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CUPRATE MEDIATED ALLYLIC SUBSTITUTIONS ON VINYLEPOXIDES AND CONJUGATE ADDITIONS ON 2-PYRIDONES

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CUPRATE MEDIATED ALLYLIC SUBSTITUTIONS ON VINYLEPOXIDES AND CONJUGATE ADDITIONS ON 2-PYRIDONES

A Thesis
Presented to
the Graduate School of
Clemson University

In Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy
Chemistry

by
Yaxin Huang
May 2012

Accepted by:
R Karl Dieter, Committee Chair
Rhett Smith
Bill Pennington
Gautam Bhattacharyya
ABSTRACT

Regioselective control in allylic substitution reactions of vinylepoxides is difficult due to the competition between $S_N$2- substitution and $S_N$2'- allylic substitution pathway. Although excellent $S_N$2'/$S_N$2- and anti/syn- ratios were achieved by CuCN derived organozinc cuprates on $\gamma,\delta$-epoxy-$\alpha,\beta$-enoates, application of this methodology to the vinylepoxide, $\text{trans-1-}$(tert-butyldimethylsilyloxy)-2,3-epoxy-4-hexene, is explored. Dialkyzinc reagents mediated by catalytic amounts of CuCN provide excellent regio-(S$_N$2'/S$_N$2) and diastereo-(olefinic $E/Z$ and anti/syn-) selectivity with $n$-Bu, Et and $t$-Bu ligands, while reduced $E/Z$ and S$_N$2'/S$_N$2- ratios were achieved with aromatic ligands (e.g., furyl and Ph). The assignment of regio- and stereoisomers were achieved by alternative syntheses of the authentic compounds. The epoxide opening allylic alcohol products were activated by conversion to allylic acetates or phosphates, which underwent allylic substitution reaction with lithium cyanocuprate in a highly anti-$S_N$2'-controlled fashion. As a result of this sequential bis-allylic substitution, the synthesis of compounds with two contiguous stereogenic centers was realized.

While many methods were reported for the synthesis of 2,3-dihydro-4-pyridone derivatives, access to substituted 2-piperidones from 2-pyridones is still underdeveloped because of their low reactivity towards conjugate additions and the difficulty in control of regioselectivity. $N$-Boc-2-pyridone underwent conjugate addition with CuI derived lithium dialkylcuprate with modest to excellent 1,4/1,6- regioselectivities, and various ligands ($n$-Bu, $s$-Bu, $t$-Bu, Me and Ph) were transferred in low to modest yields. Various organolithium reagents were added to the pyridinium salt derived from $N$-benzyl-2-
pyridone in low to modest yields, with poor to modest 1,4,1,6-regioselectivities. One pot synthesis of 3,4-dihydro-2-pyridones was realized in excellent diastereoselectivity.

A facile (three steps) and efficient (65% over three steps) synthesis of enantiopure mono-substituted bicyclic amidines was developed. Alkylation of these mono-substituted amidines provided bis-substituted bicyclic amidines in modest yields (55%) and with decent diastereoselectivities (88:12). These chiral bicyclic amidines are potential organocatalysts for asymmetric addition such as acetoxybromination or halolactonization reactions based on our preliminary result from DBU and other literature reports. Success on DBU alkylation in high yields (up to 88%) and with various ligands (Me, Et and Bn) provides a promising methodology for synthesis of multi-alkylated (e.g., bis and tri-susbtituted) chiral cyclic amidines.
DEDICATION

This work is dedicated to my parents, Mr. Min Huang and Mrs. Junhui Liu, for their never-ending support in my pursuit of this degree and tremendous encouragement in times of difficulty.
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I would like to thank Dr. Karl Dieter for giving me the opportunity to conduct research in the field of organic synthetic chemistry. Over the past seven years, Dr. Dieter has taught me not only the knowledge of organic chemistry but also the meaning of scientific scrutiny and dedication for science. His enthusiasm towards chemistry greatly encouraged me in time of frustration and his never–giving-up attitude brought me motivation to keep moving on. It is his guidance and mentorship that shaped me into a young chemist equipped with the experience and skills for the years to come.

I am grateful to Dr. Gautam Bhattacharyya, Dr. Bill Pennington and Dr. Rhett Smith for their important suggestions and criticisms in many of my research projects, valuable advices on the preparation of this manuscript, willingness to write recommendations for me. I am also in debt to Dr. Julia Brumaghim for many advices on the preparation of my thesis and on my future career. I would like to specially thank Ms. Barbara Lewis for her never-ending encouragement and understanding during the years I worked as a teaching assistant. Ms. Lewis’s word of encouragement and affirmation is what brought me through the stressful moments in the teaching class as well as in my research laboratory. I would also like to thank many other people in chemistry department for this work cannot be completed without their help. These include Dr. Alex Kitaygorodskiy for his assistance with NMR spectra, Dianne Harris for her help with purchasing chemicals, Robin Wilmott for her great help with laboratory supplies and many other items, Frances Miller and Laura Hupp for their effort to provide equipment and safety for our laboratory.
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Allylic Substitution on Vinylepoxides

1.1 Overview of Allylic Substitution

Allylic substrates are useful synthons because they can undergo either $S_N^2$- or $S_N^{2'}$- allylic substitution reactions, although the control of regioselectivity and stereoselectivity can be problematic depending upon substrate structure and reagent. An allylic substitution is a substitution reaction occurring at either the $\alpha$ or $\gamma$ position of an allylic system, corresponding to either positional stability or rearrangement of the original double bond. The incoming nucleophile may attack the same carbon bearing the leaving group, or it may attack at the $\gamma$ position with corresponding rearrangement of the double bond (Scheme 1.1).

**Scheme 1.1** General $S_N^2$- and $S_N^{2'}$- Allylic Substitutions

\[
\begin{array}{c}
\begin{array}{c}
R \quad \beta \\
\gamma \\
\alpha \\
\end{array}
+ \quad \text{Nu}^- \quad \text{catalyst}
\end{array}
\quad \rightarrow \quad \begin{array}{c}
\begin{array}{c}
R \quad \beta \\
\gamma \\
\alpha \\
\end{array}
+ \quad \begin{array}{c}
\begin{array}{c}
\text{Nu} \quad \beta \\
\gamma \\
\alpha \\
\end{array}
\end{array}
\end{array}
\]

\[S_N^2 \quad S_N^{2'}\]

\[LG = \text{Br, Cl, OAc, CO}_2R, -\text{OPO(OEt)}_2, -\text{O(CO)NHR}\]

Currently there are many metal reagents that can catalyze allylic substitution reactions including palladium, copper, nickel, rhodium, iridium, platinum, molybdenum,
iron and tungsten based reagents.\textsuperscript{3} Of usefulness and feasibility in organic synthesis, organocopper and organopalladium reagents are most often used because of their reliability for the control of regio- and stereoselectivities.\textsuperscript{4-6} There are many reported examples using organocopper reagents in allylic substitution reactions. One significant advantage of organocopper reagents is that they can be obtained from a variety of organometallic reagents (e.g., organolithium, organozinc, organomagnesium, organoaluminum and organotitanium reagents) and thus enables cuprate to carry various functionalized transferable ligands. Another advantage of organocopper reagents is that excellent $S_N2'$- regioselectivities can be achieved in allylic substitution reactions by judicious choice of organocuprate reagents, solvents, counter ions, stoichiometry of the copper salt, and leaving groups.\textsuperscript{2}

1.2 Regioselectivity

Allylic substitution can proceed by either $S_N2'$- or $S_N2$- pathways. In the proposed mechanism (Scheme 1.2), Cuprate undergoes oxidative addition of allylic substrate 1 to form a $\sigma$-allyl copper complex at the $\gamma$ carbon, and this $\gamma$-complex can undergo a rapid reductive elimination to afford the $\gamma$-alkylation product ($S_N2'$), or undergo isomerization through a $\pi$-allyl complex to form a $\gamma$-allyl copper complex at the $\alpha$ carbon, which leads to the $\alpha$-alkylation product ($S_N2$) after reductive elimination.
Regioselectivity in these allylic substitution reactions could be affected by several factors including the nature of the leaving groups, geometry of substrates (e.g., E and Z olefin isomers), nature of the cuprate reagents, copper catalysts, solvent systems and reaction temperature.

1.21 Substrate Influence

The regioselectivity can be influenced by the types of leaving groups and steric hindrance on the allylic substrates. Among many leaving groups, phosphates and perfluorobenzoates demonstrate excellent $S_N2'$ selectivities.

1.211 Different Leaving Groups

Allylic Acetates

Allylic acetates generally suffer from lower reactivity in cuprate allylic substitutions than the corresponding allylic halides$^{7,8}$, mesylates$^{9,10}$, or phosphates$^{11}$. Several examples illustrate that allylic acetates sometimes give lower $S_N2'$ selectivities.
than other allylic substrates (e.g., allylic halides). Schmid observed that in copper
catalyzed Grignard reagent promoted allylic substitution reactions, allylic bromide gave
better S\textsubscript{N}2'-selectivities than the corresponding allylic acetate (Scheme 1.3), the reason
was not uncertain.\textsuperscript{12}

\textbf{Scheme 1.3 Allylic Substitutions of 2}

\begin{center}
\begin{align*}
\text{H}_3\text{CO} & \xrightarrow{\text{RMgBr}} \text{H}_3\text{CO} \\
\text{(R = C}_{15}\text{H}_{31}) & \text{cat. Li}_2\text{CuCl}_4 \\
\text{THF, -78 °C} & \text{H}_3\text{CO} + \text{H}_3\text{CO} \\
\text{X} & \text{S}_{\text{N}2}':\text{S}_{\text{N}2}
\end{align*}
\end{center}

\text{3} : \text{4}

\begin{center}
\begin{tabular}{l|c}
\text{X} & \text{2.5:97.5} \\
\text{OAc} & \text{91:9} \\
\text{Br} & \\
\end{tabular}
\end{center}

\textbf{Allylic Halides and Allylic Mesylates}

Various cuprate reagents (e.g., R\textsubscript{2}CuLi, R\textsubscript{2}CuZnX, RCu•BF\textsubscript{3}) were reported to
react regioselectively with allylic halides, and allylic chlorides generally gave higher
S\textsubscript{N}2'-selectivity than bromides or iodides.\textsuperscript{11,13,14} While allylic chlorides gave poor to
modest regioselectivity when reacting with Li or Mg cuprates (i.e., R\textsubscript{2}CuLi or
R\textsubscript{2}CuMgX),\textsuperscript{15} much improved regioselectivity was achieved using Zn cuprates or with
BF\textsubscript{3} additives.\textsuperscript{16} Allylic mesylates undergo allylic substitution reactions using cuprate
reagents (e.g., R\textsubscript{2}CuLi, R\textsubscript{2}CuLi•BF\textsubscript{3}, RCuCNLi, RCuCNLi•BF\textsubscript{3}) giving similarly high
regioselectivity.

Nakamura and coworkers reported excellent S\textsubscript{N}2'- selectivity for allylic
chlorides\textsuperscript{16} and they found that while S\textsubscript{N}2'-/S\textsubscript{N}2- regioselectivity depends largely on the
nature of the organocuprate reagent, the stereoselectivity of the allylic substitution reactions is very sensitive to the substrate structure (Table 1.1 and Table 1.2). An alkyl group (i.e., Me) and an alkoxy group (i.e., OBn) on the δ position of the allylic substrates did not demonstrate much difference in the regioselectivity under these reaction conditions, suggesting that coordination effects (e.g., coordination of the counter ion of the cuprate to the oxygen on the δ-alkoxy group) is either absent during the reaction process or has little impact on the regioselectivity. It should be pointed that the actual structures of reactive species for these zinc cuprates are still unclear\textsuperscript{17,18} and the formula R\textsubscript{2}CuZnCl only reflects the relative stoichiometries of R\textsubscript{2}Zn and CuCN.

\textbf{Table 1.1} Allylic Substitutions of 5 using Various Cuprates

\begin{center}
\begin{tabular}{llll}
entry & cuprate & \% yield & \(S_N2'/S_N2\) (7:6) \\
1 & Bu\textsubscript{2}CuLi & 87 & 37:63 \\
2 & Bu\textsubscript{2}CuZnCl\cdotLiCl & 83 & 95:5 \\
3 & Bu\textsubscript{2}Ti(O\textsubscript{t}Pr\textsubscript{3})Li/ cat. Cu\textsuperscript{a} & 91 & 99:1 \\
4 & BuCu\cdotBF\textsubscript{3} & 92 & 98:2 \\
5 & Me\textsubscript{2}CuZnCl\cdotLiCl & 72 & 98:2 \\
\end{tabular}
\end{center}

\textsuperscript{a}6 mol \% CuI\cdot2LiCl
Table 1.2 Allylic Substitutions of 8 using Various Cuprates

<table>
<thead>
<tr>
<th>entry</th>
<th>cuprate</th>
<th>% yield</th>
<th>$S_N2'/S_N2$ (10:9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bu$_2$CuLi</td>
<td>61</td>
<td>12:88</td>
</tr>
<tr>
<td>2</td>
<td>Bu$_2$CuZnCl•LiCl</td>
<td>100</td>
<td>98:2</td>
</tr>
<tr>
<td>3</td>
<td>Bu$_2$Ti(O$i$Pr)$_3$Li/ cat. Cu$^a$</td>
<td>92</td>
<td>99:1</td>
</tr>
<tr>
<td>4</td>
<td>BuCu•BF$_3$</td>
<td>87</td>
<td>99:1</td>
</tr>
<tr>
<td>5</td>
<td>Bu$_2$Zn/ cat. Cu$^b$</td>
<td>80</td>
<td>98:2</td>
</tr>
<tr>
<td>6</td>
<td>Me$_2$CuZnCl•LiCl</td>
<td>98</td>
<td>90:10</td>
</tr>
</tbody>
</table>

$^a$6 mol% CuI•2LiCl $^b$6 mol% CuBr•Me$_2$S

Allylic Phosphates

In many cases, allylic phosphates provide excellent anti-$S_N2'$- selectivity with various cuprate reagents including Li (e.g., RCuCNLi, R$_2$CuLi)$^{19}$, Mg (e.g., RCuCNMgX, R$_2$CuMgX)$^{20}$, Zn (e.g., RCuCNZnCl)$^{21}$, Ti [e.g., RTi(O-i-Pr)$_3$/cat. CuI•2LiCl]$^{22}$ and Al (e.g., R$_3$Al/cat. CuCN)$^{23}$ cuprates. Allylic phosphates were reported to give higher $S_N2'$- selectivity than the corresponding halides.$^{7,23}$ (+) Trans-carvyl chloride 11a gave lower $S_N2'$-/ $S_N2$- selectivity (89:11) than the corresponding phosphate 11b (95:5, Scheme 1.4) under the same reaction conditions.
Scheme 1.4 Allylic Substitution Reactions of Carvyl Derivative 11

Geranyl chlorides 13a gave reduced $S_N 2'$-$S_N 2$- regioselectivity (90:10)

compared to the phosphate 13b (97:3) when reacting with aluminum cuprate reagent (Scheme 1.5). More importantly, allylic phosphates are synthetically useful in that they can be generated readily from the corresponding allylic alcohols.

Scheme 1.5 Allylic Substitution Reactions of Geranyl Derivative 13

Also, Yamamoto\textsuperscript{24} reported clean $S_N 2'$- or $S_N 2$- control with allylic phosphates achieved by changing the catalyst in the reaction. Allylic phosphate 15 reacts with $n$-butyl magnesium bromide in THF with different catalysts. Iron and Nickel catalysts strongly favor $S_N 2$- product 16, while copper catalysts strongly favor $S_N 2'$- product 17 (Scheme 1.6).
Knochel and coworkers reported a highly anti-\(S_N2\)'-selective allylic substitution using allylic pentafluorobenzoates with Zn cuprates. Pentafluorobenzoate 18, which can be generated readily from the corresponding allylic alcohol, reacted with polyfunctionalized zinc reagents in the presence of stoichiometric amounts of CuCN•2LiCl in a highly regio- and stereocontrolled fashion (Scheme 1.7).

**Scheme 1.7 Allylic Substitutions of Allylic Pentafluorobenzoate 18**

Steric hindrance on the substrates also plays a role in the regioselectivity of allylic substitution reactions. Substituents on the olefin could reduce the \(S_N2\)'-selectivity, as
reported by Anderson for allylic acetates\textsuperscript{26} and Dieter’s report on allylic phosphates.\textsuperscript{19} In the former study, allylic acetates with a di-substituted γ carbon (e.g., 22) present a higher steric hindrance for the reductive elimination of a Cu(III) σ-complex to occur at the γ position, compared to a terminal olefin 20, and thus gave diminished $S_N2'$-/SN$_2$- selectivity (Scheme 1.8). In another example, Dieter reported allylic phosphates reacted with various $N$-carbamoyl cuprates. Poor to modest $S_N2'$-/SN$_2$- selectivities were achieved when a primary allylic phosphate 26 was used, while secondary allylic phosphate 24 gave very good $S_N2'$-/SN$_2$- selectivities. In this study, the different $S_N2'$- or SN$_2$- selectivity is a combinative result of steric hindrance of the substrates (i.e., primary vs secondary phosphate) and steric hindrance of the cuprate reagents (i.e., a bulky $\alpha$-di[$N$-carbamoyl]-alkyl]cuprate).\textsuperscript{19}
Scheme 1.8 Steric Effects on Regioselectivity

\[ \text{Me}_2\text{CuLi} \quad \text{Et}_2\text{O}, -10^\circ\text{C} \rightarrow \]
\[ \text{Me}_2\text{CuLi} \quad \text{Et}_2\text{O}, -10^\circ\text{C} \rightarrow \]

<table>
<thead>
<tr>
<th>Cuprate</th>
<th>( \text{S}<em>\text{N}2/\text{S}</em>\text{N}2 )</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{N}^2\text{CuLi} ) ( \text{Boc} )</td>
<td>94:6</td>
<td>86</td>
</tr>
<tr>
<td>( \text{N}^2\text{CuCNLi} ) ( \text{Boc} )</td>
<td>93:7</td>
<td>70</td>
</tr>
<tr>
<td>( \text{N}^2\text{CuLi} ) ( \text{Boc} )</td>
<td>94:6</td>
<td>86</td>
</tr>
<tr>
<td>( \text{N}^2\text{CuLi} ) ( \text{Boc} )</td>
<td>100:0</td>
<td>100</td>
</tr>
<tr>
<td>( \text{N}^2\text{CuLi} ) ( \text{Boc} )</td>
<td>89:11</td>
<td>93</td>
</tr>
<tr>
<td>( \text{N}^2\text{CuCNLi} ) ( \text{Boc} )</td>
<td>77:23</td>
<td>68</td>
</tr>
<tr>
<td>( \text{N}^2\text{CuLi} ) ( \text{Boc} )</td>
<td>58:42</td>
<td>93</td>
</tr>
<tr>
<td>( \text{N}^2\text{CuLi} ) ( \text{Boc} )</td>
<td>0:100</td>
<td>87</td>
</tr>
</tbody>
</table>
1.213 Summary of Substrate Effect on Regioselectivity

Allylic acetates demonstrate the best results when reacting with Mg cuprates (RCuCNMgX or R₂CuMgX, X = Cl, Br), while they are often inert towards zinc cuprates (i.e., R₂Zn/ cat. CuCN)\textsuperscript{27} and give poor regioselectivity using lithium cuprates (e.g., R₂CuLi)\textsuperscript{28,29}. While good to excellent S\textsubscript{N}2' selectivities are observed for allylic mesylates and chlorides, they occasionally suffer from poor E/Z ratios and also excellent diastereoselectivity seems to be limited to specific substrates such as γ-mesyloxy-α,β-enoates.\textsuperscript{7,9} Allylic phosphates and pentafluorobenzoates generally give excellent anti-S\textsubscript{N}2'-selectivity when reacting with various cuprate reagents including Li, Mg, Zn, Al, Ti cuprates (RCuCNM and R₂CuM, M = Li\textsuperscript{19}, MgCl or MgBr\textsuperscript{7,20,30}, ZnCl\textsuperscript{21,31,32}, AlR\textsubscript{2}\textsuperscript{23}), and they generally demonstrate higher regioselectivity than corresponding chlorides. Readily generated from allylic alcohols, allylic phosphates are more synthetically useful than allylic halides.

1.22 Cuprate Reagents and Additives

The regioselectivity in allylic substitution reactions can be influenced by the nature of the cuprate reagents and different additives in the reaction media. Depending on the types of counter ions (e.g., RCuCNM, M = Li, MgCl, ZnCl), stoichiometry of the copper salt (R₂CuM vs RCuCNM, M = Li or MgCl) and the reaction solvent (dimer in ether and ion pairs in THF vide infra), the actual reacting cuprate species could vary. The use of Lewis acids (i.e., TMSCl or BF\textsubscript{3}) can also influence the outcome of S\textsubscript{N}2'/S\textsubscript{N}2-regioselectivity.
1.221 Cuprate Reagents

Structure of Cuprate Reagents

Over the past two decades the structures of cuprate reagents have been intensively studied. Several models for the structures of cuprates in solutions (e.g., diethyl ether, THF) were also proposed, and the dimer structure in ether and the solvent separated ion pair structures for the Gilman cuprates were confirmed by NMR spectroscopy\textsuperscript{33} and X-ray scattering experiments (i.e., XANES and EXAFS)\textsuperscript{34-38}. It is now well accepted that lithium organocuprates including Gilman cuprates (i.e., \(R_2\text{CuLi} \cdot \text{LiX}, X = \text{CN or I}\)) and alkyl(cyano)cuprates (i.e., \(RCuNC\text{Li} \cdot \text{LiX}, X = \text{CN or I}\)) exist as contact ion pairs (CIP) in weakly solvating solvents (e.g., \(\text{Et}_2\text{O}\) or \(\text{Me}_2\text{S}\)), which form either a homodimer or hetero-aggregate (Figure 1.1), while solvent separated ions pair (SSIP) are present in solvents (e.g., THF, crown ether) that strongly coordinate to lithium cations. However, the actual structure of the reactive copper species is still unclear.

**Figure 1.1** Structures of Gilman Reagents in \(\text{Et}_2\text{O}/\text{THF}\)

![Diagram of structures](image_url)
Proposed Structures for Higher Order Cuprates

Lipshutz first used the term “higher order” (HO) cuprate to describe a cuprate reagent prepared from two equivalents of an alkyllithium reagent and one equivalent of CuCN. This cuprate reagent sometimes demonstrates higher reactivity than traditional lower order Gilman cuprates (i.e., R$_2$CuLi•LiX, X = Cl, Br, I) and thus was suggested as having the stoichiometry as R$_2$CuCNLi$_2$. Later, X-ray crystallography studies suggested that these cuprates should be indicated as R$_2$CuLi•LiCN to better reflect their structures. By carrying out comparison studies of $^{13}$C-$^{13}$C scalar coupling constants and multiplicity patterns in THF, Bertz and coworkers found that these “higher order” cuprates (R$_2$CuLi•LiCN) strike an equilibrium between contact ion pairs (CIP) and solvent separated ion pairs (SSIP, 29, Figure 1.2) with only small amount of CIPs in THF. Moreover, Gschwind found that in diethyl ether these “higher order” cuprates present mainly as homodimer where a cyano group (CN) of LiCN is coordinated to the lithium from the homodimer (30a, Figure 1.2), although possible structures of heterodimers (30b and 30c, Figure 1.2) cannot be excluded.
**Figure 1.2** Possible Structures of “Higher Order” Cuprates in Solutions

X-Ray crystal structures of cuprates obtained by Koten\(^{45}\) and Boche\(^{46}\), along with EXAFS- and XANES studies\(^{37,38,40}\) and quantum chemical calculations\(^{47-49}\) also agreed that these “higher order” cuprates are merely lower order Gilman cuprates, which are complexed with one equivalent of LiCN (i.e., \(R_2CuLi\cdotLiCN\)).\(^{50}\)

**Gilman Cuprate vs Alkyl(cyano)cuprate (trans Effect)**

Cuprate reagents usually react with allylic substrates in an \(anti\)-S\(_N\)2\(^{-}\)-fashion \((\textit{vide infra})\).\(^{51,52}\) For lithium cuprates, the Gilman reagents (i.e., \(R_2CuLi\cdotLiX\), \(X = Cl, Br, I\)) usually provide poorer S\(_N\)2\(^{-}\)-selectivity than alkyl(cyano)cuprates (i.e., \(RCuCNLi\)) for allylic epoxides\(^{53,54}\) or allylic chlorides\(^{16}\). This is because the alkyl(cyano)cuprate reagents undergo a fast reductive elimination, while Gilman cuprates may undergo an isomerization of the initially formed \(\sigma\)-allyl copper complex. Marshall reported that lithium cuprates [i.e., Gilman and alkyl(cyano)cuprates] reacted with vinylepoxide \(31\) in
Et₂O at 0 °C (Scheme 1.9), and lithium alkyl(cyano)cuprate provided strong preference for the S₉²⁻ product (85:15) while the Gilman reagent gave poor regioselectivity (41:59). The same difference in regioselectivity between alkyl(cyano)cuprates and Gilman cuprates was also observed with Mg cuprate reactions by Backvall and coworkers.²⁸

**Scheme 1.9 Cuprate Opening of Vinylepoxide 31**

![Scheme 1.9 Cuprate Opening of Vinylepoxide 31](image)

Many studies were carried out to account for this observed different regioselectivity for the Gilman cuprate and alkyl(cyano)cuprate reagents. In the early 1990s, Backvall proposed a well accepted hypothesis for the observed regioselectivity²⁸ where a cuprate reagent [Gilman or alkyl(cyano)cuprate] undergoes oxidative addition of an allylic substrate 34 to form a σ-allyl complex Cu(III) species 35 at the γ-position (Scheme 1.10). When an electron withdrawing group (i.e., X = CN, Cl) is bonded to the copper atom [i.e., in an alkyl(cyano)cuprate], this Cu(III) complex is known to undergo a fast reductive elimination to afforded the S₉²⁻ product.⁸,₅₅-₅⁷ When a Gilman cuprate is used (i.e., X = R’), the rate of reductive elimination is then greatly reduced and the γ-Cu(III) σ-allyl complex 35 can then equilibrate with an α-Cu(III) σ-allyl complex 37,
which upon reductive elimination would provide the $S_N2$- product 38. Backvall point out that the rate of reductive elimination is the key to the rise of $S_N2'/-S_N2$- regioselectivity (faster reductive elimination favors $S_N2'$- pathway) and that alkyl(cyano)cuprates undergo a faster reductive elimination step than the Gilman cuprates. The regioselectivity for the Gilman cuprate reactions is highly influenced by the stability of the two Cu(III) complexes. A primary Cu(III) complex (i.e., 37) is more stable than a secondary Cu(III) complex (i.e., 35) because the steric hindrance between the R’ group on the copper and a H on the methylene group is minimized, and it gives the $S_N2$- product (i.e., 38) as the major product. Likewise, adding a bulky substituent on the $\alpha$-position or/and replacing R group with H can drive the equilibrium towards the $\gamma$-complex 35, which upon reductive elimination gives the $S_N2'$- product (i.e., 36).

**Scheme 1.10** Backvall’s Mechanism of $S_N2$- and $S_N2'$- Pathways
In order to better understand the detailed reaction mechanism, Nakamura and coworkers developed a new model to better explain the regioselectivity for both Gilman and alkyl(cyano)cuprates, using calculated energy levels of several possible reaction intermediates and transition states (Scheme 1.11).\textsuperscript{58,59} Allylic substrate 34 reacts with a Gilman cuprate to form a \(\pi\)-allyl Cu(III) transition state 39 upon oxidative addition, which releases the leaving group (Y) to form intermediate 40. Reductive elimination can occur at either the \(\gamma\)-position leading to the \(S_N2'\) product or the \(\alpha\)-position to afford the \(S_N2\) product. Nakamura stated that the electronic effect of the substituent on the allylic substrate (e.g., R group) is the most important in controlling regioselectivity, whereas the steric effect plays a minor role.\textsuperscript{58} In a case where \(R = H\) and intermediate 40 is therefore symmetrical, one would expect equal proportion of \(S_N2'\) and \(S_N2\) product, and this is consistent with experimental observations by Goering.\textsuperscript{60}

**Scheme 1.11** Nakamura’s Mechanism for Gilman Cuprate Mediated Allylic Substitutions

\[
\begin{array}{c}
\text{R}^2\text{CuMe} \\
\text{Y}
\end{array}
\quad
\begin{array}{c}
\text{R}^2\text{CuMe} \\
\text{Y}
\end{array}
\quad
\begin{array}{c}
\text{R}^2\text{CuMe} \\
\text{Y}
\end{array}
\quad
\begin{array}{c}
\text{R}^2\text{CuMe} \\
\text{Y}
\end{array}
\]

In a case where an alkyl(cyano)cuprate is used, the oxidative addition of the cuprate to allylic substrate 34 can give two types of Cu(III) \(\pi\)-allyl transition states 43 and
45 (Scheme 1.12). Transition state 43 releases the leaving group Y to afford an enyl [σ + π] Cu(III) complex 44 which gives S_N2'- product 36 upon reductive elimination.

Similarly, transition state 45 would lead to S_N2- product 38. Transition state 43 is lower in energy than 45 because the electron donating group R’ is trans to the leaving group Y (trans effect: the effect of a coordinated group upon the rate of substitution reactions of ligands opposite to it\(^{61}\)) in 43. This is rationalized by having the Cu-R’ σ-orbital overlapping with the electron deficient C-Y anti-bonding orbital (σ* C-Y), and therefore the S_N2'- product is favored for the alkyl(cyano)cuprate reagents. Nakamura stated that this trans effect plays the most important role in the S_N2'- preference in the alkyl(cyano)cuprate allylic substitution reactions.

**Scheme 1.12** Nakamura’s Mechanism for Alkyl(cyano)cuprate Allylic Substitutions
In agreement with Backvall’s hypothesis, Nakamura states that the rate of reductive elimination for alkyl(cyano)cuprates is faster than the Gilman cuprates because of the electron withdrawing CN group. However, while both Backvall and Nakamura state that the origin of the regioselectivity for Gilman cuprate occurs at the reductive elimination step, Nakamura states that the electronic effect of the $\alpha/\gamma$-substituent(s) plays a significant role in the regioselectivity for Gilman cuprate, whereas Backvall suggests that steric hindrance of the Cu(III) $\sigma$-allyl complexes determines the regioselectivity. As for the regioselectivity of the alkyl(cyano)cuprate reagents, Nakamura states that the regioselectivity originated from the geometries of the Cu(III) transition states in the oxidative addition step and that the trans effect plays a significant role, whereas Backvall ascribes the regioselectivity of alkyl(cyano)cuprates to a fast reductive elimination step (caused by an electron withdrawing CN group on Cu) of the initially formed $\gamma-\sigma$-allyl complex.

The regioselectivity of allylic acetate substitution reactions is very sensitive to the nature of the nucleophile and the catalyst. For example, Backvall noticed that Mg cuprates generally gave better $S_N2'/S_N2$- selectivity than Li cuprates towards allylic acetates (Scheme 1.13). Geranyl acetate 47 reacted with lithium cuprates (e.g., BuCuCNLi and Bu$_2$CuCNLi$_2$) and magnesium cuprates [e.g., BuCuCNMgBr and Bu$_2$CuCN(MgBr)$_2$] reagents. While the Mg cuprates gave almost exclusively $S_N2'$-product, the lithium cuprates gave poor regioselectivity ($S_N2:S_N2'=50:50$~$68:32$). Goering also reported lower $S_N2'/S_N2$- regioselectivity in lithium cuprates in diethyl ether.
with allylic acetates than magnesium cuprates, although no explanation was given in either report.

**Scheme 1.13 Allylic Substitutions of Geranyl Acetate 47 with Various Cuprates**

![Scheme 1.13 Allylic Substitutions of Geranyl Acetate 47 with Various Cuprates](image)

<table>
<thead>
<tr>
<th>Reagent</th>
<th>1:99</th>
</tr>
</thead>
<tbody>
<tr>
<td>BuCu(CN)MgBr</td>
<td></td>
</tr>
<tr>
<td>Bu₂CuMgBrMgCNBr</td>
<td>1:99</td>
</tr>
<tr>
<td>BuCuCNLi</td>
<td>50:50</td>
</tr>
<tr>
<td>Bu₂CuLi:LiCN</td>
<td>68:32</td>
</tr>
</tbody>
</table>

Zinc alkylcuprates provide lower reactivity than lithium alkyl(cyano)cuprates in these allylic substitution reactions. Copper mediated or copper catalyzed reactions of organozinc reagents with allylic halides, mesylates, phosphates, pentafluorobenzoates and epoxides afford anti-SN₂’-products in a highly regio- and stereo-controlled fashion. Unlike Li and Mg cuprates, the structure of Zn and Ti cuprate species are still unclear. Knochel and coworkers employed dialkylzinc reagents in reactions with cyclic allylic phosphate 48a or allylic pentafluorobenzoate 48b in the presence of stoichiometric amounts of CuCN•2LiCl to afford exclusively the SN₂’-product in high yields and enantioselectivities (Scheme 1.14).
Scheme 1.14 Enantioselective Allylic Substitutions of 48

\[
\begin{align*}
\text{Pent}_2\text{Zn} \\
\text{CuCN-2LiCl 1.1 equiv} \\
\text{THF:NMP 3:1} \\
-30^\circ\text{C to -10^\circ C} \\
\end{align*}
\]

only S\text{N}2'

<table>
<thead>
<tr>
<th>LG</th>
<th>% yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>48a OPO(OEt)_2</td>
<td>90</td>
<td>94</td>
</tr>
<tr>
<td>48b OCOC_6F_5</td>
<td>91</td>
<td>93</td>
</tr>
</tbody>
</table>

1.222 Lewis Acid Effect

Several Lewis acids were reported to promote S\text{N}2’- pathways in cuprate allylic substitutions. Yamamoto discovered the anti- S\text{N}2’- enhancement effect of BF\text{3} reagents, and RCu•BF\text{3} is now called the “Yamamoto’s reagent”. Nakamura later discovered similar enhancement of regio- and stereoselectivity with other Lewis acids including Ti, and Zn reagents (Table 1.3). The detailed mechanism for this effect is still uncertain, and is probably through chelation effect of the Lewis acids to the copper species.\textsuperscript{14}
Table 1.3 Allylic Substitutions of 49

<table>
<thead>
<tr>
<th>entry</th>
<th>reagent</th>
<th>additive</th>
<th>% yield</th>
<th>SN2'/SN2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-Bu2CuLi</td>
<td>-</td>
<td>87</td>
<td>37:63</td>
</tr>
<tr>
<td>2</td>
<td>n-BuCu•BF3</td>
<td>BF3</td>
<td>92</td>
<td>98:2</td>
</tr>
<tr>
<td>3</td>
<td>n-Bu2CuZnCl•LiCl</td>
<td>ZnCl2</td>
<td>85</td>
<td>99:1</td>
</tr>
<tr>
<td>4</td>
<td>n-Bu2Ti(OiPr)3Li/</td>
<td>-</td>
<td>91</td>
<td>99:1</td>
</tr>
<tr>
<td></td>
<td>cat CuI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Me2CuZnCl•LiCl</td>
<td>ZnCl2</td>
<td>72</td>
<td>98:2</td>
</tr>
</tbody>
</table>

Flemming also reported R₃Al as Lewis acids serving the same function. Geranyl phosphate 50 reacted with trialkylaluminum reagents (R₃Al) under CuCN catalysis to afford high SN2'-regioselectivity (SN2'/SN2 > 95:5, Scheme 1.15). However, two equivalents of trimethylaluminum are required to achieve excellent regioselectivity and high yields. This presumably involves an aluminum cuprate reagent and a second molecule of trialkylaluminum acting as a Lewis acid.

Scheme 1.15 Allylic Substitutions of 50 with Aluminum Cuprates

<table>
<thead>
<tr>
<th>R</th>
<th>% yield</th>
<th>SN2'/SN2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>93</td>
<td>97:3</td>
</tr>
<tr>
<td>Et</td>
<td>82</td>
<td>96:4</td>
</tr>
<tr>
<td>nPr</td>
<td>75</td>
<td>96:4</td>
</tr>
<tr>
<td>tBu</td>
<td>62</td>
<td>95:5</td>
</tr>
</tbody>
</table>
1.223 Cu Salts

Copper (I) cyanide seems to be the most effective catalyst to enhance the regioselectivity in these allylic substitution reactions (vide supra). Yamamoto and coworker used 2-decenyl-1-diphenylphosphate (51) to react with the Grignard reagent \( \text{n-BuMgCl} \) under the catalysis of various copper salts, and found that \( \text{CuCN} \cdot 2\text{LiCl} \) gave the highest \( \text{S}_{\text{N}}2' \)-selectivity (99:1), while \( \text{CuOTf} \) and \( \text{CuSCN} \) favored the \( \text{S}_{\text{N}}2 \)-pathway (Scheme 1.16).\(^{24}\) These results may suggest that the rates of reductive elimination in these allylic substitution reactions follow this trend: \( \text{RCuCNMgCl} \gg \text{RCuXMgCl} \) \((X = \text{Cl, Br}) \gg \text{R}_2\text{CuMgCl} \) (from \( \text{CuOTf} \) or \( \text{CuSCN} \)).

Scheme 1.16 Allylic Substitution of 51 using Various Cu Catalysts

Similarly, outstanding regioselectivity enhancement by \( \text{CuCN} \) was also observed by Chong.\(^{29}\) Allylic acetate 54 reacted with various cuprate reagents to afford \( \text{S}_{\text{N}}2' \)-product 55 and \( \text{S}_{\text{N}}2 \)-product 56 (Scheme 1.17). While lithium di-\( n \)-butylcuprate gave
exclusively the $S_N 2$- product, copper (I) salt catalyzed Grignard reagent gave increased amounts of the $S_N 2'$- product with CuCN giving excellent $S_N 2'$- selectivity (96:4).

**Scheme 1.17** CuI and CuCN Catalyzed Cuprate Reaction of 54

![Scheme 1.17](image)

1.23 Solvent Effects

Solvent systems in these copper mediated allylic substitution reactions played a role in the control of regioselectivity. Backvall, Calo, and Marshall separately reported that while Li and Mg cuprates tend to promote $S_N 2'$- pathway in diethyl ether, THF gave increased amount of the $S_N 2$- products. They attribute this solvent effect to the formation of different organocopper species, which is due to different lithium ion coordination ability of these solvents (e.g., Et$_2$O and THF), and the specific structures of reactive species are still under investigation.

Backvall and coworkers studied the allylic substitution of Mg cuprate reagents on geranyl acetate 57 in both Et$_2$O and THF (**Table 1.4**), and they found that in Et$_2$O both alkyl(cyano)cuprate (i.e., BuCuCNMgBr) and Gilman-type cuprate (i.e.,
Bu$_2$CuMgBr•MgCNBr) gave almost exclusively the S$_{N2}'$- product (entry 1 and 3). In THF, however, the alkyl(cyano)cuprate gave excellent S$_{N2}'$- selectivity with poor yield (15%, entry 2), while the Gilman-type cuprate (Bu$_2$CuMgBr•MgCNBr) gave completely reversed result affording exclusively the S$_{N2}$- product (entry 4).

**Table 1.4** Allylic Substitution Reactions of Acetate 57 in Et$_2$O and THF

<table>
<thead>
<tr>
<th>entry</th>
<th>cuprate</th>
<th>solvent</th>
<th>$S_{N2}'$ / $S_{N2}$</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$n$-BuCuCNMgBr</td>
<td>Et$_2$O</td>
<td>&gt;99:1</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>$n$-BuCuCNMgBr</td>
<td>THF</td>
<td>&gt;99:1</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>$n$-Bu$_2$CuMgBr•MgCNBr</td>
<td>Et$_2$O</td>
<td>&gt;99:1</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>$n$-Bu$_2$CuMgBr•MgCNBr</td>
<td>THF</td>
<td>1:99</td>
<td>61</td>
</tr>
</tbody>
</table>

This contrast of two different solvents for cyano-Gilman type cuprate (R$_2$CuLi•LiCN) is probably due to the different structures of cuprate aggregates in Et$_2$O and THF. Although little was known about the actual reacting species of lithium alkyl(cyano)cuprate (i.e., RCuCNLi•LiCN) in Et$_2$O solutions, X-ray studies performed by Boche$^{46}$ and Power$^{66}$ provided the solid state structure of lithium alkyl(cyano)cuprate (RCuCNLi•LiCN) crystallized in Et$_2$O (Figure 1.3, a). A recent electrospray ionization mass spectrometry study on lithium alkyl(cyano) cuprate and Gilman cuprate in diethyl ether identified the anions to be Li$_{n-1}$Cu$_n$R$_n$(CN)$_n$ and Li$_{n-1}$Cu$_n$R$_{2n}$ respectively.$^{67}$ The
homodimeric structure of cyano-Gilman reagent (R₂CuLi•LiCN) in Et₂O was determined by $^{13}$C and $^{15}$N NMR spectroscopy, EXAFS and XANES experiments and quantum chemical calculations (Figure 1.3, b). In THF, however, both alkyl(cyano)cuprates and cyano-Gilman cuprates exist as solvent separated ion pairs (Figure 1.3, c and d).

**Figure 1.3** Structures of Alkylcyano and Cyano-Gilman Cuprates in Et₂O and THF

![Diagram](image-url)

Excellent S$_N$2'- selectivities (>99:1) were achieved for alkyl(cyano)cuprate in both THF and Et₂O (entry 1-2) in spite of the different structures of the actual reactive species, suggesting that solvent effect was not playing a significant role in this case.
Several literature reports have suggested that an electron withdrawing group (i.e., CN, Cl, I, Br) on the copper atom would destabilize the transition state and thus leads to a fast reductive elimination step, which favors the $S_{N}2'$- alkylation.\(^{8,55-57,70}\) Therefore, this excellent $S_{N}2'$- selectivity observed in Et$_2$O indicated that cyano group (CN) is still bonded to the copper atom after the oxidative addition step for alkyl(cyano)cuprate. In both Et$_2$O and THF, the *trans* effect on the transition state would play a significant role: the conformer with incoming alkyl group *trans* to the leaving group (OAc) would be more stable and give $S_{N}2'$- product upon reductive elimination (Scheme 1.18).
For cyano-Gilman cuprate, the solvent effects played an significant role in the regioselectivity. The homodimeric cuprate $\text{Bu}_2\text{CuMgBr}\cdot\text{MgCNBr}$ (Figure 1.3, b) in ether gave excellent $S_N2'$- preference although the reason was not discussed. In THF, however, almost exclusive $S_N2$- product was formed for cyano-Gilman type cuprate ($\text{Bu}_2\text{CuMgBr}\cdot\text{MgCNBr}$) in THF and this could be explained by the rate of reductive elimination step of dialkyl copper (III) species. Because of the identical alkyl groups on
the copper (Bu), two \([\sigma + \pi]\) enyl complexes 65 and 66 would be formed upon oxidative addition (Scheme 1.19).

