Cu-Catalyzed Enantioselective Allylic Substitutions with Organomagnesium and Organoaluminum Reagents Promoted by N-Heterocyclic Carbenes for the Formation of Quaternary Stereogenic Centers

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Boston College
The Graduate School of Arts and Sciences
Department of Chemistry

Cu-CATALYZED ENANTIOSELECTIVE ALLYLIC SUBSTITUTIONS WITH ORGANOMAGNESIUM AND ORGANOALUMINUM REAGENTS PROMOTED BY N-HETEROCYCLIC CARBENES FOR THE FORMATION OF QUATERNARY STEREOGENIC CENTERS

A thesis

By

KYOKO MANDAI

Submitted in partial fulfillment of the requirements for the degree of Master of Science

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Cu-Catalyzed Enantioselective Allylic Substitutions with Organomagnesium and Organoaluminum Reagents Promoted by N-Heterocyclic Carbenes for the Formation of Quaternary Stereogenic Centers

Kyoko Mandai
Thesis Advisor: Professor Amir H. Hoveyda

Abstract

Chapter One: An overview of Cu-catalyzed enantioselective allylic substitutions with organometallic reagents.

Chapter Two: Development of Cu-catalyzed enantioselective allylic alkylations of allylic chlorides with Grignard reagents for the formation of all-carbon quaternary stereogenic centers is disclosed.

Chapter Three: Development of Cu-catalyzed enantioselective allylic substitutions of allylic phosphates with alkyl, aryl and heterocyclic aluminum reagents for the formation of quaternary stereogenic centers is discussed.
Acknowledgements

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Table of Contents

Chapter 1: Cu-Catalyzed Enantioselective Allylic Substitutions with Organometallic Reagents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-1 Introduction</td>
<td>1</td>
</tr>
<tr>
<td>1-2 Cu-Catalyzed Enantioselective Substitutions for the Formation of Quaternary Stereogenic Centers</td>
<td>5</td>
</tr>
<tr>
<td>1-3 Cu-Catalyzed Enantioselective Allylic Alkylations with Grignard Reagents</td>
<td>15</td>
</tr>
<tr>
<td>i) Thiolate-Based Chiral Ligands</td>
<td>15</td>
</tr>
<tr>
<td>ii) Phosphine-Based Chiral Ligands</td>
<td>17</td>
</tr>
<tr>
<td>iii) Ferrocenyld-Based Phosphine Ligand</td>
<td>20</td>
</tr>
<tr>
<td>iv) NHC-Based Chiral Ligand</td>
<td>21</td>
</tr>
<tr>
<td>1-4 Cu-Catalyzed Enantioselective Allylic Substitutions with Organoaluminum Reagents</td>
<td>23</td>
</tr>
<tr>
<td>1-5 Conclusions</td>
<td>26</td>
</tr>
</tbody>
</table>

Chapter 2: Development of Cu-Catalyzed Enantioselective Allylic Alkylations with Grignard Reagents for the Formation of All-Carbon Quaternary Stereogenic Centers

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-1 Project Perspective</td>
<td>27</td>
</tr>
<tr>
<td>2-2 Studies towards Cu-Catalyzed EAA Reactions with Secondary Alkyl Grignard Reagents</td>
<td>28</td>
</tr>
<tr>
<td>2-2-1 Preliminary Studies for Cu-Catalyzed EAA with i-PrMgCl</td>
<td>28</td>
</tr>
<tr>
<td>2-2-2 Cu-Catalyzed EAA of Me-, Et-, and n-Bu-Substituted Allylic Chlorides with i-PrMgCl, c-HexMgCl, and c-PentMgCl</td>
<td>30</td>
</tr>
</tbody>
</table>
Chapter 3: Development of Cu-Catalyzed Enantioselective Allylic Substitutions with Alkyl, Aryl, and Heterocyclic Aluminum Reagents for the Formation of Quaternary Stereogenic Centers

3-1 Project Perspective.................................................................70
3-2 Cu-Catalyzed EAA with Trialkylaluminum Reagents......................72
  3-2-1 Preliminary Studies with Et₃Al...........................................72
  3-2-2 Cu-Catalyzed EAA with (i-Bu)₃Al........................................80
3-3 n-Butyl Additions...................................................................81
3-4 Additions of Various Aryl Groups and Heterocycles with Readily Available Aluminum Reagents.........................................................83
  3-4-1 Initial Studies of the Reactions with R₂AlPh..........................85
    i) Examination of Alkyl Groups on R₂AlPh................................85
    ii) Ligand and Temperature Screening......................................86
    iii) Preparation of Et₂AlPh.....................................................91
3-4-2 Additions of Various Aryl Groups and Heterocycles .................. 96
   i) Aryl Additions ................................................................. 96
   ii) Additions of Heterocycles ............................................. 98

3-4-3 Cu-Catalyzed Allylic Substitutions of Various Allylic Phosphates .. 100
   i) Si-Substituted Allylic Phosphate ...................................... 100
   ii) Aryl-Substituted Allylic Phosphate ............................... 102

3-5 Conclusions ........................................................................ 103

3-6 Experimental ........................................................................ 104
Chapter One

Cu-Catalyzed Enantioselective Allylic Substitutions
with Organometallic Reagents

1-1 Introduction

Catalytic enantioselective allylic substitution reactions of activated olefins with organometallic reagents offer a versatile and effective method for enantioselective C-C bond formations in organic synthesis.\(^1\) For decades, many efforts have been extensively made to develop practical methods catalyzed by various late transition metals. Palladium-based complexes, one of most common catalyst systems, are often used with a stabilized, soft nucleophile such as a malonate. Complementary, copper-based complexes can promote allylic substitutions with nonstabilized, hard nucleophiles, such as alkylmetals, in the form of organomagnesium, zinc, and aluminum reagents.\(^2\)

\[
\begin{align*}
\text{R}_1 \begin{array}{c} \text{LG} \end{array} \overset{\text{chiral ligand}} \text{Cu} \overset{\text{alkylmetal}} \rightarrow & \text{R}_2 \begin{array}{c} \text{alkyl} \end{array} \begin{array}{c} \text{chiral S}_{\text{N}}2 \text{ product} \end{array} + \text{R}_2 \begin{array}{c} \text{alkyl} \end{array} \begin{array}{c} \text{achiral S}_{\text{N}}2 \text{ product} \end{array}
\end{align*}
\]

---


An allylic substitution of a carbon nucleophile can proceed through two pathways (see eq 1). Addition can occur either at the carbon bearing a leaving group by an S_N2 process or at the allylic position through an S_N2’ mode. A Cu-catalyzed reaction in the presence of a chiral ligand can afford the S_N2’ product enantioselectively. A mechanism of Cu-catalyzed enantioselective allylic alkylation (EAA) with Grignard reagents has been proposed by Bäckvall et al. (Figure 1).^3 The reaction begins with the formation of a π-complex B between an allylic substrate A and a Cu(I) cuprate. Coordination of cuprate is anti to the leaving group according to the report by Corey et al. (Figure 2).^4 An oxidative addition forms the Cu(III)-η¹ complex C. When ligand L is electron-withdrawing (e.g. CN or Cl), the reductive elimination step is facilitated to smoothly generate the S_N2’ product (path 1). The Cu(III) complex C can, however, isomerize to the Cu(III) π-allyl complex D. Subsequent reductive elimination of Cu(III)-η¹ complex E could deliver the S_N2 product (path 2). Effective enantioselective allylic substitution protocols need to address the regioselectivity of above mentioned S_N2’ and S_N2 products and enantioselectivity of the S_N2’ product. The obtained S_N2’ product contains a functionalizable terminal olefin. In addition to cross-coupling reactions, a terminal olefin can be derivatized to various units (Figure 3).^5 Hydroboration or ozonolysis followed by NaBH₄ reduction will provide products with primary alcohols bearing stereogenic centers (a or b). Ketones can be

---

Figure 1. Proposed Reaction Mechanism for Cu-Catalyzed EAA with Grignard Reagent

Figure 2. Allignment of Alkyl Cuprate and Allylic Substrate
introduced by Wacker oxidation (c). Additionally, Ru-catalyzed oxidation delivers carboxylic acid (d). The development of an efficient metal-catalyzed enantioselective allylic substitution requires a catalyst to be capable of furnishing an $S_{N}2'$ product selectively in high enantiomeric excess. We set out to develop an efficient and practical method for Cu-catalyzed allylic substitution for the preparation of compounds containing all carbon quaternary stereogenic centers with organomagnesium and organoaluminum reagents. The following section will account recent discoveries for the preparation of products bearing quaternary stereogenic centers obtained in Cu-catalyzed allylic substitutions. The disclosures of the substitution reaction with Grignard reagents and

\[ R_1^{+} \text{alkyl} \]

\[ OH \]

\[ R_2 \text{alkyl} \]

\[ \text{Hydroboration} \]

\[ 9-\text{BBN then NaOH, H}_2\text{O} \]

\[ \text{Ru-Catalyzed Oxidation} \]

\[ \text{RuCl}_3, \text{NaIO}_4, \text{MeCN/CCl}_4/\text{H}_2\text{O} \]

\[ \text{Ozonolysis/Reduction} \]

\[ 1. \text{O}_3 2. \text{NaBH}_4 \]

\[ R_1^{+} \text{alkyl} \]

\[ \text{Wacker Oxidation} \]

\[ \text{PdCl}_2, \text{CuCl}, \text{O}_2, \text{DMF/H}_2\text{O} \]

\[ R_1^{+} \text{alkyl} \]

\[ \text{Figure 3. Functionalizations of } S_{N}2' \text{ Product Bearing a Terminal Olefin} \]
organoaluminum reagents will be introduced.

1-2 Cu-Catalyzed Enantioselective Substitutions for the Formation of Quaternary Stereogenic Centers

Through Cu-catalyzed enantioselective allylic substitution, there are opportunities to synthesize tertiary or all-carbon quaternary stereogenic centers. Construction of sterically congested quaternary stereogenic centers in catalytic and enantioselective processes is of great importance in organic synthesis and the identification of efficient and practical methods is an ongoing effort. In recent years, efforts have concentrated in the development of effective and general chiral catalysts. Studies with respect to the construction of quaternary stereogenic centers through copper catalyzed enantioselective allylic substitution with organometallic nucleophiles, such as organozinc and organomagnesium reagents, will be discussed.

---

The first example for accessing quaternary stereogenic centers through Cu-catalyzed enantioselective allylic alkylation with dialkylzinc reagents has been developed in these laboratories. Chiral amino acid-based ligands were applied to EAA of Me-substituted cinnamyl phosphates under copper catalysis.\(^7\) The amino acid-based ligand can be readily prepared from commercially available materials in five steps. Due to its high modularity, the ligand was modified and optimized for the reaction system. The most efficient catalyst system was discovered through high throughput screening. As shown in Scheme 1, \(\sigma\text{-Oi-Pr}\) substituted pyridyl Shiff base 3 in the combination with

\[\text{Scheme 1. Cu-Catalyzed EAA of Aryl-Substituted Allylic Phosphates with Chiral Amino Acid-Based Ligands}\]

![Scheme 1. Cu-Catalyzed EAA of Aryl-Substituted Allylic Phosphates with Chiral Amino Acid-Based Ligands](image)

\[\text{Me} \quad \text{OP(O)(OEt)}_2 \quad \text{10 mol % CuCN} \quad \text{Me} \quad \text{OP(O)(OEt)}_2 \quad \text{10 mol % CuCN} \]

\[\begin{align*}
\text{3} & \quad \text{BH} \quad \text{2} \\
\text{3 eqv Et}_2\text{Zn} & \quad \text{THF, -78 °C, 24 h} & \quad \text{Me} & \quad \text{OP(O)(OEt)}_2 & \quad \text{10 mol % CuCN} & \quad \text{THF, -78 °C, 48 h} \\
\text{1. 10 mol % CuCN} & \quad \text{2. KOH, aq EtOH, 80 °C} & \quad \text{3 eqv } \left(\text{Me} \quad \text{OP(O)(OEt)}_2\right) & \quad \text{Zn} & \quad \text{Me} & \quad \text{OP(O)(OEt)}_2 & \quad \text{10 mol % CuCN} \\
\end{align*}\]

\(82\%\) overall (3 steps) \(82\%\) ee

CuCN catalyzed the addition of dialkylzinc reagents to trisubstituted allylic phosphate generating all-carbon quaternary stereogenic centers with high regio- (>98:<2 S<sub>N</sub>2':S<sub>N</sub>2) and enantioselectivities (78-90% ee). Notably, this method was highlighted in the synthesis of the fish deterrent, sporochnol (6, eq 3). The alkylation of 4 in the presence of ligand 5 followed by deprotection yielded sporochnol (6) in 82% ee and 82% overall yield.

Subsequently, our laboratory has discovered that chiral amino acid-based ligand derived from a salicyl aldehyde in combination with a Cu salt. Alkylations of di- and trisubstituted phosphates with dialkylzinc reagents are promoted with more efficiency (Scheme 2).<sup>8</sup> Allylic phosphate 1, bearing a phenyl group, undergoes highly regioselective in the presence of salicyl-based ligand 7 (92% ee for 2) than with pyridyl-based ligand 3 in eq 2 (78% ee for 2). Higher efficiency of ligand 7 in

**Scheme 2. Cu-Catalyzed EAA of Aryl, Alkenyl and Alkynyl Allylic Phosphates**

Cu-catalyzed EAA allows the reaction to be performed at an elevated reaction temperature (-15 °C with ligand 7 vs -78 °C with ligand 3). Cu-catalyzed EAA with pyridyl-based ligand 3 had been somewhat limited to aromatic substrates; the alkylation of aliphatic phosphates, however, can be achieved in use of salicyl derived ligands. Enantioselective formation of quaternary stereogenic centers in diene 8 and enyne 9 occurs with enantioselectivities (82% ee and 91% ee, respectively) with high regiocontrol (>98:<2 \( \text{SN}_{2}:\text{SN}_{2} \)). A transition state model in this system was proposed (Figure 4). The initial formation of Cu(I)-ligand complex followed by the addition of the dialkylzinc reagent generates chiral Cu(I) cuprate complex. Association of chiral cuprate complex and the allylic phosphate forms the catalyst-substrate complex 10. The favored positioning of the substrate in the complex 10 is influenced by the interaction between the large and small substituents of the substrate and the ligand.

![Figure 4. Proposed Transition State Model](image-url)
These Cu-complexes with amino acid-based ligands could also be employed to form all-carbon quaternary stereogenic centers in the alkylations of $\alpha,\beta$-unsaturated esters bearing a trisubstituted olefins and $\gamma$-phosphates (Scheme 3). The generation of a quaternary stereogenic center adjacent to a carbonyl group is of particular synthetic utility and a number of approaches have been studied to provide solutions. Initial studies of Cu-catalyzed EAA of $\alpha,\beta$-unsaturated esters led us to identify dipeptide Schiff base 11 as

Scheme 3. Cu-Catalyzed EAA of Dialkylzinc Reagents to Unsaturated Esters with Amino Acid-Based Ligands

![Scheme 3 Diagram]

an optimal alternative to ligand 7 in Scheme 2. The reaction in the presence of ligand 11 and (CuOTf)$_2$·C$_6$H$_6$ proceeds with the highly regio- and enantioselective addition of a variety of alkyl groups including ethyl (12), long-chain alkyl groups (13 and 14), and sterically hindered isopropyl group (15) in up to >98:<2 $S_N2'$::$S_N2$ with up to 90% ee. Since allylic alkylation with Ph$_2$Zn resulted in <30% conversion after 24 h, due to lower nucleophilicity of the zinc reagent, an alternative approach to obtain phenyl-substituted all-carbon quaternary stereogenic centers was taken. In the presence of ligand 16, esters 17, and 18 containing phenyl groups were successfully delivered in up to 94% ee with >98:<2 $S_N2'$::$S_N2$. It is noteworthy that only 10 mol % of catalyst ((CuOTf)$_2$·C$_6$H$_6$) is enough to promote the EAA compared to the previous system (5 mol % Cu in Scheme 3 vs 10 mol % Cu in Scheme 2). The utility of this class of products was demonstrated by functionalization of 18 to provide amine 21 and biologically active 22 (Scheme 4).
Phenyl-substituted product 18, obtained in the enantioselective allylic alkylation, was converted to aldehyde 19. Aldehyde 19 is a key intermediate to β-amino acid 21 and aromatase inhibitor, aminogluthethimide 22 through unsaturated diester 20.

In addition to amino acid-based ligands, chiral N-heterocyclic carbenes (NHCs) have been developed as efficient ligands for enantioselective transformations including Cu-catalyzed enantioselective allylic alkylation. In 2004 and 2005, two classes of chiral NHC ligands were disclosed and employed in the Cu-catalyzed EAA of trisubstituted allylic phosphate 1 with dialkylzinc reagents.11 With reactions with NHC-based ligands,

**Scheme 5.** Comparison between Different Chiral Ligands in Cu-Catalyzed EAA with Dialkylzinc Reagent

the *in situ* generation of the active chiral catalyst from air-stable NHC-Ag complex and a Cu salt was found to be effective and selective. Scheme 5 summarizes the comparison between a amino acid-based ligand and NHC-based ligands in Cu-catalyzed EAA. The allylic alkylation is promoted in the presence of 2.5 mol % of dimeric binaphthyl-based NHC-Ag complex (CuOTf)$_2$·C$_6$H$_6$ (5 mol % NHC-Cu complex is present in the reaction) to afford the same levels of regio- and enantioselectivities (91% ee vs 92 % ee compared to amino acid-based ligand 7). Biphenoxy-based NHC-Ag complex affords the enantiomerically enriched olefin within 2 h with an increase in enantioselectivity (97% ee with 1 mol % dimeric NHC-Ag complex and 2 mol % of air-stable, commercially available and unpurified CuCl$_2$·2H$_2$O). We are able to isolate air-stable NHC-Cu complex through the reaction of NHC-Ag complex and a Cu salt. As

**Scheme 6.** Comparison between *in situ* Generated and Preformed NHC-Cu Complexes

\[
\begin{align*}
\text{Me} & \quad \text{PO(OEt)}_2 \\
1 & \quad \text{NHC-based catalyst} \\
& \quad 3 \text{ equiv (i-Pr)}_2\text{Zn} \\
& \quad \text{THF, -15 °C, 12 h} \\
& \quad 1 \text{ mol % NHC-Ag 24} \\
& \quad 2 \text{ mol % CuCl}_2\cdot2\text{H}_2\text{O} \\
& \quad >98\% \text{ conv} \\
& \quad >98:<2 \text{ } S_N^2::S_N^2 \\
& \quad 98\% \text{ ee} \\
25 & \quad \text{Me} \quad \text{i-Pr} \\
& \quad 1 \text{ mol % Cu} \\
& \quad \text{(CuOTf)}_2\cdot\text{C}_6\text{H}_6 \\
& \quad >98\% \text{ conv} \\
& \quad >98:<2 \text{ } S_N^2::S_N^2 \\
& \quad 97\% \text{ ee}
\end{align*}
\]
shown in Scheme 6, identical selectivities were observed in the allylic alkylation of 25 in the presence of isolated in situ-generated NHC-Cu complexes.

Subsequently, our laboratory reported an efficient method for the enantioselective synthesis of allyl silanes bearing a quaternary stereogenic center through a Cu-catalyzed allylic substitution in the presence of NHC-Cu complexes and alkyl- and arylzinc reagents.\textsuperscript{12} Aryl additions to Si-substituted allylic phosphate 27 are effectively promoted in the presence of sulfonate-based NHC-Ag complex 28\textsuperscript{13} and (CuOTf)\textsubscript{2}·C\textsubscript{6}H\textsubscript{6}; this is the first example of aryl addition through Cu-catalyzed enantioselective allylic substitution (Scheme 7). Aryl-substituted allyl silanes 29 and 30 were delivered with high regio- and enantioselectivities (>98:<2 S\textsubscript{N2}':S\textsubscript{N2}, 85 and 90% ee, respectively).

\textbf{Scheme 7.} Cu-Catalyzed Enantioselective Allylic Arylation of Vinyl Silanes with Diarylzinc Reagents


Only one example outside of our laboratory; a method for Cu-catalyzed EAA has been reported for the formation of products containing all-carbon quaternary stereogenic centers. In 2008, Hong and coworkers reported the allylic alkylation with Grignard reagents catalyzed by chiral monodentate NHC-Cu complexes.\textsuperscript{14} They used a chiral bisisoquinoline-based NHC-Cu complex \textit{33}, which is employed in alkylations of naphthyl-containing pivalate \textit{31} with ethylmagnesium bromide (eq 4). Notably, this is the first example of the use of Grignard reagent in generation of an all-carbon quaternary stereogenic center in Cu-catalyzed EAA. In EAA, the reaction of allylic pivalate \textit{31} performed at 0 °C results in \textit{32} obtained with good regioselectivity and moderate enantioselectivity (85:15 \textit{S}$_{N2}$:\textit{S}$_{N2}$ with 76% ee).

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

1-3 Cu-Catalyzed Enantioselective Allylic Alkylations with Grignard Reagents

Grignard reagents have been widely used as versatile carbon nucleophiles due to their ease of preparation, atom economy, and high reactivity. The first catalytic enantioselective allylic substitution reaction employed Grignard reagents. Since then, many efforts have been made towards development of Cu-catalyzed enantioselective allylic alkylations with Grignard reagents, along with chiral ligands.

i) Thiolate-Based Chiral Ligands

The arenethiolatocopper(I) complex 36 in Scheme 8 was used to promote the first example of Cu-catalyzed EAA by Bäckvall and van Koten et al. in 1995. Their contribution is significant since they found that the selectivity levels of the reaction are remarkably influenced by many factors: the coordination ability of the leaving groups, solvent, addition of the reagents, addition rate of the Grignard reagents, and temperature.

