Nickel-Catalyzed Coupling Reactions and Synthetic Studies toward ent-Dioxepandehydrothyrsiferol via an Epoxide-Opening Cascade

by

Sze-Sze Ng

B. S. with Honors, Chemistry
University of Texas at Austin, 2003

Submitted to the Department of Chemistry
in Partial Fulfillment of the Requirements
for the Degree of

DOCTOR OF PHILOSOPHY
IN ORGANIC CHEMISTRY

at the

Massachusetts Institute of Technology

June 2008

© 2008 Massachusetts Institute of Technology
All rights reserved

Signature of Author

______________________________________________________________

Department of Chemistry

April 25, 2008

Certified by ____________________________

Timothy F. Jamison
Associate Professor of Chemistry
Thesis Supervisor

Accepted by ____________________________________________

Robert W. Field
Chairman, Department Committee on Graduate Students
This doctoral thesis has been examined by a committee in the Department of Chemistry as follows:

Professor Mohammad Movassaghi  ________________________________________________ Chairman

Professor Timothy F. Jamison _____________________________________________________ Thesis Supervisor

Professor Gregory C. Fu __________________________________________________________
To my family and David
ABSTRACT

Nickel-Catalyzed Coupling Reactions


Most asymmetric transition metal-catalyzed methods of preparing enantiomerically enriched allylic alcohols rely on chiral ligands. The nickel-catalyzed allene–aldehyde coupling exploits the axial chirality in 1,3-disubstituted allenes in achieving asymmetric induction. When a chiral allene binds to a transition metal catalyst, the allene establishes a chiral environment around the metal center. This can possibly create a new stereocenter in a coupling product. Indeed, enantiomerically enriched allenes couple with aromatic aldehydes and triethylsilane in the presence of a nickel-carbene catalyst to provide selectively a Z-allylic alcohol with an enantiomeric excess identical to that of the starting chiral allene (eq 1).

\[
\begin{align*}
\text{H} & \rightleftharpoons \text{H} & \text{Ar} & \text{O} & \text{H} & \text{Ni} & (\text{cod})_2 & \text{IPr} & \text{Et}_3 & \text{Si} & \text{H} & \text{Ar} & \text{OSi} & \text{Et}_3 & \text{R}^2 \\
\text{R}^1 & \rightleftharpoons \text{R}^2 & & & & & & & & & & & & & & (1)
\end{align*}
\]

There is considerable interest to prepare allylic alcohols from simple alkenes because of their wide availability and ease of handling, as compared to alkenyl metal reagents, which are most commonly used to obtain allylic alcohols. It was reported in literature that a nickellacycle could be obtained from a mixture of nickel, \(\alpha,\omega\)-enal, and a silyl triflate. Under appropriate conditions, \(\beta\)-hydride elimination could occur to provide an allylic alcohol product. The nickel(0) catalyst could be regenerated in the presence of a base. Ethylene and terminal alkenes are appropriate substrates for this transformation (eqs 2 and 3). Either allylic or homoallylic alcohol product can be obtained from terminal alkenes by using appropriate ligands for the nickel catalyst (eq 3).
Synthetic studies of ent-dioxepandehydrothyrsiferol via an Epoxide-Opening Cascade

Dioxepan-dehydrothyrsiferol is a marine polycyclic ether natural product isolated from the red algae Laurencia viridis. Synthesis of the fused six-seven-seven cyclic ether in ent-dioxepan-dehydrothyrsiferol through an epoxide-opening cascade strategy was explored. Formation of the strained tetrahydropyran ring in ent-dioxepan-dehydrothyrsiferol directly from an epoxide-opening cascade of triepoxide allylic alcohol proved to be difficult. Alternatively, a δ-lactone was obtained using an epoxide-opening cascade of triepoxide tert-butyl ester. The furan side chain was installed via a Suzuki coupling.

Thesis Supervisor: Timothy F. Jamison

Title: Associate Professor of Chemistry
PREFACE

Portions of this thesis have appeared in the following articles that were co-written by the author, and are reproduced in part with permission from:


Part of the nickel-catalyzed alkene–aldehyde coupling was contributed by Dr. Chun-Yu Ho.

Part of the synthesis of *ent*-dioxpendehydrothrysiferol was contributed by Jessica Tanuwidjaja.

X-ray crystal structure data was collected by Dr. Peter Müller.

ORTEP diagrams were generated by Dr. David Laitar.
ACKNOWLEDGMENTS

Five years in graduate school have gone by quickly, I owe the following people who trained me to be an organic chemist.

Working with Professor Bimal Banik was my first opportunity to connect textbook chemistry to real synthetic problem in the laboratory and he sparked my interest in organic chemistry.

Professor Michael Krische was my inspiring undergraduate research advisor whom I admired and I always think of him as one of my role models.

Professor Timothy Jamison influenced me most as my academic and career advisor. He has been very liberal and always encouraging in letting me explore my projects in anyway I determined reasonable. My ideas were not always bright but he always provided guidance when I needed it. One most important lesson I learnt working with Tim was to be objective and not to give up easily. Try everything possible and anything that seemed unlikely but somehow still have 1% chance that it would work. Never assume a theory was wrong until proven by an experiment. Tim was also kind and funny. Every once in a while he would have a comment that made my day. He also cared very much about my career development. He has given me every opportunity to meet and talk to chemists working in industry through fellowship conferences.

In Tim’s lab I also had the opportunity to learn from skillful senior chemists (Carmela Molinaro, Johann Chan, Betsy Colby, Tim Heffron, Karen Miller, Sejal Patel, Chudi Ndubaku, Ryan Moslin, Neil Langille, Jason Ho and others). Their experience and tricks were passed along to others and me and will be passed along for generations of chemists to come in Tim’s lab.

Professor Gregory Fu and Professor Mohammad Movassaghi were both insightful and provided honest opinions and suggestions for my thesis over the years.

I also had the opportunity to work with Jason Chun-Yu Ho, who is now a professor in the Chinese University of Hong Kong. I have learnt a great deal of practical organic chemistry skills from him. He has contributed immensely in the development of nickel-catalyzed coupling of alkenes and aldehydes and has provided insightful interpretation of experimental data. I also want to mention that he is a true master of column chromatography.

And to all of you working with me in the lab (Jeff Byers, Lucas Brändli, Victor Gehling, Andrew Lauer, Aaron Van Dyke, Kristin Schleicher, Brian Underwood, Ivan Vilotijevic, Chris Morten, Jessica Tanuwidjaja, Brian Sparling, and Ngan Nguyen). Even though most of you do not work in my project you have helped by giving me constructive comments throughout the way. Jokes and all the mess-ups we came up with every day were part of my experience to become a better chemist! I also wish Jessica success in her upcoming projects after working with me for one semester. She has been careful and productive in her work and has made significant contribution to our project.

To my family, their financial support for my education was a tremendous help. They also taught me to be independent. And David Laitar, from whom I found companionship and
happiness when I was in graduate school. He has brought me excitement every day. David is also a gifted chemist; I admire his intellect and his dedication to perfection in everything he does.
# TABLE OF CONTENTS

**Abbreviations.**

---

### Chapter 1. Nickel-Catalyzed Reductive Coupling of Allenes and Aldehydes.  
13

- Introduction 14
- Nickel-Catalyzed Reductive Coupling Reactions 14
- Proposed Nickellacycle Intermediate in Nickel-Catalyzed Reductive Coupling Reactions 15
- Evaluation of Experimental Parameters 17
- Deuterium Labeling Experiment 31
- References 33
- Experimental Section 37
- $^1$H NMR and $^{13}$C NMR Spectra 63

### Chapter 2. Nickel-Catalyzed Coupling of Alkenes, Aldehydes and Silyl Triflates.  
97

- Introduction 98
- Nickel-Catalyzed Coupling of Ethylene and Aldehydes 101
- Ligand-Dependent Regioselectivity in the Coupling of Terminal Alkenes and Aldehydes 103
- Effects of the Base 107
- Source of Nickel 110
- Substrate Scope 111
- Discussion 120
- References 130
- Experimental Section 135
- $^1$H NMR and $^{13}$C NMR Spectra 181

### Chapter 3. Synthetic Studies toward ent-Dioxepeatrothyrsiferol via an Epoxide-Opening Cascade.  
237

- Introduction 238
- Evaluation of Epoxide-Opening Substrates 250
- Synthesis of the Tricyclic Ether Fragment via an Epoxide-Opening Cascade 258
- Coupling of the Tricyclic Ether Fragment with the Tetrahydrofuran Fragment 262
- Installation of a Bromine Atom to the Terminal Oxepane 271
- References 275
- Experimental Section 279
- $^1$H NMR and $^{13}$C NMR Spectra 315

---

**Curriculum Vitae.**  
369
ABBREVIATIONS

Ac   acetyl
Acac acetoacetate
Anis anisyl (methoxy-phenyl)
Ar aryl
atm atmospheres
BBN 9-borabicyclo[3.3.1]nonane
BINAP 2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
Bn benzyl
Boc tert-butoxy carbonyl
BRSM based on recovered starting material
Bu butyl
°C degree (Celsius)
cat. catalytic
cod cyclooctadiene
COSY correlated spectroscopy
Cp cyclopentadiene
CSA camphorsulfonic acid
Cy cyclohexyl
Cyp cyclopentyl
δ chemical shift in parts per million
DBU 1,8-diazabicyclo[5.4.0]-7-undecene
DCC dicyclohexylcarbodiimide
DCM dichloromethane
DEAD diethylazodicarboxylate
DET diethyltartrate
DHF dihydrofuran
DHP dihydropyran
DIBAL diisobutylaluminum hydride
DMA dimethylacetamide
DMAP 4-dimethylaminopyridine
DMF N,N’-dimethylformamide
DMI 1,3-dimethyl-2-imidazolidinone
DMM dimethoxy methane
DMP Dess Martin periodinane
DMPU 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO dimethyl sulfoxide
dr diastereomeric ratio
ee enantiomeric excess
ESI electron spray ionization
Et ethyl
Et3B triethylborane
EtO ethoxy
Et2O diethylether
EtOAc ethyl acetate
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyr</td>
<td>pyridine</td>
</tr>
<tr>
<td>R</td>
<td>any substituents</td>
</tr>
<tr>
<td>sat.</td>
<td>saturated</td>
</tr>
<tr>
<td>SiO₂</td>
<td>silica gel</td>
</tr>
<tr>
<td>t&lt;sub&gt;R&lt;/sub&gt;</td>
<td>retention time</td>
</tr>
<tr>
<td>t&lt;sup&gt;-Bu&lt;/sup&gt;</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>temp</td>
<td>temperature</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyl dimethylsilyl</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TES</td>
<td>triethylsilyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>tetrahydropyran</td>
</tr>
<tr>
<td>TIPS</td>
<td>triisopropylsilyl</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>Ts</td>
<td>tosyl</td>
</tr>
<tr>
<td>TsOH</td>
<td>para-toluenesulfonic acid</td>
</tr>
<tr>
<td>wt</td>
<td>weight</td>
</tr>
</tbody>
</table>
Chapter 1

Nickel-Catalyzed Reductive Coupling of Allenes and Aldehydes
Introduction

Nickel-Catalyzed Reductive Coupling Reactions

While palladium is far more popular than nickel in cross coupling reactions such as Suzuki coupling, nickel is more often used in the intermolecular coupling of two different unsaturated functional groups (such as an alkyne and an aldehyde) in the presence of a reducing agent (reductive coupling, Scheme 1).\(^1\)\(^2\) In the presence of a catalytic amount of nickel and a reducing agent, a carbon–carbon bond is formed between an electron-rich component (e.g. alkyne, 1,3-enyne, 1,3-diene, allene, etc.) and an electrophilic component (e.g. aldehyde, epoxide, enone, etc.). Some of these couplings are summarized in Table 1. A commonly proposed mechanism for these reductive couplings involves oxidative cyclization, sigma bond metathesis, and reductive elimination (Scheme 1).

Scheme 1

![Scheme 1 Diagram](image-url)
These nickel-catalyzed coupling reactions have advantages over existing methods. In a single operation simple functional groups such as an alkyne are added directly to an electrophile. This one-step protocol is more convenient as compared to a more traditional approach, which would involve hydrometallation of an alkyne followed by addition of the alkenyl metal to an aldehyde. The nickel-catalyzed reductive coupling approach is also generally more convenient than preparing the corresponding Grignard reagent and adding it to the desired electrophiles. Finally, the use of nickel in the presence of a chiral ligand also provides enantiomerically enriched coupling product in many cases.

Table 1. Examples of Nickel-Catalyzed Reductive Coupling Reactions

<table>
<thead>
<tr>
<th>electron-rich function group</th>
<th>electrophilic functional group</th>
<th>reducing agent</th>
<th>product examplea</th>
<th>referenceb</th>
</tr>
</thead>
<tbody>
<tr>
<td>alkyne</td>
<td>aldehyde</td>
<td>Et3B</td>
<td>OR</td>
<td>2c, 2d*, 2e*</td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>Et3SiH</td>
<td></td>
<td>2f, 2g*</td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>CrCl2</td>
<td></td>
<td>2h</td>
</tr>
<tr>
<td>&quot;</td>
<td>epoxide</td>
<td>Et3B</td>
<td>OR</td>
<td>2i</td>
</tr>
<tr>
<td>1,3-ene</td>
<td>aldehyde</td>
<td>Et3B</td>
<td></td>
<td>2j, 2k*</td>
</tr>
<tr>
<td>&quot;</td>
<td>epoxide</td>
<td>Et3B</td>
<td></td>
<td>2j</td>
</tr>
<tr>
<td>1,3-diene</td>
<td>aldehyde</td>
<td>Et2Zn</td>
<td></td>
<td>2i</td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>Et3B</td>
<td></td>
<td>2i</td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>Et3SiH</td>
<td></td>
<td>2l, 2m*</td>
</tr>
</tbody>
</table>

*a Dashed line indicates the site of carbon–carbon bond formation. b asterisk indicates a reference to the asymmetric version.
Proposed Nickellacycle Intermediate in Nickel-Catalyzed Reductive Coupling Reactions

A commonly proposed mechanism for nickel-catalyzed reductive couplings involves a nickellacycle intermediate (Scheme 1). A nickellacycle can be obtained from oxidative addition of two \( \pi \) ligands to a Ni(0) species (Scheme 2). This step is termed oxidative cyclization or oxidative coupling. Oxidative cyclization can occur between two identical \( \pi \) ligands or two different \( \pi \) ligands. For example, two cyclopropenes can add to nickel to form a nickellacyclopentane. Coupling of 1:1 mixture of ethylene and carbon dioxide with nickel afforded a nickellalactone. Coupling of butyne and benzaldehyde yielded a nickelladihydrofuran. Nickellacycle formation is a fundamental concept in nickel chemistry and has been proposed in many nickel-catalyzed reactions. Examples are [2+2] cycloaddition of alkene, cyclotrimerization of alkyne, as well as nickel-catalyzed reductive coupling reactions.

\[ \text{Scheme 2} \]

\[ \begin{align*}
\text{\( \pi \) ligand A} & \quad + \quad \text{\( \pi \) ligand B} & \xrightarrow{\text{Ni(0)Ln}} & \text{nickellacycle} \\
\text{example: (A \neq B)} & \quad \text{Me} \quad \text{Me} & + & \quad \text{Me} \quad \text{Me} & \xrightarrow{\text{Ni(0)Ln}} & \text{Me} \quad \text{Me} \\
\text{example: (A \neq B)} & \quad \text{H}_2\text{C}=\text{CH}_2 & + & \quad \text{CO}_2 & \xrightarrow{\text{Ni(0)Ln}} & \text{Me} \quad \text{Me} \\
\text{example: (A \neq B)} & \quad \text{Me} \quad \text{Me} & + & \quad \text{Ph} \quad \text{H} & \xrightarrow{\text{Ni(0)Ln}} & \text{Me} \quad \text{Me} \\
\text{example: (A \neq B)} & \quad \text{Me} \quad \text{Me} & + & \quad \text{Ph} \quad \text{H} & \xrightarrow{\text{Ni(0)Ln}} & \text{Me} \quad \text{Me} \\
\text{example: (A \neq B)} & \quad \text{Me} \quad \text{Me} & + & \quad \text{Ph} \quad \text{H} & \xrightarrow{\text{Ni(0)Ln}} & \text{Me} \quad \text{Me} \\
\end{align*} \]
In the case of a nickel-catalyzed reductive coupling, the proposed oxidative cyclization step typically involves oxidative addition of an electron-rich \( \pi \) component (e.g. alkyne, enyne, allene, etc.) and an electrophilic \( \pi \) component (e.g. aldehyde, enone, carbon dioxide etc.) and would result in a Ni(II) nickellacycle intermediate.\(^2\) To regenerate the Ni(0) catalyst the Ni(II) nickellacycle needs to be reduced. Nickellacycle is known to undergo reactions such as \( \beta \)-hydride elimination, reductive elimination, and sigma bond metathesis (see Scheme 1 for an example).\(^4k,6\) In a typically proposed mechanism of nickel-catalyzed reductive coupling, formation of nickellacycle is always followed by a sigma bond metathesis. Triethylborane, alkylsilanes, and diethylzinc are the most common reagents to promote sigma bond metathesis in nickel-catalyzed reductive coupling.\(^2\) Study by Mori and Sato on their nickel-catalyzed coupling of 1,3-dienes and aldehydes supported this mechanism.\(^6f,6g\) Ogoshi has recently isolated a nickelladihyrofuran from an oxidative cyclization of nickel with butyne and benzaldehyde (Scheme 2).\(^4k\) This nickelladihydrofuran could be reduced by dimethylzinc to yield a butyne–benzaldehyde reductive coupling product, again consistent with the standard proposed mechanism.

*Transition-Metal Catalyzed Allene–Aldehyde Couplings.*

Prior to our studies, the majority of intramolecular and intermolecular reactions of simple allenes and aldehydes involved the union of one of the sp\(^2\)-hybridized carbons of the allene with the carbonyl group of the aldehyde, affording homoallylic alcohols in the case of multi-component coupling reactions\(^9,10,11\) and, in allenylmetal addition reactions, homopropargylic alcohols.\(^12\) With enantiomerically enriched allenylmetal reagents, enantiomerically enriched homopropargylic alcohols can be obtained.\(^12c,12d\) Highly enantioselective transition metal-
catalyzed coupling of simple unactivated allenes with aldehydes was not available. Only one attempt has been reported, with enantiomeric excess less than 24%.\textsuperscript{10c,10i}

Our nickel-catalyzed allene–aldehyde coupling is unique from existing methods and addressed the enantioselectivity problems as mentioned above. Enantiomerically enriched allylic alcohols were obtained with the same enantiomeric excess as the starting allenes via a chirality transfer process.\textsuperscript{13,14}

**Evaluation of Experimental Parameters.**

Triethylborane (Et\textsubscript{3}B) and alkylsilanes are functional group-tolerant reducing agents in several nickel-catalyzed reactions, such as reductive coupling reactions of a diene, an alkyne, or an enyne with an aldehyde, ketone, or epoxide.\textsuperscript{2} Thus the development of a reductive coupling reaction between an allene and an aldehyde commenced with evaluation of these reducing agents. A mixture of cyclohexylallene (1\textsubscript{a}), aldehyde, Ni(cod), tricyclopentylphosphine, and a reducing agent provided two major coupling products 2 and 3 (Table 2).

The nickel-catalyzed allene–aldehyde coupling displayed reducing agent-dependent regioselectivity. With triethylborane as the reducing agent, allylic alcohol 2\textsubscript{a} predominated over 3\textsubscript{a} in the coupling of allene 1\textsubscript{a} and isobutyraldehyde (Table 2, entry 1). Switching the reducing agent from triethylborane to triethylsilane (Et\textsubscript{3}SiH) afforded geminally disubstituted allylic ether 3\textsubscript{b} as the exclusive three-component coupling product, along with products corresponding to hydrosilylation of the allene (entry 2). Trisubstituted allylic ether 2\textsubscript{b} was not observed in the NMR spectrum of the crude reaction mixture. Several commercially available silanes were examined next. tert-Butyldimethylsilane (t-BuMe\textsubscript{2}SiH) provided a similar yield of 3\textsubscript{c} (entry 3). Triisopropylsilane (i-Pr\textsubscript{3}SiH) afforded 3\textsubscript{d} only upon heating (entry 4). Under similar conditions
other common silanes did not provide 3 in significant yields. Since regioselectivity was excellent with a silane as the reducing agent, alkylsilanes were used in further evaluation of the nickel-catalyzed allene–aldehyde coupling.

### Table 2. Reducing Agent-Dependent Regioselectivity

<table>
<thead>
<tr>
<th>entry</th>
<th>reducing agent</th>
<th>R¹</th>
<th>yield (%)a,b</th>
<th>2:3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Et₃B</td>
<td>i-Pr</td>
<td>50</td>
<td>89:11 (R² = H) (2a:3a)</td>
</tr>
<tr>
<td>2</td>
<td>Et₃SiH</td>
<td>i-Pr</td>
<td>51</td>
<td>5:95 (R² = Et₃Si) (2b:3b)</td>
</tr>
<tr>
<td>3d</td>
<td>t-BuMe₂SiH</td>
<td>i-Pr</td>
<td>53</td>
<td>5:95 (R² = t-BuMe₂Si) (2c:3c)</td>
</tr>
<tr>
<td>4e/f</td>
<td>t-Pr₂SiH</td>
<td>Cy</td>
<td>24</td>
<td>5:95 (R² = t-Pr₂Si) (2d:3d)</td>
</tr>
</tbody>
</table>

a General procedure: To a solution of Ni(cod)₂ (10 mol%) and Cyp₃P (10 mol%) were added the reducing agent (200 mol%) and the aldehyde (200 mol%). Allene 1a (100 mol%) in THF was added to the reaction mixture over 8 to 12 h. The reaction mixture was stirred 18 h at room temperature. b Isolated yield. c Ni(cod)₂ (20 mol%) and Cyp₃P (40 mol%) were used. d Cyp₃P (20 mol%) were used. e The reaction was heated to 50 °C in toluene. f 300 mol% of reducing agent was used.