Nakamura has shown that the rate of reductive elimination is mainly controlled by electronic effect of the substituents and, to a less degree, by steric effect. Based on Nakamura’s calculation, for a substituted allylcopper (III) intermediate where the substituent is on C1, an electron-donating alkyl (R) group demonstrates a lower activation energy of reductive elimination at C3 than C1 whereas a hydrogen (H) the activation energy for reductive elimination is equal at C1 and C3. As a result, the presence of two electron donating alkyl groups increases the activation energy of reductive elimination at the \(\gamma\) position, leaving a strong preference for the \(S_N2\)-pathway.

**Scheme 1.19** Mechanism of Gilman Cuprate Reaction with 57
1.24 Summary

Allylic phosphates and perfluorobenzoates seem to be the best leaving groups, for they strongly favor the \textit{anti-} $S_N2'$- pathway and generally give excellent $S_N2'$- and \textit{anti-} selectivity in stoichiometric or catalytic cuprate reactions.\textsuperscript{7,20,24,25,30,32} They are good leaving groups and often give good to excellent chemical yields with Li, Zn, Mg, Ti, and Al cuprate reagents (i.e., either $RCuCNM$ or $R_2CuM$, $M = Li, MgCl (MgBr), ZnCl, AlR_2$) in allylic substitution reactions. Moreover, they can be readily generated from the allylic alcohols.

Zinc cuprates ($R_2Zn/CuX$, $X = CN, I$) seem to work the best for allylic phosphates in that they generally provide better $S_N2'$- regioselectivity, compared to Li ($R_2CuLi$ or $RCuCNLi$) and Mg ($R_2CuMgBr$ or $RCuCNMgBr$) cuprates. Organozinc reagents generally undergo copper salt catalyzed allylic substitutions with excellent regio- ($S_N2'$-) and stereocontrol (\textit{anti-}). A combination of CuCN salt and Et$_2$O as solvent gives rise to the highest $S_N2'$- selectivity. Copper cyanide (CuCN) generally provides better regioselectivity than other copper salts. The use of Lewis acids (i.e., BF$_3$) can favor the $S_N2'$- pathway.

1.3 Stereoselectivity

The stereoselectivity in an allylic substitution reaction includes olefinic $E/Z$ ratio, enantioselectivity and/or diastereoselectivity (i.e., \textit{anti-}/\textit{syn-} ratio).
1.31 Olefinic E/Z Ratio

The olefinic E/Z ratio is largely dependent upon the geometry of the allylic substrates, and to a less degree, upon the nature of the leaving groups.

1.311 Substrate Geometry

The olefinic E/Z ratio is governed by the geometry of the allylic substrates. Allylic substrate can undergo anti-\textit{S}_2'- substitution starting with two conformers (Scheme 1.20). Conformer 67a gives rise to the \textit{E} isomer while conformer 67b gives the \textit{Z} isomer. Transition state 68 is more stable because of a smaller A$^{1,3}$ strain between two hydrogens than that in transition state 69 (H and R$^1$ group), and in accordance with the Curtin-Hammett principle$^{71}$ the \textit{E} product is favored.

\begin{center}
\textbf{Scheme 1.20} Reaction Pathways of 67a and 67b
\end{center}
1.312 Leaving Group Effect

The $E/Z$ ratio is also affected by the leaving groups and phosphates generally give better $E/Z$ ratios than chlorides or mesylates.\textsuperscript{7} Yamamoto used allylic chloride 70a, mesylates 70b, and phosphate 70c for allylic substitution reactions with prenyl Grignard reagent in the presence of CuCN•2LiCl, and found out that while chloride and mesylates gave poor $E/Z$ ratio (46:55–55:45), the phosphate gave excellent results (96:4, Scheme 1.21). One possible explanation is the higher energy in the Z isomer caused by the gauche configuration between the leaving group LG and the methyl group, and the energy difference is magnified by using a more bulky leaving group (e.g., a phosphate) and thus gives higher $E$ preference. It is also noteworthy that allylic substitution reaction occurred at the carbon $\gamma$ to the chloride of substrate 70a, suggesting a higher reactivity of this allylic chloride over the allylic acetate.
**Scheme 1.21** Reaction of 70a-c with Mg Cuprates

\[
\begin{align*}
&\text{70a-c} \\
\text{(CH}_3\text{)}_2\text{C}=\text{CHCH}_2\text{MgCl (3 equiv)} \\
\text{THF, CuCNZLiCl (3 equiv)} \\
\text{-78 or 0 °C} \\
\text{71}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Substrate</th>
<th>LG</th>
<th>R</th>
<th>% yield</th>
<th>E/Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>70a</td>
<td>Cl</td>
<td>Ac</td>
<td>90</td>
<td>46:54</td>
</tr>
<tr>
<td>70b</td>
<td>OMs</td>
<td>TBS</td>
<td>68</td>
<td>55:45</td>
</tr>
<tr>
<td>70c</td>
<td>OPO(OEt)₂</td>
<td>TBS</td>
<td>94</td>
<td>96:4</td>
</tr>
</tbody>
</table>

**1.32 Anti/Syn- Ratio**

Anti/Syn- ratio is significantly governed by stereoelectronic effect, and to a less degree by chelation effect.

**1.321 Corey’s Model**

In order to find out the origin of anti-/syn- selectivity in the allylic substitution reactions, the transition state of these copper catalyzed allylic substitution reactions were investigated. Copper reagents are known for their capacity to facilitate anti- S_N 2’-substitutions in allylic substrates (e.g., acetates, phosphates, epoxides). E.J. Corey and Boaz proposed a molecular orbital overlap rationalization, which proposed the possible origins of such anti- selectivities.\(^7\) In Corey’s model, the filled d\(^{10}\) orbital of copper,
which is the HOMO of the nucleophile, can interact with the LUMO of the allylic substrate comprised of the \textit{anti}-bonding orbital ($\pi^*$) of the double bond and the \textit{anti}-bonding orbital ($\sigma^*$) of C-O bond (Figure 1.4). The approach of the cuprate is from the \textit{anti}-direction of the leaving group, thereby affording an \textit{anti}-S$_N$2'- derived product.

\textbf{Figure 1.4} Corey’s Model for Cuprate \textit{anti}-S$_N$2'- Substitution$^{51}$

\begin{center}
\begin{tikzpicture}

\begin{center}
\text{\textit{anti} - approach}
\end{center}
\end{tikzpicture}
\end{center}

\textbf{1.322 Felkin-Ahn Model}

Nakamura investigated the diastereoselectivity of organocopper mediated S$_N$2'-substitution reactions with allylic chlorides having a chiral center at the $\delta$-position (Scheme 1.22). In their study, substrate 73 reacted with various organocopper reagents affording excellent diastereoselectivities ($ds$).
They ascribed this high diastereoselectivity to purely steric effects and used a Felkin-Ahn model for the rationalization of this stereoselectivity. The large group (phenyl) is oriented perpendicular to the olefin, and the R group is coming from the least hindered position (from a direction which is eclipsed with the H in the back) (75, Scheme 1.23). The experimental observations are consistent with this prediction.

In order to confirm that steric control is the only factor and that a chelation effect did not play a role in the diastereoselectivity, several δ-oxygenated allylic substrates were also examined. They found out that exclusive anti addition product was obtained for all
entries except for substrate 77 and 78 (Table 1.5), probably due to the little steric differences between the alkoxy group (OR^2) and the alkyl group (R^1). Different types [i.e., R^2CuZnCl, R^2Cu•Ti(OiPr)_3, RCu•BF_3] of cuprate reagents demonstrate little impact on the diastereoselectivities, but significantly influenced the regioselectivity (Bu^2CuLi vs other cuprate, entry 7 vs 3-6) for the reason discussed above. Most importantly, allylic chloride with a chelating inhibiting group (OTIPS) 80 did not diminish the diastereoselectivity (entry 8) suggesting that chelation effects were not active in the control of stereoselectivity and steric effects alone are effective enough to provide exclusive diastereococontrol. However, no experiment was performed in Et_2O, which better facilitate the chelation of cations to oxygen.
Table 1.5 Regio- and Stereoselective Allylic Substitutions of 77-80

![Reaction Scheme]

- **77**: $R^1 = \text{Me}, R^2 = \text{MOM}$
- **78**: $R^1 = \text{\textsuperscript{\textdegree}Pent}, R^2 = \text{MOM}$
- **79**: $R^1 = \text{\textsuperscript{\textdegree}Pr}, R^2 = \text{Bn}$
- **80**: $R^1 = \text{\textsuperscript{\textdegree}Pr}, R^2 = \text{TIPS}$

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>cuprate</th>
<th>%yield</th>
<th>$S_N2'/S_N2$</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>77</td>
<td>$\text{Bu}_2\text{CuLi/ZnCl}_2$</td>
<td>79</td>
<td>98:2</td>
<td>65:35</td>
</tr>
<tr>
<td>2</td>
<td>78</td>
<td>$\text{Bu}_2\text{CuLi/ZnCl}_2$</td>
<td>90</td>
<td>90:10</td>
<td>70:30</td>
</tr>
<tr>
<td>3</td>
<td>79</td>
<td>$\text{Bu}_2\text{CuLi/ZnCl}_2$</td>
<td>100</td>
<td>98:2</td>
<td>100:0</td>
</tr>
<tr>
<td>4</td>
<td>79</td>
<td>$\text{Bu}_2\text{Zn/ cat. Cu}_a$</td>
<td>80</td>
<td>98:2</td>
<td>100:0</td>
</tr>
<tr>
<td>5</td>
<td>79</td>
<td>$\text{Bu}_5\text{Ti(O}^{\text{\textsuperscript{\textdegree}Pr})_3/ cat. Cu}_b$</td>
<td>92</td>
<td>99:1</td>
<td>100:0</td>
</tr>
<tr>
<td>6</td>
<td>79</td>
<td>$\text{BuCu•BF}_3$</td>
<td>87</td>
<td>99:1</td>
<td>100:0</td>
</tr>
<tr>
<td>7</td>
<td>79</td>
<td>$\text{Bu}_2\text{CuLi}$</td>
<td>61</td>
<td>12:88</td>
<td>100:0</td>
</tr>
<tr>
<td>8</td>
<td>80</td>
<td>$\text{Bu}_2\text{CuLi/ZnCl}_2$</td>
<td>93</td>
<td>98:2</td>
<td>100:0</td>
</tr>
</tbody>
</table>

\(^a 6 \text{ mol\% CuBr•Me}_2\text{S} \quad ^b 6 \text{ mol\% Cul•2LiCl}\)

1.4 Vinylepoxides

Vinylepoxides are useful synthons since they can be opened at three different reaction sites, and are a subset of allylic substrates.\(^51\)

1.4.1 Introductions of Vinylepoxides

Nucleophilic attack of the nucleophile to a vinylepoxide can occur at three different sites (Scheme 1.24): attacking at the least hindered carbon A of vinylepoxide 81 will give the $S_N2$- product 82, which is not commonly observed and this site is
generally attacked by soft nucleophiles (e.g., malonates);\textsuperscript{73} attack at site B gives rise to the regioisomeric S\textsubscript{N}2- product 83, which is common when hard nucleophiles are used such as organometallic reagents (e.g. organolithium, Grignard and organoaluminum reagents).\textsuperscript{2} While the hard-soft acid-base theory is basically a pragmatic rule allowing the prediction of the stability of different acid-base adducts, it demonstrates a close relationship with electronegativity and charge density of the species and therefore in general, species having relatively high charge densities are hard and those having low charge densities are soft. Attack of a nucleophile at site C, which is often observed in copper catalyzed reactions, will afford the S\textsubscript{N}2'- substitution product 84. The regioselective attacks of the nucleophiles largely depend on the types of nucleophiles being used. Attack at site B and C is found useful in natural product synthesis while attack at site A can lead directly to the formation of allylic alcohols.\textsuperscript{51,74-77} It is therefore of great interest to develop new synthetic methodologies to control the regio- and stereoselectivities of these vinylepoxide opening reactions.

**Scheme 1.24 Allylic Substitution Pathways on Vinylepoxide 81**
1.42 Regioselectivity

The *trans* effect of the Cu(III) intermediate is an important factor determining the regioselectivity in cuprate allylic substitution reactions with vinylepoxides (vide supra).\(^{59}\) Other than that, substituents on the oxirane ring were found to strongly disfavor the $S_N2$-pathway. Marshall and coworkers examined various allylic epoxides and reacted them with lithium alkyl(cyano)cuprates (i.e., MeCuCNLi, **Scheme 1.25**). They found that substituents on the oxirane ring, either at the $\alpha$ or $\beta$ position, gave exclusively the $S_N2'$-product, suggesting steric hindrance plays a significant role in regioselectivity.\(^{54,78}\)

**Scheme 1.25** Substituent Effect of Regioselectivity for 85-87

1.43 $E$/Z Selectivity

The olefinic $E$/Z ratio obtained from various vinylepoxide opening reactions seems to be greatly affected by the geometry of the allylic substrate and substituents on the allylic system. Marshall found that if the substituent on the oxirane ring is $\beta$ to the
C=C double bond, then almost exclusively $E$ product will be formed; if the substituent is $\alpha$ to the double bond, then a mixture of $E$ and $Z$ product will be formed (Scheme 1.26).\textsuperscript{54,78}

**Scheme 1.26 Substituent Effect for $E/Z$ Selectivity**

Marshall ascribed this observed $E$ preference to A\textsuperscript{1,3} strain in the reaction transition states (Scheme 1.27). For epoxide 88, the cis- transition state 94 is strongly disfavored because of a strong A\textsuperscript{1,3} strain between a H and a tertiary carbon, whereas in the trans- transition state 93 only a small A\textsuperscript{1,3} strain between two Hs, so only the $E$ isomer 89 was obtained. However, for epoxide 90, there is A\textsuperscript{1,3} strain in the trans- transition state 95 between a H and a Me group and in the cis- transition state 96 between a H and a secondary carbon, and the energy level difference between these two conformers is greatly reduced and hence a mixture of both $E$ and $Z$ (75:25) isomeric products is obtained.
Scheme 1.27 Transition States 93-96

\[ \text{E-trans 93} \]

\[ \text{E-cis 94} \text{ Strongly disfavored} \]

\[ \text{E-trans 95} \]

\[ \text{E-cis 96} \text{ disfavored} \]
1.43 Anti-/Syn- Selectivity

Although in most cases anti- substitution is observed and an explanation was given by Corey (vide supra),72 there are a few examples where the syn- substitution pathway occurs. Marshall, Trometer, and Cleary published in 1989 a report on the addition of different methylcuprate reagents to Geranyl derived vinyloxiranes 97-100.54 In these allylic opening reactions, the type of cuprate reagent used in these reactions did not cause much difference in the anti-/syn- stereoselectivities, although lithium alkyl(cyano)cuprate seemed to provide somewhat higher anti- diastereomeric ratios than the Gilman reagent. Moreover, these reaction conditions still left a lot room for the improvement for anti : syn ratio (Table 1.6).

While anti-S\textsubscript{N}2'- products were still the major diastereomers with E isomeric substrates 97 and 98 (70:30~88:12), the Z isomeric substrates 99 and 100 surprisingly gave predominantly syn-S\textsubscript{N}2'- opening products, with excellent syn/anti ratio for hydroxyl compound 99 (>97:3 for both methods).
**Table 1.6 Diastereoselective Opening of 97-100**

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>cuprate&lt;sup&gt;a&lt;/sup&gt;</th>
<th>% yield</th>
<th>anti : syn</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>97</td>
<td>Me₂CuLi</td>
<td>81</td>
<td>84:16</td>
</tr>
<tr>
<td>2</td>
<td>97</td>
<td>MeCuCNLi</td>
<td>84</td>
<td>88:12</td>
</tr>
<tr>
<td>3</td>
<td>98</td>
<td>Me₂CuLi</td>
<td>77</td>
<td>70:30</td>
</tr>
<tr>
<td>4</td>
<td>98</td>
<td>MeCuCNLi</td>
<td>81</td>
<td>75:25</td>
</tr>
<tr>
<td>5</td>
<td>99</td>
<td>Me₂CuLi</td>
<td>75</td>
<td>3:97</td>
</tr>
<tr>
<td>6</td>
<td>99</td>
<td>MeCuCNLi</td>
<td>88</td>
<td>1:99</td>
</tr>
<tr>
<td>7</td>
<td>100</td>
<td>Me₂CuLi</td>
<td>78</td>
<td>18:82</td>
</tr>
<tr>
<td>8</td>
<td>100</td>
<td>MeCuCNLi</td>
<td>79</td>
<td>16:84</td>
</tr>
</tbody>
</table>

<sup>a</sup> Me₂CuLi was prepared from MeLi and CuI in THF/Et₂O (4:1), MeCuCNLi was prepared from MeLi and CuCN in Et₂O.

This preference likely arises from the significant directing effect of the terminal hydroxyl group on the Z isomer 99, which undergoes Li coordination to the oxygen on the epoxide ring and terminal hydroxyl group (Scheme 1.28). This chelation effect is observed in both pure Et₂O and Et₂O/THF mixed solvent, although in pure Et₂O slightly higher syn- preference was observed (99:1 vs 97:3, entry 5 and 6). This is also in accordance with the fact that lithium cuprates [Gilman and alkyl(cyano)cuprate] are present as contact ion pairs (CIP) in Et₂O and Li is still bonded to the copper atom.
In summary, the $E/Z$ stereoselectivity is largely dependent upon the geometry of the transition state arising from the substituents on the allylic system, while cuprate reagents have little impact on the outcome. The anti-syn- ratio is significantly governed by stereoelectronic effect and to a less extend by chelation effects.
Conjugate Addition of Organometallic Reagents to 2-Pyridones

2.1 Conjugate Addition Introduction

Reactions forming carbon-carbon bonds are one of the most important organic reactions and conjugate addition to α,β-unsaturated systems is a powerful tool to reach this goal. These conjugate addition reactions involve a Michael acceptor and a nucleophile (e.g., organometallic reagents). Michael acceptors include α, β-unsaturated aldehydes, ketones, esters and amides. The common nucleophiles include organometallic reagents and other non-carbon Michael donors such as amines, alkoxides and sulfides. One of the most frequently used organometallic reagents in 1,4-conjugate addition reactions is organocopper reagents, which can be derived from organolithium, organozinc, organomagnesium and many other organometallic reagents. The conjugate addition of an organocuprate reagent to a Michael substrate gives a stabilized carbanion, which upon protonation gives rise to β-substituted product (path a); the same carbanion can react with an electrophile $E^+$ to form an α,β-disubstituted product (path b). If the electrophile is an aldehyde, three stereogenic centers are formed in the tandem 1,4-addition-aldol reaction pathway (path c) (Scheme 1.29). It should be noted that these tandem conjugate addition enolate alkylation reactions (paths b and c) are sometimes problematic and generally give low yields due to the lower reactivity of copper enolates towards electrophiles compared to lithium enolates.
**Scheme 1.29 Different Pathways for Cuprate Conjugate Additions**

Other than organocopper reagents, a variety of organometallic reagents were found to serve as nucleophiles in conjugate addition reactions including zinc, magnesium, aluminum and boron based reagents. Also, transition metals such as nickel, cobalt, palladium and titanium afford catalysts that are found to effectively facilitate these transformations. Organocopper reagents, however, are the most frequently used organometallic reagents in 1,4-addition reactions.

### 2.2 Conjugate Addition to 2-Pyridones

The pyridone ring is an important precursor for the synthesis of 3,4-dihydro-2-pyridones or substituted 2-piperidinones, which form the backbones for many
biologically active compounds and natural products.\textsuperscript{93-100} It is also a general template for the synthesis of a broad range of \textit{N}-heterocycles such as piperidines, pyridines, quinolizidines, and indolizidine alkaloids.\textsuperscript{101,102} Though several methodologies have been reported for the synthesis of substituted 2-piperidinones,\textsuperscript{103-107} there are only a few literature reports on the synthesis of multisubstituted 3,4-dihydro-2-pyridone systems.\textsuperscript{108,109} These known literature procedures still suffer from limited numbers of substrates and types of nucleophiles. Therefore the synthesis of diverse multi-substituted 3,4-dihydro-2-pyridones still remains a challenge to synthetic chemists.

\section*{2.21 Conjugate Addition to 5,6-Dihydro-2-pyridones}

5,6-Dihydro-2-pyridinones were employed in copper salt mediated stereoselective 1,4-conjugate addition reactions, with excellent diastereoselectivity depending on the \textit{N}-protecting group and the cuprate reagents. Perrio and coworkers prepared 3,4-dimethyl-5,6-dihydro-2(1H)-pyridinones (101), which underwent 1,4-conjugate addition reactions in the presence of copper bromide dimethyl sulfide complex (CuBr•Me\textsubscript{2}S) providing only one diastereomer.\textsuperscript{107} It is noteworthy that \textit{N}-Boc (Boc = tert-butoxycarbonyl) analogues gave lower chemical yields (39~60\%) than the \textit{N}-methyl analogues (58~78\%), which was caused by the degradation of the \textit{N}-Boc substrates in the reaction medium (\textbf{Table 1.7}). Interestingly, the chemical yields of the cuprate reagent towards the \textit{N}-methyl substrate followed the order: Me > \textit{n}-Bu > Ph, whereas the reactivity towards \textit{N}-Boc substrate followed opposite order: Ph > \textit{n}-Bu > Me.
Table 1.7 Conjugate Addition of Cuprate to 101

![Chemical structure of 101 and 102](image)

<table>
<thead>
<tr>
<th>entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>R</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>Ph</td>
<td>58</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>Me</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>n-Bu</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>Boc</td>
<td>Ph</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>Boc</td>
<td>Me</td>
<td>39</td>
</tr>
<tr>
<td>6</td>
<td>Boc</td>
<td>n-Bu</td>
<td>54</td>
</tr>
</tbody>
</table>

<sup>a</sup> R<sup>1</sup>Li (10 equiv), CuBr•SMe<sub>2</sub> (5 equiv), TMSCl (3.2 equiv)

It’s known that introduction of an electron withdrawing group at the α position will greatly enhance the reactivity of α,β-unsaturated lactams.<sup>110-115</sup> Amat and coworkers reported the introduction of a carbonyl group at the α-position of indolyl α,β-unsaturated lactam 103 where the analogue lactam without the carbonyl was totally unreactive towards the nucleophiles (Table 1.8).<sup>116</sup> Various nucleophiles including tris(methylthio)methyl lithium (entry 1), the enolates derived from methyl bis(methylthio)acetate (entry 2) and methyl (phenylsulfinyl)acetate (entry 3) gave modest yields (50-62%).
### Table 1.8 Conjugate Additions to 103

<table>
<thead>
<tr>
<th>entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>nucleophile</th>
<th>% yield</th>
<th>trans : cis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(MeS)&lt;sub&gt;3&lt;/sub&gt;CH, n-BuLi</td>
<td>50</td>
<td>17:83</td>
</tr>
<tr>
<td>2</td>
<td>(MeS)&lt;sub&gt;2&lt;/sub&gt;CHCOOMe, NaH</td>
<td>62</td>
<td>77:23</td>
</tr>
<tr>
<td>3</td>
<td>PhSOCH&lt;sub&gt;2&lt;/sub&gt;COOMe, NaH</td>
<td>50</td>
<td>nd&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>All reaction were performed in THF, -78 °C, 2-7 h. <sup>b</sup>Not determined.

Cuprate reagents were reported to be effective nucleophiles in the conjugate addition to α-carbonyl-α, β-unsaturated lactams (e.g., 106). Moloney reported a conjugate addition to enantiopure bicyclic unsaturated lactams using lithium diorganocuprates in poor to modest yields (Scheme 1.30),<sup>115</sup> suggesting the low reactivity of such 5,6-dihydro-2-pyridones (106) under these reaction conditions. It should be noted that the same order of chemical yields for these lithium cuprate reactions (Ph > n-Bu > Me) as reported by Perrio<sup>107</sup> was observed.
Carreira reported a similar 1,4 conjugate addition reaction to 5-substituted-5,6-dihydro-2-(1H)-pyridone 108.\textsuperscript{117} In this reaction, a disubstituted lactam 109 was formed in 75% yield in an 83:17 diastereomeric ratio (Scheme 1.31). 2-Piperidinone 109 served as an important intermediate in the synthesis of (±)-Strychnofoline. It should be noted, however, only allyl cuprates, which are much more reactive than alkylcuprates, were employed in this study.

\textbf{Scheme 1.31 Conjugate Additions to 108}

2.22 Conjugate Addition to 2-Pyridones

Kunz and coworkers first reported the synthesis of 4-substituted-2-piperidinones using Grignard reagents (Table 1.9).\textsuperscript{118} They achieved excellent diastereoselectivity
(>98:2) and regioselectivity (>95:5) by using Grignard reagents (entry 1~10) and cuprate reagents (entry 11~13) with a 2-pyridone containing a chiral auxiliary.

Table 1.9 Copper Catalyzed Grignard Conjugate Additions to 110

<table>
<thead>
<tr>
<th>entry</th>
<th>reagent</th>
<th>yield (%)</th>
<th>dr R/S</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtMgCl</td>
<td>54</td>
<td>99:1</td>
</tr>
<tr>
<td>2</td>
<td>n-PrMgCl</td>
<td>68</td>
<td>99:1</td>
</tr>
<tr>
<td>3</td>
<td>i-PrMgCl</td>
<td>88</td>
<td>1:99</td>
</tr>
<tr>
<td>4</td>
<td>n-BuMgCl</td>
<td>75</td>
<td>99:1</td>
</tr>
<tr>
<td>5</td>
<td>t-BuMgCl</td>
<td>22</td>
<td>1:99</td>
</tr>
<tr>
<td>6</td>
<td>n-DecMgCl</td>
<td>55</td>
<td>99:1</td>
</tr>
<tr>
<td>7</td>
<td>c-C₆H₁₁MgCl</td>
<td>79</td>
<td>1:99</td>
</tr>
<tr>
<td>8</td>
<td>BenzylMgCl</td>
<td>34</td>
<td>99:1</td>
</tr>
<tr>
<td>9</td>
<td>PhenylMgCl</td>
<td>76</td>
<td>99:1</td>
</tr>
<tr>
<td>10</td>
<td>ButenylMgCl</td>
<td>86</td>
<td>99:1</td>
</tr>
<tr>
<td>11</td>
<td>n-Bu₂CuLi</td>
<td>64</td>
<td>99:1</td>
</tr>
<tr>
<td>12</td>
<td>t-Bu₂CuLi</td>
<td>39</td>
<td>92:8</td>
</tr>
<tr>
<td>13</td>
<td>n-Hex₂CuLi</td>
<td>93</td>
<td>99:1</td>
</tr>
</tbody>
</table>

Reagents and conditions: (a) Me₃SiOTf, 1h, CH₂Cl₂, room temp, 2, 6-lutidine, RMgX, CH₂Cl₂, room temp, 1-2h; (b) TMSCl, THF, 1h, room temp, R₂CuLi, THF, -78 °C to room temp.

They specifically designed an N-galatosyl group as the chiral auxiliary for the diastereoselective and regioselective attack of the nucleophile on the 2-pyridone or
pyridinium salt resulting from the 2-pyridone. An equilibrium mixture of two rotamers of the starting 2-pyridone (110a and 110b) was established (**Scheme 1.32**). Rotamer 110b was favored because the electrostatic repulsion (dipole interaction) between the lactam carbonyl group and the carbonyl on the pivaloyl group was minimized. Nucleophile attack occurred exclusively at the 4-position because the 6-position is sterically hindered by the bulky N-galactosyl group. Surprisingly, reversed diastereoselectivity was observed in some reactions (entry 3, 5, 7), but the reason was not discussed.

**Scheme 1.32** Rotamers of 110

Sosnicki reported the allylation of 2-pyridone substrates using lithium allyldibutylmagnesate reagents. N-allyl-2-pyridone 112 reacted with lithium allyldi-n-butylmagnesate to form conjugate addition product 113 (1,6-) and 114 (1,4-). All reactions gave good regioselectivity (> 92:8) except for entry 3 (**Table 1.10**). Using Grubbs catalyst, these 1,6-bisallyl-2-piperidinones were successfully converted into bicyclic δ-lactams 115. While good to excellent 1,4/1,6-regioselectivity was achieved in these 1,4-conjugate addition reactions, a major drawback is that only the allyl group could be used as a transferable ligand.
Table 1.10 Conjugate Additions of Lithium Allyldi-\textit{n}-butylmagnesiate to 112

\[
\begin{array}{cccc}
\text{entry}^a & \text{R}^1 & \text{R}^2 & \text{113:114} & \text{total yield (\%)} \\
1 & D & \text{Allyl} & 95:5 & 82 \\
2 & \text{TMS} & \text{Allyl} & 93:7 & 81 \\
3 & \text{Cl} & \text{Allyl} & 87:13 & 66 \\
4 & \text{PhS} & \text{Allyl} & 98:2 & 76 \\
5 & \text{Allyl} & \text{Allyl} & 92:8 & 72 \\
\end{array}
\]

\[a\] Reactions were run at -72 °C in THF.

The same lithium allyldi-\textit{n}-butylmagnesiate reacted with \textit{N}-benzyl-2-pyridone (116) to afford 3,6-dihydro-2-pyridone 117 in good yield (83\%) with excellent 1,6-regioselectivity (95:5).\cite{119} Again, the allyl group was the only successful transferable ligand in conjugate addition reactions to these 2-pyridone substrates (Scheme 1.33).
Introduction of an electron withdrawing group at the α-position for 2-pyridones is also reported to facilitate the conjugate addition reactions. Chang and coworker reported regioselective conjugate additions of Grignard reagents to 3-tosyl-N-benzyl-2-pyridones (118) in THF at room temperature to afford 4,5,6-trisubstituted 2-piperidinones (119). These reactions demonstrated exclusive 1,4- regioselectivity, however, because of the steric hindrance of an ethyl group at the 6-position.

**Scheme 1.34** Grignard Conjugate Additions to 118

Similarly, Hiroya reported that a 3-methoxycarbonyl –N-Boc (and N-benzyl) -2-pyridone underwent conjugate addition with an enol ether in the presence of a Lewis acid (Scheme 1.35). 3-Methoxycarbonyl-N-benzyl-2-pyridone **120a** reacted with enol ether
in the presence of Et₂AlCl (1.1 equiv) at – 40 °C to give rise to the conjugate addition product 122 (40%, 1,4-) and 123 (11%, 1,6-) with good diastereoselectivity (91:9). 3-Methoxycarbonyl-N-Boc-2-pyridone 120b reacted with enol ether 121 in the presence of Me₃Al (0.15 equiv) at -78 °C and gave exclusively the 1,4-conjugate addition product 122b (56%) with the same diastereoselectivity (91:9).

Scheme 1.35 Conjugate Additions to 120a-b

2.23 Conjugate Addition to N-Boc-4-Pyridone

Fenghai and Dieter reported the conjugate addition reaction of various organometallic reagents to N-Boc-4-pyridone 124 (Table 1.11). Lithium cuprates (alkylcyano or Gilman cuprate) bearing various ligands (i.e., n-Bu, Me, s-Bu, t-Bu and Ph) were readily added to the substrate (67-80%, entry 1-6). Lithium zincates with or without CuCN can also added to N-Boc-4-pyridone in modest yields, while addition of 1.0 equivalent of CuCN gave increased yield (70% vs 63% entry 7 vs 8). Grignard reagents were readily added and n-Bu, i-Pr, Et and Ph ligands all gave good yields (85-90%, entry 10, 11, 13, 14) while Me gave reduced yields (40%, entry 12) due to its lower reactivity. It’s interesting that both lithium zincates and Grignard reagents underwent smooth
conjugate addition reactions even in the absence of copper salts, which were generally considered crucial for such conjugate additions.\textsuperscript{123}

Table 1.11 Conjugate Additions to 124

<table>
<thead>
<tr>
<th>entry\textsuperscript{a}</th>
<th>RM</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$n$-BuCuCNLi</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>$n$-Bu$_2$CuLi</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>Me$_2$CuLi</td>
<td>69</td>
</tr>
<tr>
<td>4</td>
<td>$s$-Bu$_2$CuLi</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>t-Bu$_2$CuLi</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>Ph$_2$CuLi</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>$n$-Bu$_3$ZnLi</td>
<td>63</td>
</tr>
<tr>
<td>8</td>
<td>$n$-Bu$_3$ZnLi/ CuCN(1.0)</td>
<td>70</td>
</tr>
<tr>
<td>9</td>
<td>$n$-BuMgCl(1.0)/CuCN (0.1)</td>
<td>79</td>
</tr>
<tr>
<td>10</td>
<td>$n$-BuMgCl (1.0)</td>
<td>90</td>
</tr>
<tr>
<td>11</td>
<td>$i$-PrMgCl</td>
<td>86</td>
</tr>
<tr>
<td>12</td>
<td>MeMgCl</td>
<td>40</td>
</tr>
<tr>
<td>13</td>
<td>EtMgCl</td>
<td>89</td>
</tr>
<tr>
<td>14</td>
<td>PhMgCl</td>
<td>85</td>
</tr>
</tbody>
</table>

\textsuperscript{a}All reaction were run in THF at -78 °C.
### 2.24 TMSCl’s Acceleration Effect in Conjugate Addition Reactions

It’s noteworthy that trimethylchlorosilane (TMSCl) could facilitate these conjugate addition reactions in polar solvents (e.g. THF). First observed by Nakamura and coworkers in 1984, trimethylchlorosilane (TMSCl) showed its striking effect on accelerating organocopper reagents in conjugate additions to α, β-unsaturated carbonyl compounds. By the addition of TMSCl to the reaction, Dieter and coworkers reported conjugate addition of various α-carbamoylalkylcuprate reagents to α, β-alkenyl-, α, β-alkynyl-, α, β-γ-alkenyl-, α, β-γ, δ dienyl carboxylic acid derivatives, α,β-alkenyl nitriles, and α,β-alkenyl sulfoxides. In their study, conjugate addition of α-carbamoylalkylcuprates to carboxylic acid derivatives occurred smoothly in the presence of TMSCl, especially when dialkylcuprates alone failed completely (Scheme 1.36).

**Scheme 1.36** TMSCl’s Acceleration in Conjugate Additions

| 1. s-BuLi 2.0 equiv, THF, (-)-sparteine |
| 2. CuCN 2LiCl 1.0 equiv, -55 °C |
| 3. -78 °C, TMSCl 5.0 equiv |

There were several proposed mechanisms for this acceleration effect of TMSCl in organocopper mediated conjugate additions (Scheme 1.37). Corey and Boaz proposed a hypothesis of inner sphere electron-transfer, where the enolate-like intermediate generated from the 1,4- addition of the copper species was trapped with the silylation reagent (TMSCl), which is an irreversible step (route A); Another
mechanism proposed by Lipshutz\textsuperscript{128} involves a combined factor of the Lewis acidity and basicity of TMS\textsubscript{Cl} towards the enone and cuprate cluster, respectively, where the chlorine atom (Cl) would coordinate to the lithium (Li) on the cuprate and the silicon (Si) could serve as a Lewis acid towards the oxygen (O) on the enone (\textsubscript{131}), and therefore enhance the reactivity of the cuprate reagent (route B); a more recent mechanism, proposed by Bertz and Snyder\textsuperscript{129}, argues that a coordinate between the chloride and copper (\textsubscript{130}) could be present with an absence of a silylation of oxygen (route C), even though recent experimental data show such coordination is quite small\textsuperscript{130}. Through calculations and theoretical studies, Snyder and Bertz suggested that TMS\textsubscript{Cl} reduces the energy level of the transition state through a chlorine (Cl) coordination to a Cu(III) complex (\textsubscript{130}), and thus causes a faster reductive elimination step and eventually accelerates the conjugate addition reaction. They also found that by adding strong coordinative solvent such as hexamethylphosphoramide (HMPA) to the reaction medium stabilizes the Cu(III) d-\pi* complex by solvent coordination to the copper atom (\textsubscript{130a}) and consequently increases the energy barrier for the consequent reductive elimination step and thus serves as a “retarding reagent” in the cuprate conjugate addition reactions.\textsuperscript{129} Snyder later reported that without such solvent stabilization a trialkylcopper species has no or little existence in the reaction pathway and that a neutral tetracoordinated copper species is the essential intermediate (vide infra).\textsuperscript{131}
Scheme 1.37 Possible Explanations for TMSCI’s Acceleration Effect

Although all these proposed mechanisms agree on the correlation between the coordination of TMSCI (either to the oxygen atom or copper atom) and the enhancement of the reaction rate, none of them seem to provide a direct answer for the actual reaction pathway. Singleton and coworker, by measuring kinetic isotopic effects for $^2$H and $^{13}$C NMR spectra, concluded that the rate determining step of the 1,4-conjugate addition reaction is the reductive elimination step.
2.3 Pyridinium Salts

Comins and Akiba were the first to report the highly regioselective addition of Grignard reagents / cuprate reagents to \( N \)-ethoxycarbonylpyridinium salt 134 and \( N \)-\( t \)-butyldimethylsilyl pyridinium salts 135.\(^{134-136}\) In the reactions of both pyridinium salts, excellent 1,4-/1,2- regioselectivities (98.8:1.2~100:0 for both 134 and 135) were achieved (Scheme 1.38).

**Scheme 1.38 Conjugate Additions to Pyridinium Salts 134 and 135**

\[
\begin{align*}
\text{ClCO}_2\text{Et} & \quad \text{RCuBF}_3 \\
\text{\( \begin{array}{c}
\text{N} \\
\text{O} \\
\text{Et}
\end{array} \)} & \quad \text{\( \begin{array}{c}
\text{N} \\
\text{O} \\
\text{Et}
\end{array} \)}
\end{align*}
\]

\[
\begin{align*}
r^\text{Bu} & : 99.5:0.5 \quad 68 \\
r^\text{Hex} & : 99.7:0.3 \quad 66 \\
\text{PhCH}_2\text{CH}_2 & : 100:0 \quad 55 \\
r^\text{Bu} & : 99.7:0.3 \quad 38 \\
\text{Ph} & : 99:1 \quad 59
\end{align*}
\]

\[
\begin{align*}
r^\text{Bu} & : 99.6:0.4 \quad 68 \\
r^\text{Hex} & : 99.5:0.5 \quad 62 \\
\text{PhCH}_2\text{CH}_2 & : 98.9:1.1 \quad 64 \\
r^\text{Bu} & : 98.8:1.2 \quad 58 \\
\text{Ph} & : 99.7:0.3 \quad 59
\end{align*}
\]
Next, Comins and coworkers developed the addition reactions of Grignard reagents to chiral 1-acyl-4-methoxypyridinium salts with good to excellent diastereoselectivities.\textsuperscript{137-139} 4-Methoxy-3-(triisopropylsilyl)pyridine (140) reacted readily with the chloroformate derived from chiral alcohols to provide a chiral 1-acylpyridinium salt 141, which reacted with various Grignard reagents affording diastereoenriched addition products 142 (Table 1.12). These 2-substituted-1-acyl-2,3-dihydro-4-pyridones (142) were quite useful for a sequential 1,4-conjugate addition, as well as in the synthesis of more complex alkaloids.\textsuperscript{138}
Table 1.12 Conjugate Additions to Pyridinium Salt 141

<table>
<thead>
<tr>
<th>entry</th>
<th>R*OCOCl</th>
<th>RMgX</th>
<th>% yield</th>
<th>de</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>143</td>
<td>Ph</td>
<td>81</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>143</td>
<td>Bu-C≡C-</td>
<td>76</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>143</td>
<td>p-Tol</td>
<td>89</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>144</td>
<td>c-hex</td>
<td>81</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>144</td>
<td>p-Tol</td>
<td>64</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>144</td>
<td>vinyl</td>
<td>75</td>
<td>90</td>
</tr>
</tbody>
</table>

When indolyl or pyrrolyl Grignard reagents and chloroformate derivatives of the chiral alcohol trans-2-(α-cumyl)cyclohexanol (TCC) were used, these dihydropyridones 145a and 145b were formed with 48~50% enantiomeric excess (ee) upon the removal of the chiral auxiliary.
The synthesis of several biologically active natural products (e.g., aspidospermidine, strychnine, eburnammonine and smipine) bearing a highly functionalized piperidine ring (Figure 1.6) could be realized from these enantioenriched 2-indolyl/pyrrolyl substituted pyridones.\textsuperscript{138}

Figure 1.6 Natural Products Bearing a Highly Functionalized Piperidine Ring\textsuperscript{138}
2.4 Regiochemistry

Several regioisomers could be formed in the conjugate addition reactions to $\alpha,\beta,\gamma,\delta$-unsaturated diene systems: 1,2-, 1,4- and 1,6- adducts, and the control of exclusive 1,4- addition can be achieved by using Yamamoto’s reagent (RCu•BF$_3$) while lithium dialkylcuprates often give 1,6- addition products.$^5$

2.4.1 1, 4- vs 1, 2- Addition

The reaction of lithium di-$n$-butyl cuprate with enones in toluene afforded primarily 1,2- addition products.$^{140}$ Smith and coworkers found that addition of diethyl ether or dimethyl sulfide to the reaction mixture can promote 1,4- addition and afford excellent 1,4-: 1,2- regioselectivity (Table 1.13). In their studies, 4, 4a, 5, 6, 7, 8-hexahydro-4a-methyl-2(3H)-naphthalenone (146), 2-cyclohexen-1-one (147) and 3, 5, 5-trimethyl-2-cyclohexen-1-one (148) were chosen to react with lithium di-$n$-butyl cuprate in toluene. The reactions proceeded to afford mostly the 1,2- adducts in the absence of diethyl ether ($1,2:1,4 = 66:34$~$98:2$). An increased amount of the 1,4- addition products were observed upon addition of one equivalent of diethyl ether while addition of two equivalents of diethyl ether gave an excellent preference of 1,4- addition over 1,2-addition ($1,2:1,4 = 5:95$~$1:99$).$^{140}$
Table 1.13 Conjugate Additions of $^n$BuLi to 146-148

<table>
<thead>
<tr>
<th>enone</th>
<th>molar equiv of ether</th>
<th>product ratio</th>
<th>1,2- addition</th>
<th>1,4- addition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>146</td>
<td>0</td>
<td>98</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>93</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>147</td>
<td>0</td>
<td>66</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>27</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>148</td>
<td>0</td>
<td>95</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>78</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5</td>
<td>95</td>
<td></td>
</tr>
</tbody>
</table>

One explanation of such solvent effects on the regioselectivity was the stabilization of a Cu(III) intermediate in ether (Scheme 1.39). In a generally accepted mechanism for the conjugate addition of cuprate reagents to enones, the trialkyl copper species 149 was hardly observed without any solvent stabilization.\textsuperscript{140,141} Schleyer and
coworkers performed *ab initio* calculations for trialkylcopper species and found that “oxygen-coordinated trimethylcopper species was kinetically stable although thermodynamically much less than the reaction product”.\textsuperscript{142} Snyder also reported that without solvent stabilization, the trialkyl copper has little or no existence and was unlikely to serve as a key intermediate (vide supra).\textsuperscript{131} Smith therefore proposed that a solvent stabilized Cu (III) species \textbf{150} was involved in the reaction process and underwent a facile reductive elimination to afford the 1,4-conjugate addition product.