![Scheme 8. Chiral Arenethiolatocopper(I) and Ferrocenethiolatocopper(I)-Catalyzed EAA with Grignard Reagents](image-url)
The protocols are highly $S_N2'$ selective when $\text{Et}_2\text{O}$ was used (higher than 90:10 $S_N2'$:$S_N2$). Screening various leaving groups, such as acetate, pivalate, CF$_3$-substituted carbonate, and phosphate, led to an acetate providing to be optimal in terms of enantioselectivity. After optimization of the reaction conditions, the highest enantioselectivity is obtained under the reaction conditions shown in Scheme 8. The allylic alkylation of allylic acetate 34 in the presence of 14 mol % of copper complex 36 at 0 °C affords only $S_N2'$ $n$-Bu addition product 35 in 42% ee. It should be noted that the Grignard reagent and a solution of 34 need to be added separately to a solution of 36 at the same rate. The intermediate of the alkylation with arenethiolatocopper(I) complex 39 is shown in Figure 5. It is proposed that the coordination of carbonyl oxygen of the allylic acetate to the complex 36 through cationic magnesium iodide. When in situ-generated arenethiolatocopper(I) complex; from arenethiolatolithium 37 and copper iodide, is used, the enantioselectivity of the products does not change significantly (40% ee with $>98:<2$ $S_N2'$:$S_N2$). Improved enantioselectivity could be obtained by ferrocenethiolatocopper(I) complex derived from ferrocenethiolatolithium 38 and copper iodide (64% ee).  

![Figure 5. Proposed Intermediate 39 in Complex (36)-Catalyzed EAA of Allylic Acetate](image)

ii) Phosphine-Based Chiral Ligands

Parallel to above mentioned studies, Alexakis and coworkers developed an EAA of alkyl Grignard reagents catalyzed by phosphine-based ligands and a copper salt (Scheme 9).\(^\text{17}\) Cu-catalyzed allylic alkylation of cinnamyl chloride 40 with EtMgBr in the presence of ligand 42 and CuCN proceeded and resulted in ethylated product 41 in 96:4 \(S_N^2\):\(S_N^2\) with 73% ee. When the copper salt is changed to CuTC (copper thiophene 2-carboxylate), the enantioselectivity is increased to 82% ee. As Bäckvall and van Koten discussed, various parameters including solvent, leaving group, copper source and addition rate of the Grignard reagents can be tuned to achieve selectivity.\(^\text{15}\) The phosphoramidite ligand 43 in combination with CuTC did not promote the reaction with a increase in selectivity.

\[\text{Scheme 9. Cu-Catalyzed EAA with Phosphine-Based Ligands}\]

\[\text{Scheme 9. Cu-Catalyzed EAA with Phosphine-Based Ligands}\]

\[\text{Scheme 9. Cu-Catalyzed EAA with Phosphine-Based Ligands}\]

---

(91:9 $S_N2':S_N2$ with 79% ee). The alkylation in the presence of binaphthyl-phosphoramide ligand 44 and CuTC is significantly improved to give 41 in 99:1 $S_N2':S_N2$ with 96% ee. This new chiral phosphoramide ligand 44 was applied to synthesis of a precursor 46 of (+)-naproxen 47 known as nonsteroidal anti-inflammatory drug (Scheme 10). Methyl addition to allylic chloride 45, in the presence of ligand 44 and copper bromide, affords 46 in 90:10 $S_N2':S_N2$ with 93% ee.

Recently, phosphine-based chiral ligands were applied to the Cu-catalyzed EAA of vinyl boronic esters to synthesize enantiopure $\alpha$-substituted allyl boronates. Hall and coworkers fine-tuned the reaction conditions discovered by Alexakis and coworkers utilizing a catalytic amount of a phosphoramide ligand and CuTC. Slow addition of Grignard reagent over 4 h is required for optimal enantioselectivities. For example, reaction of boronic ester 48 with EtMgBr in the presence of 2.5 mol % chiral ligand 50 and 2 mol % CuTC in CH$_2$Cl$_2$ proceeds to afford 49 selectively (9:1 $S_N2':S_N2$ and 87% ee). The increased enantioselectivity was observed when ligand 51 was employed with

similar regiocontrol (7:1 S$_{N}2$' : S$_{N}2$ and 92% ee, Scheme 11). They also demonstrate that a chiral allylic boronate 52 reacts with benzaldehyde to form homoallylic alcohol 53 in 18:1 $E$:Z in 92% ee (eq 5).
iii) Ferrocenyl-Based Phosphine Ligand

The research group of Feringa has demonstrated that \((R,S)\)-taniaphos 54 to introduce high regio- and enantioselectivities for the addition of various Grignard reagents in CH\(_2\)Cl\(_2\) at -78 °C (Scheme 12).\(^5,19\) Aromatic and aliphatic allylic bromides are alkylated to afford 55 and 56 in up to 98:2 S\(_{2}N_2\)':S\(_{2}N_2\) with up to 98% ee. The synthesis of chiral allylic ester 57 (97:3 S\(_{2}N_2\)':S\(_{2}N_2\), 98% ee) was also attained in one step; it is noteworthy that allylic alkylation occurs faster than Grignard addition to the flanking ester. Furthermore, Cu-catalyzed EAA with Grignard reagents of allylic bromides was successfully accomplished to deliver products 58 and 59 containing a benzyl ether and a

![Scheme 12. Cu-Catalyzed EAA with Ferrocenyl-Based Phosphine Ligand](image)

\(^{19}\) (a) López, F.; van Zijl, A. W.; Minnaard, A. J.; Feringa, B. L. Chem. Commun. 2006, 409-411.
silyl ether, as well as compound 60 bearing a protected amine group with high selectivities (>95:<5 S<sub>2</sub>':S<sub>2</sub> and 92-95% ee). Most of the products were obtained in high yield (72-97%).

iv) NHC-Based Chiral Ligands

Okamoto and coworkers first introduced the use of NHC-Cu catalysts in EAA with alkyl Grignard regents. The optimal chiral NHC copper chloride complex 64 bears the stereogeneticity adjacent to the carbene (Scheme 13). It was found that a 2-pyridyloxy group serves as a better leaving group over a chloride or a carbonate (acetate is comparable to 2-pyridyloxy group). The best result in their report is an alkylation of Z-allylic ether ((Z)-61) with n-hexMgBr, in the presence of 1 mol % NHC-Cu complex 64, provides the S<sub>N</sub>2' product 62 in 98:2 S<sub>N</sub>2':S<sub>N</sub>2 with 70% ee. When the E-allylic ether

---

Scheme 13. Cu-Catalyzed EAA with NHC-Cu Complex

---

((E)-61) is used, the same conditions afford the opposite enantiomer 63 as the major product in moderate regio- and enantioselectivities (86:14 S_N2':S_N2 with 60% ee). Based on this observation, they postulated that the identity of the major active catalyst, as shown in Figure 6, could be an ate-complex (iii) generated via a NHC-Cu alkyl complex (ii). Both could be active but one faster. The transition state model is shown as 65. They proposed that the ate-complex (iii) would react with the substrate (allylic acetate in this case) through a seven-membered cyclic structure which consists of coordination between Cu and C-C double bond of the substrate and chelation between Cu, leaving group, and MgX cation.

\[ \text{Figure 6. Proposed Active Catalysts and Transition State Model} \]
1-4 Cu-Catalyzed Enantioselective Allylic Substitutions with Organoaluminum Reagents

There are several reports regarding Cu-catalyzed enantioselective allylic substitution with organoaluminum reagents. In 2000, the first attempt to utilize organoaluminum reagents as carbon nucleophiles was reported by Woodward and coworkers. Cu-catalyzed EAA of allylic chloride 66 with Et₃Al in the presence of ligand 68 and a Cu(I) salt delivers the product with 8% ee (12% conversion, eq 6).²¹ While diethylzinc is used, however, selectivity increases (>98% conversion, 60% ee).

Recently, our laboratory disclosed a synthesis of the unusual siphonariid metabolite baconipyrone C through a double EAA with Me₃Al.²² In the initial studies using allylic phosphate rac-69 as a model substrate (eq 7), the reaction catalyzed by NHC-Ag complex 28 and CuCl₂·2H₂O with Me₂Zn affords no desired product (<2% conversion). When the alkylation with more Lewis acidic and nucleophilic Me₃Al proceeds to 95% conversion

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with high regio- (>98:<2 $S_{N2}':S_{N2}$), moderate diastereo- (1.5:1 dr) and high enantioselectivity (89% ee). For the synthesis of baconipyrene C 73, double EAA was carried out in the presence of NHC-Ag complex 28, CuCl$_2$:2H$_2$O and Me$_3$Al to furnish the desired product 72 in 61% yield with >98% ee (Scheme 14).

**Scheme 14.** Cu-Catalyzed Double EAA with Trimethylaluminum towards the Total Synthesis of Baconipyrene C
The EAA protocol and the viability of aluminum reagents were further investigated through the study of the catalytic enantioselective vinyl additions to allylic substrates.\textsuperscript{23} The vinylaluminum reagents are readily prepared from hydroalumination of alkynes with commercially available, inexpensive dibal-H stereoselectively (only the $E$ isomer is generated). As shown in Scheme 15, the vinyl addition of trisubstituted allylic phosphates in the presence of a Cu salt and NHC-Ag complex 28 and modified NHC-Ag complex 74\textsuperscript{23} affords the $S_N2'$ products with high selectivity (87->98% ee). The reactions of allylic phosphates affords aryl-substituted 1,4-diene 75, bicyclic diene 76, and tris(homoallylic) ether 77 in $>$98% conversion (up to 92% yield) with excellent regio- and

\textit{Scheme 15. Cu-Catalyzed Enantioselective Allylic Vinyl Addition with Vinylaluminum Reagents}

\begin{center}
\begin{tikzpicture}[scale=0.8]
\node at (0,0) {\textbf{Scheme 15. Cu-Catalyzed Enantioselective Allylic Vinyl Addition with Vinylaluminum Reagents}}; \node at (4,0) {1 equiv dibal-H}; \node at (4,-1.5) {hexanes, 55 $^\circ$C, 5 h}; \node at (0,-2.5) {\textit{R}}; \node at (2,-2.5) {\textit{OPO(OEt)}_2}; \node at (4,-2.5) {\textit{Al(i-Bu)}_2}; \node at (6,-2.5) {\textit{R}}; \node at (8,-2.5) {\textit{R}}; \node at (10,-2.5) {\textit{R}}; \node at (0,-6) {\textit{Ph}}; \node at (2,-6) {\textit{Ag}}; \node at (4,-6) {\textit{Ag}}; \node at (6,-6) {\textit{74}}; \node at (8,-6) {\textit{75}}; \node at (10,-6) {\textit{76}}; \node at (12,-6) {\textit{77}}; \node at (4,-7) {\textit{87\%}}; \node at (6,-7) {\textit{89\%}}; \node at (8,-7) {\textit{92\%}}; \node at (4,-8) {\textit{>98<2 S_N2':S_N2}}; \node at (6,-8) {\textit{>98<2 S_N2':S_N2}}; \node at (8,-8) {\textit{>98<2 S_N2':S_N2}}; \node at (4,-9) {\textit{>96\% ee}}; \node at (6,-9) {\textit{87\% ee}}; \node at (8,-9) {\textit{93\% ee}}; \end{tikzpicture}
\end{center}

enantioselectivities (>98:<2 S\textsubscript{N2}’:S\textsubscript{N2}, up to >98% ee). This procedure is amenable to large scale without the use of glovebox techniques.

1-5 Conclusions

Cu-catalyzed enantioselective allylic substitution has been developed as an efficient and powerful tool to construct stereogenic centers. Development of effective chiral catalysts significantly improved the scope and nucleophiles to be used, rendering this class of reactions useful. Recent efforts have shown the ability to generate sterically demanding quaternary stereogenic centers, in addition to the reaction using facile and readily accessible nucleophiles, such as Grignard reagents and organoaluminum reagents, affording a variety of molecules bearing tertiary stereogenic centers. The next step we should challenge will be to establish practical and efficient systems to prepare for quaternary stereogenic centers by means of effective new chiral catalysts and carbon nucleophiles affording products with high regio- and enantioselectivities.
Chapter Two

Development of Cu-Catalyzed Enantioselective Allylic Alkylations with Grignard Reagents for the Formation of All-Carbon Quaternary Stereogenic Centers

2-1 Project Perspective

It has been demonstrated in these laboratories that Cu-catalyzed allylic alkylations of α,β-unsaturated esters with dialkylzinc reagents in the presence of a chiral amino acid-based ligand and a copper salt afford products containing highly functionalized all-carbon quaternary stereogenic centers. ¹ Due to improved atom economy and readily accessibility of Grignard reagents, in comparison with dialkylzinc reagents, we envisioned that a catalytic enantioselective transformation utilizing Grignard reagents would be highly practical. As shown in Table 1, commercially available Grignard

<table>
<thead>
<tr>
<th></th>
<th>Mg (Grignard Reagents)ᵃ</th>
<th>Zn (Zinc Reagents)ᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeMgCl</td>
<td>$23/mol</td>
<td>Me₂Zn $1122/mol</td>
</tr>
<tr>
<td>EtMgCl</td>
<td>$84/mol</td>
<td>Et₂Zn $130/mol</td>
</tr>
<tr>
<td>i-BuMgCl</td>
<td>$108/mol</td>
<td>Ph₂Zn $11057/mol</td>
</tr>
<tr>
<td>PhMgCl</td>
<td>$20/mol</td>
<td></td>
</tr>
</tbody>
</table>

ᵃ Commercially available from Aldrich, 2.0 M or 3.0 M solution in THF. ᵇ Commercially available from STREM.

reagents are much less expensive than the corresponding commercially available
dialkylzinc reagents (e.g. MeMgCl is $23/mol vs Me₂Zn is $1122/mol).

2-2 Studies towards Cu-Catalyzed EAA Reactions with Secondary Alkyl
Grignard Reagents

2-2-1 Preliminary Studies for Cu-Catalyzed EAA with i-PrMgCl

Our investigation of Cu-catalyzed enantioselective allylic alkylations has been
focused on the synthetic utility of allylic chlorides and phosphates bearing esters, utilized
in our previous reports, with organozinc and secondary alkyl Grignard reagents. ¹ ² In situ
generation of NHC-Cu complexes through transmetalation between NHC-Ag complexes
and a Cu salt has allowed us to investigate the effect of various NHCs. We examined the
Cu-catalyzed EAA of Me-substituted t-butyl ester 4 with i-PrMgCl in the presence of
NHC-Ag complexes 1-3 ³ (Chart 1) and CuCl₂·2H₂O in THF at -78 °C. Results of the
initial study in Cu-catalyzed EAA with i-PrMgCl are summarized in Table 2. It was found
that allylic chloride 4, in the absence of catalysts, did not react with i-PrMgCl at -78 °C
within 30 min (entry 1, Table 2). The reaction was promoted in the presence of 2.5 mol %
CuCl₂·2H₂O to afford S₂N2’ and S₂N2 products 6a and 7a in a 10:90 ratio with >98%
conversion (entry 2, Table 2). EAA of allylic chloride 4 in the presence of 2.5 mol % of
chiral naphthyl-derived NHC-Ag complex 1 provides the desired product 6a with 35:65

---

$S_{N2}':S_{N2}$, and in -33% ee (entry 3, Table 2). Sulfonate-containing NHC-Ag complex 3 provided the products with improved regioselectivity, 53:47 $S_{N2}':S_{N2}$, but with similar levels of enantioselectivity (-31% ee, entry 5). A remarkable improvement was observed in the reaction with phenoxy-based NHC-Ag complex 2; EAA proceeded to afford the

![Chart 1. Chiral Bidentate NHC-Ag Complexes](image)

**Table 2. Initial Studies of Cu-Catalyzed EAA with i-PrMgCl**

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>$i$-PrMgCl (equiv)</th>
<th>NHC-Ag (mol %)</th>
<th>Cu (mol %)</th>
<th>conv (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>$S_{N2}':S_{N2}$ (6:7)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee 6 (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$t$-Bu; 4</td>
<td>2</td>
<td>none</td>
<td>none</td>
<td>&lt;2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>$t$-Bu; 4</td>
<td>2</td>
<td>none</td>
<td>2.5</td>
<td>&gt;98</td>
<td>10:90</td>
<td>0</td>
</tr>
<tr>
<td>3&lt;sup&gt;d&lt;/sup&gt;</td>
<td>$t$-Bu; 4</td>
<td>2</td>
<td>1; 2.5</td>
<td>2.5</td>
<td>&gt;98</td>
<td>35:65</td>
<td>-33</td>
</tr>
<tr>
<td>4</td>
<td>$t$-Bu; 4</td>
<td>2</td>
<td>2; 2.5</td>
<td>2.5</td>
<td>&gt;98</td>
<td>67:33</td>
<td>94</td>
</tr>
<tr>
<td>5&lt;sup&gt;d&lt;/sup&gt;</td>
<td>$t$-Bu; 4</td>
<td>2</td>
<td>3; 2.5</td>
<td>2.5</td>
<td>&gt;98</td>
<td>53:47</td>
<td>-31</td>
</tr>
<tr>
<td>6</td>
<td>$t$-Bu; 4</td>
<td>1.5</td>
<td>2; 0.5</td>
<td>0.5</td>
<td>&gt;98</td>
<td>73:27</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>Me; 5</td>
<td>1.5</td>
<td>2; 0.5</td>
<td>0.5</td>
<td>&gt;98</td>
<td>86:14</td>
<td>95</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions were performed under N<sub>2</sub> atm. <sup>b</sup> Determined by analysis of 400 MHz $^1$H NMR spectra. <sup>c</sup> Determined by GLC analysis. <sup>d</sup> Reaction was performed for 1 h.
product 6a in a 67:37 ratio of SN2':SN2 with 6a in 94% ee (entry 4). The allylic alkylation could be improved using 0.5 mol % CuCl₂·2H₂O and 0.5 mol % NHC-Ag complex 2 to provide the desired product 6a with increased, yet moderate, regioselectivity (73:27 SN2':SN2) and in 96% ee (entry 6, Table 2). Changing the size of the ester group on the substrate from a t-butyl ester to a methyl ester further enhanced the regioselectivity to 87:13 SN2':SN2 while maintaining high enantioselectivity (6b in 95% ee, entry 7, Table 2).

2-2-2 Cu-Catalyzed EAA of Me-, Et-, and n-Bu-Substituted Allylic Chlorides with i-PrMgCl, c-HexMgCl, and c-PentMgCl

We continued to investigate EAA with secondary alkyl Grignard reagents, such as isopropyl-, cyclopentyl-, and cyclohexylmagnesium chlorides (i-PrMgCl, c-pentMgCl, and c-hexMgCl, respectively), to allylic chlorides bearing methyl esters 5, 8, and 9. Results are highlighted in Table 3. All reactions proceed to >98% conversion within 30 min at –78 °C with 0.5 mol % catalyst loading. Cu-catalyzed EAA with i-PrMgCl and c-hexMgCl provided SN2’ products with high enantioselectivities and moderate regioselectivities in all cases (94->98% ee, 68:32 to 88:12 SN2':SN2, entries 1-6, Table 3). Results illustrated in entries 1-6 indicate that allylic chlorides bearing longer alkyl substituents R (Me vs Et and n-Bu) at the α-position deliver products with higher enantioselectivities, but lower regioselectivities. Alkylations with c-pentMgCl leads to desired products 15, 16, and 17 in high enantioselectivities (90-96% ee), but the reactions
suffer from low regioselectivities (less than 48:52 S_N2:S_N2', entries 7-9). Moreover, the reaction of allylic chloride 5 with c-pentMgCl was not reproducible and provided 25% of byproduct 18 (representative result is presented in entry 7).

