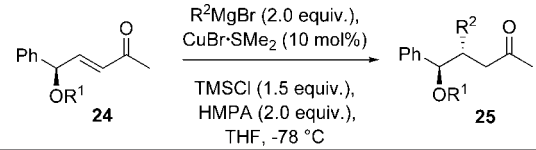



R: Ph, $p$-$MeOC_6H_4$, $p$-$FC_6H_4$, $p$-$ClC_6H_4$, $mp$-$(MeO)_2C_6H_3$, $(OCH_2O)C_6H_3$, $m$-$MeO(OCH_2O)C_6H_2$; yield: 70-95%; de: >90%

Kornienko et al. have examined the DCA of Grignard reagents to a series of chiral γ-substituted α,β-unsaturated esters. Excellent diastereoselectivity was achieved in the addition of substituted phenyl Grignard reagents to γ-alkoxy substrate **18** (Scheme 9).[25m] The addition products could be converted to **20**, an intermediate in the synthesis of pancratistatins (**21**, Scheme 10).[25n] Similarly addition of substituted aryl Grignard reagents to protected γ-amino-α,β-unsaturated esters **22** yielded the syn addition products **23** with excellent yields and diastereoselectivity (Scheme 11).[25p]

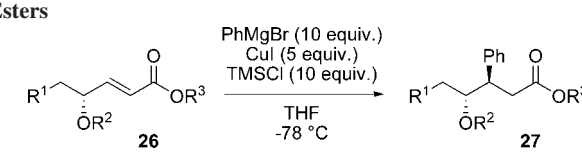
The study by Raczko[25g] of the DCA to sterically demanding and to chelating γ-alkoxy-substituted linear α,β-unsaturated ketones provides some insight into the factors governing the stereochemical outcome of the CA to γ-substituted-*E*-α,β-unsaturated ketones and esters. It is apparent that chelating alkoxy moieties were essential in inducing anti stereoselectivity. With the chelating BOM-protective group, in place of the sterically demanding TBDPS-protective group, the anti addition products were obtained with high diastereoselectivity (Table 1).

**Table 1. DCA to Chiral γ-Alkoxy Acyclic Ketones**




| entry | $R^1$ | $R^2$ | yield (%) | de (%) |
|---|---|---|---|---|
| 1 | TBDPS | Me | 85 | 24 |
| 2 | TBDPS | Ph | 86 | 20 |
| 3 | TBDPS | vinyl | 86 | 58 |
| 4 | BOM | Me | 92 | 86 |
| 5 | BOM | Ph | 84 | 88 |
| 6 | BOM | vinyl | 90 | 92 |

**Table 2. DCA to Chiral γ-Alkoxy-substituted α,β-Unsaturated Esters**




| entry | $R^1$ | $R^2$ | $R^3$ | yield (%) | de (%) |
|---|---|---|---|---|---|
| 1 | H | Bn | Me | 89 | 68 |
| 2 | OBn | Bn | Me | 94 | 87 |
| 3 | OTBDPS | Bn | Me | 88 | >96 |
| 4 | OTBDPS | MOM | Et | 80 | >96 |
| 5[a] | OTBDPS | Bn | Me | 87 | 23 |
| 6[a] | OBn | Bn | Me | 72 | 47 |
| 7[a] | H | Bn | Me | 65 | 55 |

[a] Addition to *Z*-α,β-unsaturated ester.

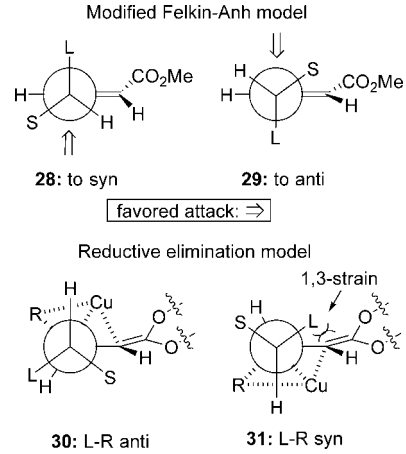



**Figure 3.** Modified Felkin-Anh model and new reductive elimination model for the DCA reaction. S: small group, L: large group.

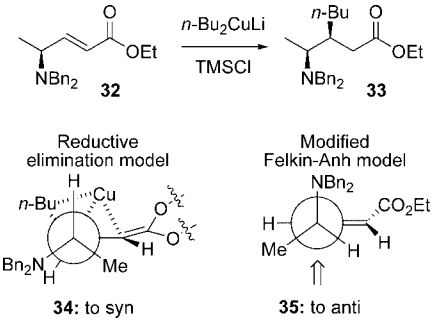



**Figure 4.** Reductive elimination model for the DCA reaction to $\gamma$-amino-$\alpha,\beta$-unsaturated esters.

Following a similar approach, Kornienko and co-workers investigated DCA to $\gamma,\delta$-*bis*-alkoxy substituted acyclic $\alpha,\beta$-unsaturated esters (Table 2).[25o] These studies demonstrated the necessity for sterically demanding substituents at the $\delta$-position in achieving high stereoselectivity (compare entries 1, 2 and 3). Interestingly, protection of the $\gamma$-alkoxy group by either a MOM (entry 4) or Bn group (entry 3) provided similar results. This observation led to the conclusion that coordination to the methoxy moiety of the MOM protecting group has little influence on the diastereoselectivity of the reaction. It should be noted that the use of *Z*-$\alpha,\beta$-unsaturated esters led to addition products with low diastereoselectivity (entries 5−7).

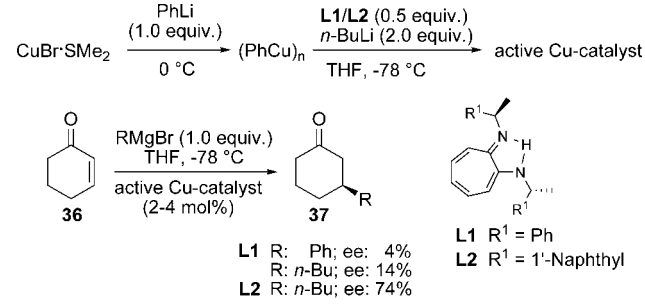
The modified Felkin-Anh model[27] (Figure 3) used previously in predicting the stereochemical outcome of DCA reactions proved to be of limited use, primarily in its ability to predict the stereochemical outcome for the $\gamma$-amino-$\alpha,\beta$-unsaturated esters (Figure 4). This lack of accuracy prompted Kornienko and co-workers[25o] to propose a reductive elimination model to account for the results obtained with $\gamma$-substituted $\alpha,\beta$-unsaturated esters and ketones.

### 2.1.3. Conclusions and Perspective

With the toolbox of chiral auxiliaries developed to date, most of the more frequently encountered multifunctional building blocks can be accessed with high levels of diastereocontrol. Future advances in this area are thus expected to be directed toward the identification of less expensive alternatives to the auxiliaries available at present.[28]

The development of methods for DCA that take advantage of the stereochemical features of the substrates is of particular interest. The methods, introduced recently, to access polypropionate and amino alcohol motifs are of considerable utility in organic synthesis. Thus, further insight provided by the data available on the DCA to chiral substrates will prove invaluable in the development of catalytic methods to access each individual diastereoisomer of important acyclic structural motifs. Balancing the level of substrate and catalyst control in stereoselective addition reactions to provide products with multiple stereocenters (match−mismatch effects) continues to be an important challenge in the field of stereoselective synthesis. This is especially true for the motifs containing multiple stereogenic centers that are encountered frequently in biologically relevant compounds. Furthermore, the reductive elimination model proposed recently appears to allow for increased accuracy in the prediction of the stereochemical outcome of these DCA reactions.

**Scheme 12. First Examples of Asymmetric Induction in the Catalytic CA of Grignard Reagents**




## 2.2. Enantioselective Conjugate Addition (ECA)

The major part of this review is concerned with enantioselective conjugate addition reactions of Grignard reagents using catalytic amounts of chiral Cu-complexes.

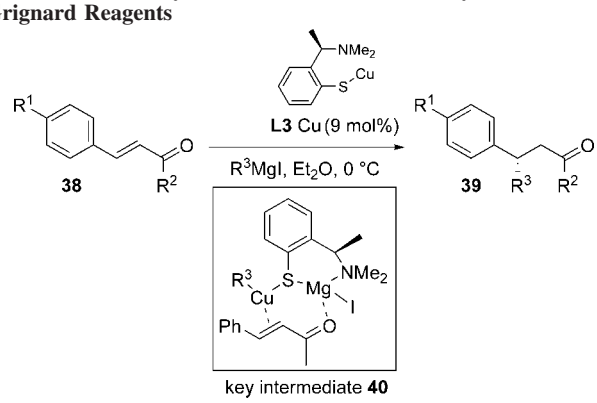
### 2.2.1. Cu-Catalyzed 1,4-ECA

**2.2.1.1. Early Studies on Catalyzed ECA.** The first example of a catalyzed ECA of Grignard reagents was reported by Lippard and co-workers in 1988.[29] In this seminal contribution the authors demonstrate the possibility of asymmetric induction in the CA of Grignard reagents using catalytic amounts of a chiral ligand. Improvements to the regio- (1,4- vs 1,2-addition) and enantioselectivity (up to 14%) were obtained for the CA of *n*-BuMgBr to cyclohexenone using 2 to 4 mol % of catalyst. The chiral catalyst was based on chiral bidentate *N*,*N*′-dialkyl-substituted aminotroponeimine ligands depicted in Scheme 12 (**L1** and **L2**) with CuBr·$SMe_2$ as the metal source and PhLi or *n*-BuLi to form the active complex.

Although the selectivity was low initially, additives were soon found by Lippard and co-workers,[29a] that allowed for a significant improvement in enantioselectivity. Most notably, HMPA and silyl reagents accelerated the CA of organocuprates and provided an improvement in enantioselectivity.[29b]

In 1991 van Koten and co-workers introduced the chiral bidentate aryl-thiolate-ligated Cu-complex (**L3** Cu) as a catalyst for the CA of Grignard reagents (Table 3).[30] It was shown that high regio- and modest enantioselectivity could be obtained in the CA of MeMgI to benzylidene acetone using 9 mol % of the arenethiolato Cu(I)-complex **L3** Cu (entries 1−3). However, the reaction proved to be sensitive to the reaction conditions[31] including changes in solvent and substrate. Furthermore, in order to achieve the highest level

**Table 3. Chiral Aryl-Thiolate Cu (L3 Cu)-Catalyzed ACA of Grignard Reagents**




| entry | $R^1$ | $R^2$ | $R^3$ | ee (%) |
|---|---|---|---|---|
| 1 | H | Me | Me | 76 |
| 2 | H | *i*-Pr | Me | 72 |
| 3 | Cl | Me | Me | 69 |
| 4 | CN | Me | Me | 13 |
| 5 | OMe | Me | Me | 56 |
| 6 | H | *t*-Bu | Me | 45 |
| 7 | H | Ph | Me | 0 |
| 8 | H | Me | *n*-Bu | 45 |
| 9 | H | Me | *i*-Pr | 10 |

of regio- and enantioselectivity both Grignard reagent and enone were added together in a continuous manner to the catalyst.

The use of THF rather than $Et_2O$ resulted in no enantioselectivity. Similarly, the use of Grignard reagents other than MeMgI or the use of other substrates resulted in lower enantioselectivity (entries 4−9). In contrast with the results obtained by Lippard and co-workers,[29b] the use of additives such as silyl compounds and HMPA resulted in a decrease in both regio- and enantioselectivity.

However, the enantioselectivity of the CA of MeMgI to benzylidene acetone was improved by using toluene as a solvent. In addition, the reaction proceeded with only 3 mol % of catalyst **L3** Cu.[30d] Model studies indicated that $[CuSAr(R)]_3$ reacts with $R^2MgX$ to form the aggregate $[CuR^2]_4[Mg(SAr(R))_2]_2$. It was proposed that from this aggregate intermediate **40** is formed through interaction with the substrate. The enone binds the dinuclear Cu−Mg arenethiolate unit with the olefinic bond coordinating to Cu and the carbonyl oxygen binding to Mg. From this complex the alkyl moiety of the Grignard reagent is transferred to the $\beta$-position of the enone.

Another chiral thiol-based catalyst was reported by Spescha and Rihs[32] in 1991 for the CA of RMgX (R = *n*-Bu, Ph) to several $\alpha,\beta$-unsaturated carbonyl compounds. This catalyst was prepared *in situ* from chiral thioglucofuranose **L4**, CuI·$SBu_2$ and *n*-BuLi (Scheme 13). The highest ee (60%) was obtained for the CA of *n*-BuMgBr to cyclohexenone using a 4 mol % catalyst loading in $Et_2O$ at −78 °C.

The reproducibility of the enantioselectivity in this ECA was improved by the presence of TEMPO, which is proposed

**Scheme 13. Cu-Catalyzed ACA of Grignard Reagents Using the Thioglucofuranose Ligand L4**

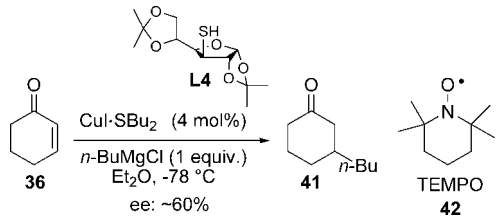
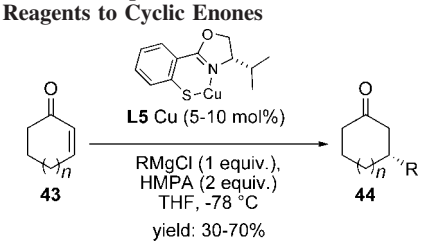
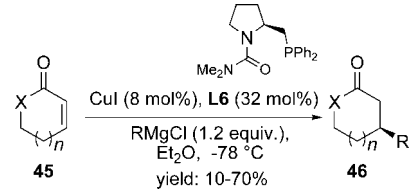



**Table 4. Thiolate-Complex (L5 Cu) Used in the ACA of Grignard Reagents to Cyclic Enones**




| entry | *n* | R | ee (%) |
|---|---|---|---|
| 1 | 1 | *n*-Bu | 60 |
| 2 | 1 | *i*-Pr | 72 |
| 3 | 0 | *n*-Bu | 16 |
| 4 | 0 | *i*-Pr | 37 |
| 5 | 2 | *n*-Bu | 83 |
| 6 | 2 | *i*-Pr | 87 |

**Table 5. Cu-Catalyzed ACA of Grignard Reagents Using an Aminophosphine-Based Catalyst (L6)**



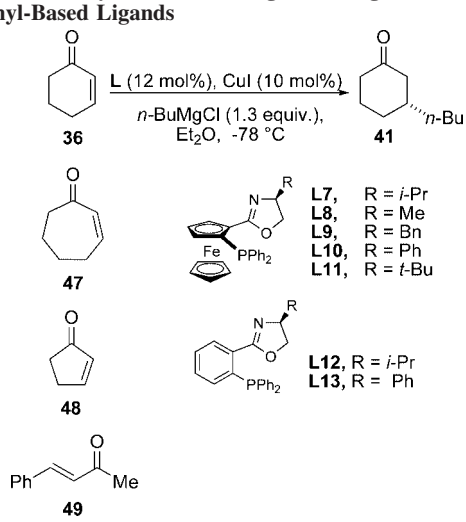

| entry | *n* | X | R | ee (%) |
|---|---|---|---|---|
| 1 | 1 | $CH_2$ | Et | 73 |
| 2 | 1 | $CH_2$ | *n*-Pr | 72 |
| 3 | 1 | $CH_2$ | *n*-Bu | 90 |
| 4 | 1 | $CH_2$ | *n*-hexyl | 92 |
| 5 | 1 | $CH_2$ | $BnCH_2$ | 87 |
| 6 | 2 | $CH_2$ | *n*-Bu | 81 |
| 7 | 1 | O | *n*-Bu | 91 |
| 8 | 1 | O | *n*-hexyl | 90 |
| 9 | 0 | $CH_2$ | *n*-Bu | 42 |
| 10 | 1 | $CH_2$ | Me | 5 |
| 11 | 1 | $CH_2$ | Ph | 4 |
| 12 | 1 | $CH_2$ | Bn | 12 |
| 13 | 1 | $CH_2$ | *i*-Pr | 4 |

to react with excess *n*-BuLi that was used for preparation of the catalyst. *n*-BuLi can engage in the direct 1,4-CA to the substrate leading to a racemic product. A decrease in both the regio- and enantioselectivity was observed with replacement of *n*-BuMgCl by *n*-$Bu_2Mg$ and with THF as a solvent in place of $Et_2O$. These effects are most likely due to changes in the Schlenk equilibrium resulting in the formation of other aggregated species.

An important improvement in the CA of Grignard reagents was achieved by Zhou and Pfaltz[33] with the introduction of a structural analogue (i.e., **L5** Cu, Table 4) of the arenethiolate Cu(I)-complex developed by van Koten and co-workers.[30c] The primary change in the structure of the catalyst is the more rigid chiral moiety (oxazoline vs dimethylbenzylamine). Cu(I) thiolate-complex **L5** Cu proved to be the most efficient catalyst for cyclic enones with the best results observed in THF in the presence of 2 equiv of HMPA at low temperature. High regioselectivity and moderate enantioselectivity was obtained in the CA of *n*-Bu (entry 1) and *i*-Pr (entry 2) Grignard reagents. Omitting HMPA or using $Et_2O$ as solvent both resulted in a loss of enantioselectivity. Furthermore, addition of silyl derivatives did not affect the enantioselectivity.

This catalyst system allows for the ECA of *i*-PrMgCl and *n*-BuMgCl to several cyclic enone substrates (entries 3−6)

**Table 6. Cu-Catalyzed ECA of Grignard Reagents Using Ferrocenyl-Based Ligands**




| entry | substrate | L | yield (%) | regioselectivity (%)[a] | ee (%) |
|---|---|---|---|---|---|
| 1 | **36** | **L7** | 80 | 91 | 83 |
| 2 | **36** | **L8** | 68 | 83 | 81 |
| 3 | **36** | **L9** | 97 | >99 | 82 |
| 4 | **36** | **L10** | 97 | >99 | 83 |
| 5 | **36** | **L11** | 87 | 99 | 46 |
| 6[b] | **36** | **L12** | 77 | 98 | 26 |
| 7 | **36** | **L13** | 6 | 9 | 0 |
| 8 | **47** | **L10** | 82 | >99 | 92 |
| 9 | **48** | **L10** | 82 | >99 | 65 |
| 10 | **49** | **L10** | 61 | 99 | 81 |

[a] Regioselectivity: [1,4/(1,4 + 1,2)] × 100. [b] Enantiomer of catalyst used and enantiomer of product obtained.

with the highest enantioselectivity obtained for the CA of *i*-PrMgCl to 2-cycloheptenone (87%, entry 6). In several cases it was necessary to increase the catalyst loading to 10 mol % to improve yields. For acyclic enones, enantioselectivity below 20% was obtained using this system.