\textbf{Scheme 1.39} Ether Stabilization of Cu (III) Intermediate

2.42 1,4- vs 1,6- Addition

Although cuprate reagents generally afford 1,4- conjugate addition products, conjugate additions involving substrates with extended multiple bond systems (1,6-, 1,8-, etc) have been less thoroughly studied.\textsuperscript{5,143-145} Ever since the first discovery of 1,6-
conjugate addition with organocuprate reagents by Yamamoto in 1982, the control of regioselectivity (1,6- over 1,4- addition) has remained a challenge for synthetic chemists. In Yamamoto’s study, methyl sorbate was reacted with different organocuprate reagents (Scheme 1.40). While n-butylcopper and boron trifluoride gave predominately 1,4- addition product; lithium di-n-butylcuprate afforded exclusively 1,6-adduct. The alkyl copper and boron trifluoride (RCu·BF₃) combination was named Yamamoto reagents. An intermediate involving the coordination of BF₃ to the carbonyl group is likely to promote this 1,4- regioselectivity.

Scheme 1.40 Regioselective Conjugate Additions to 151

1,6-conjugate addition of cuprate reagents to acceptor-substituted enynes has been investigated intensively over the last few years because of their convenience in synthesizing functionalized allenes (Scheme 1.41). For example, the lithium dialkyl cuprate R₂CuLi can react with the enyne in either a 1,4- or 1,6- conjugate addition pathway. Upon treatment of the resulting enolate can react with an electrophile (E-X) to afford a substituted allene or a 1,3- butadiene derivative.
Surprisingly, for these acceptor-substituted enynes 154, the regioselectivity was hardly influenced by the size of the transferable ligand on the cuprate reagents. As shown in Scheme 1.42, even though a tert-butyl group already occupied the terminal alkyne position, the incoming t-butyl group on the cuprate reagent still showed a strong preference for 1,6-addition over 1,4-addition in spite of the large steric hindrance affording the 1,6-adduct 160 in 69~91% yields. This regioselectivity, however, was still limited to these acceptor-substituted enynes, and the specific mechanism is yet to be established.
The nature of the cuprate reagents also played a significant role in the control of regioselectivity. While Gilman reagents \( \text{R}_2\text{CuLi} \) and cyano-Gilman cuprates \( \text{R}_2\text{CuCN} \cdot \text{LiCN} \) generally provided the 1,6-adduct as the major product; the combined reagents of \( \text{RCu/TMSI} \), as well as silylcuprate \( \text{Li}[\text{Cu}(\text{R}_3\text{Si})_2] \) afforded preferably 1,4-conjugate addition products.\(^{150}\) Solvent, on the other hand, greatly influenced the regioselectivity. As seen in Scheme 1.43, the Gilman cuprate reacted with 2-en-4-ynoate \( 159a \) in different solvents and afforded different results: in THF the reaction proceeded smoothly in a predominantly 1,6-addition fashion, whereas in ether with the same cuprate reagent, the reaction afforded 1,6-reduction product \( 162 \), which is quite unusual. The detailed mechanism of this reaction is still uncertain.\(^{151}\)}
In summary, N-substituted-2-pyridones and N-substituted-5,6-dihydro-2-pyridones typically demonstrate poor conjugate addition reactivity towards organometallic nucleophiles (e.g., cuprate reagents). Successful examples of conjugate addition are limited to carefully designed substrates (such as introduction of an electron withdrawing group at the α-position or conversion into a pyridinium salt), and more reactive nucleophiles (i.e., allyl cuprates). Large excess of organometallic nucleophiles are also often required to complete this reaction. While high stereoselectivities can be achieved by the help of chiral auxiliaries, the results of regioselectivity is largely subjected to solvent polarity and choice of cuprate reagents.
References


(93)  Smith, D. Comprehensive Organic Chemistry; Pergamon, 1979; Vol. 4.


CHAPTER TWO
REGIO- AND STEREOSELECTIVITIES IN THE REACTIONS OF ORGANOMETALLIC REAGENTS WITH VINYLEPOXIDES

Introduction

Allylic substitution reactions are useful organic reactions and they are a common methodology for C-C bond formation. Although cuprate mediated allylic substitution reactions provide a powerful methodology for the regio-, diastereo-, and enantioselective construction of carbon-carbon bonds, the extent of these selectivities is often dependent upon the cuprate reagent, substrate substitution pattern, leaving group, solvent, and temperature.\textsuperscript{1-5} The \textit{anti}-S\textsubscript{N}2’-substitution (allylic substitution with rearrangement) reaction pathway predominates,\textsuperscript{6} and \textit{syn}-S\textsubscript{N}2’-substitution is largely limited to allylic carbamates\textsuperscript{7,8} and \textit{o}-diphenylphosphinobenzoates (\textit{o}-DPPB)\textsuperscript{9}. While this reliable reactivity pattern is an attractive feature of these cuprate mediated allylic substitutions, the method is often limited by modest regio- and/or diastereoselectivities. In early work, Marino\textsuperscript{10,11} and Lipshutz\textsuperscript{12} showed that lithium and zinc alkyl(cyano)cuprates (i.e., R\textit{Cu}CNM, M= Li, Zn) generally gave superior \textit{S}\textsubscript{N}2’-regioselectivity in reactions with cyclic epoxyalkenes compared to other cuprate reagents, and allylic \textit{o}-diphenylphosphinobenzoates give exceptional \textit{syn}- diastereoselectivity. Breit and coworkers reported the highly regio- (S\textsubscript{N}2’) and diastereoselective (\textit{syn}-) allylic
substitution reactions of allylic o-diphenylphosphinobenzoate 1 with Grignard reagents and copper (I) salts (Scheme 2.1).  

**Scheme 2.1** o-DPPB Directed syn-S_N^2' Substitution

**Scheme 2.1** o-DPPB Directed syn-S_N^2' Substitution

Nevertheless, the reliability of the alkyl(cyano)cuprate protocol is often substrate dependent and the o-DPPB methodology utilizes an expensive auxiliary and is limited to allylic esters. Marino reported allylic substitution reaction of cyclic vinyl epoxide 4 where the regioselectivity is highly dependent on the substituents on the substrates. Exclusive S_N^2'- product was obtained when the γ-position is occupied by an octenyl group whereas a methyl group gave poor regioselectivity (Scheme 2.2). The recently introduced picolinoxy group gives excellent S_N^2'-allylic substitution with (Z)-alkenes, but poor regioselectivity with (E)-alkenes.
A limited number of studies have explored 1,2-asymmetric induction in copper mediated allylic substitution\textsuperscript{16-23}, and conjugate addition reactions\textsuperscript{24-28} arising from a pre-existing stereogenic center adjacent to the alkene moiety.

**Scheme 2.2 Substrate Dependent Regioselectivity**

Regioselective control is more difficult in vinyl oxiranes (i.e., epoxides) where the \( \text{S}_2\)\textsuperscript{2} substitution reaction becomes more competitive with the \( \text{S}_2\)\textsuperscript{2}′-allylic substitution pathway.\textsuperscript{29,30} In a series of studies, Marshal examined a wide range of substituted, non-conjugated, and oxygen functionalized vinyl oxiranes delineating the effects of substrate structure.\textsuperscript{30} Organozinc cuprates\textsuperscript{31,32} and tri-substitued epoxides suppressed \( \text{S}_2\)\textsuperscript{2}-substitution, but mixtures of (\( E\)) and (\( Z\))-olefins were often obtained (Table 2.1).
Table 2.1 Cuprate Reactions of Tri-substituted Epoxides

<table>
<thead>
<tr>
<th>Substrate</th>
<th>% Yield</th>
<th>anti:syn</th>
<th>E/Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-olefin, trans-epoxide</td>
<td>76</td>
<td>91:9</td>
<td>75:25</td>
</tr>
<tr>
<td>Z-olefin, trans-epoxide</td>
<td>97</td>
<td>98:2</td>
<td>16:84</td>
</tr>
<tr>
<td>E-olefin, cis-epoxide</td>
<td>76</td>
<td>97:3</td>
<td>98:2</td>
</tr>
<tr>
<td>Z-olefin, cis-epoxide</td>
<td>71</td>
<td>90:10</td>
<td>97:3</td>
</tr>
</tbody>
</table>

Studies by Yamamoto\textsuperscript{31} on the epoxyenoate of methyl sorbate achieved the highest $S_N2'$-selectivity with CuCN derived methylcuprates, while later studies by Miyashita\textsuperscript{32} showed that enhanced regio and diastereoselectivities could be achieved with dialkylzinc reagents in the presence of CuCN in DMF (Table 2.2). The vast majority of these studies on vinyl oxiranes focused on methylcuprate reagents for transfer of the methyl group. $S_N2$-opening of the vinyl oxirane ranges from a minor occurrence to a significant one, and is chiefly limited by choice of substrate structure and utilization of CuCN derived cuprate reagents.
**Table 2.2** Cuprate Reactions of Epoxy Enoates 9a and 9b

\[
\begin{align*}
9a & \quad R = \text{Me}, \quad R^1 = \text{Me} \\
9b & \quad R = \text{nBu}, \quad R^1 = \text{Et}
\end{align*}
\]

<table>
<thead>
<tr>
<th>substrate</th>
<th>reagent</th>
<th>% yield</th>
<th>10:11</th>
<th>10 anti: syn</th>
<th>11 anti: syn</th>
</tr>
</thead>
<tbody>
<tr>
<td>9a</td>
<td>Me₂CuLi(^{a})</td>
<td>58</td>
<td>21:79</td>
<td>71:29</td>
<td>96:4</td>
</tr>
<tr>
<td>9a</td>
<td>Me₂CuLi•BF(_3)(^{a})</td>
<td>54</td>
<td>24:76</td>
<td>45:55</td>
<td>63:37</td>
</tr>
<tr>
<td>9a</td>
<td>MeCuCNLi(^{a})</td>
<td>71</td>
<td>68:32</td>
<td>99:1</td>
<td>97:3</td>
</tr>
<tr>
<td>9b</td>
<td>Me₂Zn/CuCN (0.2 equiv)(^{b})</td>
<td>81</td>
<td>95:5</td>
<td>&gt;95:5</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^{a}\)Reactions were run in Et\(_2\)O. \(^{b}\)Reaction was run in DMF.

\(\alpha,\beta\)-Enoates containing a \(\gamma\)-mesyloxy or tosylxy leaving group give significantly better \(S_N2'\)-regioselectivities than the corresponding epoxides in cuprate mediated allylic substitutions.\(^{33-36}\) Cuprates derived from simple alkylithium reagents and CuCN required addition of BF\(_3\)Et\(_2\)O for clean reactions, while the corresponding zinc cuprates did not. Transferable ligands were limited to simple alkyl ligands and the reactions gave either recovered starting material or reductive cleavage of the leaving group with acetate or benzoate nucleofuges. Nevertheless, vinyl \(\gamma\)-butyrolactones were reported to undergo \(anti-S_N2'\)-substitutions with alkylcyanocuprates. More recently we reported high regio- and stereoselectivities for sequential and tandem allylic substitutions on \(\gamma\)-chboro-\(\delta\)-acyloxy-\(\alpha,\beta\)-enoates (Scheme 2.3),\(^{37}\) and the strategy has been extended to the use of R\(_3\)Al/CuCN reagent combinations.\(^{38}\)
Scheme 2.3 Allylic Substitution Reactions of γ-Chloro-δ-acyloxy-α,β-enoate 12

\[
\begin{align*}
&\text{1. } R^1\text{MgX (1.0 equiv)} \\
&\quad \text{CuCN (0.3-2.0 equiv)} \\
&\quad \text{CH}_2\text{Cl}_2
\\
&\text{2. } \text{RMgX (2.0 equiv)} \\
&\quad \text{X = Cl, Br}
\end{align*}
\]

\[R^1 = \text{''Bu, Et; } R = \text{ Et, ''Bu, 'Pr}
\]

68-85% (dr = 92:8-98:2)

In summary, S_N2'-substitution is facilitated by phosphate^{39-44} and perfluorobenzoate leaving groups^{45,46}, CuCN derived cuprates^{10-12,17,36}, Mg^{21,22,41,43}, Zn^{32,36}, and Ti^{18,19} cuprates, and by steric hindrance^{21,30} about the leaving group, although exceptions abound.^{43,44} Temperature variations can effect reversal of S_N2/S_N2'-selectivity for sp^2-hybridized transferable ligands. What emerges from these portraits is a useful reaction for chirality transfer that is limited by substrate structure reducing the generality of the strategy. While the o-DPPB strategy is general, it precludes the direct use of readily available enantioenriched vinyl oxiranes containing two C-O bonds that can be exploited for sequential or tandem allylic substitution reactions. Having achieved excellent regio- and diastereoselectivity in cuprate mediated bis-allylic substitution reactions on 4-chloro-5-acetoxy-2,3-hexenoate^{37}, we set out to develop procedures for achieving similar selectivities on the complementary vinyl oxiranes. We sought to develop general procedures for the reaction of vinyl oxiranes with a range of cuprate reagents. We choose a vinyl oxirane containing a protected alcohol functionality. We restricted the study to disubstituted epoxides containing a methyl substituent so as to pose the greatest challenge to the methodology.
Results

Epoxy enoate 9 contains an electron deficient alkene that might be more reactive towards cuprate reagents and thus bias the inherent regio- and diastereoselectivities. For comparison, the cuprate mediated sequential bis-allylic substitution reactions of trans-1-(tert-butyldimethylsilyloxy)-2,3-epoxy-4-hexene (14) were also examined (Table 2.4). Treatment of epoxide 14 with cuprate or zincate reagents gave a mixture of products arising via allylic anti-$S_N2'$-substitution (i.e., 15-17) and $S_N2$-substitution (i.e., 18). The $^{13}$C-NMR spectrum for the reaction mixture of 14 with n-butylcuprates displayed four sets of olefinic carbon absorptions, which proved difficult to assign unambiguously to possible structures. Consequently, several possible stereo- and regioisomers of 15a were prepared for structural assignments (Scheme 2.4).

Scheme 2.4 Possible Products of Allylic Opening of 14

![Scheme 2.4 Possible Products of Allylic Opening of 14](image)

The syn-diastereomer of 15a (i.e., 16a) was readily prepared from dienol 19 via epoxidation, alcohol silylation and anti-$S_N2'$ substitution with lithium dimethylcuprate (Scheme 2.5) and displayed identical $^1$H, $^{13}$C, and GC-MS data to that obtained for 15a. Careful $^{13}$C measurements at 125 MHz resolved the diastereomeric carbinol [δ 72.9
(anti), 73.0 (syn)] and one of the diastereomeric olefinic [δ 139.7 & 126.2 (anti), 139.8 & 126.3 (syn)] absorptions and control experiments revolving around mixing samples of 15a and 16a in various proportions confirmed both the assignments and the calculated amounts via $^{13}$C NMR-peak heights.

**Scheme 2.5 Synthesis of Diastereomer 16a**

\[
\begin{align*}
\text{m-CPBA (1.3 equiv)} & \quad \text{NaHCO}_3, \text{CH}_2\text{Cl}_2 \\
\text{-20 °C, 2 h (90%) } & \quad \text{TBDMSCI} \\
\text{Imidazole (2.0 equiv)} & \quad \text{CH}_2\text{Cl}_2, \text{rt, 12 h (90%)} \\
\hline
\text{19} & \quad \text{20} \\
\text{16a} & \quad \text{21}
\end{align*}
\]

*Cis*-alkene 17a was prepared from the known 1,1-dibromoalkene 22 via in situ acetylide formation and trapping with ethyl glyoxal to afford 23. Reduction of the alkyne and ester functional groups in 23 followed by protection of the primary alcohol as the tert-butyldimethylsilyl ether (Scheme 2.6) afforded 17a as a 50:50 mixture of anti and syn diastereomers.
Scheme 2.6 Synthesis of *cis*-Alkene 17a

The non-allylic S$_N$2-substitution product 28 was prepared by alkylation of ethyl hexanoate with crotonaldehyde to afford 26 followed by ester reduction (27) and silylation of the primary alcohol (Scheme 2.7) and shown not to be a product of these reactions.

Scheme 2.7 Synthesis of Regioisomer 28
The allylic S_N2-substitution product 18 was not synthesized and its structure was established by COSY NMR experiments. Since 15a and 16a initially displayed overlapping ¹³C absorptions at 75 MHz, there remained a fifth set of olefinic absorptions unaccounted for. Considering the possibility of silyl migration, silyl regioisomer 15' was prepared via silylation of 15a (t-BuMe₂SiOTf, 2,6-lutidine, CH₂Cl₂) followed by chemoselective desilylation of the primary alcohol [pyridinium p-toluene sulfonate (0.3 equiv), MeOH] confirming the presence of this product in the reaction mixtures (Scheme 2.8).

**Scheme 2.8 Synthesis of Silyl- Migration Isomer 15'**

Reaction of lithium dialkylcuprates with epoxide 14 gave allylic alcohols in modest yields with good E:Z selectivity, good to excellent anti:syn diastereoselectivity and excellent regioselectivity (Table 2.3, entries 1-3), although the reaction could be capricious. Utilization of lithium n-butyl(cyano)cuprate gave low to modest yields of 15a.
with excellent regioselectivity, good to excellent anti:syn diastereoselectivities (entries 4-6) and modest to good E:Z selectivity. Use of HMPA as an additive diminished the E:Z stereoselectivity and increased the amount of silyl migration while maintaining excellent anti:syn diastereoselectivity and regioselectivity (entry 7). The low yields were reflected in recovered starting material (i.e., 14).

Although °Bu₂Zn with catalytic amounts of CuCN in DMF or THF gave excellent S_N2':S_N2- regio- and anti:syn- diastereoselectivities, the protocol gave modest E:Z selectivity when conducted at elevated temperatures (entries 8-14). Utilization of lower temperatures gave excellent selectivities across all levels irrespective of whether the reaction mixture was allowed to slowly warm to room temperature (entry 10) or quenched at low temperature (entries 11-12). The reaction was complete in one hour at -35 °C (9 hrs at -78 °C) with a significant decrease in the E:Z selectivity (entry 12) while still retaining excellent regioselectivity and anti:syn diastereoselectivity. The stoichiometric use of CuCN also gave diminished E:Z selectivity while retaining excellent diastereo- and regioselectivity (entry 15). The use of Et₂Zn and catalytic quantities of CuCN gave uniformly excellent selectivities across the board in both DMF and THF (entries 16 & 17, respectively). Addition of five equivalents of LiBr had little effect (entry18). The t-Bu₂Zn reagent in the presence of CuCN gave modest E:Z selectivity and excellent regio- and anti:syn diastereoselectivity (entry 19) while the heteroaryl (entries 20-21) and aryl (22-23) zinc reagents gave modest chemical yields, modest regioselectivity (i.e., ~ 75:25), excellent anti:syn diastereoselectivity and variable
$E:Z$ selectivity. Ph$_2$Zn gave excellent $E:Z$ selectivity with substoichiometric amounts of CuCN and reduced selectivity with stoichiometric amounts of CuCN.

The use of Grignard reagents in the presence of CuCN generally gave modest to excellent selectivities across the board (entries 24-33), which were sensitive to solvent composition and transferable ligand. The $n$-BuMg reagent gave excellent $E:Z$ selectivity and anti:syn diastereoselectivity in THF but modest regioselectivity (entry 24) while the use of diethyl ether showed enhanced $E:Z$ selectivity and reduced the latter two selectivities (entries 25-26). By contrast, the $E:Z$ selectivity was reduced in THF (entry 30-31) and enhanced in Et$_2$O (entries 32-33) for EtMgCl. In the latter solvent (i.e., Et$_2$O:THF, 10:1, v/v) all selectivities were uniformly excellent (entries 32-33). The use of an Et$_2$O:THF (10:1) solvent mixture also improved both the anti:syn diastereoselectivity and the regioselectivity in the reactions of $n$-BuMgCl/CuCN (entries 27-28), although the use of Et$_2$O:Et$_3$N (20:1) significantly degraded both the anti:syn-diastereoselectivity and the S$_N$2':S$_N$2-regioselectivity (entry 29).

Table 2.3 Copper Mediated Reactions of 14
<table>
<thead>
<tr>
<th>entry</th>
<th>cuprate</th>
<th>solvent</th>
<th>T °C(hr)</th>
<th>% yield</th>
<th>E: Z</th>
<th>dr (% yield)</th>
<th>S_N2⁺: S_N2⁻</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>°Bu₂CuLi (1.0)</td>
<td>THF</td>
<td>-78 (12)</td>
<td>52</td>
<td>90:10</td>
<td>83:17 (2%)</td>
<td>98:2</td>
</tr>
<tr>
<td>2</td>
<td>°Bu₂CuLi (1.0)</td>
<td>THF</td>
<td>-78 (12)</td>
<td>70</td>
<td>88:12</td>
<td>93:7 (2%)</td>
<td>94:6</td>
</tr>
<tr>
<td>3</td>
<td>°Bu₂CuLi (1.0)</td>
<td>THF</td>
<td>-78 (12)</td>
<td>55</td>
<td>88:12</td>
<td>93:7 (8%)</td>
<td>97:3</td>
</tr>
<tr>
<td>4</td>
<td>°BuCuCNLi (1.0)</td>
<td>THF</td>
<td>-78 (12)</td>
<td>24</td>
<td>90:10</td>
<td>87:13 (14%)</td>
<td>99:1</td>
</tr>
<tr>
<td>5</td>
<td>°BuCuCNLi (1.0)</td>
<td>THF</td>
<td>-78 (12)</td>
<td>N/A</td>
<td>91:9</td>
<td>87:13 (8%)</td>
<td>99:1</td>
</tr>
<tr>
<td>6</td>
<td>°BuCuCNLi (1.0)</td>
<td>THF</td>
<td>-78 (12)</td>
<td>14</td>
<td>90:10</td>
<td>88:12 (12%)</td>
<td>99:1</td>
</tr>
<tr>
<td>7</td>
<td>°BuCuCNLi (1.0)</td>
<td>THF/PA</td>
<td>-78 (12)</td>
<td>44</td>
<td>76:24</td>
<td>98:2 (23%)</td>
<td>100:0</td>
</tr>
<tr>
<td>8</td>
<td>°Bu₂Zn/ CuCN (0.2)</td>
<td>DMF</td>
<td>-23 (12)</td>
<td>40</td>
<td>82:18</td>
<td>100:0 (18%)</td>
<td>96:4</td>
</tr>
<tr>
<td>9</td>
<td>°Bu₂Zn/ CuCN (0.2)</td>
<td>THF</td>
<td>-23 (12)</td>
<td>77</td>
<td>88:12</td>
<td>100:0 (17%)</td>
<td>99:1</td>
</tr>
<tr>
<td>10</td>
<td>°Bu₂Zn/ CuCN (0.2)</td>
<td>THF</td>
<td>-78 (12)</td>
<td>89</td>
<td>91:9</td>
<td>96:4</td>
<td>99:1</td>
</tr>
<tr>
<td>11</td>
<td>°Bu₂Zn/ CuCN (0.2)</td>
<td>THF</td>
<td>-78 (9)</td>
<td>N/A</td>
<td>91:9</td>
<td>99:1</td>
<td>99:1</td>
</tr>
<tr>
<td>12</td>
<td>°Bu₂Zn/ CuCN (0.2)</td>
<td>THF</td>
<td>-78 (8)</td>
<td>54</td>
<td>94:6</td>
<td>100:0</td>
<td>100:0</td>
</tr>
<tr>
<td>13</td>
<td>°Bu₂Zn/ CuCN (0.2)</td>
<td>THF</td>
<td>-35 (1)</td>
<td>N/A</td>
<td>84:16</td>
<td>100:0</td>
<td>96:4</td>
</tr>
<tr>
<td>14</td>
<td>°Bu₂Zn/ CuCN (0.2)</td>
<td>THF</td>
<td>-35 (1)</td>
<td>87</td>
<td>85:15</td>
<td>100:0</td>
<td>97:3</td>
</tr>
<tr>
<td>15</td>
<td>°Bu₂Zn/ CuCN (1.0)</td>
<td>THF</td>
<td>-78 (12)</td>
<td>81</td>
<td>88:12</td>
<td>100:0</td>
<td>99:1</td>
</tr>
<tr>
<td>16</td>
<td>Et₂Zn/ CuCN (0.2)</td>
<td>DMF</td>
<td>-23 (12)</td>
<td>53</td>
<td>92:8</td>
<td>100:0</td>
<td>99:1</td>
</tr>
<tr>
<td>17</td>
<td>Et₂Zn/ CuCN (0.2)</td>
<td>THF</td>
<td>-78 (12)</td>
<td>54</td>
<td>94:6</td>
<td>100:0</td>
<td>94:6</td>
</tr>
<tr>
<td>18</td>
<td>Et₂Zn/ CuCN(0.2)/ LiBr(5.0)</td>
<td>THF</td>
<td>-78 (12)</td>
<td>47</td>
<td>91:9</td>
<td>94:6</td>
<td>99:1</td>
</tr>
<tr>
<td>19</td>
<td>°Bu₂Zn/ CuCN (0.2)</td>
<td>THF</td>
<td>-78 (12)</td>
<td>56</td>
<td>86:14</td>
<td>96:4</td>
<td>100:0</td>
</tr>
<tr>
<td>20</td>
<td>Furyl₂Zn/ CuCN (0.2)</td>
<td>THF</td>
<td>-78 (12)</td>
<td>41</td>
<td>50:50</td>
<td>97:3</td>
<td>75:25</td>
</tr>
<tr>
<td>21</td>
<td>Furyl₂Zn/ CuCN (1.0)</td>
<td>THF</td>
<td>-40 (12)</td>
<td>47</td>
<td>67:33</td>
<td>98:2</td>
<td>74:26</td>
</tr>
<tr>
<td>22</td>
<td>Ph₂Zn/ CuCN (0.2)</td>
<td>THF</td>
<td>0 (12)</td>
<td>40</td>
<td>94:6</td>
<td>91:9</td>
<td>74:26</td>
</tr>
<tr>
<td>23</td>
<td>Ph₂Zn/ CuCN (1.0)</td>
<td>THF</td>
<td>0 (12)</td>
<td>58</td>
<td>85:15</td>
<td>97:3</td>
<td>72:28</td>
</tr>
<tr>
<td>24</td>
<td>°BuMgCl(1.2)/ CuCN (0.2)</td>
<td>THF/Et₂O</td>
<td>-78 (12)</td>
<td>70</td>
<td>91:9</td>
<td>100:0</td>
<td>88:12</td>
</tr>
<tr>
<td>25</td>
<td>°BuMgCl(1.2)/ CuCN (0.2)</td>
<td>Et₂O</td>
<td>-78 (12)</td>
<td>75</td>
<td>100:0</td>
<td>79:21</td>
<td>71:29</td>
</tr>
<tr>
<td>26</td>
<td>°BuMgCl(1.2)/ CuCN (0.2)</td>
<td>Et₂O</td>
<td>-78 (12)</td>
<td>79</td>
<td>97:3</td>
<td>72:28</td>
<td>69:31</td>
</tr>
<tr>
<td>27</td>
<td>°BuMgCl(1.2)/ CuCN (0.2)</td>
<td>Et₂O/THF</td>
<td>-78 (12)</td>
<td>87</td>
<td>96:4</td>
<td>98:2</td>
<td>93:7</td>
</tr>
<tr>
<td>28</td>
<td>°BuMgCl(1.2)/ CuCN (0.2)</td>
<td>Et₂O/THF</td>
<td>-78 (12)</td>
<td>64</td>
<td>96:4</td>
<td>99:1</td>
<td>88:12</td>
</tr>
<tr>
<td>Reaction</td>
<td>Catalyst</td>
<td>Solvent</td>
<td>Yields</td>
<td>E:Z</td>
<td>anti:syn</td>
<td>Regio</td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>----------</td>
<td>---------</td>
<td>--------</td>
<td>------</td>
<td>---------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>BuMgCl(1.2)/CuCN (0.2)</td>
<td>THF</td>
<td>78:82</td>
<td>92:8</td>
<td>50:50</td>
<td>61:39</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>EtCuCNMgCl (1.0)</td>
<td>Et₂O/Et₃N</td>
<td>78:22</td>
<td>85:15</td>
<td>91:9</td>
<td>93:7</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>EtMgCl (1.2)/CuCN(0.2)</td>
<td>THF</td>
<td>78:22</td>
<td>88:12</td>
<td>97:3</td>
<td>88:12</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>EtCuCNMgCl (1.0)</td>
<td>Et₂O/THF</td>
<td>67:33</td>
<td>94:6</td>
<td>98:2</td>
<td>93:7</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>EtMgCl (1.2)/CuCN(0.2)</td>
<td>Et₂O/THF</td>
<td>76:24</td>
<td>93:7</td>
<td>98:2</td>
<td>91:9</td>
<td></td>
</tr>
</tbody>
</table>

- **a** The reactions were run at -78 °C and then allowed to slowly warm to room temperature and stirred for the indicated time unless otherwise noted.  
- **b** Yields based upon isolated products purified by column chromatography.  
- **c** The E:Z ratios [(15+15')+16] were determined from 13C NMR peak heights for the olefinic carbon atoms.  
- **d** Diastereomeric ratios (15+15':16) were determined from 13C-NMR ratios (125MHz) for the olefinic carbon absorptions.  
- **e** Regioisomeric ratios (15-17):18 were determined from 13C-NMR ratios for the olefinic carbon absorptions and compared against the 1H-NMR ratios for the methyl absorptions.  
- **f** The diol (21%) arising from desilylation of 15 was also obtained.  
- **g** Vinyl oxirane 14 was recovered: entry 4 (34%); entry 7 (15%); entry 8 (30%).  
- **h** The reaction was quenched at the indicated temperature after the indicated time in parenthesis.  
- **i** Vinyl oxirane 14 (22%) was recovered.  
- **j** Lithium halide free zinc reagents were employed.  

Lithium tri-n-butylzincate gave poor regioselectivity at elevated temperatures (Table 2.4, entry 1) and modest selectivity with reversal of regiochemistry in non-polar solvents (entries 3-4), although excellent regioselectivity was obtained in THF at room temperature (entry 2). Excellent E:Z selectivity and poor anti:syn diastereoselectivity was obtained in all cases for the allylic S_N2'-substitution pathway with reversal to syn-selectivity at higher temperatures. Silyl migration occurred at higher temperatures and in polar solvents (entries 1-2). Tri-methylzincate was unreactive at room temperature and when heated to reflux in THF gave poor S_N2':S_N2- regioselectivity (entry 5).
Table 2.4 Zincate Mediated Reactions of 14

<table>
<thead>
<tr>
<th>entry</th>
<th>zincate</th>
<th>solvent</th>
<th>T °C (hr)</th>
<th>% yield$^a$</th>
<th>E: Z$^b$</th>
<th>dr (% yield $^{15}$)$^c$</th>
<th>$S_N^2$:$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$^{n}$Bu$_3$ZnLi (1.5)</td>
<td>THF</td>
<td>66 (12)</td>
<td>49$^c$</td>
<td>95:5</td>
<td>34:66 (14)</td>
<td>70:30</td>
</tr>
<tr>
<td>2</td>
<td>$^{n}$Bu$_3$ZnLi (1.5)</td>
<td>THF</td>
<td>25 (12)</td>
<td>69</td>
<td>92:8</td>
<td>63:37 (11)</td>
<td>99:1</td>
</tr>
<tr>
<td>3</td>
<td>$^{n}$Bu$_3$ZnLi (1.5)</td>
<td>Et$_2$O</td>
<td>25 (12)</td>
<td>92</td>
<td>97:3</td>
<td>74:26</td>
<td>19:81</td>
</tr>
<tr>
<td>4</td>
<td>$^{n}$Bu$_3$ZnLi (1.5)</td>
<td>hexane</td>
<td>25 (12)</td>
<td>82</td>
<td>98:2</td>
<td>70:30</td>
<td>15:85</td>
</tr>
<tr>
<td>5</td>
<td>Me$_3$ZnLi (1.5)</td>
<td>THF</td>
<td>66 (12)</td>
<td>53</td>
<td>97:3</td>
<td>-</td>
<td>58:42</td>
</tr>
</tbody>
</table>

$^a$ Yields based upon isolated products purified by column chromatography. $^b$ The E:Z ratios [(15+15$^e$+16): 17] were determined from $^{13}$C NMR peak heights for the olefinic carbon atoms. $^c$ Diastereomeric ratios for 15 (i.e., 15:16) were determined from $^{13}$C-NMR ratios (125MHz) for the olefinic carbon absorptions. $^d$ Regioisomeric ratios (15-17):18 were determined from $^{13}$C-NMR ratios for the olefinic carbon absorptions and compared against the $^1$H-NMR ratios for the methyl absorptions. $^e$ Homoallylic alcohol was also obtained (8%). Vinyloxirane (24%) was also recovered.

Protection of the alcohol in 15a as the acetate or phosphate gave 30a-b, respectively, which were subjected to a second copper mediated allylic substitution (Table 2.5). Zinc cuprates were unreactive (entry 1) with 30a. Although EtCuCNMgCl gave excellent regio- and diastereoselectivity, it displayed low reactivity with acetate 30a giving substantial amounts of recovered starting material and cleavage of the acetate moiety in 30a in THF and THF/CH$_2$Cl$_2$ (entry 2-3), $^{n}$Bu cuprate ($^n$BuCuCNMgCl) gave
improved yield (60%) in CH₂Cl₂ (entry 4) suggesting the important role of THF in these acetate cleavage reactions. Similar patterns of cleavage reactions in THF were observed in diethylcuprate (Et₂CuMgCl, entry 5-6) and di-n-butyl cuprate (n-Bu₂CuMgCl, entry 10) although a preference of S₉N2-regioselectivities was also observed. Diethyl cuprate (Et₂CuMgCl) gave good yield in excellent S₉N2'-regioselectivity and anti-diastereoselectivity in CH₂Cl₂ (entry7). In CH₂Cl₂ and Et₂O, i-Pr₂CuMgCl gave selectivities identical to n-Bu₂CuMgCl showing no effect of the increased ligand size (entries 8-9), although a slight improvement in the anti:syn ratio was observed in Et₂O.

n-Bu₂CuMgCl gave similar results in Et₂O, ¹BuOMe and CH₂Cl₂ with excellent regioselectivities and modest diastereoselectivities (entry 11-13), although higher chemical yield was obtained in CH₂Cl₂ (entry 13). Lithium cyanocuprate (n-BuCuCNLi) failed to provide any desired product, giving starting material recovery and acetate cleavage product (entry 14).

Next we examined cuprate reactions of allylic phosphate, which generally gives high regio and diastereoselectivity in allylic substitution reactions. Although recovered starting material and acetate cleavage products were obtained with acetate 30a, the best results were obtained with lithium alkyl(cyano)cuprates (e.g., RCuCNLi, R = Et, n-Bu, s-Bu) where good chemical yields and excellent S₉N2'-regioselectivity and anti:syn-diastereoselectivity could be achieved in THF with phosphate 30b (entry 17-20).

Reaction of phosphate 30b with Gilman reagent in THF gave low yield due to cleavage of phosphate group with excellent regio and diastereoselectivity (entry 15) and similar results were observed in n-BuCuCNLi in Et₂O (entry 16). Utilization of the bulky t-Bu
ligand afforded S$_{N}$2-selectivity (entry 22) while the phenyl reagent gave diminished S$_{N}$2’-selectivity and excellent *anti*:syn-diastereoselectivity (entry 21). Reaction of PhLi and substoichiometric amounts of CuCN gave excellent S$_{N}$2-selectivity but low chemical yields (entry 23).

**Table 2.5** Copper Mediated Reactions of 30a and 30b

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>reagent (equiv)</th>
<th>solvent$^a$</th>
<th>% yield$^b$</th>
<th>$S_N2'$:$S_N2^c$</th>
<th>dr 31 or (32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30a</td>
<td>$^{n}$Bu$_2$Zn(2.0)/CuCN (1.0)</td>
<td>THF</td>
<td>0$^i$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>30a</td>
<td>EtCuCNMgCl (2.0)</td>
<td>THF</td>
<td>30$^d$</td>
<td>95:5</td>
<td>97:3</td>
</tr>
<tr>
<td>3</td>
<td>30a</td>
<td>EtCuCNMgCl (2.0)</td>
<td>CH$_2$Cl$_2$/THF 4:1</td>
<td>36$^d$</td>
<td>99:1</td>
<td>94:6</td>
</tr>
<tr>
<td>4</td>
<td>30a</td>
<td>$^{n}$BuCuCNMgCl (1.1)</td>
<td>Et$_2$O</td>
<td>60$^i$</td>
<td>94:6</td>
<td>85:15</td>
</tr>
<tr>
<td>5</td>
<td>30a</td>
<td>Et$_2$CuMgCl (2.0)</td>
<td>THF</td>
<td>25$^e$</td>
<td>20:80</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>30a</td>
<td>Et$_2$CuMgCl (2.0)</td>
<td>CH$_2$Cl$_2$/THF 4:1</td>
<td>49$^e$</td>
<td>57:43</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>30a</td>
<td>Et$_2$CuMgCl (1.0)</td>
<td>CH$_2$Cl$_2$</td>
<td>86</td>
<td>99:1</td>
<td>84:16</td>
</tr>
<tr>
<td>8</td>
<td>30a$^k$</td>
<td>$^{i}$Pr$_2$CuMgCl (1.0)</td>
<td>CH$_2$Cl$_2$</td>
<td>64</td>
<td>98:2</td>
<td>87:13</td>
</tr>
<tr>
<td>9</td>
<td>30a</td>
<td>$^{i}$Pr$_2$CuMgCl (1.0)</td>
<td>Et$_2$O</td>
<td>75</td>
<td>97:3</td>
<td>93:7</td>
</tr>
<tr>
<td>10</td>
<td>30a</td>
<td>$^{n}$Bu$_2$CuMgCl (1.1)</td>
<td>THF</td>
<td>52$^d$</td>
<td>17:83</td>
<td>(100:0)</td>
</tr>
<tr>
<td>11</td>
<td>30a</td>
<td>$^{n}$Bu$_2$CuMgCl (1.1)</td>
<td>Et$_2$O</td>
<td>73</td>
<td>95:5</td>
<td>89:11</td>
</tr>
<tr>
<td>12</td>
<td>30a</td>
<td>$^{n}$Bu$_2$CuMgCl (1.1)</td>
<td>$^{t}$BuOMe</td>
<td>72</td>
<td>98:2</td>
<td>89:11</td>
</tr>
<tr>
<td>13</td>
<td>30a</td>
<td>$^{n}$Bu$_2$CuMgCl (1.1)</td>
<td>CH$_2$Cl$_2$</td>
<td>90</td>
<td>96:4</td>
<td>83:17</td>
</tr>
<tr>
<td>14</td>
<td>30a</td>
<td>$^{n}$BuCuCNLi (1.3)</td>
<td>THF</td>
<td>0$^h$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

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Reactions were conducted at -78 °C and then allowed to warm to room temperature and stirred for 12 h. Based upon isolated products purified by column chromatography. Determined from \(^{13}\)C-NMR absorption peak heights for the olefinic carbon atoms. Starting acetate [entry (%): 1-2 (50-59%); 14 (15%)], and the alcohol from acetate cleavage were recovered [entry (% yield): 1-2 (4-9%); 14 (19%)]. Alcohol from acetate cleavage was obtained [entry (% yield): 3 (65%); 5 (51%)]. Commercial EtLi was employed and LiI (1.0 equiv) was added to the reaction mixture. Starting material (50%) and acetate cleavage product (25%) were obtained. Starting material recovered (30%). Starting material recovered (25%). Only starting material was recovered. Similar results were obtained with the Et analog (i.e., Et replacing \(\text{^n}\)Bu) of 30a [53% yield, 31:32 = 98:2, dr 17 = 85:15]. Starting material recovered (15% for entry 16).