Table 3. Cu-Catalyzed Enantioselective Allylic Alkylations with Secondary Alkyl Grignard Reagents

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>(alkyl)MgCl</th>
<th>product</th>
<th>S_{N2}:S_{N2}</th>
<th>ee (%)</th>
<th>yield (%)</th>
<th>byproduct (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>5</td>
<td>6b</td>
<td>86:14</td>
<td>95</td>
<td>74</td>
<td>&lt;2</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>8</td>
<td>10</td>
<td>86:14</td>
<td>97</td>
<td>41</td>
<td>&lt;2</td>
</tr>
<tr>
<td>3</td>
<td>n-Bu</td>
<td>9</td>
<td>11</td>
<td>76:24</td>
<td>&gt;98</td>
<td>52</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>5</td>
<td>12</td>
<td>88:12</td>
<td>94</td>
<td>88</td>
<td>&lt;2</td>
</tr>
<tr>
<td>5</td>
<td>Et</td>
<td>8</td>
<td>13</td>
<td>81:19</td>
<td>96</td>
<td>78</td>
<td>&lt;2</td>
</tr>
<tr>
<td>6</td>
<td>n-Bu</td>
<td>9</td>
<td>14</td>
<td>68:32</td>
<td>98</td>
<td>64</td>
<td>&lt;10</td>
</tr>
<tr>
<td>7&lt;sup&gt;o&lt;/sup&gt;</td>
<td>Me</td>
<td>5</td>
<td>15</td>
<td>43:57</td>
<td>90</td>
<td>nd</td>
<td>25</td>
</tr>
<tr>
<td>8</td>
<td>Et</td>
<td>8</td>
<td>16</td>
<td>48:52</td>
<td>94</td>
<td>42</td>
<td>&lt;2</td>
</tr>
<tr>
<td>9</td>
<td>n-Bu</td>
<td>9</td>
<td>17</td>
<td>31:69</td>
<td>96</td>
<td>29</td>
<td>&lt;2</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reactions were performed under N₂ atm. >98% conv in all cases. <sup>b</sup>Determined by analysis of 400 MHz <sup>1</sup>H NMR spectra. <sup>c</sup>Determined by GLC analysis. <sup>d</sup>Isolated yields of the pure S_N2' product. <sup>e</sup>Only unknown byproduct was obtained. <sup>f</sup>Byproduct is nd=not determined.
2-2-3 Additional Studies of Cu-Catalyzed EAA with c-PentMgCl towards Improvement of Regioselectivity

Enantioselective additions of isopropyl and cyclohexyl Grignard reagents to trisubstituted allylic chlorides (5, 8, and 9) generate enantiomerically enriched products in moderate to good regioselectivities (up to 88:12 SN₂’:SN₂ and up to >98% ee, entries 1-6 in Table 3). In the case of cyclopentyl additions, however, regioselectivities are problematic (~1:1 SN₂’:SN₂) although enantioselectivities are high (90 to 96% ee, entries 7-9, Table 3). Thus, we decided further investigation of the Cu-catalyzed EAA with c-pentMgCl was needed.

i) Screening of Chiral Ligands for Cu-Catalyzed EAA with c-PentMgCl

In our initial studies of the reaction conditions for Cu-catalyzed EAA allylic chloride 4 with i-PrMgCl, we found that different NHC ligand classes could have significant influence over both regio- and enantioselectivities of the SN₂’ products (see entries 3-5, Table 1). We focused our attention towards the screening of chiral NHC ligands in the Cu-catalyzed EAA of allylic chloride 5 with c-pentMgCl in order to improve regioselectivity. Within this context, chiral monodentate NHC-Ag complexes 19-23 have been recently developed in these laboratories (Chart 2). As illustrated in Table 4, methoxy-substituted NHC-Ag complex 19 is ineffective in controlling regio- and enantioselectivities of the transformation (48:52 SN₂’:SN₂ and 81% ee, entry 1). When the methoxy substituent R removed as in NHC-Ag complex 20, regioselectivity can be
improved to 71:29 $S_N2\cdot S_N2$ (entry 2, Table 4). When NHC-Ag complex 21, bearing an ortho diethyl-substituted phenyl group, is employed, the regioselectivity of the transformation is significantly improved, affording the desired product 15 in a 85:15 ratio of $S_N2\cdot S_N2$ and in high enantioselectivity (90% ee). Sterically demanding triisopropyl phenyl-substituted NHC-Ag complex 22 affords the product with lower regio- and

![Chart 2. Chiral Monodentate NHC-Ag Complexes](image)

**Table 4.** Screening of Chiral NHC-Ag Complexes in Cu-Catalyzed EAA with $\cdot$-PentMgCl$^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>NHC-Ag</th>
<th>$S_N2\cdot S_N2^{b,c}$</th>
<th>yield (%)$^d$</th>
<th>ee (%)$^e$</th>
<th>byproduct (%)$^f$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>48:52</td>
<td>-</td>
<td>81</td>
<td>&lt;30</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>71:29</td>
<td>-</td>
<td>80</td>
<td>&lt;30</td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td>82:18</td>
<td>52</td>
<td>90</td>
<td>29</td>
</tr>
<tr>
<td>4</td>
<td>22</td>
<td>16:84</td>
<td>-</td>
<td>4</td>
<td>&lt;35</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>63:37</td>
<td>-</td>
<td>87</td>
<td>&lt;40</td>
</tr>
</tbody>
</table>

$^a$ Reactions were performed under N$_2$ atm. >98% conv in all cases. $^b$ Determined by analysis of 400 MHz $^1$H NMR spectra $^c$ Determined by GLC analysis. $^d$ Isolated yield of mixtures of $S_N2$ and $S_N2$ products.
enantioselectivities (16:84 $S_N2':S_N2$ with 4% ee, entry 4). Furthermore, in contrast to the reaction in the presence of NHC-Ag complex 21, employment of NHC-Ag complex 23, bearing an additional isopropyl group on the biphenyl moiety, led to lower selectivities in the alkylation of allylic chloride 5 (63:37 $S_N2':S_N2$ and 87% ee, entry 5).

ii) Examination of Byproduct Formation in Cu-Catalyzed EAA with c-PentMgCl

Studies initiated to discover the optimal monodentate NHC ligand for Cu-catalyzed EAA with c-pentMgCl led to the observation of the formation of non-negligible amounts of byproduct (up to 40%, entries 1-7 in Table 3), albeit the reaction proceeded with improved regioselectivity and in high enantioselectivity. Reduction product 18 has been known to arise as a byproduct in Cu-catalyzed EAA with bidentate NHC-Ag complex 2. In addition to reduction product 18, when monodentate NHC-Ag complexes 19-23 were used in EAA of allylic chlorides with c-pentMgCl, an unexpected byproduct was obtained. The byproduct was isolated and assigned to be

---

**Scheme 1. Plausible Pathway to Generate Compound 25**

1. $\text{MeO}^-\text{cyclohexene-MgCl} + \text{MeO}^-5\text{Me}^-\text{Me}^-\text{Cl} \xrightarrow{\text{metal-halogen exchange}} \text{MeO}^-\text{cyclohexene-MgCl} + \text{MeO}^-\text{cyclohexene-Cl}$
2. $\text{MeO}^-\text{cyclohexene-MgCl} \xrightarrow{\text{Allylic alkylation}} \text{MeO}^-\text{cyclohexene-MgCl} + \text{MeO}^-\text{cyclohexene-Cl}$

---
compound 25 (Scheme 1). A plausible pathway for generation of compound 25 is illustrated in Scheme 1. Allylic chloride 5 may be transformed to allylic magnesium chloride 24 through metal-halogen exchange which can participate in allylic alkylation of 5 to afford byproduct 25 by way of a $S_N2'$ process. One possible mechanism by which allylic magnesium chloride can be generated is through a radical pathway. However, when the reaction is performed in the presence of one equivalent of styrene as a radical scavenger, the amount of byproduct 25 was not reduced (eq 1). Further studies are required to elucidate the basis for generation of 25 in reactions with monodentate NHC-Ag complexes.

In order to identify the optimal reaction conditions, the ratio of NHC-Ag complex to the Cu salt, which generates NHC-Cu complex in situ, were investigated. To achieve high selectivity, a 2:1 ratio of NHC-Ag complex to the Cu salt is required. We suspected that excess NHC-Ag complex may be responsible for the generation of byproduct 25. Hence, we prepared and isolated monodentate NHC-Cu complex 26 through transmetalation of NHC-Ag complex 21 (eq 2). As eq 3 shows, the reaction proceeded in the presence of 0.5 mol % NHC-Cu complex 26 to deliver 15 with lower regio- and enantioselectivities than those observed with in situ-combined NHC-Ag

complex and Cu salt (30:70 SN\textsuperscript{2}:SN\textsubscript{2} with 80% ee vs 82:18 SN\textsuperscript{2}:SN\textsubscript{2} with 90% ee, entry 3, Table 3). Nevertheless, the amount of byproduct 25 was suppressed to 9%. The reaction was then carried out in the presence of 0.5 mol % NHC-Ag complex 21 and 0.5 mol % NHC-Cu complex 26 (eq 4). This composition of catalysts is likely to present in reactions with \textit{in situ}-generated NHC-Cu catalyst. The reaction affords a nearly 1:1 ratio of SN\textsuperscript{2}:SN\textsubscript{2} with the SN\textsuperscript{2} product 15 isolated in 83% ee, along with generation of 17% of the byproduct 25 (eq 4). When 1 mol % AgCl is added to an EAA in the presence of 0.5 mol % NHC-Cu complex 26, the SN\textsubscript{2} product is predominantly observed with the SN\textsuperscript{2} product isolated in 72% ee with 10% byproduct formed (34:66 SN\textsuperscript{2}:SN\textsubscript{2}, eq 5). These

\textbf{Scheme 2.} Preparation of Monodentate NHC-Cu Complex and Investigation of Cu-Catalyzed EAA with c-PentMgCl

![Scheme 2](image-url)
investigations demonstrate that the use of isolated NHC-Cu complex \textbf{26} can reduce the amount of byproduct \textbf{25}, however, regio- and enantioselectivities suffer.

2-2-4 Applications of Monodentate NHC-Ag and NHC-Cu Complexes for Cu-Catalyzed EAA with \(c\)-PentMgCl, \(i\)-PrMgCl, and \(c\)-HexMgCl

Chiral monodentate NHC-Ag complex \textbf{21} was applied to enantioselective cyclopentyl addition to allylic chlorides \textbf{8} and \textbf{9}, as well as to isopropyl and cyclohexyl addition to allylic chlorides \textbf{5}, \textbf{8}, and \textbf{9}. In order to reduce the generation of byproduct, the reaction of allylic chlorides with various Grignard reagents were also carried out in the presence of monodentate NHC-Cu complex \textbf{26}, the data from which is summarized in Table 5. Comparing the reactions in the presence of bidentate NHC-Ag complex \textbf{2} and monodentate NHC-Ag complex \textbf{21}, we found that, for the most part, regioselectivities obtained from reactions with bidentate NHC-Ag complex \textbf{21} were superior to those resulting from NHC-Ag complex \textbf{2} (74:26 to 92:8 \(S_N2\)‘:\(S_N2\) with Condition B vs 31:69 to 88:12 \(S_N2\)‘:\(S_N2\) with Condition A, Table 4). Moderate to highly enantiomerically enriched products were achieved. Alkylations with \(i\)-PrMgCl in the presence of bidentate NHC-Ag complex \textbf{2} provide slightly improved enantioselectivity compared with monodentate NHC-Ag complex \textbf{21} (95->98% ee vs 78-95% ee, entries 1-3). Isolated NHC-Cu complex \textbf{26} afforded the product in lower selectivities than \textit{in situ}-generated NHC-Cu complex generated from NHC-Ag complex \textbf{21} and CuCl\(_2\)\(\cdot\)2H\(_2\)O; however, in these reactions, the amount of byproduct is diminished (e.g. Reaction of \(c\)-pentMgCl with Condition B
generated 29% of byproduct while the reaction performed under Condition C generated 5% byproduct, entry 4). In addition, we compared results between Cu-catalyzed EAA and the previously reported Cu-free EAA$^2$ (Condition A, B, and C vs Condition D, Table 4). For example, Cu-catalyzed reaction of 5 with $i$-PrMgCl requires only 0.5 mol % Cu salt and 1 mol % chiral NHC ligand to achieve complete conversion within 30 min. The corresponding Cu-free reaction requires higher catalyst loading (5 mol % vs 0.5 mol %) and longer reaction times to obtain significant conversion (24-60 h vs 0.5 h). As shown in Table 5, Cu-catalyzed EAA with Grignard reagents is more efficient than the related Cu-free processes. Higher regioselectivities are, however, observed generally in Cu-free EAA reactions (Condition D).
Table 5. Comparison between Cu-Catalyzed and Cu-Free EAA with Grignard Reagents

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>(alkyl)MgCl</th>
<th>Cu-catalyzed EAA&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cu-free EAA&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>S&lt;sub&gt;n&lt;/sub&gt;2&lt;sup&gt;{2}&lt;/sup&gt;:S&lt;sub&gt;n&lt;/sub&gt;2&lt;sup&gt;{2}&lt;/sup&gt; (%)</td>
<td>ee (%)</td>
<td>bypd&lt;sup&gt;d&lt;/sup&gt; (%)</td>
</tr>
<tr>
<td>1</td>
<td>Me</td>
<td>5</td>
<td>86:14</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>8</td>
<td>86:14</td>
<td>41</td>
</tr>
<tr>
<td>3</td>
<td>n-Bu</td>
<td>9</td>
<td>76:24</td>
<td>52</td>
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<tr>
<td>4</td>
<td>Me</td>
<td>5</td>
<td>36:64</td>
<td>42</td>
</tr>
<tr>
<td>5</td>
<td>Et</td>
<td>8</td>
<td>48:52</td>
<td>29</td>
</tr>
<tr>
<td>6</td>
<td>n-Bu</td>
<td>9</td>
<td>31:69</td>
<td>29</td>
</tr>
<tr>
<td>7</td>
<td>Me</td>
<td>5</td>
<td>88:12</td>
<td>88</td>
</tr>
<tr>
<td>8</td>
<td>Et</td>
<td>8</td>
<td>81:19</td>
<td>78</td>
</tr>
<tr>
<td>9</td>
<td>n-Bu</td>
<td>9</td>
<td>68:32</td>
<td>64</td>
</tr>
</tbody>
</table>

bypdt = byproduct. <sup>a</sup>Reactions were performed under N<sub>2</sub> atm. >98% conv in all cases. <sup>b</sup>Reactions were performed under N<sub>2</sub> atm. <sup>c</sup>Determined by analysis of 400 MHz<sup>1</sup>H NMR spectra. <sup>d</sup>Determined by GLC analysis. <sup>e</sup>Isolated yield of pure S<sub>n</sub>2<sup>{2}</sup> product. <sup>f</sup>Total yield of S<sub>n</sub>2<sup>{2}</sup> and S<sub>n</sub>2 products. <sup>g</sup>Cyclopropane product derived from conjugate addition of the Grignard reagent followed by displacement of the chloride by the enolate. <sup>h</sup>Reduction product 18. <sup>i</sup>Byproduct is only compound 25. <sup>j</sup>The mixture of reduction product 18 and compound 25.
2-3 Cu-Catalyzed EAA of Various Trisubstituted Substrates with i-PrMgCl

We have demonstrated the Cu-catalyzed EAA of \( \alpha \)-alkyl-\( \gamma \)-chloro-\( \alpha,\beta \)-unsaturated methyl esters with secondary alkyl Grignard reagents and disclosed that the use of monodentate NHC-Ag complex 21 leads to efficient reactions with improved regioselectivities while maintaining high enantioselectivities. In addition to the reaction of allylic chlorides bearing an ester group, we examined Cu-catalyzed EAA of aromatic and aliphatic substrates with \( i \)-PrMgCl to generate all-carbon quaternary stereogenic centers. First, we began our studies by searching both an optimal NHC ligand and an appropriate leaving group for the trisubstituted substrate (Table 6). The reaction of allylic chloride 28 in the presence of NHC-Ag complex 2 provides the product in high enantioselectivity (93% ee), but with low regioselectivity (41:59 \( S_N2' : S_N2 \), entry 1); Low regio- and enantioselectivities are obtained in the presence of NHC-Ag complex 3 (41:59 \( S_N2' : S_N2 \), 17% ee, entry 2). Monodentate NHC-Ag complex 20 affords the product in low regio- and enantioselectivities as well (23:77 \( S_N2' : S_N2 \) with 70% ee, entry 3). NHC-Ag complex 21, which serves as an optimal ligand in Cu-catalyzed EAA of allylic chlorides bearing methyl esters with secondary alkyl Grignard reagents, affords the product in excellent enantioselectivity (90% ee), albeit with low regioselectivity (28:72 \( S_N2' : S_N2 \), entry 4). Subsequently, Cu-catalyzed EAA of allylic phosphate 29 and allylic acetate 30 in the presence of NHC-Ag complexes 2 and 20 were investigated in order to determine whether improved selectivities could be obtained. The reaction of 29 affords \( S_N2' \) products in about 30:70 \( S_N2' : S_N2 \) and in 20 to 66% ee (entries 5 and 6) and allylic acetate 30 delivers
only the $S_N2$ product in low conversions (<63% conversion, entries 7 and 8). EAA of cyclohexyl allylic chloride 31 was also studied with NHC-Ag complexes 2 and 20 and the reactions resulted in the product obtained with low regioselectivities but in good enantioselectivities (12:88 $S_N2'$:$S_N2$ with 86% ee, entry 9 and 3:97 $S_N2'$:$S_N2$ with 82% ee, entry 10).

Table 6. Cu-Catalyzed EAA of Trisubstituted Substrates with $i$-PrMgCl$^\text{a}$

<table>
<thead>
<tr>
<th>entry</th>
<th>Substrate</th>
<th>NHCl-Ag (mol %)</th>
<th>time (h)</th>
<th>conv (%)$^b$</th>
<th>$S_N2$:$S_N2'$</th>
<th>ee (%)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me 28</td>
<td>2; 0.5</td>
<td>2.5</td>
<td>&gt;98</td>
<td>41;59</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>20; 1</td>
<td>30</td>
<td>&gt;98</td>
<td>23;77</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>Ph-Cl</td>
<td>20; 1</td>
<td>30</td>
<td>&gt;98</td>
<td>28;72</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>Me 29</td>
<td>20; 1</td>
<td>12</td>
<td>&gt;98</td>
<td>26;74</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>Ph-Cl</td>
<td>20; 1</td>
<td>12</td>
<td>&gt;98</td>
<td>29;71</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>Ph-Cl</td>
<td>20; 1</td>
<td>12</td>
<td>&gt;98</td>
<td>26;74</td>
<td>66</td>
</tr>
<tr>
<td>7</td>
<td>Me 30</td>
<td>20; 1</td>
<td>12</td>
<td>20</td>
<td>&lt;2;98</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>Me 31</td>
<td>20; 1</td>
<td>12</td>
<td>63</td>
<td>&lt;2;98</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>Me 31</td>
<td>20; 1</td>
<td>5</td>
<td>96</td>
<td>3;97</td>
<td>82</td>
</tr>
</tbody>
</table>

$^a$Reactions were performed under N$_2$ atom. $^b$Determined by analysis of 400 MHz $^1$H NMR spectra. $^c$Determined by GLC analysis.
2-4 Cu-Catalyzed EAA with Primary Alkyl and Phenyl Grignard Reagents

Following the EAA with secondary alkyl Grignard reagents, we examined reactions of allylic chlorides (4, 5, 32, and 8) with primary alkyl Grignard reagents. As illustrated in Table 7, alkylations of 4 with EtMgCl in the presence of NHC-Ag complexes

**Table 7. Screening of Monodentate NHC-Ag Complexes for Cu-Catalyzed EAA with Primary Alkyl Grignard Reagents**

<table>
<thead>
<tr>
<th>entry</th>
<th>Product</th>
<th>NHC-Ag (mol %)</th>
<th>S_{2-S}^{2%}</th>
<th>ee (%)</th>
<th>byproduct (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>2; 0.5</td>
<td>92:8</td>
<td>59</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>t-BuO</td>
<td>20; 1</td>
<td>95:5</td>
<td>54</td>
<td>&lt;5</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>21; 1</td>
<td>91:9</td>
<td>62</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>t-BuO</td>
<td>2; 0.5</td>
<td>90:10</td>
<td>63</td>
<td>&lt;2</td>
</tr>
<tr>
<td>5</td>
<td>t-BuO</td>
<td>20; 1</td>
<td>87:13</td>
<td>69</td>
<td>&lt;2</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>21; 1</td>
<td>87:13</td>
<td>64</td>
<td>&lt;2</td>
</tr>
<tr>
<td>7</td>
<td>MeO</td>
<td>20; 1</td>
<td>90:10</td>
<td>58</td>
<td>&lt;2</td>
</tr>
<tr>
<td>8</td>
<td>t-BuO</td>
<td>20; 1</td>
<td>92:8</td>
<td>62</td>
<td>&lt;2</td>
</tr>
<tr>
<td>9</td>
<td>MeO</td>
<td>20; 1</td>
<td>97:3</td>
<td>70</td>
<td>&lt;2</td>
</tr>
</tbody>
</table>

*Reactions were performed under N₂ atom. *b Determined by analysis of 400 MHz ¹H NMR spectra. *c Determined by GLC analysis. *d Only reduction product 18 was obtained.
2, 20, and 21 proceeded to deliver the product in high regioselectivities (91:9-95:5 SN2’:SN2) but in moderate enantioselectivities (54-62% ee, entries 1-3). Additions of \( n\)-BuMgCl proceed in the presence of NHC-Ag complexes 2, 20, and 21 to provide in 87:13 to 90:10 SN2’:SN2 with 63-69% ee (entries 4-6). Methyl ester 5 was employed in the reaction with NHC-Ag complex 20 to afford the desired product 35 with the same regioselectivity as 34 but in lower enantioselectivity (90:10 SN2’:SN2, 58% ee, entry 7). Enantioselective \( n\)-butyl addition to Et-substituted allylic chloride 32 in the presence of NHC-Ag complex 20 proceeded with high regioselectivity but was moderately enantioselective (92:8 SN2’:SN2 with 62% ee, entry 8). EAA of smaller methyl ester 8, compared to \( tert\)-butyl ester 32, provided 37 with improved regio- and enantioselectivities (97:3 SN2’:SN2, 70% ee, entry 9 vs 92:8 SN2’:SN2, 62% ee, entry 8). Through studying additions of EtMgCl and \( n\)-BuMgCl, we discovered highly regioselective reactions (up to 97:3 SN2’:SN2), however, enantioselectivities could not be improved beyond 70% ee.