Tomioka and co-workers have obtained high enantioselectivity (up to 92%, Table 5) in the CA of organocuprates formed using *n*-BuMgCl in the presence of stoichiometric amounts of chiral aminophosphine **L6.**[34] In a subsequent detailed study they demonstrated that a catalyst loading of 32 mol % of chiral **L6** and 8 mol % Cu salt in $Et_2O$ provided optimal efficiency. With polar solvents (such as THF and DMS) considerably lower enantioselectivity was obtained. As mentioned before the counterion can have a major influence on the outcome of the Cu-catalyzed ECA of Grignard reagents. Iodide was identified as the most suitable counterion in the catalyzed reaction while for the stoichiometric reaction cyanide was the counterion of choice. The halide of the Grignard reagent is also critical. The highest efficiency in terms of yield, regio- and enantioselectivity was obtained using a chloride-based Grignard reagent. Notably, the use of *n*-$Bu_2Mg$ in place of *n*-BuMgCl still provided high enantioselectivity (92%), albeit with lower regioselectivity.

In addition to optimization of the reaction conditions, Tomioka and co-workers[34] studied the scope of their system with respect to Grignard reagent and enones. High enantioselectivity and moderate to good yields were obtained using linear Grignard reagents (Et, *n*-Pr, *n*-Bu, *n*-hexyl, $BnCH_2$, entries 1−5) for the CA to cycloheptenone (entry 6) and dihydropyranone (entries 7, 8). For CA to cyclopentenone moderate enantioselectivity was obtained (entry 9). Finally, MeMgCl, aryl, benzyl and branched (entries 10−13) Grignard reagents provided much lower enantio- and regioselectivity. The lower enantio- and regioselectivity was not due to decomposition of the catalyst as the chiral phosphine ligand could be recovered and reused without loss of enantioselectivity. The mechanism and the exact nature of the chiral catalyst involved remain to be elucidated for this system. Prior to 2003, the results obtained by Tomioka and co-workers[34] represented the state of the art with regard to enantioselectivity (92%). However, a major drawback of this system is the high catalyst loading required (32 mol %).

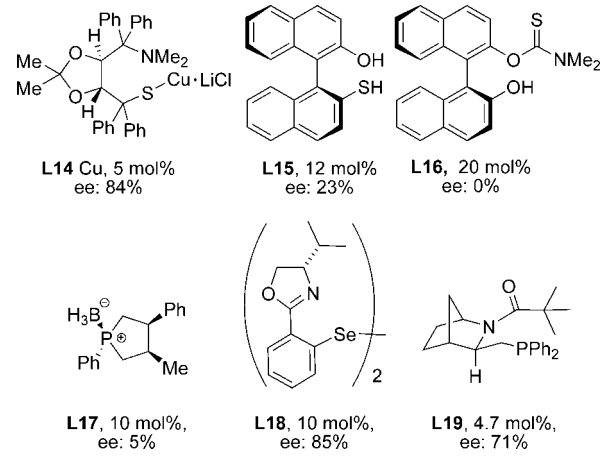



**Figure 5.** Ligands used in the Cu-catalyzed ECA of Grignard reagents depicted with highest ee value obtained. **L14**;[36a] **L15** and **L16**;[36b,c] **L17**;[36d] **L18**;[36e] **L19**.[36f]

Stangeland and Sammakia[35] achieved asymmetric induction in the Cu-catalyzed CA of Grignard reagents by combining planar chirality and a stereogenic center in the ligand structure (Table 6). With 12 mol % of the chiral ligand **L7** and 10 mol % of CuI in $Et_2O$ the product of the addition of *n*-BuMgCl to cyclohexenone **36** was obtained in good yield and 83% ee (entry 1). A slight reduction in enantioselectivity (74%) was observed when additives (HMPA, TMSCl or MeI) were present; whereas in THF the reaction was barely enantioselective (6%). Variation in the ligand structure showed that the enantioselectivity was insensitive to the size of the alkyl group in the oxazoline ring (entries 2−4) with the exception of the *t*-Bu substituted oxazoline **L11** (entry 5). With the benzyl **L9** and phenyl **L10** oxazoline ligands, however, a substantial increase in regioselectivity (up to 10 times) was observed. In the absence of planar chirality little if any enantioselectivity was observed (entries 6 and 7).

The scope of the ACA of Grignard reagents to enones was investigated using ligand **L10**. As observed with the ligand developed by Tomioka et al.,[34] the highest enantioselectivity (92%) was obtained for addition of *n*-BuMgCl to cycloheptenone **47** (entry 8). For cyclopentenone **48** (entry 9), a lower ee of 65% was obtained, in accordance with a trend in stereoselectivity observed frequently in catalysis upon changing from a 6- to a 5-membered cyclic enone.[8,12,35] Interestingly, the use of acyclic enone **49** yielded similar results to those obtained for the cyclic systems (61% yield and 81% ee, entry 10).

A broad range of structurally diverse chiral ligands in combination with a Cu source were tested in the CA of Grignard reagents (for example **L14**−**L19**, Figure 5). For these ligands good regioselectivity, albeit typically poor to modest enantioselectivity, has been obtained.[36] In particular, the aminothiol ligand (**L14**) by Seebach and co-workers[36a] and the diselenide oxazoline ligand (**L18**) by Braga and co-workers[36e] show promising levels of enantioselectivity.

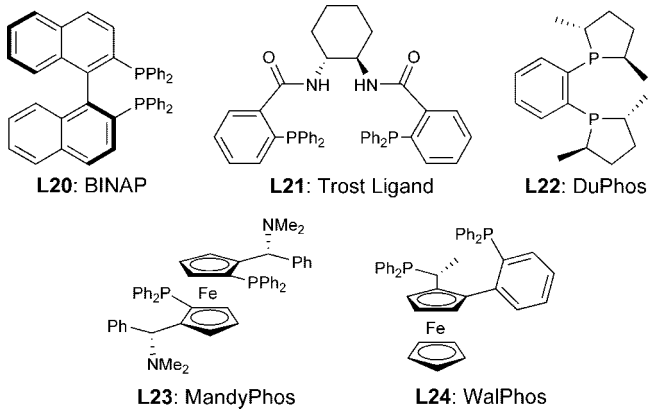



**Figure 6.** Chiral diphosphine ligands.

**2.2.1.2. Catalytic ECA to Enones.** It is apparent from the studies described above that (i) the reactivity of the Grignard reagent does not preclude Cu-catalyzed enantioselective alkyl transfer i.e. the ACA can compete with the noncatalyzed carbon−carbon bond-forming reaction. (ii) Appreciable levels of enantioselectivity can be reached with several, structurally diverse, chiral ligands. (iii) The catalyzed ECA of Grignard reagents is frequently highly sensitive to changes in solvent, concentration, temperature and the rate of addition of reagents. (iv) A pronounced substrate dependence is observed. (v) Enantioselectivity, although promising in some cases, had not reached the levels required for general application in synthetic organic chemistry. (vi) Several chiral and achiral Cu-complexes that are active in catalyzing the ECA of Grignard reagents appear to be present under many of the catalysis conditions employed. Furthermore, for the CA reaction it was observed that nonligated Cu salts are capable of catalyzing the CA reaction of Grignard reagents to enones. Therefore, it is necessary that a chiral ligand coordinates strongly to the Cu(I) ion to avoid nonstereoselective catalysis by free Cu(I) in solution.

Although chiral diphosphine ligands (Figure 6) have dominated the field of asymmetric catalysis over the last 30 years,[1] until recently these ligands were not reported to be effective in the conjugate addition of Grignard reagents. Most of the ligands used previously in the CA of Grignard reagents incorporate a P, S or Se atom in combination with a N or O donor atom to coordinate selectively with the Cu and Mg in the catalytically active complex. In principle, diphosphines do not fulfill the paradigm of the *metal-differentiating coordination concept*.[37] Indeed, as part of a screening program Feringa and co-workers[11] observed that the bidentate phosphine ligands such as BINAP (**L20**), Trost ligand (**L21**), and DuPhos (**L22**) provided poor enantioselectivity in the ACA of Grignard reagents (Figure 6).

Among the most important of the bidentate ligands in asymmetric catalysis are the ferrocenyl diphosphine ligands,[38] in particular TaniaPhos (**L25**, Figure 7)[38a,b] and JosiPhos (**L30**).[38c,d] In recent years, these ligands have been used especially for enantioselective hydrogenation reactions and have proven to be successful in a variety of other asymmetric transformations as well.[38e–g] Moreover, ferrocenyl-based ligands showed promising enantioselectivity in the Cu-catalyzed conjugate addition of dialkylzinc reagents to enones.[35,38h]

Initial results with ferrocenyl-based diphosphines[38d,39] indicated their potential for CA of Grignard reagents (45% ee with MandyPhos (**L23**, Figure 6) and 70% ee with WalPhos (**L24**)) and formed the basis for the breakthrough in the catalyzed ECA of Grignard reagents made in 2004.[11]

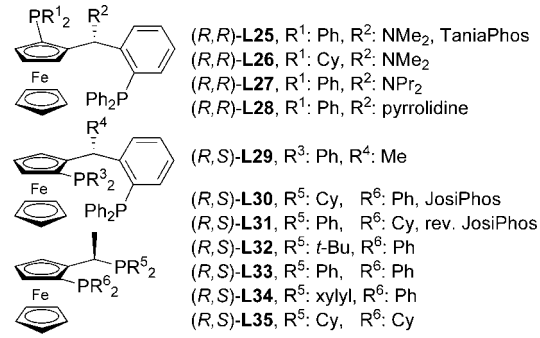



**Figure 7.** Chiral ferrocenyl ligands. Cy: *c*-hexyl.

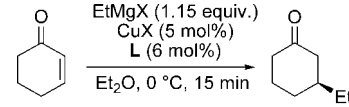
It was soon established that, among the ferrocenyl ligands (Figure 7) tested for the ECA of Grignard reagents to cyclic enones, the highest enantioselectivity was obtained with the ligand TaniaPhos (**L25**).[11]

With TaniaPhos (Table 7, entries 1−3) high enantioselectivity and moderate regioselectivity were obtained in the Cu(I)-catalyzed CA of EtMgCl to cyclohexenone. Optimization of reaction conditions for the model system depicted in Table 7 identified that the use of 5 mol % of CuCl and 6 mol % of TaniaPhos **L25** at 0 °C in $Et_2O$ with EtMgBr provided both excellent regio- and enantioselectivity (entry 4).

Conversion was complete in 15 min using these conditions. Furthermore, 95% regio- and 96% enantioselectivity was obtained. Analogues of TaniaPhos were tested under these conditions to identify the key structural features of the catalyst. Replacing the phenyl groups with cyclohexyl groups (**L26**, entry 5) led to a large decrease in enantioselectivity. Surprisingly, variation of the amine substituent $R^2$ (**L27**, entry 6 and **L28**, entry 7) had little effect on the enantioselectivity. By contrast, replacement of the amine group by a methyl group (**L29**, entry 8) reduced the enantioselectivity as well as the regioselectivity. With the JosiPhos ligand (**L30**, entry 9) the opposite enantiomer was obtained with lower enantioselectivity.

The CA of a series of Grignard reagents to cyclohexenone was examined under these reaction conditions (Table 8). For RMgBr reagents with linear alkyl chains (R = Et, Me, *n*-Pr, *n*-Bu; entries 1−4) the CA products **37** were obtained with excellent enantioselectivity (90−96% ee). The substitution pattern was found to have a major influence on the enantio-

**Table 7. Cu-Catalyzed ECA of Grignard Reagents to Cyclohexenone with Ferrocenyl-Based Catalysts**

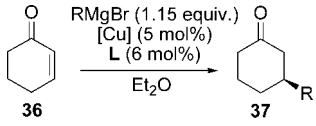



36 50

| entry | EtMgX | X | L | regioselectivity (%)[a] | ee (%) | *R*/*S* |
|---|---|---|---|---|---|---|
| 1 | EtMgCl | I | **L25** | 43 | 93 | *R* |
| 2 | EtMgCl | Br | **L25** | 61 | 95 | *R* |
| 3 | EtMgCl | Cl | **L25** | 71 | 95 | *R* |
| 4 | EtMgBr | Cl | **L25** | 95 | 96 | *R* |
| 5 | EtMgBr | Cl | **L26** | 80 | 10 | *R* |
| 6 | EtMgBr | Cl | **L27** | 96 | 94 | *R* |
| 7 | EtMgBr | Cl | **L28** | 92 | 93 | *R* |
| 8 | EtMgBr | Cl | **L29** | 69 | 45 | *R* |
| 9 | EtMgBr | Cl | **L30** | 93 | 30 | *S* |

[a] Regioselectivity: [1,4/(1,4 + 1,2)] × 100.

**Table 8. Cu-Catalyzed ECA of Grignard Reagents to Cyclohexenone**

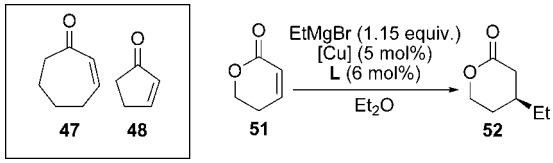



36 37

| entry | R | [Cu] | L | regioselectivity (%)[a] | ee (%) |
|---|---|---|---|---|---|
| 1 | Et | CuCl | **L25** | 95 | 96 |
| 2 | Me | CuCl | **L25** | 83 | 90 |
| 3 | *n*-Pr | CuCl | **L25** | 81 | 94 |
| 4 | *n*-Bu | CuCl | **L25** | 88 | 96 |
| 5 | *i*-Pr | CuCl | **L25** | 78 | 1 |
| 6 | *i*-Bu | CuCl | **L25** | 62 | 33 |
| 7 | *i*-amyl | CuCl | **L25** | 76 | 95 |
| 8 | $CH_2Bn$ | CuCl | **L25** | 80 | 77 |
| 9 | 4-Cl-*n*-Bu | CuCl | **L25** | 79 | 85 |
| 10 | *i*-Pr | CuBr·$SMe_2$ | **L30** | 99 | 54 |
| 11 | *i*-Bu | CuBr·$SMe_2$ | **L30** | 99 | 92 |
| 12 | Ph | CuBr·$SMe_2$ | **L30** | 50 | 40 |

[a] Regioselectivity: [1,4/(1,4 + 1,2)] × 100.

**Table 9. Cu-Catalyzed ECA of Grignard Reagents to Cyclic Enones**




47 48 51 52

| entry | substrate | L | regioselectivity (%)[a] | ee (%) | *R*/*S* |
|---|---|---|---|---|---|
| 1 | **47** | **L25** | 80 | 87 | *R* |
| 2 | **47** | **L30** | 96 | 78 | *S* |
| 3 | **48** | **L25** | 69 | 6 | *S* |
| 4 | **48** | **L30** | 99 | 82 | *R* |
| 5 | **48** | **L32** | 99 | 92 | *R* |
| 6 | **51** | **L25** | 99 | 47 | *R* |
| 7 | **51** | **L30** | 99 | 79 | *S* |
| 8 | **51** | **L32** | 99 | 82 | *S* |

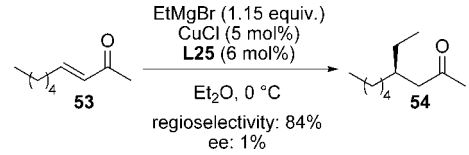
[a] Regioselectivity: [1,4/(1,4 + 1,2)] × 100.

selectivity achieved. With Grignard reagents containing branched alkyl chains (in particular *i*-Pr and *i*-Bu Grignard reagents) CA proceeded with low enantioselectivity (entries 5, 6). *i*-AmylMgBr afforded the 1,4-addition product with 95% ee (entry 7). Grignard reagents substituted at the $\beta$- or $\delta$-position also afforded good enantioselectivity (entries 8 and 9). With the ligand JosiPhos (**L30**), the CA of *i*-PrMgBr and *i*-BuMgBr provided excellent regiocontrol (99%) albeit with moderate (54%, entry 10) to high enantioselectivity (92%, entry 11). The JosiPhos-based catalyst system shows only modest enantioselectivity for the CA of PhMgBr (entry 12).[40]

For the CA of simple alkylMgBr to other cyclic enones and unsaturated lactones the same conditions can be used to reach modest to high enantioselectivity (Table 9). However, the ferrocenyl diphosphine ligand that provides optimum results is dependent on the specific structure of the cyclic substrate.