The stereochemistry of syn-stereoisomers 31 was confirmed by conversion of 31f into alcohol 35 and comparison of its NMR spectrum with that of the anti-isomer 34, which could be prepared from readily available 13 (Scheme 2.9). To this end, reduction of ester 13, followed by tosylation and deoxygenation of the resultant primary alcohol afforded 33, which gave the (R*/S*) diastereomer 34, upon ozonolysis of 33 followed by reductive work-up. Ozonolysis of 31f with reductive workup gave the (R*/R*) diastereomer 35, which displayed different \(^{13}\)C-NMR absorptions from that of 34.
**Scheme 2.9 Stereochemical Assignments**

\[
\text{Scheme 2.9 Stereochemical Assignments}
\]

**Reactions:**

1. **Scheme 31:**
   - Reaction: \( \text{O}_3, \text{MeOH} \) followed by \( \text{NaBH}_4 \)
   - Yield: 80% overall

2. **Scheme 13:**
   - Reaction: \( \text{LiAlH}_4, \text{Et}_2\text{O} \) reflux, 70%
   - Additional steps: 1. TsCl, Pyridine rt. 12 h (100%), 2. LiAlH\(_4\), Et\(_2\)O (55%)

**Products:**

- **31 → 35**
- **13 → 33 → 34**
- **13 → 33 → 34**
Discussion

The mechanistic framework for understanding regio- and stereocontrol in copper mediated allylic substitution reactions involves the preference for anti-$S_N2'$-attack of the cuprate reagent on the allylic substrate guided by interactions of the copper $d_{x-y}$ orbital with the alkene $\pi^*$ and $\sigma^*_{C-LG}$ orbitals\textsuperscript{6,48,49} followed by either partitioning between two $\sigma$-allyl copper complexes via the intermediacy of a $\pi$-allyl complex\textsuperscript{50} or regioselective reductive elimination from the $\pi$-allyl complex itself or an enyl $[\sigma + \pi]$ complex\textsuperscript{49,51}. For the copper-catalyzed reactions of Grignard reagents and allylic substrates, conditions favoring rapid reductive elimination (e.g., leaving group, substrate structure) favor $S_N2'$-allylic substitution, while slower reductive elimination allows partitioning between the initial $\sigma$-allyl complex leading to $S_N2'$-substitution and the $\sigma$-allyl copper complex leading to $S_N2$-substitution, which may be favored on steric grounds.\textsuperscript{50} Computationaly, Nakamura and co-workers have shown that alkyl(cyano)cuprates pass through a lower energy transition state when the electron rich alkyl group is trans (i.e., trans effect) to the leaving group resulting in a cis-orientation of the copper transferable ligand and the allyl group in the $\sigma$-complex leading to $S_N2'$-substitution and an unfavorable trans-orientation in the $\sigma$-complex leading to $S_N2$-substitution accounting for the significantly higher $S_N2'$-regioselectivity observed for these reagents.\textsuperscript{48,49}

The fact that excellent regioselectivities are achieved with dialkylzinc reagents in the presence of stoichiometric or catalytic quantities of CuCN raises questions as to the nature of these zinc cuprate reagents. The excellent $S_N2'$-regioselectivity obtained with
these reagents coupled with Nakamura’s computational study\textsuperscript{49} suggest formation of a zinc alkyl(cyano)cuprate reagent [i.e., RCu(CN)ZnR] rather than formation of a zinc dialkylcuprate [i.e., R$_2$CuZn(CN)$_2$] under conditions catalytic in copper.\textsuperscript{18} These experimental results are also consistent with the supposition that chelation effects are minimal in the reactions involving zinc cuprate reagents. Although dialkylzinc reagents are generally monomers reflecting the reluctance of zinc to participate in alkyl or aryl bridging, the reagents readily coordinate to donor atoms (e.g., ethers).\textsuperscript{52} It should be noted that Nakamura performed gas phase calculations\textsuperscript{49} and that both lithium and magnesium cuprates appear to be monomeric SSIP in THF and dimeric CIP in Et$_2$O,\textsuperscript{53-55} while the structural elements of zinc cuprates\textsuperscript{54-56} appear to be unstudied. Although neither solution or solid state structures have been elucidated for the zinc cuprates, our results point to structural differences in either the reactive zinc cuprate species or in the transition state structures relative to the lithium and magnesium cuprates.

Alkyl (i.e., Et, $^n$Bu, $^t$Bu) cuprate mediated allylic substitution on epoxide\textsuperscript{14} follows the normal patterns. Lithium dialkylcuprates give good to excellent $S_N2'$-regioselectivity [88 to 96\% regioisomeric excess (re)] governed by steric effects in the copper(III) intermediate\textsuperscript{36} (Scheme 2.10). As predicted by the trans-effect, use of lithium alkyl(cyano)cuprates gives increased $S_N2'$-regioselectivity (≥98\% re), which is also observed by use of dialkylzinc reagents and sub-stoichiometric amounts of CuCN (92 - ≥98\% re). Similar high $S_N2'$-regioselectivities are also achieved with magnesium alkyl(cyano)cuprates (86\% re) while alkyl Grignard reagents and 20 mol\% of CuCN display poor to modest regioselectives (38-82\% re). The $S_N2'$-regioselectivity decreases
along the series $\text{RCuCNLi} \ (\geq 98\% \ \text{re}) > \text{R}_2\text{Zn/CuCN} \ (0.2-1.0 \ \text{equiv})\ [88-\geq 98\% \ \text{re}] > \text{R}_2\text{CuLi} \ (88-96\% \ \text{re}) > \text{RCuCNMgX} \ (86\% \ \text{re})$ for the alkylcuprates.

**Scheme 2.10 Cu(III) Intermediate 36**

The $\pi$-face selectivity and subsequent *anti*:*$\text{syn}$ diastereomeric ratios for the $\text{S}_\text{N}2'$-substitution products are modest for the lithium dialkylcuprates (66-86% de) and good for the zinc cuprates at low temperatures (82-88% de) and the magnesium cuprates in THF or $\text{Et}_2\text{O}$:THF (5:1) [86-\geq 98% de]. Poor diastereomeric ratios (44-58% de) are obtained for $n$-$\text{BuMgCl/CuCN} \ (0.2 \ \text{equiv})$ in $\text{Et}_2\text{O}$ suggesting the importance of chelation effects.

Thus *anti*:*$\text{syn}$ diastereoselectivity decreases along the series $\text{R}_2\text{Zn/CuCN} \ (0.2-1.0 \ \text{equiv}) \ (92-\geq 98\% \ \text{de}), \text{RMgX/CuCN} \ (0.2-1.0 \ \text{equiv}) \ [82-\geq 98\% \ \text{de} \ \text{in THF or} \ \text{Et}_2\text{O}:\text{THF} \ (5:1)]$, $\text{RCuCNLi} \ (74-96 \ \text{de}) > \text{R}_2\text{CuLi} \ (66-86 \ \text{de})$. With the magnesium cuprates, *anti*:*$\text{syn}$-distereoselectivity is greater in THF than in $\text{Et}_2\text{O}$ and provides evidence against isomerization of intermediate cuprate complexes via SSIP and for chelation effects between cuprate reagent and substrate.
Thus, anti:syn-diastereoselectivity is modest to good for lithium dialkylcuprates in THF, excellent for zinc and magnesium cuprates in THF and poor for magnesium cuprates in Et₂O, although for the latter excellent S₈2'-regioselectivity can be restored by use of small amounts of THF (i.e., Et₂O:THF, 10:1) but not with Et₃N (i.e., Et₂O:Et₃N, 10:1; 1:1 dr). These observations suggest that diastereoselectivity in these allylic substitutions of epoxide 14 are governed by a combination of electronic and steric interactions, chelation effects and perhaps cuprate reactivity. In considering cuprate and/or the intermediate Cu(III) reactivity, the rate for oxidative addition and reductive elimination generally move in opposite directions with respect to electronic effects of the copper ligands. Regioselectivity, on the other hand, is govern by steric and electronic effects in the cuprate ligand of 36, the trans-effect for the alkylcyanocuprates (i.e., 36, L = CN), and the rate of reductive elimination.

The E/Z geometry of the product allylic alcohols derived from epoxide 14 appears to be largely determined by allylic strain in the transition states. In the ground state, the conformer leading to the trans-alkene displays A₁,₂-strain while the conformer leading to the cis-alkene displays A₁,₃-strain (Scheme 2.12), which usually exhibits the higher strain energy. The transition state geometries will undoubtedly alter the energy differences.
between the two types of allylic strain. Although not universally observed, the amount of 
Z-isomer (Table 2.3) generally increases at higher temperatures, in more polar solvents 
(e.g., THF/HMPA > THF > Et₂O), and with increasing size of the transferable ligand 
(e.g., iBu, Ph > aBu > Et). Additionally, there appears to be some dependence upon the 
cuprate counter ion (i.e., Li ~ Mg > Zn). These observations suggest that non-polar 
solvents, smaller transferable ligands and zinc cuprates favor a tighter transition state 
geometry magnifying the energy differences between the A¹,³ and A¹,²-steric interactions.

**Scheme 2.12 Allylic Strain in Epoxide 14 and Resultant TS**

The stereoselective substitution reactions of 30a-b have several potential control 
elements that may govern the stereochemical outcome of the reaction. These include the 
newly introduced stereogenic center, the stereo electronic preference for anti-S_N2' 
pathways, and A¹,³-strain at both stereogenic allylic centers. Observed 
diastereoselectivities in S_N2'-products obtained from allylic substrates containing a δ- 
stereogenic center have been rationalized by both modified Felkin-Ahn³⁶,⁵⁸ and A¹,³- 
strain⁵⁸ models. More recently a reductive elimination model²⁸ has been proposed for
conjugate addition reactions to γ-oxy-α,β-enoates (Scheme 2.13). In all instances, syn-31 is observed as the major product indicating that the dominant stereo controlling element is the strong stereoelectronic preference for anti-S_{N2}′ substitution, which is diminished slightly in the reactions of dialkymagnesium cuprates with 30a. The syn:anti-diastereoselectivity for the magnesium cuprates is solvent and cuprate reagent dependent, and could reflect cuprate structure and/or chelation of the cuprate reagent with the leaving group. In THF, these cuprates are expected to be solvent separation ion pairs and in less polar solvents homodimers, and this is consistent with reaction at the ester carbonyl in THF. In the modified Felkin-Ahn and reductive elimination models drawn to reflect the dominant anti-S_{N2}′-stereoelectronic control, steric hinderance for approach of the cuprate reagent is minimized at the expense of A^{1,3}-strain in the transition state conformation, while in the A^{1,3}-strain model the A^{1,3}-strain is minimized at the expense of an increased steric interaction for the approaching cuprate reagent (Scheme 2.13). Although all three models under the anti-S_{N2}′ constraint predict the same diastereomer, the preference for S_{N2}-substitution with tBuCuCNLi overrides the trans-effect for RCuCNLi reagents favoring S_{N2}′-pathways and points to the A^{1,3}-model as the more predictive one.

Regioselectivity in the reactions of 30a-b are sensitive to cuprate reagent, solvent, and size of the transferable ligand. The magnesium and lithium phenyl- and alkyl(cyano)cuprates give S_{N2}′-selectivity that diminishes significantly for phenyl (75:25, A = 2.8 kcal/mol)\textsuperscript{59} and reverses for tBu (14:86, A = 5.4 kcal/mol )\textsuperscript{59} reflecting A-values consistent with the A^{1,3}-strain model (Scheme 2.13). The magnesium
dialkycuprates and Ph₂CuLi give SN₂-selectivity in THF and SN₂’-selectivity in less polar solvents (i.e., Et₂O, CH₂Cl₂, tBuOMe) and for the magnesium cuprates reacting with 30a SN₂-selectivity is proportional to the amount of THF present in the solvent mixture. This is reminiscent of the ion-pair model for SN₂:SN₂’-selectivity proposed by Cram.

**Scheme 2.13 Models for Diastereocontrol in Allylic Substitutions of 31**

**(A) Modified Felkin-Ahn Model**

**(B) Reductive-Elimination Model**

**(C) A¹,3-Strain Model**
Summary

The regio- and stereoselectivities of the reactions of organometallic reagents with vinylepoxide 14 and allylic phosphate 30 were examined. The regioselectivity of the epoxide opening reaction is largely dependent on the steric and electronic effect of the allyl ligand of the Cu(III) species, the trans-effect for the cyanocuprates, and the rate of reductive elimination. The diastereoselectivity, however, is governed by a combination of electronic and steric effects, chelation effects and possibly cuprate reactivity whereas the $E/Z$ ratio seems to be controlled by allylic strain (i.e., $A_{1,2}^{1,2}$ and $A_{1,3}^{1,3}$) in the transition states. Epoxide opening product 15 was readily converted into allylic phosphate 30, which reacted with various lithium cyanocuprate to afford two contiguous stereogenic centered compounds in a highly regio- and diastereocontrolled fashion.
Experimental

**General:** NMR spectra were recorded as CDCl$_3$ solutions on Bruker AC-500 or JOEL 500 MHz instruments. The $^1$H NMR chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (TMS) or CHCl$_3$ (δ = 7.26) as internal standard. The $^{13}$C NMR chemical shifts are reported as δ values in parts per million (ppm) downfield from TMS and referenced with respect to CDCl$_3$ signal (triplet, centerline δ = 77.00 ppm). Infrared (IR) spectra were recorded on a Nicolet IR-200 FT-IR or Nicolet IR-100 FT-IR spectrometer as neat samples. Gas chromatography-mass spectrometry measurements were performed on a Shimadzu GC-2010 GC coupled to a GCMS-QP2010 mass spectrometer. Analytical thin layer chromatography (TLC) was performed on Scientific Adsorbents Inc. silica gel plates, 200 μ mesh with F$_{254}$ indicator. Visualization was accomplished by UV light (254 nm), and/or a 10% ethanol solution of phosphomolybdic acid. Flash column chromatography was performed with 200-400 μ mesh silica gel. Elemental analyses were determined by Atlantic Microlab Inc., Norcross, GA, USA from flash column chromatography purified samples. The chemical yields are of materials isolated by flash column chromatography.

**Materials:** All reaction flasks were oven-heated over 12 hours prior to use. All reactions were conducted under positive argon atmosphere using flasks fitted with rubber septa and sealed with Parafilm™. -40 °C or lower reaction temperature was achieved by using cold bath prepared from dry-ice/ isopropanol mixture. THF and diethyl ether were distilled.
from sodium benzophenone ketyl. Methanol was distilled from CaH₂. Other solvents including dichloromethane, ¹BuOMe, toluene, etc were used as received. Copper salts including CuCN and CuI were used from commercial bottles without any further purification. LiCl and ZnBr₂ were flame dried over a propane torch over 10 minutes under argon prior to use. n-BuLi (2.5 M in hexanes), s-BuLi (0.66 in cyclohexane), t-BuLi (1.6 M in pentane), MeLi (1.6 M in diethyl ether) and PhLi (1.8 M in hexanes)) were commercially available and were titrated using s-BuOH and 1,10-phenanthroline monohydrate in THF prior to use. Et₂Zn (1.0 M in hexanes), n-BuMgCl (2.0 M in diethyl ether), i-PrMgCl (1.65 M in THF) and EtMgCl (2.0 M in THF) were used directly from commercial source.

**(E) 2, 3-Epoxy-1-(1, 1-dimethylethylidimethylsiloxy)-4-hexene (14).** To a solution of starting epoxy alcohol (1.12 g, 9.64 mmol) in dichloromethane (60 mL) was sequentially added triethylamine (1.947 g, 19.28 mmol, 2.0 equiv), imidazole (1.311 g, 19.28 mmol, 2.0 equiv), and dimethylaminopyridine (20 mg). The mixture was cooled to 0 °C, and a solution of t-BuMe₂SiCl (1.43 g, 9.64 mmol, 1.0 equiv) in dichloromethane (20 mL) was added dropwise over a period of 30 minutes. The mixture was gradually warmed up to room temperature over 12 hours and H₂O (20 mL) was added. The aqueous phase was extracted with dichloromethane (3x30 mL), dried over MgSO₄, and concentrated in vacuo to afford an oil. Flash column chromatography on silica gel (petroleum ether:diethyl ether:NEt₃, 97:2:1) afforded 2.01 g (91%) of 14 as a colorless oil: ¹H NMR
(500 MHz, CDCl₃) δ 5.94 (dq, J = 15.6, 6.4 Hz, 1H), 5.22 (ddq, J = 15.6, 8.25, 1.85 Hz, 1H), 3.84 (dd, J = 11.9, 3.2 Hz, 1H), 3.69 (dd, J = 12.35, 4.55 Hz, 1H), 3.24 (dd, J = 8.25, 2.3 Hz, 1H), 3.00-2.98 (m, 1H), 1.74 (dd, J = 5.05, 1.8 Hz, 3H), 0.90 (s, 9H), 0.07 (d, J = 4.1 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 131.9, 128.1, 63.2, 60.2, 56.1, 25.9, 18.4, 17.9, -5.3.

(E) (2R*, 5S*) 1-[(1, 1-Dimethylethylidimethylsilyloxy)-5-methylnon-3-en-2-ol (15a).

**General Procedure E**: Copper (I) cyanide (90 mg, 1.0 mmol, 0.2 equiv) was dispersed in 40 mL of anhydrous THF, the flask was cooled to -78 °C, and a solution of n-Bu₂Zn (10.0 mmol, 2.0 equiv) (previously prepared from n-BuLi and ZnBr₂) in THF was added dropwise. The mixture was stirred at -78 °C for 15 minutes before treatment with a solution of 14 (1.14 g, 5.0 mmol, 1.0 equiv) in THF (2.0 mL). After 12 hours, H₂O (10 mL) was added, and the reaction mixture was filtered through Celite, extracted with ether (3 x 30 mL), dried over MgSO₄, and then concentrated in vacuo to afford a crude oil. Flash column chromatography (silica gel, ether:petroleum ether, 5:95, v/v) afforded 15a (1.19 g, 83%): IR (neat) 3436 (br, s), 2958 (s), 2930 (s), 2859 (s), 2244 (w), 1463 (m), 1382 (m), 1255 (m), 1111 (m), 1007 (w), 909 (w), 837 (m), 778 (m), 734 (m) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.63 (dd, J = 15.55, 7.8 Hz, 1H), 5.35 (dd, J = 15.6, 6.85 Hz, 1H), 4.11 (dt, J = 10.3, 3.2 Hz, 1H), 3.61 (dd, J = 10.1, 3.65 Hz, 1H), 3.42 (dd, J = 10.1, 7.75 Hz, 1H), 2.12-2.09 (m, 1H), 1.31-1.20 (m, 7H), 0.98 (d, J = 6.85 Hz, 3H), 0.91 (s, 9H), 0.88 (t, J = 6.9 Hz, 3H), 0.08 (s, 6H); ¹³C
NMR (125 MHz, CDCl$_3$) $\delta$ 139.7, 126.2, 72.9, 67.4, 36.5, 29.5, 25.9, 22.8, 19.3, 18.3, 14.1, -5.3, -5.4; mass spectrum, EI, m/z (relative intensity), 287 (0.01), 175 (17), 137 (16), 117 (20), 105 (75), 95 (43), 81 (52), 75 (100), 73 (61), 69 (68), 55 (53). Anal. Calcd. for C$_{16}$H$_{34}$O$_2$Si: C, 67.07; H, 11.96. Found: C, 66.92; H, 11.89.

(E) (2R*, 5S*) 1-[(1, 1-Dimethylethylidimethylsilyloxy)-5-methylhept-3-en-2-ol (15b). General Procedure F: Copper (I) cyanide (90 mg, 1.0 mmol, 0.2 equiv) was dispersed in 40 mL of anhydrous THF, cooled to -78 °C, and a solution of Et$_2$Zn (10.0 mmol, 2.0 equiv) in hexanes was added dropwise. The mixture was stirred at -78 °C for 15 minutes before treatment with a solution of 14 (1.14 g, 5.0 mmol, 1.0 equiv) in THF (2.0 mL). After 12 hours, 10 mL of H$_2$O was added, and the reaction mixture was filtered through Celite, extracted with ether (3x30 mL), dried over MgSO$_4$, and then concentrated in vacuo to afford a crude oil. Flash column chromatography (silica gel, ether:petroleum ether, 10:90, v/v) afforded 15b (1.00 g, 78%): IR (neat) 3436 (br, s), 2091 (br), 1646 (s), 1462 (w), 1383 (w), 1256 (w), 1110 (w), 734 (w) cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.61 (dd, $J = 15.55$, 7.8 Hz, 1H), 5.34 (dd, $J = 15.6$, 6.85 Hz, 1H), 4.11 (dt, $J = 3.7$, 2.75 Hz, 1H), 3.61 (dd, $J = 10.1$, 3.65 Hz, 1H), 3.43 (dd, $J = 10.05$, 8.25 Hz, 1H), 2.56 (s, 1H), 2.06-1.98 (m, 1H), 1.33-1.24 (m, 2H), 0.97 (d, $J = 6.4$ Hz, 3H), 0.90 (s, 9H), 0.84 (t, $J = 7.35$ Hz, 3H), 0.07 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 139.4, 126.5, 73.0, 67.4, 38.1, 29.4, 25.9, 19.8, 18.3, 11.7, -5.3, -5.4; mass spectrum, EI, m/z (relative intensity),
241 (0.05), 201 (2), 131 (27), 109 (89), 89 (57), 75 (100), 73 (73), 67 (51), 57 (33). Anal. Calcd. for C_{14}H_{30}O_{2}Si: C, 65.06; H, 11.70. Found: C, 64.85; H, 11.84.

\((E)\) (2\(R^*\), 5\(R^*\)) 1-[(1, 1-Dimethylethylidimethylsilyl)oxy]-5, 6, 6-trimethylhept-3-en-2-ol (15c). Employing General Procedure E, 15c was prepared in 56\% yield after flash column chromatography (silica gel, ether:petroleum ether, 5:95, v/v): IR (neat) 3436 (br, s), 2959 (m), 2860 (w), 1647 (s), 1112 (m), 837 (m), 778 (m) cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.61 (dd, \(J = 15.15\), 8.7 Hz, 1H), 5.27 (dd, \(J = 15.1\), 6.4 Hz, 1H), 4.05-4.03 (m, 1H), 3.53 (dd, \(J = 10.05\), 3.65 Hz, 1H), 3.35 (dd, \(J = 9.65\), 7.8 Hz, 1H), 2.44 (d, \(J = 2.3\) Hz, 1H), 1.85-1.79 (m, 1H), 0.87 (d, \(J = 6.9\) Hz, 3H), 0.83 (s, 9H), 0.76 (s, 9H), 0.00 (s, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 136.9, 128.0, 73.0, 67.4, 47.0, 32.7, 27.4, 25.9, 18.3, 15.3, -5.3, -5.4; mass spectrum, EI, \(m/z\) (relative intensity), 269 (0.04), 229 (0.7), 155 (17), 137 (23), 105 (31), 89 (58), 81 (95), 73 (67), 57 (100).

\((E)\) (2\(R^*\), 5\(R^*\)) 1-[(1, 1-Dimethylethylidimethylsilyl)oxy]-5-furylex-3-en-2-ol (15d). Difurlylzinc [(2-furyl)_2Zn] was prepared in the following fashion: at -78 °C, \(n\)-BuLi (0.86 mL, 2.1 mmol, 2.0 equiv) was added dropwise to a solution of furan (144 mg, 2.1 mmol, 2.0 equiv) in 5.0 mL of THF, the solution was warmed up to 0 °C and maintained at that temperature for 1.5 hour. The mixture was then added to a -78 °C solution of ZnBr\(_2\) (238 mg, 1.05 mmol, 1.0 equiv) in 3.0 mL of THF, and the mixture was stirred for
20 minutes at -78 °C, Employing **General Procedure E**, 15d was obtained in 47% yield as a mixture of diastereomers (50:50) after flash column chromatography (silica gel, ether:petroleum ether, 10:90, v/v): IR (neat) 3501 (br, s), 2983 (s), 2874 (m), 1445 (m), 1383 (m), 1298 (w), 1130 (m), 934 (w), 845 (w), 794 (w), 738 (w) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.34 (d, J = 1.5 Hz, 1H), 7.32 (d, J = 1.0 Hz, 1H, diastereomer), 6.31-6.30 (m, 1H), 6.02 (d, J = 3.0 Hz, 1H), 6.00 (d, J = 3.5 Hz, 1H, diastereomer), 5.88 (ddd, J = 16.0, 7.5, 1.5 Hz, 1H), 5.51 (ddd, J = 15.5, 6.5, 1.0 Hz, 1H), 5.58 (dt, J = 10.0, 1.0 Hz, 1H, diastereomer), 5.44 (dd, J = 12.0, 8.5 Hz, 1H, diastereomer), 4.60 (dt, J = 3.5, 1.0 Hz, 1H, diastereomer), 4.18 (dt, J = 9.0, 4.0 Hz, 1H), 3.89-3.87 (m, 1H, diastereomer), 3.65 (dd, J = 10.0, 3.5 Hz, 1H), 3.70 (dd, J = 10.0, 3.5 Hz, 1H, diastereomer), 3.57-3.55 (m, 1H), 3.47 (ddd, J = 17.5, 7.5 Hz, 1H), 2.63 (d, J = 2.8 Hz, 1H), 2.51 (d, J = 2.8 Hz, 1H, diastereomer), 1.38 (d, J = 7.0 Hz, 3H), 0.92 (s, 9H), 0.10 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 158.3, 141.1, 134.9, 128.4, 110.1, 104.1, 72.5, 67.2, 36.1, 25.9, 19.4, 18.8, -5.2, -5.3 and (158.4, 141.1, 135.5, 128.0, 110.0, 103.8, 68.6, 66.8, 32.3, 25.9, 18.3, 18.2, -5.2, -5.2, diastereomer); mass spectrum, EI, m/z (relative intensity), 282 (20), 281 (73), 221 (15), 147 (19), 105 (17), 75 (69), 73 (100).

***(E) (2R*, 5R*) 1-[(1, 1-Dimethylethyl(dimethylsilyl)oxy]-5-phenylhex-3-en-2-ol (15e).***

Employing **General Procedure E**, 15e was prepared in 42% yield after flash column chromatography (silica gel, ether:petroleum ether, 5:95, v/v): IR (neat) 3351 (br, s), 2957 (s), 2929 (s), 2858 (s), 2361 (w), 1596 (w), 1472
(m), 1254 (m), 1072 (m), 837 (s), 699 (s) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.24-7.11 (m, 5H), 5.88 (ddd, J = 15.55, 6.85, 0.95 Hz, 1H), 5.37 (ddd, J = 15.55, 6.4, 1.35 Hz, 1H), 4.12-4.06 (m, 1H), 3.55 (dd, J = 10.1, 3.7 Hz, 1H), 3.42-3.35 (m, 1H), 3.36 (dd, J = 10.1, 7.8 Hz, 1H), 2.63 (s, 1H), 1.29 (d, J = 6.85 Hz, 3H), 0.83 (s, 9H), 0.00 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 145.5, 138.2, 128.5, 127.3, 127.2, 126.2, 72.9, 67.2, 42.2, 25.9, 21.2, 18.4, -5.2, -5.3; mass spectrum, EI, m/z (relative intensity), 291 (0.01), 275 (0.2), 231 (2), 157 (96), 143 (42), 131 (89), 129 (91), 105 (82), 91 (49), 89 (66), 75 (100), 73 (97).

(E) 2,3-Epoxy-1-(1,1-dimethylethylidimethylsiloxy)-non-4-ene (21). Using the same experimental procedure as was used in the preparation of 14, 21 was prepared in 90% from the corresponding epoxy alcohol which was prepared from (E, E) 2,4-nonadien-1-ol using a published procedure⁶⁰: IR (neat) 3356 (br, s), 2957 (s), 2929 (s), 2858 (s), 1643 (w), 1463 (w), 1254 (m), 1098 (s), 837 (s), 778 (cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.84 (dt, J = 15.1, 6.9 Hz, 1H), 5.11 (dd, J = 15.1, 8.2 Hz, 1H), 3.77 (dd, J = 11.9, 3.2 Hz, 1H), 3.62 (dd, J = 12, 4.6 Hz, 1H), 3.16 (dd, J = 8.2, 2.3 Hz, 1H), 2.92-2.89 (m, 1H), 1.98 (dt, J = 6.9, 6.9 Hz, 2H), 1.31-1.21 (m, 4H), 0.82 (s, 9H), 0.82-0.80 (m, 3H), 0.00 (d, J = 4.1 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 137.3, 126.8, 63.2, 60.3, 56.3, 32.0, 31.0, 25.9, 22.2, 18.3, 13.9, -5.3; mass spectrum, EI, m/z (relative intensity), 256 (0.3), 255 (1.1), 214 (11), 213 (62), 143 (30), 117 (15), 97 (15), 89 (24), 75 (57), 73 (57), 55 (100).
**1,1-Dibromo-3-methyl-1-heptene (22)** was prepared according to a published experimental procedure\textsuperscript{61-63} in 71% yield.
(2R*, 5S*) and (2S*, 5S*) Ethyl 2-Hydroxy-5-methyl-3-nonoynoate (23). 1,1-Dibromoalkene 22 (774 mg, 2.87 mmol, 1.0 equiv) was dissolved in dry THF (4 mL) and the mixture was cooled to -78 °C before adding a n–BuLi (3.0 mL, 7.5 mmol, 2.5 equiv, 2.5 M in hexane) solution dropwise. The resulting solution was stirred at -78 °C for 1 hour and then allowed to gradually warm to room temperature and stirred for another 30 minutes. Then the mixture was cooled to -78 °C again and treated with a solution of ethyl glyoxalate (freshly distilled, 33 mol % in toluene) in THF (10 mL) and the reaction mixture was kept at -78 °C for 2 more hours before quenching with a saturated aqueous NH₄Cl solution (10 mL). After extraction of the aqueous phase with ether (3 x 25 mL), the combined organic phase was dried over MgSO₄ and concentrated in vacuo to afford a colorless oil. Flash column chromatography (silica gel, hexane:EtOAc, 85:15, v/v) afforded pure 23 (243 mg, 38%) as a 50:50 mixture of diastereomers: ¹H NMR (500 MHz, CDCl₃) δ 4.82 (d, J = 1.4 Hz, 1H), 4.36-4.24 (m, 2H), 3.02 (s, 1H), 2.49-2.42 (m, 1H), 1.46-1.27 (m, 6H), 1.33 (t, J = 6.9 Hz, 3H), 1.15 (d, J = 7.3 Hz, 3H), 0.90 (t, J = 6.9 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 170.8, 90.9, 75.7, 62.5, 61.6, 36.2, 29.4, 25.8, 22.4, 20.6, 14.0, 14.0.

(Z) (2S*, 5S*) and (Z) (2R*, 5S*) 5-Methyl-3-nonene-1, 2-diol (24a). Alcohol 23 (210 mg, 1.36 mmol) was dissolved in dry MeOH (7 mL) and to the mixture was added quinoline (0.1 mL) and Lindlar’s catalyst (20 mg). The resulting mixture was stirred vigorously under an
atmosphere of H₂ for 3 h before diluting with ether (20 mL), and was then filtered through a pad of Celite and solvent was removed in vacuo to afford crude 24 (212 mg) as a yellow oil. The crude material (80 mg, 1.0 equiv) was dissolved in dry ether (8 mL) and lithium aluminum hydride (43 mg, 2.0 equiv) was cautiously added at 0 °C. The mixture was refluxed for 2 h before cautiously quenching with 10 drops of water at 0 °C and EtOAc (30 mL) was added to dilute the solution whereupon the resulting mixture was stirred for 5 minutes until it became clear. The aqueous phase was extracted with EtOAc (3 x 25 mL), and the organic phase was dried over MgSO₄ and concentrated in vacuo to afford 24a (48 mg, 75%) as a yellow oil. Crude 24a was used in the next step without further purification.

(Z) (2R*, 5S*) and (Z) (2S*, 5S*) 1-[(1,1-Dimethylethyl(dimethylsilyl)oxy]-5-methyl-non-3-en-2-ol (17a) was prepared (52%) as a pair of diastereomers (58:42) from 24a using the same experimental procedure used to prepare 14: IR (neat) 3393 (br, m), 2957 (s), 2928 (s), 2859 (s), 1463 (m), 1377 (w), 1253 (m), 1105 (s), 838 (s), 779 (m) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) as a pair of diastereomers (58:42) δ 5.38-5.26 (m, 2H), 4.49-4.45 (m, 1H), 3.63-3.56 (m, 1H), 3.43 (dd, J = 10, 8.5 Hz, 1H), 2.59 (d, J = 1.5 Hz, 1H), 2.53 (d, J = 1.5 Hz, 1H diasteromer) 2.49-2.40 (m, 1H), 1.35-1.18 (m, 6H), 1.00 (d, J = 7 Hz, 3H), 0.96 (d, J = 7 Hz, 3H diastereomer) 0.93 (s, 9H), 0.93-0.88 (m, 3H), 0.10 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) (diastereomer) δ 140.8 (140.4), 126.4 126.1, (68.8) 68.5, (67.3) 67.1, (37.1) 37.0, 32.7 (32.6), 29.9 (29.6), 25.9, 22.8, (21.6) 21.3, 18.3, 14.0 (14.0),
-5.3, -5.4; mass spectrum, EI, m/z (relative intensity), 268 (0.12), 171 (1), 137 (22), 131 (22), 105 (39), 95 (45), 89 (63), 8 1(74), 75 (100), 73 (73), 57 (26).

(E) (2R*, 3S*) and (E) (2S*, 3S*) 2-n-Butyl-4-hexene-1, 3-diol (27). Diisopropylamine (528 mg, 5.22 mmol, 1.2 equiv) was dissolved in THF (20 mL) at 0 °C whereupon it was treated with n-BuLi (1.91 mL, 4.78 mmol, 2.5 M in hexane, 1.1 equiv) dropwise. After 15 minutes, the resultant solution was cooled to -78 °C and ethyl hexanoate (626 mg, 4.35 mmol, 1.0 equiv) was added slowly. The mixture was stirred at -78 °C for 1 hour before a solution of crotonaldehyde (457 mg, 6.53 mmol, 1.5 equiv) in THF (5 mL) was added dropwise and the mixture was allowed to warm to room temperature over 2 h before quenching with a saturated aqueous NH₄Cl solution (10 mL). After ether extraction (3 x 30 mL), drying over MgSO₄ and removal of solvent in vacuo, 26 was obtained as a colorless oil. Without further purification, this oil was dissolved in THF (28 mL), and lithium aluminum hydride (320 mg, 8.42 mmol, 2.0 equiv) was added with caution at 0 °C. The resulting suspension was then heated at reflux for 3 h and then quenched with water (1.0 mL). The aqueous phase was extracted with ether (3 x 30 mL), the combined organic phase was dried over MgSO₄, and then concentrated in vacuo to afford 27 consisting of a 1 : 1 mixture of diastereomers (450 mg, 60% over 2 steps): ¹H NMR (300 MHz, CDCl₃) δ 5.79-5.50 (m, 2H), 4.31 (dd, J = 6, 3 Hz, 1H, diastereomer) 4.09 (t, J = 9 Hz, 1H), 3.88 (dd, J = 9, 3 Hz, 1H), 3.75-3.61 (m, 2H), 2.57 (s, 2H), 1.76-1.73 (m, 3H), 1.40-1.18 (m, 6H), 0.95-0.88 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ
(diastereomer) 133.2 (130.7), 128.1 (128.0), 77.7 (76.3), 64.8 (64.5), 45.1 (44.8), 29.7
(29.4), 27.7 (26.2), 22.9 (22.9), 17.8 (17.7), 14.0 (14.0).

\((E)\ (2R^*,\ 3S^*)\) and \((E)\ (2S^*,\ 3S^*)\) \(1\{1,1\text{-Dimethylethylidimethylsilyl}oxy\}\)-2-\(n\)-butyl-4-hexen-3-ol (28).

\[
\begin{align*}
&\text{OH} \\
&\text{OTBS}
\end{align*}
\]

Dil 27 (450 mg, 2.6 mmol, 1.0 equiv) was dissolved in dichloromethane (20 mL) and imidazole (265 mg, 2.6 mmol, 1.5 equiv) and \(t\)-BuMe\(_2\)SiCl (392 mg, 3.9 mmol, 1.0 equiv) were added sequentially at 0 \(^\circ\)C. The reaction mixture was stirred for 12 hours before quenching with water (10 mL). After extraction of the aqueous layer with ether and drying the organic layer over MgSO\(_4\), 28 was obtained as a colorless oil consisting of a 1 : 1 mixture of diastereomers (390 mg, 52%). IR (neat) 3413 (br, s), 2956 (s), 2931 (s), 1471 (m), 1379 (w), 1255 (s), 1091 (s), 967 (m), 837 (s), 776 (s) cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.67-5.55 (m, 1H), 5.49-5.40 (m, 1H), 4.02-3.96 (t, \(J = 5.5\) Hz, 1H), 3.86-3.82 (d, \(J = 9.6\) Hz, 1H), 3.56-3.51 (dd, \(J = 10.1, 6.0\) Hz, 1H), 1.65 (s, 3H), 1.25-1.11 (m, 6H), 0.88-0.74 (m, 5H), 0.82 (s, 9H), 0.00 (s, 6H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) (diastereomer) 133.3 (131.1), (126.9) 126.8, 76.6 (75.8), (65.4) 65.2, (44.8) 44.7, (29.8) 29.6, 27.9, 25.9, 23.0, 18.2 (17.9), 14.1, -5.5, -5.6; mass spectrum, EI, \(m/z\) (relative intensity), 285 (0.01), 269 (0.05), 229 (4), 211 (3), 145 (13), 137 (6), 105 (77), 95 (12), 81 (17), 75 (100), 73 (29).
(E) (25®, 5R®) 2-[(1,1-Dimethylethylidimethylsilyl)oxy]-5-methylnon-3-en-1-ol (15a’).

Starting allylic alcohol 15a (110 mg, 0.38 mmol, 1.00 equiv) was dissolved in dichloromethane (3.5 mL), whereupon 2, 6- lutidine (61 mg, 0.57 mmol, 1.50 equiv) and tert-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (132 mg, 0.50 mmol, 1.31 equiv) was sequentially added to the reaction flask at 0 °C. The reaction mixture was gradually warmed to room temperature over 1 hour and then quenched with 2 drops of MeOH, followed by addition of water (10 mL). Extraction of the aqueous phase with ether, drying with MgSO₄, and concentrated in vacuo afforded the bis-sylated diol (146 mg) as a colorless oil, which was used in the next step without further purification. The crude material (44 mg, 0.11 mmol, 1.0 equiv) was dissolved in dry MeOH (2 mL) and pyridium p-toluenesulfonate (10 mg, 0.03 mmol, 0.3 equiv) was added at room temperature. The resulting mixture was stirred at room temperature for 12 hours before water (5 mL) was added. The aqueous phase was extracted with ether, and the combined organic phase was dried over MgSO₄ and concentrated in vacuo. Purification by column chromatography (SiO₂, diethyl ether : hexane, 5 : 95, v/v) afforded 15a’ (16 mg, 49% over 2 steps) as a colorless liquid: IR (neat) 3414 (br, s), 2958 (s), 2929 (s), 2858 (s), 2360 (w), 1463 (m), 1377 (w), 1254 (m), 1102 (m), 1056 (m), 972 (m), 837 (s), 778 (s), 670 (w) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.56 (ddd, J = 16, 8, 1 Hz, 1H), 5.34 (ddd, J = 15, 7, 1 Hz, 1H), 4.18 (dt, J = 7, 4 Hz, 1H), 3.52 – 3.39 (m, 2H), 2.15 – 2.08 (m, 1H), 2.00 (dd, J = 8.5, 5 Hz, 1H), 1.32-1.18 (m, 6H), 0.99 (d, J = 6.5 Hz, 3H), 0.93 (s, 9H), 0.93-0.88 (t, J = 7.5 Hz, 3H), 0.09 (d, J = 11.5 Hz, 6H); ¹³C
NMR (125 MHz, CDCl$_3$) $\delta$ 139.4, 127.7, 74.6, 67.2, 36.4, 36.3, 29.5, 25.8, 22.7, 20.3, 18.1, 14.0, -4.0, -4.7; mass spectrum, El, $m/z$ (relative intensity), 267 (0.02), 255 (13), 229 (4), 175 (24), 159 (11), 119 (13), 117 (76), 115 (15), 103 (49), 81 (22), 75 (84), 73 (100), 55 (54).

(E) (4S*, 5S*) (1, 1-Dimethylethyl)dimethyl[(4-n-butyl-5-methyl-2-nonenyl)oxy]silane (31b).

**General procedure G:** In a 25 mL round bottom flask flushed with argon, starting alcohol 15a (287 mg, 1.0 mmol) was dissolved in 3 mL anhydrous THF and the mixture was cooled to -78 °C in a dry ice bath. The mixture was slowly treated with n-BuLi (0.41 mL, 2.45 M in hexane, 1.0 mmol) stirred for 10 minutes, warmed up to -40 °C and stirred for 30 minutes, and then cooled down to -78 °C whereupon a solution of diethyl chlorophosphate (183 mg, 1.05 mmol) in 3.0 mL of THF was added dropwise. The resulting solution was then stirred at -78 °C for 1 hour, and then at -40 °C for 30 minutes. Meanwhile, in a separate round bottom flask, LiCl (111 mg, 2.6 mmol, flame dried) and CuCN (117 mg, 1.3 mmol) were dissolved in anhydrous THF (5.0 mL), the mixture was then cool to -78 °C, and n-BuLi (1.3 mmol, 2.45 M in hexane) was added dropwise. This mixture was stirred at -78 °C for 45 minutes before adding to the previously prepared reaction mixture dropwise at -78 °C. The reaction mixture was kept at -78 °C for 2 hours before gradually warming to room temperature over 12 hours. Saturated aqueous
ammonium chloride solution (10 mL) was used to quench the reaction mixture, followed by extraction with diethyl ether (3 x 25 mL). The organic phase was dried over MgSO₄, and concentrated in vacuo to afford an oil as crude product. Flash column chromatography on silica gel (ether:petroleum ether, 1:99, v/v) afforded 221 mg of pure 31b (68%): IR (neat) 2956 (s), 2927 (s), 2857 (s), 1462 (m), 1379 (m), 1253 (m), 1103 (m), 1060 (w), 973 (w), 836 (w), 776 (w) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.42-5.30 (m, 2H), 4.08 (d, J = 3.65 Hz, 2H), 1.88-1.82 (m, 1H), 1.48-1.00 (m, 13H), 0.84 (s, 9H), 0.84-0.78 (m, 6H), 0.71 (d, J = 6.85 Hz, 3H), 0.00 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 132.7, 130.2, 64.2, 46.7, 36.8, 34.9, 32.5, 30.1, 29.7, 26.0, 23.1, 22.9, 18.5, 15.5, 14.3, 14.2, -4.9, -5.0; mass spectrum, EI, m/z (relative intensity), 325 (0.01), 269 (81), 185 (19), 171 (41), 115 (31), 101 (29), 75 (100), 73 (70), 55 (20).