Solvent and ligand effects were briefly examined in the nickel-catalyzed coupling of allene 1a and isobutyraldehyde (Table 3). While toluene, ethyl acetate (EtOAc), and methanol (MeOH) could also be used (entries 4-8), tetrahydrofuran (THF) was the most suitable solvent for this coupling reaction (entries 2-3). The nickel/ligand ratio was also found to be an important variable. The reductive coupling afforded less than 5% allylic ether 3b without a supporting ligand (entry 1). A 1:1 ratio of Ni(cod)₂ and tricyclopentylphosphine (Cyp₃P) was optimal, regardless of the choice of solvent (entries 2, 4, 6, 8). Only bulky, electron-rich, and monodentate phosphines such as Cyp₃P and Cy₃P were compatible ligand for the nickel-catalyzed allene–aldehyde coupling. Smaller and bidentate phosphines afforded only a trace amount of coupling products. The N-heterocyclic carbene IPr, which is also a bulky and
electron rich monodendate ligand, was also an excellent ligand but only with aromatic aldehydes (vide infra). The yield of the coupling product could be increased further simply by using a greater amount of aldehyde and silane (Table 4).

Table 3. Evaluation of Solvents and Ligand Ratios

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand (mol%)</th>
<th>solvent</th>
<th>yield (%) a, b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>THF</td>
<td>&lt;5</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>THF</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>THF</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>EtOAc</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>EtOAc</td>
<td>21</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>MeOH</td>
<td>36</td>
</tr>
<tr>
<td>7</td>
<td>20</td>
<td>MeOH</td>
<td>27</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>toluene</td>
<td>46</td>
</tr>
</tbody>
</table>

a General procedure: To a solution of Ni(cod)₂ (10 mol%) and Cy₃P were added Et₂SiH (200 mol%) and the aldehyde (200 mol%). Allene 1a (100 mol%) in THF was added to the reaction mixture over 4 h. The reaction mixture was stirred 18 h at room temperature. b Isolated yield.
Table 4. Nickel-Catalyzed Reductive Coupling of Terminal Allenes with Aldehydes

\[
\begin{align*}
R^1 & \quad \rightarrow \quad R^2 \quad \rightarrow \quad R_3 \text{SiH} \\
\text{Ni(cod)}_2 & \quad \text{Cyp}_3 \text{P} \\
\text{THF} & \quad \rightarrow \\
R^1 & \quad \text{OSiR}_3
\end{align*}
\]

1a: R\(^1\) = Cy, R\(^2\) = H  
1b: R\(^1\) = R\(^2\) = n-C\(_3\)H\(_{11}\)  
1c: R\(^1\) = Ph, R\(^2\) = H

<table>
<thead>
<tr>
<th>entry</th>
<th>allene</th>
<th>aldehyde</th>
<th>silane</th>
<th>product</th>
<th>yield (%) (^{a,b})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>i-Pr</td>
<td>Et(_3)SiH</td>
<td><img src="image" alt="Structure" /></td>
<td>3b</td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>&quot;</td>
<td>t-BuMe(_2)SiH</td>
<td><img src="image" alt="Structure" /></td>
<td>3c</td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>Cy</td>
<td>Et(_3)SiH</td>
<td><img src="image" alt="Structure" /></td>
<td>3e</td>
</tr>
<tr>
<td>4</td>
<td>&quot;</td>
<td>&quot;</td>
<td>t-BuMe(_2)SiH</td>
<td><img src="image" alt="Structure" /></td>
<td>3f</td>
</tr>
<tr>
<td>5</td>
<td>&quot;</td>
<td>&quot;</td>
<td>i-Pr(_3)SiH</td>
<td><img src="image" alt="Structure" /></td>
<td>3d</td>
</tr>
<tr>
<td>6</td>
<td>&quot;</td>
<td>Ph</td>
<td>t-BuMe(_2)SiH</td>
<td><img src="image" alt="Structure" /></td>
<td>3g</td>
</tr>
<tr>
<td>7</td>
<td>1b</td>
<td>i-Pr</td>
<td>t-BuMe(_2)SiH</td>
<td><img src="image" alt="Structure" /></td>
<td>3h</td>
</tr>
<tr>
<td>8</td>
<td>&quot;</td>
<td>Cy</td>
<td>&quot;</td>
<td><img src="image" alt="Structure" /></td>
<td>3i</td>
</tr>
<tr>
<td>9</td>
<td>&quot;</td>
<td>n-Bu</td>
<td>&quot;</td>
<td><img src="image" alt="Structure" /></td>
<td>3j</td>
</tr>
<tr>
<td>10</td>
<td>1c</td>
<td>Ph</td>
<td>&quot;</td>
<td><img src="image" alt="Structure" /></td>
<td>3k</td>
</tr>
</tbody>
</table>

\(^a\) General procedure: See experimental section. \(^b\) Isolated yield. \(^c\) Heated to 50 °C in toluene. \(^d\) Cyp\(_3\)P was replaced by iPr. \(^e\) Cyp\(_3\)P was employed as the ligand. Yield was determined by NMR of the crude mixture versus DMF as an external standard.
The scope of nickel-catalyzed reductive coupling of allenes and aldehydes was also evaluated. The catalyst system derived from Ni(cod)$_2$ and Cyp$_3$P promoted the coupling of allenes 1a, 1b and 1c with various aliphatic aldehydes in good yield and excellent regioselectivity when a trialkylsilane (Et$_3$SiH or t-BuMe$_2$SiH) was employed as a reducing agent (Table 4). In all cases, carbon–carbon bond formation occurred at the sp–hybridized carbon (rather than the sp$^2$–hybridized carbons) of the allenes (regioselectivity). Homoallylic alcohol products were not observed in any case. The more hindered double bond reacted with the aldehyde, rather than the less substituted double bond in all cases as well (entries 1-10). This site selectivity was not affected by the steric bulk around the allene. Allene 1b, possessing two geminal alkyl substituents, also underwent coupling with aliphatic aldehydes with the same sense of site selectivity as 1a and 1b (Table 3, entries 7–9).

The size of the silane affected the yield of the coupling product significantly. Switching from t-BuMe$_2$SiH to Et$_3$SiH lowered the yield substantially (Table 3, entries 1–4) due to competing hydrosilylation of the allene; more hydrosilylation of allene was observed in the latter case. This phenomenon might be related to the relative size of those two organosilanes. Triisopropylsilane (i-Pr$_3$SiH), however, appeared to be too bulky for either the coupling or hydrosilylation to occur efficiently (entry 5).

Coupling of allene 1a and 1c with aromatic aldehyde such as benzaldehyde proceeded with higher yield when IPr was used as ligand instead of Cyp$_3$P (entries 6, 10). N-heterocyclic carbene IPr also seemed to limit oligomerization of allene better than Cyp$_3$P. With Cyp$_3$P as the supporting ligand, oligomerization of 1c was pronounced, and 3k was obtained in only 5% yield (entry 10). Nevertheless, this problem was alleviated when Cyp$_3$P was replaced by IPr (entry 10), and the same regioselectivity and site selectivity was observed as with Cyp$_3$P.
The nickel-catalyzed reductive coupling of allenes and aldehydes provides a method for obtaining allylic alcohols that complements Grignard reactions between alkenyl magnesium halides and aldehydes. One example clearly demonstrated this feature of the nickel-catalyzed coupling was the synthesis of epoxy allylic alcohol 3l (Scheme 3).\textsuperscript{17a} It was reported by Forsyth that \(\gamma\)-epoxy aldehyde cannot react with propenyl magnesium bromide to yield the corresponding allylic alcohol product.\textsuperscript{17b} On the other hand, \(\gamma\)-epoxy aldehyde derived from farnesol coupled with allene 1d to provide epoxy allylic ether 3l in reasonable yield when a stoichiometric amount of nickel was used.\textsuperscript{17c}

Scheme 3

A few chiral ligands (4a-4e) were evaluated for enantioselectivity in the nickel-catalyzed allene–aldehyde coupling (Scheme 4). In the coupling of cyclohexyllallene and benzaldehyde, chiral \(N\)-heterocyclic carbenes 4a and 4b provided good yield of coupling product 3g but in no cases were enantiomeric excess more than 24\%. Since the catalyst control strategy did not provide good asymmetric induction, focus was directed to a substrate control strategy. 1,3-disubstituted allenes are axially chiral. Chirality transfer from chiral allene to the product might be possible in the nickel-catalyzed allene–aldehyde coupling.
Enantiomerically enriched 1,3-disubstituted allene (aS)-4,5-nonadiene (5a, 95% ee) was chosen as the first substrate to study the chirality transfer process in the nickel-catalyzed allene–aldehyde coupling. (aS)-4,5-nonadiene (5a) has the same substituent at both ends of the allene, therefore minimizing the number of possible coupling products. It was readily prepared in enantiomerically enriched form from the corresponding enantiomerically enriched propargyl alcohol.18

A ligand-dependent chirality transfer process was observed in the nickel-catalyzed reductive coupling of (aS)-4,5-nonadiene (5a) and benzaldehyde (Table 5). Using standard coupling conditions developed for terminal allenes, enantiomerically enriched 5a coupled with benzaldehyde to afford product 6a in 77% yield and with >95:5 Z/E selectivity (Table 5, entry 1).
However, while the starting allene had an enantiomeric excess (ee) of 95%, the ee of the product in the coupling reaction was substantially lower (62%). We thus conducted another evaluation of supporting ligands in this transformation with the aim of finding one that was not only efficacious, but also transferred the axial chirality of the allene to the product to a greater extent than Cyp₃P did. N-heterocyclic carbene IPr provided a solution to the erosion of enantiomeric purity that we observed using Cyp₃P (entries 2-7).

**Table 5. Ligand-Dependent Chirality Transfer**

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>yield 6a (%) a,b</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 c</td>
<td>Cyp₃P</td>
<td>77</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>IPr</td>
<td>78</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>IPrHCl, Cs₂CO₃</td>
<td>65</td>
<td>23</td>
</tr>
<tr>
<td>4</td>
<td>IPrHCl, KOt-Bu</td>
<td>71</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>SIPrHBF₄, KOt-Bu</td>
<td>36</td>
<td>95</td>
</tr>
<tr>
<td>6 d</td>
<td>IPr</td>
<td>88</td>
<td>95</td>
</tr>
<tr>
<td>7 d</td>
<td>IPr</td>
<td>80 c</td>
<td>95</td>
</tr>
</tbody>
</table>

a General procedure: To a solution of Ni(cod)₂ (20 mol%) and ligand (40%) were added Et₂SiH (300 mol%) and the aldehyde (300 mol%). Allene 5a (100 mol%) in THF was added to the reaction mixture over 4.5 h. The reaction mixture was stirred 8 h at room temperature. b NMR yield versus DMF as an external standard. In all cases, the Z/E selectivity was >95:5 (¹H NMR of unpurified reaction mixture). c 20 mol% Cyp₃P was used. d Allene 5a was added at –78 °C in one portion, and the mixture was allowed to warm to ambient room temperature. e Isolated yield of 6a.

The method of generating the catalytically competent ligand (the “free carbene”) from an imidazolium salt precursor had significant effects on both yield and the degree of chirality transfer (Table 5, entries 2-5). In all cases in which the free carbene was generated in situ (entries...
3-5), either the yield or ee of the product was lower than that obtained with Cyp₃P (entry 1). However, using of the free carbene IPr itself afforded the product in near identical yield as Cyp₃P and with complete transfer of chirality, giving product of 95% ee (entry 2).

Slow addition of the allene to the other components of the reaction in THF at ambient room temperature was used during the early stages of development of this transformation in order to minimize side reactions involving allene–allene coupling (Table 5, entries 1-5). We later found that these byproducts were suppressed by adding the allene to the reaction mixture at reduced temperature (−78 °C). The need for slow addition was thus obviated, and this modification also resulted in a further increased yield (Table 5, entries 6-7).

With the use of an NHC ligand, homoallylic products arising from reaction of the benzaldehyde at the sp² carbons of the allene 5a could be detected in the unpurified reaction mixtures (¹H NMR). In the case at hand, the ratio of the allylic product to the sum of all homoallylic products was nevertheless still rather high (94:6). The latter were removed by straightforward column chromatography (SiO₂).

The configuration of allylic ether 6a was determined by a Mosher’s ester analysis (Scheme 5). Removal of the Et₃Si group (TBAF/THF) from racemic 6a and esterifying with the R enantiomer of the Mosher acid provided a mixture of two diastereomeric esters. This sequence was repeated with the 95% ee product. ¹H NMR analysis of both products indicated that the vinylic proton of the major diastereomer of the ester formed using the enantiomerically enriched material was upfield (5.45 ppm) relative to that of the minor diastereomer (5.51 ppm). These results suggested that the configuration of the product 6a from the nickel-catalyzed coupling of (aS)-allene 5a and benzaldehyde was R.
With reaction conditions in hand that provided a good chemical yield of highly enantiomerically enriched material in the multicomponent coupling reaction, the scope of this novel transformation was examined (eq 1 and Table 6). In all cases examined, the degree of chirality transfer was 100%, and the $Z/E$ selectivity was uniformly $>95:5$.  

$$\begin{align*}
\ce{H=CH} & \quad \ce{CH=CH} & \quad \ce{H=CH} \\
R_1 & \quad \ce{CH=CH} & \quad R_2 \\
& \quad \ce{Ar} & \\
& \quad \ce{R_3SiH} & \quad \text{cat. Ni(cod)$_2$, IPr} \\
& \quad \ce{THF} & \\
& \quad \ce{Ar} & \quad \ce{R_1R_2SiR_3} \\
\end{align*} \quad \text{(1)}$$
<table>
<thead>
<tr>
<th>entry</th>
<th>allene</th>
<th>product</th>
<th>allylic: homoallylic</th>
<th>yield (allylic)</th>
<th>site selectivity</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂-n-Pr-n-Pr</td>
<td>n-Pr-n-Pr</td>
<td>6a</td>
<td>94:6</td>
<td>80%, &gt;95:5</td>
<td>n.a.</td>
</tr>
<tr>
<td>2</td>
<td>5a</td>
<td>n-Pr-n-Pr</td>
<td>6b</td>
<td>90:10</td>
<td>70%, &gt;95:5</td>
<td>n.a.</td>
</tr>
<tr>
<td>3</td>
<td>5a</td>
<td>n-Pr-n-Pr</td>
<td>6c</td>
<td>95:5</td>
<td>74%, &gt;95:5</td>
<td>n.a.</td>
</tr>
<tr>
<td>4</td>
<td>5a</td>
<td>n-Pr-n-Pr</td>
<td>6d</td>
<td>93:7</td>
<td>75%, &gt;95:5</td>
<td>n.a.</td>
</tr>
<tr>
<td>5</td>
<td>5a</td>
<td>n-Pr-n-Pr</td>
<td>6e</td>
<td>90:10</td>
<td>56%, &gt;95:5</td>
<td>n.a.</td>
</tr>
<tr>
<td>6</td>
<td>5a</td>
<td>n-Pr-n-Pr</td>
<td>6f</td>
<td>90:10</td>
<td>66%, &gt;95:5</td>
<td>n.a.</td>
</tr>
<tr>
<td>7</td>
<td>Cy-n-Pr-n-Pr</td>
<td>n-Pr-n-Pr</td>
<td>6g</td>
<td>93:7</td>
<td>76%, &gt;95:5</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>8</td>
<td>5b</td>
<td>n-Pr-n-Pr</td>
<td>6h</td>
<td>90:10</td>
<td>68%, &gt;95:5</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>9</td>
<td>5b</td>
<td>n-Pr-n-Pr</td>
<td>6i</td>
<td>93:7</td>
<td>65%, &gt;95:5</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>10</td>
<td>t-Bu-n-Pr-n-Pr</td>
<td>t-Bu-n-Pr</td>
<td>6j</td>
<td>85:15</td>
<td>40%, &gt;95:5</td>
<td>&gt;95:5</td>
</tr>
</tbody>
</table>

Table 6. Nickel-Catalyzed Coupling of Chiral Allenes and Aldehydes<sup>a</sup>

<sup>a</sup> See eq 1. Standard conditions: To a solution of Ni(cod)<sub>2</sub> (20 mol%), IPr (40 mol%) in THF at −78 °C were added the allene (100 mol%, 0.5 mmol), aldehyde (300 mol%), and silane (300 mol%). The mixture was warmed to ambient room temperature over 6 h, stirred 12 h, and purified by chromatography (SiO₂). Absolute configuration determined by Mosher ester analysis. See Supporting Information. <sup>b</sup> Ratio of allylic to the sum of all homoallylic products. <sup>c</sup> Determined by <sup>1</sup>H NMR of unpurified reaction mixtures. <sup>d</sup> Isolated yield of allylic alcohol shown. <sup>e</sup> Determined by chiral HPLC. <sup>f</sup> <sup>1</sup>H NMR of crude reaction mixture indicated a 94:6 ratio of 6f:6a (reductive dechlorination).
A methyl group para to the carbonyl of the aldehyde had little effect on both the allylic:homoallylic selectivity and the Z/E selectivity (Table 6, entries 1 and 3), whereas an ortho methyl substituent resulted in slightly diminished reaction yield (70%) and slight increased in the amount of homoallylic products formed (90:10, entry 2).

The nickel-catalyzed allene–aldehyde coupling is compatible with ethers, esters, and aryl chlorides (Table 6, entries 4-6). An electron-donating MeO group in the para position had little effect on the transformation (entry 4), but an electron-withdrawing CO$_2$Me substituent reduced the chemical yield to 56% and the allylic:homoallylic selectivity to 90:10 (entry 5). In the case of a para Cl substituent (entry 6), a small amount of 6a, corresponding to reductive dechlorination of 6f, could be detected by $^1$H NMR analysis of the crude reaction mixture ($6f$:6a = 94:6), but this impurity was easily removed by SiO$_2$ chromatography.

We next examined coupling reactions of enantiomerically enriched 1,3-allenes in which the two allene substituents were different, adding yet another selectivity variable in these reactions, site selectivity. In other words, two different allylic products are possible, depending upon which double bond of the allene reacts (Table 6, entries 7-10).

(aS)-1-Cyclohexyl-1,2-butadiene (5b, 98% ee), prepared using a similar sequence to that for (aS)-4,5-nonadiene (5a), underwent multicomponent coupling in 76% yield with benzaldehyde under the catalytic reaction conditions used in the previous examples (Table 6, entry 7). The ratio of allylic to homoallylic products was similarly high (93:7), as were both the Z/E selectivity and the enantiomeric purity of the product (6g, 98% ee). On the issue of site selectivity, a single allylic product was isolated, corresponding to exclusive reaction of the more hindered double bond of the allene.
These trends and high selectivity were preserved in analogous coupling reactions employing different organosilanes (Table 6, entries 8-9). The reactions leading to allylic products 6h and 6i proceeded with excellent allylic:homoallylic selectivity, in good yield, and with high enantio-, Z/E-, and site selectivity. These results also demonstrate a degree of flexibility as to which silyl “protective group” is incorporated into the product.

The coupling of (aS)-1-tert-butyl-1,2-butadiene (5c), benzaldehyde, and Et₃SiH afforded 6j in reduced yield and allylic:homoallylic selectivity, but with the same level of Z/E-, enantio-, and site selectivity as that observed in all other cases (Table 6, entry 10).

The nickel/IPr catalyst system can differentiate the two alkyl groups on the allene only when the two alkyl groups have significant steric difference. As discussed in the case of allenes 5b and 5c, both allenes coupled with benzaldehyde with high site selectivity (i.e., only one allylic ether product was observed). This demonstrated that the nickel/IPr system could differentiate between a branched alkyl group and a methyl group. On the other hand, there was no differentiation between unbranched alkyl group and a methyl group. For example, the coupling of racemic n-hexyl-buta-1,2-diene (5d, Scheme 6) with benzaldehyde and triethylsilane yielded a 50:50 mixture of allylic ether products (6k and 6l).

**Scheme 6**

\[
\text{cat. Ni(cod)₂, IPr} + \text{Et₃SiH} \rightarrow 6k : 6l = 50:50 (73\% \text{ yield})
\]
Deuterium Labeling Experiment

A deuterium labeling experiment was carried out to confirm the role of triethylsilane as a reducing agent. A previous experiment was repeated (Table 6, entry 7), using Et₃SiD (97% D) in place of Et₃SiH (Scheme 7). Slightly lower allylic:homoallylic selectivity (89:11) was observed, but ²H-6g had the same ee, Z/E ratio, and site selectivity as 6g. Moreover, deuterium incorporation occurred at a single site and with >95:5 diastereoselectivity. This confirmed the hydride on triethylsilane was incorporated into the coupling product.

The configuration of the deuterium labeled stereogenic center was assigned as R by the sequence shown in Scheme 7. The triethyldisilyl group of labeled coupling product ²H-6g was removed with tetrabutylammonium fluoride, and ozonolysis of the double bond afforded hydroxyketone 7 in near quantitative yield. Lead tetraacetate cleavage of this functional group pair provided 2-deuterio-2-cyclohexylacetic acid (8). Esterification of 8 with methyl (R)-mandelate (DCC, DMAP) yielded 9. Comparison of the ¹H NMR spectra of this compound to those of (+/−)-9 and the corresponding unlabeled ester allowed for assignment of the labeled stereogenic center as the R configuration.²⁰

Scheme 7
The general observation of the nickel-catalyzed allene–aldehyde coupling (Tables 4 and 6) and the result of the deuterium labeling experiment (Scheme 7) can be accounted for by the sequence of events proposed in Scheme 8. Of the four isomeric 1:1:1 complexes of Ni, IPr (L), and allene 5b (A-1, A-2, A-3, and A-4), only A-1 places the large Ni-L complex on the less hindered allene face and less substituted double bond. The sense of induction may be explained by benzaldehyde coordination away from the methyl group with the Ph group placed between L and (cyclohexyl)methylidene (B). Oxidative cyclization gives metallacycle C.

**Scheme 8**

We believe that there is a direct link between the selectivity for the Z alkene geometry and the sense of induction of deuterium labeling. Sigma bond metathesis between C and Et₃SiD could afford η³-allyl-Ni complex D. Reductive elimination with retention leads to the observed Z alkene and R configuration at the labeled carbon. Conversely, the alternative complex (E) gives the opposite sense of selectivity in both cases (E and S, respectively). Our explanation for the absence of this product is the severe 1,3-interaction between the Me and Cy groups present in E.
Finally, the overall site selectivity (reduction of the more hindered double bond of the allene) could be explained by the reductive elimination step between the hydride and the allyl group on nickel. If nickel complex D was trigonal planar, either the small hydride or the large ligand on nickel would be underneath the cyclohexyl group on the allyl group. Based on a steric argument the hydride rather than the ligand would be next to the cyclohexyl group. Therefore reductive elimination placed the hydride to the allyl carbon with the cyclohexyl group to afford 6g.