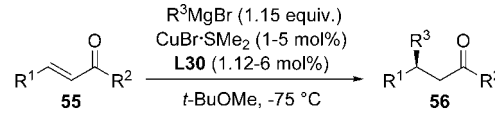
Several ferrocenyl diphosphine ligands afford enantioselectivities over 70% in the Cu-catalyzed CA of Grignard reagents to cycloheptenone. TaniaPhos (**L25**) and JosiPhos (**L30**) gave the product with 87% (entry 1) and 78% ee (entry 2), respectively, albeit with opposite configurations. For cyclopentenone, the JosiPhos-type ligands provided better regio- and enantioselectivity than the TaniaPhos-type ligands (entries 3−5). For example, with ligand **L32** the 1,4-adduct

**Scheme 14. Initial Results for Cu-Catalyzed ACA of Grignard Reagents to Acyclic Enones**




53 54

**Scheme 15. Cu-Catalyzed ECA of Grignard Reagents to Acyclic Enones**

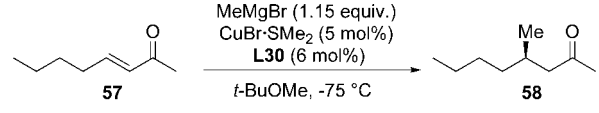



55 56

$R^1$: Me, *n*-Pr, *n*-Bu, *n*-pentyl; $R^2$: Me, *n*-Bu;
$R^3$: Me, Et, *n*-Pr, *n*-Bu, *i*-Bu, *i*-amyl, 4-Cl-*n*-Bu
regioselectivity: 88-98%; ee: 86-98%; 21 examples

For $R^1$: 2-thienyl, 2-furyl; regioselectivity: 66-74%; ee: 96-97%
For $R^2$: *t*-Bu; regioselectivity: 54%; ee: 40%
For $R^3$: *i*-Pr; regioselectivity: 92%; ee: 48%
For $R^3$: Ph; regioselectivity: 62%; ee: 76%

**Scheme 16. Cu-Catalyzed ECA of MeMgBr to 3-Octen-2-one**

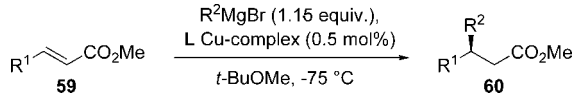



57 58

could be obtained with 99% regioselectivity and 92% ee (entry 5). In accordance with the observations of Stangeland and Sammakia,[35] for the CA to cycloheptenone or cyclopentenone, respectively, a reversal of the sense of the asymmetric induction was observed. For $\alpha,\beta$-unsaturated lactones the JosiPhos ligand (**L30**) and the related chiral phosphine **L32** provided higher enantioselectivity (79% and 82% ee, entries 6 and 7, respectively) than that obtained with TaniaPhos **L25** (47% ee, entry 8). For these cyclic substrates further improvements in the enantioselectivity of the reaction, in comparison to the selectivity obtained for cyclohexenones, still remain a challenge.

An important challenge in the field of catalyzed ECA of Grignard reagents is the expansion of the scope of the catalyst system to address acyclic $\alpha,\beta$-unsaturated enones. Although the products of CA of organometallic reagents to acyclic enones are important subunits of biologically active molecules, there was a paucity of highly enantioselective catalyzed routes for their preparation.[41] Notable exceptions are the Cu-catalyzed CA of dialkylzinc reagents[8] described by Hoveyda and co-workers[42a] and that of Nakamura and co-workers.[42b] A complementary approach reported by Lipshutz and co-workers and Buchwald and co-workers relies on a Cu-catalyzed asymmetric conjugate reduction of $\beta,\beta$-disubstituted enones.[38f,43] However, a general method based on the asymmetric CA of organomagnesium reagents to acyclic enones was, until recently, unavailable.[44] Initial studies were carried out using the catalyst system that showed success in the CA of EtMgBr to cyclic enones. For the linear substrate *E*-3-nonen-2-one, the combination of TaniaPhos (**L25**) and CuCl at 0 °C provided the 1,4-addition product (Scheme 14). However, the lack of enantioselectivity and low regioselectivity obtained demonstrates once again the strong dependence of the outcome of the CA reaction on the structure of the substrate.

**Table 10. Cu-Catalyzed ACA of Grignard Reagents to α,β-Unsaturated Esters**




| entry | $R^1$ | $R^2$ | L | yield (%)[a] | ee (%) |
|---|---|---|---|---|---|
| 1 | Me | *n*-Bu | **L30** | 92 | 95 |
| 2 | Me | homoallyl | **L30** | 67 | 85 |
| 3 | Me | *i*-pentyl | **L30** | 90 | 96 |
| 4 | *n*-Pr | Et | **L30** | 99[b] | 93 |
| 5 | $CH_2OBn$ | Et | **L30**[c] | 85 | 86 |
| 6 | *i*-Bu | *n*-Bu | **L30**[c] | 99[b] | 92 |
| 7 | *c*-hexyl | Et | **L31**[c] | 86 | 98 |
| 8 | 2-furyl | Et | **L31** | 90 | 95 |
| 9 | Ph | Et | **L31**[d] | 94 | 98 |
| 10 | Ph[e] | Et | **L31**[f] | 90 | 53[g] |
| 11 | *n*-Pr | Me | **L31**[c] | 19[b] | 93 |

[a] Regioselectivity: [1,4/(1,4 + 1,2)] x 100 was over 98% in all examples. [b] Conversion. [c] 2.5 mol % catalyst was used. [d] 1.5 mol % catalyst was used. [e] Addition to the *Z*-α,β-unsaturated ester. [f] 5.0 mol % catalyst and 1.5 equiv of EtMgBr were used. [g] Product has opposite configuration compared to product obtained from addition to the *E*-α,β-unsaturated ester.

However, the combination of the JosiPhos ligand (**L30**) and CuBr·$SMe_2$ provided high selectivity in the CA of linear alkyl Grignard reagents to a range of aliphatic linear enones in *t*-BuOMe at −75 °C (Scheme 15).[45]

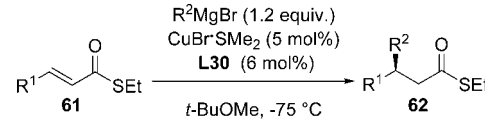
An especially notable example is the addition of MeMgBr to simple acyclic enones (Scheme 16). For this CA the corresponding 1,4-adducts could be obtained with 94−98% ee, even with a catalyst loading of 1 mol %. The scope of the Cu-catalyzed asymmetric CA includes aromatic and γ-substituted aliphatic acyclic enones.[45]

**2.2.1.3. Catalytic ECA to Esters and Thioesters.** Acyclic α,β-unsaturated esters are a particularly important substrate class in the CA of organometallic reagents due to the synthetic versatility of the chiral ester products. However, until recently progress with these substrates was limited. Use of ACA in organic synthesis has primarily relied on chiral auxiliary methods (see section 2.1.1).[46] The lower intrinsic reactivity of α,β-unsaturated esters relative to the corresponding enones of the acyclic unsaturated systems may account for this paucity of versatile methods.[47]

Recent advances have shown that the ACA of alkylMgBr to linear α,β-unsaturated methyl esters catalyzed by CuBr•$SMe_2$ and either JosiPhos (**L30**) or **L31** can provide the 1,4-addition products in high yield and enantioselectivity for a wide range of substrates (Table 10).[48] At 0.5 mol% catalyst loading these systems allow for the addition of linear alkyl (e.g., entry 1), as well as *i*-pentyl and homoallyl Grignard reagents (entry 2 and 3), to a wide range of α,β-unsaturated methyl esters. For the less hindered electrophiles, i.e. those without branching at the γ-position, the Cu-complex of **L30** afforded the best results (entry 1−6). For γ-branched (entry 7) or aryl-substituted α,β-unsaturated methyl esters (entry 8 and 9) the Cu-complex of **L31** provided the optimum results. Importantly, the Cu-complex of **L30** could be recovered from the crude reaction mixture and reused repeatedly without loss of activity.[49] Furthermore, the *Z*-enoates afforded the opposite enantiomer of the addition product to that obtained with the *E*-enoates albeit with lower enantioselectivity (entry 10).

A limitation of this method is the addition of the relatively unreactive methyl Grignard reagent that gave high enantioselectivity (93%, entry 11) but low conversion (19%). Since the CA of MeMgBr is an important target due to its potential application in the synthesis of biologically active compounds (*vide infra*), the more electrophilic and readily accessible α,β-unsaturated thioesters were employed.[50] With the JosiPhos (**L30**) ligand, the Cu-catalyzed CA of MeMgBr to a wide range of α,β-unsaturated thioesters was complete within 2 h at −75 °C (Table 11).

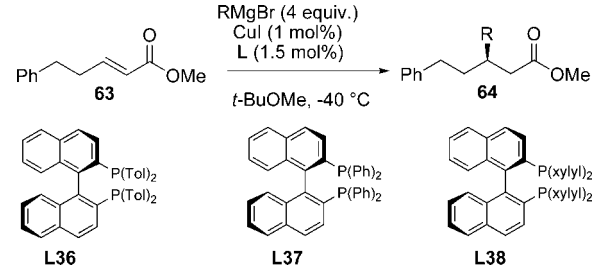
**Table 11. Cu-Catalyzed ACA of Grignard Reagents to α,β-Unsaturated Thioesters**




| entry | $R^1$ | $R^2$ | yield (%)[a] | ee (%) |
|---|---|---|---|---|
| 1 | *n*-pentyl | Me | 90 | 96 |
| 2 | *n*-Bu | Me | 93 | 95 |
| 3 | *n*-Pr | Me | 92 | 96 |
| 4 | Et | Me | 92 | 92 |
| 5 | $(CH_2)_3OBn$ | Me | 84 | 95 |
| 6 | Ph | Me | 65 | 95 |
| 7 | *n*-pentyl | Et | 89 | 86 |
| 8 | Et | *n*-Pr | 87 | 85 |
| 9 | Me | *n*-Bu | 90 | 90 |
| 10 | *n*-pentyl | *i*-Pr | 93 | 25 |
| 11 | *n*-pentyl | *i*-Bu | 80 | 15 |

[a] Regioselectivity: [1,4/(1,4 + 1,2)] × 100 was over 99% in all examples.

**Table 12. ACA of Grignard Reagents to α,β-Unsaturated Esters Catalyzed by Cu/BINAP-Complexes**

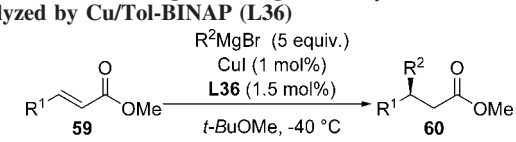



| entry | L | R | yield (%)[a] | ee (%) |
|---|---|---|---|---|
| 1 | **L36** | Et | 88 | 93 |
| 2 | **L37** | Et | 85 | 85 |
| 3 | **L38** | Et | 83 | 48 |

[a] Regioselectivity: [1,4/(1,4 + 1,2)] × 100 was over 99% in all examples.

Under these conditions the β-methyl substituted thioesters **62** and (after methanolysis) the corresponding methyl esters were obtained with excellent enantiomeric excess (up to 96%, entries 1−6). The Cu-catalyzed CA of MeMgBr furnishes the 1,4-addition products of thioester **61** exclusively and in excellent yield with complete regioselectivity and in most cases with excellent enantioselectivity. Furthermore, the CA of other linear Grignard reagents, such as EtMgBr (entry 7), *n*-PrMgBr (entry 8), and *n*-BuMgBr (entry 9) provide enantioselectivities in the range of 85−90%. However, bulky Grignard reagents, such as *i*-PrMgBr (entry 10) and *i*-BuMgBr (entry 11), gave poor enantioselectivity under these conditions. The higher reaction rate observed for the methyl adducts obtained from the α,β-unsaturated thioesters compared with their respective oxoester analogues is most probably due to their inherent electronic properties. Those properties are more similar to those of the corresponding enones.[51,52]

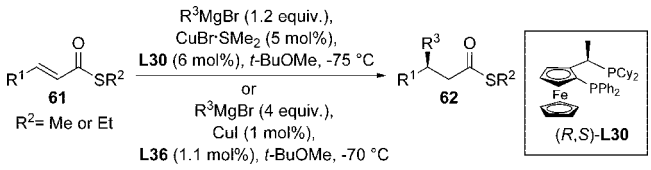
**Table 13. ACA of Grignard Reagents to α,β-Unsaturated Esters Catalyzed by Cu/Tol-BINAP (L36)**




| entry | $R^1$ | $R^2$ | yield (%)[a] | ee (%) |
|---|---|---|---|---|
| 1 | $CH_2Bn$ | Me | 20 | 98 |
| 2 | $CH_2Bn$ | Et | 88 | 93 |
| 3 | $CH_2Bn$ | *n*-Pr | 90 | 92 |
| 4 | $CH_2Bn$ | *i*-Pr | 89 | 91 |
| 5 | $CH_2Bn$ | *n*-Bu | 90 | 92 |
| 6 | $CH_2Bn$ | *n*-pentyl | 86 | 90 |
| 7 | $CH_2Bn$ | *n*-heptyl | 89 | 92 |
| 8 | $CH_2Bn$ | *i*-Bu | 91 | 86 |
| 9 | $CH_2Bn$ | homoallyl | 90 | 94 |
| 10 | Me | Et | 83 | 74 |
| 11 | *n*-Pr | Et | 85 | 87 |
| 12 | *i*-Pr | Et | 90 | 95 |
| 13 | Ph | Et | 90 | 93 |
| 14 | $CH_2Bn$[b] | Et | 86 | 94[c] |
| 15 | $CH_2OBn$ | Et | 83 | 73 |
| 16 | $CH_2OBn$[b] | Et | 86 | 87[c] |
| 17 | furyl | Et | 80 | 85 |

[a] Regioselectivity of the 1,4-:1,2-addition was in all cases over 99:1. [b] Addition to the *Z*-α,β-unsaturated ester. [c] Provides a product with the opposite configuration compared to the product obtained from addition to the *E*-α,β-unsaturated ester.

**Table 14. ACA of Grignard Reagents to α,β-Unsaturated Thioesters Catalyzed by the Cu/JosiPhos and Cu/Tol-BINAP-Complexes**

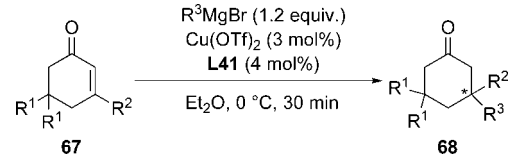



| | | | | Tol-BINAP (**L36**) | | JosiPhos (**L30**) | |
|---|---|---|---|---|---|---|---|
| entry | $R^1$ | $R^2$ | $R^3$ | yield (%)[a,b] | ee (%) | yield (%)[a] | ee (%) |
| 1 | Ph | Me | Me | 88 | 94 | 65 (90) | 95 |
| 2 | *p*-$ClC_6H_4$ | Et | Me | 93 | 99 | 60[c] (95) | >99[c] |
| 3 | *p*-$MeC_6H_4$ | Et | Me | 34 (39) | 99 | 33 (75) | >99 |
| 4 | *p*-$MeOC_6H_4$ | Et | Me | 15 (22) | 96 | 24 (35) | 93 |
| 5 | *n*-pentyl | Et | *i*-Pr | 89 | 65 | 93 | 25 |
| 6 | *n*-pentyl | Et | *i*-Bu | 95 | 94 | 80 | 15 |
| 7 | Me | Et | *n*-Bu | 94 | 74 | 90 | 90 |
| 8 | *n*-pentyl | Et | Me | 90 | 93 | 90 | 96 |
| 9 | *i*-Pr | Et | Me | 82 | 99 | – | – |
| 10 | $CH_2OTBDPS$ | Et | Me | 95 | 83 | 95 | 98 |

[a] Regioselectivity 1,4-:1,2-addition in all cases over 99:1. [b] Conversion between parentheses were not 99%. [c] Reaction performed on methylthioester.

The complementary use of TaniaPhos (**L25**) and JosiPhos-type ligands (**L30** and **L32**) in combination with a Cu source have proven to be a considerable advance in the development of protocols for the CA of Grignard reagents that are directly applicable in organic synthesis.[13] These catalyst systems cover a broad range of substrates, such as α,β-unsaturated cyclic and acyclic enones, esters and thioesters, and provide high regio- and enantioselectivity. A further advantage of these methods is the low catalyst loading required, the robustness of the reaction to traces of water and dioxygen and the use of air-stable preformed Cu-complexes of the chiral ligands (*vide infra*). That is not to say that these methods are a panacea to ACA as several challenges remain.

**Table 15. NHC Ligand/Cu-Catalyzed ECA**




| entry | $R^1$ | $R^2$ | $R^3$ | conversion (%) | ee (%) |
|---|---|---|---|---|---|
| 1 | H | Et | Me | 98 | 68 |
| 2 | H | Me | *n*-Bu | 100 | 77 |
| 3 | H | Me | *i*-Bu[a] | 100 | 96 |
| 4 | H | Me | homoallyl[a] | 91 | 90 |
| 5 | H | Me | *i*-Pr[b] | 100 | 77 |
| 6 | H | Me | *c*-pentyl[a] | 100 | 85 |
| 7 | H | Me | *t*-Bu[a] | 0 | – |
| 8 | H | Me | Et | 99 | 80 |
| 9 | Me | Me | Et | 93 | 71 |
| 10 | H | *i*-Bu | Et | 98 | 81 |
| 11 | H | Ph | Et | 98 | 72 |
| 12 | H | homoallyl | Et | 94 | 69 |
| 13 | H | Me | Ph[a] | 72 | 66 |

[a] Reaction performed at −30 °C. [b] Reaction performed at −18 °C.

In particular more efficient catalytic systems should be developed for the addition of Grignard reagents to several cyclic enones and for the addition of α-branched-, vinyl-, allyl- and phenyl Grignard reagents.

A complementary and efficient catalyst system for the CA of Grignard reagents to α,β-unsaturated esters was recently reported by Wang et al.[53] This catalyst is based on CuI complexed with Tol-BINAP derivatives **L36**−**L38** (Table 12). The ligand **L36** gives much better results (entry 1) than the phenyl (**L37**, entry 2) or xylyl analogues (**L38**, entry 3).

Under the reaction conditions, i.e. 1.5 mol % of Tol-BINAP (**L36**) and 1 mol % of CuI in *t*-BuOMe at −40 °C, the ACA of a range of Grignard reagents could be performed with enantioselectivity of up to 95% (Table 13, entries 1−9).[53] The major differences compared with the systems based on ferrocenyl phosphine ligands[13] are that higher enantioselectivity can be achieved in the CA of *i*-PrMgBr and unsaturated Grignard reagents.