(E) (4S*, 5S*) (1, 1-Dimethylethyl)dimethyl[(4-1-methylethyl-5-methyl-2-heptenyl)oxy]silane (31c).

**General Procedure H:** In a 25 mL round bottom flask flushed with argon, CuCN (45 mg, 0.5 mmol) was dispersed in 10 mL dichloromethane, and starting material 30a (300 mg, 1.0 mmol) was added at room temperature. The mixture was stirred for 5 minutes before cooling to -78 °C, whereupn i-PrMgCl (1.65 M in THF, 1.0 mmol, 0.61 mL) was then added dropwise. The reaction mixture was stirred at -78 °C for 2 hours before gradually warming up to room temperature over 12 hours. Saturated aqueous NH₄Cl solution (10 mL) was used to quench the reaction mixture, followed by
extraction with dichloromethane (3 x 25 mL), drying the organic phase over MgSO₄.

After concentration in vacuo and flash column chromatography of the resulting oil on silica gel (100% petroleum ether) 151 mg of the pure product 31c was obtained (53% yield): IR (neat) 2958 (s), 2857 (s), 1462 (m), 1254 (m), 1100 (m), 1057 (w), 976 (w), 836 (m), 776 (m) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.41-5.26 (m, 2H), 4.08 (d, J = 6 Hz, 2H), 1.61-1.47 (m, 2H), 1.23-1.12 (m, 5H), 0.83 (s, 9H), 0.82-0.77 (m, 8H), 0.73 (d, J = 3 Hz, 3H), 0.70 (d, J = 3 Hz, 3H), 0.00 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 131.3, 130.8, 64.1, 53.7, 35.4, 33.2, 29.4, 28.6, 26.0, 23.1, 21.2, 20.6, 18.5, 15.4, 14.3, -5.0, -5.1; mass spectrum, EI, m/z (relative intensity), 283 (0.02), 227 (71), 171 (23), 157 (35), 143 (68), 115 (36), 95 (36), 75 (100), 73 (85), 57 (24).

(E) (4S*, 5S*) (1,1-Dimethylethyl)dimethyl[(4-ethyl-5-methyl-2-nonenyl)oxy]silane (31a).

Employing General Procedure H, 31a was prepared in 81% yield after flash column chromatography (silica gel, ether:petroleum ether, 1:99, v/v): IR (neat) 3434 (br, s), 2958 (s), 2929 (s), 2858 (m), 1638 (br), 1462 (m), 1253 (m), 1103 (m), 836 (s), 775 (m) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.50 (dt, J = 15, 5 Hz, 1H), 5.42 (dd, J = 14.5, 9 Hz, 1H), 4.17 (dd, J = 5, 1.5 Hz, 2H), 1.89-1.82 (m, 1H), 1.50-1.22 (m, 9H), 0.93 (s, 9H), 0.91 (t, J = 3 Hz, 3H), 0.86 (t, J = 7.5 Hz, 3H), 0.81 (d, J = 7 Hz, 3H), 0.09 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 132.2, 130.4, 64.1, 48.6, 36.4, 34.8, 29.6, 26.0, 25.4, 23.0, 18.4, 15.4, 14.1, 12.3, -5.0, -5.1; mass spectrum, EI, m/z (relative intensity), 283
(0.3), 241 (24), 143 (12), 115 (11), 75 (100), 73 (27). Anal. Calcd. for \( \text{C}_{18}\text{H}_{38}\text{OSi} \): C, 72.41; H, 12.83. Found: C, 72.68; H, 12.85.

\((E) (4S^*, 5S^*) (1,1-\text{Dimethylethyl})\text{dimethyl}[(4-1-\text{methylpropyl}-5-\text{methyl-2-}
\text{nonenyloxy})\text{silane} (31d).}

Employing General procedure G, 31d was prepared in 70% yield as a pair of diastereomers (53:47) after flash column chromatography (silica gel, 100% petroleum ether): IR (neat) 2958 (s), 2928 (s), 2857 (m), 1462 (m), 1378 (m), 1254 (m), 1101 (m), 853 (w), 774 (w) cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.50-5.42 (m, 1H), 5.41-5.34 (m, 1H), 4.18 (d, \(J = 5.05\) Hz, 2H), 1.77-1.05 (m, 11H), 0.93 (s, 9H), 0.91-0.77 (m, 12H), 0.1 (s, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) (minor diastereomer) \(\delta\) (131.2) 131.1, (131.1) 130.9, 64.1 (64.0), 52.2 (51.1), (35.5) 35.2, (34.8) 34.7, (33.1) 32.9, 29.7, 29.5 (29.2), 27.5 (26.7), 26.0 (25.9), 23.2 (23.1), 18.5 (17.0), (16.4) 16.2, (15.2) 14.3, 11.4 (11.3), -5.0; mass spectrum, EI, \(m/z\) (relative intensity), 311 (0.2), 269 (19), 143 (15), 75 (100), 73 (32).

\((E) (2R^*, 5S^*) (1,1-\text{Dimethylethyl})\text{dimethyl}[(2-1,1-\text{dimethylethyl}-5-\text{methyl-3-}
\text{nonenyloxy})\text{silane} (32e).}

Employing General procedure G, 32e was prepared in 67% yield after flash column chromatography (silica gel, ether:pentane ether, 1:99, v/v) along with
11% of the S?2’- product: IR (neat) 2957 (s), 2928 (s), 2858 (m), 1464 (m), 1363 (m), 1253 (m), 1101 (s), 1022 (w), 1003 (w), 853 (m), 774 (w) cm\(^{-1}\), \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.24-5.18 (m, 2H), 3.73 (dd, \(J = 10, 4.1\) Hz, 1H), 3.50 (dd, \(J = 10.1, 7.8\) Hz, 1H), 2.15-2.03 (m, 1H), 1.82-1.76 (m, 1H), 1.30-1.17 (m, 6H), 0.94 (d, \(J = 6.4\) Hz, 3H), 0.86 (s, 9H), 0.85 (s, 9H), 0.92-0.82 (m, 3H), 0.00 (s, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 139.0, 127.9, 64.0, 55.6, 37.0, 37.0, 32.3, 29.8, 28.4, 26.1, 23.0, 21.1, 18.4, 14.2, -5.1, -5.2; mass spectrum, EI, \(m/z\) (relative intensity), 325 (0.03), 269 (83), 213 (100), 199 (36), 115 (29), 89 (79), 75 (99), 73 (95), 57 (90). S?2’- product: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.50 (dd, \(J = 15.0, 10.5\) Hz, 1H), 5.34 (dt, \(J = 15.1, 5\) Hz, 1H), 4.09 (dd, \(J = 5.5, 1.4\) Hz, 2H), 1.70-1.62 (m, 1H), 1.59 (d, \(J = 10.6\) Hz, 1H), 1.22-1.10 (m, 6H), 0.83 (s, 9H), 0.81 (s, 9H), 0.82-0.76 (m, 3H), 0.73 (d, \(J = 6.9\) Hz, 3H), 0.00 (s, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 131.6, 129.3, 64.1, 56.3, 37.8, 33.6, 32.4, 29.8, 28.8, 26.0, 23.0, 18.5, 17.1, 14.3, -4.9.

\((E)\) (4S*, 5S*) (1,1-Dimethylethyl)dimethyl[(4-phenyl-5-methyl-2-nonenyloxy)silane (31f).

Employing General procedure G, 31f was prepared in 85% yield after flash column chromatography (silica gel, ether:petroleum ether, 1:99, v/v): IR (neat) 2957 (s), 2928 (s), 2856 (m), 1461 (w), 1377 (w), 1258 (m), 1099 (m), 835 (w), 775 (w) cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.25-7.22 (m, 2H), 7.18-7.10 (m, 3H), 5.80 (dd, \(J = 15.1, 9.6\) Hz, 1H), 5.51 (dt, \(J = 15.1, 5.5\) Hz, 1H),
4.10 (d, $J = 5.05$ Hz, 2H), 3.03 (t, $J = 8.25$ Hz, 1H), 1.78-1.70 (m, 1H), 1.30-1.15 (m, 6H), 0.85 (s, 9H), 0.88-0.76 (m, 6H), 0.00 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 144.7, 132.5, 130.4, 128.3, 128.1, 125.9, 63.9, 54.8, 37.9, 34.4, 29.3, 26.0, 22.9, 18.5, 17.0, 14.2, -5.0; mass spectrum, EI, m/z (relative intensity), 346 (0.02), 289 (25), 205 (14), 191 (14), 130 (24), 129 (63), 114 (22), 91 (24), 75 (100), 73 (66).

$^{(E)} (2R^*, 5S^*)$ (1,1-Dimethylethyl)dimethyl[(2-phenyl-5-methyl-3-nonenyl)oxy]silane (32f).

In a round bottom flask flushed with argon, starting alcohol 15a (197 mg, 0.69 mmol, 1.0 equiv) was dissolved in 3.0 mL of anhydrous THF, the mixture was cooled to -78 °C in a dry ice bath, and n-BuLi (0.29 mL, 2.40 M, 0.69 mmol, 1.0 equiv) was added dropwise. The mixture was stirred for 10 minutes, then warmed to -40 °C for 30 minutes, whereupon diethyl chlorophosphate (126 mg, 0.72 mmol, 1.05 equiv) in 3.0 mL of THF was added at -78 °C dropwise. The resulting solution was stirred at -78 °C for 50 minutes, then at -40 °C for 50 minutes. Meanwhile, in a separate round bottom flask, CuCN (25 mg, 0.27 mmol, 0.39 equiv) dispersed in 3.0 mL of THF was cooled to -78 °C, then treated with PhLi (0.52 mL, 1.7M in di-n-butylether, 0.89 mmol, 1.3 equiv) dropwise, stirred for 30 minutes at -78 °C before adding to the previous reaction flask at -78 °C. The combined reaction mixture was kept at -78 °C for 2 hours before gradually warming to room temperature over 12 hours. Saturated aqueous ammonium chloride solution (10 mL) was
used to quench the reaction mixture, followed by extraction with diethyl ether (3 x 25 mL). The organic phase was dried over MgSO₄, and concentration in vacuo to afford an oil as crude product. Flash column chromatography on silica gel (ether:petroleum ether, 2:98, v/v) afforded 107 mg of pure 32f (45% yield): ¹H NMR (500 MHz, CDCl₃) δ 7.34-7.21 (m, 5H), 5.65-5.60 (dd, J = 15.6, 7.35 Hz, 1H), 5.44-5.43 (dd, J = 15.1, 7.35 Hz, 1H), 3.80 (dd, J = 7.3, 3.65 Hz, 2H), 3.46 (q, J = 7.35 Hz, 1H), 2.18-2.11 (m, 1H), 1.34-1.22 (m, 6H), 1.01 (d, J = 6.9 Hz, 3H), 0.88 (s, 9H), 0.92-0.86 (m, 3H), 0.00 (d, J = 9.6 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 142.9, 138.3, 128.5, 128.3, 128.2, 126.3, 67.7, 51.3, 36.9, 36.8, 29.7, 26.0, 22.9, 20.8, 18.4, 14.2, -5.3, -5.4.

(E) (2S*, 3S*) 2-n-Butyl-3-ethyl-4-hexen-1-ol (37). Ethyl-2-n-butyl-3-ethyl-4-

hexenoate (13) (1.0 g, 4.4 mmol) was dissolved in 20 mL of anhydrous ether, cooled to 0 °C in an ice-bath whereupon lithium aluminum hydride (168 mg, 4.4 mmol) was added slowly to the reaction flask. The mixture was heated at reflux for 12 hours, and then cooled in an ice-bath, whereupon 1 mL of H₂O was added cautiously, the reaction mixture was diluted with 20 mL of ether, filtered through Celite, dried over MgSO₄ and concentrated in vacuo to afford a crude oil. Flash column chromatography on silica gel (ether:petroleum ether, 5:95, v/v) afforded 570 mg (70%) of pure 37: IR (neat) 3400 (br, s), 2958 (s), 2929 (s), 2872 (m), 1456 (m), 1377 (m), 1041 (m), 970 (m) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.49-5.44 (m, 1H), 5.28-5.22 (m, 1H), 3.63 (dd, J = 11, 4.5 Hz, 1H), 3.57 (dd, J = 10.5, 6.5 Hz, 1H), 2.11-2.04 (m, 1H), 1.70
(dd, $J = 6.5, 1.5$ Hz, 3H), 1.52-1.13 (m, 9H), 0.91 (t, $J = 7$ Hz, 3H), 0.86 (t, $J = 7$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 133.1, 126.5, 64.6, 46.1, 44.9, 30.3, 26.4, 25.3, 23.1, 18.0, 14.1, 12.4; mass spectrum, EI, $m/z$ (relative intensity), 184 (0.3), 137 (9), 97 (10), 82 (18), 69 (17), 67 (18), 83 (63), 55 (100).

(E) (2S*, 3S*) 1-Tosyloxy-2-n-butyl-3-ethyl-4-hexene (38). (E) 2-n-Butyl-3-ethyl-4-hexen-1-ol (37) (560 mg, 3.0 mmol) was dissolved in 10 mL of dry pyridine and $p$-toluenesulfonyl chloride (1145 mg, 6.0 mmol) was added in one portion at room temperature. After stirring at room temperature for 12 hours, the reaction mixture was quenched with 10 mL of H$_2$O, extracted with ether (3 x 25 mL), and the organic phase was dried over MgSO$_4$, and concentrated in vacuo to afford 38 as an oil (924 mg, 100%). The crude material was used for the next step without any purification: IR (neat) 2959 (s), 2931(s), 2873 (m), 1458 (m), 1364 (s), 1178 (s), 1098 (m), 962 (s), 834 (s), 667 (s) cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.82 (d, $J = 6.5$ Hz, 2H), 7.37 (d, $J = 8$ Hz, 2H), 5.18-5.13 (m, 1H), 5.01-4.96 (m, 1H), 4.00 (dd, $J = 9.5, 4.5$ Hz, 1H), 3.84 (dd, $J = 10, 7.5$ Hz, 1H), 2.47 (s, 3H), 2.00-1.92 (m, 1H), 1.57 (dd, $J = 6.5, 1.5$ Hz, 3H), 1.39-1.06 (m, 9H), 0.86 (t, $J = 7$ Hz, 3H), 0.79 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 144.6, 139.3, 131.1, 129.7, 128.0, 127.5, 71.7, 44.8, 41.8, 29.9, 26.3, 25.0, 22.9, 21.6, 17.9, 13.9, 12.2; mass spectrum, EI, $m/z$ (relative intensity), 281 (0.3), 225 (0.6), 207 (0.8), 166 (14), 137 (75), 109 (43), 96 (31), 95 (31), 91 (51), 83 (84), 82 (71), 81 (51), 67 (42), 55 (100).
(E) \((4R^*, 5S^*)\)-4-Ethyl-5-methyl-2-nonene (33). To a suspension of lithium aluminum hydride (570 mg, 15.0 mmol, 5.0 equiv) in 15 mL diethyl ether at 0 °C was added a solution of 38 (924 mg, 3.0 mmol, 1.0 equiv) in 5 mL of ether. The mixture was stirred at room temperature for 2 hours before quenching with \(\text{H}_2\text{O} (5 \text{ mL})\). After extraction with ether (3 x 25 mL), the organic phase was dried over MgSO\(_4\) and concentrated \textit{in vacuo} to afford a colorless oil. Flash column chromatography (silica gel, 100% petroleum ether) afforded pure 33 (260 mg, 55%): IR (neat) 2960 (s), 2929 (s), 2873 (m), 2361 (w), 1457 (m), 1378 (m), 969 (m) cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.37-5.29 (m, 1H), 5.21-5.14 (m, 1H), 1.67 (dd, \(J = 6.4, 1.4 \text{ Hz}, 3\text{H}), 1.44-1.12 (m, 9\text{H}), 0.90-0.78 (m, 9\text{H}); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 134.1, 125.3, 50.4, 37.0, 33.1, 30.0, 24.2, 23.1, 18.1, 17.2, 14.2, 12.4; mass spectrum, EI, \(m/z\) (relative intensity), 168 (0.4), 126 (17), 84 (41), 83 (86), 69 (29), 55 (100).

\((2R^*, 3S^*)\) 2-Ethyl-3-methyl-1-heptanol (34). Starting material 33 (100 mg, 0.6 mmol, 1.0 equiv) was dissolved in a mixed solvent of dry methanol (10 mL) and dichloromethane (1 mL), the mixture was cooled to -78 °C, and a stream of O\(_3\) was bubbled through the solution until a faint blue color appeared. Then the O\(_3\) stream was maintained for 10 more minutes before the solution was purged with nitrogen gas for 5 minutes. The dry ice bath was removed, the reaction mixture was
warmed to room temperature and stirred for 2 more hours. Solvent was then removed by rotary evaporator, the residue was dissolved in dry ether (5 mL), and lithium aluminum hydride (240 mg, 6.0 mmol, 10.0 equiv) was added in one portion and the mixture was then stirred at room temperature for 12 hours. Water (2 mL) was slowly added to quench the excess lithium aluminum hydride followed by extraction with ether (3 x 25 mL) and concentration in vacuo to afford a colorless liquid. Flash column chromatography on silica gel (ether:petroleum ether, 5:95, v/v) afford pure 34 (80 mg, 84%) as a colorless liquid: IR (neat) 3339 (br, s), 2959 (s), 2927 (s), 2874 (s), 1463 (m), 1380 (m), 1040 (m), 962 (w) cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.56-3.48 (m, 2H), 1.63-1.56 (m, 1H), 1.34-1.03 (m, 9H), 0.88-0.81 (m, 6H), 0.76 (d, $J = 6.85$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 63.9, 47.2, 34.0, 32.7, 30.1, 23.1, 19.7, 15.7, 14.2, 12.7; mass spectrum, EI, $m/z$ (relative intensity), 140(1), 111 (13), 98 (19), 85 (68), 84 (69), 71 (87), 70 (58), 69 (65), 57 (100), 55 (96).

(2$^S$, 3$^S$) 2-Ethyl-3-methyl-1-heptanol (35). Following the protocols for the preparation of 34, pure 35 was synthesized from starting material 31 in 80% yield after flash column chromatography (silica gel, ether:petroleum ether, 5:95, v/v): IR (neat) 3338 (br, s), 2960 (s), 2928 (s), 2874 (m), 2366 (w), 1460 (w), 1379 (w), 1036 (w) cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.58 (dd, $J = 11$, 5 Hz, 1H), 3.47 (dd, $J = 11$, 6 Hz, 1H), 1.55-1.50 (m, 1H), 1.33-1.02 (m, 9H), 0.88-0.81 (m, 6H), 0.78 (d, $J = 6.85$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 63.4, 47.3, 33.9, 33.0, 30.1, 23.1, 21.4, 16.2,
14.2, 12.4; mass spectrum, EI, \textit{m/z} (relative intensity), 140 (1), 111 (12), 98 (17), 85 (69), 84 (76), 71 (86), 69 (62), 59 (31), 57 (100), 55 (95).
References


CHAPTER THREE

CONJUGATE ADDITIONS TO 2-PYRIDONES

Introduction

2-Piperidinone derivatives are present in the backbones of many biologically active compounds,\(^1^5\) and the synthetic methods for construction of substituted piperidones and piperidines are of great interest for synthetic chemists. While many methods were reported for the synthesis of 2,3-dihydro-4-pyridone derivatives,\(^6^11\) access to substituted 2-piperidinones from 2-pyridones is still underdeveloped. One major obstacle for such syntheses is the low reactivity of 2-pyridones towards Michael donors.\(^\alpha,\beta^-\) Unsaturated lactams are known for their low reactivity toward organometallic reagents (RLi, RMgX and organocuprate) in either 1,4 or 1,6- conjugate additions,\(^12^14\) and currently there are three major protocols to activate \(\alpha,\beta^-\) unsaturated lactams.

The first method involves the introduction of an electron withdrawing group [e.g., carbonyl group or \(p\)-toluenesulfonyl (tosyl) group] at the \(\alpha\) position of the \(\alpha,\beta^-\) unsaturated lactam (Figure 3.1), which results in an increased reactivity towards conjugate addition reactions.\(^12^15^20\) Various organometallic reagents (e.g., organolithium, organocuprate, Grignard reagents) were used as nucleophiles with these activated conjugated substrates.
The second protocol converts the amide carbonyl into a thiolactam (Scheme 3.1).\textsuperscript{21,22} Unsaturated lactam 1 was unreactive towards conjugate addition reactions, so conversion into a thiolactam 2 using Lawesson’s reagent greatly increased its reactivity and 2 underwent conjugate addition of dimethyl malonate giving rise to the conjugate addition product, which upon desulfurization afforded the useful tetracyclic indole alkaloid 3 (80%).
Scheme 3.1 Synthesis of Tetracyclic Indole Alkaloid 3

The third protocol involves the introduction of an electron withdrawing group on the nitrogen atom. Itoh and coworkers reported the conjugate addition reactions of \(N\)-tosyl-\(\alpha,\beta\)-unsaturated \(\delta\)-lactam 4 with MeMgI and CuI (5 mol %) in modest yields (70-74%),\(^{13}\) where an electron withdrawing tosyl group greatly increased the electron deficiency of the unsaturated system (Scheme 3.2).
To the best of our knowledge, only one example was found for the conjugate addition to N-benzyl-2-pyridone (6, Figure 3.2)\textsuperscript{23} and no literature reports were found for N-tosyl-2-pyridone (tosyl = \textit{p}-toluenesulfonyl, 7) or \textit{N}-Boc-2-pyridone (Boc = \textit{tert}-butoxycarbonyl, 8) conjugate addition. Therefore it is of great interest to investigate the reactivity of these substrates towards conjugate addition reactions.

**Figure 3.2** Examples of \textit{N}-Protected 2-Pyridones

The 1,4/1,6- regioselectivity in cuprate conjugate additions to acyclic \(\alpha,\beta,\gamma,\delta\)-unstaturated conjugate diene systems are well studied\textsuperscript{24-27} The mechanistic rationalization was first proposed by Krause\textsuperscript{24} where the cuprate would initially undergo oxidative addition to the C=C double bond adjacent to the acceptor group (e.g., carbonyl) to form a \(\sigma\)-Cu(III) complex favoring an O-Li coordination; migration of copper group to the terminal C=C double would give arise to a \(\delta\) positioned \(\sigma\)-Cu(III) intermediate, which gives 1,6- conjugate adduct upon reductive elimination. The fact that exclusively 1,6-
product was observed in these $R_2CuLi$ conjugate additions may suggest that a slower reductive elimination step for $\beta$-Cu(III) complex than that of a $\delta$-Cu(III) complex.

**Scheme 3.3** Krause’s Mechanism for 1,6- Addition

Some kinetic calculations further supported the argument of different reaction rate of two Cu(III) intermediates. Nakamura and coworkers performed density-function study and calculated the energy barrier for the reductive elimination for both Cu(III) complexes and also the activation energy required for the migration of the Cu group.\(^{28}\) The oxidative addition of $Me_2CuLi$ to penta-2,4-dienal give rise to a $\beta$-Cu(III) $\sigma$-complex, which requires an activation energy of 17.4 kcal/mol to afford 1,4- conjugate adduct upon reductive elimination, while the activation energy required for the reductive elimination of $\delta$-Cu(III) $\sigma$-complex is 13.5 kcal/mol. The rate determining step is the migration of the copper atom, which is calculated to be 16.2 kcal/mol, which is 1.2 kcal/mol below the 1,4- reductive elimination barrier.
Scheme 3.4 Kinetic Calculation for the Activation Energies

\[ \text{Me}_2\text{CuLi} \quad \xrightarrow{17.4 \text{ kcal/mol}} \quad \text{Me}_2\text{CuLi}^+ \]

\[ \text{1,4- adduct} \quad \text{16.2 kcal/mol} \quad \Downarrow \]

\[ \text{1,6- adduct} \quad 13.5 \text{ kcal/mol} \quad \Downarrow \]

\[ \Downarrow \quad -19.0 \text{ kcal/mol} \]

\[ \text{Me}_2\text{CuLi}^+ \quad \xrightarrow{13.5 \text{ kcal/mol}} \quad \text{Me}_2\text{CuLi} \]

\[ \text{exclusively} \]

\[ \text{H} \quad \xrightarrow{17.4 \text{ kcal/mol}} \quad \text{Me}_2\text{CuLi}^+ \]

\[ \text{Me}_2\text{CuLi}^+ \quad \xrightarrow{13.5 \text{ kcal/mol}} \quad \text{Me}_2\text{CuLi} \]

\[ \text{1,4- adduct} \quad \text{16.2 kcal/mol} \quad \Downarrow \]

\[ \text{1,6- adduct} \quad 13.5 \text{ kcal/mol} \quad \Downarrow \]

\[ \Downarrow \quad -19.0 \text{ kcal/mol} \]
Results

Preparation of Starting Materials

\textit{N-Boc-2-Pyridone (7)}

Using a modification of Beak’s procedure,\textsuperscript{7} \textit{N-Boc-2-pyridone} was prepared by the deprotonation of 2-hydroxypyridine (9) with sodium \textit{tert}-butoxide followed by treatment with (Boc)\textsubscript{2}O (Boc = \textit{tert}-butoxycarbonyl) (\textbf{Scheme 3.5}). Unlike the \textit{N-Boc-4-pyridone}, the synthesis of 7 is always accompanied with the \textit{O-Boc} isomeric product 10 in various amounts (19-37\%). The formation of 10 could come from the direct acylation of the oxygen atom by (Boc)\textsubscript{2}O, or it could come from the isomerization of \textit{N-Boc} compound 7 at room temperature over time, which was observed by McKillop and coworkers on \textit{N-acetyl-2-pyridone}.\textsuperscript{29} The formation of 10 and lost of material during the purification by column chromatography (Et\textsubscript{3}N activated silica gel, neutral or basic Al\textsubscript{2}O\textsubscript{3}) greatly diminished the efficiency for the preparation of 7 (up to 65\% yield was obtained).

\textbf{Scheme 3.5} Synthesis of \textit{N-Boc 2-Pyridone 7}

\[
\begin{align*}
\text{9} & \xrightarrow{1. \text{ NaH, t-BuOH, r.t., 15 min}} \text{7} + \text{10} \\
& \xrightarrow{2. \text{(Boc)}_2\text{O, 60°C, 2.5 h}} \text{7:10} = 63:37 - 81:19
\end{align*}
\]
Attempted Preparation of $N$-Pivaloyl-2-Pyridone (11)

Since 7 is susceptible to $N$-Boc cleavage under various reaction conditions (vide infra), we also attempted to synthesize $N$-pivaloyl-2-pyridone. For the same reason given by McKollip,\textsuperscript{29} our attempt to prepare $N$-pivaloyl-2-pyridone (11) was unsuccessful and exclusively the $O$-acylation product 12 was obtained (Scheme 3.6). $N$-pivaloyl-2-pyridone is extremely unstable at room temperature and isomerizes through equilibrium to $O$-pivaloyl-2-pyridone (12). Fleming also reported fast isomerization of $N$-acetyl-2-pyridone to $O$-acetyl-2-pyridone at room temperature.\textsuperscript{30}

\textbf{Scheme 3.6 Attempted Synthesis of 11}

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\includegraphics[width=\textwidth]{Scheme3.png}};
\end{tikzpicture}
\end{center}

Preparation of $N$-tosyl-2-pyridone (8)

We also decided to synthesize $N$-tosyl-2-pyridone (8), which is considered a better Michael accepter in conjugate addition reactions. While poor yields of the $N$-tosylation product were obtained by the same procedure used for the preparation of 7, deprotonation by $n$-BuLi in THF at 0 °C for 20 minutes followed by direct $p$-
toluenesulfonyl chloride (TsCl) addition, solved the problem and gave exclusively N-tosyl-2-pyrione (8) in modest yield (72%, Scheme 3.7).

**Scheme 3.7 Preparation of 8**

![Diagram](image)

<table>
<thead>
<tr>
<th>Deprotonation</th>
<th>13:8</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaH, t-BuOH</td>
<td>80:20</td>
<td>-</td>
</tr>
<tr>
<td>n-BuLi, THF</td>
<td>100</td>
<td>72%</td>
</tr>
</tbody>
</table>

Preparation of N-Benzyl-2-Pyridone (6)

Following Sieburth’s procedure, N-benzyl-2-pyridone (6) was prepared readily (86%) from 2-hydroxypyridine, BnBr and K$_2$CO$_3$ in MeOH at 65 °C for 2.5 hours (Scheme 3.8).

**Scheme 3.8 Preparation of 6**

![Diagram](image)
Conjugate Addition Reactions to N-Boc-2-Pyridone (7)

Lithium Cuprate Conjugate Additions

We first used lithium alkyl(cyano)cuprate (i.e., n-BuCuCNLi, prepared at -78 °C for one hour from one equivalent of n-BuLi and one equivalent of CuCN•2LiCl in THF) to react with 7 in the presence of TMSCl (entry 1, Table 3.1), and the reaction did not provide any desired product. Recovery of t-butylicarbonate 15 and 2-pyridone 9 suggest that the carbamate group was cleaved by a nucleophile (Scheme 3.9). n-Butyl copper (RCu•LiI, prepared from CuI at -78 °C for 1 hour) gave the 1,4-conjugate addition product 16a (14%), along with the cleavage products t-butylicarbonate (15) and 2-pyridone (9) (entry 2). In all likelihood the organocopper reagent (i.e., BuCu•LiI) was not fully formed under these reaction conditions and unreacted n-BuLi in the reaction mixture served as a strong nucleophile to cleave the carbamate group.

Scheme 3.9 Proposed Mechanism for Boc Cleavage Reaction

When the organocopper reagent (i.e., BuCu•LiI) was prepared from CuI at elevated temperature (-40 °C for 1 hour, entry 3, Table 3.1), the cleavage product of the carbamate was suppressed and the reaction only proceeded with 13% conversion with
most of the starting material recovered (71% of 7) along with the Boc migration product 10 (16%), suggesting that this organocopper reagent (n-BuCu•LiI) is not reactive enough toward 7 under these reaction conditions. In fact, Yamamoto reported the low reactivity of organocopper reagents (RCu) in the absence of a Lewis acid (i.e., BF$_3$) in conjugate addition reactions.$^{32}$ We thus turned our attention to generally more reactive lithium dialky cuprates (Gilman reagents). Using 2.0 equivalents of lithium di-$n$-butylcuprate prepared from CuCN•2LiCl in THF at -55 °C for 1 hour gave a modest 37% yield, along with the cleavage products the $t$-butyl carbonate 15 (30%), 2-pyridone 9 (17%) and the Boc migration product 10 (5%, entry 4). In this reaction, high 1,4/1,6- regioselectivity (90:10) was achieved, and the assignments of both regioisomer were made from $^1$H and $^{13}$C NMR spectra. For the 1,4- addition product 16a, a methylene group $\alpha$ to the carbonyl is split by an adjacent chiral center into two pairs of doublet of doublet peaks at 2.54 ppm ($J = 14.7$, 5.5 Hz) and 2.28 ppm ($J = 14.7$, 8.7 Hz). Also, an olefinic proton absorption at 6.64 ppm indicates the olefinic proton $\alpha$ to the N atom. For the 1,6- addition product 17a, the same methylene group shows an absorption peak at 2.96 ppm (doublet, $J = 2.3$ Hz) and indicates it is not adjacent to a chiral center but to an olefinic proton, suggesting a $\beta$, $\gamma$-unsaturated lactam 17. The 1,4/1,6- regioselectivity was determined by the integration of the olefinic protons ($\delta$ 6.64 and 5.10 for 1,4- adduct and $\delta$ 5.78 and 5.66 for 1,6- adduct) from $^1$H NMR.

Using 2.0 equivalents of the Gilman cuprate (i.e., Bu$_2$CuLi) prepared from CuI under the same conditions gave an increased yield (50%) of the 1, 4 addition product 16a with only 5% of the Boc migration product 10 (entry 5, Table 3.1). Interestingly, in
comparison to CuCN mediated reactions, carbamate cleavage product 9 and t-butyl carbonate 15 were significantly suppressed in these CuI mediated cuprate reactions, and it is possible that LiCl serves as a Lewis acid and promotes the Boc cleavage process. It’s been reported that cuprates prepared from CuI are superior to those prepared from CuCN in the conjugate addition towards α,β-unsaturated lactams, while none of the reports provided any further explanation for this observation. Reducing the equivalents of cuprate (i.e., Bu₂CuLi) to one brought increased chemical yields (68-74%, entry 6 and 7 vs entry 5, Table 3.1) likely because it diminished the cleavage products (i.e., 9 or t-butyl carbonate 15), which were probably caused by some n-BuLi present in the extra equivalent of cuprate in THF (as in entry 5). All these Gilman reagents prepared from CuI gave the same 1,4/1,6-regioselectivity (86:14) determined by ¹H NMR, which was slightly lower than that obtained with cuprates prepared from CuCN (entry 5, 6, 7 vs 4). It should be noted that Boc migration product 10 was always observed in these cuprate reactions (e.g., 16% entry 3, 5%, entry 4 and 5, 4% entry 6, 8% entry 7), indicating that starting material 7 is prone to undergo Boc migration even under mild basic conditions.

Our attempt to use a cuprate prepared from 2.0 equiv of n-BuLi and 0.66 equiv of CuI at -40 °C for 1 hour proceeded in 65% yield with very good regioselectivity (92:8, entry 8, Table 3.1), along with starting material recovery (21%) and 2-pyridone 9 (8%). This demonstrates that as low as 33% (with regard to one equivalent of n-BuLi) of copper salt is sufficient for the reaction to proceed in satisfactory yields. The observance of 2-pyridone 9 (8%) suggests that the reagent prepared is merely n-Bu₂CuLi + n-BuLi where the free n-BuLi cleaved the carbamate group of the starting material 7 (Scheme 3.8).
Encouraged by Guo’s result, we tried using \( n\)-BuLi (1.0 equiv) and CuBr\( \cdot \)Me\(_2\)S (0.5 equiv) as a copper source in THF/Me\(_2\)S mixed solvent to react with \( 7 \) at -70 °C.

Unfortunately only starting material \( 7 \) was recovered, suggesting \( 7 \) has a lower reactivity than the corresponding \( N\)-Boc-4-pyridone (entry 9). When 1.0 equivalent of the Gilman reagent (i.e., \( n\)-Bu\(_2\)CuLi prepared from CuI) was employed in Et\(_2\)O, the reaction went smoothly to afford 1,4- addition product 16a (70%) along with 1,6- addition product 17a (10%) in a similar regioselectivity (89:11, entry 10), suggesting that switching solvent from THF to Et\(_2\)O has little effect on the outcome of chemical yields or the regioselectivity for the \( n\)-butyl ligand.

Next we examined the Gilman cuprates bearing various alkyl or aromatic transferable ligands. The Gilman cuprate bearing an \( s\)-butyl group (i.e., \( s\)-Bu\(_2\)CuLi) proceeded smoothly in THF (68%) with excellent 1,4/1,6- regioselectivity (95:5, entry 11, Table 3.1), and with a 50:50 diastereoselectivity. \( t\)-Bu\(_2\)CuLi gave high regioselectivity (91:9) in modest yield (76%, entry 12) in THF, whereas diminished chemical yield (31%) and poor regioselectivity (62:38, entry 13) were obtained using the same cuprate in Et\(_2\)O. It’s noteworthy that this regioselectivity observed with \( t\)-Bu\(_2\)CuLi in Et\(_2\)O is the only example where 1,4/1,6- regioselectivity is lower than 85:15, which may arise from the contact ion pair (CIP) structure of the cuprate reagent in Et\(_2\)O. Since \( t\)-Bu is the most bulky group among the ligands investigated and gave the highest 1,6- ratio, it is assumed that the regiocontrol in ether is not significantly affected by steric effects, and is probably influenced by electronic effect, although the detailed mechanism is still unclear. Methyl
cuprate (Me$_2$CuLi) in THF gave modest 1,4/1,6- ratio (86:14) in a reduced yield (52%, entry 14) due to the lower reactivity of Me ligand than the n-Bu ligand.

Our attempts to use phenyl as the transferable ligand were mostly problematic, due to a competition reaction for the formation of homo-coupled biphenyl (19). Cuprate (Ph$_2$CuLi) prepared from CuI and PhLi at -40 °C for 1 hour gave low yield (33%, entry 15) with 8% of unreacted starting material when starting 7 and TMSCl were added at -40 °C , while increased yield was achieved when 7 and TMSCl were added to the same cuprate at 0 °C (44%, entry 16). Cuprate (i.e., Ph$_2$CuLi) prepared from CuCN in diethyl ether at -40 °C for 30 minutes gave a better conversion of the starting material at 0 °C leading to similar regioselectivity (88:12, entry 17), however, several unidentified byproducts were also obtained suggesting it is a worse solvent than THF for these conjugate addition reactions. In conclusion, (1) Gilman reagents prepared from CuI gave satisfactory yields and good to excellent regioselectivity (86:14-95:5) for all transferable ligands. (2) Substoichiometric amounts (i.e., 33 mole %) of CuI relative to n-BuLi is sufficient to achieve good results. (3) Regioselectivity is governed by electronic effect rather steric effect, and perhaps by solvent polarity. (4) Me and Ph gave low chemical yields due to low reactivity and formation of biphenyl, respectively.
Table 3.1 Cuprate Conjugate Addition to 7

<table>
<thead>
<tr>
<th>entry</th>
<th>reagent (equiv)(^a)</th>
<th>solvent</th>
<th>temp (^\circ)C</th>
<th>% yield(^b)</th>
<th>1,4:1,6(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(n)-BuCuCN(\cdot)Li (1.0)(^{d,e})</td>
<td>THF</td>
<td>-40</td>
<td>(0^{f,g,h})</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>(n)-BuCu(\cdot)Li (1.0)(^d)</td>
<td>THF</td>
<td>-40</td>
<td>(13)(^{f,g,h})</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>(n)-BuCu(\cdot)Li (1.0)</td>
<td>THF</td>
<td>-40</td>
<td>(13)(^{f,i})</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>(n)-Bu(_2)Cu(\cdot)LiCN (2.0)(^j,e)</td>
<td>THF</td>
<td>-40</td>
<td>(42)(^{g,i,h})</td>
<td>90:10</td>
</tr>
<tr>
<td>5</td>
<td>(n)-Bu(_2)CuLi (2.0)(^j)</td>
<td>THF</td>
<td>-40</td>
<td>50(^i)</td>
<td>86:14</td>
</tr>
<tr>
<td>6</td>
<td>(n)-Bu(_2)CuLi (1.0)</td>
<td>THF</td>
<td>-40</td>
<td>74(^{f,i})</td>
<td>86:14</td>
</tr>
<tr>
<td>7</td>
<td>(n)-Bu(_2)CuLi (1.0)</td>
<td>THF</td>
<td>-40</td>
<td>68(^i)</td>
<td>86:14</td>
</tr>
<tr>
<td>8</td>
<td>(n)-BuLi (2.0)/CuI (0.66)</td>
<td>THF</td>
<td>-40</td>
<td>(69)(^{f,g})</td>
<td>92:8</td>
</tr>
<tr>
<td>9</td>
<td>(n)-BuLi (1.0)/CuBr(\cdot)Me(_2)S (0.5)(^k)</td>
<td>THF/Me(_2)S</td>
<td>-70</td>
<td>0(^f)</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>(n)-Bu(_2)CuLi (1.0)(^j)</td>
<td>Et(_2)O</td>
<td>-40</td>
<td>80(^m)</td>
<td>89:11</td>
</tr>
<tr>
<td>11</td>
<td>(s)-Bu(_2)CuLi (1.2)</td>
<td>THF</td>
<td>-40</td>
<td>68(^i)</td>
<td>95:5(^n)</td>
</tr>
<tr>
<td>12</td>
<td>(t)-Bu(_2)CuLi (1.0)</td>
<td>THF</td>
<td>-40</td>
<td>76</td>
<td>91:9</td>
</tr>
<tr>
<td>13</td>
<td>(t)-Bu(_2)CuLi (1.0)(^j)</td>
<td>Et(_2)O</td>
<td>-50</td>
<td>-</td>
<td>62:38</td>
</tr>
<tr>
<td>14</td>
<td>Me(_2)CuLi (1.0)</td>
<td>THF</td>
<td>-40</td>
<td>52</td>
<td>86:14</td>
</tr>
<tr>
<td>15</td>
<td>Ph(_2)CuLi (1.0)</td>
<td>THF</td>
<td>-40</td>
<td>33(^{f,o})</td>
<td>89:11</td>
</tr>
</tbody>
</table>
Conjugate Addition of Various Lithium Triorganozincates to \(N\)-Boc-2-Pyridone 7

Next we used different lithium zincates to react with 7 in the presence of TMSCl, and the results are summarized in Table 3.2. Lithium tri-\(n\)-butylzincate (\(n\)-Bu\(_3\)ZnLi) was added smoothly (71% yield) to the starting pyridone 7 at 0 °C with good regioselectivity (90:10, entry 1). Lithium tri-\(s\)-butylzincate (\(s\)-Bu\(_3\)ZnLi) provided excellent regioselectivity (95:5, entry 2) at 0 °C but in reduced chemical yield (43%, entry 2) due to the formation of competition cleavage product 18 (38%). Interestingly, carbonate 18 was obtained as a byproduct in this reaction. A triplet absorption at 4.00 ppm in the proton NMR corresponds to the ester methylene group (OCH\(_2\)), and a carbonyl absorption at 153.8 ppm in \(^1\)\(^3\)C NMR corresponds to a carbonate carbonyl group instead of an ester carbonyl (which generally is present at 175-165 ppm). This strikes a contrast to the previous observed \(t\)-butyl benzoate 20, suggesting a different carbamate cleavage pathway. One possible explanation is an old source of \(s\)-BuLi used might been oxidized over time to \(s\)-BuOLi which cleaves the Boc group.
The t-Bu ligand gave poor regioselectivity (62:38-65:35) both at 0 °C and -40 °C (entry 3-4). In conclusion, (1) The reaction temperature does not play a significant role in the regioselectivities in these lithium zincate conjugate addition reactions, (2) While good to excellent regioselectivities were achieved for n-Bu and s-Bu groups, poor to reversed 1,4/1,6- ratios were obtained for t-Bu, (3) Poor chemical yields were obtained for most transferrable ligands due to the cleavage of the carbamate group and formation of many unidentified byproducts as determined by TLC.