The allylic substitution of allylic chloride 4 with PhMgCl was also attempted, at -78 °C for 0.5 h, however, no desired SN2’ product is obtained in either reaction with bidentate NHC-Ag complex 2 or monodentate NHC-Ag complex 20 (eq 6).
Conclusions

We have focused on the development of Cu-catalyzed enantioselective allylic alkylations of \( \alpha,\beta \)-unsaturated-\( \gamma \)-chloro esters with Grignard regents for the formation of all-carbon quaternary stereogenic centers. Both highly regio- and enantioselective reactions were obtained by means of bidentate NHC-Ag complex 2 in the EAA with \( i \)-PrMgCl and \( c \)-hexMgCl (up to 88:12 \( S_N2' : S_N2 \) and up to >98% ee). Reactions with \( c \)-pentMgCl proceeded efficiently and enantioselectively but with low levels of regioselectivity (up to 48:52 \( S_N2' : S_N2 \) and up to 96% ee). Application of newly developed chiral monodentate NHC-Ag complex 21 allowed the regioselectivity to be significantly improved while maintaining high enantioselectivity (up to 82:18 \( S_N2' : S_N2 \) with up to 95% ee). The byproduct 25 generated in the reaction with NHC-Ag complex 21 was identified and further investigation was conducted in order to decrease the amount of its generation. Substrates containing phenyl and cyclohexyl groups were examined for the alkylation with \( i \)-PrMgCl to afford the desired products with up to a 41:59 ratio of \( S_N2' : S_N2 \) in up to 93% ee. In addition, we have herein summarized the comparison of the results of reactions with bidentate NHC-Ag complex 2, monodentate NHC-Ag complex 21 and isolated monodentate NHC-Cu complex 26, in addition to results from the Cu-free EAA. The Cu-catalyzed EAA with primary alkyl Grignard reagents resulted in high regioselectivity but with moderate enantioselectivity (up to 97:3 \( S_N2' : S_N2 \) and up to 70% ee). Alkylation with PhMgCl does not provide any desired product in the presence of bidentate NHC-Ag complex 2 or with monodentate NHC-Ag complex 20. In order to
overcome these difficulties in Cu-catalyzed EAA with Grignard reagents, further studies into the development of the system are required.
2-6 Experimental

General. Infrared (IR) spectra were recorded on a Bruker FT-IR Alpha (ATR mode) spectrophotometer, $\nu_{\text{max}}$ in cm$^{-1}$. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). $^1$H NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CDCl$_3$: $\delta$ 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants (Hz). $^{13}$C NMR spectra were recorded on a Varian Unity INOVA 400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CDCl$_3$: $\delta$ 77.16 ppm). High-resolution mass spectrometry was performed on a Micromass LCT ESI-MS (positive mode) at the Mass Spectrometry Facility, Boston College. Enantiomer ratios were determined by GLC analysis (Alltech Associated Chiral dex GTA column (30 m x 0.25 mm) and Betadex 120 column (30 m x 0.25 mm)) in comparison with authentic racemic materials. Optical rotations were measured on a Rudolph Research Analytical Autopol IV Polarimeter. Unless otherwise noted, all reactions were carried out with distilled and degassed solvents under an atmosphere of dry N$_2$ in oven- (135 °C) and flame-dried glassware with standard dry box or vacuum-line techniques. Solvents were purified under a positive pressure of dry argon by a modified Innovative Technologies purification system: CH$_2$Cl$_2$ and Et$_2$O were purged with argon and purified by passage through two alumnia columns.
Tetrahydrofuran (Aldrich Chemical Co.) was purified by distillation from sodium benzophenone ketyl immediately prior to use unless otherwise specified. All work-up and purification procedures were carried out with reagent grade solvents (purchased from Doe & Ingalls) in air. All Grignard reagents were prepared in THF by addition of the corresponding chlorides onto magnesium turnings, which was purchased from Strem Chemicals Inc. and used as received.

■ Reagents and ligands:

\[(E)-\text{tert-Butyl 4-chloro-2-methylbut-2-enoate (4):}\] prepared according to a previously reported procedure.\(^1\)

1-Chlorobutane: purchased from Aldrich Chemical Co. and purified by distillation over MgSO₄.

Chlorocyclopentane: purchased from Aldrich Chemical Co. and purified by distillation over MgSO₄.

Chloroethane: purchased from Aldrich Chemical Co. and used as received.

Cyclohexylchloride: purchased from Aldrich Chemical Co. and purified by distillation over MgSO₄.

2-Chloropentane: purchased from Aldrich Chemical Co. and purified by distillation over MgSO₄.

Copper(II) dichloride bishydrate: purchased from Aldrich Chemical Co. and used as

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received.

\((E)\)-Methyl 4-chloro-2-ethylbut-2-enoate (8): prepared according to a previously reported procedure.²

\((E)\)-Methyl 2-(2-chloroethylidene)hexanoate (9): prepared according to a previously reported procedure.²

\((E)\)-Methyl 4-chloro-2-methylbut-2-enoate (5): prepared according to a previously reported procedure.²

NHC-Ag complex 1: prepared according to a previously reported procedure.³

NHC-Ag complex 2: prepared according to a previously reported procedure.⁴

NHC-Ag complex 3: prepared according to a previously reported procedure.⁵

Monodentate NHC-Ag complexes 19-23: prepared according to a previously reported procedure.⁶

NHC-Ag complex (21): mp = 177-179 °C; IR (neat): 3033 (w), 2970 (w), 2872 (w), 1503 (m), 1466 (m), 1451 (m), 1265 (m), 1217 (m), 1180 (m), 1055 (w), 1031 (w), 761 (m), 731 (s), 697 (s), 666 (m) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.63-7.55 (5H, m), 7.38-7.36 (1H, m), 7.3-7.0 (m).

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m), 7.31-7.17 (7H, m), 7.16-7.10 (2H, m), 7.09-7.04 (2H, m), 7.02-6.93 (2H, m), 6.33 (2H, d, \( J = 7.2 \) Hz), 6.90 (1H, dd, \( J = 8.0, 1.6 \) Hz), 5.08 (1H, d, \( J = 10.0 \) Hz), 5.07 (1H, d, \( J = 10.0 \) Hz), 2.90 (1H, td, \( J = 15.2, 7.6 \) Hz), 2.77 (1H, td, \( J = 15.2, 7.6 \) Hz), 2.38 (1H, td, \( J = 14.8, 7.2 \) Hz), 1.81 (1H, td, \( J = 15.2, 7.6 \) Hz), 1.46 (3H, t, \( J = 7.6 \) Hz), 0.92 (3H, t, \( J = 7.6 \) Hz); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \( \delta \) 204.9 (C carbene, \( J = 238.2, 17.0 \) Hz), 143.1, 141.0, 139.8, 138.9, 137.6, 137.2, 134.7, 133.9, 131.4, 130.9, 129.6, 129.5, 129.4, 129.3, 129.2, 129.1, 129.0, 128.8, 128.5, 128.2, 127.6, 127.0, 126.9, 77.4, 72.8,, 24.8, 23.8, 15.4, 15.0; LRMS (ES\(^{+}\)): Calcd for C\(_{37}\)H\(_{34}\)AgN\(_2\) [M-Cl]: 613.17, Found: 613.1. Optical Rotation: \([\alpha]_{D}^{20}\) –271.2 (c = 1.00, CHCl\(_3\)).

**Synthesis of NHC-Cu complex 26**

A flame-dried round-bottom flask was charged with NHC-Ag complex 21 (37.6 mg, 0.0578 mmol), CuCl (5.60 mg, 0.0578 mmol), and THF (2 mL) under a dry N\(_2\) atmosphere. The solution was allowed to stir at 22 °C for 12 h. After that time, the resulting mixture was passed through a plug of celite eluted with CH\(_2\)Cl\(_2\). The filtrate was concentrated and triturated with hexcane/CH\(_2\)Cl\(_2\) to afford NHC-Cu complex 26 as a white solid (23.4 mg, 0.0386 mmol, 67% yield).

**Representative experimental procedure for Cu-catalyzed enantioselective allylic alkylation of Grignard reagents to (\(E\))-methyl 4-chloro-2-methylbut-2-enoate (5):**

In an N\(_2\)-filled glovebox, an oven-dried 13 x 100 mm test tube was charged with chiral NHC-Ag complex 2 (1.80 mg, 1.50 x 10\(^{-3}\) mmol), sealed with a rubber septum and parafilm. The vessel was removed from the glovebox. To the chiral NHC-Ag complex 2,
under an N₂ atmosphere, were added THF (0.5 mL) and a solution of CuCl₂·2H₂O in THF (0.01 M, 150 µL, 1.50 x 10⁻³ mmol) and the solution was allowed to stir for 30 min. Allylic chloride 5 (44.5 mg, 0.300 mmol) in THF (0.5 mL) was added to the solution, which was allowed to stir for 10 min before cooling to -78 °C. c-HexMgCl (1.59 M in THF, 283 µL, 0.450 mmol) was added dropwise over 3 min. The mixture was allowed to stir at –78 °C for 30 min, after which the reaction was quenched by the addition of a saturated aqueous solution of NH₄Cl (0.5 mL). The resulting mixture was washed with diethyl ether (3 x 3 mL) and filtered through a short plug of MgSO₄ and silica gel. The filtrate was concentrated to provide colorless oil residue, which was purified by silica gel column chromatography with Et₂O/Pentane 1:50 to afford the colorless oil of SN₂’ product 12 in 88% yield (51.8 mg, 0.264 mmol).

(S)-tert-Butyl 2-isopropyl-2-methylbut-3-enoate (6a; This compound has been previously reported and spectra data match those described).²

¹H NMR (CDCl₃, 400 MHz): δ 5.95 (1H, dd, J = 17.6, 10.8 Hz, CH=CH₂), 5.09 (1H, dd, J = 10.8 1.2 Hz, CH=CHH), 5.03 (1H, dd, J = 17.6, 1.2 Hz, CH=CHH), 2.12–2.05 (1H, m, CH(CH₃)₂), 1.41 (9H, s, C(CH₃)₃), 1.08 (3H, s, CH₃), 0.83 (3H, d, J = 6.4 Hz, CH(CH₃)₂), 0.79 (3H, d, J = 7.2 Hz, CH(CH₃)₂); ¹³C NMR (CDCl₃, 100 MHz): δ 175.3, 141.8, 114.1, 80.3, 53.1, 34.7, 28.1, 17.8, 17.4, 14.3; Optical Rotation: [α]D²⁰ –23.2 (c = 1.00, CHCl₃) for an enantiomerically enriched sample of 96% ee.
Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (96% ee shown; chiral dex GTA column, 10 psi, 40 °C).

(S)-Methyl 2-isopropyl-2-methylbut-3-enoate (6b; This compound has been previously reported and spectra data match those described). \(^7\)

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 6.00 (1H, dd, \(J = 17.6, 10.8\) Hz, CH=CH2), 5.15 (1H, dd, \(J = 10.8, 1.2\) Hz, CH=CHH), 5.08 (1H, dd, \(J = 17.6, 1.2\)Hz, CH=CHH), 3.68 (3H, s, OCH\(_3\)), 2.14 (1H, dd, \(J = 6.8, 6.8\) Hz, CH(CH\(_3\))\(_2\)), 1.17, (3H, s, CH\(_3\)), 0.83 (3H, d, \(J = 6.8\) Hz, CH(CH\(_3\))\(_2\)), 0.82 (3H, d, \(J = 6.8\) Hz, CH(CH\(_3\))\(_2\)); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 176.6, 141.1, 114.6, 52.7, 52.0, 34.9, 17.9, 17.4, 14.5; Optical rotation: \([\alpha]_D^{20} -26.8\) (c = 0.65, CHCl\(_3\)) for an enantiomerically enriched sample of 89% ee.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (95% ee shown; chiral dex GTA column, 10 psi, 35 °C).

\(^7\) Murphy, K. E.; Hoveyda, A. H. *Org. Lett.* 2005, 7, 1255-1258.
(S)-Methyl 2-ethyl-2-isopropylbut-3-enoate (10; This compound has been previously reported and spectra data match those described).\(^\text{2}\) \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 5.99 (1H, dd, \(J = 18.0, 11.2\) Hz, CH=CH\(_2\)), 5.27 (1H, dd, \(J = 11.2, 2.8\) Hz, CH=CH\(_3\)), 5.01 (1H, dd, \(J = 18.0, 2.8\) Hz, CH=CHH), 3.69 (3H, s, OCH\(_3\)), 2.08-2.04 (1H, m, CH), 1.80-1.66 (2H, m, CH\(_2\)), 0.83-0.75 (9H, m, CH\(_3\) and (CH\(_3\))\(_2\)CH); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 176.3, 135.5, 115.7, 57.2, 51.7, 35.3, 26.6, 19.0, 16.9, 9.7; Optical Rotation: \([\alpha]_D^{20} +6.33\) (\(c = 1.80,\ \text{CHCl}_3\)) for an enantiomerically enriched sample of 97% ee.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (97% ee shown; \(\beta\)-dex column, 10 psi, 80 °C).
(S)-Methyl 2-isopropyl-2-vinylhexanoate (11; This compound has been previously reported and spectra data match those described).\(^2\) \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 6.00 (1H, dd, \(J = 18.0, 11.2\) Hz, CH=CH\(_2\)), 5.25 (1H, dd, \(J = 11.2, 1.2\) Hz, CH=CHH), 5.00 (1H, dd, \(J = 18.0,1.2\) Hz, CH=CHH), 3.68 (3H, s, OCH\(_3\)), 2.07-2.04 (1H, m, CH), 1.69-1.61 (2H, m, CH\(_2\)), 1.29-0.75 (13H, m, \(\text{CH}_2\text{CH}_2\text{CH}_3\) and CH(\(\text{CH}_3\)_2)); \(^13\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 176.4, 135.9, 115.5, 56.5, 51.7, 35.5, 33.8, 27.3, 23.4, 19.0, 16.9, 14.1; Optical Rotation: \([\alpha]_D^{20} +3.57\) (\(c = 1.27,\) CHCl\(_3\) for an enantiomerically enriched sample 96% ee.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (>98% ee shown; chiral dex GTA column, 10 psi, 70 °C).
(S)-Methyl 2-cyclohexyl-2-methylbut-3-enoate (12; This compound has been previously reported and spectra data match those previously described).\(^2\) \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 5.98 (1H, dd, \(J = 17.6, 10.8\) Hz, CH=CH\(_2\)), 5.11 (1H, dd, \(J = 10.8, 1.2\) Hz, CH=CHH), 5.03 (1H, dd, \(J = 17.6, 1.2\) Hz, CH=CHH), 3.65 (3H, s, OCH\(_3\)), 1.75-0.88 (14H, m, CH\(_3\) and CH(CH\(_2\))\(_5\)); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 176.6, 141.3, 114.4, 52.7, 52.0, 45.5, 28.3, 27.6, 26.9, 26.9, 26.6, 15.3; Optical Rotation: \([\alpha]_D^{20} -24.2\) (c = 1.00, CHCl\(_3\)) for an enantiomerically enriched sample of 94% ee.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (94% ee shown; chiral dex GTA column, 10 psi, 70 °C).
(R)-Methyl 2-cyclohexyl-2-ethylbut-3-enoate (13; This compound has been previously reported and spectra data match those described).2

\[
\begin{align*}
\text{\textsuperscript{1}H NMR (CDCl}_3, 400 \text{ MHz}): & \quad \delta 6.01 (1H, dd, J = 18.0, 11.2 \text{ Hz, CH}=\text{CH}_2), 5.23 (1H, dd, J = 11.2, 1.2 \text{ Hz, CH}=\text{CHHH}), 4.98 (1H, dd, J = 18.0, 1.2 \text{ Hz, CH}=\text{CHHH}), 3.68 (3H, s, OCH}_3), 1.83-0.87 (13H, m, \text{CH}_2\text{CH}_3 \text{ and CH(}\text{CH}_2\text{)}_3), 0.77 (3H, t, J = 7.2 \text{ Hz, CH}_2\text{CH}_3); \\
\text{\textsuperscript{13}C NMR (CDCl}_3, 100 \text{ MHz}): & \quad \delta 176.3, 136.5, 115.2, 57.3, 51.7, 46.0, 29.3, 27.2, 27.1, 26.8, 26.7, 26.1, 9.6; \text{ Optical Rotation: } [\alpha]_D^{20} +20.6 \text{ (c } = 1.85, \text{ CHCl}_3) \text{ for an enantiomerically enriched sample of 96% ee.}
\end{align*}
\]

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (96% ee shown; chiral dex GTA column, 10 psi, 90 °C).
(R)-Methyl 2-cyclohexyl-2-vinylhexanoate (14; This compound has been previously reported and spectra data match those described).\textsuperscript{2} \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): \(\delta\) 6.02 (1H, dd, \(J = 18.0, 11.2\) Hz, CH=CH\textsubscript{2}), 5.21 (1H, dd, \(J = 11.2, 1.2\) Hz, CH=CH\textsubscript{H}), 4.96 (1H, dd, \(J = 18.0, 1.2\) Hz, CH=CH\textsubscript{H}), 3.66 (3H, s, OCH\textsubscript{3}), 1.75-0.84 (20H, m, CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3} and CH(CH\textsubscript{2})\textsubscript{3}); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz): \(\delta\) 176.1, 136.8, 115.0, 56.6, 51.7, 46.2, 33.4, 29.2, 27.3, 27.2, 27.1, 26.8, 26.7, 23.4, 14.1; Optical Rotation: \([\alpha]_D^{20} +11.7\ (c = 1.02, \text{CHCl}_3)\) for an enantiomerically enriched sample of 98% ee.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (98% ee shown; chiral dex GTA column, 10 psi, 80 °C).
(R)-Methyl 2-cyclopentyl-2-methylbut-3-enoate (15). This compound has been previously reported and spectra data match those described.\(^2\) \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 6.04 (1H, dd, \(J = 17.6, 10.8\) Hz, CH=CH\(_2\)), 5.11 (1H, dd, \(J = 10.8, 1.2\) Hz, CH=CHH), 5.03 (1H, dd, \(J = 17.6, 1.2\) Hz, CH=CHH), 3.65 (3H, s, OCH\(_3\)), 2.30-2.25 (1H, m, CH), 1.59-1.22 (11H, m, CH\(_3\) and (CH\(_2\))\(_4\)); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 176.6, 140.6, 114.2, 52.0, 51.0, 47.3, 27.6, 27.4, 25.8, 25.8, 17.5; Optical Rotation: \([\alpha]_D^{20} = -20.7\) (c = 1.00, CHCl\(_3\)) for an enantiomerically enriched sample of 90% ee.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (90% ee shown; chiral dex GTA column, 10 psi, 70 °C).
(R)-Methyl 2-cyclopentyl-2-ethylbut-3-enoate (16). This compound has been previously reported and spectra data match those described.\(^2\)

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta \) 6.01 (1H, dd, \(J \) = 17.6, 10.8 Hz, CH=CH\(_2\)), 5.24 (1H, dd, \(J \) = 10.8, 1.2 Hz, CH=CHH), 5.03 (1H, dd, \(J \) = 17.6, 1.2 Hz, CH=CHH), 3.68 (3H, s, OCH\(_3\)), 2.26-2.21 (1H, m, CH), 1.74 (2H, q, \(J \) = 7.6 Hz, CH\(_2\)CH\(_3\)), 1.61-1.20 (8H, m, (CH\(_2\))\(_4\)), 0.79 (3H, t, \(J \) = 7.2 Hz, CH\(_3\)); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta \) 176.1, 136.6, 115.7, 55.6, 51.7, 47.0, 28.1, 27.8, 26.9, 25.5, 25.3, 9.6; Optical Rotation: \([\alpha]_D^{20} \) –0.30 (\(c = 0.67\), CHCl\(_3\)) for an enantiomerically enriched sample of 94% ee.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (94% ee shown; chiral dex GTA column, 10 psi, 80 °C).
(R)-Methyl 2-cyclopentyl-2-vinylhexanoate (17). This compound has been previously reported and spectra data match those described.\(^7\)

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 6.03 (1H, dd, \(J = 17.6, 11.2\) Hz, CH=CH\(_2\)), 5.24 (1H, dd, \(J = 11.2, 1.2\) Hz, CH=CHH), 5.03 (1H, dd, \(J = 17.6, 1.2\) Hz, CH=CHH), 3.67 (3H, s, OCH\(_3\)), 2.27-2.22 (1H, m, CH), 1.70-1.04 (14H, m, CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\) and CH(CH\(_2\)\(_4\)), 0.86 (3H, t, \(J = 7.2\) Hz, CH\(_3\)); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 176.3, 136.9, 115.5, 55.0, 51.8, 47.3, 35.0, 28.1, 27.2, 26.9, 25.5, 25.3, 23.4, 14.1; Optical Rotation: \([\alpha]_D^{20}\) = –5.63 (c = 1.00, CHCl\(_3\)) for an enantiomerically enriched sample of 95% ee.

Enantiomeric purity was determined by chiral GLC analysis in comparison with authentic racemic material (96% ee shown; \(\beta\)-dex column, 10 psi, 90 °C).
(S)-tert-Butyl 2-ethyl-2-methylbut-3-enoate (33, This compound has been previously reported and spectra data match those described).\textsuperscript{9} \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}); \(\delta\) 5.99 (1H, dd, \(J = 10.4, 18.0\) Hz, CH=CH\textsubscript{2}), 5.06 (2H, m, CH=CH\textsubscript{2}), 1.73 (1H, m, CH\textsubscript{3}HH), 1.55 (1H, m, CH\textsubscript{3}HH), 1.44 (9H, s, (CH\textsubscript{3})\textsubscript{3}CO), 1.20 (3H, s, (CH\textsubscript{3})(CO\textsubscript{2}t-Bu)C), 0.848 (3H, dd, \(J = 7.2, 7.2\) Hz, CH\textsubscript{3}CH\textsubscript{2}); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}); \(\delta\) 175.3, 142.5, 113.2, 80.4, 49.6, 32.2, 28.2, 20.1, 9.1; Optical Rotation: \([\alpha]_D^{20} -13.8 (c = 0.65, \text{CHCl}_3)\) for an enantiomerically enriched sample of 60% ee.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (62% ee shown; chiral dex GTA column, 10 psi, 35 \(^\circ\)C).
(S)-tert-Butyl 2-methyl-2-vinylhexanoate (34; this compound has been previously reported and spectra data match those described) \(^8\) \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 5.97 (1H, dd, \(J = 17.6, 10.8\) Hz, CH=CH\(_2\)), 5.05-5.01 (2H, m, CH=CH\(_2\)), 1.66-1.44 (2H, m, CH\(_3\)CH=CH\(_2\)CH\(_3\)), 1.41 (9H, s, (CH\(_3\))\(_3\)), 1.30-1.14 (7H, m, CCH\(_3\) and CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 0.87 (3H, t, \(J = 7.2\) Hz, CH\(_3\)); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 175.3, 142.7, 112.9, 80.3, 49.2, 39.1, 28.1, 26.9, 23.3, 20.6, 14.1; HRMS (EI\(^+\)): Calcd for C\(_{13}\)H\(_{24}\)O\(_2\): 212.1776, Found: 212.1773; Optical rotation: \([\alpha]_D^{20}\) -8.75 (\(c = 1.00\), CHCl\(_3\)) for an enantiomerically enriched sample of 60% ee.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (63% ee shown; chiral dex GTA column, 10 psi, 35 °C).