The ACA of Grignard reagents to a number of α,β-unsaturated esters was carried out under these conditions (entries 10−17). However, reduced enantioselectivity was observed with aliphatic α,β-unsaturated esters in comparison to that obtained with the JosiPhos-based system (entries 11 and 12). Interestingly, similar enantioselectivity was obtained with both *E*- and *Z*-methyl ester of 5-phenylpent-2-enoate (93% for *E*, entry 2 vs 94% for *Z*, entry 14). In contrast, for the benzyloxy substituted substrate higher enantioselectivity

**Scheme 17. NHC Ligands Used in the ECA of Grignard Reagents**

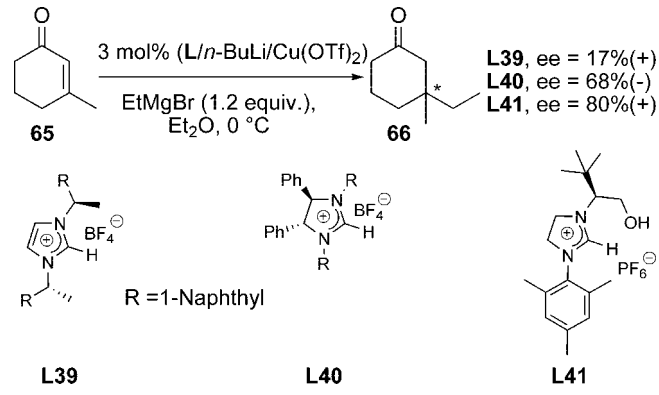
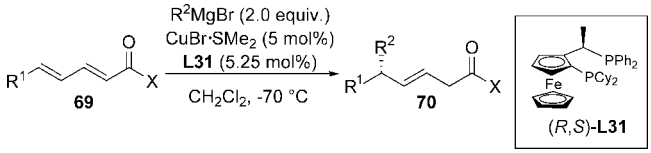


**Table 16. Cu-Catalyzed 1,6-ECA of Grignard Reagents to α,β,γ,δ-Unsaturated Esters**




| entry | $R^1$ | X | $R^2$ | regioselectivity (%)[a] | ee (%) |
|---|---|---|---|---|---|
| 1 | Me | OEt | Et | 96 | 95 |
| 2 | Me | OEt | *n*-Bu | 98 | 97 |
| 3 | Et | OEt | *n*-Bu | 98 | 96 |
| 4 | Me | OEt | homoallyl | 94 | 92 |
| 5 | Me | OEt | *i*-Pr | 98 | 72 |
| 6 | *n*-Bu | OEt | Et | 98 | 93 |
| 7 | *i*-Bu | OEt | Et | 96 | 93 |
| 8 | $CH_2Bn$ | OEt | Et | 96 | 90 |
| 9 | $CH_2OBn$ | OEt | Et | >90 | 90 |
| 10 | *i*-Pr | OEt | Et | 92 | 79 |
| 11 | $CH_2OTBDPS$ | OEt | Et | 92 | 73 |
| 12 | Et | SEt | Me | 97 | 93 |

[a] Regioselectivity 1,6- and 1,4- over 1,2-addition in all cases over 99:1

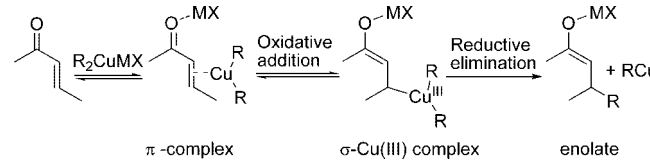
was obtained for the *Z*-enoate (73% for *E*, entry 15 vs 87% for *Z*, entry 16).

In an effort to improve the results of the ACA of MeMgBr to aromatic α,β-unsaturated thioesters Feringa and co-workers[54] identified Tol-BINAP/Cu as a more active catalyst compared to the JosiPhos/Cu system[50] used previously (Table 14, entries 1−4). Further comparison of the two catalyst systems in the ECA to α,β-unsaturated thioesters showed improved results in the addition of secondary and bulky Grignard reagents using Tol-BINAP/Cu. In contrast, for the primary organomagnesium reagents, JosiPhos/Cu was found to provide the best regio- and enantioselectivity (entries 7 and 8). Overall, it is apparent that the TolBINAP/Cu system provides superior results in the ACA to γ-substituted aliphatic substrates (entry 9), whereas the JosiPhos/Cu catalyst is superior for δ-functionalized substrates[55] (entry 10).

**2.2.1.4. Quaternary Centers through Catalytic ECA.** The construction of quaternary stereogenic centers is a major contemporary challenge in asymmetric catalysis.[56] In 2006 Alexakis and co-workers reported[57] that diaminocarbene based ligands (N-heterocyclic carbene ligand, NHC) in combination with Cu(II) triflate accelerate the CA of Grignard reagents to trisubstituted cyclic enones with moderate to high enantioselectivity. This was the first example of the application of NHC ligands to the ECA of Grignard reagents. Among the chiral NHC ligands **L39**−**L41** tested, the most promising results were obtained with imidazolidinium ligands bearing chiral moieties at the nitrogen atoms of the heterocycle (Scheme 17).

$Cu(OTf)_2$/**L41** was identified as the most effective catalyst for this reaction. Initial studies employed *n*-BuLi to deprotonate the $ImH^+$ unit of the ligand, however, better reproducibility could be achieved when the deprotonation was performed with the Grignard reagent itself. It was found that high enantioselectivity was obtained with primary Grignard reagents (Table 15, entries 1−4). However, with secondary Grignard reagents (entries 5 and 6) it was necessary to lower the temperature to −30 °C to achieve good results in the ACA reaction, while the addition of tertiary Grignard reagents does not proceed. The addition of EtMgBr was performed on a number of trisubstituted cyclohexenones affording the products with modest to good enantioselectivity (entries 8−12) and to 5- and 7-membered ring substrates reaching 46% and 82% ee, respectively. Finally, CA with PhMgBr gave modest enantioselectivity (entry 13).

**Scheme 18. Proposed Mechanism for the Stoichiometric 1,4-Addition of Organocuprates**



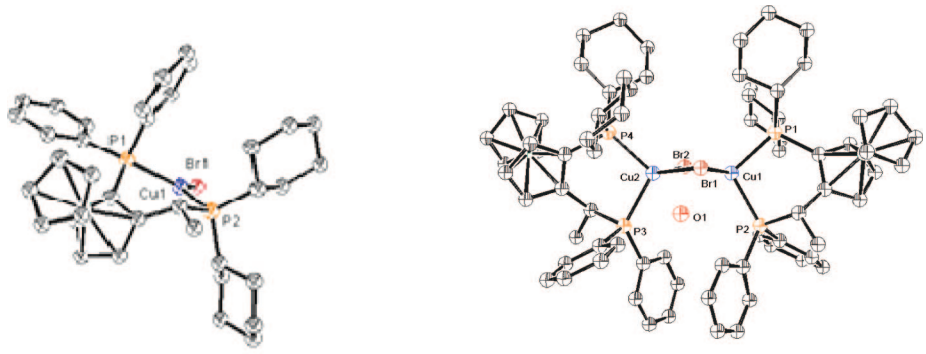

### 2.2.2. Cu-Catalyzed 1,6-ECA

Controlling regioselectivity for 1,6-conjugate addition (using extended Michael acceptors as substrates) is more complicated compared to 1,4-conjugate addition due to competing 1,2- and 1,4-addition reactions. Yamamato (for dienoates)[58] and Krause (for enynes)[59] and co-workers have shown that by tuning of the electron density on the Cu-reagent regioselective 1,4- or 1,6-addition can be achieved. This indicates that a similar fine-tuning of the catalyst could allow for regio- and stereoselective 1,6-ACA. However, until recently, the catalytic 1,6-ACA had been reported only for β-substituted[60] substrates using zinc reagents or δ-substituted substrates[61] using β-ketoesters or glycine imine as nucleophiles.

Feringa and co-workers[62] have reported the catalytic enantioselective 1,6-addition of Grignard reagents to *bis*-unsaturated esters **69**. Although with the JosiPhos (**L30**) and TaniaPhos (**L25**) ligands only decomposition of the substrate ethyl sorbate was observed, with the reversed JosiPhos (**L31**) ligand the Cu-catalyzed addition of EtMgBr provided the 1,6-addition product (Table 16, entry 1) in high regio- (96%) and enantioselectivity (95%). The rate of reaction is significantly lower than the 1,4-addition (1,6-ECA at −70 °C for 16 h vs 1,4-ECA at −75 °C for 2 h). Addition of linear alkyl Grignard reagents to ethyl sorbate could be carried out with high regio- and stereocontrol (entries 2 and 3). For this substrate the conjugate addition of homoallylic (entry 4) and *i*-Pr (entry 5) Grignard reagents provides the 1,6-addition product **70** with moderate to high stereoselectivity. Furthermore, linear alkyl as well as functionalized substrates incorporating a $CH_2$ spacer can be used in the CA with high regio- and stereoselectivity (entries 6−9). A significant decrease in enantioselectivity was observed with sterically hindered substrates (for example with a methyl substituent at the ε-position (entry 10), or with a TBDPS-protected alcohol at the ε-position (entry 11)). Regio- and enantioselective 1,6-addition of the less reactive MeMgBr to the corresponding thioester was also reported (entry 12).

### 2.2.3. Mechanism of ECA

The mechanism of the Cu-catalyzed enantioselective CA of organometallic compounds may follow principles similar to those proposed for the noncatalyzed organocuprate addition (Scheme 18).[63,64] The mechanism accepted widely for noncatalyzed organocuprate addition starts with the reversible formation of a Cu-olefin π-complex, involving d,π*-back bonding.[64d,e,i,k] This step is followed by oxidative addition to the β-carbon to form a $d^8$ Cu(III)-intermediate[64a,c,h] and ultimately reductive elimination to yield the enolate. The mechanism proposed is supported by data from kinetic studies[64b,j] including kinetic isotope effect measurements[64g,l]




**L30** Cu **L31** Cu

**Figure 8.** X-ray structure of CuBr-complexes **L30** Cu (left) and **L31** Cu (right).

and NMR spectroscopy of intermediates observed in the reaction mixture.[64d,e]

Although $\pi$-complexes of $\alpha,\beta$-unsaturated esters, ketones, and nitriles have been observed by low-temperature NMR spectroscopy,[65] a Cu(III)-intermediate had not been observed in the CA of organocuprates, and its involvement was proposed primarily on the basis of quantum chemical calculations.[66] Recent theoretical studies have indicated that a Cu(III)-intermediate could be involved in the CA of organocuprates. This potentially important intermediate was characterized for the first time by rapid injection NMR spectroscopy.[67]

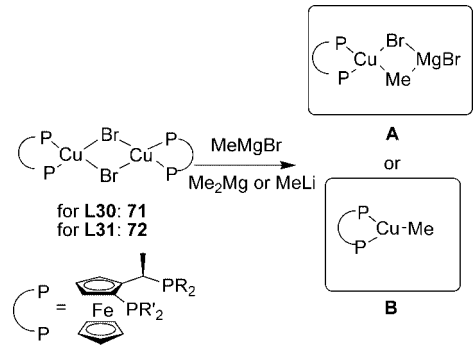
A similar mechanism for the Cu-catalyzed enantioselective CA of dialkylzinc reagents involving an oxidative addition−reductive elimination pathway has been postulated based on the spectroscopic and catalysis data available for the stoichiometric organocuprate CA reaction.[8,68] However, relatively few studies focusing on the mechanism of the enantioselective Cu-catalyzed CA of organometallic reagents have been reported to date.[69] Moreover, these studies are related exclusively to the catalytic CA of dialkylzinc reagents and have not as yet led to a generally accepted mechanism especially with regard to the rate-determining step.

The difficulties encountered in obtaining detailed structural information regarding the species formed under catalytic conditions have complicated mechanistic interpretation of data from catalysis experiments.[70] Presumably as a consequence, detailed studies of the mechanism of the reaction have not appeared frequently in the literature. The majority of the studies related to the mechanism of the Cu-catalyzed 1,4-addition postulate the transmetalation between the organometallic compounds and the Cu species as the first step in the catalytic cycle.[71,72]

Feringa and co-workers[49] have examined aspects of the reaction to explore the mechanism of the ACA of Grignard reagents. It was found that the air-stable Cu(I)-complexes can be prepared by addition of equimolar amounts of a Cu(I) salt and the chiral ligands **L30** or **L31**. The structure of the complexes was determined by X-ray analysis (Figure 8).

Electrochemical studies at −70 °C established that the oxidation potential for Cu(I) of **L31** Cu is lower than that of **L30** Cu. Hence, the difference in reactivity toward various $\alpha,\beta$-unsaturated ester substrates may be related to the energy match of the substrate and the catalyst. Furthermore, the observation of a dramatic decrease of enantioselectivity for this catalyst system in THF compared to *t*-BuOMe indicates that the Schlenk equilibrium is an important factor in the CA of Grignard reagents. The presence of bromide, either

**Scheme 19. Cu-Complexes Formed via Transmetalation of Grignard (A) or Li Reagents (B)**




in the Grignard reagent or in the Cu salt, is essential to achieve full conversion and high regio- and enantioselectivity.

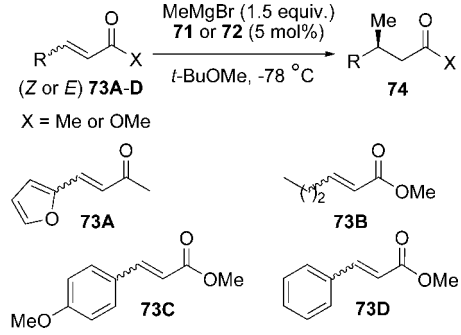
NMR studies of the actual catalytic reaction mixture identified two Cu-complexes, **A** or **B**, formed via transmetalation with Grignard reagents or organolithium compounds and established their relevance to the catalytic cycle (Scheme 19).

On the basis of these studies it was postulated that the generation of species **A**, rather than **B**, is essential to obtain high levels of regio- and enantioselectivity in the catalytic ACA of Grignard reagents to unsaturated carbonyl compounds. Furthermore, conditions (solvent, nature of halide, Cu source, additives) were established which favor formation of either of these species. Kinetic studies indicated that the rate of the ACA is dependent on the Grignard reagents, the substrate and the catalyst. The first-order dependence with respect to the catalyst is in agreement with the linear dependency of the ee of the product on the ee of the catalyst.

Another important observation for this system relates to the *E*- and *Z*-configurations of the substrates (Table 17). The ACA of EtMgBr to both *E*- and *Z*-isomers of the enone **73A** (entries 1 and 2) led to the same enantiomer in 95% ee. By contrast, for the less reactive unsaturated ester **73B** the use of the *E*- or *Z*-isomers led to opposite enantiomers with high enantioselectivity (entries 3 and 4).

ACA to the *E*-isomer of Michael substrate **73C** afforded, without reaching full conversion, the product in a high 90% ee (entry 5), while for the *Z*-isomer the product was formed with only 40% ee (entry 6). Furthermore, the CA reaction between EtMgBr and cinnamate *E*-**73D** (entry 7) or *Z*-**73D** (entry 8) gave results similar to those for substrate **73C** with respect to enantioselectivity. When the reaction was stopped before full conversion was reached, it was found that the

**Table 17. CA of EtMgBr and *Z*−*E* Isomerization of Substrates**



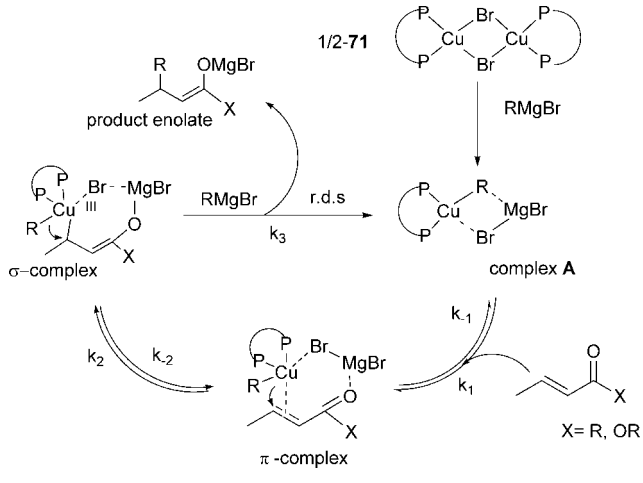

| entry | substrate | catalyst | conversion (%) | *Z*:*E* substrate | ee (%) |
|---|---|---|---|---|---|
| 1 | *E*- **73A** | **71** | 100 | − | 95 (+) |
| 2 | *Z*- **73A** | **71** | 100 | − | 95 (+) |
| 3 | *E*- **73B** | **71** | 100 | − | 90 (*R*) |
| 4 | *Z*- **73B** | **71** | 100 | − | 90 (*S*) |
| 5 | *E*- **73C** | **72** | 70 | − | 90 (+) |
| 6 | *Z*- **73C** | **72** | 77 | 1:99 | 40 (−) |
| 7 | *E*- **73D** | **72** | 100 | − | 98 (*S*) |
| 8 | *Z*- **73D** | **72** | 100 | − | 53 (*R*) |
| 9 | *Z*- **73D** | **72** | 10[a] | 94:6 | 59 (*R*) |

[a] Reaction was stopped after 10% conversion.

*Z*-isomer **73D** (entry 9) had isomerized partially to the *E*-isomer. Control experiments confirmed that the isomerization process is initiated only when both the chiral Cu-complex and the Grignard reagent are present in solution together. This suggests that the activated Cu-complex **A** may interact directly, but reversibly, with the alkene moiety allowing for *Z*−*E* isomerization of the double bond to occur. Therefore, the enantioselectivity achieved in the CA reaction is decreased. When the *Z*−*E* isomerization is much faster than the final irreversible step, leading to the product, the formation of the adduct with the same absolute configuration starting from either the *Z* or *E*-isomer occurs. Indeed, this appears to take place in the CA to enones *E*-**73A** and *Z*-**73A.**

A reaction pathway which is consistent with the catalysis, kinetic and spectroscopic data is presented in Scheme 20. The CA reaction pathway involves formation of an intermediate species through $\pi$-complexation followed by formation of a Mg enolate via a Cu(III)-intermediate. The first step in the catalytic cycle is initiated by formation of the catalyst (complex **A**). This monomeric complex **A** is formed from dimeric precatalyst **71** via transmetalation with the Grignard reagent. Most probably, complex **A** functions in a manner similar to that of organocuprates with the additional advantage that it bears a chiral diphosphine ligand which accelerates the CA process and stabilizes the reaction intermediates. This stabilization allows overcoming the background 1,2-addition and noncatalyzed racemic 1,4-addition reaction leading to racemic product.

**Scheme 20. Catalytic Cycle Proposed for the CA Addition of Grignard Reagents to α,β-Unsaturated Carbonyl Compounds**




The first step in the proposed cycle is the reversible formation of the $\pi$-complex from complex **A** and the double bond of the enone or enoate. For this intermediate, Cu coordinates to the olefinic bond, while an additional interaction between the $Mg^{2+}$ ion and the oxygen atom of the carbonyl functionality stabilizes the complex further. The importance of $Mg^{2+}$ ion is reflected in the inhibitory effects of solvent (THF), additive (dioxane) and halide (absence of bromide) on the conversion and the stereo- and regioselectivity of the reaction. The inhibition arises for the formation of species **B** upon removal of $Mg^{2+}$ ions from the system.