![Diagram of conjugate addition reaction]

**Table 3.2 Zincate Conjugate Additions to 7**

<table>
<thead>
<tr>
<th>entry</th>
<th>reagent (equiv)(^a)</th>
<th>temp °C</th>
<th>% yield(^b)</th>
<th>1,4 :1,6(^c) (16:17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-Bu(_3)ZnLi (1.1)</td>
<td>0</td>
<td>71</td>
<td>90:10</td>
</tr>
<tr>
<td>2</td>
<td>s-Bu(_3)ZnLi (1.1)</td>
<td>0</td>
<td>43(^d)</td>
<td>95:5(^e)</td>
</tr>
<tr>
<td>3</td>
<td>t-Bu(_3)ZnLi (1.0)</td>
<td>0</td>
<td>-</td>
<td>65:35</td>
</tr>
<tr>
<td>4</td>
<td>t-Bu(_3)ZnLi (1.0)</td>
<td>-40</td>
<td>-</td>
<td>62:38</td>
</tr>
</tbody>
</table>

\(^a\) All reactions were performed in THF and TMSCl (5.0 equiv) was used unless otherwise noted.\(^b\) Isolated yields. \(^c\) Regioselectivity was determined by the integration of the olefinic protons from \(^1\)H NMR. \(^d\) Carbonate 18 was obtained: entry 2 (38%), \(^e\) Diastereomeric ratio 67:33.
Conjugate Addition to N-Benzyl-2-Pyridone

Direct Conjugated Additions to N-Benzyl-2-Pyridone

N-Benzyl-2-pyridone $6$ is more inert towards conjugate addition of organometallic reagents (Table 3.3) than the N-Boc analogue $7$, due to the electron donating effect of the benzyl group reducing the electrophilicity of the pyridone ring. Thus, it requires the presence of a Lewis acid in order to proceed and complete conversion of the starting material $6$ was never achieved even with large excess of nucleophiles (i.e., 5 equivalents of $n$-Bu$_2$CuLi). Other literature reports also mentioned the requirement of a large excess of organometallic reagents for the conjugate addition to $\alpha,\beta$-unsaturated lactams.$^{37}$ While lithium di-$n$-butylcuprate (5.0 equiv) prepared from CuCN along with TMSCl (15.0 equiv) did not cause any reaction at -78 °C in THF (entry 1, Table 3.3), the same cuprate prepared from CuI gave 25% conversion of starting material $6$ and provided conjugate addition product $19\text{a}$ with good 1,4/1,6-regioselectivity (90:10, entry 2). Reactions performed at higher temperatures resulted in higher yields of the conjugate addition product (43% at -30 °C and 54% at 0 °C, entry 3 and 4), along with improved regioselectivities (93:7-96:4). The 1,4/1,6-regioselectivity was determined by the integration of the olefinic protons ($\delta$ 5.90 and 5.00 for 1,4-adduct and $\delta$ 5.73 and 5.41 for 1,6-adduct) from $^1$H NMR.

Attempts to add $n$-BuLi in different solvents (THF and toluene) with additives (TMSCl or HMPA) were unsuccessful, giving complete starting material recovery (entry 5-7). $n$-BuMgCl in the presence of TMSCl (1.0equiv) in dichloromethane added to substrate $6$ in modest yield (45%) with poor regioselectivity (54:46, entry 9), while
starting material 6 (37%) was recovered even with 4.0 equivalents of Grignard reagent.

Lithium tri-\textit{n}-butylzincate did not cause any reaction with or without TMSCl in dichloromethane (entry 10 and 11), although using BF$_3$•Et$_2$O gave conjugate addition product (28%) with poor regioselectivity (41:59, entry 12). A similar result was achieved by adding TMSCl to Bu$_3$ZnLi in THF (26%, 1,4:1,6 = 45:55, entry 13). The following conclusions were reached: (1) \textit{N}-benzyl-2-pyridone is very inert toward conjugate addition of organometallic reagents and it requires large excess of nucleophile (4-5 equivalents) and high temperature (0 °C) to proceed, although complete conversion of starting material was never achieved. (2) Cuprate reagents seem to give higher regioselectivities than Grignard reagents or zincates. (3) Addition of Lewis acids (e.g. TMSCl, BF$_3$•Et$_2$O) can promote the conjugate addition reactions of organometallic reagents (i.e., Grignard reagent and Zincates) although BF$_3$•Et$_2$O is more effective than TMSCl.
Table 3.3 Organolithium and Organozincate Conjugate Additions to 6

![Diagram of molecules 6, 19, and 20]

<table>
<thead>
<tr>
<th>entry</th>
<th>reagent (equiv)a</th>
<th>additive</th>
<th>solvent</th>
<th>temp °C</th>
<th>% conversionb</th>
<th>1,4:1,6 c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-Bu₂CuLi (5.0)d</td>
<td>TMSCl (15.0)</td>
<td>THF</td>
<td>-78</td>
<td>0e</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>n-Bu₂CuLi (5.0)f</td>
<td>TMSCl (15.0)</td>
<td>THF</td>
<td>-78</td>
<td>25g</td>
<td>90:10</td>
</tr>
<tr>
<td>3</td>
<td>n-Bu₂CuLi (5.0)f</td>
<td>TMSCl (15.0)</td>
<td>THF</td>
<td>-30</td>
<td>43g</td>
<td>96:4</td>
</tr>
<tr>
<td>4</td>
<td>n-Bu₂CuLi (5.0)f</td>
<td>TMSCl (15.0)</td>
<td>THF</td>
<td>0</td>
<td>54g,h</td>
<td>93:7</td>
</tr>
<tr>
<td>5</td>
<td>n-BuLi (1.0)</td>
<td>-</td>
<td>THF</td>
<td>-78i</td>
<td>0e</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>n-BuLi (1.0)</td>
<td>HMPA (1.5)</td>
<td>THF</td>
<td>-78i</td>
<td>0e</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>n-BuLi (3.0)</td>
<td>Sparteine (0.3)</td>
<td>Toluene</td>
<td>-78i</td>
<td>0e</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>n-BuMgCl (1.2)</td>
<td>ZnBr₂ (0.1)</td>
<td>CH₂Cl₂</td>
<td>0</td>
<td>0e</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>n-BuMgCl (4.0)</td>
<td>TMSCl (1.0)</td>
<td>CH₂Cl₂</td>
<td>0</td>
<td>45g,h</td>
<td>54:46</td>
</tr>
<tr>
<td>10</td>
<td>n-Bu₂ZnLi (1.0)</td>
<td>-</td>
<td>CH₂Cl₂</td>
<td>0</td>
<td>0e</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>n-Bu₂ZnLi (1.0)</td>
<td>TMSCl (5.0)</td>
<td>CH₂Cl₂</td>
<td>0</td>
<td>0e</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>n-Bu₂ZnLi (1.0)</td>
<td>BF₃·Et₂O (1.0)</td>
<td>CH₂Cl₂</td>
<td>0</td>
<td>28g</td>
<td>41:59</td>
</tr>
<tr>
<td>13</td>
<td>n-Bu₂ZnLi (1.0)</td>
<td>TMSCl (5.0)</td>
<td>THF</td>
<td>0</td>
<td>26g</td>
<td>45:55</td>
</tr>
</tbody>
</table>

a All reactions were performed at the specified temperature and were gradually warmed to room temperature over 12 hours unless otherwise noted. b % conversions were measured by molar ratio of the desired product against starting material calculated from the crude ³¹H NMR spectra. c Regioselectivity was determined by the integration of the olefinic protons from ¹H NMR. d Cuprate prepared from CuCN. e Only starting material 6 was recovered. f Cuprate prepared from CuI. g Starting material 6 was recovered (molar ratio against 6): entry 2 (75%), entry 3 (57%), entry 4 (33%), entry 9 (37%), entry 12 (72%), entry 13 (74%). h Oxidation product 22 was obtained (molar ratio against 6): entry 4 (3%), entry 9 (15%). i Reactions were performed at –78 °C for 2 hours and at r.t. for 12 hours. j Reactions were performed at –78 °C for 5 hours and r.t. for 12 hours.
Preparation of Pyridinium Salt 21

Next we decided to activate substrate 6 with trimethylsilyl trifluoromethanesulfonate (TMSOTf) to form a pyridinium salt 21. Many literature reports mentioned conversion of pyridine rings into pyridinium salts using ethyl chloroformate (CICOOEt) or TMSOTf significantly increased their electrophilicity toward organometallic reagents.\textsuperscript{34,35,38} When N-benzyl-2-pyridone was treated with TMSOTf in CDCl\textsubscript{3} in an NMR tube at room temperature, the reaction monitored by NMR indicated the disappearance of the starting material (a doublet at 6.69 ppm, $J = 8.3$ Hz and dd at 6.19 ppm, $J = 6.9$, 6.9 Hz) and complete formation of the pyridinium salt (a doublet at 8.61 ppm, $J = 6.0$ Hz and dd at 8.31 ppm, $J = 7.8$ Hz) in less than one minute (Scheme 3.10). The NMR spectrum of this salt stayed the same over one hour at room temperature indicating the good stability of this pyridinium salt 21 in CDCl\textsubscript{3}.

**Scheme 3.10** Preparation of Pyridinium Salt 21

Conjugate Addition to Pyridinium Salt 21

The results for conjugate addition of various organometallic reagents to 21 are summarized in Table 3.4. The Grignard reagent, $n$-BuMgCl (2.0 equiv), reacted with pyridinium salt 21 at -78 °C to afford 1,4- conjugate addition product 19 in poor yield (38%) and modest regioselectivity (62:38) with unreacted starting material (58%, entry 1)
recovered. When the reaction was performed at 0 °C an increased yield (60%) was obtained, although with reduced regioselectivity (58:42, entry 2). A small amount of oxidation product 22a was detected in these reactions, and one possible mechanism for the formation of this compound involves the initial 1,4-addition of the carbanion to the pyridinium salt 21 followed by the deprotonation of a tertiary hydrogen and a sequential cleavage of the silyl ether to form the aromatized product (Scheme 3.11).

**Scheme 3.11 Possible Mechanism for the Formation of 22a**

![Possible Mechanism for the Formation of 22a](image)

The Grignard reagent, n-BuMgCl (1.2 equiv), added to 21 in the presence of catalytic amounts of ZnBr₂, giving improved regioselectivity (71:29, entry 3). Kunz reported the conjugate addition of various Grignard reagents to TMSOTf activated 2-pyridinium salt in the presence of 2,6-lutidine with good regio- and stereocontrol.³⁹ When we employed the same condition, the reaction proceeded smoothly (71% yield), although with similarly poor regioselectivity (59:41, entry 4) along with unreacted starting material (11%), suggesting that more than two equivalents of Grignard reagent will be needed to achieve complete conversion of the starting material. The addition of CuI, however, gave only starting material recovery (entry 5) suggesting cuprate reagents (e.g., n-Bu₂CuMgCl) are less reactive than Grignard reagents towards pyridinium salt 21.
Addition of \(n\)-BuLi (2.0 equiv) to \(\text{21}\) in dichloromethane at 0 °C gave modest yield (62%) and regioselectivity (78:22, entry 6), while slightly increased regioselectivity (80:20, entry 7) was achieved when the same reaction was conducted at -78 °C. Attempts to achieve complete conversion using one equivalent of \(n\)-BuLi were unsuccessful, leading to unreacted \(\text{6}\) (22%, entry 8) and this suggested that a minimum of two equivalents alkyllithium reagent is required for complete reaction. Ethereal solvents (Et\(_2\)O or THF) significantly diminished the yields of conjugate addition reactions (0-13%, entry 9 and 10). Toluene furnishes the reaction product with similar results to that obtained in dichloromethane (61-67%, entry 11 and 12) with modest regioselectivity (75:25), suggesting that regioselectivity is not greatly influenced by solvent polarity. \(s\)-BuLi demonstrated lower yield (35%) than \(n\)-BuLi in dichloromethane, with similar 1,4/1,6- regioselectivity (80:20, entry 13). \(t\)-BuLi gave modest yield (60%) with poor regioselectivity (64:36, entry 14). The abnormally low 1,4/1,6- regioselectivity of \(t\)-Bu ligand was also seen in the \(N\)-Boc substrate \(\text{7}\) when \(t\)-Bu\(_2\)CuLi was used. No reaction product was detected for MeLi, probably due to its low reactivity (entry 15).

Interestingly, PhLi provided almost exclusively 1,6 – adduct \(\text{20e}\) in modest yields (entry 16 and 17) in spite of its large size. Increasing from one to two equivalents of PhLi gave increased chemical yield (50% vs 40%), although unreacted starting material was
recovered (20-29%) in both reactions. Lithium tri-n-butyl zincate was unreactive towards 21 at 0 °C, giving only starting material recovery (entry 18).

The regiochemistry for these organolithium conjugate addition reactions seem to be significantly influenced by the transferable ligands. While n-BuLi and s-BuLi give similarly good 1,4/1,6-ratios (80:20), t-BuLi gave reduced regioselectivity (64:26) and interestingly PhLi gave mostly 1,6-adduct. This may suggest that the outcome of regiochemistry is an combination of steric effects and electronic effects, although the detailed mechanism however is yet to be probed.

**Table 3.4 Conjugate Additions to 21**

<table>
<thead>
<tr>
<th>entry</th>
<th>RM (equiv)</th>
<th>temp °C</th>
<th>solvent</th>
<th>molar ratio 19</th>
<th>1,4:1, 6</th>
<th>Molar ratio 22</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-BuMgCl (2.0)</td>
<td>-78</td>
<td>CH₂Cl₂</td>
<td>38e</td>
<td>62:38</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>n-BuMgCl (2.0)</td>
<td>0</td>
<td>CH₂Cl₂</td>
<td>63e</td>
<td>58:42</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>n-BuMgCl (1.2) /ZnBr₂ (0.1)</td>
<td>0</td>
<td>CH₂Cl₂</td>
<td>30e</td>
<td>71:29</td>
<td>-</td>
</tr>
<tr>
<td>Entry</td>
<td>Reagent</td>
<td>Temperature</td>
<td>Solvent</td>
<td>Yield</td>
<td>Regioselectivity</td>
<td>Other Notes</td>
</tr>
<tr>
<td>-------</td>
<td>--------------------------</td>
<td>-------------</td>
<td>-----------</td>
<td>-------</td>
<td>-----------------</td>
<td>-------------</td>
</tr>
<tr>
<td>4</td>
<td>n-BuMgCl (2.0)</td>
<td></td>
<td>CH₂Cl₂</td>
<td>87°</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2,6-lutidine (2.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n-BuMgCl (2.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2,6-lutidine (2.0)</td>
<td></td>
<td>CH₂Cl₂</td>
<td>0°</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CuI (0.05)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>6</td>
<td>n-BuLi (2.0)</td>
<td>-78°F</td>
<td>CH₂Cl₂</td>
<td>86(62)</td>
<td>78:22</td>
<td>14</td>
</tr>
<tr>
<td>7</td>
<td>n-BuLi (2.0)</td>
<td>-78gı</td>
<td>CH₂Cl₂</td>
<td>72</td>
<td>80:20</td>
<td>28</td>
</tr>
<tr>
<td>8</td>
<td>n-BuLi (1.0)</td>
<td>-78°</td>
<td>CH₂Cl₂</td>
<td>61(56)</td>
<td>75:25</td>
<td>14</td>
</tr>
<tr>
<td>9</td>
<td>n-BuLi (2.0)</td>
<td>-78°</td>
<td>THF</td>
<td>0°</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>n-BuLi (2.0)</td>
<td>-78°</td>
<td>Et₂O</td>
<td>15°</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>n-BuLi (2.0)</td>
<td>-78°</td>
<td>Toluene</td>
<td>79(61)</td>
<td>75:25</td>
<td>21</td>
</tr>
<tr>
<td>12</td>
<td>n-BuLi (2.0)</td>
<td>-78gı</td>
<td>Toluene</td>
<td>67°</td>
<td>75:25</td>
<td>14</td>
</tr>
<tr>
<td>13</td>
<td>s-BuLi (2.0)</td>
<td>-78gı</td>
<td>CH₂Cl₂</td>
<td>35°</td>
<td>80:20</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>t-BuLi (2.0)</td>
<td>-78gı</td>
<td>CH₂Cl₂</td>
<td>80°</td>
<td>64:36</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>MeLi (2.0)</td>
<td>-78gı</td>
<td>CH₂Cl₂</td>
<td>0°</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>PhLi (1.0)</td>
<td>-78°</td>
<td>CH₂Cl₂</td>
<td>58(40)</td>
<td>5:95</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>PhLi (2.0)</td>
<td>-78°</td>
<td>CH₂Cl₂</td>
<td>60°</td>
<td>5:95</td>
<td>(16)</td>
</tr>
<tr>
<td>18</td>
<td>n-Bu₂ZnLi (1.1)</td>
<td>23</td>
<td>CH₂Cl₂</td>
<td>0°</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*All reactions were performed at the specified temperature and were allowed to warm up to r.t. over 12 hours unless otherwise noted. Molar ratios of the desired product against 6 were calculated from the crude 1H NMR spectra, numbers in parenthesis are isolated yields. Regioselectivity was determined by the integration of the olefinic protons from 1H NMR. Percentage of 22 (23) was determined by the molar ratio against 19 (20) calculated from the crude 1H NMR spectra. Starting material 6 was recovered (molar ratio against 19 or 20): entry 1 (58%), entry 2 (35%), entry 3 (70%), entry 4 (13%), entry 5 (100%), entry 8 (24%), entry 9 (100%), entry 10 (85%), entry 12 (19%), entry 13 (65%), entry 14 (20%), entry 15 (100%), entry 16 (42%), entry 17 (24%), entry 18 (100%). Reactions were performed at -78 °C for 5 minutes and were warmed to r.t. Reactions were kept at -78 °C for 6 hours before quenched at -78 °C. In conclusion, we herein report the regioselective conjugate additions of organometallic reagents to N-benzy-2-pyridone, and to the best of our knowledge these are the first examples to introduce alkyl (°Bu, sBu, tBu) and aryl (Ph) groups to this substrate. The reactivity of different organometallic reagents in these conjugate addition
reactions follows the order of: alkyl lithium reagents > Grignard reagents > cuprates and zincates. While cuprates (i.e., \( n\)-Bu\(_2\)CuMgCl) and zincates are completely inert towards conjugate addition to 21, two equivalents of alkyllithium is required to effect complete conversion. Reactions performed in Et\(_2\)O or THF as solvent were shown to be very inert towards these conjugate additions while dichloromethane seems to be the choice of solvent, which is consistent with Kunz’s discovery. The regioselectivity is not influenced by polarity of the solvents (dichloromethane vs toluene), but rather by the nature of organometallic reagents (alkyl lithium reagents give better regioselectivity than Grignard reagents), reaction temperature, and, to a higher degree, by the transferable ligands (e.g., PhLi gives only 1,6- adduct while \( t\)-Bu gives poorer regioselectivity than \( n\)-BuLi or \( s\)-BuLi).

**Tandem Reactions of 21**

We next added \( n\)-BuLi to pyridinium salt 21 and trapped the intermediate enolate with an electrophile (MeI) in attempts to achieve a tandem reaction which would furnish a two stereogenic centered product 24 (Table 3.5). The reaction gave tandem reaction product 24 (39%) along with monosubstituted product 19 and 20 (34% combined). It has been reported that trapping these enolates with an electrophile are generally met with low chemical yields because of the low reactivity of the enolate intermediates.\(^{40,41}\) However, it’s noteworthy that excellent diastereoselectivity (95:5) was achieved for this tandem reaction.
Table 3.5 Tandem Reactions of 6

1. TMS-OTf (1.0 equiv, DCM, rt, 15min)
2. n-BuLi (2.0 equiv), -78 °C, time
3. MeI, 0 °C

<table>
<thead>
<tr>
<th>entry</th>
<th>time</th>
<th>R’X (equiv)</th>
<th>24: 19 : 20</th>
<th>% yield (24)</th>
<th>dr (24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 h</td>
<td>MeI (4.0)</td>
<td>44:29:27</td>
<td>39%</td>
<td>95:5</td>
</tr>
<tr>
<td>2</td>
<td>2 h</td>
<td>MeI (6.0)</td>
<td>55:40:5</td>
<td>-</td>
<td>95:5</td>
</tr>
</tbody>
</table>

a All reaction were performed in dichloromethane, n-BuLi was added at -78 °C and the reaction was kept at -78 °C for 1 h (entry 1) or 2 h (entry 2). b Determined by the integration of 1H NMR of the crude product. c MeI was added at -78 °C for 1 minute and the reaction was warmed to 0 °C and gradually warm to r.t. over 12 hours. d Isolated yield, a mixture of 19 and 20 (34% combined) was also obtained. e MeI was added at 0 °C and reaction was allowed to warm to r.t. over 12 hours.

Attempts of Conjugate Addition to N-Tosyl-2-Pyridone 8

Itoh and coworkers describe an electron withdrawing tosyl group on the N-atom of an α,β-unsaturated-δ-lactam that would facilitate the conjugate addition reactions with cuprate reagents whereas N-alkyl analogues were totally inert.36 However, our attempts for conjugate addition of organocuprates failed with only recovery of starting material (entry 1 and 2, Table 3.6). Compared to an α,β-unsaturated-δ-lactam, the extra double bond in N-tosyl -2-pyridone 8 decreased its electrophilicity as a Michael acceptor. Grignard reagents without any copper salt were unsuccessful, giving recovered starting material (entry 3) while cleavage of the tosyl group occurred when more than one
equivalent of Grignard reagent was used at elevated temperature (entry 4). Unfortunately, attempts to add PhLi or PhMgCl to the activated pyridinium salt (prepared from 8 and TMSOTf in dichloromethane) were also unsuccessful, giving only the migration of the tosyl group product 25 (entry 5 and 6).

Table 3.6 Attempted Conjugate Additions to 8

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent (equiv)</th>
<th>TMSCl</th>
<th>Solvent</th>
<th>Temp °C</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-Bu₂CuLi (1.0)</td>
<td>3.0</td>
<td>THF</td>
<td>-78</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>n-Bu₂CuLi (1.1)</td>
<td>5.0</td>
<td>THF</td>
<td>-40</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>n-BuMgCl (1.1)</td>
<td>3.0</td>
<td>THF</td>
<td>-78</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>n-BuMgCl (5.0)</td>
<td>3.0</td>
<td>THF</td>
<td>23</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>PhLi (1.0)^c</td>
<td>-</td>
<td>DCM</td>
<td>-78</td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>PhMgCl (1.0)^c</td>
<td>-</td>
<td>DCM</td>
<td>-78</td>
<td>25</td>
</tr>
</tbody>
</table>

^a Cuprate prepared from CuCN•2LiCl. ^b Cuprate prepared from CuI. ^c Starting material 8 was treated with TMSOTf (1.0 equiv) at r.t. for 15 minutes in dichloromethane before RM was added.
Discussion

Regioselectivities in Cuprate conjugate additions to 6 and 7

Contrary to the often observed 1,6- regioselectivity in conjugate additions of Gilman reagents to an activated diene, the reaction on N-Boc-2-pyridone with Gilman reagent gave mostly the 1,4- conjugate addition product. This result suggest the initially formed β-Cu(III) σ-complex undergo a fast reductive elimination, likely caused by the coordination of the Cl atom on TMSCl to the copper atom forming a tetracoordinated Cu(III) species (Scheme 3.12) and thus lowers the energy barrier for reductive elimination. Similar effect of TMSCl’s role in accelerating Cu(III) reductive elimination was also reported by Snyder. Chelation of the lithium atom to enolate oxygen and R group on copper may also contribute to stabilize this Cu(III) complex. The size of the transferable ligands seems to have little effect on regioselectivity. n-Bu, s-Bu, t-Bu, Me and Ph all gave similarly good 1,4- regioselectivity (86:14-95:5) suggesting that regioselectivity is governed by electronic effects (i.e., TMSCl stabilization, chelation effects) rather than steric effects, which agrees with earlier findings by Krause. Polarity of the solvent (i.e., THF vs Et₂O) seems to have little impact on the outcome of regioselectivities (with the exception for t-Bu group).
Scheme 3.12 Proposed Reaction Pathway for Cuprate Addition to 7

Higher 1,4/1,6-regioselectivities observed for the Gilman cuprate (R$_2$CuLi) reaction with N-benzyl-2-pyridone than N-Boc-pyridone may provide evidence for the influence of O-Li coordination on regiochemistry. The coordination of lithium to the oxygen on the Boc group may stabilize δ-Cu(III) complex and therefore give rise to 1,6-adduct, whereas such stabilization is absent in the Cu(III) intermediate for N-benzyl-2-pyridone (Figure 3.4).

Figure 3.4 Stabilization of Cu(III) Complex by the Chelation of Lithium to the Boc Group
Possible Mechanism for Boc Migration Product 10

Lithium halide (e.g., LiI, LiCl) in the reaction medium can serve as a Lewis acid coordinating to the Boc carbonyl group, which in return enhances the nucleophilic attack of the lactam oxygen (Scheme 3.13). This intramolecular nucleophilic acyl substitution thus gives the Boc migration product 10.

Scheme 3.13 Proposed Mechanism for Boc Migration

Unlike its analogue, N-Boc-4-pyridone, the N-Boc-2-pyridone 7 has a carbonyl adjacent to the N- atom, and the electron withdrawing effect of this carbonyl makes the pyridone ring a better leaving group and thus more susceptible to nucleophilic attack. This N-Boc-2-pyridone 7 decomposes completely to 2-hydroxypyridine at room temperature after 30 days further showing the low stability of this compound.

Low Reactivity of N-Substituted-2-Pyridones

N-Benzyl-2-pyridone has lower reactivity towards cuprate conjugate additions than N-Boc-2-pyridone, although it demonstrates higher stability in the reaction medium. Several literature reports note the low reactivity of α, β unsaturated lactams towards conjugate additions,12-14 and introduction of an electron withdrawing group on the α position was found to increase the electrophilicity of the conjugate double bond and thus successfully facilitate conjugate addition reactions.44 Compared to N-Boc-2-pyridone, N-
benzyl pyridone is less reactive because of the electron donating effect of the benzyl group, and therefore is inert towards alkyl lithium or Grignard reagent even in large excess at room temperature.
Summary

We herein report the first examples of regioselective conjugate additions of organometallic reagents to \( N\)-Boc-2-pyridone (7) and \( N\)-Benzyl-2-pyridone (6). \( N\)-Boc-2-pyridone (7) demonstrated low reactivity towards conjugate addition of lithium cuprates and zincates and high susceptibility to Boc cleavage reactions. Lithium dialkycuprates (\( R_2 \)CuLi, one equivalent) prepared from CuI in THF or Et\(_2\)O provided the best overall results in the conjugate additions to 7 in the presence of a Lewis acid (TMSCl). \( n\)-Bu, \( s\)-Bu and \( t\)-Bu give good yields (68-80%) with good 1,4/1,6-regioselectivities (92:8-95:5) while Me and Ph gave reduced yields (44-52%), although various amounts of Boc migration product 10 were commonly observed in these cuprate conjugate additions. Lithium organozincates (\( R_3 \)ZnLi) generally demonstrate poor to modest 1,4/1,6-regioselectivities, while Grignard regents and magnesium cuprates are typically inert toward conjugate additions to 7. \( N\)-Benzyl-2-pyridone (6) demonstrated significantly lower reactivity towards various cuprate reagents (\( R_2 \)CuM or RCuCNM, \( M = Li, Mg \)), although modest chemical yields and regioselectivity were achieved by activation of 6 with TMSOTf. One pot synthesis of 3,4-disubstituted-2-pyridones was successful and gave excellent \textit{anti}-diastereoselectivity (95:5).
Experimental

**General:** $^1$H NMR and $^{13}$C NMR spectra were recorded using JOEL (500 MHz) or Bruker (500 MHz) NMR spectrometers in CDCl$_3$. The $^1$H NMR chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (TMS) or CHCl$_3$ ($\delta = 7.26$) as internal standard. The $^{13}$C NMR chemical shifts are reported as δ values in parts per million (ppm) downfield from TMS and referenced with respect to CDCl$_3$ signal (triplet, centerline $\delta = 77.00$ ppm). Analytical thin layer chromatography (TLC) was performed on Scientific Adsorbents Inc. silica gel plates, 200 μ mesh with F$_{254}$ indicator. Visualization was accomplished by UV light (254 nm), and/or a 10% ethanol solution of phosphomolybdic acid or 5% aqueous potassium permanganate solution. Flash column chromatography was performed with 200-400 μ mesh silica gel. Activated silica gel was prepared from 200-400 mesh silica gel washed with 5% Et$_3$N in petroleum ether. The isolated chemical yields are of materials isolated by flash column chromatography.

**Materials:** All reaction flasks were oven-heated over 12 hours prior to use. All reactions were conducted under positive argon atmosphere using flasks fitted with rubber septa and sealed with Parafilm™. A -40 °C or lower reaction temperature was achieved by using a cold bath prepared from dry-ice/ isopropanol mixture. THF and diethyl ether were distilled from sodium benzophenone ketyl. Methanol was distilled from CaH$_2$. Other solvents including dichloromethane, toluene, etc were used as received. Copper salts
including CuCN, Cu(I) thiophene-2-carboxylate (CuTC), Cu(OTf)₂ and CuI were used from commercial bottles without any further purification. LiCl and ZnBr₂ were flame dried over a propane torch over 10 minutes under argon prior to use. n-BuLi (2.5 M in hexanes), s-BuLi (0.66 in cyclohexane), t-BuLi (1.6 M in pentane), MeLi (1.6 M in diethyl ether) and PhLi (1.8 M in hexanes) were commercially available and were titrated using s-BuOH and 1,10-phenanthroline monohydrate in THF prior to use. Et₂Zn (1.0 M in hexanes), n-BuMgCl (2.0 M in diethyl ether) and EtMgCl (2.0 M in THF) were used directly from commercial sources. Aqueous pH = 7 buffer solution (K₂HPO₄/NaOH) was used from commercial bottles.

**General Procedure A: Conjugate Addition Reactions of Lithium**

**Alkyl(cyano)cuprates [Alkyl(iodo)cuprate] to N-Boc-2-pyridone.** CuI or CuCN•LiCl were dispersed/dissolved in freshly distilled THF (4 mL) at room temperature and the mixture was cooled to -78°C whereupon alkyl lithium (0.5 mmol, 1.0 equiv) was added dropwise through a syringe. The reaction mixture was stirred at -78 °C for one hour and was warmed to -40 °C and stirred for 5 minutes before a solution of N-Boc-2-pyridone (98 mg, 0.5 mmol, 1.0 equiv) and TMSCl (275 mg, 5.0 equiv) in THF (2 mL) was added dropwise at the same temperature. The reaction mixture was allowed to warm up to room temperature over 12 hours and was quenched with aqueous buffer solutions (pH = 7), extracted with EtOAc (3 x 30 mL). The combined organic phase was dried over MgSO₄ and concentrated in *vacuo* to afford crude **16** as a yellow oil.
General Procedure B: Conjugate Addition Reactions of Lithium Dialkylcuprates to N-Boc-2-pyridone. To a suspension/solution of CuI or CuCN•2LiCl in dry THF under argon at -40 °C, was added dropwise alkyllithium (2.4 equiv) and the mixture was stirred for 1 hour at -40 °C before a solution of N-Boc-2-pyridone (98 mg, 0.5 mmol, 1.0 equiv) and TMSCl (275 mg, 5.0 equiv) in THF (2 mL) was added dropwise at the same temperature. The reaction mixture was allowed to warm up to room temperature over 12 hours and was quenched with saturated aqueous NH₄Cl solutions, extracted with EtOAc (3 x 30 mL). The combined organic phase was dried over MgSO₄ and concentrated in vacuo to afford crude 16 as a yellow oil.

General Procedure C: Conjugate Addition Reactions of Lithium Trialkylzincates to N-Boc-2-pyridone. To a solution of ZnBr₂ (1.1 equiv., flame dried) in THF (3 mL) was added alkyllithium (3.0 or 3.3 equiv) dropwise at 0 °C. The reaction mixture was stirred at the same temperature for 30 minutes and was cooled to -78 °C (or specified reaction temperature in Table 3.2) whereupon a solution of N-Boc-2-pyridone (98 mg, 0.5 mmol, 1.0 equiv) and TMSCl (275 mg, 5.0 equiv) in THF (2 mL) was added dropwise at the specified reaction temperature in Table 3.2. The reaction mixture was allowed to warm up to room temperature over 12 hours and was quenched with NH₄Cl solutions, extracted with EtOAc (3 x 30 mL). The combined organic phase was dried over MgSO₄ and concentrated in vacuo to afford crude 16 as a yellow oil.
General Procedure D: Activation of N-Benzyl-2-pyridone with TMSOTf Followed by Conjugate Addition with Various Organometallic Reagents. Starting N-benzyl-2-pyridone (185 mg, 1.0 equiv) dissolved in dry dichloromethane (2 mL) was treated dropwise with TMSOTf (222 mg, 1.0 equiv) at room temperature while stirring. The resulting solution was stirred for 15 minutes at room temperature and was cooled to the indicated reaction temperature in Table 3.4 whereupon the organometallic reagent was added dropwise. After stirring for 12 hours at room temperature, saturated aqueous NH$_4$Cl solution was added to quench and the aqueous phase was extracted with dichloromethane (3 x 30 mL), dried over MgSO$_4$ and concentrated in vacuo to afford crude 19 as a yellow oil.

General Procedure E: Activation of N-Benzyl-2-pyridone with TMSOTf Followed by Conjugate Addition with Grignard Reagent in the Presence of 2,6-Lutidine. Starting N-benzyl-2-pyridone (185 mg, 1.0 equiv) dissolved in dry dichloromethane (2 mL) was treated dropwise with TMSOTf (222 mg, 1.0 equiv) at room temperature while stirring. The resulting solution was stirred for 30 minutes at room temperature and 2,6-lutidine (214 mg, 2.0 equiv) was added. The resulting solution was cooled to 0 °C whereupon the Grignard reagent (2.0 equiv) was added dropwise. After stirring for 12 hours at room temperature, saturated aqueous NH$_4$Cl solution was added to quench the reaction mixture and the aqueous phase was extracted with dichloromethane (3 x 30 mL), dried over MgSO$_4$ and concentrated in vacuo to afford crude 19 as a yellow oil.
**General Procedure F: Conjugate Addition Reactions of Cuprate Reagents to N-Benzyl-2-pyridone.** CuI (950 mg, 5.0 equiv) dispersed in freshly distilled THF was cooled to -35 °C whereupon nBuLi (4.1 mL, 10.0 equiv) was added dropwise. The reaction mixture was stirred for 1.5 hours at -35 °C where it became a clear yellow – green solution and was then cooled to -78 °C whereupon a solution of starting N-benzyl-2-pyridone (185 mg, 1.0 equiv) and TMSCl (1640 mg, 15.0 equiv) in 8 ml of THF (previously stirred for 30 minutes) was added slowly through a cannula. The reaction mixture was allowed to warm to room temperature over 12 hours and aqueous buffer (pH = 7) solution was added to quench. The aqueous phase was extracted with Et₂O (3 x 30 mL), dried over MgSO₄ and concentrated in vacuo to afford crude 19 as a oil.

**General Procedure G: Conjugate Addition Reactions of Organolithium Reagents to N-Benzyl-2-pyridone.** To a solution of (-)-sparteine (35 mg, 0.3 equiv) in toluene (10 mL) at -78 °C was added dropwise alkylithium reagent (3.0 equiv), and the mixture was stirred for 15 minutes at -78 °C whereupon a solution of starting N-benzyl-2-pyridone (98 mg, 1.0 equiv) and TMSCl (167 mg, 3.0 equiv) in toluene (5 mL) was added over 10 minutes. The reaction mixture was kept at -78 °C for 5 hours and was then allowed to warm to room temperature over 12 hours and was quenched with saturated aqueous NH₄Cl. The aqueous phase was extracted with dichloromethane (3 x 30 mL), and the combine organic phase was dried over MgSO₄, concentrated in vacuo to afford crude 19 as a oil.
General Procedure H: Conjugate Addition of Lithium Trialkylzincates to N-Benzyl-2-pyridone in the Presence of a Lewis Acid. ZnBr$_2$ (225 mg, 1.0 equiv, flamed dried) was dissolved in freshly distilled THF and n$^6$BuLi (3.0 mmol, 3.0 equiv) was added slowly at 0 °C. The reaction mixture was then warm to room temperature and was stirred for 30 minutes before cooled back to 0 °C whereupon a solution of starting N-benzyl-2-pyridone (98 mg, 1.0 equiv) and BF$_3$•Et$_2$O (142 mg, 1.0 equiv) (alternatively TMSCl 545 mg, 5.0 equiv was used) in THF (3 mL) was added slowly. The reaction mixture was allowed to warm to room temperature over 12 hours and saturated aqueous NH$_4$Cl solution was added to quench the reaction mixture. The aqueous phase was extracted with Et$_2$O (3 x 30 mL), dried over MgSO$_4$ and concentrated in vacuo to afford crude 19 as a oil.

$N$-Boc-2-pyridone (7): Modified from an established procedure$^7$: 2-hydroxy pyridine (1940 mg, 1.0 equiv) was dissolved in $^4$BuOH (18 mL) and was treated at room temperature with NaH (656 mg, 1.3 equiv) very slowly and with caution. The resulting white slurry was heated in a 60 °C oil bath and stirred for 15 minutes until it became homogeneous, whereupon a solution of (Boc)$_2$O (5232 mg, 1.2 equiv) in $^4$BuOH (8 mL) was added through a syringe dropwise over 12 minutes at 60 °C. The resulting mixture was then cooled to room temperature and stirred for 12 hours before water (10 mL) was cautiously added and the mixture was diluted with Et$_2$O (30 mL) and neutralized to pH = 7 with 5% HCl aqueous solution. The aqueous phase was extracted with Et$_2$O (3 x 30 mL) and the combined organic phase was dried over MgSO$_4$, concentrated in vacuo to afford crude 7 as white solid. Flash column
chromatography on silica gel (silica gel was activated with 10:90 Et$_3$N/petroleum ether prior to use, ether:petroleum ether, 20:80-45:55, v/v as eluent) afforded pure 7 (2060 mg, 53%) as white crystal: mp 76.2-77 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.55 (dd, $J$ = 7.4, 1.9 Hz, 1H), 7.22 (dd, $J$ = 7.4, 2.8 Hz, 1H), 6.49 (d, $J$ = 9.2 Hz, 1H), 6.08 (t, $J$ = 7.1 Hz, 1H), 1.60 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 161.1, 150.8, 139.9, 133.4, 123.7, 105.7, 86.3, 27.8.

t-Butyl 2-pyridyl carbonate (10): Compound 10 was isolated in the synthesis of 7 as a byproduct after column chromatography on silica gel (silica gel was activated with 10:90 Et$_3$N/petroleum ether prior to use, ether:petroleum ether, 20:80-45:55, v/v as eluent): mp 36.8-38.9 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.34 (dd, $J$ = 5.1, 1.9 Hz, 1H), 7.72 (dt, $J$ = 8.2, 2.7 Hz, 1H), 7.16 (dd, $J$ = 7.4, 5.1 Hz, 1H), 7.04 (d, $J$ = 8.3 Hz, 1H), 1.50 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 158.0, 151.1, 148.5, 139.7, 122.1, 115.9, 84.2, 27.8.

4-$n$-Butyl-3,4-dihydro-N-Boc-2-pyridone (16a)

From: $n$-Bu$_2$CuLi (CuI)

Employing General Procedure B, $n$-BuLi (1.0 mmol, 2.0 equiv, 0.4 mL of 2.5M), CuI (95 mg, 0.5 mmol, 1.0 equiv) gave 16a (94 mg, 74%) as a brown oil after column chromatography (silica gel, Et$_3$N:Et$_2$O:petroleum ether, 1:10:89, v/v): $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.64 (dd, $J$ = 8.3, 1.4 Hz, 1H), 5.10 (dd, $J$ = 8.3, 3.7 Hz, 1H), 2.55
(dd, 14.7, 5.5 Hz, 1H), 2.39-2.31 (m, 1H), 2.28 (dd, J = 14.7, 8.7 Hz, 1H), 1.43 (s, 9H),
1.30-1.18 (m, 6H), 0.78 (t, J = 7.4 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 169.4, 149.9,
125.2, 113.1, 83.8, 40.2, 34.3, 31.9, 28.7, 28.0, 22.7, 14.0.

From: $n$-BuCuILi

Employing General Procedure A, $n$-BuLi (0.5 mmol, 1.0 equiv, 0.2 mL of 2.5M), CuI
(95mg, 0.5 mmol, 1.0 equiv) gave $16a$ (14% by $^1$H NMR calculation) as a brown oil.

From: $n$-Bu$_2$CuLi (CuCN)

Employing General Procedure B, $n$-BuLi (2.0 mmol, 4.0 equiv, 0.8 mL of 2.5M),
CuCN (90 mg, 1.0 mmol, 2.0 equiv) gave $16a$ (35% by $^1$H NMR calculation) as a brown oil.