(S)-Methyl 2-methyl-2-vinylhexanoate (35). This compound has been previously reported and spectra data match those described.\(^2\)

\(\text{\(^1\)H NMR (400 MHz, CDCl}_3\):} \ \delta \ 5.99 \ (1\text{H, dd, } J = 17.6, 10.8 \text{ Hz, CH} = \text{CH}_2\), \ 5.11 \ (1\text{H, dd, } J = 10.8, 1.2 \text{ Hz, CH} = \text{CHH}), \ 5.03 \ (1\text{H, dd, } J = 17.6, 1.2 \text{ Hz, CH} = \text{CHH}), \ 3.65 \ (3\text{H, s, OCH}_3), \ 1.72-1.12 \ (9\text{H, m, CH}_3 \text{ and CH}_2\text{CH}_2\text{CH}_2), \ 0.86 \ (3\text{H, t, } J = 7.2 \text{ Hz, CH}_2\text{CH}_3); \ \text{\(^13\)C NMR (CDCl}_3, 100 \text{ MHz):} \ \delta \ 176.6, 142.0, 113.5, 52.0, 48.8, 39.1, 26.9, 23.2, 20.6, 14.1; \ \text{Optical Rotation:} \ [\alpha]_D^{20} -7.67 \ (c = 1.00, \text{CHCl}_3) \ \text{for an enantiomerically enriched sample of 58\% ee.}\)

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (58\% ee shown; chiral dex GTA column, 10 psi, 50 °C).
(S)-tert-Butyl 2-ethyl-2-vinylhexanoate (36) IR (neat): 2963 (m), 2934 (m), 2875 (m), 1725 (s), 1458 (m), 1367 (m), 1246 (m), 1172 (m), 1136 (s), 914 (w), 852 (w) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 5.99 (1H, dd, J = 17.8, 11.0 Hz, CH=CH₂), 5.14 (1H, dd, J = 11.0, 1.0 Hz, CH=CH₂), 5.05 (1H, dd, J = 17.8, 1.0 Hz, CH=CH₂), 1.69-1.58 (4H, m, C₆H₄CH₃ and CH₂CH₂CH₂CH₃), 1.43 (9H, s, C(CH₃)₃), 1.31-1.1.09 (2H, m, CH₂CH₂CH₂CH₃), 0.89 (3H, t, J = 7.2 Hz, CH₂CH₃), 0.81 (3H, t, J = 7.2 Hz, CH₂CH₂CH₂CH₃); ¹³C NMR (CDCl₃, 100 MHz): δ 175.0, 140.7, 114.0, 80.3, 53.2, 35.9, 29.2, 28.2, 26.7, 23.5, 14.2, 8.9; HRMS (ESI+): Calcd for C₁₄H₃₀NO₂ [M+NH₄]: 244.39350, Found: 244.22765; Optical Rotation: [α]D²⁰ +3.80 (c = 0.63, CHCl₃) for an enantiomerically enriched sample of 83% ee.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (62% ee shown; chiral dex GTA column, 10 psi, 45 °C)
(S)-Methyl 2-ethyl-2-vinylhexanoate (37, This compound has been previously reported and spectra data match those described).\(^2\)\(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 5.96 (1H, dd, \(J = 18.0, 10.8\) Hz, CH=CH\(_2\)), 5.16 (1H, dd, \(J = 10.8, 1.2\) Hz, CH=CH\(_2\)H), 5.05 (1H, dd, \(J = 18.0, 1.2\) Hz, CH=CHH), 3.66 (3H, s, OCH\(_3\)), 1.71 (2H, q, \(J = 7.6\) Hz, CH\(_2\)CH\(_3\)), 1.65 (2H, dd, \(J = 8.8, 8.0\) Hz, CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 1.30-1.09 (4H, m, CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 0.86 (3H, t, \(J = 7.2\) Hz, CH\(_2\)CH\(_3\)), 0.78 (3H, t, \(J = 7.2\) Hz, CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\))\(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 176.3, 140.1, 114.5, 52.9, 51.9, 35.6, 28.8, 26.6, 23.3, 14.1, 8.9; Optical Rotation: \([\alpha]_D^{20}\) +2.14 (\(c = 1.00\), CHCl\(_3\)) for an enantiomerically enriched sample of 79% ee.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (79% ee shown; chiral dex GTA column, 10 psi, 50 °C).
-BuO

Et

n-Bu
Chapter Three

Development of Cu-Catalyzed Enantioselective Allylic Substitutions with Alkyl, Aryl, and Heterocyclic Aluminum Reagents for the Formation of Quaternary Stereogenic Centers

3-1 Project Perspective

When developing Cu-catalyzed enantioselective allylic substitutions, the choice of nucleophiles is noteworthy. Ideally, a nucleophile should be reactive enough to facilitate the reaction, readily accessible, easy to prepare, and atom economical. Trialkylaluminum reagents are less expensive compared to dialkylzinc reagents (Table 1). A variety of aluminum reagents can be readily prepared from the treatment of commercially available

| Table 1. Price Comparison between Commercially Available Organometallic Reagents |
|---------------------------------|-----------------|-----------------|-----------------|
|                                | Mg (Grignard Reagents)$^a$ | Zn (Zinc Reagents)$^b$ | Al (Aluminum Reagents)$^b$ |
| MeMgCl                          | $23/mol$         | Me$_2$Zn         | Me$_3$Al        |
| EtMgCl                          | $84/mol$         | Et$_2$Zn         | Et$_3$Al        |
| i-BuMgCl                        | $108/mol$        | i-Bu$_2$Zn       | i-Bu$_3$Al      |
| PhMgCl                          | $20/mol$         | Ph$_2$Zn         |                 |

$^a$ Commercially available from Aldrich. 2.0 M or 3.0 M solution in THF. $^b$ Commercially available from STREM.
inexpensive dialkylaluminum chloride with the corresponding organolithium or Grignard reagents but so can \( \text{R}_2\text{Zn} \). In addition, we have demonstrated that \( \text{Et}_3\text{Al} \) is more reactive than \( \text{Et}_2\text{Zn} \) in Cu-catalyzed enantioselective allylic alkylation (EAA) of disubstituted allylic substrates in the context of natural product synthesis.\(^1\) Moreover, we have reported the Cu-catalyzed EAA with vinylaluminum reagents, prepared from various alkynes and dibal-H, to achieve enantioselective vinyl additions.\(^2\) In addition to allylic alkylation, Cu-catalyzed enantioselective conjugate addition reactions to cyclic enones with dialkylarylaluminum reagents have been reported, affording aryl addition products in good enantioselectivities (up to >98% ee).\(^3\) Thus, we envisioned Cu-catalyzed enantioselective allylic substitution reactions with alkyl- or arylaluminum reagents; the reactions with primary alkyl and phenyl Grignard reagents do not proceed efficiently (Chapter 2).\(^4\) To complement difficult access to enantioselective allylic substitutions with Grignard reagents, as well as to apply a variety of aluminum reagents for additions of synthetic useful units, such as aryl groups and heterocycles, through enantioselective \( \text{S}_\text{N}2' \)

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\(^4\) For ethyl and \( n \)-butyl additions, regioselectivity up to 97:3 \( \text{S}_\text{N}2' \): \( \text{S}_\text{N}2 \) with 70% ee were obtained. There was no phenyl addition in the reaction with PhMgCl.
substitution, we initiated our studies involving aluminum-based reagents in Cu-catalyzed
enantioselective allylic substitutions in the presence of chiral N-heterocyclic carbene
(NHC) complexes to generate quaternary stereogenic centers.

3-2 Cu-Catalyzed EAA with Trialkylaluminum Reagents

We first optimized the catalytic enantioselective allylic alkylations of
\(\alpha\)-methyl-\(\alpha,\beta\)-unsaturated \(t\)-butyl esters with commercially available triethylaluminum
reagents. Details for the optimization are described in this section.

3-2-1 Preliminary Studies with \(\text{Et}_3\text{Al}\)

Initially, we assessed different leaving groups for the \(\alpha,\beta\)-unsaturated \(t\)-butyl ester
under the optimal conditions found for Cu-catalyzed EAA with Grignard reagents of
allylic chlorides, addressed in Chapter 2. Reactions of allylic chloride 4 or phosphate 5
were tested in the reaction with 1.5 equivalents of \(\text{Et}_3\text{Al}\) in the presence of 1 mol %
bidentate NHC-Ag complex 2\(^{5b}\) (see Chart 1) and 0.5 mol % \(\text{CuCl}_2\cdot2\text{H}_2\text{O}\) at various

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(5) For other catalytic EAA involving chiral NHC complexes, see: (a) Larsen, A. O.; Leu, W.;
(b) Van Veldhuizen, J. J.; Campbell, J. E.; Giudici, R. E.; Hoveyda, A. H. J. Am. Chem. Soc. 2005,
127, 6877-6882. (c) Reference 1. (d) Kacprzynski, M. A.; May, T. L.; Kazane, S. A.; Hoveyda, A.
(6) 1 mol % NHC ligand and 0.5 mol % \(\text{CuCl}_2\cdot2\text{H}_2\text{O}\) was used in Cu-catalyzed EAA with Grignard
reagents.
Chapter 3, Page 73

temperatures (-15, -30, -50, and -78 °C). As data are shown in entries 1-4 in Table 2, the alkylation of allylic chloride 4 at all temperatures screened only delivers desired S_N2’ product 6 in low conversion (24-40% conversion) as a racemate. The reaction of allylic phosphate 5 does not provide improved conversion (<29% conversion, entries 5-8), however, enantioselectivities (20% ee) were obtained at -30 and -50 °C (entries 6 and 7, Table 2).
Chart 1. Chiral Bidentate NHC-Ag Complexes$^{5a,5b,8a}$

Table 2. Initial Studies of Leaving Group in Cu-Catalyzed EAA with Et$_3$Al at Various Temperatures$^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>temp (°C)</th>
<th>conv (%)$^b$</th>
<th>ee (%)$^c$</th>
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<td>&lt;5</td>
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<td>&lt;2</td>
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</table>

$^a$ Reactions were performed under N$_2$ atm. >98% $^b$ Determined by analysis of 400 MHz $^1$H NMR spectra. $^c$ Determined by GLC analysis.
At this point, reactions were examined without the catalyst to see where a racemate is produced from. When allylic phosphate 5 is treated with 1.5 equivalents of Et₃Al, <2% conversion is observed (eq 1). As shown in equation 2, 0.5 mol % CuCl₂·2H₂O catalyzes allylic alkylation to provide Sₐₙ₂’ product 6 in 34% conversion. In order to improve reactivity and selectivities, we examined a variety of NHC-Ag complexes including a monodentate NHC-Ag complex⁷ and sulfonate-based NHC-Ag complexes⁸ (Chart 2).

As shown in Table 3, when allylic chloride 4 is used, reactions with NHC-Ag complexes 2 and 7 provide 6 as a racemic product (entries 1 and 2); while increased enantioselectivity could be obtained when sulfonate-based NHC-Ag complex 3 is used (47% ee, entry 3). Reactions with allylic chloride 4, however, proceed to low conversion (18-31% conversion, entries 1-3). Next, allylic phosphate 5 was employed in EAA;

---

NHC-Ag complex 2 promoted the EAA to afford 6 in 29% conversion with low enantioselectivity (-20% ee, entry 4). Monodentate NHC-Ag complex 7 promotes the alkylation of 5 in 55% conversion accompanied by the generation of 17% S_N2 product and racemic 6 (entry 5). Cu-catalyzed EAA with NHC-Ag complex 3 proceeds to complete conversion, affording only S_N2’ product 6 (>98%) in significantly increased enantioselectivity (84% ee, entry 6). In addition, sterically modified NHC-Ag complexes 8 and 9 were employed for the reaction. These NHC-Ag complexes 8 and 9 promote the alkylation in >98% conversion with >98% S_N2’ product 6 in 86 and 82% ee, respectively (entries 7 and 9). Based on these results, NHC-Ag complex 8 was selected as an optimal ligand and reactions at various temperatures were carried out. Cu-catalyzed EAA carried out at -50 °C gives a similar result compared to -30 °C (85% ee, entry 10 vs 86% ee, entry 7). Only 28% conversion is obtained at -78 °C, furnishing 6 with slightly lower
enantioselectivity (80% ee, entry 11 vs 86% ee, entry 7). When the temperature is increased to 0 °C and to 22 °C, high enantioselectivities are still maintained (84% ee, entries 12 and 13). This initial screening was done with 2:1 ratio of NHC ligand and a Cu salt, however, catalyst prepared from 1:1 mixture of NHC ligand (0.5 mol % NHC-Ag complex in dimeric form) and CuCl₂·2H₂O (1 mol %) is effective as well, providing same enantioselectivity (86% ee, entries 7 and 8).

\[ \text{Table 3. Cu-Catalyzed Enantioselective Allylic Alkylations of Me-Substituted tert-Butyl Esters with Et}_2\text{Al}^3 \]

\[
\begin{array}{cccccc}
\text{entry} & \text{LG} & \text{NHC-Ag} (\text{mol} \%) & \text{temp (°C)} & \text{conv} (%)^b & \text{ee} (\%)^c \\
1 & \text{Cl} & 4 & 2;1 & -30 & 31 & >98:2 \\
2 & \text{Cl} & 4 & 7;2 & -30 & 18 & >98:2 \\
3 & \text{Cl} & 4 & 3;1 & -30 & 27 & >98:2 \\
4 & \text{OPO(OEt)}_2 & 5 & 2;1 & -30 & 29 & >98:2 \\
5 & \text{OPO(OEt)}_2 & 5 & 7;2 & -30 & 55 & 69:31 \\
6 & \text{OPO(OEt)}_2 & 5 & 3;1 & -30 & >98 & >98:2 \\
7 & \text{OPO(OEt)}_2 & 5 & 8;1 & -30 & >98 & >98:2 \\
8 & \text{OPO(OEt)}_2 & 5 & 8;0.5 & -30 & >98 & >98:2 \\
9 & \text{OPO(OEt)}_2 & 5 & 9;1 & -30 & >98 & >98:2 \\
10 & \text{OPO(OEt)}_2 & 5 & 8;1 & -50 & >98 & >98:2 \\
11 & \text{OPO(OEt)}_2 & 5 & 8;1 & -78 & 28 & >98:2 \\
12 & \text{OPO(OEt)}_2 & 5 & 8;1 & 0 & >98 & >98:2 \\
13 & \text{OPO(OEt)}_2 & 5 & 8;1 & 22 & >98 & >98:2 \\
\end{array}
\]

\(^a\) Reactions were performed under N₂ atm. \(^b\) Determined by analysis of 400 MHz \(^1\)H NMR spectra. \(^c\) Determined by GLC analysis.
As equation 3 shows, Et\textsubscript{3}Al to methyl ester 10 affords 11 with diminished enantioselectivities in the presence of NHC-Ag complex 3 or 8 (46% ee and 50% ee), revealing that sterically demanding ester group in allylic phosphate can lead to high enantioselectivities. Only 0.25 mol % NHC-Ag complex 8 and 0.5 mol % CuCl\textsubscript{2}\textcdot2H\textsubscript{2}O can be used (1:1 ratio of NHC ligand and a Cu salt) and the alkylation proceeds to >98% conversion within 24 h to afford the S\textsubscript{N}2' product 6 with high enantioselectivity (86% ee, eq 4). In addition to Et\textsubscript{3}Al additions, Me\textsubscript{3}Al addition to Et-substituted allylic phosphate 12 in the presence of NHC-Ag complex 3 proceeds readily to afford S\textsubscript{N}2' product \textit{ent}-6 in 71% ee (eq 5).
Since the enantioselectivity of the products is still moderate (46-86% ee), we screened various Cu(I) and Cu(II) salts (Table 4). Cu(I) and Cu(II) chlorides as well as Cu(I) and Cu(II) triflates give no significant difference in enantioselectivity (84-86% ee, entries 1-4) as compared to Cu(II) chloride bishydrate (86% ee, entry 5). The reaction with NHC-Ag complex 8 and CuCl₂·2H₂O is complete within 1 h (entry 6).

<table>
<thead>
<tr>
<th>entry</th>
<th>Cu salt</th>
<th>time (h)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl₂</td>
<td>24</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>CuCl</td>
<td>24</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OTf)₂</td>
<td>24</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>(CuOTf)₂(C₆H₆)</td>
<td>24</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>CuCl₂·2H₂O</td>
<td>24</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>CuCl₂·2H₂O</td>
<td>1</td>
<td>84</td>
</tr>
</tbody>
</table>

Reactions were performed under N₂ atm. >98% conv and >98:<2 SN₂:SN₂ in all cases determined by analysis of ¹H NMR spectra. Determined by GLC analysis. 0.25 mol % of Cu salt was used.
3-2-2 Cu-Catalyzed EAA with (i-Bu)₃Al

Based on the results of Et₃Al addition, Cu-catalyzed EAA of allylic phosphates with (i-Bu)₃Al was carried out (Table 5). The alkylation of allylic phosphate 5 with NHC-Ag complex 3 furnishes the desired SN₂’ product 13 in 66% ee (entry 1). When the alkylation is promoted by NHC-Ag complex 8 (see Chart 2), the desired product 13 is afforded with an increase of enantioselectivity (86% ee, entry 2). Lower enantioselectivities were observed in EAA of allylic phosphate 10 with NHC-Ag complexes 3 and 8 (41% ee, entry 3 and 67% ee, entry 4).

Table 5. Cu-Catalyzed EAA with (i-Bu)₃Al

<table>
<thead>
<tr>
<th>entry</th>
<th>Product</th>
<th>NHC-Ag</th>
<th>conv (%)b</th>
<th>ee (%)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>3</td>
<td>&gt;98; 24</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>8</td>
<td>&gt;98; 24</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>3</td>
<td>&gt;98; 14</td>
<td>41</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>8</td>
<td>&gt;98; 14</td>
<td>67</td>
</tr>
</tbody>
</table>

a Reactions were performed under N₂ atm. >98:<2 S_N2:S_N2 in all cases. b Determined by analysis of 400 MHz ¹H NMR spectra. c Determined by GLC analysis.
3-3  \(n\)-Butyl Additions

In Chapter 2, low enantioselectivities were observed in the Cu-catalyzed EAA with \(n\)-BuMgCl. In an effort to improve these results, we examined \(n\)-butyl addition in Cu-catalyzed EAA of allylic phosphate 5 with organoaluminum reagents. Since \((n\text{-Bu})_3\text{Al}\) is not commercially available, we prepared \(\text{R}_2\text{Al}(n\text{-Bu})\) from the reaction of commercially available dialkylaluminum chloride with \(n\text{-BuLi}\) or \(n\text{-BuMgCl}\), as depicted in equation 6. Generation of the alkylaluminum reagent can be performed in either THF or pentane. The use of pentane can precipitate generated metal salts such as \(\text{MgCl}_2\) and \(\text{LiCl}\). Aluminum reagents prepared in THF and pentane were tested in the EAA reaction with NHC-Ag complex 3 at -30 °C (entries 1-4, Table 6). Reactions with \(\text{Me}_2\text{Al}(n\text{-Bu})\) in THF provided up to 93% of undesired methylated product 16 with <10% \(n\)-Bu adduct 15 (entries 1 and 3). When the reagent is prepared in pentane, the Cu-catalyzed EAA produces more \(n\)-Bu adduct 15 with increased enantioselectivities (14% of 15 with 58% ee, entry 2 and 33% of 15 with 75% ee, entry 4); the use of \(\text{Me}_2\text{Al}(n\text{-Bu})\) prepared in pentane from \(n\text{-BuLi}\) affords the butyl addition product 15 with the highest enantioselectivity (entry 4). Next, \(\text{Et}_2\text{Al}(n\text{-Bu})\) in pentane was examined; Cu-catalyzed EAA with this reagent, in the
presence of the NHC-Cu complex derived from 3, affords the \( n \)-butyl adduct 15 and ethyl adduct 6 in a ratio of 53:47 15:6 with 76% ee (Et adduct 6 with 83% ee, entry 5). Additionally, the reaction in the presence of NHC-Ag complex 8 provides \( n \)-Bu and Et substitutions in a 61:39 ratio with improved enantioselectivities (80% ee for 15 and 85% ee for 6, entry 6). Observed enantioselectivity of the \( n \)-Bu addition product 15 from the reaction with \( \text{Et}_2\text{Al}(n\text{-Bu}) \) is significantly higher than that obtained from EAA with \( n\text{-BuMgCl} \) (69% ee of 15, Chapter 2). Since prepared aluminum reagents contains two

### Table 6. Cu-Catalyzed Enantioselective Allylic Alkylations with \( \text{R}_2\text{Al}(n\text{-Bu}) \)

<table>
<thead>
<tr>
<th>entry</th>
<th>( n\text{-Bu} ) source</th>
<th>( \text{R}_2\text{Al}(n\text{-Bu}) ) in THF or pentane</th>
<th>NHC-Ag</th>
<th>conv (%)(^b)</th>
<th>( \text{Sn}2: \text{Sn}2) (^b)</th>
<th>( 15:16 ) or 15:6(^{b,c} )</th>
<th>ee (15) (%)(^d)</th>
<th>ee (6) (%)(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( n\text{-BuMgCl} )</td>
<td>( \text{Me}_2\text{Al}(n\text{-Bu}) ) in THF</td>
<td>Me(_2)Cl or Et(_2)AlCl</td>
<td>3</td>
<td>36</td>
<td>&gt;98:2</td>
<td>7:93</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>( n\text{-BuMgCl} )</td>
<td>( \text{Me}_2\text{Al}(n\text{-Bu}) ) in pentane</td>
<td>Me(_2)Cl or Et(_2)AlCl</td>
<td>3</td>
<td>&gt;98</td>
<td>83:17</td>
<td>14:86</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>( n\text{-BuLi} )</td>
<td>( \text{Me}_2\text{Al}(n\text{-Bu}) ) in THF</td>
<td>Me(_2)Cl or Et(_2)AlCl</td>
<td>3</td>
<td>&gt;98</td>
<td>86:14</td>
<td>6:94</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>( n\text{-BuLi} )</td>
<td>( \text{Me}_2\text{Al}(n\text{-Bu}) ) in pentane</td>
<td>Me(_2)Cl or Et(_2)AlCl</td>
<td>3</td>
<td>&gt;98</td>
<td>&gt;98:2</td>
<td>33:67</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>( n\text{-BuLi} )</td>
<td>( \text{Et}_2\text{Al}(n\text{-Bu}) ) in pentane</td>
<td>Me(_2)Cl or Et(_2)AlCl</td>
<td>8</td>
<td>&gt;98</td>
<td>&gt;98:2</td>
<td>53:47</td>
<td>76</td>
</tr>
<tr>
<td>6</td>
<td>( n\text{-BuLi} )</td>
<td>( \text{Et}_2\text{Al}(n\text{-Bu}) ) in pentane</td>
<td>Me(_2)Cl or Et(_2)AlCl</td>
<td>8</td>
<td>&gt;98</td>
<td>&gt;98:2</td>
<td>61:39</td>
<td>80</td>
</tr>
</tbody>
</table>

\( ^a \) Reactions were performed under N\(_2\) atm. \( ^b \) Determined by analysis of 400 MHz \(^1\)H NMR spectra. \( ^c \) Ratio of \( n\)-butyl addition and R (Me or Et) addition. \( ^d \) Determined by GLC analysis.
similar size of sp³-hybridized carbons (ethyl and n-butyl), it is difficult to selectively transfer the desired n-butyl group.