This proposed mechanism is also consistent with the result observed in the nickel-catalyzed coupling of terminal allenes and aldehydes. The more hindered double bond was reduced to provide germinal disubstituted allylic ether products (Table 4).

Conclusion

In summary, this enantioselective, three-component coupling occurs by way of a previously unobserved process in allene–aldehyde coupling reactions and is promoted by a Ni-NHC complex that efficiently transfers the axial chirality of the allene to the product. This catalyst also possesses the qualities necessary to induce a surprising sense and degree of Z/E- and site selectivity.

References:


15) MePh₂SiH, Me₂PhSiH, (EtO)₃SiH, and Ph₂SiH₂ were screened.

16) Bu₃P, (o-anisyl)₃P, Ph₃P, NMDPP, and BINAP were screened.

17) (a) See chapter 3 of this thesis. (b) González, I. C.; Forsyth, C. J. \textit{Tetrahedron Lett.} \textbf{2000}, 41, 3805–3807. (c) As demonstrated in the coupling of allene 1b and n-butyraldehyde (Table 4, entry 9), unbranched aldehydes are not the best substrates for the nickel-catalyzed allene–aldehyde coupling. Use of stoichiometric amount of nickel provided better yield of the desired coupling product. The coupling condition used in Scheme 3 was not optimized.


19) Recent review of Mosher’s ester analysis: (a) Hoye, T. R.; Jeffrey, C. S.; Shao, F. \textit{Nature}

Experimental Section

General Information

Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of nitrogen or argon with rigid exclusion of moisture from reagents and glassware. Tetrahydrofuran and diethylether were distilled from a blue solution of sodium benzophenone ketyl. Dichloromethane and toluene were distilled over calcium hydride. Triethylsilane, triisopropylsilane and tert-butyldimethylsilane were purchased from Aldrich Chemical Co. and were saturated with nitrogen before use. Benzaldehyde was purchased from Aldrich Chemical Co. and was distilled before use. All aliphatic aldehydes were distilled over magnesium sulfate under argon before use. Bis(cyclooctadienyl)nickel(0) (Ni(cod)\textsubscript{2}) and tricyclopentylphosphine (Cyp\textsubscript{3}P) were purchased from Strem Chemicals, Inc., stored under nitrogen atmosphere and used without further purification. 1,3-Bis-(2,6-di-isopropylphenyl)imidazol-2-ylidene (IPr) was prepared according to literature procedure.\textsuperscript{1} All other chemicals were used without purification.

Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F\textsubscript{254} plates. The developed chromatogram was analyzed by UV lamp (254 nm), ethanolic phosphomolybdic acid (PMA) or potassium permanganate (KMnO\textsubscript{4}). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230-400 mesh). \textsuperscript{1}H and \textsuperscript{13}C NMR spectra were recorded on Varian 300 MHz, Varian 500 MHz or Bruker 400 MHz spectrometer in CDCl\textsubscript{3}, unless otherwise noted. Chemical shifts in \textsuperscript{1}H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constant in hertz (Hz), and integration. Chemical shifts of \textsuperscript{13}C NMR spectra are reported in ppm from the central peak of CDCl\textsubscript{3} (77.23 ppm) on the δ scale. Infrared (IR) spectra were recorded on a Perkin-Elmer 2000 FT-IR. High resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer by Dr. Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrument Facility. Chiral GC analysis was performed on a Varian CP-3800 gas chromatograph fitted with ChiralDEX B-PH, B-DA, and G-TA capillary columns. Chiral HPLC analysis was performed on a Hewlett-Packard 1100 chromatograph equipped with a variable wavelength detector and Chiralcel OD or OD-H columns. Specific Rotations ([\alpha]\textsubscript{20}D) were measured on a Perkin-Elmer 241 polarimeter at 589 nm.

Preparation of Terminal Allenes

![1a](image)

Prepared by the method of Brandsma.\textsuperscript{2} Cyclohexyl-magnesium chloride (50 mL, 100 mmol, 2 M in ether) was dissolved in anhydrous THF (80 mL) and cooled to −78 °C under argon. After 10 minutes of cooling, a THF (8 ml) solution of anhydrous lithium bromide (2 g) and anhydrous
copper (I) bromide (1 g) was added to the Grignard solution in one portion. The reaction mixture was stirred 20 min at –78 °C. Propargyl bromide (13.4 mL, 120 mmol) was dissolved in anhydrous THF (10 mL) in an oven dried round bottom flask and was cooled at –78 °C for 15 min. The propargyl bromide solution was taken up by a 50 mL syringe and added to the reaction mixture over 30 min. During this time the reaction mixture was kept below –50 °C with rigorous stirring. After the addition was complete the reaction mixture was stirred 30 min at –78 °C. The dry ice / acetone bath was removed and the reaction was allowed to warm to room temperature and stirred 3 h. The reaction mixture was poured into an aqueous NH₄Cl solution (10 g NH₄Cl, 100 mL). The mixture was extracted with 200 mL pentane. The aqueous layer was extracted again with 100 mL pentane. The combined pentane solution was washed repeatedly with water and finally with brine. The solution was dried with MgSO₄ and pentane was removed in rotavap. Purification via flash chromatography on silica followed by distillation afforded 1a (7.9 g, 65% yield).

\[ 1H \text{ NMR (500MHz, CDCl₃, } \delta): 5.10 \text{ (q, } J = 6.4 \text{ Hz, 1H), } 4.69 \text{ (dd, } J = 6.7, 3.4 \text{ Hz, 2H), } 1.99 \text{ (m, 1H), } 1.80-1.02 \text{ (m, 11H).} \]

\[ 1C \text{ NMR (125MHz, CDCl₃, } \delta): 207.6, 96.3, 75.6, 36.8, 33.2, 26.4, 26.2. \]


2-octyn-1-ol (4.3 mL, 30 mmol) and triethylamine (17 mL, 120 mmol) were dissolved in anhydrous dichloromethane (35 mL) in a 100 mL round bottom flask. The reaction mixture was stirred 10 min at –78 °C. Methanesulfonyl chloride (7 mL, 90 mmol) was added dropwise. After the addition was complete the reaction was stirred 2 h at –78 °C. The dry ice / acetone bath was replaced by a sodium chloride / ice slush bath. The reaction mixture was stirred 90 min at –10 °C. The reaction mixture was poured into water (50 mL). The organic layer was separated. The aqueous layer was extracted with dichloromethane. The combined dichloromethane solution was washed with water and dried with MgSO₄. Purification via flash chromatography on silica afforded methanesulfonic acid oct-2-ynyl ester. In an oven dried 50 mL round bottom flask magnesium turning (0.56 g) was stirred in anhydrous THF (4 mL). A few drop of 1,2-dibromoethane was added. Gentle heating was applied to initiate the reaction. \( n \)-Pentylbromide (2.84 mL, 23 mmol) was added slowly at a rate that caused and maintained a gentle reflux. When most of the magnesium vanished of more \( n \)-pentylbromide (1 mL) was added. The solution was cooled down to slightly warm (pentylmagnesium bromide was not soluble in cold THF). Meanwhile anhydrous CuBr (3.44 g, 24 mmol) and anhydrous LiBr (2.08 g, 24 mmol) were dissolved in anhydrous THF (40 mL) in an ice bath and stirred vigorously. Once the mixture became homogeneous, the warm pentyl magnesium bromide solution was added via a syringe with a thick needle. The reaction mixture was stirred rigorously for 20 min at 0 °C. The reaction mixture was cooled to –78 °C. Methanesulfonic acid oct-2-ynyl ester in anhydrous THF (30 mL) was added to the reaction mixture dropwise via a syringe pump over 30 min. Once the addition was complete, the dry ice / acetone bath was allowed to warm back to room temperature and stirred 12 h. The reaction mixture was quenched with ice cold saturated NH₄Cl (80 mL) and extracted with 250 mL hexane. The aqueous layer was extracted again with hexane until the aqueous layer became blue. The combined hexane solution was then washed two times with
saturated NH$_4$Cl, once with water (50 mL) and finally with brine (50 mL). Purification via flash column chromatography on silica afforded allene 1b (2.54 g, 47% from 2-octyn-1-ol).

$^1$H NMR (500 MHz, CDCl$_3$, δ): 4.64 (p, $J = 3.0$ Hz, 2H), 1.96-1.90 (m, 4H), 1.46-1.39 (m, 4H), 1.35-1.26 (m, 8H), 0.94-0.87 (t, $J = 7.0$ Hz, 6H).

$^{13}$C NMR (125 MHz, CDCl$_3$, δ): 205.9, 103.6, 75.4, 32.3, 31.8, 27.5, 22.8, 14.3.

IR (thin film NaCl): 2957, 2929, 2873, 2859, 1958, 843.

Prepared according to the method of Myers.$^3$ Triphenylphosphine (5 g, 15 mmol) was dissolved in THF (20 mL). The solution was cooled in a MeOH / ice bath, and diethylazodicarboxylate (DEAD) (2.4 mL, 15 mmol) was added to the solution over 1 min. The solution was stirred 10 min below –10 ºC. 1-Phenyl-2-propyn-1-ol (1.22 mL, 10 mmol) in THF (10 mL) was added. THF (5 mL) was used to rinse the rest of the alcohol into the reaction mixture. The mixture was stirred 10 min, and o-nitrobenzenesulfonyl-hydrazine$^{3b}$ (3.3 g, 15 mmol in 20 mL THF) was added. The mixture was kept below 0 ºC for 2 h and was allowed to warm to room temperature and stirred 16 h. The reaction was diluted with pentane (300 mL) and washed 5 times with ice cold water to remove THF. The mixture was dried by MgSO$_4$. Column chromatography in pentane afforded 1c as a colorless oil (250 mg, 21% yield).

$^1$H NMR (400MHz, CDCl$_3$, δ): 7.40-7.28 (m, 4H), 7.25-7.16 (m, 1H), 6.18 (t, $J = 6.8$ Hz, 1H), 5.16 (d, $J = 6.8$ Hz, 2H).
Nickel-Catalyzed Couplings of Terminal Allenes and Aldehydes

**Standard procedure A.** A 25 mL round bottom flask and a stir bar were oven-dried and brought into a glove box. Ni(cod)$_2$ (28 mg, 0.1 mmol, 10 mol%) and Cyp$_3$P (28 µL, 0.1 mmol, 10 mol%) were added to the flask. The flask was sealed with a septum and electrical tape. The sealed flask was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in THF (2 mL) at room temperature under argon and stirred 10 min at room temperature. Silane (3 mmol, 300 mol%) was added in one portion. Aldehyde (3 mmol, 300 mol%) was added in one portion. Finally allene (1 mmol, 100 mol%) in THF (8 mL) was added into the reaction mixture at room temperature via a syringe pump over 8 h. The reaction was stirred at room temperature for another 12 h. THF and other volatiles were removed under reduced pressure. The crude mixture was diluted in hexane. Purification via flash chromatography on silica afforded the allylic ether product.

**Standard procedure B.** A 10 mL round bottom flask and a stir bar were oven-dried and brought into a glove box. Ni(cod)$_2$ (7 mg, 0.025 mmol, 10 mol%) and Cyp$_3$P (7 µL, 0.025 mmol, 10 mol%) were added to the flask. The flask was sealed with a septum and electrical tape. The sealed flask was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in THF or toluene (0.5 mL) at room temperature under argon and stirred 10 min at room temperature. Silane (0.75 mmol, 300 mol%) was added in one portion. Aldehyde (0.75 mmol, 300 mol%) was added in one portion. Finally allene (0.25 mmol, 100 mol%) in THF or toluene (2 mL) was added into the reaction mixture at room temperature via a syringe pump over 3.5 h. The reaction was stirred at room temperature for another 12 h. THF and other volatiles were removed under reduced pressure. The crude mixture was diluted in hexane. Purification via flash chromatography on silica afforded the allylic ether product.

**Standard procedure C.** A 10 mL round bottom flask and a stir bar were oven-dried and brought into a glove box. Ni(cod)$_2$ (10 mg, 0.036 mmol, 15 mol%) and Cyp$_3$P (10 µL, 0.036 mmol, 15 mol%) were added to the flask. The flask was sealed with a septum and electrical tape. The sealed flask was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in THF (0.5 mL) at room temperature under argon and stirred 10 min at room temperature. Silane (0.75 mmol, 300 mol%) was added in one portion. Aldehyde (0.75 mmol, 300 mol%) was added in one portion. Finally allene (0.25 mmol, 100 mol%) in THF or toluene (3 mL) was added into the reaction mixture at room temperature via a syringe pump over 5 h. The reaction was stirred at room temperature for another 12 h. THF and other volatiles were removed under reduced pressure. The crude mixture was diluted in hexane. Purification via flash chromatography on silica afforded the allylic ether product.
The reaction of allene 1a (148 μL, 1 mmol) and isobutyraldehyde (272 μL, 3 mmol) with Ni(cod)$_2$, tricyclopentylphosphine and triethylsilane (480 μL, 3 mmol) in THF following the standard procedure A described above afforded 3b in 52% yield.

$^1$H NMR (500 MHz, CDCl$_3$, δ): 4.98 (m, 1H), 4.80 (m, 1H), 3.72 (d, $J = 6.1$ Hz, 1H), 2.00-1.00 (m, 14 H), 0.96 (t, $J = 8.0$ Hz, 9H), 0.85 (t, $J = 6.32$ Hz, 6H), 0.59 (q, $J = 7.98$ Hz, 6H).

$^{13}$C NMR (125 MHz, CDCl$_3$, δ): 149.0, 111.0, 82.0, 39.4, 35.9, 34.1, 33.7, 31.8, 26.9, 26.7, 26.6, 20.1, 17.6, 7.3, 5.2.

IR (NaCl, thin film): 3077, 2955, 2923, 2877, 2853, 1811, 1646, 1459, 1449, 1414, 1063, 1007, 904, 834, 740, 725.

HRMS-ESI (m/z): [M+Na]$^+$ calcd for C$_{19}$H$_{38}$OSiNa, 333.2584; found, 333.2593.

The reaction of allene 1a (148 μL, 1 mmol) and isobutyraldehyde (272 μL, 3 mmol) with Ni(cod)$_2$, tricyclopentylphosphine and tert-butyldimethylsilane (498 μL, 3 mmol) in THF following the standard procedure A described above afforded 3c in 71% yield.

$^1$H NMR (500 MHz, CDCl$_3$, δ): 4.98 (m, 1H), 4.80 (m, 1H), 3.70 (d, $J = 5.8$ Hz, 1H), 1.98-1.60 (m, 9H), 1.58-1.40 (m, 1H), 1.38-1.10 (m, 4H), 0.92 (s, 9H), 0.843 (dd, $J = 6.9$, 6.6, 6H), 0.04 (s, 3H), -0.02 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$, δ): 148.8, 111.1, 81.5, 39.7, 35.7, 34.2, 33.6, 31.7, 26.9, 26.7, 26.6, 26.2, 20.3, 18.5, 17.3, -4.1, -4.8.

IR (NaCl, thin film): 3077, 2957, 2927, 2855, 1647, 1463, 1251, 1057, 863, 838, 774.

HRMS-ESI (m/z): [M+Na]$^+$ calcd for C$_{19}$H$_{38}$OSiNa, 333.2584; found, 333.2590.
The reaction of allene 1a (37 µL, 0.25 mmol) and cyclohexanecarboxaldehyde (90 µL, 0.75 mmol) with Ni(cod)$_2$, tricyclopentylphosphine and triisopropylsilane (154 µL, 0.75 mmol) in toluene following the standard procedure B described above (except that 1 mL toluene was used to dissolve Ni(cod)$_2$ and tricyclopentylphosphine and the reaction was heated at 50 °C) afforded 3d in 24% yield.

$^1$H NMR (500 MHz, CDCl$_3$, δ): 4.96 (m, 1H), 4.82 (m, 1H), 3.95 (d, $J = 5.8$ Hz, 1H), 2.00-0.80 (m, 25H), 1.10 (s, 18H).

$^{13}$C NMR (100 MHz, CDCl$_3$, δ): 148.6, 110.9, 81.9, 42.8, 39.5, 35.6, 34.2, 33.8, 30.2, 28.6, 26.9, 26.8, 26.8, 26.7, 26.6, 26.7, 26.6, 26.6, 18.5, 13.1.

IR (NaCl, thin film): 3079, 2924, 2865, 2852, 1645.71, 1449, 1086, 1062, 883.

HRMS-ESI (m/z): [M + Na]$^+$ calcd for C$_{25}$H$_{48}$OSiNa, 415.3367; found, 415.3366.

The reaction of allene 1a (148 µL, 1 mmol) and cyclohexanecarboxaldehyde (361 µL, 3 mmol) with Ni(cod)$_2$, tricyclopentylphosphine and triethylsilane (480 µL, 3 mmol) in THF following the standard procedure A described above afforded 3e in 46% yield.

$^1$H NMR (500 MHz, CDCl$_3$, δ): 4.93 (m, 1H), 4.79 (m, 1H), 3.72 (d, $J = 6.7$ Hz, 1H), 2.00-0.80 (m, 24H), 0.96 (t, $J = 7.6$ Hz, 9H), 0.59 (q, 7.9 Hz, 6H).

$^{13}$C NMR (125 MHz, CDCl$_3$, δ): 148.6, 111.1, 81.8, 41.5, 39.0, 35.6, 34.1, 33.7, 30.4, 28.4, 26.9, 26.9, 26.7, 26.7, 26.6, 26.5, 7.3, 5.2.


HRMS-ESI (m/z): [M + Na]$^+$ calcd for C$_{22}$H$_{42}$OSiNa, 373.2897; found, 373.2892.
The reaction of allene 1a (148 µL, 1 mmol) and cyclohexanecarboxaldehyde (361 µL, 3 mmol) with Ni(cod)_2, tricyclopentylphosphine and tert-butyldimethylsilane (498 µL, 3 mmol) in THF following the standard procedure A described above afforded 3f in 73% yield.

1H NMR (500 MHz, CDCl₃, δ): 4.94 (m, 1H), 4.80 (m, 1H), 3.70 (d, J = 6.1 Hz, 1H), 2.00-0.80 (m, 24H), 0.91 (s, 9H), 0.03 (s, 3H), -0.02 (s, 3H).

13C NMR (125 MHz, CDCl₃, δ): 148.4, 111.2, 81.4, 41.5, 39.3, 35.6, 34.2, 33.7, 30.7, 28.1, 26.9, 26.7, 26.7, 26.6, 26.6, 26.2, 18.5, -4.1, -4.7.

IR (NaCl, thin film): 3076, 2926, 1645, 1450, 1251, 1061, 900, 837, 774.

HRMS-ESI (m/z): [M+Na]^+ calcd for C₂₂H₄₂OSiNa, 373.2897; found, 373.2893.

A 7 mL vial and a stir bar were oven-dried and brought into a glove box. Ni(cod)_2 (7 mg, 0.025 mmol, 10 mol%) and IPr (19 mg, 0.05 mmol, 20 mol%) were added to the flask. The vial was sealed with a septum and electrical tape. The sealed vial was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in THF (3 mL) at room temperature under argon and stirred 10 min at room temperature. The mixture was cooled to –78 °C. t-BuMe₂SiH (125 µL, 0.75 mmol, 300 mol%) was added in one portion. Benzaldehyde (76 µL, 0.75 mmol, 300 mol%) was added in one portion. Finally allene (37 µL, 0.25 mmol, 100 mol%) was added in one portion. The reaction was stirred 2 h at –78 °C. The dry ice / acetone bath was then covered with aluminum foil and the temperature was slowly rise to room temperature. The reaction was stirred for a total of 15 h. THF and other volatiles were removed under reduced pressure. Purification via flash chromatography on silica afforded 3g in 86% yield.

1H NMR (400 MHz, CDCl₃, δ): 7.35-7.20 (m, 5H), 5.24 (s, 1H), 5.10 (s, 1H), 4.83 (s, 1H), 1.80 (m, 1H), 1.70 (m, 6H), 1.45 (m, 1H), 1.15 (m, 3H), 0.92 (s, 9H), 0.75 (m, 2H), 0.07 (s, 3H), -0.04 (s, 3H).

13C NMR (100 MHz, CDCl₃, δ): 150.0, 143.7, 128.1, 127.1, 126.7, 110.9, 78.4, 39.5, 35.8, 33.7, 33.480, 26.8, 26.6, 26.5, 26.1, 18.5, -4.7, -4.7.


HRMS-ESI (m/z): [M + Na]^+ calcd for C₂₂H₃₈OSiNa, 367.2428; found, 367.2431.
The reaction of allene 1b (57 µL, 0.25 mmol) and isobutyraldehyde (68 µL, 0.75 mmol) with Ni(cod)$_2$, tricyclopentylphosphine and tert-butyldimethylsilane (125 µL, 0.75 mmol) in THF following the standard procedure C described above afforded 3h in 75% yield.

$^1$H NMR (500 MHz, CDCl$_3$, δ): 5.10 (m, 1H), 4.83 (m, 1H), 3.79 (bs, 1H), 1.80-1.68 (m, 2H), 1.46-1.18 (m, 22H), 0.97 (d, $J = 6.7$ Hz, 3H), 0.94 (s, 9H), 0.93-0.85 (m, 6H), 0.76 (d, $J = 6.7$ Hz, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$, δ): 154.7, 108.3, 79.7, 41.4, 36.2, 34.0, 32.5, 32.5, 30.9, 27.5, 26.7, 26.2, 22.9, 22.9, 21.4, 18.5, 14.9, 14.4, 14.3, -3.9, -4.8.

IR (NaCl, thin film): 2958, 2929, 2858, 1647, 1463, 1250, 1056, 902, 865, 839, 774.

HRMS-ESI (m/z): [M+Na]$^+$ calcd for C$_{23}$H$_{48}$OSiNa, 391.3367; found, 391.3365.

The reaction of allene 1b (57 µL, 0.25 mmol) and cyclohexanecarboxaldehyde (90 µL, 0.75 mmol) with Ni(cod)$_2$, tricyclopentylphosphine and tert-butyldimethylsilane (125 µL, 0.75 mmol) in THF following the standard procedure B described above afforded 3i in 68%.