The results indicate that $Mg^{2+}$ ions not only activate the enone (or enoate) via coordination to the oxygen atom of the substrate (Lewis acid effect) but also interact with the Cu-complex through the bridging halide. The importance of the bromide in the halide bridge to the formation of species **A** is evident from the necessity for it to be present either in the catalyst itself or in the Grignard reagent. The origin of this effect is unclear. However, the size and electronegativity of the bromide ion may be critical in achieving a balance between the stabilization of the $\pi$- and $\sigma$-complexes that are intermediates in the reaction. The formation of a $\pi$-complex may be followed by an intramolecular rearrangement to form a Cu(III)-intermediate where Cu binds to the $\beta$-carbon of the enone (or enoate) through a $\sigma$-bond. This $\sigma$-complex is in fast equilibrium with the $\pi$-complex, with an equilibrium constant between the two states depending on the stability of the Cu(III)-intermediate. Theoretical calculations indicate that this type of Cu(III)-intermediate would be unstable, and hence the thermodynamic stabilization of the Cu−substrate species and the kinetic lability toward reductive elimination are the most important factors governing the rate of C−C bond formation.[66c] The thermodynamic stabilization can be achieved by using soft donor ligands, while the kinetic lability will depend mostly on the geometry of the species formed. In the present system this is realized through a combination of the Grignard reagent and a diphosphine ligand which provides donor ligands and the necessary geometry in the $\sigma$-complex to afford excellent regio- and stereocontrol.

The proposed catalytic cycle accounts for the observed *Z*−*E* isomerization of enoates also. This isomerization provides strong evidence for the presence of a fast equilibrium between the $\pi$-complex and the Cu(III) species (the $\sigma$-complex), which is followed by the rate-limiting reductive elimination step. The observation that *Z*−*E* isomerization occurs (even in the case where the reaction between MeMgBr and the unsaturated enoate *Z*-**73C** does proceed to afford detectable amounts of the CA product) is in agreement with the mechanism proposed. Cuprate-induced isomerization of a *Z*-enone to an *E*-enone was reported previously by House[73] and was rationalized by invoking a mechanism involving the formation of a radical anion involving electron transfer from the cuprate to the enone. Similar observations were reported by Corey[64c] for CA of organocuprates, leading to the conclusion that the CA reaction of cuprate proceeds via a reversible d,$\pi$-complex and a Cu(III) adduct and that the

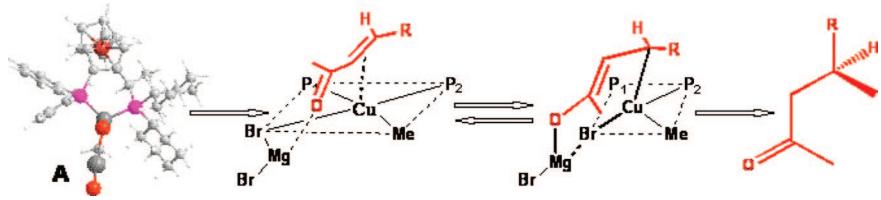



**Figure 9.** Working model for the ECA of Grignard reagents using the **L30** Cu-complex ($P_1$-diphenyl-substituted phosphine, $P_2$- dicyclohexyl-substituted phosphine).

initial electron-transfer step from cuprate to enone is not necessary. The latter proposition is in good agreement with the data obtained for the ECA system of Feringa and co-workers.[49]

Additional substitution at the α- or β-carbons of the substrate prevents formation of the 1,4-product. This observation supports the mechanism in which the alkyl Cu species **A** complexes with the alkene moiety of the substrate and in which the alkyl transfer step is rate limiting. The presence of substituents at these positions may impede coordination of the bulky diphosphine Cu complex to the double bond which renders the 1,2-addition the more favorable reaction. However, it should be noted that this mechanism probably does not hold for the Cu−carbene complexes reported by Alexakis and co-workers.[57] Detailed studies of the mechanism are required to elucidate the underlying differences between these catalyst systems.

Finally, in an attempt to rationalize the stereoselectivity for the ECA a hypothetical model was proposed by Feringa and co-workers.[49] In this model the [PM3(tm)] optimized structure for **A** (Scheme 20, complex **A**) gave a tetrahedral structure with the positioning of the Grignard reagent at the bottom face of the complex (Figure 9). This calculated structure is in accordance with the X-ray structure of the **L30** Cu-complex (Figure 8). To this complex the enone approaches from the top face, forcing a square pyramidal geometry. The enone binds in this complex on the top apical position from the least hindered side. This implies that the Me group occupies the side next to dicyclohexylphosphines moieties (P2) and the more sterically demanding BrMgBr is positioned next to the smaller diphenyl moieties (P1). This square pyramidal geometry is stabilized through interaction between Mg and the carbonyl moiety of the skewed enone and via π-complexation of the alkene moiety to the copper. In the next step a Cu(III)-intermediate is formed. In this complex the β-carbon is bound to the copper from the top face. It is proposed that in this transition structure featuring a chairlike seven-membered ring conformation the absolute configuration is already fixed. The final transfer of the Me-group from the Cu then proceeds from the bottom side to the β-carbon to give the addition product with the experimentally observed stereochemistry. However, as the authors point out, further mechanistic studies and calculations are required to validate this preliminary hypothetical model.

## 3. Asymmetric Allylic Alkylation (AAA) with Grignard Reagents

Similar to asymmetric conjugate addition, the field of asymmetric allylic alkylation has advanced tremendously in the last three decades and progress has been summarized.[3,4,7,13] Most of the earlier reviews primarily deal with AA employing a chiral catalyst. However, initial insight has been obtained by studying AA using a stoichiometric chiral source (employing chiral substrates or chiral auxiliaries).[24a,63a,74]

Catalytic enantioselective allylic alkylation (EAA) faces the same challenges as ECA. Primary requirements are to obtain synthetically useful levels of enantioselectivity and to overcome the competition of noncatalyzed reactions. For EAA these competing reactions are catalyzed $S_N2$ reactions (Scheme 2B) and noncatalyzed addition of highly active organometallic reagents leading to racemic products (either $S_N2$ or $S_N2'$).

In the following section recent advances in diastereoselective allylic alkylation (DAA) using Grignard reagents are discussed. This section is followed by a comprehensive review of developments in enantioselective allylic alkylation (EAA), i.e. addition of organometallic reagents catalyzed by chiral Cu-complexes. Both parts cover the literature starting from 1995.

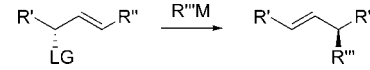
### 3.1. Diastereoselective Allylic Alkylation (DAA)[14]

For diastereoselective allylic alkylation two approaches can be used. The first approach is based on the chiral information present in a substrate to favor diastereofacial selective addition. In the second approach a chiral auxiliary (for DAA a chiral leaving group) is used to direct addition toward one enantiomer. As for the DCA only the most significant achievements from the recent years will be discussed.

#### 3.1.1. DAA to Chiral Substrates

The prominent methods for DAA all employ chiral starting materials. This is in sharp contrast to the abundant use of auxiliary methods for DCA. The majority of DAA to chiral substrates rely on anti addition to a leaving group.[24a,63a,74] These methods predominantly provide the $S_N2'$-substitution products with *E*-alkene geometry (Scheme 21).

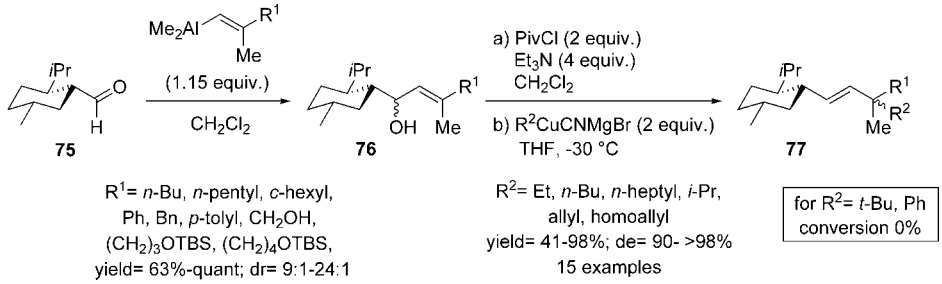
**Scheme 21. Anti Selective $S_N2'$-Substitution**



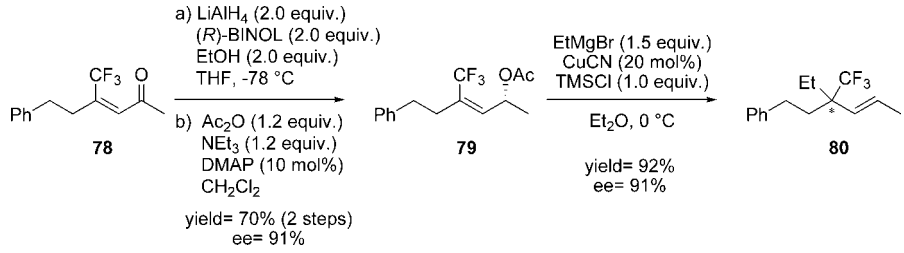

In recent years multiple examples of anti selective $S_N2'$-substitution have been reported using acetate or carbonates,[75] aziridines[76] and a variety of other leaving groups.[77] Two new methods for the synthesis of all carbon quaternary centers via anti selective $S_N2'$-substitution were published. The first method by Spino and co-workers[75b,d] features the synthesis of the substrate for the asymmetric allylic alkylation by carboalumination of a menthol-derived auxiliary. This substrate is then subjected to anti selective $S_N2'$ substitution, furnishing the alkylated products in good yield and excellent diastereoselectivity (Scheme 22).

The second method by Yamazaki and co-workers[75i] starts with enones and features subsequent asymmetric reduction and acylation to yield chiral substrates for DAA in 91% ee. Allylic alkylation via the anti $S_N2'$-mechanism then provides **80** in 92% yield (Scheme 23).

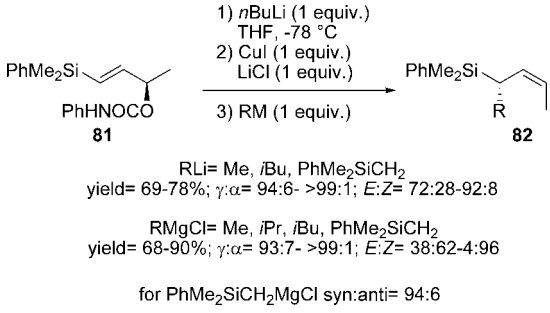
**Scheme 22. Synthesis of Quaternary Carbon Centers by Anti Selective $S_N2'$-Substitution Using a Menthol-Derived Auxiliary**




**Scheme 23. Synthesis of Quaternary Carbon Centers by Anti Selective $S_N2'$-Substitution**




**Scheme 24. Synthesis of $S_N2'$-Substitution Products with *Z*-Alkene Geometry**




Woerpel and co-workers[78] introduced a method for the preparation of $S_N2'$-products with *Z*-alkene geometry using the combination of allylic carbamates and Grignard reagents (Scheme 24).

As reported before,[79] allylic carbamates in combination with Li cuprates give the *E*-alkene $S_N2'$-products. A possible explanation for the formation of the *Z*-alkene using Grignard reagents is the subsequent formation of two intermediates (Scheme 25). The first intermediate **83** is formed using either Li or Mg cuprates. For Li reagents reductive elimination from this intermediate would give the products with *E*-alkene geometry. In view of the lower reactivity of Mg cuprates, the second intermediate **85** is formed exclusively using Grignard reagents. Anti elimination from **85** then gives the product with *Z*-alkene geometry.

Efficient syn-selective DAA[80] was developed by Breit and co-workers.[81] The directing *o*-diphenylphosphanylbenzoyl (*o*-DPPB) group was employed to create tertiary and quaternary carbon centers for several cyclic (Table 18) and acyclic substrates (Table 19) with excellent selectivities.

To obtain high levels of selectivity a minimum amount of 0.2 equiv of Cu-source is necessary (entry 2). For *E*- or *Z*-alkene geometry of the substrate opposite enantiomers of the product are obtained (entry 1 vs entry 3). Limitations for the formation of quaternary centers using this methodology are the use of *t*-Bu (entry 12) and allyl Grignard reagents. The syn-directing properties of the *o*-DPPB group are proposed to originate from phosphane coordination of the organocopper reagent. Interestingly, by oxidation of the *o*-DPPB group the syn-directing properties of the auxiliary could be switched off. This allows for anti-addition with respect to the leaving group with high regio- and diastereoselectivity (Table 20). In this way one has access to both enantiomers of the AAA product using the same enantiomer of the substrate.

In another study by Breit, Mann and co-workers[82] the directing properties of the *o*-DPPB group were further exploited for the synthesis of chiral $\beta$-branched α-amino acids (Scheme 26).

Furthermore, Hoveyda and co-workers[83] developed a heteroatom-assisted anti-selective $S_N2'$-substitution (Scheme 27). Interestingly, no copper catalysis is required.

When the alkoxy group ($OR^1$ in **96**) is replaced by an alkyl substituent or is protected as TBS ether, no reaction is observed. Thus, the heteroatom in the side chain of the substrate is required for DAA. The requirement for coordination of the Grignard reagent to the alkoxy group is further illustrated by the low conversion obtained when the intramolecular chelating Grignard reagent **100** is used. To explain the control of diastereoselectivity three possible models involving heteroatom binding to the metal were proposed (Figure 10).

### 3.1.2. DAA Employing Chiral Auxiliaries

Compared to the extensive use of auxiliaries in DCA, only a few auxiliary-based approaches[84] have been reported for DAA. The small number of successful auxiliary-based methods can be explained by the higher conformational freedom of the auxiliary when bound to the substrate (alkoxy for DAA vs ester for DCA) and the rapid development of catalytic methods for AA. After 1995 two methods featuring chiral auxiliaries were reported.

Caló and co-workers[85] uses a chiral sulfide leaving group to allow for $S_N2'$-substitution of bulky Grignard reagents (up to 98% ee, Scheme 28).

Furthermore, Breit and co-workers[86] used the *o*-diphenylphosphanylferrocene carboxylate (*o*-DPPF) auxiliary to allow addition of several Grignard reagents (up to 95% ee, Scheme 29).

**Scheme 25. Explanation for the Formation of the $S_N2'$-Substitution Products with *Z*-Alkene Geometry**

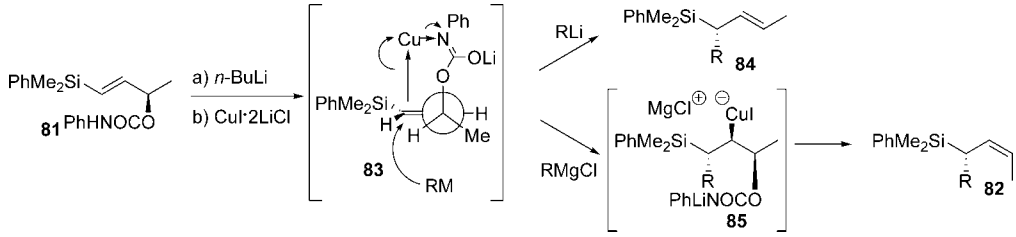
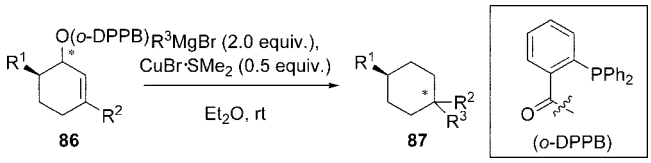



**Table 18. Syn-Selective DAA to Cyclic Substrates Using the *o*-DPPB Auxiliary**




| entry | $R^1$ | $R^2$ | $R^3$ | **86** (*R*)/(*S*) | yield (%) | $S_N2'/S_N2$ | CT[a] (%) |
|---|---|---|---|---|---|---|---|
| 1 | *i*-Pr | H | Me[b] | *S* | 85 (*S*) | | 100 |
| 2 | *i*-Pr | H | Me[b] | *R* | 86 (*R*) | | 100 |
| 3 | H | Et | Me | *S* | >95[c] (*S*) | 99:1 | 99 |
| 4 | H | Et | *n*-Bu | *S* | >95[c] (*R*) | >99:1 | 99 |
| 5 | H | Et | *i*-Pr | *S* | >95[c] (*S*) | 98:2 | 99 |
| 6 | H | Et | Ph | *S* | >95[c] (*R*) | 40:60 | 95 |

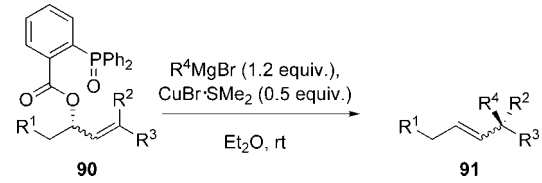
[a] Chirality transfer = [ee product/ee substrate] × 100%. [b] MeMgI was used. [c] Yield determined by GC.

### 3.1.3. Conclusions and Perspective

The synthesis of chiral synthons via anti-selective $S_N2'$-substitution with Grignard reagents is well established. However, the necessity to work with chiral starting materials is an obvious drawback. The newly developed "switchable" syn-directing *o*-DPPB auxiliary introduced by Breit and co-workers is a significant improvement in this respect. Using this auxiliary, in combination with the anti-directing oxidized analogue, synthesis of a single stereoisomer of a substrate is required to allow access to both enantiomers of the AA products. Furthermore, the recently developed methods to obtain quaternary carbon centers are of eminent synthetic value as current catalytic methods for AA do not provide access to quaternary centers.

Finally, the use of chiral auxiliaries for DAA is quite limited. In view of the rapid development of catalytic methods for AA, that can easily compete with any chiral auxiliary-based method, it is not to be expected that extensive research will be devoted to the development of new chiral auxiliaries.