3-4 Additions of Various Aryl Groups and Heterocycles with Readily Available Aluminum Reagents

As presented in the previous section, the versatility of readily accessible aluminum reagents can be utilized to introduce various substituents to quaternary stereogenic centers. We have shown that Cu-catalyzed EAA in the presence of in situ-generated NHC-Cu complexes with PhMgCl did not provide the desired product (Chapter 2). There is only one example for Cu-catalyzed EAA to access products containing aryl-substituted quaternary stereogenic centers utilizing arylzinc reagents.⁵ The disclosure by Tomioka et al. in 2008 shows an example of Cu-catalyzed allylic aryl addition, in the presence of CuTC and proline-based chiral ligand, with Grignard reagents to form a tertiary stereogenic center.⁹ Among the few reports for the formation of stereogenic centers bearing aryl groups through catalytic enantioselective allylic alkylation, Iridium can be used to catalyze the reaction reported by Alexakis et al. in 2009 (Scheme 1).¹⁰

---

accomplished the construction of tertiary stereogenic centers bearing aryl groups with \textit{in situ}-generated arylzinc reagents; low regioselectivity was observed (16:84-63:37 \(S_N2':S_N2\)) with enantioselectivities up to 91\% ee. We, then, began to investigate NHC-Cu catalyzed allylic substitution of aryl addition, as well as heterocycle addition utilizing the versatility of organoaluminum reagents.

\textbf{Scheme 1. Ir-Catalyzed EAA with \textit{in situ}-Generated Arylzinc Reagents from Aryl Grignard Reagents}\textsuperscript{10}

\[
\begin{align*}
\text{4.4 mol \% Ligand 17} & \rightarrow \text{1.5 equiv ArMgBr} \\
\text{2 mol \% \([\text{IrCl(cod)}]_2\)} & \rightarrow \text{THF, 22 °C, 16-20 h} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ar} & \rightarrow \text{Sn2'} \\
16:84 - 63:37 \text{Sn2':Sn2} & \text{up to 91\% ee} \\
\end{align*}
\]
3-4-1 Initial Studies of the Reactions with R₂AlPh

i) Examination of the Alkyl Groups on R₂AlPh

We prepared three types of aluminum reagents from the reaction of commercially available PhLi in Bu₂O with dialkylaluminum chloride (Table 7); these reagents are used directly without filtration or purification in the Cu-catalyzed EAA of 5 in the presence of NHC-Ag complex 3. The results are summarized in Table 7; the addition with Me₂AlPh affords a 88:12 ratio of phenyl addition and methyl addition in 46% ee of 18 (entry 1). The reaction of Et₂AlPh affords the S_N2' product 18 exclusively in 79% ee (entry 2). The use of (i-Bu)₂AlPh in EAA results in 90% of the phenyl adduct 18 in 76% ee and 10% of

<table>
<thead>
<tr>
<th>entry</th>
<th>R₂AlPh</th>
<th>conv (%)</th>
<th>time (h)</th>
<th>18 (%)</th>
<th>alkyl addition (%)</th>
<th>18 ee (%)</th>
<th>alkyl addition ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me₂AlPh</td>
<td>&gt;98; 14</td>
<td></td>
<td>88</td>
<td>12; 16</td>
<td>46</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Et₂AlPh</td>
<td>&gt;98; 12</td>
<td></td>
<td>&gt;98</td>
<td>&lt;2; 6</td>
<td>79</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>(i-Bu)₂AlPh</td>
<td>&gt;98; 12</td>
<td></td>
<td>90</td>
<td>10; 13</td>
<td>76</td>
<td>77; 13</td>
</tr>
</tbody>
</table>

*a* Reactions were performed under N₂ atm. *b* Determined by analysis of 400 MHz ¹H NMR spectra. *c* Determined by GLC analysis.
\(i\)-Bu adduct 13 in 77% ee (entry 3). After this examination of the effect of dialkyl group of aluminum reagents, we selected Et\(_2\)AlPh as an effective nucleophile for phenyl addition.

ii) Ligand and Temperature Screening

Next, we screened chiral NHC ligands and reaction temperatures for the EAA with Et\(_2\)AlPh. We have developed various sulfonate-based NHC ligands for enantioselective C-C bond and C-B bond formations\(^\text{5d,8,11}\). Chart 3 illustrates various sulfonate-based NHC-Ag complexes employed for this study and results are summarized in Table 8. The initial screening study of NHC-Ag complexes was carried out at -30 °C (entries 1-3 and 9-18). The reaction with NHC-Ag complex 3 completed within 15 min to generate the \(\text{SN}_2'\) product of Ph addition 18 with >98:<2 (18:6) group selectivity and formed 18 in 81% ee (entry 3). Compared to the reaction with NHC-Ag complex 3, the reaction with NHC-Ag complex 2, bearing an aryloxide, is slow (13% conversion after 15 min), however, enhanced selection of Ph addition with high regioselectivity is obtained (>98:<2 Ph:Et, >98% \(\text{SN}_2'\), and 72% ee, entry 1). Monodentate NHC-Ag complex 7 provides only Ph addition product 18, however, low regioselectivity (83:17 \(\text{SN}_2'\):\(\text{SN}_2\)) and poor

---

enantioselectivity of the desired S<sub>N</sub>2' product 18 were observed (14% ee, entry 2).

According to the above observation, sulfonate-based NHC ligands are more suitable for this transformation than monodentate NHC ligands or phenoxy-based NHC ligands. We

**Table 8. Ligand and Temperature Screen for Cu-Catalyzed EAA with Et<sub>2</sub>AlPh<sup>a</sup>**

<table>
<thead>
<tr>
<th>entry</th>
<th>NHC-Ag; mol %</th>
<th>temp (°C)</th>
<th>conv (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>time (h)</th>
<th>18:6&lt;sup&gt;b&lt;/sup&gt;</th>
<th>S&lt;sub&gt;N&lt;/sub&gt;2:S&lt;sub&gt;N&lt;/sub&gt;2&lt;sup&gt;b&lt;/sup&gt;</th>
<th>18 ee (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2; 0.5</td>
<td>-30</td>
<td>13; 0.25</td>
<td>&gt;98:2</td>
<td>&gt;98:2</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>7; 1</td>
<td>-30</td>
<td>&gt;98:12</td>
<td>83:17</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3; 0.5</td>
<td>-30</td>
<td>&gt;98:0.25</td>
<td>&gt;98:2</td>
<td>&gt;98:2</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3; 0.5</td>
<td>-50</td>
<td>87:12</td>
<td>88:12</td>
<td>&gt;98:2</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3; 0.5</td>
<td>-78</td>
<td>41:12</td>
<td>&gt;98:2</td>
<td>&gt;98:2</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3; 0.5</td>
<td>-15</td>
<td>&gt;98:0.25</td>
<td>&gt;98:2</td>
<td>&gt;98:2</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>3; 0.5</td>
<td>0</td>
<td>&gt;98:0.25</td>
<td>&gt;98:2</td>
<td>&gt;98:2</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>3; 0.5</td>
<td>22</td>
<td>&gt;98:0.25</td>
<td>&gt;98:2</td>
<td>&gt;98:2</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>19; 0.5</td>
<td>-30</td>
<td>61:0.25</td>
<td>&gt;98:2</td>
<td>&gt;98:2</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>20; 0.5</td>
<td>-30</td>
<td>&gt;98:12</td>
<td>&gt;98:2</td>
<td>&gt;98:2</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>21; 0.5</td>
<td>-30</td>
<td>76:0.25</td>
<td>&gt;98:2</td>
<td>&gt;98:2</td>
<td>74</td>
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</tr>
<tr>
<td>12</td>
<td>22; 0.5</td>
<td>-30</td>
<td>36:0.25</td>
<td>92:8</td>
<td>&gt;98:2</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>23; 0.5</td>
<td>-30</td>
<td>&gt;98:0.25</td>
<td>&gt;98:2</td>
<td>83:17</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>24; 0.5</td>
<td>-30</td>
<td>65:0.25</td>
<td>&gt;98:2</td>
<td>&gt;98:2</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>25; 0.5</td>
<td>-30</td>
<td>13:0.25</td>
<td>&gt;98:2</td>
<td>&gt;98:2</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>8; 0.5</td>
<td>-30</td>
<td>&gt;98:12</td>
<td>&gt;98:2</td>
<td>&gt;98:2</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>9; 0.5</td>
<td>-30</td>
<td>&gt;98:0.25</td>
<td>&gt;98:2</td>
<td>&gt;98:2</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>26; 0.5</td>
<td>-30</td>
<td>&gt;98:0.25</td>
<td>97:3</td>
<td>&gt;98:2</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions were performed under N<sub>2</sub> atm.  <sup>b</sup> Determined by analysis of 400 MHz <sup>1</sup>H NMR spectra.  
<sup>c</sup> Determined by GLC analysis.  <sup>d</sup> 18 was isolated in 98% yield.
turned our attention to screen modified sulfonate-based NHC ligands in order to further improve enantioselectivity. Various NHC ligands were investigated with varying steric structure. NHC ligand 19, which has two methyl groups at meta position on aromatic ring, catalyzes the EAA with lower reactivity after 15 min but enantioselectivity is maintained.
(61% conversion and 77% ee, entry 9). More sterically hindered Et groups at ortho position on aromatic ring of NHC-Ag complex 20 promotes the formation of the product 18 in 74% ee (entry 10). One of ortho substituents of aryl group in NHC-Ag complex 19 was then replaced by phenyl group and the reaction with NHC-Ag complex 21 promotes the EAA to 76% conversion to 18 after 15 min with 75% ee (entry 11). NHC-Ag complex 22 bearing a sterically demanding triisopropyl phenyl group resulted in the product formation in considerable diminution of both reactivity and enantioselectivity and some amount of ethyl addition product 6 is obtained (36% conversion in 15 min, 92% of 18 with 10% ee, and 8% of 6, entry 12). NHC-Ag complex 23 bearing an isopropyl group at the ortho position of the aromatic ring promotes Cu-catalyzed EAA but is not regio- or enantioselective (>98% conversion, 83:17 Sₜ₂’:Sₜ with 45% ee, entry 13). NHC-Ag complex 24 with dit-butyl phenyl moiety on meta position promotes the alkylation with low efficiency (65% conversion and 50% ee, entry 14). The reaction with NHC-Ag complex 25 containing an unsubstituted phenyl group did not promote the EAA efficiently possibly due to instability of NHC-Ag complex, but delivering 18 in 13% conversion with 76% ee (entry 15). Furthermore, chiral NHC complexes 8, 9, and 26, of which one of the phenyl groups on the NHC is removed, were tested in the reaction. The reaction promoted
by NHC-Ag complex 8 does not improve the enantioselectivity of the product 18 (75% ee, entry 16 vs 81% ee, entry 3). NHC-Ag complexes containing 2,4-diethyl- and 2,4-diisopropyl-substituted phenyl group, 9 and 26, leads to lower enantioselectivity (71% ee, entry 17 and 38% ee, entry 18). Next, the reaction promoted by NHC-Ag complex 3 was carried out at various temperatures. When the reaction is carried out at temperatures lower than -30 °C, reactivity and enantioselectivity are decreased and 12% of ethyl addition was observed in the reaction at -50 °C (entries 4 and 5). Reactions at elevated temperatures, such as -15, 0, and 22 °C, are efficient but enantioselectivity of the product 18 is moderate (74-76% ee, entries 6-8 vs 81% ee, entry 3).

Under the optimal reaction conditions, phenyl additions of methyl ester substrate 10 and ethyl-substituted substrate 12 were investigated. Phenyl addition to allylic phosphate 10 proceeds to complete conversion only to the desired product 27 within 15 min with 45% ee (eq 7). The reaction of allylic phosphate 12 furnishes 28 with 82% ee (eq 8).
iii) Preparation of Et₂AlPh

The next study was initiated due to the moderate enantioselectivity of the products (<81% ee) of the EAA of phenyl addition. The preparation of arylaluminum reagents is facile. In addition to Method A in Table 9, phenyllithium is generated from the treatment of phenyl bromide and \( n \)-butyllithium through lithium-halogen exchange followed by transmetalation between lithium and aluminum (Method B in Table 9). Since a variety of aryl halides are available, a variety of aluminum reagents can be prepared and used as nucleophiles in allylic substitution. This could be important to expand the induction of various aryl groups, including heterocycles. As shown in Table 9, the result obtained from
the optimized phenyl addition in the previous section is also included for comparison (entry 1). During the preparation of Et₂AlPh solution, LiCl, which is soluble in THF, is precipitated out by the addition of pentane, let to settle and the supernatant solution is used in the reaction. Since LiCl can be Lewis acid, we thought that if LiCl remained in the

**Table 9. Cu-Catalyzed EAA with Et₂AlPh^a**

<table>
<thead>
<tr>
<th>Method</th>
<th>Reaction Conditions</th>
<th>Yield</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1 equiv Et₂AlCl, pentane, 22 °C, 12 h</td>
<td>&gt;98 %</td>
<td>&gt;98:0 %</td>
</tr>
<tr>
<td>B</td>
<td>1 equiv n-BuLi (in hexane), THF, 22 °C, 12 h</td>
<td>&gt;98 %</td>
<td>&gt;98:0 %</td>
</tr>
<tr>
<td>C</td>
<td>1 equiv Et₂AlCl, pentane, 22 °C, 12 h</td>
<td>&gt;98 %</td>
<td>&gt;98:0 %</td>
</tr>
</tbody>
</table>

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^a Reactions were performed under N₂ atm. >98:0 % Stéphany. The amount of hexane from Li reagent is included as pentane. ^b Determined by analysis of 400 MHz 1H NMR spectra. ^c Determined by GLC analysis. nd = not determined.
solution, it might coordinate to the substrate or in situ-generated NHC-Cu complex and decrease enantioselectivity of the desired products. We found that additional LiCl (1 equiv and 5 equiv) present in the EAA reaction leads to significantly decreased enantioselectivity (40% ee, entry 2 and 21% ee, entry 3). When Et₂AlPh is prepared by Method B in a 1:1 mixture of THF and pentane, the formation of 18 is slow and not enantioselective (50% conversion after 20 h and 18% ee, entry 4). In order to reduce the amount of LiCl in the solution of Et₂AlPh through precipitation, the amount of THF, which is used for the lithium-halogen exchange, was decreased and larger amount of pentane was used (~7:1 pentane:THF). The reaction with the aluminum reagents proceeds to >98% conversion within a shorter reaction time (5 h, entry 5 vs 20 h, entry 4), affording the desired product 18 with improved enantioselectivity (73% ee, entry 5). When Et₂O instead of THF is used, the reaction affords a large amount of ethyl addition (7:93 18:6, entry 6). Unexpectedly, low enantioselectivity for 18 (55% ee) and good enantioselectivity for 6 (84% ee) were observed (entry 6). The use of a small amount of Et₂O (~7:1 pentane:Et₂O) also facilitated ethyl addition (6 in 87% ee, entry 7). Additionally, Bu₂O, which is contained in commercially available PhLi, was examined and the EAA in a mixture of pentane and Bu₂O (~7:1 ratio) produced predominately 18 in 79% ee (entry 8).
This result is almost identical to the best one shown in entry 1 in Table 9. Et₂AlPh from the treatment of PhMgCl with Et₂AlCl was also prepared (Method C). PhMgCl was freshly prepared in THF and mixed with Et₂AlCl. The allylic substitution with the resulting aluminum reagent is not efficient or enantioselective (19% conversion and 2% ee, entry 9). To precipitate and remove the \textit{in situ}-generated MgCl₂, 1 equivalent 1,4-dioxane was added to the aluminum reagent solution (entry 10). 1,4-Dioxane interacts with MgCl₂ to form MgCl₂·1,4-dioxane complex, which can be precipitated and removed. The reaction with a solution of the corresponding aluminum reagents affords 18 in 72% ee (entry 10). As shown in equation 9, when 1,4-dioxane is used as a solvent, this reagent provides a highly-efficient EAA reaction delivering 18 in 79% ee within 0.5 h.¹²

(¹²) The EAA with the aluminum reagent from PhMgBr gave similar enantioselectivity but the reaction was slightly slower (68% conv with 78% ee within 0.5 h).
As mentioned above, additives can trap metal salts, which are dissolved in the solution of aluminum reagent to give improved enantioselectivity in the EAA reaction.\textsuperscript{13}

Based on this idea, we examined some additives to complex LiCl. \(N,N,N',N'-\text{Tetramethyl-1,2-ethylenediamine (TMEDA)}\) is known to chelate to LiCl. We hypothesized that chelation of TMEDA to LiCl in solution would avoid the interaction of LiCl with the catalyst or substrate to enhance the enantioselectivity of the allylic alkylation products. As shown in eq 10, the allylic alkylation with the aluminum reagents, when 1 equiv of TMEDA is added, leads to <29\% conversion to 18 with 55\% ee. The use of the aluminum reagent containing 3 equiv of TMEDA did not provide the allylic substitution possibly due to TMEDA coordinating to copper.

3-4-2  Additions of Various Aryl Groups and Heterocycles

i)  Aryl Additions

 Arylaluminum reagents can be readily prepared by the reaction of Et₂AlCl and aryllithium, which is generated from the reaction of an aryl halide with n-BuLi in pentane (scheme in Table 10). These aluminum reagents can be applied to Cu-catalyzed enantioselective allylic substitutions of allylic phosphates in the presence of an NHC-Ag complex to construct all-carbon quaternary stereogenic centers bearing a variety of aryl groups. Results in Cu-catalyzed enantioselective addition of aryl groups are presented in Table 10. The reaction was performed in the presence of 0.5 mol % NHC-Ag complex 3 and 1 mol % CuCl₂·2H₂O at -30 °C. Sterically demanding o-tolyl group can be introduced effectively in 1 h, but enantioselectivity is low (39% ee for 29, entry 1). The addition of methoxy-substituted phenyl group provides the product 30 with good enantioselectivity (81% ee, entry 2) with 72% yield. Reaction with Et₂Al(p-CF₃C₆H₄) in the presence of NHC-Ag complex 3 affords the desired product 31, within 1 h, in 57% ee (entry 3).¹⁴ It is noteworthy that biphenol based-NHC-Ag complex 2 delivers the product with higher enantioselectivity (66% ee, entry 4 vs 57% ee, entry 3) when slightly excess amount of the

(14) The reaction in absence of the NHC ligand provides 38% conversion with >98% aryl addition and >98:<2 S₃N₂':S₃N₂ within 1 h. Thus 1:1.5 ratio of Cu salt and NHC ligand was employed.
NHC-Ag complex 2 is used (1.5:1 ratio of NHC ligand:CuCl₂·2H₂O).