$^1$H NMR (500 MHz, CDCl$_3$, δ): 5.06 (m, 1H), 4.83 (m, 1H), 3.76 (bs, 1H), 1.90-1.00 (m, 28H), 0.94 (s, 9H), 0.90 (m, 6H), 0.03 (s, 3H), 0.03 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$, δ): 154.2, 108.4, 79.8, 41.2, 41.1, 36.2, 34.2, 32.5, 32.5, 32.1, 27.4, 27.1, 27.0, 26.8, 26.6, 26.3, 25.5, 22.9, 22.925, 18.5, 14.4, 14.3, -3.9, -4.7.

IR (NaCl, thin film): 2929, 2856, 1647, 1463, 1251, 1103, 902, 835, 774.

HRMS-ESI (m/z): [M+Na]$^+$ calcd for C$_{26}$H$_{52}$OSiNa, 431.3680; found, 431.3700.
The reaction of allene 1b (57 µL, 0.25 mmol) and n-butyraldehyde (68 µL, 0.75 mmol) with Ni(cod)$_2$, tricyclopentylphosphine and tert-butyldimethylsilane (125 µL, 0.75 mmol) in THF following the standard procedure C described above afforded 3j in 35% yield.

$^{1}$H NMR (500 MHz, CDCl$_3$, δ): 5.09 (bs, 1H), 4.76 (bs, 1H), 3.97 (t, $J = 4.9$ Hz, 1H), 1.90-1.82 (m, 1H), 1.55-1.20 (m, 23H), 0.92 (s, 9H), 0.88 (m, 6H), 0.05 (s, 3H), 0.01 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$, δ): 156.0, 107.6, 75.8, 40.7, 39.1, 35.9, 34.7, 32.5, 27.4, 26.9, 26.2, 22.9, 18.8, 18.5, 14.4, 14.3, -4.2, -4.7.

IR (NaCl, thin film): 2958, 2930, 2858, 1646, 1463, 1255, 1085, 902, 836, 774.

HRMS-ESI (m/z): [M + Na]$^+$ calcd for C$_{22}$H$_{48}$OSiNa, 391.3367; found, 391.3350.

The reaction of phenylallene 1c (121 µL, 1 mmol) and benzaldehyde (305 µL, 3 mmol) with Ni(cod)$_2$, IPr (78 mg, 0.2 mmol) and tert-butyldimethylsilane (498 µL, 3 mmol) in THF following the standard procedure A (described above except that tricyclopentylphosphine was replaced by IPr) afforded 3k in 56% yield.

$^{1}$H NMR (400 MHz, CDCl$_3$, δ): 7.43-7.33 (m, 4H), 7.30 (t, $J = 7.4$ Hz, 3H), 7.22 (t, $J = 7.3$ Hz, 1H), 7.10 (d, $J = 7.0$, 2H), 5.35 (s, 1H), 5.19 (s, 1H), 4.71 (d, $J = 1.4$ Hz, 1H), 3.39 (d, $J = 16.1$ Hz, 1H), 3.05 (d, $J = 16.1$ Hz, 1H), 0.97 (s, 9H), 0.09 (s, 3H), -0.02 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$, δ): 151.8, 143.3, 139.7, 129.6, 128.4, 128.2, 127.3, 126.6, 126.1, 112.1, 77.8, 37.6, 26.1, 18.5, -4.7, -4.8.


HRMS-ESI (m/z): [M + Na]$^+$ calcd for C$_{22}$H$_{30}$OSiNa, 361.1958; found, 361.1959.
Preparation of chiral allenes

\[
\text{H} \quad \leftrightarrow \quad \text{H} \\
\text{n-Pr} \quad \text{n-Pr} \\
(aS)-5a
\]

Prepared using the same method as 5b and 5c from (S)-non-5-yn-4-ol, which was prepared by lipase resolution using the procedure described below (60% yield from (S)-non-5-yn-4-ol, 95% ee by chiral GC). The absolute configuration was assigned by comparing the specific rotation of 5a with the literature value\(^4\) and is also consistent with the Lowes-Brewster rule.\(^5\)

\(^1\)H NMR (400 MHz, CDCl\(_3\), \(\delta\)): 5.07 (m, 2H), 1.97 (m, 4H), 1.44 (sextet, \(J = 7.3\) Hz, 4H), 0.94 (t, \(J = 7.3\) Hz, 6H).

\(^13\)C NMR (100 MHz, CDCl\(_3\), \(\delta\)): 204.2, 90.8, 31.4, 22.7, 13.9.


\([\alpha]^{20}_D +64.0\) (c 1.00, CHCl\(_3\))

\([\alpha]^{20}_D +84.7\) (c 0.72, EtOH)

Literature \([\alpha]^{20}_D +80.0\) (c 0.69, EtOH)\(^4\)

Chiral GC analysis: (Chiraldex B-PH, 35 °C isotherm, 0.1 mL/min): \(t_R(aR) = 74.7\) min; \(t_R(aS) = 81.2\) min.

Preparation of (+/−)-4-cyclohexyl-but-3-yn-2-ol. Carbon-tetrabromide (73 g, 220 mmol) was dissolved in anhydrous dichloromethane (150 mL). The solution was cooled to 0 °C, triphenylphosphine (115 g, 440 mmol) was added. The mixture was stirred 30 min at 0 °C. Cyclohexanecarboxaldehyde (10 mL, 110 mmol) was added and the reaction mixture was slowly warmed to room temperature and stirred 12 h. The brown precipitate was removed by filtering the CH\(_2\)Cl\(_2\) solution through silica gel and the silica gel was washed with hexane. Evaporation of the solvents gave an oil with white precipitate. The crude was diluted with hexane and filtered through silica gel to yield a colorless oil (2,2-dibromo-vinyl)-cyclohexane (21.62 g, 74% yield). It was used without further purification. (2,2-Dibromo-vinyl)-cyclohexane (9.18 g, 34 mmol) was dissolved in anhydrous THF (40 mL) and was cooled to −78 °C. Methyllithium (55 mL, 88 mmol, 1.6 M in ether) was added to the solution over 5 min and the mixture was stirred 2.5 h at −78 °C. Acetaldehyde was added in one portion and the mixture was stirred 1.5 h and was warmed to room temperature. The reaction was quenched with water and extracted with diethyl ether (80 mL), which was washed with water and dried with MgSO\(_4\). Column chromatography afforded a yellow oil of (+/−)-4-cyclohexyl-but-3-yn-2-ol (4.9 g, 94% yield).
Preparation of enantiomerically enriched (S)-4-cyclohexyl-but-3-yn-2-ol by lipase resolution. In an oven-dried round bottom flask, (+/–)-4-cyclohexyl-but-3-yn-2-ol (2.28 g, 15 mmol) was dissolved in anhydrous pentane (50 mL) at room temperature. 4Å molecular sieves (approximately half the volume of the solvent), Amano lipase AK from *Pseudomonas fluorescens* (2 g) followed by freshly distilled vinyl acetate (4 mL, 40 mmol) were added. The slurry was stirred 5 h at room temperature. NMR of the crude reaction mixture indicated that the ratio of acetate to alcohol was approximately 1:1. The mixture was stirred for 30 more minutes, filtered through celite and washed with pentane. Column chromatography afforded (S)-4-cyclohexyl-but-3-yn-2-ol (1.1 g, 99% yield based on 50% conversion) that was at least 98% ee according to Mosher’s ester analysis. The absolute configuration was determined by Mosher’s ester analysis. It was consistent with the specific rotations of similar compounds prepared from the same method.

1H NMR (400 MHz, CDCl₃, δ): 4.53 (m, 1H), 2.42-2.30 (m, 1H), 1.9-1.2 (m, 10H), 1.43 (d, J = 6.5 Hz, 3H).

13C NMR (100 MHz, CDCl₃, δ): 89.0, 82.3, 58.8, 32.8, 29.1, 26.0, 25.1.

IR (NaCl, thin film): 3333, 2931, 2854, 2240, 1449, 1158, 1078, 897.

HRMS-ESI (m/z): [M + Na]+ calcd for C₁₀H₁₆ONa, 175.1093; found, 175.1094.

[α]₂⁰ D –23.0 (c 1.00, CHCl₃)

Mosher’s ester analysis: (+/–)-4-cyclohexyl-but-3-yn-2-ol was converted into a pair of diastereomers of (R)-Mosher’s esters (DCC, DMAP, (R)-Mosher’s acid, CH₂Cl₂). The methyl doublets (δ 1.50 and 1.56 ppm) of the two diastereomers were well resolved by 1H NMR and were assigned according to the method of Mosher.

The enantiomerically-enriched alcohol was then converted to (R)-Mosher’s ester, and a doublet was observed at δ 1.56 ppm. Therefore, 4-cyclo-hexyl-but-3-yn-2-ol prepared from lipase resolution had an absolute configuration of (S).
Prepared using the method of Myers. Triphenylphosphine (5 g, 15 mmol) was dissolved in THF (20 mL). The solution was cooled in a MeOH / ice bath, and diethylazodicarboxylate (DEAD) (2.4 mL, 15 mmol) was added to the solution over 1 min. The solution was stirred 10 min below –10 °C. (S)-4-cyclohexyl-but-3-yn-2-ol (1.52 g, 10 mmol) in THF (10 mL) was added. THF (5 mL) was used to rinse the rest of the alcohol into the reaction mixture. The mixture was stirred 10 min, and o-nitrobenzenesulfonyl-hydrazine (3.3 g, 15 mmol in 20 mL THF) was added. The mixture was kept below 0 ºC for 2 h and was allowed to warm to room temperature and stirred 16 h. The reaction was cooled to 0 ºC, diluted with pentane (200 mL) and washed 10 times with ice cold water to remove THF. Column chromatography in pentane afforded 5b (0.95 g, 70% yield, 98% ee based on chiral GC analysis). The absolute configuration of the allene was determined based on the absolute configuration of the alcohol and was consistent with Lowes-Brewster rule. The spectral data are consistent with literature values.

1H NMR (400 MHz, CDCl₃, δ): 5.09 (m, 1H), 5.04 (m, 1H), 2.00-1.91 (m, 1H), 1.80-1.00 (m, 10H), 1.65 (dd, J = 3.4, 7.0 Hz, 3H).
13C NMR (100 MHz, CDCl₃, δ): 203.7, 96.7, 86.5, 37.4, 33.3, 26.4, 26.3, 15.0.
[α]²⁰D + 76.7 (c 1.46, CHCl₃)
Chiral GC analysis: (Chiraldex B-DA, 60 ºC isotherm, 1.5 mL/min): tᵣ(aS) = 21.1 min; tᵣ(aR) = 22.6 min.

Preparation of (+/-)-5,5-dimethyl-hex-3-yn-2-ol. THF (80 mL) was cooled to –78 ºC. tert-butylacetylene (7.35 mL, 60 mmol) was added. MeLi (56 mL, 90 mmol, 1.6 M in diethylether) was added via a syringe pump over 10 min. The mixture was stirred 1 h at –78 ºC. Acetaldehyde (6.7 mL, 120 mmol) was added. The mixture was stirred at –78 ºC for one more hour and warmed to room temperature. The reaction was cooled to 0 ºC and quenched with water. The cold mixture was diluted with diethylether (150 mL) and washed two times with water. The ether solution was dried by MgSO₄ and was filtered through silica gel. The silica gel was washed with diethyl ether. The NMR of the crude reaction mixture indicated 5,5-dimethyl-hex-3-yn-2-ol along with some cyclotrimer of acetaldehyde. (53.4 mmol alcohol based on NMR integration, 89% yield). The crude product was used without further purification.
Preparation of (S)-5,5-dimethyl-hex-3-yn-2-ol by lipase resolution. Prepared using the same lipase resolution procedure as described above (lipase, 4Å MS, vinylacetate, pentane, room temperature, 5.5 h. 88.5% isolated yield. > 98% ee based on chiral GC analysis and Mosher’s ester analysis).

\[
\begin{align*}
1^H \text{NMR (} & 400 \text{ MHz, } CDCl_3, \delta): 4.49 (q, J = 6.5 \text{ Hz, } 1H), 2.1 (bs, 1H), 1.39 (d, J = 6.5 \text{ Hz, } 3H), 1.19 (s, 9H). \\
13^C \text{ NMR (} & 100 \text{ MHz, } CDCl_3, \delta): 92.9, 80.9, 68.1, 58.6, 31.2, 25.0. \\
\text{IR (NaCl, thin film): } & 3336, 2971, 2237, 1363, 1263, 1125, 1050, 973, 882. \\
[\alpha]_{D}^{20} & = -27.3 (c 1.06, CHCl_3)
\end{align*}
\]

Mosher’s ester analysis: (+/-)-5,5-dimethyl-hex-3-yn-2-ol was converted into a pair of diastereomers of (R)-Mosher’s esters (DCC, DMAP, (R)-Mosher’s acid, CH\textsubscript{2}Cl\textsubscript{2}). The methyl doublets (\(\delta = 1.48\) and 1.54 ppm) and \(t\)-Bu singlets (\(\delta = 1.19\) and 1.21 ppm) of the two diastereomers were well resolved by \(^1\)H NMR and were assigned according to the method of Mosher.\(^7\)

The enantiomerically enriched alcohol was converted to (R)-Mosher’s ester. A doublet was observed at \(\delta = 1.54\) ppm, and a singlet was observed at \(\delta = 1.19\) ppm. Therefore, 5,5-dimethyl-hex-3-yn-2-ol prepared from lipase resolution had an absolute configuration of (S).

Chiral GC analysis: (Chiraldex B-PH, 60 °C isotherm, 0.3 mL/min): \(t_R(S) = 69.0\) min; \(t_R(R) = 72.3\) min.

Prepared using the same method as described above for 5b. After the removal of THF by an aqueous workup, the pentane solution was filtered through a pad of silica gel to remove most of the by-products. The pentane was removed by rotavap at atmospheric pressure, and the last traces of pentane were removed by fractional distillation. Finally, the product was separated from the crude mixture by distilling under high vacuum at room temperature, collecting in a cooled flask, affording 60% of 5c. The absolute configuration of the allene was assigned based on the absolute configuration of the alcohol and was consistent with Lowes-Brewster rule.\(^5\)
**1H NMR (400 MHz, CDCl₃, δ):** 5.12 (quintet, 6.8 Hz, 1H), 5.06 (dq, 3.3, 6.42 Hz, 1H), 1.67 (dd, 3.3, 6.9 Hz, 3H), 1.04 (s, 9H).

**13C NMR (100 MHz, CDCl₃, δ):** 202.1, 102.6, 87.4, 31.9, 30.4, 15.1.

**IR (NaCl, thin film):** 2962, 1962, 1462, 1363, 1192, 873, 725.

\[ [\alpha]_{20}^D +67.7 \ (c \ 1.24, \ CHCl_3) \] (consistent with similar compounds)

Prepared using the same method as 5b and 5c from (+/-)-dec-3-yn-2-ol.

**1H NMR (400 MHz, CDCl₃, δ):** 5.04 (m, 2H), 1.96 (m, 2H), 1.65 (dd, 5.2, 10 Hz, 3H), 1.45-1.23 (m, 8H), 0.90 (t, 6.4 Hz, 3H).

**13C NMR (100 MHz, CDCl₃, δ):** 204.9, 90.5, 85.2, 31.9, 29.3, 29.1, 28.9, 22.9, 14.8, 14.3; IR (NaCl, thin film): 2963, 2928, 2857, 1967, 1460.

**HRMS-ESI (m / z):** [M + Na]⁺ calcd for C₁₀H₁₈Na, 138.1403; found, 138.1406.

**Nickel-Catalyzed Reductive Coupling of Chiral Allenes and Aldehydes**

**General procedure.** A 25 mL round bottom flask and a stir bar were oven-dried and brought into a glove box. Ni(cod)₂ (28 mg, 0.1 mmol, 20 mol%) and IPr (78 mg, 0.2 mmol, 40 mol%) were added to the round bottom flask, the flask was sealed with a septum, and the sealed flask was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in THF (7.5 mL) under argon and stirred 10 min at room temperature. The solution was cooled to −78 °C in a dry ice / acetone bath. After 10 min of cooling, triethylsilane (240 µL, 1.5 mmol, 300 mol%), tert-butyldimethylsilane (250 µL, 1.5 mmol, 300 mol%), or dimethylphenylsilane (233 µL, 1.5 mmol, 300 mol%), as specified below, was added in one portion. Next the aldehyde (1.5 mmol, 300 mol%) was added in one portion. The mixture was stirred 5 min at −78 °C. The allene (0.5 mmol, 100 mol%) was added to the reaction mixture in one portion. The reaction was kept in the dry ice / acetone bath and the bath was allowed to warm to room temperature over 6 h. The reaction was stirred an additional 12 h at room temperature. ¹H NMR of an aliquot of the crude (after filtering through a plug of silica) indicated the allylic alcohol was the major coupling product along with minor impurities assigned as various homoallylic alcohols. The ratio of the allylic to homoallylic products was determined by the ¹H NMR integration of spectrum of the crude mixture (Refer to Table 6 for the ratio). THF and excess silane were removed under reduced pressure and the crude mixture was diluted in hexane. Purification via flash chromatography on silica afforded the allylic ether coupling product.
The reaction of (aS)-nona-4,5-diene (5a) (82 µL, 0.5 mmol) and benzaldehyde (152 µL, 1.5 mmol) with Ni(cod)₂, IPr and triethylsilane in THF following the general procedure described above afforded 6a in 77% isolated yield and 95% ee as determined by chiral HPLC. The absolute configuration of the stereocenter was determined by Mosher’s ester analysis to be R. The olefin geometry was determined to be Z by a nOe experiment (see below).

1H NMR (500 MHz, CDCl₃, δ): 7.16-7.40 (m, 5H); 5.76 (s, 1H); 5.24 (t, J = 7.3 Hz, 1H); 2.27 (q, J = 7.5 Hz, 2H); 2.02 (m, 1H); 1.74 (m, 1H); 1.51 (sextet, J = 7.5 Hz, 2H); 1.14-1.34 (m, 4H); 1.01 (t, J = 6.7 Hz, 3H); 0.97 (t, J = 7.6 Hz, 9H); 0.81 (t, J = 7.0 Hz, 3H); 0.64 (q, J = 7.9 Hz).
13C NMR (100 MHz, CDCl₃, δ): 144.5, 141.9, 128.0, 126.5, 125.6, 125.4, 71.3, 31.0, 30.4, 29.6, 23.6, 22.9, 14.34, 14.26, 7.11, 7.07.

IR (NaCl, thin film): 2957, 2875, 1458, 1063, 742, 698.
HRMS-ESI (m / z): [M + Na]+ calcd for C₂₂H₃₈OSiNa, 369.2584; found, 369.2588.

[α]²⁰D –75.2 (c 1.07, CHCl₃)

Chiral HPLC analysis: Analysis was performed on the corresponding free alcohol, obtained by the deprotection of 6a (TBAF, THF): (Chiralcel OD, hexanes: 2-propanol, 99:1, 1.0 mL/min): tᵣ(S) = 9.7 min; tᵣ(R) = 10.8 min.

Mosher’s ester analysis: (+/-)-6a was first converted into the free alcohol (TBAF, THF) and was then converted into a pair of diastereomers of (R)-Mosher’s esters (DCC, DMAP, (R)-Mosher’s acid, CH₂Cl₂). The vinyl triplets (δ 5.45 and 5.51 ppm) of the two diastereomers were well resolved by 1H NMR and were assigned according to the method of Mosher. The enantiomerically-enriched 6a was then converted to (R)-Mosher’s ester using the same procedure. The vinyl triplet was observed at δ 5.46 ppm. Therefore 6a had an absolute configuration of (R).

NOE DIFF experiment: Pre-saturation of the carbinol proton of 6a gave no nOe to the vinylic proton (δ 5.24 ppm), but 13% nOe was observed for the allylic protons indicated (δ 2.27 ppm). These results supported a Z olefin geometry.
The reaction of (aS)-nona-4,5-diene (5a) (82 µL, 0.5 mmol) and o-tolualdehyde (174 µL, 1.5 mmol) with Ni(cod)₂, IPr and triethylsilane in THF following the general procedure described above afforded 6b in 66% yield and 95% ee as determined by chiral HPLC. The absolute configuration of the stereocenter was assigned as R in analogy to 6a and 6j whose configurations were established by Mosher’s ester analysis.⁷

1H NMR (400 MHz, CDCl₃, δ): 7.71 (bd, J = 7.6 Hz, 1H), 7.21 (bt, J = 7.4 Hz, 1H), 7.13 (dt, J = 1.4, 7.4 Hz, 1H), 7.04 (bd, J = 7.4 Hz, 1H), 5.75 (s, 1H), 5.20 (t, J = 6.6 Hz, 1H), 2.38-2.22 (dq, J = 7.5, 14.8 Hz, 2H), 2.20 (s, 3H), 1.91 (ddt, J = 1.1, 5.4, 10.32 Hz, 1H), 1.65 (ddt, J = 1.0, 6.7, 9.8 Hz, 1H), 1.49 (sextet, J = 6.9 Hz, 2H), 1.16 (m, 3H), 1.03 (t, J = 5.6 Hz, 4H), 0.94 (t, J = 8.0 Hz, 9H), 0.77 (t, J = 7.1 Hz, 3H), 0.60 (q, J = 7.5 Hz, 6H).

13C NMR (100 MHz, CDCl₃, δ): 142.2, 139.1, 134.2, 129.8, 126.9, 126.7, 126.5, 125.6, 69.1, 31.7, 30.6, 30.5, 23.5, 22.8, 19.6, 14.4, 14.2, 7.1, 5.2.

IR (NaCl, thin film): 2957, 2875, 1462, 1061, 1006, 744.

HRMS-ESI (m / z): [M + Na]+ calcd for C₂₃H₄₀OSiNa, 383.2741; found, 383.2737.

[α]²⁰_D –75.2 (c 1.25, CHCl₃)

Chiral HPLC analysis: Analysis was performed on the corresponding free alcohol, obtained by the deprotection of 6b (TBAF, THF) (Chiralcel OD, hexanes: 2-propanol, 99:1, 1.0 mL/min): t_R(S) = 11.4 min; t_R(R) = 14.1 min.

The reaction of (aS)-nona-4,5-diene (5a) (82 µL, 0.5 mmol) and p-tolualdehyde (177 µL, 1.5 mmol) with Ni(cod)₂, IPr and triethylsilane in THF following the general procedure described above afforded 6c in 74% yield and 95% enantiomeric excess as determined by chiral HPLC. The absolute configuration of the stereocenter was assigned as R in analogy to 6a and 6j whose configuration were established by Mosher’s ester analysis.