**Table 20. Anti-Selective DAA to Acyclic Substrates Using the Oxidized *o*-DPPB Auxiliary**




| entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | yield (%) | $S_N2'/S_N2$ | *E*:*Z* **91** | CT[a] (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | Me | H | Me | *n*-Bu | 92 | 94:6 | >99:1 | 100 |
| 2 | Me | H | Me | *t*-Bu | 68 | 75:25 | >99:1 | 76 |
| 3 | Me | H | Me | Ph | 86 | 93:7 | >99:1 | 97 |
| 4[c] | OTBDMS | Me | $CO_2Et$ | Et | 85 | >99:1 | >99:1 | 100 |
| 5[c] | OTBDMS | Me | $CO_2Et$ | *i*-Pr | 94 | 97:3 | >95:5 | 100 |
| 6[c] | OTBDMS | Me | $CO_2Et$ | *n*-Bu | 87 | >98:2 | >98:2 | 100 |

[a] Chirality transfer = [ee product/ee substrate]x 100%. [c] Enantiomer of **90** was used, and enantiomer of **91** was obtained.

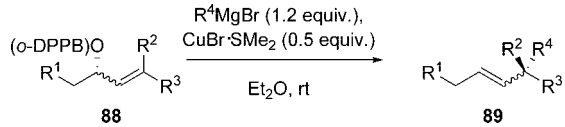
## 3.2. Enantioselective Allylic Alkylation (EAA)

The major part of the AA part of this review is concerned with enantioselective allylic alkylation reactions of Grignard reagents using catalytic amounts of chiral Cu-complexes.

### 3.2.1. Cu-Catalyzed EAA

The development of highly enantioselective transition metal-catalyzed allylic alkylation reactions has enjoyed widespread attention over recent decades.[3,4,7,13] These powerful reactions provide access to optically active building

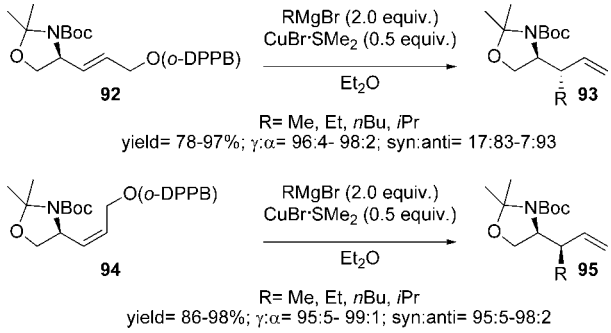
**Table 19. Syn-Selective DAA to Acyclic Substrates Using the *o*-DPPB Auxiliary**



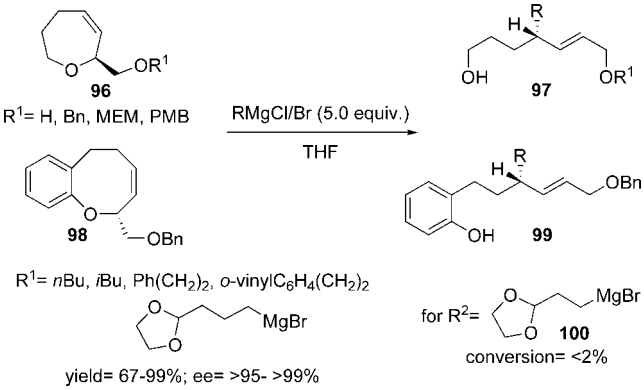

| entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | *E*/*Z* **88** | yield (%) | $S_N2'/S_N2$ | *E*:*Z* **89** | CT[a] (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Me | H | Ph | Me | *E* | 92 | >99:1 | >98:2 | 100 |
| 2[b] | Me | H | Ph | Me | *E* | 85 | 96:4 | 95:5 | 100 |
| 3 | Me | H | Ph | Me | *Z* | 92 | 99:1 | >98:2 | 96 |
| 4 | Me | H | Me | *n*-Bu | *E* | 96 | 98:2 | >99:1 | 99 |
| 5 | Me | H | Me | 3-pentyl | *E* | 90 | 97:3 | >99:1 | 99 |
| 6 | Me | H | Me | *t*-Bu | *E* | 96 | 97:3 | >99:1 | 82 |
| 7 | Me | H | Me | Ph | *E* | 94 | 98:2 | >99:1 | 97 |
| 8 | Me | H | Me | homoallyl | *E* | 80 | 95:5 | >99:1 | 97 |
| 9[c] | OTBDMS | Me | $CH_2OPMB$ | Et | *E* | 86 | >99:1 | >99:1 | 100 |
| 10[c] | OTBDMS | Me | $CH_2OPMB$ | *i*-Pr | *E* | 89 | >99:1 | >99:1 | 100 |
| 11[c] | OTBDMS | Me | $CH_2OPMB$ | *t*-Bu | *E* | 53 | >99:1 | >99:1 | 100 |
| 12[c] | OTBDMS | Me | $CH_2OPMB$ | Bn | *E* | 90 | 14:86 | 80:20 | 91 |

[a] Chirality transfer = [ee product/ee substrate] × 100. [b] 0.2 equiv of $CuBr \cdot SMe_2$ was used. [c] Enantiomer of **88** was used, and the enantiomer of **89** was obtained.

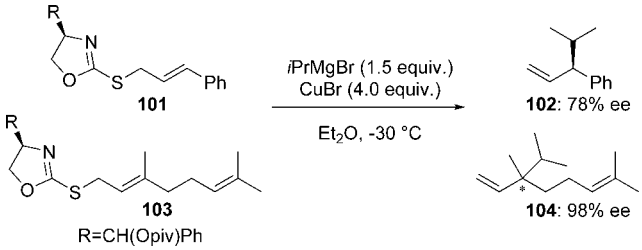
**Scheme 26. Synthesis of Chiral β-Branched α-Amino Acids by $S_N2'$-Substitution**



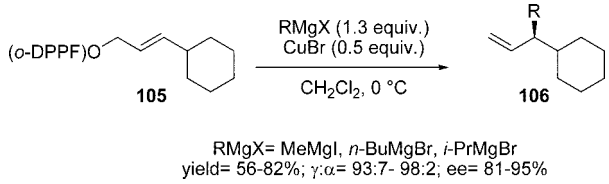

**Scheme 27. Heteroatom Copper-Free Anti-Selective $S_N2'$-Substitution**




**Scheme 28. DAA Using a Chiral Sulphide Leaving Group**




**Scheme 29. DAA Using a Chiral *o*-DPPF Leaving Group**




blocks employed frequently in the synthesis of complex natural products and molecules of pharmaceutical interest. In addition to the well-established allylic alkylation using soft-carbon nucleophiles, in recent years methods based on the use of enolates and hard organometallic based carbon nucleophiles have emerged.[4]

The first breakthrough in Cu-catalyzed asymmetric allylic alkylation reactions with Grignard reagents was reported in 1995 by Bäckvall, van Koten and co-workers.[87] The addition

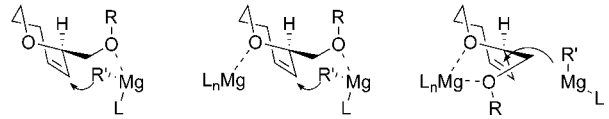
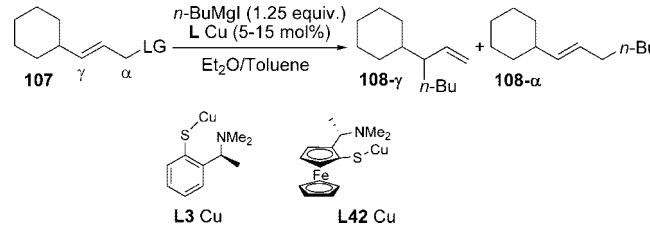


**Figure 10.** Three possible methods for heteroatom coordination.

**Table 21. Cu-Catalyzed AAA of *n*-BuMgI to 107 Using L3/Cu or L42/Cu**




| entry | LG | L | yield (%) | γ:α | e (%) |
|---|---|---|---|---|---|
| 1 | OAc | **L3** | 100 | 100:0 | 42 |
| 2 | OCO(*t*-Bu) | **L3** | 100 | 100:0 | 25 |
| 3 | $OPO(OEt)_2$ | **L3** | 100 | 92:8 | 10 |
| 4 | $OCOCF_3$ | **L3** | 81 | 90:10 | 9 |
| 5[a] | OAc | **L42** | 88 | 98:2 | 64 |

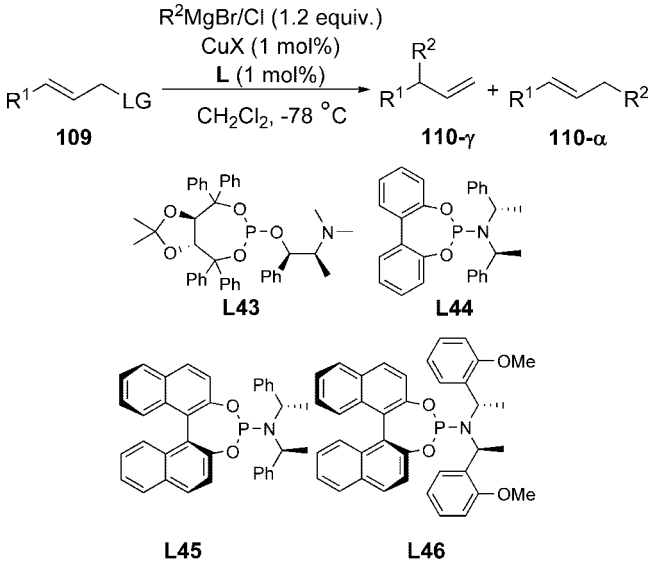
[a] 1.5 equiv of *n*-BuMgI was used.

of *n*-BuMgI to substrate **107** in the presence of a catalytic amount (14 mol %) of an arenethiolato-Cu species (**L3**/Cu) provided the branched product **108**-γ in quantitative yield with excellent regioselectivity and moderate enantioselectivity (42%, Table 21, entry 1). As with the ACA reaction, the AAA reaction proved to be sensitive to changes in temperature, order of addition of the reagent, solvent, ligand/metal ratio and the coordinating abilities of the leaving group in terms of both regio- and enantioselectivity (entries 2−4). Subsequently, these results were improved upon using a ferrocene thiolato-Cu (**L42**/Cu) catalyst providing **108**-γ in good yield, excellent regioselectivity and 64% ee (entry 5).[88,89] Extensive structural modification of the ferrocenyl moiety in **L42**/Cu has thus far proven to be unsuccessful in increasing the enantioselectivity of the reaction.[90] Subsequent studies focused initially on the use of $R_2Zn$ reagents for AAA. High enantioselectivity was achieved with several acyclic substrates and dialkylzinc reagents.[91]

Alexakis et al.[92] have tested different ligand classes including phosphites and phosphoramidites to address the selectivity issues impeding the development of the Cu-catalyzed AAA of Grignard reagents. Phosphite ligand **L43**, CuCN and EtMgCl at −78 °C in $CH_2Cl_2$ provided quantitative conversion of substrate **109** to **110**-γ with excellent regioselectivity albeit in racemic form (Table 22, entry 1). Further studies showed that for $R^1$ = Ph and LG = Cl, the AAA could proceed in high yield and high regio- and good enantioselectivity (94% yield, 94:6 regioselectivity, 73% ee, entry 2). The enantioselectivity could be improved further by using CuTC (Cu(I)-thiophene-2-carboxylate) instead of CuCN, providing AAA products with enantioselectivity of up to 82% (entry 3). The complex formed from ligand **L43** and CuTC proved to be an effective catalyst for $S_N2'$-substitution with several linear and secondary Grignard reagents with typically ∼50% enantioselectivity. Further studies[93] revealed that **L44** performed better than **L43** when secondary Grignard reagents were used (entry 6 vs 5), and branched products were obtained in high yields and enantioselectivity. The highest selectivity was obtained using the phosphoramidite ligand **L45** (entry 7).

The observation that phosphoramidite/Cu-complexes catalyzed AAA with high levels of regio- and enantioselectivity prompted an in-depth investigation of this class of ligands. Alexakis and co-workers reported[94,95] that with **L46** a selective Cu-catalyzed AAA reaction occurs with an enan-

**Table 22. Cu-Catalyzed AAA with Phosphite and Phosphoramidite Ligands**



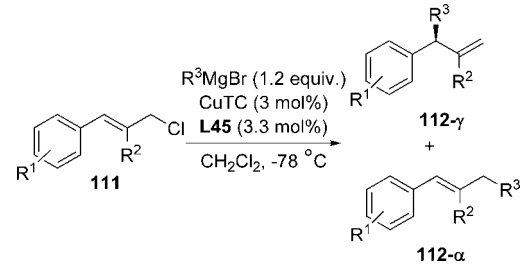

| entry | $R^1$ | LG | $R^2$ | X | L | yield (%) | γ:α | ee (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | *c*-hexyl | OAc | Et | CN | **L43** | 100 | 100:0 | 0 |
| 2 | Ph | Cl | Et | CN | **L43** | 94 | 94:6 | 73 |
| 3 | Ph | Cl | Et | TC | **L43** | 97 | 94:6 | 82 |
| 4 | *p*-$MeOC_6H_4$ | Cl | *i*-Pr | TC | **L44** | 98 | 91:9 | 86 |
| 5 | *c*-hexyl | Cl | *i*-Pr | TC | **L43** | 100[a] | 83:17 | 13 |
| 6 | *c*-hexyl | Cl | *i*-Pr | TC | **L44** | 95 | 99:1 | 68 |
| 7 | *c*-hexyl | Cl | *i*-Pr | TC | **L45** | 100[a] | 99:1 | 74 |
| 8 | Ph | Cl | Et | TC | **L46** | 86[a] | 99:1 | 96 |
| 9 | Ph | Cl | 4-pentenyl | TC | **L46** | 81[a] | 91:9 | 96 |
| 10 | *c*-hexyl | Cl | Et | TC | **L46** | 82[a] | >99:1 | 91 |
| 11 | Ph | Cl | Me | Br | **L46** | 100[a] | 89:11 | 96 |

[a] Conversion.

tioselectivity as high as 96% when the substrate cinnamyl chloride is used (entries 8 and 9). A range of linear Grignard reagents could be used with excellent regio- and enantioselectivity. Cyclic aliphatic substrates were converted to the desired branched products with only a slight decrease in enantioselectivity (entry 10). Substitution with MeMgBr remained problematic as experienced for the ECA reaction. Although MeMgBr substitution products were obtained generally with excellent enantioselectivity, the regioselectivity in all cases was moderate. Slow addition of MeMgBr over the course of several hours served to increase the regioselectivity typically from 40/60 to 85/15 ratios in favor of the optically active branched products (γ:α 89:11, entry 11) for aromatic substrates bearing electron-withdrawing and -donating substituents.[96] It was proposed that this experimental protocol avoids the formation of Gilman-type cuprates that may lead to a loss of selectivity.[97] The scope of the reaction was extended to β-disubstituted allylic halide substrates[98] (Table 23). A series of biphenol- and binaphthol-based phosphoramidite ligand/Cu-complexes were tested in the AAA to β-methylcinnamyl chloride with slow addition of EtMgBr. The products were formed with varying γ:α ratios and a high enantiomeric excess (up to 98% ee, entry 1) was obtained with **L45**/CuTC. Other Grignard reagents provided the branched products with equally good results (entries 2−4).

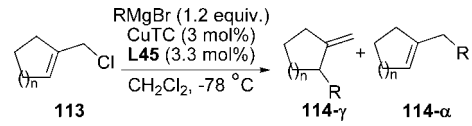
Electron-donating and -withdrawing substituents on the aromatic ring were tolerated, providing the products in good yield, γ:α ratio and enantioselectivity (entries 5, 6). For $R^2$ = Et, the reaction proceeded as for the methyl-substituted substrate (entry 7). For another class of β-disubstituted allylic

**Table 23. Cu-Catalyzed AAA of β-Disubstituted Allylic Chlorides**




| entry | $R^1$ | $R^2$ | $R^3$ | yield(%) | γ:α | ee (%) |
|---|---|---|---|---|---|---|
| 1 | H | Me | Et | 87 | 92:8 | 98 |
| 2 | H | Me | *n*-pentyl | 83 | 83:17 | 96 |
| 3 | H | Me | homoallyl | 84 | 89:11 | 97 |
| 4 | H | Me | 4-pentenyl | 87 | 87:13 | 96 |
| 5 | *p*-Cl | Me | Et | 87 | 92:8 | 96 |
| 6 | *p*-Me | Me | Et | 85 | 84:16 | 96 |
| 7 | H | Et | Et | 83 | 83:17 | 92 |

**Table 24. Cu-Catalyzed AAA of Cyclic β-Disubstituted Allylic Chlorides**




| entry | *n* | R | yield (%) | γ:α | ee (%) |
|---|---|---|---|---|---|
| 1 | 1 | *n*-hexyl | 91 | 92:8 | 98 |
| 2 | 1 | $CH_2Bn$ | 99[a] | 97:3 | 98 |
| 3 | 1 | $(CH_2)_4O$-*t*-Bu | 60 | 98:2 | 98 |
| 4 | 2 | *n*-hexyl | 83 | 97:3 | 98 |
| 5 | 2 | homoallyl | 67 | 97:3 | 99 |
| 6 | 2 | $CH_2Bn$ | 78 | 85:15 | 99 |

[a] Conversion.

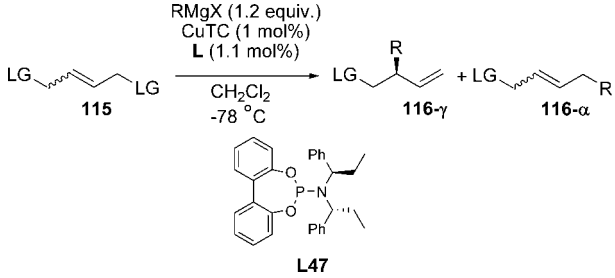
substrates, the aliphatic endocyclic allylic chlorides, the addition of a range of Grignard reagents with 3 mol % of the Cu catalyst proceeded selectively toward γ substitution and delivered products in excellent enantiomeric excess (up to 99%). For the five-membered ring substrate **113**, the enantiomeric excess (98%) obtained was not depending on the organomagnesium reagent used (Table 24, entries 1−3).

Six-membered ring allylic chlorides were converted with equally good γ:α ratios and enantioselectivity (entries 4−6). The selectivity obtained for six-membered ring allylic chlorides was the highest using substrate **113** and homallylMgBr (entry 5).