Table 10. Cu-Catalyzed EAA with Arylaluminum Reagents to Ester Substrates

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>NHC-Ag mol %</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Image" /></td>
<td>3; 0.5</td>
<td>1</td>
<td>74</td>
<td>39</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Image" /></td>
<td>3; 0.5</td>
<td>1</td>
<td>72</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Image" /></td>
<td>3; 0.5</td>
<td>1</td>
<td>nd</td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Image" /></td>
<td>2; 0.75</td>
<td>1.5</td>
<td>88</td>
<td>66</td>
</tr>
</tbody>
</table>

* Reactions were performed under N₂ atm, >98% conv, >98<2 S/N₂:S₂, and >98% Aryl addition in all cases determined by analysis of 400 MHz ¹H NMR spectra. * Yields of isolated, purified products. * Determined by GLC analysis. nd = not determined.
i) Additions of Heterocycles

In addition to various aryl groups, allylic substitution of aluminum reagents bearing heterocycles is synthetically undeveloped but is of great importance to synthesize biologically active molecules. The preparation of aluminum reagents including functional groups is facile because a wide range of lithium reagents and Grignard reagents are available. Furthermore, reactions of aluminum reagents can be led to C-C bond formation to generate various stereogenic centers. Lithium reagents can be generated through lithium-halogen exchange as well as through ortho-lithiation and direct lithiation using \( n\)-BuLi (or \( t\)-BuLi). It should be noted that aluminum reagents containing a pyrrole or pyridine from the corresponding bromides were prepared and used in Cu-catalyzed allylic substitution, however, the reaction did not proceed (<2% conversion). It could be partially due to azophilic copper. We turned our attention to aluminum reagents containing furyl and dithianyl groups and prepared from the corresponding lithium reagents through eq 11 or 12 in Table 11. Cu-catalyzed allylic substitution reaction of allylic phosphate 6 is summarized in Table 11. Furyl addition in the presence of 0.5 mol % NHC-Ag complex 3 and 1 mol % CuCl\(_2\)-2H\(_2\)O affords the desired \( S_N2'\) product 34 in >98% conversion after 1 h with 81% ee (entry 1). Improved enantioselectivity is observed when sterically
demanding NHC-Ag complex 20, bearing a diethyl phenyl group, is employed (86% ee, entry 2). Furthermore, sterically congested NHC-Ag complex 22 enhances enantioselectivity up to 98% ee (entry 3). In the case of addition of dithianyl group, the reaction in the presence of NHC-Ag complex 3 was sluggish and not enantioselective.

Table 11. Addition of Heterocycles in Cu-Catalyzed Enantioselective Allylic Substitutions

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>NHC-Ag mol %</th>
<th>conv (%)</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>3; 0.5</td>
<td>&gt;98; 1</td>
<td>nd</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>t-BuO</td>
<td>20; 0.5</td>
<td>&gt;98; 1</td>
<td>nd</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>22; 0.5</td>
<td>&gt;98; 1</td>
<td>90</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>3; 0.5</td>
<td>52; 14</td>
<td>nd</td>
<td>0</td>
</tr>
</tbody>
</table>

*Reactions were performed under N₂ atm. >98% addition of heterocycles in all cases. Determined by analysis of 400 MHz ¹H NMR spectra. Yields of isolated, purified products. Determined by GLC analysis. nd=not determined.
(52% conversion after 14 h, entry 4). The presence of sulfur in the reaction might be
detrimental due to thiophilicity of copper. Furan addition was accomplished highly
enantioselectively.

3-4-3 Cu-Catalyzed Allylic Substitutions of Various Allylic Phosphates

i) Si-Substituted Allylic Phosphate

Cu-catalyzed enantioselective allylic substitutions with aluminum reagents
containing aryl or heterocyclic groups were further expanded to include a Si-substituted
substrate. Results are illustrated in Scheme 2. We have reported phenyl and
\( p\text{-OMe-phenyl} \) addition to trisubstituted vinyl silane \( 36 \) and obtained up to 90% ee.\(^{5d} \)
Sulfonate-based NHC-Ag complex \( 3 \) was found to be an optimal ligand for allylic
substitution with aluminum reagents; 2 mol % of \textit{in situ}-generated NHC-Cu complex
from 1 mol % NHC-Ag complex \( 3 \) and 2 mol % CuCl\(_2\)·2H\(_2\)O is required to promote the
reaction efficiently. Phenyl addition with phenylaluminum reagent, prepared from
commercially available PhLi and Et\(_2\)AlCl, furnishes the desired product \( 37 \) in >98%
conversion (65% yield) within 3 h with high enantioselectivity (92% ee). In the case of
\( p\text{-OMe-phenyl} \) addition, the allylic substitution is slower than phenyl addition (76%
conversion vs >98% conversion within 3 h), and better enantioselectivity was achieved (93% ee) as compared to the diarylzinc system (90% ee is reported). The addition of \( o \)-OMe phenyl group was much slower than the addition of \( p \)-OMe phenyl group (63% conversion within 15 h) with 36% ee for the product 39. Additionally, the allylic substitution of furan proceeds to complete conversion within 1 h with moderate enantioselectivity (73% ee for the product 40).

**Scheme 2.** Cu-Catalyzed Enantioselective Allylic Substitutions of Allyl Silane with Various Aluminum Reagents

| Method A: \( \text{PhLi} \rightarrow 1 \text{ equiv } \text{Et}_2\text{AlCl} \) | \( \text{Et}_2\text{AlPh} + \text{LiCl} \)
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Method A:</strong></td>
<td>( \text{Et}_2\text{AlCl} )</td>
</tr>
<tr>
<td></td>
<td>pentane</td>
</tr>
<tr>
<td></td>
<td>-78 to 22 °C, 12 h</td>
</tr>
<tr>
<td><strong>Method B:</strong></td>
<td>( \text{ArBr} \rightarrow 1 \text{ equiv } \text{Et}_2\text{AlCl} )</td>
</tr>
<tr>
<td></td>
<td>pentane</td>
</tr>
<tr>
<td></td>
<td>-78 to 22 °C, 12 h</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PhMe₂Si</th>
<th>OPO(OEt)₂</th>
<th>PhMe₂Si</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>( \text{36} )</td>
<td>Me</td>
</tr>
</tbody>
</table>

\[ \text{3 equiv } \text{Et}_2\text{AlAr} \]

\[ \text{1 mol % } \text{NHC-Ag 3} \]
\[ \text{2 mol % } \text{CuCl}_2 \cdot 2\text{H}_2\text{O} \]

\[ \text{THF, -30 °C, 1-15 h} \]

\[ \text{No ethyl addition} \]
\[ >98\% \text{ conv, } 92\% \text{ ee} \]
\[ (3 \text{ h}) \]

\[ >98\% \text{ conv, 65\% 92\% ee} \]
\[ (3 \text{ h}) \]

\[ 76\% \text{ conv, 93\% ee} \]
\[ (3 \text{ h}) \]

\[ 63\% \text{ conv, 47\% 36\% ee} \]
\[ (15 \text{ h}) \]

\[ >98\% \text{ conv, 73\% ee} \]
\[ (1 \text{ h}) \]
ii) Aryl-Substituted Allylic Phosphate

We turned our interest to an aryl substituted allylic phosphate, which has been used for Cu-catalyzed EAA of dialkylzinc reagents with amino acid-based chiral ligands and NHC-based ligands.\(^\text{(15)}\) There is only one example of an all-carbon stereogenic center bearing two aryl groups, which is synthesized from Cu-catalyzed EAA with Et\(_2\)Zn of diaryl-substituted allylic phosphate.\(^\text{5b}\) The reaction of allylic phosphate 41 with Et\(_2\)AlPh in the presence of NHC-Ag complex 3 generates 74\% of the desired product 42 along with 29\% of ethyl addition product 43. Product 42 was obtained in 80\% ee. The NHC-Ag complex 8 leads to the selective formation of 42 with the improved enantioselectivity (89\% ee).

\[\text{Me} \quad \text{PhLi} \quad \text{Et}_2\text{AlCl} \quad \text{pentaene} \quad -78 \text{ to } 22 ^\circ \text{C} \quad 12 \text{ h} \quad \text{LiCl} \]

\[\begin{align*}
\text{41} & \xrightarrow{1 \text{ equiv Et}_2\text{AlCl}} \quad \text{Me}\_\text{Et} \quad \text{PhBr} \\
\text{3 equiv Et}_2\text{AlPh} & \quad 0.5 \text{ mol } \% \text{ NHC-Ag 3 or 8} \\
1 \text{ mol } \% \text{ CuCl}_2 \cdot 2\text{H}_2\text{O} & \quad \text{THF, } -30 ^\circ \text{C, 3 h} \\
\rightarrow & \quad \text{Me}\_\text{Et} \quad \text{PhBr} \\
\end{align*}\]

\[\text{42} \quad \text{Br} \quad \text{Br} \quad \text{43} \]

\[\text{>98\% conv, 71\%, 74:26} \quad \text{42:43, >98<2} \quad \text{S} \_\text{P}^2 \_\text{P} \_\text{S}^2, 80\% \text{ ee (with 3)}\]

\[\text{>98\% conv, 48\%, >98} \quad \text{S} \_\text{P}^2 \_\text{P} \_\text{S}^2, 89\% \text{ ee (with 8)}\]

3-5 Conclusions

We have developed Cu-catalyzed enantioselective allylic substitutions with readily accessible aluminum reagents in the presence of sulfonate-based NHC-Ag complexes and CuCl$_2$$\cdot$2H$_2$O for the formation of quaternary stereogenic centers. Not only alkyl addition, but aryl and furyl additions have been demonstrated. Moreover, we have shown the first example for Cu-Catalyzed enantioselective allylic substitutions of a furyl group leading to products containing all carbon quaternary stereogenic centers. The reaction with aluminum reagents is highly regioselective (>$98:<2$ S$_N2$:S$_N2$) and high enantioselectivities can be obtained (up to 98% ee). A variety of modified sulfonate-based NHC-Ag complexes has been examined. Synthetically useful nucleophiles were introduced adjacent to functionalizable ester, aryl, and silane groups. Additionally, we investigated preparation of aluminum reagents bearing alkyl, aryl, and heterocyclic groups in this study. These studies will be expanded to the addition of various requisite substituents to other electrophiles.
3-6 Experimental

General. Infrared (IR) spectra were recorded on a Bruker FT-IR Alpha (ATR mode) spectrophotometer, \( \nu_{\text{max}} \) in cm\(^{-1}\). Bands are characterized as broad (br), strong (s), medium (m), and weak (w). \(^1\)H NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CDCl\(_3\): \( \delta \) 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constants (Hz). \(^{13}\)C NMR spectra were recorded on a Varian Unity INOVA 400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CDCl\(_3\): \( \delta \) 77.16 ppm). High-resolution mass spectrometry was performed on a Micromass LCT ESI-MS (positive mode) at the Mass Spectrometry Facility, Boston College. Enantiomer ratios were determined by GLC analysis (Alltech Associated Chiral dex GTA column (30 m x 0.25 mm) and Betadex 120 column (30 m x 0.25 mm)) and high-performance liquid chromatography (HPLC) with a Shimadzu chromatograph (Chiral Technologies Chiralcel OD (4.6 x 250 mm), Chiral Technologies Chiralcel OB-H (4.6 x 250 mm), Chiral Technologies Chiralcel OJ-H (4.6 x 250 mm), or Chiral Technologies Chiralpak AD (4.6 x 250 mm)) in comparison with authentic racemic materials. Optical rotations were measured on a Rudolph Research Analytical Autopol IV Polarimeter.
Unless otherwise noted, all reactions were carried out with distilled and degassed solvents under an atmosphere of dry N₂ in oven- (135 °C) and flame-dried glassware with standard dry box or vacuum-line techniques. All work-up and purification procedures were carried out with reagent grade solvents (purchased from Doe & Ingalls) in air.

**Reagents and ligands:**

**9-Borabicyclo[3.3.1]nonane dimmer:** prepared according to a previously reported procedure.¹

**2-Bromoanisole:** purchased from Aldrich Chemical Co. and purified by distillation over CaH₂.

**4-Bromoanisole:** purchased from Aldrich Chemical Co. and purified by distillation over CaH₂.

**Bromobenzene:** purchased from Aldrich Chemical Co. and purified by distillation over CaCl₂.

**(E)-3-(2-Bromophenyl)but-2-enyl diethyl phosphate (41):** prepared according to a previously reported procedure.²

**2-Bromotoluene:** purchased from Aldrich Chemical Co. and purified by distillation over CaCl₂.

---

1-Bromo-4-(trifluoromethyl)benzene: purchased from Aldrich Chemical Co. and purified by distillation over CaH₂.

(E)-tert-Butyl 4-chloro-2-methylbut-2-enoate (4): prepared according to a previously reported procedure.³

(E)-tert-Butyl 4-(diethoxyphosphoryloxy)-2-ethylbut-2-enoate (12): prepared according to a previously reported procedure.⁴

(E)-tert-Butyl 4-(diethoxyphosphoryloxy)-2-methylbut-2-enoate (5): prepared according to a previously reported procedure.⁴

n-Butyllithium: purchased from Strem Chemicals Inc. (15% in hexanes) and titrated before use.

Copper(II) dichloride bishydrate: purchased from Aldrich Chemical Co. and used as received.

Dibutylether: purchased from Aldrich Chemical Co. and distilled over sodium before use.

Diethylaluminum chloride: purchased from Aldrich Chemical Co, and used as received.

Diisobutylaluminum chloride: purchased from Aldrich Chemical Co, and used as received.

Diisobutylaluminum chloride: purchased from Aldrich Chemical Co, and used as received.

---

(E)-3-(Dimethyl(phenyl)silyl)but-2-enyl diethyl phosphate (36): prepared according to a previously reported procedure.⁵

1,4-Dioxane: purchased from Aldrich Chemical Co. and purified by distillation over sodium before use.

1,3-Dithiane: purchased from Aldrich Chemical Co. and purified by recrystallization from MeOH before use.

Furan: purchased from Aldrich Chemical Co. and purified by distillation over sodium.

Hydrogen peroxide (35% wt solution in water): purchased from Aldrich Chemical Co. and used as received.

(E)-Methyl 4-(diethoxyphosphoryloxy)-2-methylbut-2-enoate (10): prepared according to a previously reported procedure.⁴

NHC-Ag complex 1: prepared according to a previously reported procedure.⁶

NHC-Ag complex 2: prepared according to a previously reported procedure.⁷

NHC-Ag complex 3: prepared according to a previously reported procedure.⁸

NHC-Ag complex 7: prepared according to a previously reported procedure.⁹

NHC-Ag complex 8: prepared according to a previously reported procedure.¹⁰

NHC-Ag complex 9: prepared according to a previously reported procedure.\textsuperscript{11}

**Pentane:** purified through Cu and alumina columns under a positive pressure of dry argon by a modified Advanced ChemTech purification system.

**Phenyllithium:** purchased from Acros Organics (2.0 M in Bu\(_2\)O) and titrated before use.

**Phenylmagnesium chloride:** prepared from the reaction of chlorobenzene and Mg tunings in THF.

**Tetrahydrofuran:** purchased from Aldrich Chemical Co. and distilled under N\(_2\) from sodium benzophenone ketyl.

**TMEDA:** purchased from Aldrich Chemical Co. and purified by distillation over CaH\(_2\).

**Triethylaluminum:** purchased from Strem Chemicals Inc. and used as received.

**Triisobutylaluminum:** purchased from Strem Chemicals Inc. and used as received.

**Trimethylaluminum:** purchased from Aldrich Chemical Co. and used as received.

\textbf{Representative experimental procedure for Cu-catalyzed enantioselective allylic alkyations of trialkylaluminum reagents to (E)-tert-Butyl 4-(diethoxyphosphoryloxy)-2-methylbut-2-enoate (5):}

In an N\(_2\)-filled glovebox, an oven-dried 10 x 50 mm vial was charged with chiral NHC-Ag complex 8 (1.58 mg, 1.50 x 10\(^{-3}\) mmol, 0.5 mol %), sealed with a rubber septum and parafilm. The vessel was removed from the glovebox. To the chiral NHC-Ag complex 8 under a nitrogen atmosphere were added THF (0.5 mL) and a solution of

CuCl₂·2H₂O (0.01M, 30 µL, 3.00 x 10⁻³ mmol, 1.0 mol %) in THF and the solution was allowed to stir for 30 min. (E)-tert-Butyl 4-(diethoxyphosphoryloxy)-2-methylbut-2-enolate 5 (92.5 mg, 0.300 mmol) in THF (0.5 mL) was added to the solution, which was allowed to stir for 10 min before allowing to cool to -78 °C. Triethylaluminum (51.3 µL, 0.45 mmol) (PYROPHORIC, USE EXTREME CAUTION) was added dropwise through a syringe. The vial was transferred to a -30 °C cryocool. After 1 h, the reaction was quenched by the addition of a saturated aqueous solution of Rochelle’s salt (5 mL). The resulting mixture was washed with diethyl ether (3 x 3 mL) and filtered through a short plug of MgSO₄ and silica gel. The filtrate was concentrated to provide colorless oil residue, which was purified by silica gel column chromatography with Et₂O/Pentane 1:50 to afford the colorless oil of S_N2’ product 6 in 74% yield (40.9 mg, 0.222 mmol).

- **Representative experimental procedure for the preparation of diethyl-n-butylaluminum:** prepared according to a previously reported procedure¹¹ except diethylaluminum chloride and n-butyllithium were used.

- **Representative experimental procedure for the preparation of diethylphenylaluminum (Method A):** prepared according to a previously reported procedure¹¹ except diethylaluminum chloride was used.

- **Representative experimental procedure for the preparation of functionalized arylaluminum reagents (Method B):** prepared according to a previously reported
procedure\textsuperscript{11} except diethylaluminum chloride was used.

\section*{Representative experimental procedure for the preparation of functionalized arylaluminum reagents (Method C):} Phenylmagnesium chloride (6.67 mL, 10.0 mmol, 1.5 M in THF) were added through a syringe to a flame-dried round bottom flask equipped with a stir bar at $-78$ °C (dry ice/acetone bath). Pentane (5 mL) followed by Et$_2$AlCl (1.25 mL, 10.0 mmol) was added through syringes and the solution was allowed to warm to 22 °C and stir for 12 h. The resulting mixture was a clear yellow solution (1.29 M) containing MgCl$_2$ solid that had precipitated out of the solution. The solution was allowed to stand for 30 min to assist with settling of solid MgCl$_2$.

\section*{Representative experimental procedure for the preparation of diethylfurylaluminum reagents:} Furan (727 µL, 10.0 mmol) and THF (1.4 mL) were added to a flame-dried round bottom flask equipped with a stir bar through syringes. The solution was allowed to cool to $-78$ °C (dry ice/acetone bath). $n$-Butyllithium (1.61 M in hexane, 6.21 mL, 10.0 mmol) was added through a syringe and the solution was allowed to stir at 0 °C for 1 h. Pentane (5.6 mL) followed by Et$_2$AlCl (1.38 mL, 11.0 mmol) was added through syringes and the solution was allowed to warm to 22 °C and stir for 12 h. The resulting mixture was a clear yellow solution of diethyl(2-furyl)aluminum (0.653 M) containing LiCl solid that had precipitated out of the solution. The solution was allowed to stand for 30 min to assist with settling of solid LiCl.
Representative experimental procedure for Cu-catalyzed enantioselective allylic substitutions of dialkylphenylaluminum reagents to \((E)\text{-}\text{tert}-\text{Butyl} 4\text{-}(\text{diethoxyphosphoryloxy})\text{-}2\text{-methylbut-2-enoate (5)}\): In an \(\text{N}_2\) filled glove box, NHC-Ag complex 3 (0.75 mg, \(7.5 \times 10^{-4}\) mmol) was weighed out to an oven-dried 13 x 100 mm test tube, which sealed with a septum and removed from the glove box. THF (0.5 mL) and a solution of CuCl\(_2\cdot2\text{H}_2\text{O}\) in THF (0.02 M, 75\(\mu\)L, \(1.50\times 10^{-3}\) mmol) were added and the solution was allowed to stir for 30 min at 22 °C. \((E)\text{-}\text{tert}-\text{Butyl} 4\text{-}(\text{diethoxyphosphoryloxy})\text{-}2\text{-methylbut-2-enoate 5 (46.2 mg, 0.15 mmol)}\) in THF (0.5 mL) was added and the solution was allowed to stir for 10 min at 22 °C and cool to \(-78\) °C (acetone/dry ice bath). A solution of \(\text{Et}_2\text{Al(p-OMeC}_6\text{H}_4)\) (0.616 M, 730 \(\mu\)L, 0.45 mmol) was added slowly through a syringe. The reaction was transferred to a \(-30\) °C cryocool for 1h. At this time, the reaction solution was quenched by the addition of a saturated aqueous solution of Rochelle’s salt (2 mL), washed with Et\(_2\)O (3 x 1 mL), and filtered through a short plug of MgSO\(_4\) and silica gel. The filtrate was concentrated to provide colorless oil residue, which was purified by silica gel column chromatography with Et\(_2\)O/pentane 1:30 to afford the colorless oil of \(\text{S}_2\text{N}^2\) product 18 (34.4 mg, 0.131 mmol, 87% yield).
(R)-tert-Butyl 2,4-dimethyl-2-vinylpentanoate (13). IR (neat): 2954 (w), 1724 (s), 1367 (m), 1246 (m), 1136 (s), 914 (m), 851 (m) cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃): \(\delta\) 5.99 (1H, dd, \(J = 17.6, 10.4\) Hz, CH=CH₂), 5.04 (1H, dd, \(J = 17.6, 0.8\) Hz, CH=CH₂), 5.01 (1H, dd, \(J = 10.8, 0.8\) Hz, CH=CH₂), 1.67-1.62 (2H, m, CH₂CH(CH₃)₂), 1.48-1.44 (1H, m, CH₂CH(CH₃)₂), 1.41 (9H, s, C(CH₃)₃), 1.22 (3H, s, CH₃), 0.87 (6H, t, \(J = 6.4\) Hz, CH₂CH(CH₃)₂); \(^13\)C NMR (100 MHz, CDCl₃): \(\delta\) 175.6, 143.4, 112.7, 80.4, 49.1, 48.1, 28.1, 25.3, 24.5, 24.0, 20.9; HRMS (ESI+): Calcd for C₁₃H₂₅O₂ \([\text{M+H}]\): 213.18545, Found: 213.18641; Optical Rotation: \([\alpha]_{D}^{20} +27.5\) (c = 0.63, CHCl₃) for an enantiomerically enriched sample of 77% ee.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (86% ee shown; chiral dex GTA column, 10 psi, 50 °C).
(R)-Methyl 2,4-dimethyl-2-vinylpentanoate (14). IR (neat): 2954 (w), 2871 (w), 1733 (s), 1462 (w), 1228 (m), 1138 (s), 917 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 6.02 (1H, dd, J = 17.6, 10.4 Hz, CH=CH₂), 5.05 (1H, dd, J = 17.6, 0.8 Hz, CH=CH₂), 5.05 (1H, dd, J = 10.8, 0.8 Hz, CH=CH₂), 3.64 (3H, s, OCH₃), 1.68-1.65 (2H, m, CCH₂CH(CH₃)₂), 1.55-1.49 (1H, m, CCH₂CH(CH₃)₂), 1.24 (3H, s, CH₃CO), 0.84 (6H, ddd, J = 15.2, 4.0, 2.4 Hz, CCH₂CH(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃): δ 176.9, 142.7, 113.2, 52.0, 48.4, 48.3, 25.1, 24.4, 23.6, 21.0; HRMS (ESI+): Calcd for C₁₀H₁₉O₂ [M+H]: 171.13850, Found: 171.13827; Optical Rotation: [α]D²⁰ +13.6 (c = 0.69, CHCl₃) for an enantiomerically enriched sample of 41% ee.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (67% ee shown; chiral dex GTA column, 10 psi, 50 °C).
(R)-tert-Butyl 2-methyl-2-phenylbut-3-enoate (18; This compound has been previously reported and spectra data match those previously described).\(^\text{12}\) \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.27 (5H, m, ArH), 6.37 (1H, dd, \(J = 17.6, 10.8\) Hz, CH=CH\(_2\)), 5.25 (1H, dd, \(J = 10.8, 1.2\) Hz, CH=CHH), 5.13 (1H, dd, \(J = 17.6, 1.2\) Hz, CH=CHH), 1.58 (3H, s, CH\(_3\)), 1.41 (9H, s, (CH\(_3\))\(_3\)CO); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 174.0, 144.3, 141.7, 128.4, 126.7, 126.5, 114.6, 81.1, 54.4, 28.0, 23.6; Optical Rotation: \([\alpha]_D\)\(^{20}\) +3.49 (c = 1.06, CHCl\(_3\)) for an enantiomerically enriched sample of 81\% ee.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (82\% ee shown; \(\beta\)-dex column, 15 psi, 90°C).