1H NMR (500 MHz, CDCl₃, δ): 7.24 (d, J = 7.9 Hz, 2H), 7.11 (d, J = 7.6 Hz, 2H), 5.74 (s, 1H), 5.22 (t, J = 7.0 Hz, 1H), 2.34 (s, 3H), 2.27 (q, J = 7.3 Hz, 2H), 2.03 (m, 1H), 1.74 (m, 1H), 1.50 (sextet, J = 7.3 Hz, 2H), 1.38-1.18 (m, 4H), 1.00 (t, J = 7.3 Hz, 3H), 0.97 (t, J = 7.9 Hz, 9H), 0.82 (t, J = 7.0 Hz, 3H), 0.63 (q, J = 7.9 Hz, 6H).

13C NMR (125 MHz, CDCl₃, δ): 142.0, 141.5, 136.0, 128.7, 125.6, 125.1, 71.2, 31.0, 30.3, 29.6, 23.6, 22.9, 21.3, 14.33, 14.28, 7.1, 5.1.

IR (NaCl, thin film): 2957, 2875, 1458, 1073, 1006, 741.

HRMS-ESI (m / z): [M + Na]+ calcd for C₂₃H₄₀OSiNa, 383.2741; found, 383.2737.

[α]²⁰_D –83.8 (c 1.05, CHCl₃)
Chiral HPLC analysis: Analysis was performed on the corresponding free alcohol, obtained by the deprotection of 6c (TBAF, THF): (Chiralcel OD, hexanes: 2-propanol, 100:0, 1.5 mL/min): t_R(R) = 37.7 min; t_R(S) = 49.1 min.

The reaction of (aS)-nona-4,5-diene (5a) (82 µL, 0.5 mmol) and p-anisaldehyde (183 µL, 1.5 mmol) with Ni(cod)_2, IPr and triethylsilane in THF following the general procedure described above afforded 6d in 75% yield and 95% enantiomeric excess as determined by chiral HPLC. The absolute configuration of the stereocenter was assigned as R in analogy to 6a and 6j whose configuration were established by Mosher’s ester analysis.

1H NMR (400 MHz, CDCl_3, δ): 7.28 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 5.73 (s, 1H), 5.23 (t, J = 7.2 Hz, 1H), 3.82 (s, 3H), 2.26 (q, J = 7.6 Hz, 2H), 2.05 (m, 1H), 1.76 (m, 1H), 1.50 (sextet, J = 7.2 Hz, 2H), 1.40-1.15 (m, 4H), 1.01 (t, J = 7.2 Hz, 3H), 0.98 (t, J = 8.0 Hz, 9H), 0.84 (t, J = 7.0, 3H), 0.64 (q, J = 7.6 Hz, 6H).

13C NMR (100 MHz, CDCl_3, δ): 158.3, 142.1, 136.7, 126.7, 125.1, 113.4, 71.0, 55.4, 31.0, 30.3, 29.6, 23.6, 22.9, 14.33, 14.28, 7.1, 5.1.

IR (NaCl, thin film): 2956, 2875, 1510, 1464, 1246, 1071, 741.

HRMS-ESI (m / z): [M + Na]^+ calcd for C_{23}H_{40}O_2SiNa, 399.2690; found, 399.2688.

[α]_D^{20} = -67.5 (c 1.14, CHCl_3)

Chiral HPLC analysis: Analysis was performed on the corresponding free alcohol, obtained by the deprotection of 6d (TBAF, THF): (Chiralcel OD, hexanes: 2-propanol, 99:1, 1.0 mL/min): t_R(R) = 14.3 min; t_R(S) = 17.0 min.

The reaction of (aS)-nona-4,5-diene (5a) (82 µL, 0.5 mmol) and methyl 4-formylbenzoate (246 µL, 1.5 mmol) with Ni(cod)_2, IPr and triethylsilane in THF following the general procedure described above afforded 6e in 56% yield (co-eluted with a small amount of homoallylic alcohol minor products) and 95% ee as determined by chiral HPLC. The absolute configuration of the stereocenter was assigned as R in analogy to 6a and 6j whose configuration were established by Mosher’s ester analysis.

1H NMR (500 MHz, CDCl_3, δ): 7.98 (d, J = 7.5 Hz, 2H), 7.43 (d, J = 8.0, 2H), 5.79 (s, 1H), 5.26 (t, J = 7.0 Hz, 1H), 3.90 (s, 3H), 2.28 (q, J = 7.1 Hz, 2H), 1.95 (m, 1H), 1.72 (m, 1H), 1.55 (sextet, J = 7.0 Hz, 2H), 1.30-1.10 (m, 4H), 1.01 (t, J = 7.0 Hz, 3H), 0.96 (t, J = 7.6 Hz, 9H), 0.79 (t, J = 7.3 Hz, 3H), 0.63 (q, J = 7.9 Hz, 6H).
The reaction of (aS)-nona-4,5-diene (5a) (82 µL, 0.5 mmol) and p-chlorobenzaldehyde solution (211 µL aldehyde, 1.5 mmol in 1 mL THF) with Ni(cod)₂, IPr and triethylsilane in THF following the general procedure described above yielded 6f in 65% yield and 1% of dechlorinated product, ie, 6a (total 66% isolated yield, ratio of 6f : 6a in crude NMR is 94:6) and 95% ee as determined by chiral HPLC. The absolute configuration of the stereocenter was assigned as R in analogy to 6a and 6j whose configuration were established by Mosher’s ester analysis.

\[ \alpha \] _D ^{20} -108.6 (c 1.28, CHCl₃)

Chiral HPLC analysis: Analysis was performed on the corresponding free alcohol, obtained by the deprotection of 6e (TBAF, THF): (Chiralcel OD, hexanes: 2-propanol, 95:5, 1.0 mL/min): t_R(R) = 7.5 min; t_R(S) = 19.7 min.

The reaction of 5b (68 mg, 0.5 mmol) and benzaldehyde (152 µL, 1.5 mmol) with Ni(cod)₂, IPr and triethylsilane in THF following the general procedure described above afforded 6g in 76% isolated yield and 98% ee as determined by chiral HPLC. The absolute configuration of the stereocenter was assigned as R in analogy to 6a and 6j whose configuration were established by Mosher’s ester analysis.
Mosher’s ester analysis. The olefin geometry was determined to be Z by a nOe experiment (see below).

$^1$H NMR (500 MHz, CDCl$_3$, δ): 7.35 (d, $J = 7.6$ Hz, 2H), 7.29 (t, $J = 7.3$ Hz, 2H), 7.20 (t, $J = 7.3$ Hz, 1H), 5.79 (s, 1H), 5.30 (q, $J = 7.0$ Hz, 1H), 1.88 (d, $J = 6.7$ Hz, 3H), 1.80 (dd, $J = 6.5$, 14.5 Hz, 1H), 1.68 (dd, $J = 7.0$, 14.5 Hz), 1.64-1.54 (m, 6H), 1.28-1.18 (m, 1H), 1.12-1.00 (m, 3H), 0.97 (t, $J = 7.9$ Hz, 9H), 0.76-0.58 (m, 1H), 0.64 (q, $J = 7.9$ Hz, 6H).

$^{13}$C NMR (125 MHz, CDCl$_3$, δ): 144.6, 140.8, 128.0, 126.5, 125.6, 124.0, 120.4, 70.9, 39.2, 36.1, 33.8, 33.5, 27.0, 26.7, 13.9, 7.1, 5.1.

IR (NaCl, thin film): 2954, 2921, 1449, 1091, 1064, 863, 737.

HRMS-ESI (m / z): [M + Na]$^+$ calcd for C$_{23}$H$_{38}$OSiNa, 381.2584; found, 381.2589.

[$\alpha$]$_{20}^D$ –58.0 (c 1.12, CHCl$_3$)

Chiral HPLC analysis: Analysis was performed on the corresponding free alcohol, obtained by the deprotection of 6g (TBAF, THF): (Chiralcel OD-H, hexanes: 2-propanol, 99:1, 1.0 mL/min): $t_R$(S) = 11.3 min; $t_R$(R) = 17.4 min.

NOE DIFF experiment: Pre-saturation of the carbinol proton (δ 5.79 ppm) of 6g gave no nOe to the vinylic proton (δ 5.30 ppm). A 10.7% nOe to the methyl group, however, was observed. Similarly, pre-saturation of the methyl protons (δ 1.88 ppm) did not show any nOe to the cyclohexyl protons. A 4.5% nOe to the carbinol proton (δ 5.79 ppm), however, was observed.

The reaction of 5b (68 mg, 0.5 mmol) and benzaldehyde (152 µL, 1.5 mmol) with Ni(cod)$_2$, IPr and tert-butyldimethyl-silane in THF following the general procedure described above afforded 6h in 68% isolated yield and 98% ee as determined by chiral HPLC. The absolute configuration of the stereocenter was assigned as R in analogy to 6a and 6j whose configuration were established by Mosher’s ester analysis.

$^1$H NMR (400 MHz, CDCl$_3$, δ): 7.40-7.10 (m, 5H), 5.80 (s, 1H), 5.31 (q, $J = 7.0$ Hz, 1H), 1.88 (d, $J = 7.0$ Hz, 3H), 1.77 (dd, $J = 7.1$, 14.8 Hz, 1H), 1.66 (dd, $J = 7.0$, 14.6 Hz, 1H), 1.57 (m, 6H), 1.30-0.50 (m, 5H), 0.96 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$, δ): 144.5, 140.5, 127.9, 126.5, 125.6, 124.5, 120.5, 71.1, 39.1, 35.9, 33.8, 33.5, 26.9, 26.6, 18.6, 13.8, -4.6, -4.8.

IR (NaCl, thin film): 2926, 2854, 1449, 1252, 1090, 1064, 876, 835, 775, 698.

HRMS-ESI (m / z): [M + Na]$^+$ calcd for C$_{23}$H$_{38}$OSiNa, 381.2584; found, 381.2595

[$\alpha$]$_{20}^D$ –55.9 (c 1.11, CHCl$_3$)

Chiral HPLC analysis: Analysis was performed 6h without the deprotection of the silane protected alcohol: (Chiralcel OD-H, hexanes: 2-propanol, 100:0, 0.8 mL/min): $t_R$(R) = 4.1 min; $t_R$(S) = 4.4 min.
The reaction of 5b (68 mg, 0.5 mmol) and benzaldehyde (152 µL, 1.5 mmol) with Ni(cod)₂, IPr and dimethylphenylsilane in THF following the general procedure described above afforded 6i in 65% isolated yield and 98% ee as determined by chiral HPLC. The absolute configuration of the stereocenter was assigned as R in analogy to 6a and 6j whose configuration were established by Mosher’s ester analysis.

1H NMR (500 MHz, C₆D₆, δ): 7.66-7.61 (m, 2H), 7.49 (d, J = 7.6 Hz, 2H), 7.24-7.18 (m, 5H), 7.09 (t, J = 7.3 Hz, 1H), 5.89 (s, 1H), 5.25 (q, J = 6.7 Hz, 1H), 2.02 (dd, J = 7.0, 14.7 Hz, 1H), 1.93 (dd, J = 7.0, 14.7 Hz, 1H), 1.74-1.58 (m, 5H), 1.56 (d, J = 7.0 Hz, 3H), 1.35 (m, 1H), 1.10 (m, 3H), 0.82-0.60 (m, 2H), 1.57 (s, 3H), 1.55 (s, 3H).

13C NMR (100 MHz, CDCl₃, δ): 144.0, 139.9, 138.2, 133.8, 129.7, 127.99, 127.96, 126.6, 125.6, 121.1, 71.4, 39.1, 36.1, 33.8, 33.5, 26.9, 26.6, 13.6, -0.9, -1.0.

IR (NaCl, thin film): 2921, 2850, 1449, 1428, 1251, 1118, 1088, 1057, 881, 785, 737, 698.

HRMS-ESI (m / z): [M + Na]⁺ calcd for C₂₅H₃₄OSiNa, 401.2271; found, 401.2265.

[α]D²⁰ –19.0 (c 1.00, CHCl₃)

Chiral HPLC analysis: Analysis was performed on the corresponding free alcohol, obtained by the deprotection of 6i (TBAF, THF): (Chiralcel OD-H, hexanes: 2-propanol, 99:1, 1.0 mL/min): tR(S) = 11.3 min; tR(R) = 17.4 min.

The reaction of 5c (55 mg, 0.5 mmol) and benzaldehyde (152 µL, 1.5 mmol) with Ni(cod)₂, IPr and triethylsilane in THF following the general procedure described above afforded 6j in 40% isolated yield (co-eluted with a homoallylic alcohol minor product) and 98% ee as determined by chiral HPLC. The absolute configuration of the stereocenter was determined by Mosher’s ester analysis to be R.

1H NMR (500 MHz, CDCl₃, δ): 7.34 (d, J = 7.6 Hz, 2H), 7.29 (t, J = 7.3 Hz, 2H), 7.20 (t, J = 7.3 Hz, 1H), 5.72 (s, 1H), 5.46 (q, J = 7.0 Hz, 1H), 1.91 (d, J = 7.0 Hz, 3H), 1.86 (d, J = 14.6 Hz, 1H), 1.77 (d, J = 14.6 Hz, 1H), 0.95 (t, J = 7.9 Hz, 9 H), 0.80 (s, 9H), 0.61 (qd, J = 2.4, 7.6 Hz, 6H).

13C NMR (125 MHz, CDCl₃, δ): 144.7, 140.5, 127.8, 126.4, 125.9, 122.9, 71.7, 43.3, 30.7, 22.7, 14.0, 6.9, 4.9.

IR (NaCl, thin film): 2954, 1463, 1091, 1065, 1006, 742.

HRMS-ESI (m / z): [M + Na]⁺ calcd for C₂₁H₃₆OSiNa, 355.2428; found, 355.2427.

[α]D²⁰ –29.8 (c 1.14, CHCl₃)

Chiral HPLC analysis: Analysis was performed on the corresponding free alcohol, obtained by the deprotection of 6j (TBAF, THF): (Chiralcel OD-H, hexanes: 2-propanol, 99:1, 1.0 mL/min): tR(S) = 10.4 min; tR(R) = 13.3 min.
Mosher’s ester analysis: (+/−)-6j was first converted into the free alcohol (TBAF, THF) and then into a pair of diastereomers of (R)-Mosher’s esters (DCC, DMAP, (R)-Mosher’s acid, CH₂Cl₂). The vinylic quartets (δ 5.63 and 5.70 ppm) and the t-Bu singlets (δ 0.76 and 0.80 ppm) of the two diastereomers were well resolved by ¹H NMR and were assigned according to the method of Mosher.⁷ The enantiomerically enriched 6j was then converted to (R)-Mosher’s ester using the same procedure. The vinylic quartet was observed at δ 5.64 ppm, and the t-Bu singlet was observed at δ 0.75 ppm. Therefore, 3a had an absolute configuration of (R).

The reaction of 5d (13.8 mg, 0.1 mmol) and benzaldehyde (32 µL, 0.3 mmol) with Ni(cod)₂ (5.5 mg, 0.02 mmol, 20 mol%), IPr (16 mg, 0.04 mmol, 40 mol%) and triethylsilane (50 µL, 0.3 mmol, 300 mol%) in THF (1.5 ml) following general procedure described above afforded 6k and 6l in 1:1 ratio in 73% yield as determined by NMR versus an internal standard.

6k:
¹H NMR (500 MHz, CDCl₃, δ): 7.35 (d, J = 6.9 Hz, 2H), 7.29 (t, J = 7.6 Hz, 2H), 7.20 (t, J = 7.3 Hz, 1H), 5.79 (s, 1H), 5.34 (q, J = 7.0 Hz, 1H), 1.99 (m, 1H), 1.86 (d, J = 7.0 Hz, 1H), 1.73 (m, 1H), 1.36-1.10 (m, 10 H), 0.97 (t, J = 8.2, 9H), 0.86 (t, J = 7.0 Hz, 3H), 0.63 (q, J = 7.6 Hz, 6H).
¹³C NMR (125 MHz, CDCl₃, δ): 144.6, 143.1, 128.0, 126.5, 125.6, 118.9, 70.7, 32.1, 30.0, 29.8, 29.5, 28.7, 22.9, 14.4, 13.8, 7.1, 5.1.

6l:
¹H NMR (500 MHz, CDCl₃, δ): 7.36 (d, J = 7.0 Hz, 2H), 7.29 (t, J = 7.3 Hz, 2H), 7.20 (t, J = 7.0 Hz, 1H), 5.78 (s, 1H), 5.23 (t, J = 7.0 Hz, 1H), 2.29 (m, 2H), 2.10 (sextet, J = 7.6 Hz, 1H), 1.73 (sextet, J = 7.6 Hz, 1H), 1.52-1.28 (m, 8 H), 0.96 (t, J = 8.2, 9H), 0.92 (t, J = 7.0 Hz, 3H), 0.87 (t, J = 7.3 Hz, 3H), 0.63 (q, J = 7.6 Hz, 6H).
¹³C NMR (125 MHz, CDCl₃, δ): 144.6, 143.1, 128.0, 126.5, 125.7, 124.7, 71.3, 32.1, 30.5, 29.6, 28.3, 22.9, 22.3, 14.4, 12.8, 7.1, 5.1.
Deuterium Labeling Experiment

\( ^2 \text{H-6g} \) was converted to a mandelic acid ester 9 to determine the absolute configuration of the deuterated stereocenter using \(^1 \text{H NMR} \) by Parker’s method.\(^{10} \) The same mandelic acid derivative was also prepared by Fleming\(^{11} \) and was also analyzed by the method of Parker.

The reaction of 5b (68 mg, 0.5 mmol) and benzaldehyde (152 \( \mu \)L, 1.5 mmol) with Ni(cod)\(_2\), IPr and triethylsilane-d (239 \( \mu \)L, 1.5 mmol) in THF, following the general procedure described above afforded \( ^2 \text{H-6g} \) (111 mg, 64% yield) in 98% ee as determined by chiral HPLC and > 95:5 dr as determined by \(^1 \text{H NMR} \).

\(^1 \text{H NMR} \) (500 MHz, CDCl\(_3\), \( \delta \)): 7.35 (d, \( J = 8.0 \) Hz, 2H), 7.28 (t, \( J = 7.5 \) Hz, 2H), 7.19 (t, \( J = 7.5 \) Hz, 1H), 5.78 (s, 1H), 5.28 (q, \( J = 6.9 \) Hz, 1H), 1.87 (d, \( J = 7.0 \) Hz, 3H), 1.76 (bd, \( J = 6.6 \) Hz, 1H), 1.62-1.52 (m, 6H), 1.26-1.16 (m, 1H), 1.12-1.00 (m, 3H), 0.95 (t, \( J = 7.9 \) Hz, 9H), 0.76-0.58 (m, 1H), 0.62 (q, \( J = 7.9 \) Hz, 6H).

\(^{13} \text{C NMR} \) (125 MHz, CDCl\(_3\), \( \delta \)): 144.6, 140.7, 127.9, 126.5, 125.6, 120.4, 70.9, 38.8 (t, \( J = 19.5 \) Hz), 36.0, 33.8, 33.5, 26.9, 26.6, 13.9, 7.1, 5.1.

IR (NaCl, thin film): 2920, 1448, 1090, 1064, 731.

HRMS-ESI (m / z): \([\text{M + Na}]^+ \) calcd for C\(_{23}\)H\(_{37}\)DOSiNa, 382.2647; found, 382.2643.

\([\alpha]^{20}_D -57.8 \) (c 1.02, CHCl\(_3\)).

Chiral HPLC analysis: Analysis was performed on the deprotected \( ^2 \text{H-6g} \) (TBAF, THF): (Chiralcel OD-H, hexanes: 2-propanol, 99:1, 1.0 mL/min): \( t_R(S) = 11.1 \) min; \( t_R(R) = 17.3 \) min.
2H-6g (96 mg, 0.27 mmol) was stirred 30 min in TBAF (1 mL, 0.5 mmol, 0.5M in THF). The mixture was diluted in diethylether and washed with water. The ether solution was dried in MgSO₄, and the solvent was removed under reduced pressure. The crude was dissolved in CH₂Cl₂ (5 mL) and cooled to −78 °C. Ozone was bubbled through the solution for 20 min, and the solution turned blue. After purging with oxygen (2 min) triphenylphosphate (157 mg, 0.6 mmol in 5 mL CH₂Cl₂) was added in one portion at −78 °C, stirred 5 min, and warmed to room temperature. CH₂Cl₂ was removed under reduced pressure. Column chromatography first with 20% CH₂Cl₂ / hexane removed triphenylphosphate. A gradient of 10-20% EtOAc / Hexane afforded 7 (62 mg, 99% yield) in > 95:5 dr as determined by ¹H NMR.

¹H NMR (400 MHz, CDCl₃, δ): 7.40-7.27 (m, 5H), 5.04 (d, J = 4.4 Hz, 1H), 4.43 (d, J = 4.5 Hz, 1H), 2.14 (dt, J = 2.0, 6.9 Hz, 1H), 1.90-0.55 (m, 11H).

¹³C NMR (100 MHz, CDCl₃, δ): 209.3, 138.1, 129.1, 128.8, 127.7, 80.2, 45.2 (t, J = 19.0 Hz), 34.0, 33.2, 26.2, 26.1, 26.0.

IR (NaCl, thin film): 3458, 2923, 2851, 1711, 1450, 756, 670.

[α]²⁰D +231.7 (c 1.23, CHCl₃).

8

A 7 mL glass vial was charged with 7 (60 mg, 0.26 mmol) and lead tetraacetate (115 mg, 0.26 mmol). The vial was purged with nitrogen, CH₂Cl₂ (2.5 mL, saturated with nitrogen) was added. The reaction mixture was stirred 8 h at room temperature, and the CH₂Cl₂ solution was passed through a dry silica gel column (purged with argon) and eluted with CH₂Cl₂ (saturated with argon) under argon to remove benzaldehyde and other low polarity byproducts. 8 and a minor impurity were eluted with 30% ethylacetate / hexane. Column chromatography with a gradient of 5%-30% EtOAc / hexane afforded 8 (14 mg, 38% yield).

¹H NMR (400 MHz, CDCl₃, δ): 12.2-11.0 (bs, 1H), 2.21 (bd, J = 6.5 Hz, 1H), 1.85-1.65 (m, 6H), 1.40-0.80 (m, 5H).