From: $n$-BuLi 2.0/ CuI 0.66

To a suspension of CuI (63 mg, 0.66 equiv) in dry THF under argon at -40 °C, was added
dropwise $n$-BuLi (2.0 equiv) and the mixture was stirred for 1 hour at -40 °C before a
solution of $N$-Boc-2-pyridone (98 mg, 0.5 mmol, 1.0 equiv) and TMSCl (275 mg, 5.0
equiv) in THF (2 mL) was added dropwise at the same temperature. The reaction
mixture was allowed to warm up to room temperature over 12 hours and was quenched
with saturated aqueous NH$_4$Cl solutions, extracted with EtOAc (3 x 30 mL). The
combined organic phase was dried over MgSO$_4$ and concentrated in vacuo to afford $16a$
(65% by $^1$H NMR calculation) as yellow powder.
From: $n$-Bu$_3$ZnLi

Employing modified General Procedure C, $n$-BuLi (1.65 mmol, 3.3 equiv, 0.67 mL of 2.5 M) was used, and starting material and TMSCl was added at -78 °C and stirred for 5 minutes before warmed to 0 °C and was allowed to warm to room temperature over 12 hours. After flash column chromatography (silica gel, Et$_3$N: Et$_2$O:petroleum ether, 1:10:89, v/v) pure 16a (90mg, 71%) was obtained as a brown oil.

6-$n$-Butyl-3,6-dihydro-$N$-Boc-2-pyridone (17a): Pure 17a (10%) was isolated along with 16a employing General Procedure B and in Et$_2$O solvent as a yellow oil: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.78 (dd, $J$ =9.6, 4.6 Hz, 1H), 5.66 (dt, $J$ = 9.6, 3.7 Hz, 1H), 4.58-4.52 (m, 1H), 2.96 (d, $J$ = 2.3 Hz, 2H), 2.71-2.65 (m, 2H), 1.43 (s, 9H), 1.26-1.11 (m, 4 H), 0.78 (t, $J$ = 6 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 169.4, 152.2, 127.0, 121.8, 83.2, 57.0, 35.7, 35.0, 28.1, 27.0, 22.7, 14.1.

4-(1-Methylpropyl)-3,4-dihydro-$N$-Boc-2-pyridone (16b)

From: $s$-Bu$_2$CuLi (CuI)

Employing General Procedure B, $s$-BuLi (1.2 mmol, 2.4 equiv, 1.82 mL of 0.66 M) gave 16b (86mg, 68%) after column chromatography (silica gel, Et$_3$N: Et$_2$O:petroleum ether, 1:10:89, v/v) as a yellow oil: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.72 (dd, $J$ = 6.5, 1.9 Hz, 1H), 5.10 (dd, $J$ = 8.3, 3.2 Hz, 1H), 2.55-2.37 (m, 3H), 1.47 (s, 9H), 1.42-1.32 (m, 3H),
0.82 (t, J = 7.4 Hz, 3H), 0.81 (dd, J = 6.4, 3.2 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$

169.8, 149.9, 126.1 (125.7), 112.2 (110.9), 83.8, 38.1 (38.0), 36.7 (36.5), 36.6, 28.0, 26.3,
15.5 (15.4), 11.6.

From: $s$-Bu$_3$ZnLi

Employing modified General Procedure C, $s$-BuLi (1.65 mmol, 3.3 equiv, 2.5 mL of 0.66 M) was used, and starting material and TMSCl was added at -78 °C and stirred for 5 minutes before warmed to 0 °C and was allowed to warm to room temperature over 12 hours. After flash column chromatography (silica gel, Et$_3$N: Et$_2$O:petroleum ether, 1:10:89, v/v) pure 16b (54 mg, 43%) was obtained as a yellow oil.

4-(1,1-Dimethylethyl)-3,4-dihydro-N-Boc-2-pyridone (16c)

From: $t$-Bu$_2$CuLi (CuI)

Employing General Procedure B, $t$-BuLi (1.1 mmol, 2.2 equiv, 0.55 mL of 2.0 M) was used and 16c (96 mg, 76%) was obtained as a yellow oil after flash column chromatography (silica gel, Et$_3$N: Et$_2$O:petroleum ether, 1:10:89, v/v): $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6. 71 (dd, J = 8.7, 1.9 Hz, 1H), 5.12 (dd, J = 8.2, 3.7 Hz, 1H), 2.51 (dd, J = 15.1, 6.9 Hz, 1H), 2.43 (dd, J = 15.6, 8.3 Hz, 1H), 2.18-2.12 (m, 1H), 1.43 (s, 9H), 0.80 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 169.9, 149.8, 126.1, 110.2, 83.8, 42.4, 36.2, 33.3, 28.0, 26.8.
Employing General Procedure C, t-BuLi (1.5 mmol, 3.0 equiv, 0.75 mL of 2.0 M) at -40 °C gave 16c (70% by $^1$H NMR calculation) as a yellow oil.

4-Phenyl-3,4-dihydro-N-Boc-2-pyridone (16d)

Employing General Procedure B, PhLi (1.0 mmol, 2.0 equiv, 0.57 mL of 1.75M) at 0 °C gave 16d (45 mg, 33%) after flash column chromatography (silica gel, Et$_3$N: Et$_2$O:petroleum ether, 1:5:94, v/v) as a yellow oil: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.27-7.13 (m, 5H), 6.89 (dd, $J$ = 8.3, 1.9 Hz, 1H), 5.30 (dd, $J$ = 8.2, 3.7 Hz, 1H), 3.74-3.70 (m, 1H), 2.84 (dd, $J$ = 15.1, 6.4 Hz, 1H), 2.67 (dd, $J$ = 15.1, 9.2 Hz, 1H), 1.48 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 168.2, 149.9, 142.0, 129.0, 127.3, 127.1, 126.5, 111.7, 84.2, 42.4, 38.3, 28.1.

4-Methyl-3,4-dihydro-N-Boc-2-pyridone (16e)

Employing General Procedure B, MeLi (1.1 mmol, 2.2 equiv, 0.69 mL of 1.6 M) at 0 °C gave 16e (65 mg, 52%) a brown oil after flash column chromatography (silica gel, Et$_3$N: Et$_2$O:petroleum ether, 1:15:84, v/v): $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.61 (dd, $J$ = 8.3, 1.9 Hz, 1H), 5.04 (dd, $J$ = 8.3, 3.2 Hz, 1H), 2.55-2.46(m, 2H), 2.22 (dt, $J$ = 8.8, 5.5 Hz, 1H), 1.42 (s, 9H), 0.96(d, $J$ = 6.9 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 169.2, 149.9, 125.0, 114.4, 83.8, 42.1, 28.0, 27.0, 20.1.
From: Me$_3$ZnLi

Employing **General Procedure C**, MeLi (1.5 mmol, 3.0 equiv, 0.94 mL of 1.6 M) at -40 °C gave **16e** (65% by $^1$H NMR calculation) as a brown oil.

**N-Benzyl-2-pyridone (6):** Employing an established procedure$^{31}$, 2-hydroxy pyridine (500 mg, 1.0 equiv) dissolved in dry MeOH (8 mL) was treated sequentially with K$_2$CO$_3$ (1380 mg, 2.0 equiv) and BnBr (1283 mg, 1.5 equiv) at room temperature while stirring. The mixture was then heated to reflux for 2.5 hours was filtered through Celite and solvent was removed by rotavapor. The residue was diluted with water (10 mL), and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic phase was dried over MgSO$_4$ and then concentrated in *vacuo* to afford crude 6 as a white solid. Flash column chromatography (silica gel, EtOAc:petroleum ether, 50:50, v/v) afforded pure 6 (795 mg, 86%) as a white solid: mp 68.5 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.29-7.22 (m, 7H), 6.59 (d, $J$ = 8.3 Hz, 1H), 6.08 (dd, $J$ = 6.9, 6.9 Hz, 1H), 5.10 (s, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 162.8, 139.6, 137.3, 136.3, 129.0, 128.2, 128.1, 121.2, 106.6, 52.1.

**4-n-Butyl-3,4-dihydro-N-benzyl-2-pyridone (19a):**

From nBuMgCl reaction with pyridinium salt

Employing **General Procedure D**, n-BuMgCl (2.0 mmol, 2.0 equiv, 1.0 mL of 2.0 M) at -78 °C gave **19a** (38% by $^1$H NMR calculation) as a yellow oil.
From \(n\)-BuMgCl reaction with pyridinium salt

Employing **General Procedure D**, \(n\)-BuLi (2.0 mmol, 2.0 equiv, 0.83 mL of 2.5 M) at -78 °C gave 19a (58 mg, 48%) and 20a (17 mg, 14%) after column chromatography (silica gel, MeOH:dichloromethane, 1:99, v/v): \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.26-7.15 (m, 5H), 5.90(dd, \(J = 7.8, 1.4\) Hz, 1H), 5.00(dd, \(J = 7.3, 3.7\) Hz, 1H), 4.60 (s, 2H), 2.58 (dd, \(J = 15.6, 6.4\) Hz, 1H), 2.43-2.36 (m, 1H), 2.29 (dd, \(J = 15.6, 9.2\) Hz, 1H), 1.36-1.14 (m, 6H), 0.81 (t, \(J = 6.9\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 169.5, 137.4, 128.7, 128.4, 127.7, 127.5, 111.8, 48.8, 37.8, 34.4, 32.0, 28.8, 22.7, 14.1.

From \(n\)-Bu_2CuLi

Employing **General Procedure F**, \(n\)-BuLi (10.0 mmol, 10.0 equiv, 4.0 mL of 2.5 M) and CuI (950 mg, 5.0 equiv) at 0 °C gave 19a (64% by \(^1\)H NMR calculation) as a yellow oil.

From \(n\)-Bu_3ZnLi

Employing **General Procedure H**, \(n\)-BuLi (3.0 mmol, 3.0 equiv), ZnBr\(_2\) (225 mg, 1.0 equiv) and BF\(_3\)•Et\(_2\)O (142 mg, 1.0 equiv) at 0 °C gave 19a (28% by \(^1\)H NMR calculation) as a yellow oil.

**6-n-Butyl-3,6-dihydro-N-benzyl-2-pyridone (20a):** 20a was isolated in the synthesis of 19a employing **General Procedure F**: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.29-7.16 (m, 5H),
5.73 (dt, $J = 10.1$, 3.7 Hz, 1H), 5.62-5.58 (m, 1H), 5.41 (d, $J = 15.1$ Hz, 1H), 3.89 (d, $J = 15.2$ Hz, 1H), 3.83-3.77 (m, 1H), 2.97 (d, $J = 3.2$ Hz, 2H), 1.66-1.44 (m, 2H), 1.24-1.09 (m, 4H), 0.80 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 168.6, 137.2, 128.7, 127.9, 127.4, 126.4, 122.6, 56.7, 46.5, 32.9, 32.6, 25.6, 22.7, 14.1.

4-Methyl-N-benzyl-2-pyridone (22a): Compound 22a was isolated in the synthesis of 19a employing General Procedure D: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.34-7.26 (m, 5H), 7.15 (d, $J = 6.9$ Hz, 1H), 6.42 (s, 1H), 6.00 (dd, $J = 6.9$, 1.8 Hz, 1H), 5.12 (s, 2H), 2.42 (t, $J = 7.8$ Hz, 2H), 1.58-1.52 (m, 2H), 1.38-1.31 (m, 2H), 0.92 (t, $J = 7.3$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 162.9, 155.6, 136.7, 136.3, 128.9, 128.2, 128.0, 118.8, 108.2, 51.5, 35.0, 31.3, 22.3, 13.9.

4-(1-Methylpropyl)-3,4-dihydro-N-benzyl-2-pyridone (19b): Employing General Procedure D, s-BuLi (1.0 mmol, 2.0 equiv, 1.51 mL of 0.66 M) at -78 °C gave 19b (35% by $^1$H NMR calculation): $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.26-7.14 (m, 5H), 5.95 (t, $J = 6.9$ Hz, 1H), 4.95 (dt, $J = 7.8$, 3.2 Hz, 1H), 4.59 (d, $J = 4.1$ Hz, 2H), 2.55-2.35 (m, 3H), 1.39-1.28 (2H), 1.21-1.04 (m, 1H), 0.80 (t, $J = 7.8$ Hz, 3H), 0.77 (d, $J = 6.4$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 169.8, 137.3, 129.1 (128.8), 128.7, 127.9, 127.5, 110.7 (109.3), 48.8, 38.5 (38.2), 36.8 (36.7), (35.5) 33.9, 26.3 (26.2), (15.5) 15.4, 11.
6-Phenyl-3,6-dihydro-N-benzyl-2-pyridone (20c): Employing General Procedure D, PhLi (0.5 mmol, 1.0 equiv, 0.28 mL of 1.8 M) at -78 °C gave 20c (52 mg, 40%) as a yellow crystal after column chromatography (silica gel, EtOAc:petroleum ether, 25:75-50:50, v/v): mp 115.9-116.6 °C \( ^1H \) NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.31- 7.09 (m, 10H), 5.69-5.58 (m, 2H), 5.53 (d, \( J = 15.2 \) Hz, 1H), 4.73 (q, \( J = 4.2 \) Hz, 1H), 3.33 (d, \( J = 15.2 \) Hz, 1H), 3.22-3.08 (m, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 167.7, 140.2, 136.9, 129.2, 128.7, 128.3, 128.2, 127.5, 127.1, 126.5, 120.6, 61.8, 46.4, 32.2.

3-Methyl-4-\( n \)-butyl-3,4-dihydro-N-benzyl-2-pyridone (24): To a solution of N-benzyl-2-pyridone (93mg, 1.0 equiv) in dry dichloromethane (4 mL) was added TMSOTf (112 mg, 1.0 equiv) at room temperature while stirring. The mixture was stirred at room temperature for 15 minutes before cooled to -78 °C whereupon it was treated dropwise with \(^n\)BuLi (0.41 mL, 2.0 equiv). After stirred for an addition hour at -78 °C, the reaction mixture was treated with MeI (284 mg, 4.0 equiv) dropwise at that temperature and was then immediately warmed to 0 °C and was allowed to warm to room temperature over 12 hours. Saturated aqueous NH\(_4\)Cl solution was added and the aqueous phase was extracted with dichloromethane (3 x 30 mL). The combined organic phase was dried over MgSO\(_4\) and concentrated to afford an oil. Flash column chromatography (silica gel activated with Et\(_3\)N, EtOAc:petroleum ether, 5:95, v/v) afforded 24 (50 mg, 39%) as a yellow oil.
NMR (500 MHz, CDCl₃) δ 7.23-7.12 (m, 5H), 5.86 (d, $J = 7.8$ Hz, 1H), 4.98 (dd, $J = 7.8$, 5.0 Hz, 1H), 4.60 (d, $J = 2.8$ Hz, 2H), 2.43-2.37 (m, 1H), 2.02-1.98 (m, 1H), 1.32-1.14 (m, 6H), 1.14 (d, $J = 7.4$ Hz, 3H), 0.78 (t, $J = 6.9$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl₃) δ 172.8, 137.5, 128.7, 127.7, 127.5, 127.4, 109.8, 49.0, 41.4, 39.2, 33.8, 28.5, 22.9, 16.3, 14.1.
References


CHAPTER FOUR
SYNTHESES OF ENANTIOENRICHED BICYCLIC AMIDINES

Introduction

Amidines are of great interest for their broad application in organic synthesis and for their biological activities applicable for the pharmaceutical industry.\(^1\) While bicyclic amidines [e.g., 1,5-diazabicyclo[4.3.0]non-5-ene (DBN, 1) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 2), Figure 4.1] serve as Lewis bases to promote acylation reactions of amines and alcohols due to their high Lewis basicity,\(^4,5\) they can also be used as nucleophiles in many organic reactions.\(^6-8\) Aggarwal discovered that DBU is a superior catalyst for promoting Baylis-Hillman reactions, which usually suffer from low reaction rate with other organocatalysts.\(^9\) Moreover, development of chiral amidines (e.g., 3 and 4) was shown to be of value since they have been shown to successfully catalyze kinetic resolution of alcohols.\(^10\) They also serve as ligands for transitional-metal-based catalysts to promote asymmetric reactions with excellent enantioselectivities.\(^11-13\)
Birman reported acylation reactions of alcohols promoted by various bicyclic amidine catalysts.\textsuperscript{14} Methanol reacted with acetic anhydride in the presence of diisopropylethylamine to afford methyl acetate under the catalysis of various organocatalysts (Table 4.1). They found that the sizes of both rings in these bicyclic amidines have significant impact on the catalytic activity in these acylation reactions, and DBN and other 5,6- membered bicyclic amidines were the most effective catalysts (entry 1, 2 and 5) whereas DBU demonstrated much lower catalytic activity (entry 3). Chiral catalysts 5 and 6 were used, however, just to compare their catalytic activity with achiral catalysts (i.e., DBU and DBN).\textsuperscript{14}
Table 4.1 Acylation of MeOH by Cyclic Amidines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Catalyst load (mol %)</th>
<th>$T_{1/2}$ $^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DBN 1</td>
<td>1</td>
<td>40 min</td>
</tr>
<tr>
<td>2</td>
<td>DBN 1</td>
<td>5</td>
<td>4 min</td>
</tr>
<tr>
<td>3</td>
<td>DBU 2</td>
<td>5</td>
<td>12 h</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>5</td>
<td>38 min</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>6</td>
<td>12 min</td>
</tr>
</tbody>
</table>

$^a$Time required to achieve 50% conversion of starting material monitored by $^1$H NMR.

Dieter’s group developed DBU catalyzed acetoxybromination and 1,2-electrophilic additions promoted by $N$-bromosuccinimide (NBS) to styrenes and cycloalkenes. Several imines can catalyze the acetoxybromination reactions with as little as 2% catalyst loading. In the DBU catalyzed 1,2 electrophilic addition reactions, various nucleophiles (OMe, BnS, PhS, ONO, N$_3$, CN, SCN) were successfully introduced to styrene in a diastereoselective (anti-) and regioselective fashion (Table 4.2).
Table 4.2 DBU Catalyzed Acetoxybromination of Styrene

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nu (equiv)</th>
<th>Acid (equiv)</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OAc</td>
<td>AcOH</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>OAc&lt;sup&gt;a&lt;/sup&gt;</td>
<td>AcOH</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>MeOH (10)</td>
<td>-</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>MeOH (10)</td>
<td>AcOH (1.0)</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>MeOH (10)</td>
<td>Citric acid (0.33)</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>BnSH (10)</td>
<td>AcOH (1.0)</td>
<td>37</td>
</tr>
<tr>
<td>7</td>
<td>PhSH (10)</td>
<td>AcOH (1.0)</td>
<td>56</td>
</tr>
<tr>
<td>8</td>
<td>NaNO&lt;sub&gt;2&lt;/sub&gt; (1.1)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td>95</td>
</tr>
<tr>
<td>9</td>
<td>NaN&lt;sub&gt;3&lt;/sub&gt; (1.1)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td>85</td>
</tr>
<tr>
<td>10</td>
<td>NaCN (1.1)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td>95</td>
</tr>
<tr>
<td>11</td>
<td>KSCN (1.1)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td>80</td>
</tr>
</tbody>
</table>

<sup>a</sup> 10 mol% of DBU was used.  
<sup>b</sup> TMSCl/ H<sub>2</sub>O was used to generate the corresponding acid in situ.

In these reactions, the amidine catalyst (i.e., DBU) serves as a Lewis base to promote the transfer of bromine to the olefin in the presence of a nucleophile. Dieter suggested a DBU-NBS complex (Figure 4.2) is formed in the reaction pathway, and bromine is released by an acid (e.g., AcOH). Up till now, zero or little (10% ee) enantioselectivities were obtained for these 1,2 electrophilic addition reactions by using chiral imine catalysts. Exploration and syntheses of effective chiral imine catalysts is important, and chiral diazobicycloalkene derivatives may be promising candidates.
Chiral Cyclic Amidines

Chiral cyclic amidines have been successfully utilized as organocatalysts in bromoacetoxylation of alkenes and halolactonization of unsaturated carboxylic acids.\textsuperscript{11,16-19} Grossman reported the first example of reagent controlled asymmetric halolactonization with poor enantioselectivity (15\% ee)\textsuperscript{20}. Birman, on the other hand, reported kinetic resolution of alcohols by bicyclic amidine derivatives.\textsuperscript{10} Although examples achieving good to excellent enantiomeric excess (up to 90\% ee) are reported for halolactonization reactions,\textsuperscript{16} these asymmetric halolactonization reactions are still considered difficult and low enantioselectivities are often obtained (24\% ee, Scheme 4.1)\textsuperscript{17,21} and the successful examples are often limited to chlorolactonization\textsuperscript{18} or to specific substrates (e.g., conjugated Z enynes)\textsuperscript{22}.

**Scheme 4.1** Stoichiometric Asymmetric Bromolactonization\textsuperscript{17}
So far, little has been achieved for effective enantioselective organocatalysts for asymmetric 1,2-electrophilic additions to alkenes (e.g., haloacetoxylation), and low enantioselectivities\textsuperscript{23} are often obtained in comparison to organometallic (e.g., Pd\textsuperscript{24}, Ru\textsuperscript{25}, Ti\textsuperscript{26}) catalysts. For example, Braddock reported that chiral amidines failed to provide any enantioselectivity for asymmetric bromoacetoxylation.\textsuperscript{11}

Asymmetric induction is still challenging in these alkene functionalization reactions, and so far most of these halolactonizations and haloacetoxylations suffer low enantioselectivities.\textsuperscript{11,23} Reasons include: 1. It is hard to identify the proper chiral catalysts, which allows the transfer of chirality (enantioselective delivery of the halonium ion);\textsuperscript{16} 2. The enantioenriched halonium-olefin complex may racemize through a rapid olefin-olefin halogen exchange and lose its chiral information.\textsuperscript{27,28} Therefore the development of highly effective organocatalysts for such asymmetric synthesis is of great interest to synthetic chemists.

**Synthesis of Amidines and Bicyclic Amidines**

Currently there are several reports on the synthesis of bicyclic amidines,\textsuperscript{12,29-35} which generally fall into two major categories.

**First Pathway**

The first pathway involves the cyclization of a lactam (e.g., 2-piperidinone or 2-pyrrolidinone) bearing aminoalkyl side chain on the nitrogen (Scheme 4.2). Several dehydrating reagents were reported to facilitate this transformation including SiCl\textsubscript{4},\textsuperscript{36} POCl\textsubscript{3},\textsuperscript{37} TiCl\textsubscript{4} and p-toluenesulfonic acid\textsuperscript{39}. However, brutal reaction conditions, large
excess of dehydrating reagent and/or extended reaction time are usually required for such cyclizations.²⁹

**Scheme 4.2 Cyclization of N-β-Amino and N-γ-Amino Lactams**

Phosphorus oxychloride was reported to be an effective dehydrating reagent. Bai and coworkers reported the synthesis of imidazole analog ⁹ utilizing the cyclization of acetyl protected pyridine ⁸. Although the reaction proceed smoothly in modest yield (72%), vigorous reaction condition (81 °C, 12 hours) and excess amount of POCl₃ (4.0 equiv) were required **(Scheme 4.3)**. Moreover, the substrate for this cyclization is limited to N-aryl amides.³⁷

**Scheme 4.3 POCl₃ Promoted Cyclization of 8**

Silicon tetrachloride (SiCl₄) is also an effective dehydrating reagent.⁴⁰ Bourguignon reported SiCl₄ as an effective dehydrating reagent to facilitate the cyclization of o-phenylenediamine.³⁶ In this reaction, N-aryl lactam ¹⁰ was heated at
reflux with SiCl₄ and Et₃N in dichloromethane to afford cyclization product 11, whereas POCl₃ as dehydrating reagent failed (Scheme 4.4). However, it required long reaction time (4 days) to complete the reaction.

**Scheme 4.4 SiCl₄ Promoted Cyclization of 10**

![Scheme 4.4 SiCl₄ Promoted Cyclization of 10](image)

An improved experimental procedure to shorten the reaction time on these cyclization reactions was later reported by the same group.⁴¹ Utilization of microwave radiation (heated at 180 °C by microwave for 10 min) completed the cyclization in 10 minutes with 72% yield (Scheme 4.5). Similar to POCl₃ cyclization reactions, the scope of these reaction conditions are limited to N-aryl lactams.

**Scheme 4.5 Cyclization under Microwave/SiCl₄**

![Scheme 4.5 Cyclization under Microwave/SiCl₄](image)

*TiCl₄ and TsOH Method*

Yamamoto reported the synthesis of bicyclic amidine 15 from N-aminopropyl lactam 14, where titanium chloride TiCl₄ was used as the dehydrating reagent (Scheme 4.6).³⁹ Similarly, Oediger reported the use of catalytic amounts of p-toluenesulfonic acid
(TsOH) to promote the synthesis of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN 1, 88%) upon cyclization.\textsuperscript{38} It should be noted that brutal reaction conditions were used to complete these cyclizations (140 °C, 9-12 hours).

**Scheme 4.6 Cyclization of 14 and 16**

![Scheme 4.6](image)

Shibasaki reported an interesting facile synthesis of bicyclic amidines utilizing \( N \)-azidopropyl lactams (e.g., 17, Scheme 4.7).\textsuperscript{29} This method provided an opportunity to achieve a range of bicyclic amidines bearing five, six or seven membered rings in desirable yields under relatively mild reaction conditions (oxalyl bromide 1.0 equiv, 0 °C to rt for 4 hours). However, this procedure is limited to substrates bearing a \( N \)-azidoalkyl side chain.
Scheme 4.7 Cyclization of N-Azidopropyl Lactam 17

Second Pathway

The second pathway utilizes an imino ether or imino thioether to react with amine hydrobromide/ chloride salt and then cyclize by intramolecular attack of the lactam nitrogen (Scheme 4.8). Imino ether 18 or imino thioether 18a are conveniently prepared from lactams or thiolactams (accessed by treatment of lactams with Lawesson’s reagent\textsuperscript{42-44} reacting with neat dimethyl sulfate or with Meerwein’s reagent (i.e., triethylxonium tetrafluoroborate, Et\textsubscript{3}O• BF\textsubscript{4}) in dichloromethane.\textsuperscript{45} Compounds 18 and 18a can then react with an amine hydrochloride salt 19 to afford amidine 20, which is then cyclized by thionyl chloride or potassium carbonate to provide bicyclic amidines 21.
Yamamoto reported synthesis of bicyclic amidines 22 using imino ether 20 to react with bromopropylamine hydrobromide \([\text{Br}(\text{CH}_2)_3\text{NH}_2\cdot\text{HBr}]\) followed by cyclization in the presence of potassium carbonate.\(^\text{39}\) The reaction proceeded in modest yields (55-56%). The starting imino ethers were readily prepared from the corresponding lactams and triethylxonium tetrafluoroborate \((\text{Et}_3\text{O}^+\text{BF}_4^-)\). This procedure enables the formation of macrocyclic amidines (i.e., thirteen membered rings).
Birman and coworkers demonstrated that bicyclic amidines (e.g., DBU, DBN) and bicyclic isothioureas (e.g., 26) are highly effective achiral organocatalysts in acylation reactions (vide supra).10,14 Elegant syntheses of these bicyclic compounds were made possible by treatment of an imino ether with an amino acid hydrochloride (or treatment of a 4,5-dihydro-2-methylthio-thiazole hydroiodide with an amino acid), followed by intermolecular cyclization using thionyl chloride or potassium carbonate. Employment of a chiral amino acid facilitates the synthesis of a chiral thiourea 26, and use of 2-methoxypyrroline 28 or S-methylvalerolactim with β or γ amino acids realized the syntheses of different size rings (i.e., 30, 31, 32). These transformations, however, typically suffer from poor chemical yields (16-44%).
Scheme 4.10 Synthesis of Bicyclic Amidines 26, 30, 31 and 32

Syntheses of enantiopure bicyclic amidines often suffer from low chemical yields and long synthetic routes.\textsuperscript{46,47} Due to the drawbacks of the existing procedures such as low chemical yields and requirement for harsh reaction conditions, it is of interest to design facile synthesis of bicyclic amidines under mild reaction conditions.

Figure 4.3 Enantiopure Bicyclic Amidines
Results and Discussion

Synthesis of Bicyclic Amidines from Aziridines

Our first attempt was to synthesize an \(N\)-protected aziridine from \(\beta\)-amino acids, followed by opening of the aziridine ring with sodium amide, cleavage of the \(N\)-protecting group and eventually cyclization using dehydrating reagents (vide supra, Scheme 4.11). Due to the convenience of removing a \(N\)-Boc group (usually under mild acid conditions), (L)-valinol 35 was readily converted into Boc protected alcohol 36 using a standard protection procedure, which was then transformed into aziridine 37 upon the treatment of a base (20% KOH). Although there are several examples of ring opening of similar aziridines,\(^{48-50}\) our attempts for ring opening of 37 with 2-pyrrolidone or sodium 2-pyrrolidinone all failed, giving starting material recovery with loss of material. In fact, several research groups have previously reported the low reactivity of \(N\)-Boc aziridines due to the poor electron withdrawing group (Boc).\(^{51}\) These Boc aziridines are very prone to lose the Boc group under different reaction conditions (i.e., high temperature, presence of a strong base, or prolonged reaction time).\(^{52}\)

Scheme 4.11 Attempted Synthesis of 38 from \(N\)-Boc Aziridine 37

\[
\begin{align*}
35 & \quad \overset{a}{\longrightarrow} \quad 36 \quad \overset{b}{\longrightarrow} \quad 37 \quad \overset{c}{\longrightarrow} \quad 38 \\
\text{a. (Boc)\textsubscript{2}O, NEt\textsubscript{3}, Dioxane/H\textsubscript{2}O, rt, 24h; b. TsCl, KOH, ether, reflux 4h; c. 2-piperidone, KOH, DMSO, 40 ^\circ C, 16h or sodium 2-pyrrolidinone.}
\end{align*}
\]
Alternatively we synthesized the N-tosyl aziridine 40 (Scheme 4.12), which is chemically more stable under basic reaction conditions and generally demonstrates higher reactivity than its N-Boc analogues. Using an established procedure, the amino alcohol was converted into bis-tosyl-protected 39 by reacting with TsCl in pyridine for 24 hours. The source and dryness of both pyridine and p-toluenesulfonyl chloride is very critical to the outcome of this reaction, and we found that good chemical yields of the bis-tosyl protected product 39 were obtained only when recrystallized TsCl and dry pyridine (dried for 12 hours with molecular sieves or freshly distilled) were used, and that trace amounts of moisture in the reagents (e.g., pyridine) would lead to mono-tosyl protected byproduct. Tosylate 39 was then smoothly converted into aziridine 40 by treatment with potassium hydroxide in benzene. It should be noted that one group reported a one step synthesis of 40 from amino alcohol 35 by the treatment of TsCl, NEt₃ and dimethylaminopyridine (DMAP) in dichloromethane. We found, however, that this procedure was rather unreliable and the reaction is always accompanied with various amounts of mono-protected byproduct and/or incomplete formation of aziridine 40.

Ring opening reaction of aziridine 40 was then developed based on Righi’s procedure. Deprotonation of 2-pyrrolidinone by NaH (1.1 equiv) in N,N-dimethylformamide (DMF) afforded the sodium salt of 2-pyrrolidinone, which was then treated with aziridine 40 at 70 °C in DMF for 12 hours to afford ring opening product 41 (64%). Although Gardiner reported the promotion of a Lewis acid [i.e., Ti(O\text{Pr})₄] in the ring opening reactions, addition of this Lewis acid [i.e., Ti(O\text{Pr})₄] did not provide any improvement on the outcome of this reaction.
The removal of the \( N \)-tosyl group requires harsh reaction conditions due to the low reactivity of sulfonamides to hydrolysis. Following established literature reports\(^{57,58}\), our initial attempts to use HCl/AcOH or Mg/MeOH to cleave the tosyl group were unsuccessful giving only recovered starting material. Finally, \( N \)-tosyl compound 41 was reacted with 48\% hydrobromic acid and phenol at reflux (130 °C) for 12 hours\(^{59-61}\) to afford amine 42 (34-60\%) in high purity and no further purification was necessary for the next step.

Unfortunately, the subsequent attempts to cyclize this \( N \)-\( \beta \)-amino-pyrrolidin-2-one 42 were unsuccessful. Si\( \text{Cl}_4 \)^{36,41} and PO\( \text{Cl}_3 \)^{37,62} were reported to be effective dehydrating reagents for the imine formation reactions and several cyclic amidines were prepared by these reagents. When amine 42 was reacted with Si\( \text{Cl}_4 \) only starting material was recovered, and the PO\( \text{Cl}_3 \) reaction was very sluggish and many unidentified byproducts were formed. Although several literature reports state that by refluxing the similar amine substrate in xylene with molecular sieves (4A) in the presence of catalytic amount of \( p \)-toluenesulfonyl acid (TsOH) can afford imine cyclization products (vide supra),\(^{38,63,64}\) this procedure did not provide any desire product 43. We assume that 5,5 bicyclic compounds have great ring strain and are therefore hard to form.

We also looked into the synthesis of 5,6 bicyclic compounds by opening the aziridine ring with a 6 membered 2-piperidone ring. To our disappointment, the effort to cyclize \( N \)-\( \beta \)-amino-2-piperidinone 45 with dehydrating reagents (xylene/cat. TsOH, Si\( \text{Cl}_4 \) or PO\( \text{Cl}_3 \)) met with no success. However, it is noteworthy that with prolonged reaction times (20-24 hours), clean cyclization product 46 was isolated as the only product.
However, controlling the reaction to complete cyclization seems fairly difficult and the reaction is not always reproducible (e.g., a mixture of tosyl cleavage product 45 and cyclic amidine 46 was obtained in some reactions). We assume that HBr served as dehydrating reagent and promoted this imine formation.

Due to the low yields of the sulfonamide hydrolysis and unreliability of the cyclization step, a search for a facile and efficient synthesis of cyclic amidines is very necessary.
Next, we focused our attention on the synthesis of amidines from imino ethers or imino thioethers. 2-Piperidone was readily converted into a thiolactam 48 using Lawesson’s reagent heated at reflux in THF (Scheme 4.13). Methylation of 48 using dimethyl sulfate ($\text{Me}_2\text{SO}_4$) afforded imino thioether 49 in good yield (85-92%). Several different experimental procedures have been reported for amidine formation from an
amine and an imino ether,\textsuperscript{10,65} and our attempts to react imino thioether 49 with (L)-valinol under various conditions (reflux in dry methanol or ethanol\textsuperscript{10} or stirring at room temperature in dichloromethane\textsuperscript{65}) met with no success and gave only recovered starting material. Running the reaction in DMF at 80 °C afforded the amidine 50 in low yield (15%) along with decomposition of the amidine 50 during purification (flash column chromatography on neutral Al\textsubscript{2}O\textsubscript{3}). Efforts to use microwave conditions\textsuperscript{41} turned out to be unreliable and the imine hydrolysis product 47 is always present in various amounts. Lactam 47 is difficult to remove from the crude product because of its high boiling point and it’s presence is problematic for the next cyclization step. Consequently, when crude reaction product mixture containing 50 and 47 was reacted with mesyl chloride or tosyl chloride in the presence of t-BuOK in the effort to cyclize the imine, only starting material was recovered.

Fortunately, we quickly learned that by converting the amino group of valinol into a hydrochloride salt 51 facilitated the imine formation in good yield (75\%). Successful examples of using the ammonium salt in these imine formation reactions have been reported, although none has mentioned the superiority of amine salt over free amine in these reactions or given any explanation.\textsuperscript{14,66,67}
Alternatively, 2-piperidone can react directly with dimethyl sulfate (MgSO$_4$) to afford imino ether 49a, which was then reacted with valinol hydrochloride salt 51 to afford the amidine salt 52, and upon cyclization with thionyl chloride provided enantiopure cyclic amidine 46. Compound 46 was synthesized in three steps and in satisfactory yield (65% over three steps). By reacting 49a with leucinol hydrochloride, an $i$-Bu substituted cyclic amidine 46a was also obtained. It is noteworthy that although successful examples of preparation of 5-membered imino ethers were reported,$^{68,69}$ our attempts to synthesize this compound from 2-pyrrolidinone and MgSO$_4$ were unsuccessful.
Scheme 4.14 Three Step Syntheses of Amidine 46 and 46a

By using different amino acids and/or lactams, bicyclic amidines bearing five, six or seven membered rings can be prepared.

Scheme 4.15 Syntheses of Five, Six or Seven Membered Bicyclic Amidines

Alkylation of DBU

We examined the alkylation reactions of DBU and introduced various ligands on the 6 position in good yields. One group discovered the alkylation of DBU and DBN and synthesized amidines bearing polymers which are used for carbon dioxide trapping and releasing, but only benzyl chloride and its polymeric derivatives were used for
alkylation. Another group reported alkylation of DBU with alkyl halides and carbonyl compounds such as ketone and aldehydes. However, the latter procedure faced low chemical yields for acyl or alkyl chlorides (38-45%), while modest yield was obtained for an alkyl bromide (75%). We explored the scope of this alkylation reaction (e.g., introduction of various alkyl groups), intending to increase the yields and to adapt this alkylation methodology to the previous synthesis of bicyclic amidines.

DBU was first treated with n-BuLi dropwise at 0 °C for 1 hour before addition of an electrophile (e.g., benzyl bromide) and 5% hydrochloric acid was used to work-up the reaction after overnight stirring. This procedure afforded exclusive the hydrochloride salt 54a (45%, entry 1, Table 4.3) of the desired product, which was formed from the product 53 during the acidic aqueous work-up. The poor yield suggested the loss of the ionic salt in water. When t-BuLi was employed for the deprotonation and pH = 7 buffer was used to work-up the reaction mixture, the desire product 53 was obtained (53%, entry 2). Still, some material was lost probably due to some salt formed, which was washed away during aqueous work-up. In an effort to minimize formation of salt 54, we used aqueous NaOH solution (20%) to basify the salt, and observed the expected increase in yield (88%, entry 3) of the desired alkylation product 53a. Alkylation with methyl iodide give a 50:50 mixture of salt 54b and desired methylation product 53b (51% combined yield, entry 4) when the reaction was quenched with pH=7 buffer solution, while the methylation product 53b (55%, entry 5) was obtained exclusively when the crude mixture was washed with base (NaOH 20%). Ethyl iodide gave increased yield (75%, entry 6) compared to methyl iodide under the same reaction conditions and furnished alkylation
product 53c. It should be noted that different deprotonating reagents (i.e., \(n\)-BuLi and \(t\)-BuLi) have little effect on the yields, while the proper work-up procedures is critical for high chemical yields of these alkylation reactions. Although a previous report states that aqueous work-up procedures on bicyclic amidines are undesirable because of the high solubility of DBU and its derivatives in water,\(^{39}\) we successfully achieved modest to good yields (55-88\%) under carefully designed work up procedures.

Table 4.3 Alkylation of DBU

<table>
<thead>
<tr>
<th>entry(^a)</th>
<th>RLi</th>
<th>R-X (equiv)</th>
<th>quenching solution</th>
<th>% yield(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(n)-BuLi</td>
<td>BnBr (1.5)</td>
<td>5% HCl</td>
<td>(45%)</td>
</tr>
<tr>
<td>2</td>
<td>(t)-BuLi(^b)</td>
<td>BnCl (1.5)</td>
<td>Ph=7 buffer</td>
<td>53%</td>
</tr>
<tr>
<td>3</td>
<td>(t)-BuLi</td>
<td>BnCl (1.5)</td>
<td>20%NaOH</td>
<td>88%</td>
</tr>
<tr>
<td>4</td>
<td>(t)-BuLi(^b)</td>
<td>MeI (1.5)</td>
<td>Ph=7 buffer</td>
<td>(51%)(^d)</td>
</tr>
<tr>
<td>5</td>
<td>(t)-BuLi</td>
<td>MeI (1.5)</td>
<td>20%NaOH</td>
<td>55%</td>
</tr>
<tr>
<td>6</td>
<td>(t)-BuLi</td>
<td>EtI (1.5)</td>
<td>20%NaOH</td>
<td>75%</td>
</tr>
</tbody>
</table>

\(^a\) All deprotonations were performed with alkyllithium (1.0 equiv) in THF at 0 °C for 1 hour unless otherwise noted. \(^b\) 0.5 Hour for deprotonation. \(^c\) Yields in parenthesis are the isolated yields of the HCl salt 54. \(^d\) A 50:50 mixture of 53 and 54 was isolated.
Sequential alkylation reactions with mono-alkylated DBU were performed. 6-Benzyl-1,8-diazabicyclo[5,4,0]undec-7-ene (53a) was deprotonated with t-BuLi at 0 °C in THF followed by the treatment of various alkyl (i.e., Me, Et, Allyl and Bn) halides. A 10% KOH aqueous solution was used to work up the reaction mixture after 12 hours of stirring to afford the bis-alkylated product in modest to good yields. Although the mass spectrum plot (MS) indicated the bis-alkylation was successful, the actual structures of these bis-alkylated products have not yet been confirmed. Two possible structures include the alkylation at the benzyl methylene carbon (i.e., 55) and the alkylation at the 9-position on the DBU ring (i.e., 56). An X-ray crystallography experiment is under way to verify the actual structures of these compounds. It is noteworthy that bis-methylated and bis-ethylated products were obtained (according to MS data) when the deprotonated substrate was treated with 2.0 equivalents of MeI or EtI, suggesting the formation of alkyammonium salts (i.e., 57 or 58).
Table 4.4 2nd Step Alkylation of DBU

<table>
<thead>
<tr>
<th>entry</th>
<th>R'-X</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeI</td>
<td>51%</td>
</tr>
<tr>
<td>2</td>
<td>EtI</td>
<td>62%</td>
</tr>
<tr>
<td>3</td>
<td>Allyl bromide</td>
<td>50%</td>
</tr>
<tr>
<td>4</td>
<td>BnCl</td>
<td>68%</td>
</tr>
</tbody>
</table>

All reactions were deprotonated by t-BuLi (1.0 equiv) at 0°C for 0.5 h in THF, and were quenched by 10% KOH solution after 12 h unless otherwise noted. Isolated yields. 2.0 equiv of t-BuLi and 4.0 equiv of MeI were used, reaction was quenched by aqueous NH4OH solution. A bis-methylated product was detected by MS analysis, % yield was based on the molecular weight of the ammonium salt (55•MeI). A bis-ethylated product was detected by MS analysis. % yield was based on the molecular weight of the ammonium salt (55•EtI). Obtained as a mixture of diastereomers (80:20 calculated from intensity of 13C NMR absorption).