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(R)-Methyl 2-methyl-2-phenylbut-3-enoate (27; This compound has been previously reported and spectra data match those described).\textsuperscript{11}

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 7.33 (2H, m, ArH), 7.25 (3H, m, ArH), 6.40 (1H, dd, \(J = 17.2, 10.4\) Hz, CH=CH\textsubscript{2}), 5.29 (1H, dd, \(J = 10.4, 0.8\) Hz, CH=CHH), 5.15 (1H, dd, \(J = 17.6, 0.8\) Hz, CH=CHH), 3.71 (3H, s, CH\textsubscript{3}O), 1.64 (3H, s, CH\textsubscript{3}C); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 175.4, 143.6, 141.0, 128.6, 127.0, 126.5, 115.2, 54.0, 52.5, 23.7.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (45% ee shown; Chiralcel OJ-H column, 99.5/0.5 hexanes/i-PrOH, 0.5 mL/min, 220 nm).
(R)-tert-Butyl 2-ethyl-2-phenylbut-3-enoate (28; This compound has been previously reported and spectra data match those described).\(^\text{12}\)\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.29 (2H, m, ArH), 7.23 (2H, m, ArH), 6.35 (1H, dd, \(J = 17.6, 10.8\) Hz, CH=CH\(_2\)), 5.25 (1H, dd, \(J = 11.2, 1.2\) Hz, CH=CHH), 4.97 (1H, dd, \(J = 17.6, 1.2\) Hz, CH=CHH), 2.15 (1H, dq, \(J = 14.0, 7.6\) Hz, CHHCH\(_3\)), 2.06 (1H, dq, \(J = 13.6, 7.2\) Hz, CHHCH\(_3\)), 1.39 (9H, s, (CH\(_3\))\(_3\)CO), 0.84 (3H, dd, \(J = 7.2\) Hz, CH\(_3\)CH\(_2\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ 173.6, 142.7, 140.3, 128.1, 127.4, 126.6, 115.7, 81.0, 58.5, 29.5, 28.0, 9.5; Optical Rotation: \([\alpha]_D^{20}\) -12.4 (\(c = 1.00,\) CHCl\(_3\)) for an enantiomerically enriched sample of 82% ee.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material obtained from the derived methyl ester derivative, which was prepared by deprotection of \(t\)-butyl ester with trifluoroacetic acid in CH\(_2\)Cl\(_2\), followed by methylation of the derived acid with MeI and K\(_2\)CO\(_3\) in DMF (83% ee shown; chiral dex GTA column, 15 psi, 90 °C).
(R)-tert-Butyl 2-methyl-2-o-tolybut-3-enoate (29). IR (neat): 2978 (w), 1724 (s), 1458 (w), 1367 (m), 1251 (m), 1161 (m), 1104 (m), 920 (w), 846 (w), 752 (w) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.28-7.26 (1H, m, ArH), 7.16-7.11 (3H, m, ArH), 6.51 (1H, dd, J = 17.6, 10.8 Hz, CH=CH₂), 5.11 (1H, dd, J = 10.4, 0.8 Hz, CH=CH₂), 4.79 (1H, dd, J = 17.6, 1.2 Hz, CH=CH₂), 2.19 (3H, s, ArCH₃), 1.60 (3H, s, CCH₃), 1.39 (9H, s, C(CH₃)₃); HRMS (ESI+): Caled for C₁₆H₂₆N₁O₂ [M+NH₄]: 264.19635, Found: 264.19612; Optical Rotation: [α]D²⁰ +0.38 (c = 2.00, CHCl₃) for an enantiomerically enriched sample of 36% ee.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material obtained from the derived methyl ester derivative, which was prepared by deprotection of t-butyl ester with trifluoroacetic acid in CH₂Cl₂, followed by
methylation of the derived acid with MeI and K₂CO₃ in DMF (36% ee shown; Chiralcel OJ-H column, 99.8/0.2 hexanes/i-PrOH, 0.5 mL/min, 254 nm).

\[(R)-\text{tert-Butyl 2-(4-methoxyphenyl)-2-methylbut-3-enoate (30). IR (neat): 2979 (w), 1721 (s), 1610 (w), 1510 (s), 1510 (s), 1367 (m), 1247 (s), 1161 (s), 1122 (s), 1034 (m), 920 (w), 831 (m) cm}^{-1}; \text{^1H NMR (400 MHz, CDCl}_3\text{): }\delta 7.19 (2H, d, J = 8.8 Hz), 6.84 (2H, d, J = 9.2 Hz), 6.37 (1H, dd, J = 17.6, 10.4 Hz), 5.22 (1H, dd, J = 10.8, 1.2 Hz), 5.11 (1H, dd, J = 17.2, 0.8 Hz), 3.78 (3H, s), 1.54 (3H, s), 1.40 (9H, s); \text{^13C NMR (100 MHz, CDCl}_3\text{): }\delta 174.2, 158.3, 142.0, 136.3, 127.7, 114.3, 113.7, 81.0, 55.4, 53.7, 28.0, 23.6; HRMS (ESI+): Calcd for C_{16}H_{26}N_{1}O_{3} [M+NH\textsubscript{4}]: 280.19127, Found: 280.19137; Optical Rotation: [\alpha]_{D}^{20} -4.11 (c = 1.72, CHCl\textsubscript{3}) for an enantiomerically enriched sample of 82% ee.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material obtained from the derived methyl ester derivative, which was prepared
by deprotection of \( t \)-butyl ester with trifluoroacetic acid in \( \text{CH}_2\text{Cl}_2 \), followed by methylation of the derived acid with MeI and \( \text{K}_2\text{CO}_3 \) in DMF (82\% ee shown; Chiralcel OB-H column, 99.8/0.2 hexanes/i-PrOH, 0.5 mL/min, 220 nm).

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\text{(R)-tert-Butyl 2-methyl-2-(4-(trifluoromethyl)phenyl)but-3-enoate (31). IR (neat):} \\
\begin{align*}
1725 \text{ (m), } & 1369 \text{ (m), } 1324 \text{ (s), } 1253 \text{ (m), } 1161 \text{ (s), } 1121 \text{ (s), } 1078 \text{ (s), } 1016 \text{ (s), } 924 \text{ (m), } 842 \text{ (m) cm}^{-1}; \\
\text{H NMR (400 MHz, CDCl}_3\text{:} \\
7.56 \text{ (2H, d, } J = 8.8 \text{ Hz, ArH), } 7.38 \text{ (2H, d, } J = 8.4 \text{ Hz, ArH),} \\
6.33 \text{ (1H, dd, } J = 17.6, 17.2 \text{ Hz, CH=CH}_2\text{), } 5.30 \text{ (1H, d, } J = 11.6 \text{ Hz, CH=CH}_2\text{), } 5.15 \text{ (1H,} \\
3.15 \text{ (1H, d, } J = 17.6 \text{ Hz, CH=CH}_2\text{), } 1.58 \text{ (3H, s, CH}_3\text{), } 1.41 \text{ (9H, s, C(CH}_3\text{)}_3\text{);} \\
\text{C NMR (100 MHz, CDCl}_3\text{): } \delta 173.3, 148.3, 140.9, 127.1, 125.4, 115.5, 81.7, 54.5, 28.0, 23.6; \text{ HRMS (ESI+:} \\
\text{Calcd for } \text{C}_{16}\text{H}_{23}\text{F}_3\text{N}_1\text{O}_2 \text{ [M+NH}_4\text{:} 318.16809, \text{ Found: } 318.16931; \text{ Optical Rotation:} \\
[\alpha]_D^{20} +2.30 \text{ (c } = 1.57, \text{ CHCl}_3\text{) for an enantiomerically enriched sample of 66\% ee.} 
\end{align*}
\]
Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (66% ee shown; β-dex column, 15 psi, 90 °C).

(R)-tert-Butyl 2-(furan-2-yl)-2-methylbut-3-enoate (34). IR (neat): 2980 (w), 1729 (s), 1368 (m), 1253 (m), 1155 (s), 1116 (m), 1012 (w), 929 (w), 801 (w), 733 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.35-7.33 (1H, m), 6.29 (1H, dd, J = 3.2, 1.6 Hz), 6.27 (1H, dd, J = 17.6, 10.8 Hz), 6.13 (1H, dd, J = 3.2, 0.8 Hz), 5.20 (1H, dd, J = 10.4, 0.8 Hz), 5.09 (1H, dd, J = 17.2, 0.8 Hz), 1.59 (3H, s), 1.40 (9H, s); ¹³C NMR (100 MHz, CDCl₃): δ 172.1, 156.2, 141.8, 139.3, 114.9, 110.2, 106.0, 81.5, 51.2, 28.0, 21.6; HRMS (ESI⁺): Calcd for C₁₃H₁₉O₃ [M+H]: 223.13342, Found: 223.13287; Optical Rotation: [α]₀²⁰ -2.38 (c = 1.00, CHCl₃) for an enantiomerically enriched sample of 98% ee.
Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (98% shown; chiral dex GTA, 10 psi, 50 °C).

\((S)\)-tert-Butyl 2-(1,3-dithian-2-yl)-2-methylbut-3-enolate (35). IR (neat): 2977 (w), 1727 (s), 1367 (m), 1248 (m), 1160 (s), 1101 (m), 919 (w), 848 (m), 672 (w); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 6.05 (1H, dd, \(J = 13.8, 8.4 \text{ Hz}\)), 5.26 (1H, d, \(J = 8.4 \text{ Hz}\)), 5.21 (1H, d, \(J = 13.8 \text{ Hz}\)), 2.40-2.88 (6H, m), 1.46 (9H, s), 1.41 (3H, s); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 170.9, 138.2, 115.0, 80.7, 55.9, 53.2, 30.5, 30.3, 27.0, 25.0, 15.7.

Enantiomeric purity was determined by GLC analysis in comparison with authentic racemic material (chiral dex GTA, 10 psi, 55 °C).
(R)-Dimethyl(phenyl)(2-phenylbut-3-en-2-yl)silane  (37; This compound has been previously reported and spectra data match those described). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.37-7.06 (10H, m, ArH), 6.47 (1H, dd, $J = 17.2$, 10.8 Hz, CH=CH$_2$), 5.09 (1H, dd, $J = 10.8$, 1.6 Hz, CH=CHH), 4.94 (1H, dd, $J = 17.2$, 1.2 Hz, CH=CHH), 1.46 (3H, s, CH$_3$), 0.24 (3H, s, SiCH$_3$), 0.23 (3H, s, SiCH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 145.5, 143.1, 136.6, 135.0, 129.2, 127.9, 127.4, 126.6, 124.7, 111.4, 37.6, 19.0, -5.1, -5.2; Optical rotation: $[\alpha]_D^{20}$-15.7 ($c = 1.00$, CHCl$_3$) for an enantiomERICally enriched sample of 92% ee.

Enantiomeric purity was determined by HPLC analysis of the derived alcohol, obtained from the derived alcohol derivative, which was prepared by hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H$_2$O$_2$ (92% ee shown; Chiralcel OD column, 98/2 hexanes/i-PrOH, 1.0 mL/min, 220 nm).
(R)-(2-(4-Methoxyphenyl)but-3-en-2-yl)dimethyl(phenyl)sila

e (38; This compound has been previously reported and
spectra data match those described). $^8$ $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.38-7.26 (5H, m, 
ArH), 6.99 (2H, d, $J = 8.8$ Hz, ArH), 6.76 (2H, d, $J = 8.8$ Hz, ArH), 6.41 (1H, dd, $J = 
17.2$, 10.8 Hz, CCH), 5.07 (1H, dd, $J = 10.8$, 1.6 Hz, CHCHH), 4.98 (1H, dd, $J = 17.2$, 
1.2 Hz, CHCHH), 3.78 (3H, s, OCH$_3$), 1.43 (3H, s, CCH$_3$), 0.24 (3H, s, SiCH$_3$), 0.23 (3H, 
s, SiCH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 157.0, 143.4, 137.7, 136.9, 135.1, 129.3, 127.7, 
127.5, 113.4, 111.3, 55.4, 36.8, 19.4, -5.0, -5.0; Optical Rotation: $[\alpha]_D^{20} -22.9$ ($c = 2.22$, 
CHCl$_3$) for an enantiomerically enriched sample of 94% ee sample.

Enantiomeric purity was determined by HPLC analysis of the derived alcohol, obtained 
from the derived alcohol derivative, which was prepared by hydroboration of the terminal 
olefin with 9-BBN, followed by oxidation with H$_2$O$_2$ (94% ee shown; Chiralpak AD 
column, 99:1 hexanes/i-PrOH, 1.0 mL/min, 220 nm).
(R)-(2-(2-Methoxyphenyl)but-3-en-2-yl)dimethyl(phenyl)silane (39). IR (neat): 3068 (w), 2995 (w), 2954 (w), 1488 (m), 1460 (w), 1427 (w), 1241 (s), 1110 (m), 1028 (m), 896 (s), 769 (s), 734 (s), 734 (s) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.33-7.31 (2H, m), 7.26-7.21 (3H, m), 7.12-7.07 (2H, m), 6.86-6.82 (1H, m), 6.17 (1H, d, \(J = 8.0\) Hz), 6.56 (1H, dd, \(J = 17.6, 10.4\) Hz), 4.96 (1H, dd, \(J = 10.8, 1.6\) Hz), 4.84 (1H, dd, \(J = 17.2, 1.6\) Hz), 3.51 (3H, s), 1.43 (3H, s), 0.29 (3H, s), 0.19 (3H, s); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ 157.1, 144.5, 140.0, 135.1, 134.2, 128.4, 127.8, 127.3, 126.5, 120.6, 110.3, 109.9, 54.0, 39.4, 20.6, -5.0, -5.0; HRMS (ESI\(^+\)): Calcd for C\(_{19}\)H\(_{25}\)O\(_1\)Si\(_1\) [M+H]: 297.16747, Found: 297.16744; Optical Rotation: \([\alpha]\)\(_D\)\(^{20}\) -6.05 (\(c = 0.50, \text{CHCl}_3\)) for an enantiomerically enriched sample of 36% ee.

Enantiomeric purity was determined by HPLC analysis of the derived alcohol, obtained from the derived alcohol derivative, which was prepared by hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H\(_2\)O\(_2\) (36% ee shown; Chiralcel OD column, 99/1 hexanes/i-PrOH, 1.0 mL/min, 220 nm).
(R)-3-(Dimethyl(phenyl)silyl)-3-(2-methoxyphenyl)butan-1-ol.

IR (neat): 2955 (w), 1489 (w), 1244 (s), 1111 (s), 1031 (m), 817 (s), 750 (w), 701 (w) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.32-7.20 (5H, m, ArH), 7.12 (1H, dd, J = 8.0, 1.6 Hz, ArH), 6.97 (1H, dd, J = 7.6, 1.6 Hz, ArH), 6.85 (1H, dt, J = 15.0, 7.6, 1.2 Hz, ArH), 6.71 (1H, dd, J = 8.4, 1.2 Hz, ArH), 3.57 (1H, m, CH₂OH), 3.50 (3H, s, OCH₃), 3.05 (1H, m, CH₂OH), 3.03 (1H, ddd, J = 15.2, 9.6, 6.0 Hz, CH₂OH), 1.71 (2H, ddd, J = 14.8, 9.2, 5.6 Hz, CH₂CH₂OH), 1.36 (3H, s, CH₃), 0.23 (3H, s, SiCH₃), 0.15 (3H, s, SiCH₃); ¹³C NMR (100 MHz, CDCl₃): δ 133.4, 129.3, 123.4, 123.3, 122.1, 121.1, 115.3, 104.9, 61.1, 55.2, 48.9, 33.3, 24.3, 18.4, -9.5, -9.8; HRMS (ESI+): Calcd for C₁₉H₃₀N₁O₂Si₁ [M+NH₄]: 332.20458, Found: 332.20437
(R)-(2-(Furan-2-yl)but-3-en-2-yl)dimethyl(phenyl)silane  (40).

IR (neat): 3079 (w), 3050 (w), 3010 (w), 2959 (w), 2929 (w), 1624 (w), 1500 (w), 1192 (m), 1160 (w), 1015 (w), 923 (w), 901 (w), 833 (m), 816 (s), 772 (m), 723 (s), 699 (s), 654 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.37-7.27 (6H, m), 6.28-6.27 (1H, m), 6.26 (1H, dd, J = 17.6, 10.8 Hz), 5.77-5.76 (1H, m), 5.03 (1H, dd, J = 10.8, 1.6 Hz), 4.84 (1H, dd, J = 17.6, 1.2 Hz), 1.35 (3H, s), 0.36 (3H, s), 0.30 (3H, s); ¹³C NMR (100 MHz, CDCl₃): δ 159.9, 140.6, 140.4, 136.3, 134.6, 129.2, 127.3, 111.2, 110.3, 103.4, 35.8, 17.7, -4.9, -5.0; HRMS (ESI+): Calcd for C₁₆H₂₁O₁Si₁ [M+H]: 257.13617, Found: 257.13660; Optical Rotation: [α]D²⁰ -4.00 (c = 1.37, CHCl₃) for an enantiomerically enriched sample of 70 % ee.

Enantiomeric purity was determined by HPLC analysis of the derived alcohol, obtained from the derived alcohol derivative, which was prepared by hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H₂O₂ (73% ee shown; Chiralcel OJ-H column, 95/5 hexanes/i-PrOH, 0.5 mL/min, 220 nm).
(R)-1-Bromo-2-(2-phenylbut-3-en-2-yl)benzene (42). IR (neat): 3083 (w), 3057 (w), 3023 (w), 2976 (w), 1633 (w), 1599 (w), 1491 (w), 1463 (w), 1445 (w), 1424 (w), 1368 (w), 1074 (m), 917 (m), 752 (s), 698 (s) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.60 (1H, dd, \(J = 8.0, 1.6\) Hz), 7.52 (1H, dd, \(J = 8.0, 1.6\) Hz), 7.32 (1H, td, \(J = 7.2, 1.6\) Hz), 7.28–7.23 (2H, m), 7.21–7.16 (1H, m), 7.19–7.08 (3H, m), 6.66 (1H, dd, \(J = 17.6, 10.8\) Hz), 5.19 (1H, dt, \(J = 10.8, 0.8\) Hz), 4.98 (1H, dd, \(J = 17.2, 0.8\) Hz), 1.87 (3H, s); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 147.5, 146.2, 145.2, 135.8, 129.8, 128.6, 128.3, 127.3, 127.0, 125.9, 124.4, 113.5, 51.6, 26.7; HRMS (ESI\(^+\)): Calcd for C\(_{16}\)H\(_{16}\)Br [M+H]: 287.04354, Found: 287.04393; Optical Rotation: \([\alpha]_D\)^{20} –17.28 (c = 0.567, CHCl\(_3\)) for an enantiomerically enriched sample of 89% ee.

Enantiomeric purity was determined by HPLC analysis of the derived alcohol, obtained from the derived alcohol derivative, which was prepared by hydroboration of the terminal olefin with 9-BBN, followed by oxidation with H\(_2\)O\(_2\) (89% ee shown; Chiralcel OD column, 95/5 hexanes/i-PrOH, 1.0 mL/min, 220 nm).