¹³C NMR (100 MHz, CDCl₃, δ): 180.0, 41.8 (t, J = 19.5 Hz), 34.8, 33.2, 33.1, 26.3, 26.2.

IR (NaCl, thin film): 2925, 2852, 1705, 1414, 1295.
Acid 8 (12 mg, 0.084 mmol), methyl-(R)-mandelate (21 mg, 0.09 mmol), dicyclohexylcarbodiimide (26 mg, 0.126 mmol), 4-(dimethyl)-aminopyridine (2 mg, 0.016 mmol) was dissolved in CH₂Cl₂ (1.5 mL) and stirred 12 h at room temperature. The crude reaction mixture was filtered through a plug of silica, and the silica was washed with CH₂Cl₂. Column chromatography in 1%-5% EtOAc / hexane afforded 9 (15.6 mg, 52% yield). ¹H NMR indicated slight erosion of dr (> 90:10) at the deuterated stereocenter as compared to ²H-6g before conversion to 9. The deuterated stereocenter was assigned to be of the R configuration, according to the method of Parker,¹⁰ and the analysis was consistent with Fleming’s result.¹¹ (Refer to ¹H NMRs of ¹H-9, 9 and (+/–)-9 for comparison of chemical shifts).

¹H NMR (400 MHz, C₆D₆, δ): 7.48 (d, J = 6.9 Hz, 2H), 7.07 (t, J = 6.0 Hz, 2H), 7.03 (t, J = 7.4 Hz, 1H), 6.10 (s, 1H), 3.18 (s, 3H), 2.20 (dt, J = 1.7, 6.9 Hz, 1H), 1.92-1.80 (m, 1H), 1.80 -1.68 (m, 2H), 1.61-1.42 (m, 3H), 1.22-1.07 (m, 2H), 1.07-0.91 (m, 1H), 0.90-0.75 (m, 2H).
¹H NMR (400 MHz, CDCl₃, δ): 7.50-7.40 (m, 2H), 7.44-7.37 (m, 3H), 5.93 (s, 1H), 3.73 (s, 3H), 2.35 (bd, J = 6.9 Hz, 1H), 1.90-1.60 (m, 6H), 1.55-0.90 (m, 5H).
¹³C NMR (125 MHz, CDCl₃, δ): 172.7, 169.6, 134.1, 129.4, 129.0, 127.8, 74.4, 52.8, 41.6 (t, J = 20.0 Hz), 35.0, 33.11, 33.08, 26.3, 26.2.
IR (NaCl, thin film): 2923, 2850, 1760, 1742, 1215, 1163.

Prepared using the same method as 9 except that (±)-5b was used to give a 1:1 mixture of diastereomers of 9.

¹H NMR (400 MHz, C₆D₆, δ): 7.48 (d, J = 7.2 Hz, 2H), 7.07 (t, J = 7.0 Hz, 2H), 7.04 (t, J = 7.1 Hz, 1H), 6.11 (s, 2H), 3.18 (s, 6H), 2.20 (dt, J = 1.8, 6.9 Hz, 1H), 2.12 (dt, J = 1.8, 7.1 Hz, 1H), 1.92-1.80 (m, 1H), 1.80-1.68 (m, 2H), 1.61-1.42 (m, 3H), 1.22-1.07 (m, 2H), 1.07-0.91 (m, 1H), 0.90 -0.75 (m, 2H).
¹H NMR (400 MHz, CDCl₃, δ): 7.50-7.40 (m, 2H), 7.44-7.37 (m, 3H), 5.93 (s, 1H), 3.73 (s, 3H), 2.35 (dt, J = 1.9, 6.9 Hz, 1H), 2.30 (bd, J = 1.8, 7.0 Hz, 1H), 1.90-1.60 (m, 6H), 1.55-0.90 (m, 5H).
¹³C NMR (125 MHz, CDCl₃, δ): 172.7, 169.6, 134.1, 129.4, 129.0, 127.8, 74.4, 52.8, 41.6 (t, J = 20.0 Hz), 35.0, 33.11, 33.08, 26.3, 26.2.
IR (NaCl, thin film): 2923, 2850, 1760, 1742, 1215, 1163.
Cyclohexylacetic acid (31.3 mg, 0.22 mmol), methyl-(R)-mandelate (33.2 mg, 0.2 mmol), dicyclohexylcarbodiimide (61.9 mg, 0.3 mmol) and 4-(dimethylamino)-pyridine (2.4 mg, 0.02 mmol) were mixed together and dissolved in anhydrous CH₂Cl₂ (2 mL). The mixture was stirred 6 h at room temperature. The CH₂Cl₂ solution was filtered through a plug of silica, the silica was washed with CH₂Cl₂. The filtrate was concentrated and column chromatography afforded ¹H-9 (45.1 mg, 78% yield).

¹H NMR (400 MHz, C₆D₆, δ): 7.46 (d, J = 7.2 Hz, 2H), 7.10-7.00 (m, 3H), 6.09 (s, 1H), 3.18 (s, 3H), 2.22 (dd, J = 7.1, 14.9 Hz, 1H), 2.12 (dd, J = 7.1, 14.9 Hz, 1H), 1.86 (m, 1H), 1.73 (m, 2H), 1.60-1.40 (m, 3H), 1.22-1.10 (m, 2H), 1.10-0.90 (m, 1H), 0.90-0.75 (m, 2H).

¹H NMR (500 MHz, CDCl₃, δ): 7.50-7.35 (m, 5H), 5.93 (s, 1H), 3.73 (s, 3H), 2.37 (dd, J = 7.0, 15.0 Hz, 1H), 2.31 (dd, J = 7.0, 14.9 Hz, 1H), 1.92-1.61 (m, 6H), 1.36-0.60 (m, 5H).

¹³C NMR (100 MHz, CDCl₃, δ): 172.6, 169.6, 134.1, 129.4, 128.9, 127.7, 74.4, 52.7, 41.9, 35.0, 33.1, 26.3, 26.2.

IR (NaCl, thin film): 2925, 2852, 1760, 1743, 1450, 1216, 1159, 1114, 1044, 734.

HRMS-ESI (m / z): [M + Na]⁺ calcd for C₁₇H₂₂DO₄Na, 313.1410; found, 313.1400.

[α]²⁰D –90.3 (c 1.03, CHCl₃).
References:


\[
\begin{align*}
\text{O} & \quad \text{Si-BrMe}_2 \\
\end{align*}
\]

\[
\text{CDCl}_3
\]
CDCl\textsubscript{3}

Current Data Parameters

- Sample: 6-05-004-006
-掃描数: 5
-スキャン: 1

1H-NMR Parameters

- CDCl\textsubscript{3}
- n-Pr
- n-Pr
- a-S-5a

1H-NMR

- δ 7.50 ppm
- J 8.25 Hz
- δ\textsuperscript{TMS} 400.1597 MHz

13C-NMR Parameters

- δ 17.56 ppm
- δ\textsuperscript{TMS} 100.1597 MHz

13C-NMR

- δ 31.38 ppm
- δ\textsuperscript{TMS} 100.1597 MHz

13C-NMR

- δ 5.46 ppm
- δ\textsuperscript{TMS} 100.1597 MHz

13C-NMR

13C-NMR

- δ 22.08 ppm
- δ\textsuperscript{TMS} 100.1597 MHz

13C-NMR

- δ -6.51 ppm
- δ\textsuperscript{TMS} 100.1597 MHz

13C-NMR

- δ -74.82 ppm
- δ\textsuperscript{TMS} 100.1597 MHz
Chapter 2

Nickel-Catalyzed Coupling of Alkenes and Aldehydes
Introduction

Alkenes are one of the most versatile, utilized, and readily available classes of functional groups. Simple alpha olefins are produced in megaton scale each year industrially, highlighting the importance of these organic feedstocks.\textsuperscript{1} Several indispensable transformations utilize olefins, such as Ziegler-Natta polymerization,\textsuperscript{2} the Heck reaction,\textsuperscript{3a-e} Wacker oxidation,\textsuperscript{3a} hydroformylation,\textsuperscript{3a} hydrometallation,\textsuperscript{3a} alkene cross-metathesis,\textsuperscript{4} epoxidation\textsuperscript{5} and dihydroxylation.\textsuperscript{5}

Transition Metal-Catalyzed Coupling of Alkenes and Aldehydes

Transition metal-catalyzed intermolecular reductive and alkylative coupling reactions have emerged as useful methods for the preparation of alcohol and amine derivatives. Nickel, palladium, rhodium and ruthenium catalysts have been found to be particularly effective in the intermolecular coupling of alkynes, 1,3-enynes, 1,3-dienes, allenes, enoate esters, enones, and enals with aldehydes, ketones, epoxides, glyoxylate esters, and imines.\textsuperscript{8-11} A variety of reducing agents have been used in these reductive couplings, such as triethylborane, organozinc reagents, organosilanes, and molecular hydrogen. As yet, however, simple, unactivated alkenes such as ethylene and 1-octene have not been reported to undergo analogous catalytic reductive coupling reactions.

As a part of our program directed toward developing C–C bond forming reactions of “off-the-shelf”, simple starting materials, we became very interested in catalytic alkene–aldehyde coupling processes. Intramolecular versions of this transformation have been reported, such as transition metal-catalyzed cyclizations of enals and enones. For example, the titanium-catalyzed intramolecular reductive cyclization of enals and enones was first reported by Buchwald and Crowe.\textsuperscript{12a-b} Recently Ogoshi has demonstrated a nickel-catalyzed cyclization of enones.\textsuperscript{12c} α,ω-
Enals also undergo cyclization by way of a radical process\textsuperscript{13} and also in a Lewis acid-catalyzed carbonyl-ene reaction.\textsuperscript{7}

Intermolecular coupling of unactivated alkenes and aldehydes is commonly mediated by a transition metal (stoichiometric) or accomplished by way of a carbonyl-ene reaction.\textsuperscript{7,15} An interesting process developed by Woerpel combined an alkene and an aldehyde through a silver-catalyzed silylene transfer reaction.\textsuperscript{16}

\textit{Oxametallacycle of alkenes and aldehydes}

Formation of an oxametallacycle through the oxidative coupling of simple alkenes and ketones has been observed with several transition metals such as titanium, zirconium and rhodium.\textsuperscript{14} These studies suggested that transition metal-catalyzed, intermolecular coupling of alkenes and aldehydes would be feasible under the appropriate conditions. Ogoshi recently observed that Lewis acids such as a silyl triflate and trimethylaluminum facilitated the formation of an oxanickellacycle through cyclization of $\alpha,\omega$-enals and $\alpha,\omega$-enones.\textsuperscript{17} We proposed that if the intermolecular coupling of an alkene and an aldehyde occurred, the nickel–alkyl bond could undergo a $\beta$-hydride elimination, followed by the removal of triflic acid from nickel to regenerate the nickel catalyst (Figure 1). This mechanistic framework also resembles that in the Heck reaction, a very important example of a catalytic coupling of an alkene and an electrophile.\textsuperscript{3a-e}
Figure 1. Proposed pathway for a nickel-catalyzed alkene–aldehyde coupling.

Carbonyl-Ene Reactions

The carbonyl-ene reaction has historically been the most direct method to combine simple alkenes and carbonyl compounds to provide homoallylic alcohol products. Recent efforts in this area have focused on asymmetric induction through the use of Lewis acids and chiral ligands, such as (bisoxazoline)CuX₂, (pybox)ScX₃, and (BINAP)TiX₂ complexes.¹⁸a-¹⁸f Typically the alkenes that are employed in intermolecular carbonyl-ene reactions are 1,1-disubstituted and trisubstituted olefins. With respect to the carbonyl component, electron-deficient enophiles such as glyoxylates, glyoxamides, and chloral are generally more efficient than simple aromatic and aliphatic aldehydes. In fact, since the report of the carbonyl-ene reaction in 1943⁷a there have been only a few scattered examples of intermolecular ene reactions between monosubstituted alkenes and simple aromatic and aliphatic aldehydes.¹⁹

To summarize, Lewis acid-catalyzed carbonyl-ene reactions are typically not feasible for the most readily available alkene and aldehyde building blocks. Part of the nickel-catalyzed coupling of alkenes and aldehydes described herein is thus complementary in scope to the carbonyl-ene...
reaction; monosubstituted alkenes couple with simple aldehydes to provide a carbonyl-ene-type product in high yield.

**Nickel-Catalyzed Coupling of Ethylene and Aldehydes**

Our investigations commenced with the simplest olefin, ethylene, and benzaldehyde. After a brief examination of phosphorous-based additives, we found that a combination of Ni(cod)$_2$, tris-(o-methoxyphenyl)-phosphine ((o-anisyl)$_3$P), triethylamine, and triethyilsilyl triflate (Et$_3$SiOTf) promoted the coupling of ethylene with a variety of aldehydes. In all cases a triethylsilyl ether of an allylic alcohol is obtained in good to excellent yield (Table 1), providing ready access to a class of allylic alcohol derivatives that have been used in cross metathesis reactions, for example.$^4$

Under 1 atm of ethylene, simple aromatic aldehydes such as benzaldehyde and $p$-tolylaldehyde undergo efficient coupling (entries 1–2). Ortho substitution on the aromatic aldehyde does not appear to deter the coupling process (entry 3), and notably, acid-sensitive heteroaromatic aldehydes such as 1-methyl-2-indolecarboxaldehyde (entry 8) and 2-furaldehyde (entry 9) are tolerated, even in the presence of Lewis acidic silyl triflates. As an additional advantage, other common silyl triflates can be used in the coupling reaction, providing orthogonal protection of the hydroxyl group when necessary (entries 5–7).
Table 1. Nickel-Catalyzed Coupling of Ethylene, Aldehydes, and Silyl Triflates

![Chemical Structure]

<table>
<thead>
<tr>
<th>entry</th>
<th>R (aldehyde)</th>
<th>R$_3$SiOTf</th>
<th>product</th>
<th>isolated yield (%)</th>
<th>entry</th>
<th>R (aldehyde)</th>
<th>R$_3$SiOTf</th>
<th>product</th>
<th>isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Et$_3$SiOTf</td>
<td>1a</td>
<td>82 (65)</td>
<td>8</td>
<td>Et$_3$SiOTf</td>
<td>1b</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>p-tolyl</td>
<td>Et$_3$SiOTf</td>
<td>1b</td>
<td>88 (65)</td>
<td>9</td>
<td>2-furyl</td>
<td>Et$_3$SiOTf</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>o-tolyl</td>
<td>Et$_3$SiOTf</td>
<td>1c</td>
<td>93 (64)</td>
<td>10</td>
<td>Et$_3$SiOTf</td>
<td>1f</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>p-anisyl</td>
<td>Et$_3$SiOTf</td>
<td>1d</td>
<td>95 (65)</td>
<td>11</td>
<td>Et$_3$SiOTf</td>
<td>1k</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2-naphthyl</td>
<td>Me$_3$SiOTf</td>
<td>1e</td>
<td>95 (83)</td>
<td>12</td>
<td>piv</td>
<td>Et$_3$SiOTf</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2-naphthyl</td>
<td>nBuMe$_3$SiOTf</td>
<td>1f</td>
<td>60</td>
<td>13</td>
<td>cyclohexyl</td>
<td>Et$_3$SiOTf</td>
<td>81 (40)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2-naphthyl</td>
<td>nBuMe$_3$SiOTf</td>
<td>1g</td>
<td>67</td>
<td>14</td>
<td></td>
<td>Et$_3$SiOTf</td>
<td>25 (34)</td>
<td></td>
</tr>
</tbody>
</table>

* Standard procedure: Ni(cod)$_2$ (20 mol%) and (o-anisyl)$_3$P (40 mol%) were dissolved in 2.5 mL toluene under argon. Ethylene (balloon, 1 atm) was substituted for argon. Triethylamine (600 mol%), the aldehyde (100 mol%, 0.5 mmol), and Et$_3$SiOTf (175 mol%) were added. The reaction mixture was stirred 6-18 h at 23 °C. * (o-anisyl)$_3$P was replaced by Cy$_3$PhP. * (o-anisyl)$_3$P was replaced by Ph$_3$P. * Yields determined by $^1$H NMR using DMF as a standard. * Conducted under 2 atm of ethylene. * Stirred at room temperature for 30 h.

Remarkably, sterically demanding tertiary aliphatic aldehydes such as pivaldehyde and 2,2-dimethyl-3-oxo-propionic acid methyl ester couple with ethylene with the same efficacy as benzaldehyde (entries 12 and 13). Enolizable aldehydes are not appropriate substrates in this system, however, since they react rapidly with the silyl triflate and triethylamine to form silyl enol ethers. The coupling of ethylene with cyclohexanecarboxaldehyde is fast enough, however, that a significant amount of coupling product is observed and can be isolated (entry 14).
Tris-\((o\text{-methoxyphenyl})\)-phosphine is the ligand of choice for the ethylene–aldehyde coupling. Other phosphines such as dicyclohexylphenylphosphine and triphenylphosphine provide lower yield under the same reaction conditions (entries 1–5, 13).

An interesting electronic effect is observed in these coupling reactions. Electron-rich aromatic aldehydes are more efficient substrates than electron-poor aromatic aldehydes. Among the four \textit{para}-substituted aromatic aldehydes examined, electron-donating \textit{para}-substituents (–Me and –OMe) improve the yield of the coupling reaction (entries 2 and 4). Electron-withdrawing \textit{para}-substituents (–CF₃ and –CO₂Me) suffer from incomplete conversion, even after prolonged reaction time (entries 10–11). In such cases, products resulting from a pinnacol coupling are observed but are not observed in any other example.

**Ligand-Dependent Regioselectivity in the Coupling of Terminal Alkenes and Aldehydes**

The encouraging results in these ethylene–aldehyde coupling reactions prompted us to examine the scope of the alkenes in detail. Unlike ethylene, 1-octene can afford more than one possible coupling product depending on where the new carbon–carbon bond is formed. The examination of a series of ligands revealed several interesting observations regarding ligand-dependent regioselectivity.

Under similar reaction conditions as the ethylene–aldehyde cases, 1-octene and benzaldehyde undergo coupling in the presence of Ni(cod)₂, a ligand, triethylamine, and Et₃SiOTf. Two distinct types of coupling products are typically observed, namely a 1,1-disubstituted allylic alcohol product (A) and a homoallylic alcohol product (H). Different classes of phosphine ligands favor one or the other coupling products, as summarized in Tables 2 and 3.
The ratio of the allylic to the homoallylic products is opposite for trialkylphosphines in which all alkyl groups are linear (entries 1 and 2), relative to those in which the three alkyl groups are branched (entries 3–5) or tertiary (entry 6). Among six trialkylphosphines with very similar electron-donating abilities,\textsuperscript{20a} tri-\textit{n}-butylphosphine, the smallest of the trialkylphosphines examined, favors the homoallylic alcohol product while tricyclohexylphosphine and tri-\textit{t}-butylphosphine, the largest among these, favor the 1,2-disubstituted allylic product. However, these sterically demanding ligands are not nearly as effective, affording the coupling products in low yield.

*Table 2. Ligand-Dependent Regioselectivity: Electron-Rich Phosphines*\textsuperscript{a}

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>cone angle (b)</th>
<th>(\nu_{CO}) (b)</th>
<th>yield (2b') (c)</th>
<th>yield (2b) (c)</th>
<th>ratio (2b':2b) (d)</th>
<th>combined yield (2b'-2b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(n-Bu)_3P</td>
<td>132</td>
<td>1915</td>
<td>11%</td>
<td>27%</td>
<td>29:71</td>
<td>38%</td>
</tr>
<tr>
<td>2</td>
<td>(n-Oct)_3P</td>
<td>107</td>
<td>1915</td>
<td>7%</td>
<td>14%</td>
<td>23:77</td>
<td>21%</td>
</tr>
<tr>
<td>3</td>
<td>(i-Pr)_3P</td>
<td>160</td>
<td>1915</td>
<td>11%</td>
<td>2%</td>
<td>85:15</td>
<td>13%</td>
</tr>
<tr>
<td>4</td>
<td>Cy_3P</td>
<td>10%</td>
<td>10%</td>
<td>3%</td>
<td>78:22</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Cy_3P</td>
<td>170</td>
<td>1915</td>
<td>13%</td>
<td>3%</td>
<td>81:19</td>
<td>16%</td>
</tr>
<tr>
<td>6</td>
<td>(i-Bu)_3P</td>
<td>182</td>
<td>1915</td>
<td>7%</td>
<td>2%</td>
<td>78:22</td>
<td>9%</td>
</tr>
<tr>
<td>7</td>
<td>Cy_2PhP</td>
<td>162</td>
<td>1915</td>
<td>37%</td>
<td>16%</td>
<td>70:30</td>
<td>53%</td>
</tr>
<tr>
<td>8</td>
<td>Cy_2(o-tol)P</td>
<td>181</td>
<td>1917</td>
<td>30%</td>
<td>5%</td>
<td>86:14</td>
<td>35%</td>
</tr>
<tr>
<td>9</td>
<td>Cy_2(o-Ph-Ph)P</td>
<td>32%</td>
<td>22%</td>
<td>60:40</td>
<td>54%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Cy_2FcP</td>
<td>14%</td>
<td>2%</td>
<td>88:12</td>
<td>16%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(\textsuperscript{a}\) Standard procedure: Ni(cod)\(_2\) (20 mol%) and a ligand (40 mol%) were dissolved in 1.5 mL toluene. Alkene (500 mol%), triethylamine (600 mol%), the aldehyde (100 mol%, 0.25 mmol) and Et\(_3\)SiOTf (175 mol%) were added. The reaction mixture was stirred 18 h at 23 °C. \(\textsuperscript{b}\) See ref. 20. \(\textsuperscript{c}\) Yields determined by \(^1\text{H}\) NMR using DMF as a standard. \(\textsuperscript{d}\) Ratio was determined by \(^1\text{H}\) NMR of the crude reaction mixture. \(\textsuperscript{e}\) 48 h reaction time. \(\textsuperscript{f}\) 1250 mol% alkene was used.
Notably, replacing one of the alkyl substituent of the tricyclohexylphosphine with a phenyl ring dramatically improves the yield (53% vs 16%; Table 2, entries 5 and 7) with a slightly diminished A:H ratio. Other aryldicyclohexylphosphines also display a similar yield enhancement (entries 8 and 9, as compared to entries 4–6). The bulky and electron-rich dicyclohexylferrocenylphosphine, however, seems to be more closely related to tri-\textit{i}-butylphosphine, (poor yield for both the allylic and homoallylic alcohol products, entry 10). All of the sterically demanding dicyclohexylaryl derivatives examined favor the allylic alcohol product, and dicyclohexylphenylphosphine is the optimal ligand in terms of yield and selectivity.