Simple difunctionalized substrates used in this transformation offer considerable versatility toward further synthetic applications.[99] In particular the 1,4-*bis*-halo-2-butenes **115** provide valuable synthetic intermediates after allylic alkylation. *E*- and *Z*-isomers of 1,4-*bis*-halo-2-butene **115** were examined in the asymmetric allylic substitution with *c*-hexylMgCl catalyzed by a biphenol- or binaphthol-based phosphoramidite/CuTC-complex. The combination of *E*-1,4-*bis*-halo-2-butene and CuTC/**L47** (3 mol %) provided **116**-γ in good yield, full regioselectivity and 77% ee (Table 25, entry 1).

Allylic alkylation of *Z*-**115** generally provided products in significantly lower ee compared to *E*-**115** (entry 2 vs 3). Several primary Grignard reagents could be used providing good enantioselectivity of up to 85% ee (entries 4−6) in the allylic substitution of substrate **115** with **L45** or **L46**. Allylic substitutions performed on *E*-dibromo substrates gave similar or better results in terms of enantioselectivity than the

**Table 25. Cu-Catalyzed AAA of 1,4-Bishalo-2-butenes**




| entry | 83 | LG | R | X | L | yield (%)[a] | ee (%) |
|---|---|---|---|---|---|---|---|
| 1 | *E* | Cl | *c*-hexyl | Cl | **L47**[b] | >99[c] | 77 |
| 2 | *E* | Cl | *c*-hexyl | Cl | **L45** | 98 | 75 |
| 3 | *Z* | Cl | *c*-hexyl | Cl | **L45** | 87[c] | 31 |
| 4 | *E* | Cl | $CH_2Bn$ | Br | **L45** | 98 | 78 |
| 5 | *E* | Cl | *n*-Bu | Br | **L46**[b] | 55 | 85 |
| 6 | *E* | Cl | $(CH_2)_4O$-*t*-Bu | Br | **L46** | 80 | 85 |
| 7 | *E* | Br | $(CH_2)_2CH{=}C(CH_3)_2$ | Br | **L46** | 70 | 94 |

[a] In all cases γ:α 100:0. [b] 3 mol % of catalyst was used. [c] Conversion.

dichloro-derivatives with phosphoramidite **L45** and **L46**. The highest selectivity was obtained using CuTC/**L46** (3 mol %) yielding **116-γ** in 70% yield and 94% ee (entry 7). When dialkylzinc reagents were employed in place of the Grignard reagents, products were obtained with moderate ee (typically 50%). The facile conversion of the remaining chloride or bromide functionalities, e.g. via the Finkelstein reaction with NaI, demonstrated the synthetic versatility of products obtained via this route.

The potential of providing useful chiral building blocks for complex molecule synthesis from the Cu-catalyzed AAA to linear substrates is evident from the results in Tables 22, 23 and 25. However, the conversion of simple linear aliphatic substrates to yield optically active acyclic building blocks was lacking until recently. Feringa and co-workers have employed the ACA catalyst derived from JosiPhos (**L30**)/ $CuBr{\cdot}SMe_2$ (*vide infra*) (5 mol %) as a catalyst in *t*-BuOMe for the AA of cinnamyl bromide **117** with MeMgBr, affording the corresponding products with good regio- and enantioselectivity (Scheme 30).[100]

When other Grignard reagents such as EtMgBr (Table 26, entry 1) or aliphatic allylic bromides were applied the regio- and enantioselectivity of the reactions were significantly lower. Only a moderate increase in the selectivity of these transformations was obtained through optimization of reaction conditions. With the related TaniaPhos **L25** ligand (6 mol%) and $CuBr{\cdot}SMe_2$ (5 mol%) the allylic alkylation of substrates **119** with EtMgBr in *t*-BuOMe provided only modest regioselectivity and an ee of 32% (entry 2). The selectivity was improved considerably using $CH_2Cl_2$ instead of *t*-BuOMe, providing the desired γ-substituted product in high yield, good regioselectivity and excellent enantioselectivity (92%, 81:19 and 95%, respectively, entry 3). Catalyst loadings could be reduced to 1 mol % without an affect on

**Scheme 30. Addition of MeMgBr to Cinnamyl Bromide 117**

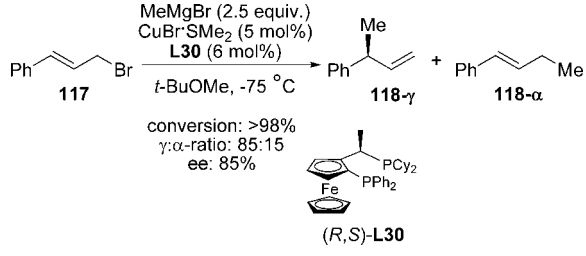
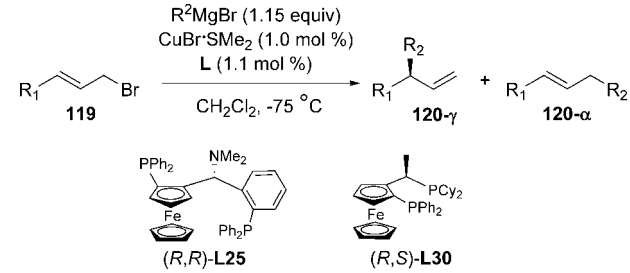



**Table 26. Cu-Catalyzed AAA with Ferrocenyl-Based Ligands**




| entry | $R^1$ | $R^2$ | L | yield (%) | γ:α | ee (%) |
|---|---|---|---|---|---|---|
| 1[a,b] | Ph | Et | **L30** | >98[c] | 38:62 | 56 |
| 2[a,b] | Ph | Et | **L25** | >98[c] | 31:69 | 32 |
| 3[a] | Ph | Et | **L25** | 92 | 81:19 | 95 |
| 4 | Ph | *n*-Bu | **L25** | 92 | 87:13 | 94 |
| 5 | Ph | homoallyl | **L25** | 93 | 91:9 | 95 |
| 6 | Ph | Me | **L25** | 91 | 97:3 | 98 |
| 7 | *p*-$ClC_6H_4$ | Me | **L25** | 95 | 99:1 | 97 |
| 8 | *p*-$CO_2MeC_6H_4$ | Me | **L25** | 94 | 98:2 | 97 |
| 9 | 1-naphthyl | Me | **L25** | 87 | >99:1 | 96 |
| 10 | *n*-Bu | Me | **L25** | 99 | >99:1 | 92 |
| 11 | *n*-Bu | Et | **L25** | 99 | >99:1 | 93 |
| 12 | $CH_2OBn$ | Me | **L25** | 94 | >99:1 | 92 |
| 13[a] | $CH_2OTBDPS$ | Me | **L25** | 72 | >95:5 | 94 |
| 14 | $CH_2N(Tos)Boc$ | Me | **L25** | 96 | >95:5 | 95 |

[a] 5 mol % catalyst. [b] Reaction in *t*-BuOMe. [c] Conversion.

the selectivity. Under these conditions a series of aryl-substituted allylic bromides were converted using EtMgBr with comparable selectivity. Furthermore, the allylic substitution of **119** could be performed with *n*-BuMgBr (entry 4) and unsaturated Grignard reagents (entry 5), providing the corresponding products with excellent enantioselectivity (up to 95% ee) and good regioselectivity (up to 91:9). Importantly, MeMgBr was used successfully as a nucleophile with almost complete control of regio- and enantioselectivity (entries 6−9).

The TaniaPhos-based catalyst proved particularly effective in the AAA to linear aliphatic allylic bromides affording almost exclusively γ-products with an enantioselectivity of up to 93% (entries 10 and 11). The synthetic applicability of Cu-catalyzed AAA reactions was enhanced further by performing this transformation on protected substrates containing oxygen or nitrogen groups.[101] In those cases products were obtained with high yields, near complete regioselectivity and in excellent enantioselectivity (entries 12−14). Several of these reactions were performed on a preparative scale (7.5 mmol) without loss of yield or regio- or enantioselectivity. The presence of a benzyloxy group is tolerated, and the substitution could be performed with a wide range of linear (Me, Et, *n*-Bu and *n*-pentyl) and functionalized (homoallyl and phenylethyl) Grignard reagents with equal efficiency. The bulky TBDPS protecting group was tolerated (entry 13) and in the case of MeMgBr led to even higher enantioselectivity (94%), albeit with slightly lower yields (72%) compared to benzyl-protected substrates. A doubly protected amine moiety is also compatible with this catalyst system (entry 14)

Feringa and co-workers have investigated AAA to functionalized substrates bearing heteroatoms at the γ-position instead of at the δ-position.[102,103] This reaction, the so-called *hetero*allylic asymmetric alkylation (*h*-AAA), is fundamentally different compared to other allylic substitutions reported in the literature[3,4] since the heteroatom is connected directly to the olefinic double bond (Figure 11).

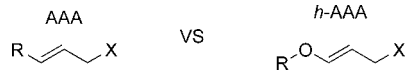
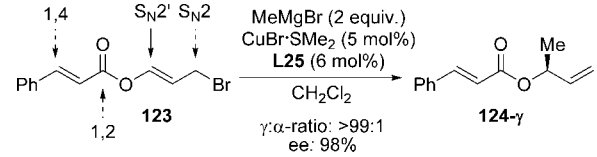



**Figure 11.** Asymmetric allylic alkylation (AAA) and *hetero*-allylic asymmetric allylic alkylation (*h*-AAA).

The catalyzed allylic alkylation of **121** ($R^1$ = Ph, $R^2$ = H) with MeMgBr provided the $\gamma$-product 1-buten-3-ol ester **122**-$\gamma$, the simplest of protected chiral allylic alcohols, in 85% yield, 98% ee (Table 27, entry 1) and with complete regioselectivity. Although, typically 5 mol % catalyst loading was employed, the catalyst loadings could be reduced to as low as 0.05 mol % without a decrease in either yield or regio- or stereoselectivity.

Surprisingly, the use of *t*-BuOMe as the solvent led largely (entry 2) to the formation of the undesired α-regioisomer at a relatively slow rate (36% conversion, 12 h). Furthermore, an intriguing example of a reversal in regioselectivity was observed when the reaction was carried out below −80 °C. Whereas at −74 °C the reaction provides exclusively the $\gamma$-product, at lower temperatures the undesired $S_N2$ product is formed in increasing amounts (entries 1, 3 and 4). Formation of both the $\gamma$- and α-substituted allylic esters appears to be Cu-catalyzed since in the absence of Cu neither of these products was formed. At higher temperatures the enantioselectivity was largely preserved (90% ee, −15 °C, entry 5). A range of Grignard reagents containing simple alkyl moieties, long alkyl chains and unsaturated alkyl groups were used successfully with excellent regio- and enantioselectivity (entries 6−9). However, the catalyst derived from CuBr·$Me_2$ and TaniaPhos (**L25**) did not provide $S_N2'$-substitution with $sp^2$-hybridized, secondary and bulky Grignard reagents. $\beta$-Substituted substrates provided predominantly **122**-α, but a combination of ligand **L45** with CuTC and slow addition of the Grignard reagent, presumably preventing the formation of Gilman-type cuprates, again resulted in high yield and high ee but with modest regioselectivity (entries 10 and 11). The excellent $\gamma$-selectivity of the catalyst system was illustrated with cinnamyl derivatives **123** which can undergo 1,4-addition, 1,2-addition, $S_N2'$ and $S_N2$ substitution (Scheme 31). This catalyzed conversion provided exclusively the $S_N2'$-products (i.e., **124**-$\gamma$), with excellent regio- and enantioselectivity (entries 12−13).

**Scheme 31. Possible Points of Addition/Substitution by MeMgBr on the Cinnamyl Derivative 123 and the Selectivity Observed**

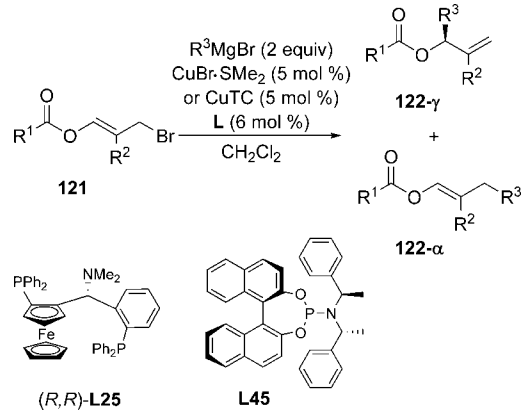



Recently Carousi and Hall reported[104] a method for the *h*-AAA reaction using 3-halopropenylboronates as substrates. The highest enantioselectivity was obtained using $CH_2Cl_2$ as the solvent with slow addition of EtMgBr as the nucleophilic reagent and with CuTC as the Cu source (Scheme 32).

The ligands **L46** or **L48** (5.5 mol%), CuTC (5.0 mol%) with 2,2-dimethylpropanediol boronate provided the $\gamma$-product with excellent selectivity. Carousi and Hall reported a dependency on the counterion. For instance, 3-bromopropenylboronates provided lower enantioselectivity and lower $S_N2'/S_N2$ ratios. Furthermore, a one-pot procedure was developed for the stereoselective aldehyde allylation based on the $\gamma$-product. This procedure yielded homoallylic alcohols with near perfect chirality transfer.

Okamoto and co-workers reported the AAA reactions of Grignard nucleophiles using catalysts derived from CuCl and

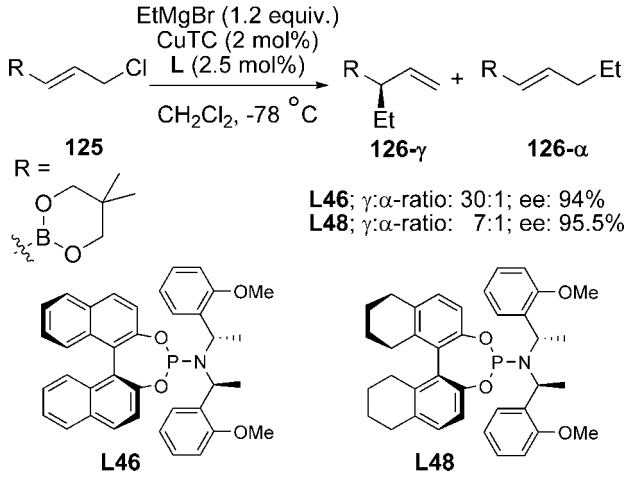
**Table 27. Cu-Catalyzed *h*-AAA with Grignard Nucleophiles**




| entry | $R^1$ | $R^2$ | $R^3$ | L | temp (°C) | yield (%) | γ:α | ee (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | Ph | H | Me | **L25** | −74 | 85 | 99:1 | 98 (+) |
| 2[a] | Ph | H | Me | **L25** | −73 | 36 | 8:92 | − |
| 3 | Ph | H | Me | **ent-L25** | −82 | 67 | 79:21 | 94 (−) |
| 4 | Ph | H | Me | **L25** | −85 | 76 | 37:63 | − |
| 5 | Ph | H | Me | **L25** | −15 | 76 | 99:1 | 90 (+) |
| 6 | Ph | H | Et | **L25** | −75 | 87 | >99:1 | 98 |
| 7 | Ph | H | homoallyl | **L25** | −75 | 96 | >99:1 | 97 |
| 8 | Ph | H | $CH_2Bn$ | **L25** | −75 | 93 | >99:1 | 93 |
| 9 | Ph | H | *n*-octadecyl | **L25** | −75 | 93 | >99:1 | >95 |
| 10 | Ph | Me | Et | **L45** | −75 | 97 | 2.5:1 | 97 |
| 11 | Ph | Me | *n*-pentyl | **L45** | −75 | 96 | 2:1 | 97 |
| 12 | styryl | H | Me | **L25** | −73 | 80 | >99:1 | 98 |
| 13 | styryl | H | Et | **L25** | −73 | 80 | >99:1 | 98 |

[a] Reaction in *t*-BuOMe.

**Scheme 32. Cu-Catalyzed *h*-AAA to Allylic Boronates**




C2-symmetric NHC ligands.[105,106] Treatment of 4-siloxy-2-buten-1-ol derivative **127** with *n*-hexylMgBr in the presence of Cu-complexes of chiral NHC ligands (**L49**, 5 mol%) in $Et_2O$ at 0 °C provided the $\gamma$-substituted $S_N2'$-products $\gamma$-**128** quantitatively, albeit with low to moderate enantiomeric excess (Table 28).

Catalysts with sterically demanding *N*-substituents gave the highest levels of asymmetric induction. Introduction of additional C2-chirality into the heterocyclic component of NHC resulted in an inversion or a decrease in the enantioselectivity obtained. Allylic acetates and 2-pyridyl ethers were appropriate leaving groups in the substrates suitable for this catalytic system (entries 1, 3 and 4), whereas carbamates (entry 2), carbonates and chlorides provided products with low ee. Inversion of product configuration was observed when *E*-allylic substrates were used instead of the *Z*-isomers.

## 4. Application of Catalytic ECA and EAA with Grignard Reagents in Synthesis

In this section tandem reactions leading to complex building blocks and the use of catalytic ECA and EAA methods employing Grignard reagents in total syntheses will be reviewed.

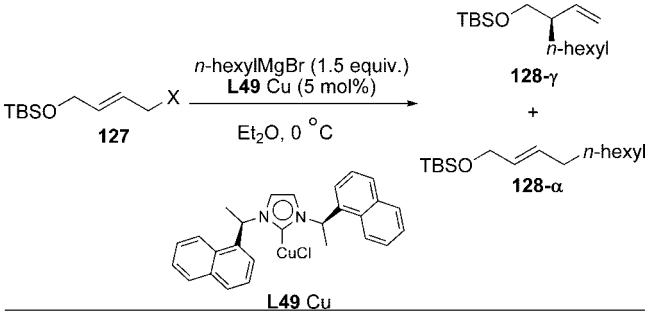
### 4.1. ECA-Aldol Reactions

Tandem reactions are attracting increasing interest in the chemical community because of their potential atom efficiency and their ability to increase structural diversity and stereochemical complexity rapidly in a stereocontrolled manner.[107] ECA-trapping reactions have been applied to the addition of zinc reagents with subsequent trapping of the zinc enolate.[6b,108] Since Mg-enolates show different levels of reactivity, ECA of Grignard reagents and subsequent reactions of the intermediate enolate with aldehydes provides an important alternative and provides access to new synthetic building blocks with multiple stereogenic centers.