Alkylation of Cycloamidine 46

Next we performed the alkylation of 46 in an effort to synthesis bis-alkylated bicyclic amidines. Compound 46 was deprotonated with t-BuLi (1.1 equivalent) and was then treated with an electrophile (i.e., BnCl). When the reaction was carried out at 0°C, benzyl alkylation product 59 was obtained in 55% yield with 75:25 diastereoselectivity.
No improvement of chemical yield or diastereoselectivity was obtained at reduced temperature (76:24 for -78 °C, entry 2). The addition of a chiral base (i.e., sparteine) to the reaction mixture provided slightly increased diastereoselectivity (88:12), although with similar chemical yield (55%, entry 3). Attempts to further improve the diastereoselectivity by reducing the deprotonation temperature met with no success providing slightly diminished dr (entry 4). Addition of TMEDA provided the similar result to sparteine (dr = 81:19, entry 5), and these additives (i.e., sparteine and TMEDA) have been known for their promotion in enantio- or diastereoselectivity in asymmetric alkylation reactions.\textsuperscript{72-74} Et\textsubscript{2}O did not provide improvement on the diastereoselectivity (77:23, entry 6), and in a mixed solvent system (THF/ether 1:6, entry 7) the reaction did not give any desired alkylation product suggesting ether is not an effective solvent for this asymmetric alkylation. This, however, is contradictory to previous literature reports.\textsuperscript{73,74} It is noteworthy that loss of diastereoselectivities were observed after these bis-alkylated amidines were purified though column chromatography (silica gel or Al\textsubscript{2}O\textsubscript{3}).
Table 4.5 Alkylation of Amidine 46

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>additive</th>
<th>temp 1</th>
<th>temp 2</th>
<th>% yield</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>No</td>
<td>0</td>
<td>0</td>
<td>55</td>
<td>75:25</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>No</td>
<td>-78</td>
<td>-78</td>
<td>53</td>
<td>76:24</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>Sparteine</td>
<td>-78</td>
<td>-78~25</td>
<td>n/a</td>
<td>82:18</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>Sparteine</td>
<td>-100</td>
<td>-100</td>
<td>n/a</td>
<td>75:25</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>TMEDA</td>
<td>-78</td>
<td>-78~25</td>
<td>53</td>
<td>81:19</td>
</tr>
<tr>
<td>6</td>
<td>Et₂O/THF</td>
<td>Sparteine</td>
<td>-78</td>
<td>-78~25</td>
<td>n/a</td>
<td>77:23</td>
</tr>
<tr>
<td>7</td>
<td>Et₂O/THF</td>
<td>TMEDA</td>
<td>-78</td>
<td>-78~25</td>
<td>0³</td>
<td>-</td>
</tr>
</tbody>
</table>

*Deprotonation were performed by 'BuLi (1.1 equiv) at the specified temperature in THF for 1h, the electrophile was added at the same temperature and the mixture was stirred for 5.5 h unless otherwise noted. ü Deprotonation for 3h. ² Diminished dr were obtained after column chromatography purification: entry1 (57:43), entry3 (70:30), entry6 (67:37). No desired product detected, unidentified byproducts were obtained.

Attempts for a Second Step Alkylation

Our attempts for a second step alkylation (¹BuLi and MeI in THF) were not successful, giving only recovered starting material with diminished diastereoselectivity (68:32, Scheme 4.16). This probably suggested the reaction was proceeded successfully with deprotonation and enolate formation, whereas the consequent alkylation of the enolate with electrophile failed.
Scheme 4.16 Attempted Second Step Alkylation

1. $^t$BuLi, THF, 0 °C, 1h
2. MeI, 0 °C
Summary

In conclusion, a facile (three steps) and efficient (65% over 3 steps) synthesis of enantioenriched mono-substituted bicyclic amidines was developed. Alkylation of these mono-substituted amidines provided bis-substituted bicyclic amidines in modest yields (55%) and with decent diastereoselectivities (88:12). These chiral bicyclic amidines may be used as organocatalysts for asymmetric addition such as acetoxybromination or halolactonization reactions based on our preliminary result from DBU and other literature reports. Successful alkylation of DBU in high yields (up to 88%) and with various alkyl (Me, Et and Bn) halides provides a promising methodology for the synthesis of multi-alkylated (e.g., bis and tri-substituted) chiral cyclic amidines.
**Experimental**

**General:** $^1$H NMR and $^{13}$C NMR spectra were recorded using JOEL (500 MHz) or Bruker (500 MHz) NMR spectrometers in CDCl$_3$. The $^1$H NMR chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (TMS) or CHCl$_3$ (δ = 7.26) as internal standard. The $^{13}$C NMR chemical shifts are reported as δ values in parts per million (ppm) downfield from TMS and referenced with respect to CDCl$_3$ signal (triplet, centerline δ = 77.00 ppm). Analytical thin layer chromatography (TLC) was performed on Scientific Adsorbents Inc. silica gel plates, 200 μ mesh with F$_{254}$ indicator. Visualization was accomplished by UV light (254 nm), and/or a 10% ethanol solution of phosphomolybdic acid or 5% aqueous potassium permanganate solution. Flash column chromatography was performed with 200-400 μ mesh silica gel or neutral aluminum oxide (Al$_2$O$_3$). Activated silica gel was prepared from 200-400 mesh silica gel washed with 5% Et$_3$N in petroleum ether. The isolated chemical yields are of materials isolated by flash column chromatography.

**Materials:** All reaction flasks were oven-heated over 12 hours prior to use. All reactions were conducted under positive argon atmosphere using flasks fitted with rubber septa and sealed with Parafilm™. -40 °C or lower reaction temperature was achieved by using cold bath prepared from dry-ice/isopropanol mixture. -100 °C Cold bath was made from diethyl ether/dry ice mixture. THF and diethyl ether were distilled from sodium benzophenone ketyl. Methanol was distilled from CaH$_2$. $N,N$-dimethyl formamide was
distilled from MgSO₄. Pyridine was dried over freshly baked molecular sieves (4A) for 24 hours prior to use. Other solvents including dichloromethane, toluene, etc were used as received. p-Toluenesulfonyl chloride (TsCl) was recrystallized from the commercial source before use. n-BuLi (2.5 M in hexanes) and t-BuLi (1.6 M in pentane) were commercially available and were titrated using s-BuOH and 1,10-phenanthroline monohydrate in THF prior to use.

**L-Valinol (35):** From an established procedure⁷⁵, L-valinol was prepared from L-valine in 81% yield: ¹H NMR (500 MHz, CDCl₃) δ 3.71 (dd, J = 11.0, 4.0 Hz, 1H), 3.38 (dd, J = 10.5, 9.0 Hz, 1H), 2.84 (s, 3H), 2.70-2.64 (m, 1H), 1.70-1.62 (m, 1H), 0.97 (d, J = 6.5 Hz, 3H), 0.96 (d, J = 7 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 64.7, 58.6, 31.6, 19.4, 18.5.

**(S)-2-(4-Methylphenylsulfonylamino)-1(4-methylsulfonyloxy)-3-methylbutane (39):** Employed an established procedure⁵³. In a 50 mL round bottom flask was placed L-valinol (515 mg, 5.0 mmol, 1.0 equiv) and pyridine (7.0 mL) was added. To the solution TsCl (2483 mg, 2.6 equiv) and dimethylaminopyridine (20 mg, 0.01 equiv) were added at 0 °C while stirring and the resulting solution was stirred for 24 hour before quenched with AcOH (1 mL) and diluted with water (20 mL). The aqueous phase was extracted with EtOAc (3 x 30 mL) and the combined organic layer was washed sequentially with water and brine before dried with MgSO₄, filtered, and concentrated in vacuo. Column chromatography (silica gel,
dichloromethane:petroleum ether, 40:60-75:25, v/v) afforded pure 39 (1.9 g, 92%) as white crystal: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.72 (dd, \(J = 12.5, 8\) Hz, 4H), 7.37 (d, \(J = 8.5\) Hz, 2H), 7.29 (d, \(J = 8\) Hz, 2H), 4.61 (s, 1H), 4.04 (dd, \(J = 10, 3.5\) Hz, 1H), 3.83 (dd, \(J = 10, 5\) Hz, 1H), 3.19-3.14 (m, 1H), 2.49 (s, 3H), 2.45 (s, 3H), 1.91-1.85 (m, 1H), 0.80 (d, \(J = 7\) Hz, 3H), 0.77 (d, \(J = 6.5\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 145.2, 143.6, 137.4, 132.3, 130.0, 129.7, 128.0, 127.1, 69.3, 57.7, 29.0, 21.7, 21.6, 18.9, 18.0.

(S)-N-(p-Toluenesulfonyl)-2-isopropylaziridine (40): Employed an established procedure\(^{76}\). Starting material 39 (600 mg, 1.5 mmol, 1.0 equiv) was dispersed in benzene (6 mL) and an aqueous KOH (2.4 mL, 20%) solution was added at room temperature. The resulting mixture was stirred at room temperature for 2 hours before was diluted with water (6 mL) and was extracted with EtOAc (3 x 30 mL). The combined organic phase was washed with water and brine, dried over MgSO\(_4\) and concentrated in vacuo to afford crude 40 (250 mg, 72%) as a powder. Crude 40 was used in the next step without any purification: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.76 (d, \(J = 8.3\) Hz, 2H), 7.27 (d, \(J = 8.3\) Hz, 2H), 2.55 (d, \(J = 7.4\) Hz, 1H), 2.47-2.42 (m, 1H), 2.38 (s, 3H), 2.03 (d, \(J = 4.6\) Hz, 1H), 1.38-1.30 (m, 1H), 0.83 (d, \(J = 6.9\) Hz, 3H), 0.72 (d, \(J = 6.9\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 144.6, 135.2, 129.7, 128.0, 46.4, 32.8, 30.2, 21.8, 19.7, 19.2.

1-(2S-p-Toluenesulfonylamino-3-methyl)-butylpyrrolidin-2-one (41): Employed an established procedure\(^{55}\). In a round bottom flask was placed 2-pyrrolidone (384 mg, 4.5
mmol, 2.5 equiv) and DMF (3 mL) was added to dissolve. While stirring, NaH (121 mg, 2.8 equiv) was added in one portion at room temperature and the mixture was stirred at 70 °C for 15 minutes before a solution of aziridine 40 (430 mg, 1.0 equiv) in DMF (5 mL) was added dropwise. The resulting solution was stirred at 70 °C for 12 hours and was cooled to room temperature whereupon water (10 mL) was added to quench. The aqueous layer was extracted with EtOAc (4 x 35 mL) and the organic layer was washed with brine, dried over MgSO₄ and concentrated in vacuo. Column chromatography (silica gel, MeOH:dichloromethane, 0-3%,v/v) afforded pure 41 (476 mg, 64%) as a white crystal: 

$^1$H NMR (500 MHz, CDCl₃) $\delta$ 7.76 (d, $J = 8.5$ Hz, 2H), 7.31 (d, $J = 8$ Hz, 2H), 5.31 (d, $J = 7$ Hz, 1H), 3.59 (dd, $J = 14$, 10.5 Hz, 1H), 3.39-3.32 (m, 1H), 3.23 (dd, $J = 6.5$, 6.5 Hz, 2H), 2.88 (dd, $J = 14.5$, 3.5 Hz, 1H), 2.44 (s, 3H), 2.31-2.24 (m, 1H), 2.15-2.08 (m, 1H), 1.93-1.84 (m, 2H), 1.69-1.62 (m, 1H), 0.84 (d, $J = 4.5$ Hz, 3H), 0.82 (d, $J = 4.5$ Hz, 3H); 
$^{13}$C NMR (125 MHz, CDCl₃) $\delta$ 176.8, 143.0, 138.6, 129.5, 127.0, 58.1, 47.9, 43.9, 31.3, 30.5, 21.5, 18.2, 17.9, 17.6.

1-(2S-p-Toluenesulfonylamino-3-methyl)-butylpiperidin-2-one (44): 44 was prepared using the same procedure for the preparation of 41: $^1$H NMR (500 MHz, CDCl₃) $\delta$ 7.74 (d, $J = 8.5$ Hz, 2H), 7.29 (d, $J = 6.5$ Hz, 2H), 5.85 (d, $J = 6$ Hz, 1H), 4.03 (dd, $J = 14$, 11 Hz, 1H), 3.41-3.35 (m, 1H), 3.18-3.07 (m, 2H), 2.64 (dd, $J = 14$, 3.5 Hz, 1H), 2.42 (s, 3H), 2.30 (dt, $J = 18$, 6 Hz, 1H), 2.15 (dt, $J = 18$, 6.5 Hz, 1H), 1.96-1.89 (m, 1H), 1.72-1.56
(m, 3H), 1.46-1.38 (m, 1H), 0.84 (d, J = 4.5 Hz, 3H), 0.82 (d, J = 4.5 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 172.1, 142.8, 138.7, 129.5, 127.0, 58.3, 48.6, 47.8, 32.0, 31.6, 22.6, 21.4, 20.7, 18.4, 17.5.

1-(2S-Amino-3-methyl)-butylpyrrolidin-2-one (42): Employed an established procedure$^{49,61}$. A 25 mL round bottom flask containing starting material 41 (433 mg, 1.0 equiv), PhOH (361 mg, 3.0 equiv) and HBr aqueous solution (6 mL, 48%) was heated to 130 °C in an oil bath. After 8 hours of refluxing the heat bath was removed and the reaction flask was cooled to 0 °C whereupon dichloromethane (15 mL) and 5% HCl (15 mL) were added. The aqueous phase was extracted with dichloromethane (2 x 25 mL) the combined organic phase was then washed 5% HCl (4 x 10 mL). The aqueous phases were combined and basified with KOH pellets until it became basic by pH strips, and was further extracted with dichloromethane (5 x 30 mL). All the organic phase was combined, washed with brine, dried over Na$_2$SO$_4$ and concentrated in vacuo to afford crude 42 (140 mg, 60%) as a yellow oil: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.51-3.32 (m, 3H), 3.11 (dd, J = 12, 6 Hz, 1H), 2.77 (dt, J = 9, 6 Hz, 1H), 2.41 (t, J = 9 Hz, 2H), 2.08-1.98 (m, 2H), 1.67-1.55 (m, 1H), 1.51 (s, 2H), 0.95 (d, J = 6 Hz, 3H), 0.92 (d, J = 6 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 175.8, 54.6, 48.0, 47.7, 31.8, 31.0, 19.4, 18.1, 17.0.

1-(2S-Amino-3-methyl)-butylpiperidin-2-one (45): 45 was prepared using the same procedure for the preparation of 42: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.52 (q, J = 9.2 Hz,
1H), 3.24 (t, J = 9.6, 1H), 3.07-3.02 (m, 1H), 2.78-2.70 (m, 2H), 2.42-2.35 (m, 1H), 2.29-2.23 (m, 1H), 1.76-1.50 (m, 6H), 0.96 (d, J = 6.9 Hz, 3H), 0.80 (d, J = 6.9 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 163.9, 70.0, 55.3, 48.4, 33.5, 26.3, 23.8, 22.5, 19.7, 18.7.

2-Piperidinethione (48): Employed an established procedure$^{77}$. In a 25 mL round bottom flask, 2-pyperidinone (100 mg, 1.0 equiv) and Lawesson’s reagent (242 mg, 0.6 equiv) was dissolved in THF (6 mL). The mixture was then heated to reflux on an oil bath for 1.5 hours before was cooled to room temperature. The solvent was removed by rotavapor and column chromatography (silica gel, EtOAc:Petroleum ether, 40:60,v/v) of the residue afforded pure 48 (120 mg, 95%) as a yellow solid: $^1$H NMR (500 MHz, CDCl$_3$) δ 9.05 (s, 1H), 3.31 (s, 2H), 2.84 (t, J = 6.0 Hz, 2H), 1.78-1.62 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 202.6, 44.8, 39.2, 20.8, 20.2.

2,3,4,5-Tetrahydro-6-(methylthio)-Pyridine (49): Employed an established procedure$^{78}$. To a 25 mL round bottom flask containing thiolactam (116 mg, 1.0 equiv) was added MeSO$_4$ (neat, 141 mg, 1.1 equiv) dropwise at 0 ºC. The mixture was stirred at room temperature for 24 hours before diluted with Et$_2$O (15 mL) and was washed with K$_2$CO$_3$ solution (20%,wt/wt, 3 x 15 mL) and brine. The organic phase was dried over Na$_2$SO$_4$, filtered and carefully concentrated in vacuo to afford crude 49 (85-92%) as a colorless oil. Crude 49 was used in the next step without any further purification: $^1$H NMR (500 MHz, CDCl$_3$) δ 3.60-3.57 (m, 2H), 2.24-2.20 (m,
2H), 2.20 (s, 3H), 1.68-1.62 (m, 2H), 1.61-1.55 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 165.8, 50.6, 31.5, 22.7, 20.2, 12.0.

2,3,4,5-Tetrahydro-6-methoxy-pyridine (49a): 2-Piperidinone (600 mg, 6.0 mmol, 1.0 equiv) was placed in a round bottom flask, and Me$_2$SO$_4$ (845 mg, 6.6 mmol, 1.1 equiv) was added neat at room temperature. The resulting mixture was stirred at room temperature for 24 hours before diluted with Et$_2$O (25 mL) and was washed with an aqueous K$_2$CO$_3$ solutions (20%, wt/wt, 3 x 15 mL) and brine. The organic phase was dried over Na$_2$SO$_4$, filtered and carefully concentrated in vacuo to afford crude 49a (585 mg, 86%) as a colorless oil. Crude 49a was used in the next step without any further purification: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.63 (s, 3H), 3.50 (t, $J$ = 6.5 Hz, 2H), 2.17 (t, $J$ = 6.5 Hz, 2H), 1.76-1.70(m, 2H), 1.60-1.53 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 162.9, 58.5, 51.8, 46.7, 25.8, 22.4, 20.3.

$N$-(1S-Hydroxymethyl-2-methylpropyl)-3,4,5,6-tetrahydro-2-pyridinamine (50)

Method A: Modified from an established procedure$^{10}$. In a 25 mL round bottom flask, starting material 49 (393 mg, 1.0 equiv) and L-valinol (309 mg, 1.0 equiv) was dissolved in dry DMF (3 mL). The mixture was heat to 80 °C on an oil bath for 12 hours before being cooled to room temperature. DMF was removed by a high vacuum pump and the residue was purified by column chromatography (neutral Al$_2$O$_3$, MeOH:dichloromethane, 3-10%, v/v) to afford pure 50 (180 mg, 32%) as a oil: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.14 (t, $J$ = 8.7 Hz, 1H),
3.86 (t, $J = 7.8$ Hz, 1H), 3.82-3.78 (m, 1H), 3.37 (s, 1H), 3.22 (s, 1H), 2.37-2.33 (m, 1H), 2.26-2.23 (m, 1H), 1.71-1.59 (m, 7H), 0.87 (d, $J = 6.4$ Hz, 3H), 0.79 (d, $J = 6.4$ Hz, 3H);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 167.4, 71.9, 69.9, 41.7, 32.6, 28.0, 27.4, 23.3, 18.9, 18.1.

Method B: starting material 49 (129 mg, 1.0 equiv) and L-valinol (103 mg, 1.0 equiv) were placed in a 7 mL glass vial. The mixture was then heated for 120-300 s in a experiment microwave oven at 70-90% power. The molar ratio of starting material and product was measured by $^1$H NMR.

$N$-($1S$-Hydroxymethyl-3-methylbutyl)-3,4,5,6-tetrahydro-2-pyridinamine hydrochloride (52a): Employed an established procedure$^{14}$. To a solution of Leucinol hydrochloride (308 mg, 1.0 equiv) in MeOH (2 mL) was added 49 (260 mg, 1.0 equiv). The mixture was stirred at room temperature for 24 hours and the solvent was removed by rotavapor to afford crude 52a as an oil. 52a was used in the next step without any further purification.

(S)-8-(2-Methylpropyl)-1,7-diazabicyclo[4,3,0]non-6-ene (46a)

Employed an existing procedure$^{14}$. In a 25 mL round bottom flask, starting hydrochloride 52a was dissolved in CHCl$_3$ (4 mL) and thionyl chloride (360 mg, 1.5 equiv) was added dropwise at 0 °C. The resulting mixture was heated to reflux for 1.5 hours and was cooled to 0 °C whereupon a few drops of MeOH were added to quench. The solvent was removed by
rotavapor, and an aqueous NaOH solution (10 mL, 20%, wt/wt) was added. The aqueous layer was extracted with dichloromethane (3 x 30 mL) and the combined organic phase was dried over Na$_2$SO$_4$ and concentrated in vacuo to afford an oil. EtOH (3 mL) was then added to this residue and the mixture was refluxed for 2 hours, basified with a NaOH solution (10 mL, 20%, wt/wt) and was extracted with dichloromethane (3 x 30 mL). The combined organic phase was dried over Na$_2$SO$_4$, filtered and concentrated in vacuo to afford crude 46a as an oil. Column chromatography (basic Al$_2$O$_3$, MeOH : dichloromethane, 1-2%, v/v) afforded pure 46a (270 mg, 75%) as a colorless oil: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.94-3.86 (m, 1H), 3.40 (t, $J = 9$ Hz, 1H), 3.11 (dt, $J = 11, 5.5$ Hz, 1H), 2.89-2.83 (m, 1H), 2.74 (t, $J = 9$ Hz, 1H), 2.46 (dt, $J = 16, 5.5$ Hz, 1H), 2.36-2.32 (m, 1H), 1.83-1.75 (m, 4H), 1.66-1.58 (m, 2H), 1.31-1.20 (m, 1H), 0.95 (d, $J = 6.5$ Hz, 3H), 0.93 (d, $J = 6.5$ Hz, 3H) $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 163.7, 61.3, 58.1, 48.2, 45.9, 26.2, 25.4, 23.7, 22.8, 22.7, 22.0.

(S)-8-i-Propyl-1,7-diazabicyclo[4,3,0]non-6-ene (46): 46 was prepared (61%) from the same procedure for the preparation of 46a from valinol hydrochloride:

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.58 (dt, $J = 9.5, 9.5$ Hz, 1H), 3.31 (t, $J = 9.5$ Hz, 1H), 3.12 (dt, $J = 10.5, 5$ Hz, 1H), 2.83-2.80 (m, 1H), 2.79 (t, $J = 9.5$ Hz, 1H), 2.49-2.42 (m, 1H), 2.38-2.29 (m, 1H), 1.82-1.76 (m, 3H), 1.72-1.56 (m, 2H), 1.03 (d, $J = 6.5$ Hz, 3H), 0.87 (d, $J = 6$ Hz, 3H) $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 163.7, 69.9, 55.1, 48.3, 33.3, 26.3, 23.8, 22.2, 19.5, 18.6.
Alkylation of DBU

**General procedure A.** DBU (3.04 g, 20 mmol, 1.0 equiv) was dissolved in dry THF (80 mL) in a 250 mL round bottom flask under argon and the solution was cooled to 0 °C in an ice bath where it was treated with t-BuLi (12 mL, 20 mmol, 1.0 equiv, 1.7 M in pentane) dropwise. The mixture was stirred at 0 °C for 1 hour before it was treated dropwise with BnCl (3.81 g, 30 mmol, 1.5 equiv), and the resulting solution was allowed to gradually warm up to room temperature over 12 hours where it was quenched with an aqueous NaOH solution (10 mL, 20%, wt/wt). The aqueous phase was extracted with dichloromethane (4 x 40 mL) and the combined organic phase was washed with brine (2 x 25 mL), dried over Na₂SO₄, and concentrated in vacuo to afford crude product 53 as a yellow/brown oil.

6-Benzyl-1,8-diazabicyclo[5.4.0]undec-7-ene 53a: Employing **General procedure A**, 53a was prepared from BnCl (2.0 equiv) as a yellow oil (88%) after column chromatography (neutral Al₂O₃, MeOH:dichloromethane, 0-10%, v/v): ¹H NMR (500 MHz, CDCl₃) δ 7.21-7.08 (m, 5H), 3.50 (dd, J = 15.2, 11 Hz, 1H), 3.37-3.31 (m, 1H), 3.27-3.11 (m, 4H), 2.84 (dd, J = 14.7, 4.6 Hz, 1H), 2.64 (t, J = 7.4 Hz, 1H), 2.49 (dd, J = 13.8, 10.5 Hz, 1H), 1.83-1.77 (m, 1H), 1.70-1.62 (m, 3H), 1.57-1.54 (m, 1H), 1.40-1.34 (m, 1H), 1.25-1.20 (m, 2H);

¹³C NMR (125 MHz, CDCl₃) δ 162.6, 141.8, 129.4, 128.2, 125.7, 51.9, 48.8, 44.5, 44.4, 38.6, 30.6, 28.6, 27.8, 22.7.
6-Ethyl-1,8-diazabicyclo[5.4.0]undec-7-ene (53b): Employing General procedure A, \( \text{53b} \) was prepared from EtI (1.5 equiv) as a yellow oil (75%): \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 3.39 (dd, \( J = 14.7, 9.2 \) Hz, 1H) 3.31-3.20 (m, 2H), 3.17-3.09 (m, 2H), 2.90 (dd, \( J = 14.7, 6.0 \) Hz, 1H), 2.19 (q, \( J = 7.4 \) Hz, 1H), 1.80-1.64 (m, 5H), 1.58-1.54 (m, 1H), 1.45-1.40 (m, 2H), 1.31-1.22 (m, 2H), 0.85 (t, \( J = 7.3 \) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 162.7, 51.8, 48.9, 45.8, 44.4, 31.5, 27.9, 27.8, 25.4, 22.7, 12.7.

6-Methyl-1,8-diazabicyclo[5.4.0]undec-7-ene (53c): Employing General procedure A, \( \text{53c} \) was prepared from MeI (1.5 equiv) as a yellow oil (60%): \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 3.46 (dd, \( J = 14.7, 10.6 \) Hz, 1H), 3.35-3.31 (m, 1H), 3.24-3.14 (m, 2H), 2.88 (dd, \( J = 15.1, 5 \) Hz, 1H), 2.58-2.52 (m, 1H), 1.82-1.74 (m, 2H), 1.69-1.58 (m, 3H), 1.53-1.44 (m, 1H), 1.42-1.33 (m, 2H), 1.08 (d, \( J = 6.9 \) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 163.7, 52.1, 48.9, 43.8, 37.7, 34.3, 28.4, 27.9, 22.3, 19.2.

General Procedure B: In a round bottom flask, 6-benzyl-1,8-diazabicyclo[4,3,0]undec-5-ene \( \text{53a} \) (242 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF (4 mL) and the solution was cooled to 0 °C in an ice bath where it was treated with \( t \)-BuLi (0.6 mL, 1.0 mmol, 1.0 equiv, 1.6 M in pentane) dropwise. The mixture was stirred at 0 °C for 0.5 hour before it was treated dropwise with the corresponding alkyl halide (1.5 mmol, 1.5 equiv), and the resulting solution was allowed to gradually warm up to room temperature.
over 12 hours where it was quenched with an aqueous KOH solutions (10 mL, 10%, wt/wt). The aqueous phase was extracted with dichloromethane (4 x 20 mL) and the combined organic phase was washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo to afford the crude product 55 as a yellow oil.

6-(1-Methylbenzyl)-1,8-diazabicyclo[5.4.0]undec-7-ene (57a): Employing General procedure B, compound 57a (324 mg, 51%) was prepared from MeI (1.5 equiv) as a yellow oil: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.37-7.23 (m, 5H), 4.31 (dd, J = 15.1, 12.4 Hz, 1H), 3.95-3.89 (m, 1H), 3.71-3.65 (m, 1H), 3.56 (dd, J = 15.1, 2.8 Hz, 1H), 3.49-3.39 (m, 3H), 3.00 (s, 3H), 2.76 (d, J = 13.3 Hz, 1H), 2.18-1.81 (m, 7H), 1.46 (d, J = 6.4 Hz, 3H), 1.35-1.28 (m, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 167.3, 142.5, 128.9, 128.0, 126.9, 56.0, 52.0, 49.9, 47.1, 43.1, 37.7, 26.7, 24.9, 22.8, 20.2, 18.6.

6-(1-Ethylbenzyl)-1,8-diazabicyclo[5.4.0]undec-7-ene (57b): Employing General procedure B, compound 57b (266 mg, 62%) was prepared from EtI (1.5 equiv) as a yellow oil: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.28-7.11 (m, 5H), 4.20 (dd, J = 14.2, 13.3 Hz, 1H), 3.91-3.86 (m, 1H), 3.71-3.64 (m, 2H), 3.48-3.44 (m, 2H), 3.33-3.12 (m, 2H), 2.92-2.87 (m, 1H), 2.80 (dd, J = 13.3, 1.8 Hz, 1H), 2.10-2.04 (m, 2H), 1.97-1.64 (m, 7H), 1.16 (t, J = 7.4 Hz, 3H), 1.18-1.14 (m, 1H), 0.72 (t, J = 7.4 Hz, 3H); <sup>13</sup>C NMR (125
MHz, CDCl3) $\delta$ 166.9, 139.8, 129.0, 128.0, 127.7, 55.3, 52.2, 50.3, 47.5, 45.5, 45.5, 26.7, 25.6, 25.0, 22.6, 20.4, 14.4, 12.1.

6-(1-Benzylbenzyl)-1,8-diazabicyclo[5.4.0]undec-7-ene (55b): Employing General procedure B, compound 55b (227 mg, 68%) was prepared from benzyl chloride (1.5 equiv) as a yellow oil: $^1$H NMR (500 MHz, CDCl3) $\delta$ 7.27-7.00 (m, 10H), 4.04 (s, 1H), 3.78 (t, $J = 14.2$ Hz, 1H), 3.33-3.00 (m, 4H), 2.92-2.78 (m, 2H), 2.17 (d, $J = 12.9$ Hz, 1H), 1.92-1.41 (m, 8H), 0.88-0.82 (m, 1H); $^{13}$C NMR (125 MHz, CDCl3) $\delta$ 166.1 (165.4), 139.4, 139.4 (138.9), 129.4, 129.1, 128.9, 128.5 (128.4), 128.2, (127.3, 126.5, 126.1), 53.7 (53.6), 50.1 (49.6), 48.2 (46.3), 44.3, 40.9 (40.6), 38.0 (36.5), (28.3) 27.5, (27.2) 26.0, 22.7 (20.7), 19.1.

(5R,8S)-5-Benzyl-8-iso-propyl-1,7-diazabicyclo[4.3.0]non-6-ene (59)

Deprotonation without sparteine or TMEDA:

Starting amidine 46 (166mg, 1.0 equiv) was dissolved in THF (4 mL) in a 25 mL round bottom flask and the mixture was cooled to -78 °C where it was treated with t-BuLi (0.78 mL, 1.1 equiv, 1.4 M in pentane) dropwise. The mixture was stirred at -78 °C for 1 hour before a solution of BnCl (2.0 equiv) in THF (2 mL) was added slowly and the solution was stirred for an additional 5.5 hours at -78 °C before an aqueous NaOH (10 mL, 20 %,wt/wt) solution was added, the aqueous phase was
extracted with dichloromethane (3 x 25 mL) and the combined organic phase was washed with brine (15 mL), dried over Na₂SO₄, and concentrated in vacuo to afford the crude product as an oil.

Asymmetric deprotonation of 46 and alkylation

Starting amine 46 (166 mg, 1.0 equiv) and sparteine/TMEDA (1.65 equiv) were dissolved in the specified solvent (4 mL) and the mixture was cooled to -78 °C (or -100 C) whereupon t-BuLi (0.78 mL, 1.1 equiv, 1.4 M in pentane) was added dropwise. The mixture was stirred at the same temperature for 1.5 hours before a solution of BnBr (2.0 equiv) in the same reaction solvent (2 mL) was slowly added at -78 °C (or – 100 °C). The mixture was stirred for 2 hours at the same temperature and was quenched with a aqueous NaOH (10 mL, 20 % wt/wt) solution, the aqueous phase was extracted with dichloromethane (3 x 25 mL) and the combined organic phase was washed with brine (15 mL), dried over Na₂SO₄, and concentrated in vacuo to afford the crude product 59 as an oil. Column chromatography (Silica gel, MeOH:dichloromethane 4:96-10:90, v/v) afford pure 59 (55%) as a colorless oil: ¹H NMR (500 MHz, CDCl₃) δ 7.21-7.11 (m, 5H), 3.66-3.59 (m, 1H), 3.42-3.32 (m, 1H), 3.23 (t, J = 9.15 Hz, 1H), 3.02-2.99 (m, 1H), 2.86-2.73 (m, 2H), 2.60-2.51 (m, 2H), 0.93 (d, J = 6.85 Hz, 3H), 0.81 (d, J = 6.85 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ (166.6)166.3, 140.3 (140.2), 129.4 (129.3), (128.4) 128.3, 126.1 (126.0), 69.8 (69.7), 54.9 (54.6), 48.7 (48.5), 38.4, 38.2 (37.7), 33.2 (33.1), 26.6 (25.7), 22.3 (21.2), (19.7) 19.5, 18.3 (18.0).
References


APPENDICES
Appendix A

$^1$H and $^{13}$C NMR Spectra for Chapter Two
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<td>NMR users</td>
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<td>[ppm]</td>
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<td>Site</td>
<td>Eclipse 500</td>
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<td>DELTA_NMR</td>
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<td>1.84305234 [s]</td>
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<td>X_pulse</td>
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<td>2 [us]</td>
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<td>1.0420224 [s]</td>
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<td>X_pulser</td>
<td>3.134666667 [us]</td>
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<td>Initial_wait</td>
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X : parts per Million : 13C
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NAME  diehy_1520_C
EXPMO  2
PROCNO  1

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Date  20090115
Time  13.49
INSTRUM  spect
PROBDH  5 mm PABBO BB-
FULTLROG  zopq30
TD  65356
SOLVENT  CDCl3
N1  506
CS  0
SN  0.00
SKH  30030.029 Hz
SIFRES  0.458222 Hz
AG  1.0912410 sec
KG  3251
DT  16.650 usec
DE  6.00 usec
TE  256.0 K
D1  2.00000000 sec
d11  0.03000000 sec
DELTAC  1.89999998 sec
MCREST  0.00000000 sec
MCNRK  0.01500000 sec

--------- CHANNEL f1 ---------
NUC1  13C
F1  9.00 usec
PL1  2.00 dB
SFO1  125.7703643 MHz

--------- CHANNEL f2 ---------
CFDPUG2  waltz16
NUC2  1H
FCDP2  70.00 usec
PL2  0.00 dB
PL12  14.96 dB
PL13  16.40 dB
SFO2  500.1320005 MHz

F2 - Processing parameters
ST  32768
SF  125.7977890 MHz
MW  EM
SB  0
LB  1.00 Hz
GB  0
PC  1.00
X : parts per Million : 1H

Field_strength = 11.7473579[T] (500[MHz])
Initial_wait = 1[s]

X.acq_duration = 3.5023408[s]
Phase_present = "[us]"

X.cdomin = "[us]"
Recvr_gain = 20

X.cfreq = 506.169915521[MHz]
Relaxation_delay = 2[s]

X.coffset = 5[ppm]
Temp.set = 25[OC]

X.points = 16164

X.precans = 0

X.resolution = 0.458221899[MHz]

X.sweep = 7.29750751[MHz]

CLipped = False

Mod.return = 2

Scaes = 8

Total_scans = 8

X.90_width = 12.1[us]

X.acq_time = 2.3823488[s]
X.angle = 45[deg]

X.pulse = 6.05[us]
huang_2102_A-5.pdf

Filename = huang_2102_A-5.pdf
Author = [Redacted]
Experiment = single_pulse.exp
Sample_Id = 1
Solvent = CHLOROFORUM-D
Creation_Time = 9-MAY-2010 11:26:46
Revision_Time = 9-MAY-2010 11:28:29
Current_Time = 9-MAY-2010 11:26:37
Current = Single Pulse Experime
Data_Format = 1D COMPLEX
Dim_Title = 1H
Dim_Units = [ppm]
Dimensions = X
Site = Eclipse+ 500
Spectrum = DELTA_NMR

Field_strength = 11.7473579[T] (500[MHz])
X_0xy_duration = 2.1833488[s]
X_domain = 1H
X_freq = 500.15991551[MHz]
X_offset = 5[ppm]
X_points = 15184
X_prescan = 0
X_resolution = 0.45822189[Hz]
X_sweep = 7.55750735[Hz]
Clipped = FALSE
Mod_return = 1
Scans = 0
Total_scans = 0
X.99_width = 12.1[us]
X_avg_time = 2.1833488[s]
X_angle = 45[deg]
X_pulse = 6.05[us]
huang_2023_P-4.jdf

31a

X: parts per Million : 1H

Filename = huang_2023_P-4.jdf
Author = NMR users
Experiment = single_pulse.exp
Sample_id = 1
溶剂 = CHLOROFORM-D
Creation_time = 2023-01-10 17:24:14
Revision_time = 2023-01-10 17:26:01
Current_time = 2023-01-10 17:36:03
Comment = Single Pulse Experiment
Data_format = 1D COMPLEX
Dim_site = 15361
Dim_title = 1M
Dim_units = [ppm]
Dimensions = X
Site = Eclipse+ 500
Spectrometer = DELTA NMR
Field_strength = 11.7473579(T) (500[MHz])
Initial_wait = 1[s]
Phase_preseq = 2[us]
Recvr_gain = 15
Relaxation_delay = 2[ms]
Temp_set = 22.1[°C]
clip = FALSE
Mod_return = 1
Scans = 8
Total_scans = 8
X_00_width = 12.1[us]
X_acq_time = 2.1824395[us]
X_angle = 45[deg]
X_pulse = 6.05[us]
huang_1497_B-4.jdf

32f

Filename = huang_1497_B-4.jdf
Author = MNR users
Experiment = single_pulse_dec
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Solvent = CHLOROFORM-D
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Revision_time = 10-DEC-2008 13:10:04
Current_time = 10-DEC-2008 13:10:05
Comment = Single Pulse with No X: parts per Million : 13C
Data_format = 1D COMPLEX
Dim_size = 127850
Dim_title = 13C
Dim_units = [ppm]
Dimensions = X
Site = Eclipse: 560
Spectrometer = DELTA_NMR
Field_strength = 11.7473579[T] (500[MHz]
X_acq_duration = 1.0420224[s]
X_domain = 13C
X_freq = 500.1891521[MHz]
X_offset = 5[ppm]
X_polarization = 4
X_resolution = 0.055673277[Hz]
X_sweep = 31.446540894[MHz]
X_domain = 8H
X_freq = 500.1891521[MHz]
X_offset = 5[ppm]
Clipped = FALSE
X_acq_time = 1.0420224[s]
X_angle = 10[deg]
X_pulse = 1.31666667[us]
Initial_wait = 1[s]
Phase_preset = 2[us]
Recov_delay = 10
Relaxation_delay = 1[s]
Temp_set = 22.1[OC]

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**X**: parts per Million : 13C

- **Filesize** = huang_1969_P-4.jpg
- **Author** = NMR users
- **Experiment** = single_pulse_dec
- **Sample_id** = 1
- **Solvent** = CHLOROPHYL
- **Creation_time** = 24-MAY-2018 11:01:19
- **Revision_time** = 24-MAY-2018 11:13:35
- **Current_time** = 24-MAY-2018 11:13:35
- **Comment** = Single Pulse with Bro
- **Data_format** = 1D COMPLEX
- **Exp_label** = 13C
- **Exp_units** = ppm
- **Dimensions** = X
- **Site** = Eclipse+ 500
- **Spectrometer** = DELTA

**Field_strength** = 11.7473579 [T] (500 [Hz])
**X_acq_time** = 1.0420234 [s]
**X_angle** = 10 [deg]
**X_pulse** = 3.16466669 [us]
**Initial_wait** = 5 [s]
**Phase_wait** = 31 [us]
**Recvr_gain** = 20
**Relaxation_delay** = 3 [s]
**Temp_set** = 21.5 [°C]
Current Data Parameters
NAME diehy_1884_crude
SFKNO 2
PROCMO 1
F2 - Acquisition Parameters
Date 20100107
Time 15.46
INSTRUM spect
PLOBD 5 mm PABBO SB-
FULPROG 2ppg3D
TD 65536
SOLVENT CDC13
NS 4848
DS 0
SWH 30030.028 Hz
FIDRES 0.458222 Hz
AQ 1.0912410 sec
RG 7298.2
DM 16.650 usec
DB 6.00 usec
TE 295.0 K
D1 2.000000000 sec
D11 0.03000000 sec
DELTA 1.85599998 sec
MCREST 0.00000000 sec
MCMRK 0.01500000 sec

------- CHANNEL f1 -------
NUC1 13C
P1 9.00 usec
PL1 2.00 dB
SF01 125.7703643 MHz

------- CHANNEL f2 -------
CPDPGR2 walt16
NUC2 1H
PCPD2 70.00 usec
PL2 0.00 dB
PL12 14.96 dB
PL13 16.40 dB
SF02 500.1320005 MHz

F2 - Processing parameters
SI 32768
SF 125.757890 MHz
SW 125.757890 MHz
GSB 0
LB 1.00 Hz
PB 0
PC 1.00
Appendix B

$^1$H and $^{13}$C NMR Spectra for Chapter Three
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Appendix C

$^1$H and $^{13}$C NMR Spectra for Chapter Four
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### Spectral Data

- **Field_strength**: 11.7473579 [T] (500 [MHz])
- **X_acq_duration**: 2.1023485 [s]
- **X_domain**: 2.0125763
- **X_freq**: 500.15991521 [MHz]
- **X_offset**: 5 [ppm]
- **X_points**: 16384
- **X_precession**: 0
- **X_resolution**: 0.45922299 [Hz]
- **X_sweep**: 7.50750751 [kHz]
- **Cliped**: FALSE
- **Mod_return**: 0
- **Source**: 8
- **Total_scans**: 8

**Additional Parameters**

- **Initial_wait**: 1 [s]
- **Phase_prerest**: 21 [us]
- **Recvr_pain**: 20
- **Relaxation_delay**: 24 [s]
- **Temp_set**: 31 [C]

---

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