The pronounced ligand effects prompted us to examine other organophosphorus ligands (Table 3). Among the four triarylphosphine ligands with a similar cone angle but different para-substituents (entries 5–7 and 9),\textsuperscript{20b,20c} tris-(\textit{p}-trifluoromethyl-phenyl)-phosphine, the least electron-rich ligand of the four, has the highest H:A ratio (entry 9) whereas tri-\textit{p}-tolylphosphine, the most \(\sigma\)-electron-donating among these four ligands, has the lowest H:A ratio (entry 5).

These data suggest that a higher H:A ratio can be achieved by decreasing the electron-donating ability of the phosphine ligand. In accord with this hypothesis, ethyldiphenylphosphinite ((EtO)Ph\textsubscript{2}P) further improves the H:A ratio in the case of 1-octene and benzaldehyde (entry 8, 95:5). The hypothesis becomes even more convincing when the H:A ratio is plotted against the \(\sigma\)-electron-donating ability of various phosphines in Table 3 (Figure 2).\textsuperscript{20} Very electron deficient phosphonites and phosphites are not effective ligands, however (entries 10 and 11). It should be noted that the cone angle of the ligands also affects the observed H:A ratio. Many of the less electron-rich ligands that favor the homoallylic product in Table 3 are also among the smaller ligands.
Table 3. Ligand-Dependent Regioselectivity: Electron-Poor Phosphines

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>cone angle $^b$</th>
<th>$v_{CO}^b$</th>
<th>combined yield (2b:2b')</th>
<th>ratio (2b:2b') $^d$</th>
<th>E:Z (2b) $^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cy$_2$PhP</td>
<td>162</td>
<td>1917</td>
<td>73</td>
<td>29:71</td>
<td>n.d.</td>
</tr>
<tr>
<td>2</td>
<td>CyPh$_2$P</td>
<td>153</td>
<td>1917</td>
<td>84</td>
<td>75:25</td>
<td>91:9</td>
</tr>
<tr>
<td>3</td>
<td>(p-anisyl)$_3$P</td>
<td>194</td>
<td>1919</td>
<td>70</td>
<td>83:17</td>
<td>80:20</td>
</tr>
<tr>
<td>4</td>
<td>FcPh$_2$P</td>
<td>173</td>
<td>1920</td>
<td>78</td>
<td>92:8</td>
<td>67:33</td>
</tr>
<tr>
<td>5</td>
<td>(p-tol)$_3$P</td>
<td>145</td>
<td>1920</td>
<td>78</td>
<td>92:8</td>
<td>67:33</td>
</tr>
<tr>
<td>6</td>
<td>Ph$_3$P</td>
<td>145</td>
<td>1922</td>
<td>73</td>
<td>92:8</td>
<td>67:33</td>
</tr>
<tr>
<td>7</td>
<td>(p-F-Ph)$_3$P</td>
<td>145</td>
<td>1924</td>
<td>74</td>
<td>92:8</td>
<td>57:43</td>
</tr>
<tr>
<td>8</td>
<td>(EtO)Ph$_2$P</td>
<td>133</td>
<td>1926</td>
<td>81</td>
<td>95:5</td>
<td>75:25</td>
</tr>
<tr>
<td>9</td>
<td>(p-CF$_3$-Ph)$_3$P</td>
<td>145</td>
<td>1929</td>
<td>44</td>
<td>&gt;95:5</td>
<td>69:31</td>
</tr>
<tr>
<td>10</td>
<td>(EtO)$_2$PhP</td>
<td>121</td>
<td>1932</td>
<td>20</td>
<td>&gt;95:5</td>
<td>89:11</td>
</tr>
<tr>
<td>11</td>
<td>(PhO)$_3$P</td>
<td>128</td>
<td>1951</td>
<td>&lt;5</td>
<td>n.d</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

$^a$ Standard procedure: Ni(cod)$_2$ (20 mol%) and a ligand (40 mol%) were dissolved in 2.5 mL toluene. Alkene (1 mL), triethylamine (600 mol%), the aldehyde (100 mol%, 0.5 mmol) and Et$_3$SiOTf (175 mol%) were added. The reaction mixture was stirred 18 h at 23 °C. $^b$ See ref. 20. $^c$ Yields were determined by $^1$H NMR using DMF as a standard. $^d$ Ratio was determined by $^1$H NMR after the products were treated with TBAF. $^*$ 48 h reaction time.

Based on the results of this study, we surmised that the coupling product ratio is determined by a combined effect of the electron-donating ability and the cone angle of the phosphine ligands. High H:A ratios can be achieved by using less electron-rich phosphines with small cone angle such as (EtO)Ph$_2$P while high A:H ratios can be obtained by using electron-rich phosphines with a large cone angle such as Cy$_2$PhP.$^{22}$
Effects of the Base

Tertiary amines are the optimal bases for the nickel-catalyzed coupling of alkenes and aldehydes. Among different types of amine bases examined in ethylene couplings, only tertiary amines provide >20% yield of coupling products (Table 4, entries 1 and 3). Amines that likely are able to interact with nickel to a greater degree, such as pyridine (Table 4, entry 5 and Table 6, entry 6), are not effective. No coupling products are detected when inorganic bases are used in place of triethylamine (Table 4, entries 6–8).

Tertiary amines were further examined in the 1-octene coupling reaction (Tables 5–6), and triethylamine was consistently superior to other tertiary amines (Table 5, 1–4 and Table 6, 1–5).
Tertiary amines smaller or larger than triethylamine compromised the yield of the coupling reaction (Table 5, entries 2–4).

**Table 4.** Effect of Bases in the Ethylene–Benzaldehyde Coupling

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et$_3$N</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>Et$_3$NH</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>N-methylpyrrolidine</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>proton sponge</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>pyridine</td>
<td>12</td>
</tr>
<tr>
<td>6$^c$</td>
<td>K$_3$PO$_4$</td>
<td>&lt;5</td>
</tr>
<tr>
<td>7</td>
<td>K$_3$CO$_3$</td>
<td>&lt;5</td>
</tr>
<tr>
<td>8</td>
<td>Cs$_2$CO$_3$</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

$^a$ Standard procedure: Ni(cod)$_2$ (20 mol%) and (o-anisyl)$_3$P (40 mol%) were dissolved in 2.5 mL toluene under argon. Ethylene (balloon, 1 atm) was substituted for argon. A base (600 mol%), benzaldehyde (100 mol%, 0.5 mmol), and Et$_3$SiOTf (175 mol%) were added. The reaction mixture was stirred 18 h at 23 °C. $^b$ Yields were determined by $^1$H NMR using DMF as a standard. $^c$ Benzaldehyde was replaced by 2-naphthaldehyde and the reaction was run at 0.25 mmol scale.

The nature of the tertiary amines in determining the yield deserves further comment. It appears that a balance of the nucleophilicity, basicity, and steric bulk of the amine base is required for the coupling reaction to occur efficiently. Amines can compete with the phosphorus ligand, alkene, and aldehyde for a coordination site on nickel. A more nucleophilic (σ-electron-donating) or smaller amine might hinder the coordination of any of the other required components to the nickel catalyst. For instance, the less nucleophilic N-methylmorpholine (Table 6, entry 3) provides a better yield than N-methylpiperidine (Table 6, entry 4).

In summary, triethylamine is the best base for the nickel-catalyzed coupling of alkenes and aldehydes, probably because of a combination of low coordinating ability and appropriate basicity.
Table 5. Effect of Bases in the 1-Octene–Benzaldehyde Coupling (Cy2PhP)\textsuperscript{a}

\[
\begin{array}{cccc}
\text{entry} & \text{base} & \text{combined yield (2b' + 2b)} \text{b} & \text{ratio (2b':2b) c} \\
1 & Et3N & 61\% & 78:22 \\
2 & Et(i-Pr)2N & 10\% & 60:40 \\
3 & Cy2NMe & 20\% & 60:40 \\
4 & N-methylpyrroolidine & 7\% & 71:29 \\
5 & 2,6-lutidine & 12\% & 58:42 \\
\end{array}
\]

\textsuperscript{a} Standard procedure: Ni(cod)\textsubscript{2} (20 mol%) and Cy\textsubscript{2}PhP (40 mol%) were dissolved in 1.5 mL alkene. A base (600 mol%), benzaldehyde (100 mol%, 0.1 mmol), and Et\textsubscript{3}SiOTf (100 mol%) were added. The reaction mixture was stirred 18 h at 23 °C. \textsuperscript{b} Yields were determined by \textsuperscript{1}H NMR using DMF as a standard. \textsuperscript{c} Ratio was determined by \textsuperscript{1}H NMR of the crude reaction mixture.

Table 6. Effect of Bases in the 1-Octene–Benzaldehyde Coupling (Ph\textsubscript{3}P)\textsuperscript{a}

\[
\begin{array}{cccc}
\text{entry} & \text{base} & \text{combined yield (2b + 2b')} \text{b} & \text{ratio (2b:2b')} \text{b} & \text{ratio (E/Z) c} \\
1 & Et3N & 64\% & 92:8 & 87:13 \\
2 & Cy2NMe & 35\% & >95:5 & 71:29 \\
3 & N-methylmorpholine & 25\% & 94:6 & 69:31 \\
4 & N-methylpiperidine & <5\% & n.d. & n.d. \\
5 & N-methylpyrrolidine & <5\% & n.d. & n.d. \\
6 & DMAP & <5\% & n.d. & n.d. \\
\end{array}
\]

\textsuperscript{a} Standard procedure: Ni(cod)\textsubscript{2} (20 mol%) and Ph\textsubscript{3}P (40 mol%) were dissolved in 2.5 mL toluene. 1-octene (1 mL), a base (600 mol%), benzaldehyde (100 mol%, 0.5 mmol), and Et\textsubscript{3}SiOTf (175 mol%) were added. The reaction mixture was stirred 18 h at 23 °C. \textsuperscript{b} Yields and ratios were determined by \textsuperscript{1}H NMR using DMF as a standard. \textsuperscript{c} Ratio was determined from the desilylated product by \textsuperscript{1}H NMR.
Source of Nickel

Since the precatalyst Ni(cod)$_2$ has two chelating diene ligands (1,5-cyclo-octadiene), other nickel(II) precatalysts without alkene ligands were examined, including Ni(Ph$_3$P)$_4$, Ni(acac)$_2$/Ph$_3$P/DIBAL, Ni(Ph$_3$P)$_2$Cl$_2$/n-BuLi, and Ni(Ph$_3$P)$_2$Br$_2$/n-BuLi (Table 7). Only the Ni(acac)$_2$/Ph$_3$P/DIBAL system is as efficient as Ni(cod)$_2$/Ph$_3$P (entry 3). Ni(Ph$_3$P)$_4$ is saturated with phosphine ligand, and perhaps alkene coordination to the nickel catalyst is thus inhibited. Similarly, Ni(cod)$_2$/Cy$_2$PhP is more efficient than Ni(acac)$_2$/Cy$_2$PhP/DIBAL and Ni(Cy$_2$PhP)$_2$Cl$_2$/n-BuLi (Table 8). Therefore Ni(cod)$_2$ was used in all subsequent investigations.

Table 7. Examination of Other Nickel Precatalysts

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>yield (2b) $^b$</th>
<th>yield (2b') $^b$</th>
<th>ratio (2b:2b') $^c$</th>
<th>combined yield $^b$ (2b+2b')</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ni(cod)$_2$/Ph$_3$P</td>
<td>78%</td>
<td>6%</td>
<td>93.7</td>
<td>84%</td>
</tr>
<tr>
<td>2</td>
<td>Ni(Ph$_3$P)$_4$</td>
<td>41%</td>
<td>3%</td>
<td>93.7</td>
<td>44%</td>
</tr>
<tr>
<td>3</td>
<td>Ni(acac)$_2$/Ph$_3$P/DIBAL</td>
<td>72%</td>
<td>5%</td>
<td>93.7</td>
<td>77%</td>
</tr>
<tr>
<td>4</td>
<td>Ni(Ph$_3$P)$_2$Cl$_2$/n-BuLi</td>
<td>32%</td>
<td>2%</td>
<td>94.6</td>
<td>34%</td>
</tr>
<tr>
<td>5</td>
<td>Ni(Ph$_3$P)$_2$Br$_2$/n-BuLi</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
<td>n.d.</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

$^a$ Standard procedure: The nickel precatalyst system (20 mol%) was dissolved in 2.5 mL toluene. The alkene (1 mL), triethylamine (600 mol%), the aldehyde (100 mol%, 0.5 mmol), and Et$_3$SiOTf (175 mol%) were added. The reaction mixture was stirred 48 h at 23 °C. $^b$ Yields were determined by $^1$H NMR using DMF as a standard. $^c$ Ratios were determined by $^1$H NMR of the crude reaction mixture.
Table 8. Examination of Other Nickel Precatalysts

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>yield (2b') (^b)</th>
<th>yield (2b) (^b)</th>
<th>ratio (2b':2b) (^c)</th>
<th>combined yield ((2b'+2b)) (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ni(cod)_2 / Cy_2PhP</td>
<td>52%</td>
<td>21%</td>
<td>71:29</td>
<td>73%</td>
</tr>
<tr>
<td>2 (^d)</td>
<td>Ni(cod)_2 / Cy_2PhP</td>
<td>53%</td>
<td>20%</td>
<td>73:27</td>
<td>73%</td>
</tr>
<tr>
<td>3</td>
<td>Ni(acac)_2 / Cy_2PhP / DIBAL</td>
<td>39%</td>
<td>16%</td>
<td>71:29</td>
<td>55%</td>
</tr>
<tr>
<td>4</td>
<td>Ni(Cy_2PhP)_2Cl_2 / n-BuLi</td>
<td>21%</td>
<td>7%</td>
<td>75:25</td>
<td>28%</td>
</tr>
</tbody>
</table>

\(^a\) Standard procedure: The nickel precatalyst system (20 mol%) was dissolved in toluene. The alkene (500 mol%), triethylamine (600 mol%), the aldehyde (100 mol%), and Et_3SiOTf (175 mol%) were added. The reaction mixture was stirred 48 h at 23 °C. \(^b\) Yields were determined by \(^1\)H NMR using DMF as a standard. \(^c\) Ratios were determined by \(^1\)H NMR of the crude reaction mixture. \(^d\) 1 mL 1-octene was used.

Substrate Scope

Applying the results of the studies of ligand and base effects, the substrate scope of the nickel-catalyzed coupling of alkenes, aldehydes, and silyl triflates was next examined (Tables 9–12). In general, ethylene and monosubstituted alkenes are superior substrates in this coupling reaction, while 1,1-disubstituted alkenes and acyclic 1,2-disubstituted (cis or trans) alkenes are significantly less reactive. Trisubstituted alkenes do not react under the standard reaction conditions.

The Ni–EtOPh_2P system efficiently catalyzes the coupling of monosubstituted alkenes and simple aromatic aldehydes such as benzaldehyde (Table 9). While the couplings of ethylene with most aldehydes usually take less than 8 h to reach completion, those involving monosubstituted alkenes typically require more than 18 h (entries 2–3). Nevertheless, with EtOPh_2P as the ligand, nickel catalyzes the coupling of several monosubstituted alkenes and aldehydes in excellent
yield. The reaction is also highly regioselective and $E/Z$ selective, favoring an $E$-homoallylic alcohol product.

Aromatic aldehydes (Table 9, entries 2, 6, 9, 12), heteroaromatic aldehydes (entries 7 and 13), and sterically demanding aldehydes (entries 8 and 14) are excellent coupling partners with monosubstituted alkenes, affording an $E$-homoallylic alcohol derivative as the major product and an allylic alcohol derivative as the minor product, with a selectivity $>95:5$ in most cases. Monosubstituted aromatic aldehydes of all substitution patterns are tolerated ($ortho$-, $meta$-, and $para$-, entry 10). Aldehydes with an electron-donating substituent in the $para$ position ($p$-$MeO$–, entry 4) are more reactive than aldehydes with an electron-withdrawing group in the same position (Cl–, entry 5), consistent with the observation in the ethylene–aldehyde couplings. The product derived from $p$-chlorobenzaldehyde can be elaborated further by way of a cross-coupling reaction.

Allylbenzene is an excellent substrate, and the homoallylic products are useful styrene derivatives. The $E$-isomer is observed exclusively. Oligomerization of the coupling product is not observed, as evidenced by the excellent yield of the coupling reactions (entries 9–14).

Linear monosubstituted olefins such as propene and 1-octene are not the only terminal olefins that can participate in this nickel-catalyzed reaction (entries 1, 2, 9, 15). Alkenes with substitution at the homoallylic position couple with benzaldehyde in similar regioselectivity and $E/Z$ selectivity as in the case of 1-octene (entry 16, as compared to entry 2).
Table 9. Homoallylic Alcohols from Nickel-Catalyzed Alkene–Aldehyde Couplings\(^a\)

<table>
<thead>
<tr>
<th>entry</th>
<th>alkene</th>
<th>aldehyde</th>
<th>major product (2)</th>
<th>yield (%)</th>
<th>E,Z (2) (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>PhCHO</td>
<td>2a OSE3 Ph</td>
<td>73 (89:11)</td>
<td>n.a.</td>
</tr>
<tr>
<td>2</td>
<td>n-C(_6)H(_5)l</td>
<td>PhCHO</td>
<td>2b OSE3 Ph</td>
<td>85 (95:5)</td>
<td>75:25</td>
</tr>
<tr>
<td>3</td>
<td>p-C(_6)H(_4)l</td>
<td>PhCHO</td>
<td>2c OSE3 Ph</td>
<td>72 (&gt;95:5)</td>
<td>75:25</td>
</tr>
<tr>
<td>4</td>
<td>p-anisaldehyde</td>
<td>n-C(_6)H(_5)l</td>
<td>2d OSE3 Ph</td>
<td>85 (&gt;95:5)</td>
<td>75:25</td>
</tr>
<tr>
<td>5</td>
<td>p-Cl(C(_6)H(_4))CHO</td>
<td>n-C(_6)H(_5)l</td>
<td>2e OSE3 Ph</td>
<td>37 (&gt;95:5)</td>
<td>74:26</td>
</tr>
<tr>
<td>6</td>
<td>2-naphthaldehyde</td>
<td>n-C(_6)H(_5)l</td>
<td>2f OSE3 Ph</td>
<td>88 (&gt;95:5)</td>
<td>70:30</td>
</tr>
<tr>
<td>7</td>
<td>1-methyl-2-indole-carboxaldehyde</td>
<td>n-C(_6)H(_5)l</td>
<td>2g OSE3 Ph</td>
<td>56 (&gt;95:5)</td>
<td>83:17</td>
</tr>
<tr>
<td>8</td>
<td>i-But</td>
<td>PhCHO</td>
<td>2h OSE3 Ph</td>
<td>64 (&gt;95:5)</td>
<td>78:22</td>
</tr>
<tr>
<td>9</td>
<td>Ph</td>
<td>PhCHO</td>
<td>2i OSE3 Ph</td>
<td>86 (92:8)</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>10</td>
<td>o-anisaldehyde</td>
<td>Ph</td>
<td>2j OSE3 Ph (ortho)</td>
<td>78 (92:8)</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>11</td>
<td>m-anisaldehyde</td>
<td>Ph</td>
<td>2k OSE3 Ph (meta)</td>
<td>98 (92:8)</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>12</td>
<td>p-anisaldehyde</td>
<td>Ph</td>
<td>2l OSE3 Ph (para)</td>
<td>99 (92:8)</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>13</td>
<td>2-naphthaldehyde</td>
<td>Ph</td>
<td>2m OSE3 Ph</td>
<td>98 (92:8)</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>14</td>
<td>1-methyl-2-indole-carboxaldehyde</td>
<td>Ph</td>
<td>2n OSE3 Ph</td>
<td>98 (92:8)</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>15</td>
<td>i-But</td>
<td>PhCHO</td>
<td>2o OSE3 Ph</td>
<td>91 (92:8)</td>
<td>69:31</td>
</tr>
<tr>
<td>16</td>
<td>Me</td>
<td>PhCHO</td>
<td>2p OSE3 Ph</td>
<td>82 (&gt;95:5)</td>
<td>81:19</td>
</tr>
<tr>
<td>17</td>
<td>Me</td>
<td>Me</td>
<td>2q OSE3 Ph</td>
<td>95 (86:14)</td>
<td>n.a.</td>
</tr>
<tr>
<td>18</td>
<td>cyclohexane</td>
<td>Me</td>
<td>2r OSE3 Ph</td>
<td>99 (75:25)</td>
<td>n.a.</td>
</tr>
<tr>
<td>19</td>
<td>Me</td>
<td>Me</td>
<td>2s OSE3 Ph</td>
<td>14 (&gt;95:5)</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

\(^a\) Standard procedure: (entries 1-8, 15-18): To a solution of Ni(cod)\(_2\) (0.1 mmol) and EtOPPh\(_2\) (0.2 mmol) in toluene (2.5 mL) at 23 °C under Ar were added the alkene (0.5 mL), triethylamine (3.0 mmol), the aldehyde (0.5 mmol), and Et\(_2\)SiOTf (0.875 mmol). The mixture was stirred 48 h at room temperature and purified by chromatography (SiO\(_2\)). Entries 9-14: Ph\(_2\)P was used in place of EtOPPh\(_2\). \(^b\) Yields were determined by \(^1\)H NMR using DMF as a standard. \(^c\) See Supporting Information for structures of the minor products (2a-2p). \(^d\) Propene (1 atm) was used in place of Ar. \(^e\) Reaction time 18 h. \(^f\) Reaction temperature 35 °C. \(^g\) Fivefold larger reaction scale. \(^h\) ratio of 2:3. \(^i\) ratio of 3: (2q+2q').
Alkenes with substituents at the allylic position, on the other hand, afford different results. A homoallylic alcohol derivative is still the major coupling product in the coupling of 2-methylbutene (entry 17) and vinylcyclohexane (entry 18) with benzaldehyde. However, the minor product is an \textit{E}-1,3-disubstituted allylic alcohol, rather than the usual 1,2-disubstituted allylic alcohol obtained from the coupling of unbranched alkenes (eqs 1–2). The coupling of 3,3-dimethylbutene and benzaldehyde yields exclusively 1,3-disubstituted allylic alcohol product (eq 3). This observation maybe important in understanding the mechanism of these transformations, which is discussed in more detail in the discussion section below.