Howell et al.[109] have reported a tandem protocol for the ACA of Grignard reagents to acyclic $\alpha,\beta$-unsaturated thioesters **129** followed by an aldol reaction with a range of aldehydes to provide $\beta$-hydroxyesters **131** with high enantioselectivity (up to 95%, Table 29, entries 1−8) and diastereoselectivity (>96%). The ACA of MeMgBr to the cinnamyl thioester was used primarily because of the relatively large difference in A-value of the phenyl and methyl groups. For ACA to substrates that incorporate substituents with a smaller difference in A-value (Me vs $CH_2$OTBDPS) a complete loss of diastereoselectivity was observed (entry 9).

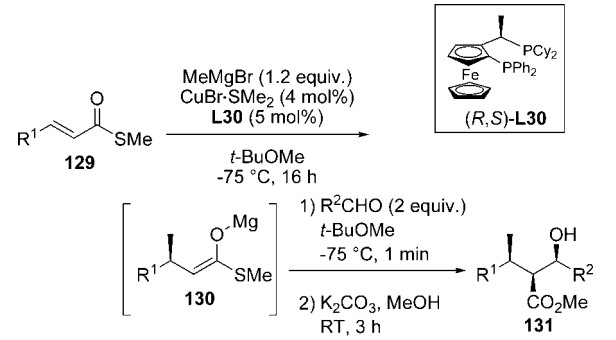
The configuration of the products can be rationalized using a Zimmerman−Traxler transition-state model in which the

**Table 28. Cu-Catalyzed AAA with Chiral NHC Ligands**




| entry | **127** | X | $\gamma$:$\alpha$ | ee (%) |
|---|---|---|---|---|
| 1 | *E* | OAc | 95:5 | 60 (*R*) |
| 2 | *E* | $OCONMe_2$ | 99:1 | 55 (*R*) |
| 3 | *E* | O-(2-pyridyl) | 98:2 | 70 (*R*) |
| 4 | *Z* | O-(2-pyridyl) | 86:14 | 60 (*S*) |

**Table 29. Tandem ACA-Aldol Reaction**




| entry | $R^1$ | $R^2$ | yield (%) | ee (%) | de (%) |
|---|---|---|---|---|---|
| 1 | Ph | Ph | 66 | 95 | >96 |
| 2 | Ph | *p*-$NO_2C_6H_4$ | 62 | 95 | >96 |
| 3 | Ph | *p*-$BrC_6H_4$ | 68 | 95 | >96 |
| 4 | Ph | *p*-$MeOC_6H_4$ | 54 | 95 | >96 |
| 5 | Ph | *n*-pentyl | 74 | 95 | >96 |
| 6 | Ph | *c*-hexyl | 76 | 95 | >96 |
| 7 | Ph | *t*-Bu | 73 | 95 | >96 |
| 8 | *p*-$ClC_6H_4$ | Ph | 49 | 99 | >96 |
| 9 | $CH_2$OTBDPS | Ph | 49 | 98 | ~0 |

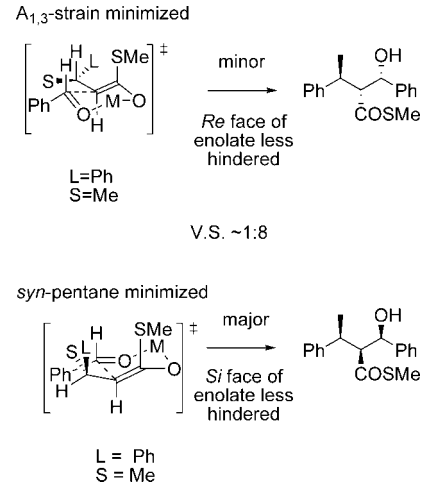
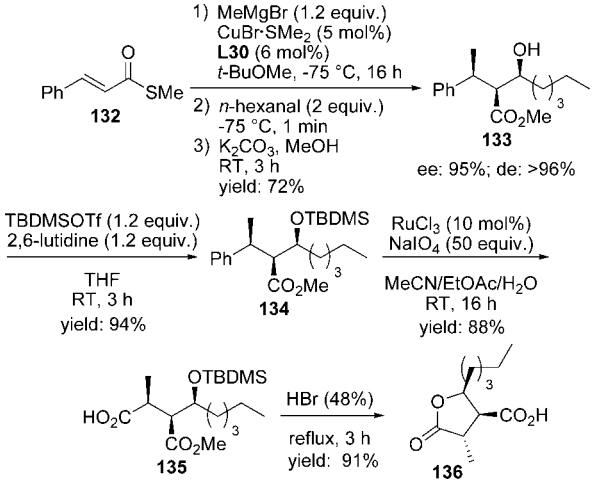
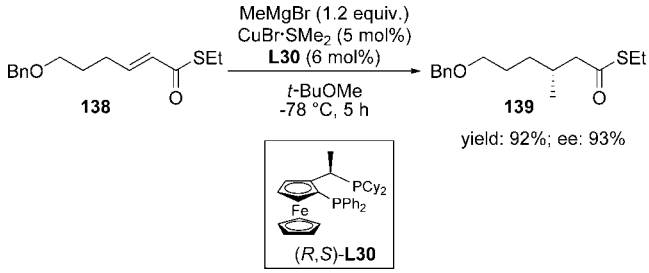



**Figure 12.** Transition-state models for anti,syn and syn,syn selectivity.

**Scheme 33. Total Synthesis of Phaseolinic Acid 136**




**Scheme 34. Cu-Catalyzed ACA to an Acyclic α,β-Unsaturated Thioester**




Z-enolate leads to all syn products as is found empirically (Figure 12). In this model minimization of the *syn*-pentane interactions in the enolate promotes *re*-facial attack, while minimization of the $A_{1,3}$-strain in the enolate would promote *si*-facial attack leading to the minor diastereoisomer.

The synthetic potential of this approach to tandem catalysis was illustrated through the total synthesis of phaseolinic acid (**136**), which was achieved in four steps (54% overall yield, 95% ee, >90% de, Scheme 33).

## 4.2. Natural Product Syntheses Featuring ECA

Effective methods to perform catalyzed ACA of Grignard reagents have become available only recently. Hence, it is unsurprising that they have not yet seen widespread application in total synthesis.

In the total synthesis of the all *syn*-β-D-mannosyl phosphomycoketide **137**[110] (Figure 13), a *Mycobacterium tuberculosis* antigen, the ACA was used to access one of the five stereocenters in 92% yield and 93% ee. This stereocenter was obtained by addition of MeMgBr to acyclic α,β-unsaturated thioester **138** using the Cu catalyst employing the (*R*,*S*)-JosiPhos **L30** ligand (Scheme 34).

The iterative protocol for the synthesis of all-*syn*-1,3-methyl arrays reported by ter Horst et al. was used in the total synthesis of (−)-lardolure **140**[50], mycocerosic acid **141**[55] and phthioceranic acid **142**[111] (Figure 14). The iterative protocol for deoxypropionates[26,112] features the catalytic

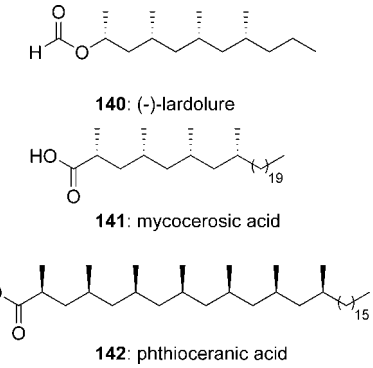
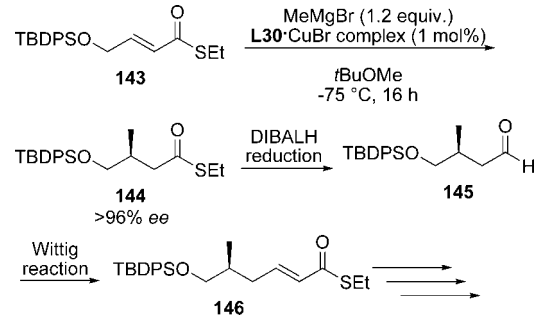



**Figure 14.** Lardolure, mycocerosic, and phthioceranic acids.

**Scheme 35. Iterative Protocol for the Synthesis of 1,3-Methyl Arrays Employing a Catalytic ACA as a Key Step**




ACA of MeMgBr to α,β-unsaturated thioesters, followed by DIBAL-H reduction of the thioester to an aldehyde and subsequent Wittig olefination to install the next α,β-unsaturated thioester moiety for a subsequent ACA (Scheme 35). The ACA is catalyzed by the preformed, recoverable Cu-complex of *R,S*-JosiPhos **L30** and CuBr·$SMe_2$. In the synthesis of mycoserosic acid four stereocenters are introduced. Each stereocenter is obtained with a stereoselectivity exceeding 96% ee. For phthioceranic acid **142** seven stereocenters are introduced via this iterative catalytic asymmetric protocol, and the selectivity for each stereocenter is again over 96% ee.

A sulfated alkene **147** (Figure 15) isolated from the Echinus *Temnopleurus hardwickii* was prepared using the 1,6-ACA.[62] This synthesis features a 1,6-ACA of a functionalized Grignard reagent to ethyl sorbate in moderate yield (34%) and high regio- (94%) and enantioselectivity (86%) using only 1.2 equiv of the Grignard reagent and a 2 mol % catalyst loading.[62]

## 4.3. Natural Product Syntheses Featuring EAA

Geurts et al. have reported a straightforward synthesis of the naturally occurring butenolide **150** (*S*)-5-ethyl-2(5H)-furanone via a simple two-step catalyzed route based on *h*-AAA reaction and subsequent ring-closing metathesis (Scheme 36).[102] Submission of the allylic bromide **148** to standard *h*-AAA conditions provided intermediate **149** in good yield and excellent enantioselectivity.

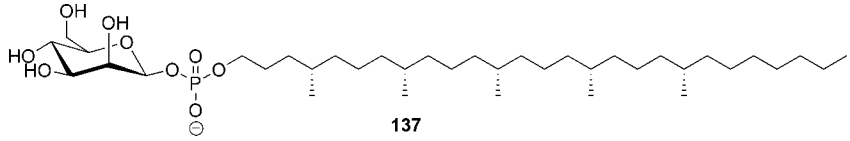



**Figure 13.** β-D-Mannosyl phosphomycoketide **137**.

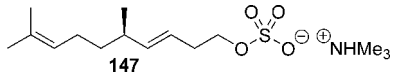
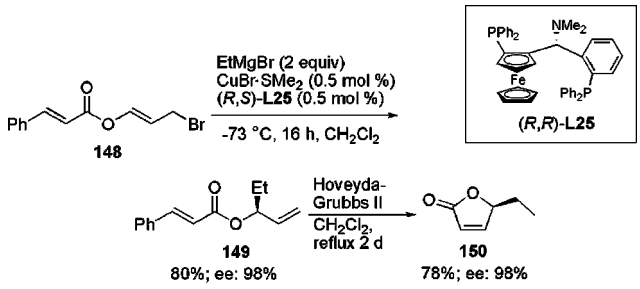
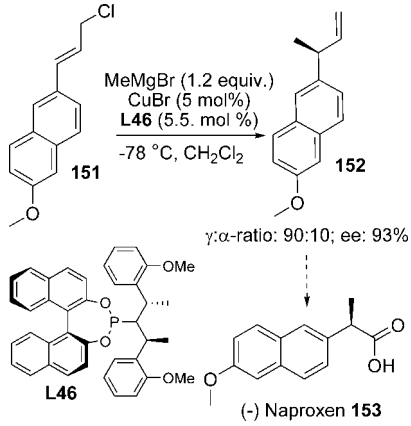



**Figure 15.** Sulfated alkene isolated from the Echinus *T. hardwickii*.

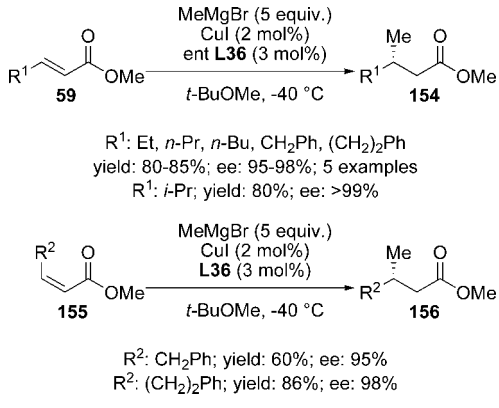
**Scheme 36. Synthesis of Butenolide 150 Employing Cu-Catalyzed *h*-AAA**




**Scheme 37. Formal Synthesis of (–)-Naproxen**




**Scheme 38. ECA of MeMgBr to α,β-Unsaturated Esters Catalyzed by Cu/Tol-BINAP (L36 or ent L36)-Complexes**




Ring-closing metathesis of **149** (78% yield, 98% ee) was accomplished at reflux with the Hoveyda−Grubbs II catalyst to produce butenolide **150**.

Recently, Alexakis et al.[96] described a formal synthesis of (−)-naproxen (**153**, Scheme 37), the enantiomer of the commercial nonsteroidal anti-inflammatory drug, based on their Cu/phosphoramidite-catalyzed AAA method.

The intermediate **152** was obtained from the naphthyl substrate **151** using 5 mol % catalyst loading and 1.2 equiv of MeMgBr at −78 °C in $CH_2Cl_2$ with good regioselectivity and excellent enantioselectivity. Oxidation of the double bond to the acid would yield (−)-naproxen **153** via a short and convenient route.

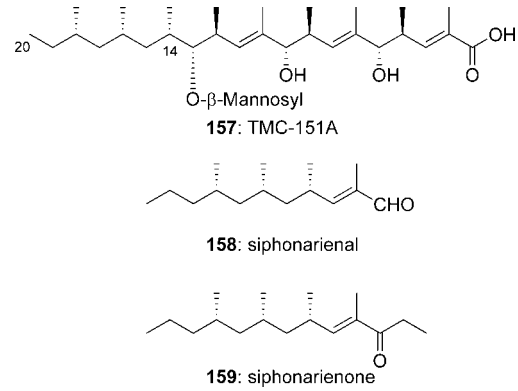



**Figure 16.** The C14−C20 fragment of antibiotic TMC-151A, siphonarienal and siphonarienone.

## 5. Conclusions and Perspective

Catalytic enantioselective C−C bond formation using highly reactive Grignard reagents has, indisputably, been one of the most challenging areas of asymmetric catalysis over the last few decades. Cu is the coinage metal of choice for asymmetric conjugate addition of Grignard reagents, which can be considered a distinct advantage compared to catalyzed C−C bond-forming reactions that rely on higher-value metal sources.

Tremendous progress and major breakthroughs have been realized over the past 4 years in enantioselective conjugate addition and allylic substitution using Grignard reagents in the presence of chiral Cu-complexes. With a wide range of substrates regio- and enantioselectivity exceeding 95% is now reached routinely, and as a consequence, these methods can be added, conveniently, to the toolbox of any practitioner of organic synthesis.

Particularly noteworthy are the addition of simple alkyl Grignard reagents (including the key reagent MeMgBr) to acyclic enones and thioesters with excellent levels of stereocontrol and the generation of quaternary centers via conjugate addition of Grignard reagents. An important extension to the burgeoning field of catalytic allylic alkylation is the possibility of using MeMgBr (and other alkyl Grignard reagents) as a hard carbon nucleophile to generate chiral allylic products that are considered highly versatile chiral synthons. Finally, the development of iterative catalytic protocols to generate acyclic structures with arrays of multiple stereocenters (in particular deoxypropionates), with full control of syn- and anti-stereochemistry governed by the chirality of the Cu-complex (catalyst control), offers tremendous opportunities in complex natural product synthesis as demonstrated in the emerging field of lipidomics.

However, several challenges remain, including catalytic asymmetric CA and AA using sterically demanding alkyl Grignard reagents as well as the use of aryl, alkenyl and alkynyl Grignard reagents. Another goal pertains to the application of functionalized Grignard reagents.[113] In facing the high reactivity of organomagnesium halides, it has been particularly rewarding to be able to tune the reactivity of the intermediate Cu-complexes through appropriate chiral ligands (diphosphines, carbenes), which has resulted ultimately in catalyst systems that can compete effectively with the uncatalyzed reaction of these organometallic reagents and the various alternative reaction pathways besides CA and AA. This holds great promise for the design of a related chiral catalyst that will ultimately tame the even more reactive organolithium reagents. Detailed mechanistic studies will guide the future interplay of noncoinage and coinage

metal species in new catalytic systems to reach the full potential of catalytic asymmetric C−C bond formation based on organometallic reagents.

## 6. Addendum

After completing the final version of this manuscript two important contributions in the field of ECA by Loh and coworkers[114]appeared. These authors reported[114a] the first addition of MeMgBr to α,β-unsaturated esters in high yields using Tol-BINAP (**L36**) and CuI. Instead of the temperature (−40 °C) previously employed to achieve ACA with the combination of this particular catalytic system and particular substrates,[53] elevated temperature (−20 °C) was used to obtain good yields and excellent enantioselectivities for a range of substrates (Scheme 38).

Furthermore, this methodology was employed for the synthesis of the C14−C20 fragment of antibiotic TMC-151A, siphonarienal and siphonarienone (Figure 16).[114b]

## 7. Acknowledgments

The excellent contributions of all past and current group members to our catalytic asymmetric synthesis program exploiting Grignard reagents is gratefully acknowledged. Their names are given in the references. We thank Dr. W. R. Browne and Dr. G. T. Carroll for critically reading the manuscript. This program was financially supported by The Netherlands Organization for Scientific Research (NWO-CW) and National Research School on Catalysis (NRSC-C)

## 8. Note Added in Proof

Very recently the original stereochemical assignment of the absolute configuration of Taniaphos **L25** and analogues **L27** and **L28** were corrected. The correct assignment for those ligands is $R,R_{Fc}$. For **L26** to our knowledge no correction has been reported. However, we assume that **L26** also should have the $R,R_{Fc}$ configuration. In this review the absolute configuration of Taniaphos and analogues has been depicted according to the revised assignment.

For **L25** and **L28** see: Ireland, T.; Grossheimann, G.; Wieser-Jeunesse, C.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 3666.

For **L27** see: Ireland, T.; Tappe, K.; Grossheimann, G.; Knochel, P. *Chem.–Eur. J.* **2008**, *14*, 3509.

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