Allylic, rather than homoallylic alcohol derivatives can be prepared by the nickel-catalyzed coupling of alkenes and aldehydes simply by substituting Cy₂PhP for EtOPh₂P (Table 10). Hence, propene couples with naphthaldehyde to provide the allylic alcohol product in good yield and with the highest selectivity (Table 10, entry 1). In contrast to the Ni–EtOPh₂P system, the homoallylic alcohol is the minor product in this case.
Once again, aromatic aldehydes and heteroaromatic aldehydes couple with straight chain monosubstituted alkenes in good yield (entries 1–2, 4). Electron-donating \( p \)-anisaldehyde is, as before, more reactive than benzaldehyde (entries 1 and 3). Therefore, based on all the data that we gathered so far, it seems to be the trend that generally electron-donating aldehydes are more reactive than electron-poor aldehydes.

There are, however, some differences in the substrate scope of the alkene in the Ni–Cy\(_2\)PhP system relative to that of the Ni–EtOPh\(_2\)P system. While branching at the homoallylic position of the alkene does not affect the coupling efficiency (entry 5), branching at the allylic position significantly attenuates the yield of the allylic alcohol product (entry 7). For example, vinylcyclohexane has a dramatically lower A:H ratio (entry 7), and the homoallylic alcohol and a 1,3-disubstituted allylic alcohol are the major products.

In a competition study, benzaldehyde undergoes coupling with a monosubstituted alkene selectively in the presence of a trisubstituted alkene (entry 6); the trisubstituted double bond is stable to the reaction conditions. Carbocyclization is not observed, nor do we observe any isomerization of the trisubstituted double bond in the coupling product. This result enables the use of a trisubstituted double bond as a masked version of other functional groups.
Table 10. Allylic Alcohols from Nickel-Catalyzed Alkene–Aldehyde Couplings

<table>
<thead>
<tr>
<th>entry</th>
<th>R¹ (alkene)</th>
<th>R² (aldehyde)</th>
<th>R₃SiOTf</th>
<th>major product</th>
<th>yield (%) b</th>
<th>ratio (2':2) c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>naphthyl</td>
<td>Et₃SiOTf</td>
<td>2r'</td>
<td>82</td>
<td>84:16</td>
</tr>
<tr>
<td>2</td>
<td>n-hexyl</td>
<td>Ph</td>
<td>Et₃SiOTf</td>
<td>2b'</td>
<td>70</td>
<td>71:29</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>α-anisyl</td>
<td>Et₃SiOTf</td>
<td>2a'</td>
<td>95</td>
<td>82:18</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>3-allyloxazolidinone</td>
<td>Et₃SiOTf</td>
<td>2k'</td>
<td>56</td>
<td>80:20</td>
</tr>
<tr>
<td>5</td>
<td>isobutyl</td>
<td>Ph</td>
<td>Et₃SiOTf</td>
<td>2n'</td>
<td>62</td>
<td>71:29</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>Ph</td>
<td>Et₃SiOTf</td>
<td>2l'</td>
<td>72</td>
<td>71:29</td>
</tr>
<tr>
<td>7</td>
<td>c-hexyl</td>
<td>Ph</td>
<td>Et₃SiOTf</td>
<td>2p'</td>
<td>5</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

a Standard procedure: Ni(cod)₂ (20 mol%), Cy₂PhP (40 mol%) were dissolved in 2.5 mL toluene. Excess alkene, triethylamine (600 mol%), the aldehyde (100 mol%, 0.5 mmol), and Et₃SiOTf (175 mol%) were added. The reaction mixture was stirred 18 h at 23 °C. b Unless specified, isolated yield of all coupling products. c Ratios were determined by ¹H NMR of the crude reaction mixture. d 1 atm propene (balloon) was used and naphthaldehyde (100 mol%) was mixed with Ni(cod)₂ and Cy₂PhP before the addition of toluene. e Yields were determined by ¹H NMR using DMF as a standard. f Isolated yield of the allylic product 2p'.

Given that heteraromatic aldehydes are competent substrates in these coupling reactions, we became interested in the effect of heteroatoms on the alkene. N-allylphthalimide, N-homoallylphthalimide and N-homoallyloxazolidinone undergo coupling in both the Ni–Cy₂PhP and Ni–EtOPH₂P systems (Table 11, entries 1–3). In particular, the coupling of N-allylphthalimide and benzaldehyde in the Ni–EtOPH₂P system affords an enamine that appears to be stable to the coupling conditions. In contrast, allylbenzoate and homoallylbenzoate esters are
much less efficient (Table 12, entries 1–4). A small amount of the allylic product is detected only with homoallylbenzoate (entry 2). When the benzoate group is further away from the terminal double bond, a better yield of the desired coupling product is observed (entry 3). These findings suggest an interaction of the heteroatoms on the alkenes to the nickel catalyst. We propose that since the oxygen on the phthalimide is less nucleophilic, it does not bind to the nickel as tightly as the benzoate oxygen. Therefore the coupling of $\textit{N}$-allylphthalimide occurs more efficiently than allylbenzoate (Table 11, entry 1 and Table 12, entry 1). As the benzoate becomes further away from the double bond, the benzoate is less likely to coordinate to the nickel catalyst, and the reactivity of the alkene is restored (Table 12, entry 3). The silyl ether-tethered alkene (entry 4) does not experience the heteroatom attenuation effect, likely for the same reason as the benzoate ester in entry 3.
Table 11. Coupling of Nitrogen-Containing Alkenes with Aldehydes

<table>
<thead>
<tr>
<th>entry</th>
<th>R¹ (alkene)</th>
<th>R² (aldehyde)</th>
<th>ligand</th>
<th>major product</th>
<th>yield (%)</th>
<th>ratio (4:4')</th>
<th>ratio (E-Z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="alkene" /></td>
<td>Ph</td>
<td>Cy₂PhP</td>
<td>4a</td>
<td>67</td>
<td>74:26</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(EtO)Ph₂P</td>
<td>4a'</td>
<td>43</td>
<td>12:88</td>
<td>60:40</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="alkene" /></td>
<td>o-anisyl</td>
<td>Cy₂PhP</td>
<td>4b</td>
<td>54</td>
<td>71:29</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ph₃P</td>
<td>4b'</td>
<td>76</td>
<td>&lt;5:95</td>
<td>83:17</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="alkene" /></td>
<td>Ph</td>
<td>Cy₂PhP</td>
<td>4c</td>
<td>60</td>
<td>83:17</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(EtO)Ph₂P</td>
<td>4c'</td>
<td>28</td>
<td>10:90</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

a Standard procedure: To a solution of Ni(cod)₂ (0.1 mmol) and ligand (0.2 mmol) in toluene (2.5 mL) at 23 °C under Ar were added the alkene (1.5 mmol), triethylamine (3.0 mmol), the aldehyde (0.5 mmol), and Et₃SiOTf (0.875 mmol). The mixture was stirred 48 h at room temperature and purified by chromatography (SiO₂). b Determined by H NMR of the crude reaction mixture using DMF as a standard. c The ratio was determined by H NMR of the mixture of E and Z homoallylic alcohols after the silyl group of the coupling product was removed by TBAF.
**Table 12. Coupling of Oxygen-Containing Alkenes with Aldehydes**

![Diagram of the coupling reaction]

<table>
<thead>
<tr>
<th>entry</th>
<th>$R^1$ (alkene)</th>
<th>$R^2$ (aldehyde)</th>
<th>ligand</th>
<th>major product</th>
<th>yield (%)</th>
<th>ratio (4:4')</th>
<th>ratio (E:Z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>Ph</td>
<td>C$_2$PhP</td>
<td>4d</td>
<td>&lt;5</td>
<td>n.d.</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(EtO)$_2$PhP</td>
<td>4d'</td>
<td>&lt;5</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Ph</td>
<td>C$_2$PhP</td>
<td>4e</td>
<td>21</td>
<td>n.d.</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(EtO)$_2$PhP</td>
<td>4e'</td>
<td>&lt;5</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>o-anisyl</td>
<td>C$_2$PhP</td>
<td>4f</td>
<td>44^d</td>
<td>73:27</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Et$_3$SiO</td>
<td>o-anisyl</td>
<td>(EtO)$_2$PhP</td>
<td>4g</td>
<td>66</td>
<td>7:93</td>
<td>50:50</td>
</tr>
</tbody>
</table>

*Standard procedure: To a solution of Ni(cod)$_2$ (0.1 mmol) and ligand (0.2 mmol) in toluene (2.5 mL) at 23 °C under Ar were added the alkene (2.5 mmol), triethylamine (3.0 mmol), the aldehyde (0.5 mmol), and Et$_3$SiOTf (0.875 mmol). The mixture was stirred 48 h at room temperature and purified by chromatography (SiO$_2$). Determined by $^1$H NMR of the crude reaction mixture using DMF as a standard. The ratio was determined by $^1$H NMR of the mixture of $E$ and $Z$ homoallylic alcohols after the silyl group of the coupling product was removed by TBAF. Isolated yield. 1.5 mmol alkene was used.*
Discussion

General Mechanistic Framework

We believe that the nickel species that catalyzes the alkene–aldehyde coupling reactions above is not functioning simply as a Lewis acid. We propose that the coupling reaction proceeds through the formation of oxanickellacycle from a nickel(0) complex (Scheme 1). A syn β-hydride elimination would afford the coupling product and a nickel–hydride species, analogous to a Heck reaction.3a-c Finally, base-promoted reductive elimination of the nickel–hydride intermediate could regenerate the nickel(0) catalyst. Note that a base-mediated β-elimination of the oxanickellacycle via an E2-like mechanism cannot be completely ruled out. Based on our observations and in analogy to the Heck reaction,3a-c we believe the nickel–hydride pathway is operative (see below).

Scheme 1

Ligand Effects

The interactions of nickel with the ligand, alkene, and aldehyde govern the assembly of the oxanickellacycle, and the oxanickellacycle in turn determines the product distribution. Scheme 2
summarizes the factors that control the product ratio in the alkene–aldehyde coupling reactions. In general, use of large phosphines favors the allylic alcohol product (A) (e.g., the coupling of 1-octene with benzaldehyde with Cy₂PhP as ligand yielded allylic alcohol as the major product.) The use of small phosphines (Bu₃P, (EtO)Ph₂P, Ph₃P, etc) on the other hand affords the homoallylic alcohol (H) as the major product.

Scheme 2

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Alkene</th>
<th>Aldehyde</th>
</tr>
</thead>
<tbody>
<tr>
<td>large cone angle and electron rich (e.g., Cy₂PhP)</td>
<td>alkene with no branching at the allylic position tolerated (e.g., propene, 1-octene)</td>
<td>smaller substituents (e.g., R = Ph)</td>
</tr>
<tr>
<td>small cone angle and electron poor (e.g., (EtO)Ph₂P)</td>
<td>branching at the allylic position tolerated (e.g., vinylcyclohexane)</td>
<td>larger substituents (e.g., R = 2-naphthyl, t-butyl)</td>
</tr>
</tbody>
</table>

Oxanickellacycle Oxanickellacycle 1 Oxanickellacycle 2 Oxanickellacycle 2

Coupling product Allylic (A) Homoallylic (H) Allylic (A')

Size of Coupling Partners

The substituents on the alkene and aldehyde also affect the ratio of the coupling products. The alkene substituents can either be closer to the ligand or the aldehyde substituent in the
oxanickellacycle. Allylic alcohol product A is obtained in a significant amount when the alkene has no branching at the allylic position. On the other hand, branching at the allylic position does not affect the coupling process when a small ligand, such as (EtO)Ph₂P, is used, and homoallylic allylic alcohol H is formed in good yield. 3,3-dimethyl-1-butene, a sterically demanding monosubstituted alkene with no allylic hydrogen, provides 1,3-disubstituted allylic alcohol A' as the sole product.

A large substituent on aldehyde favors the production of homoallylic alcohol. Less than 5% allylic alcohol product is observed when propene or 1-octene is coupled with pivaldehyde with Cy₂PhP as the ligand. In the following sections, we propose a detailed model consistent with all of these observations.

We begin by examining oxanickellacycle 1 in more detail (Scheme 3). The β-hydrogen of the oxanickellacycle 1 is not aligned with the C–Ni bond. Since β-hydride elimination generally occurs in the syn orientation, the –OSiEt₃ group must dissociate from nickel to allow bond rotation such that the β-hydrogen can align with C–Ni bond. At this stage, β-hydride elimination occurs and allylic product A is formed. The larger the phosphine ligand relative to the aldehyde substituent, the more likely oxanickellacycle 1 dominates because the alkene substituent would thus avoid severe steric repulsion with this ligand. The data shown in Table 2 support this proposal; the A:H ratio increases with the cone angle of the trialkylphosphine.
Scheme 3

Oxanickellacycle 2 accounts for the formation of homoallylic alcohol H and allylic alcohol A'. Examination of oxanickellacycle 2 reveals that although the β-hydrogen in the oxanickellacycle (H_{endo}) is not aligned with the C–Ni bond, there are β-hydrogens outside the oxanickellacycle (H_{exo}) that are appropriately poised for β-hydride elimination once a free coordination site is available (Scheme 4).\textsuperscript{3e} The preferred conformation would align R\textsuperscript{2} of the alkene trans to the C–C bond of the oxanickellacycle 2. Dissociation of one of the ligand on nickel provides a free coordination site for the syn β-hydride elimination to occur and provides the E-homoallylic alcohol H.

Scheme 4
In order for the unusual allylic alcohol (A') to form, the β-hydrogens in the oxanickellacycle (H_{endo}) must be eliminated instead of the exo-β-hydrogen (H_{exo}). Such a process requires dissociation of –OSiEt₃ and maybe favored when the exo-β-hydrogen is not aligned with the C–Ni bond, or when there is no exo-β-hydrogen (Scheme 5).

The coupling of vinylcyclohexane and benzaldehyde serves as a good example to illustrate the formation of 1,3-disubstituted allylic alcohol A' (Scheme 5). Neither R₁ nor R₂ of vinylcyclohexane is a hydrogen atom, and hence the allylic position is very sterically encumbered. The usual allylic alcohol product A is not favored because the large substituent of vinylcyclohexane will not be accommodated next to the aldehyde substituent (R) in oxanickellacycle 1 (Scheme 3) due to severe steric repulsion.

Experimental data support this theory: The coupling of vinylcyclohexane with benzaldehyde using Cy₂PhP as ligand yields only 5% of the allylic alcohol product A (Table 10, entry 7, as compared with other unbranched alkenes in Table 10, entries 1–6). Using a smaller ligand, such as (EtO)Ph₂P, the large substituents in vinylcyclohexane can be accommodated by being closer to the ligand than to the aldehyde substituent, favoring oxanickellacycle 2 (Scheme 5). The exo-β-hydrogen of the oxanickellacycle, when aligned to with C–Ni bond, induces an unfavorable steric interaction between the cyclohexyl group and the C–C bond of the oxanickellacycle. Therefore the rate of β-hydride elimination from the exo-β-hydrogen decreases, and that of the endo-β-hydrogen increases, resulting in a greater amount of the unusual E-allylic product A'. The E-double bond geometry of A' is obtained by minimizing steric repulsion during the β-H elimination step.

Alkenes without an allylic hydrogen cannot afford homoallylic alcohol products in the nickel-catalyzed alkene–aldehyde coupling reaction. For example, 3,3-dimethyl-1-butene, with no
allylic hydrogen, couples with benzaldehyde to give exclusively \(E\)-1,3-disubstituted allylic alcohol product \((A')\). Also, it appears that the steric bulk of the \(\text{tert}\)-butyl group renders formation of oxanickellacycle 1 extremely difficult, eliminating the possibility of affording 1,1-disubstituted allylic alcohol product \(A\).

**Scheme 5**

The proposed mechanistic framework is also supported by Ogoshi’s observation that cyclization of an \(\alpha,\omega\)-enal to form an oxanickellacycle is facilitated by the presence of a silyl triflate. A control experiment confirms that without silyl triflate, no coupling product is observed.

The evidence for the \(\beta\)-hydride elimination as the next step is the observation of isomerization and dimerization (hydrovinylation) of the starting olefins, which suggests the presence of a nickel–hydride (Ni–H) species, likely formed by a \(\beta\)-hydride elimination. The requirement of a base in this catalyst system also supports the presence of a Ni–H species. A \(\beta\)-hydride elimination and subsequent base-assisted removal of triflic acid (reductive elimination) from the Ni–H species regenerates the Ni(0) catalyst (Scheme 1) and may also minimize side reactions by suppressing the presence of the Ni–H species.
We do not believe the direct precursor to the oxanickellacycle in this coupling reaction is a cationic nickel (II) species. Ni\textsuperscript{2+}, Pd\textsuperscript{2+}, and Pt\textsuperscript{2+} catalysts have been reported to be effective Lewis acids for carbonyl-ene reactions.\textsuperscript{18g-i} The nickel-catalyzed coupling of alkenes, aldehydes, and silyl triflates affords carbonyl-ene-type products in good yield, but the substrate scope is entirely different from that of a Lewis acid-catalyzed carbonyl-ene reaction. While the three cationic group 10 transition metal catalysts are effective in the carbonyl-ene reaction of the more nucleophilic alkenes such as 1,1-disubstituted alkenes and the more electrophilic aldehydes such as glyoxylate esters, they do not promote the coupling of monosubstituted alkenes and simple aldehydes.

The nickel catalyst system has the opposite alkene and aldehyde substrate scopes relative to those of the carbonyl-ene reaction. The nickel–phosphine catalyst selectively reacts with monosubstituted olefins, and we observe that electron rich aldehydes, such as \(p\)-anisaldehyde, consistently provide better yield than benzaldehyde and electron-deficient aldehydes. Although this coupling reaction readily provides homoallylic alcohol products corresponding to a carbonyl-ene reaction, it is more likely that the oxanickellacycle precursor is a Ni(0) species, and probably not just a Lewis acid catalyst.

To illustrate the difference between the Ni(0)–phosphine system and a Lewis acid system, \(\beta\)-citronellene and benzaldehyde were coupled under two conditions; using a classical Lewis acid and the Ni–EtOPh\textsubscript{2}P conditions.\textsuperscript{6b} As expected, the Lewis acid-catalyzed reaction reacts at the more nucleophilic trisubstituted double bond. For the Ni–EtOPh\textsubscript{2}P system, however, the monosubstituted double bond reacts preferentially because it is the kinetically more accessible double bond. These observations are also in accord with many palladium-catalyzed reactions of
alkenes (such as Wacker oxidation and alkene hydroamination), in that a monosubstituted double bond is usually more reactive than a more substituted double bond.\textsuperscript{3a}

**Scheme 6**

The difference in substrate scope between the nickel-catalyzed alkene–aldehyde coupling and the carbonyl-ene reaction is further illustrated by competition experiments between a monosubstituted alkene and a 1,1-disubstituted alkene (Scheme 7).\textsuperscript{25-26} Equal amounts of allylbenzene and methylenecyclohexane were included in the otherwise standard coupling conditions. The coupling reaction was highly selective; 92\% of all of the coupling products detected are derived from allylbenzene. The presence of methylenecyclohexane does not change the H:A ratio of the coupling products of allylbenzene (as compared to Table 9, entry 10). A similar trend is observed between 1-octene and methylenecyclohexane (as compare to Table 9, entry 4), but the presence of excess methylenecyclohexane in the reaction mixture seems to lower the yield of the coupling reaction. This lower efficiency might be due to competition for a coordination site on nickel between monosubstituted alkenes and methylenecyclohexane.
Further evidence that supports the notion that the nickel-catalyzed coupling of alkenes, aldehydes, and silyl triflates does not involve a carbonyl-ene reaction mechanism is that ethylene, with no allylic hydrogen, also participates in this coupling reaction using the same Ni–phosphine catalyst system.

Common side reactions in these nickel-catalyzed reactions are the dimerization (hydrovinylation)\(^{27}\) and isomerization\(^{28}\) of the starting olefin. One explanation for the requirement of excess alkenes in this coupling reaction is that the terminal alkene is isomerized to an internal alkene and that this new internal alkene is not reactive in the coupling process. While isomerization of olefin is common in the coupling reaction, hydrovinylation of olefins is observed in small amounts only when the alkene–aldehyde coupling process is not efficient. The presence of a base in the coupling reaction may keep the Ni-H concentration to a minimum, thus suppressing some of these side reactions.

**Conclusion**

The nickel-catalyzed coupling of alkenes, aldehydes, and silyl triflates represents a new alternative to both allylmetal reagents and alkenylmetal reagents (Scheme 8). The parent allylmetal reagent and vinylmetal reagent can now be replaced by propene and ethylene,
respectively, using the nickel-catalyzed processes as described herein. The preparation of a
terminal, monosubstituted alkene is generally more straightforward than that of the allylmetal
species such as those shown in Scheme 8.

**Scheme 8**

<table>
<thead>
<tr>
<th>Allylmetal and alkynylmetal additions to aldehyde</th>
<th>Nickel-catalyzed alkene-aldehyde coupling reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ R^1M + \text{CHO} \rightarrow R^1\text{OH} ]</td>
<td>[ R^1\text{H} + \text{CHO} \rightarrow \text{R}^1\text{OSiEt}_3 ]</td>
</tr>
<tr>
<td>[ \text{R}^1\text{M} + \text{CHO} \rightarrow \text{R}^1\text{OH} ]</td>
<td>[ \text{R}^1\text{H} + \text{CHO} \rightarrow \text{R}^1\text{OSiEt}_3 ]</td>
</tr>
</tbody>
</table>

The transformation in this nickel-catalyzed alkene–aldehyde coupling reaction is, in effect, a
C–H functionalization reaction of the alkene, involving addition to an aldehyde. Mechanistically,
an entirely different process likely occurs, rather than oxidative addition into a C–H bond that
would be expected to have a relatively high energy activation barrier.

Unlike the related transition metal-catalyzed reductive coupling reactions developed by our
group and others, the nickel-catalyzed coupling of alkenes, aldehydes, and silyl triflates
described in this work is not an overall reductive process (Scheme 9). Thus, the coupling of an
alkene and an aldehyde, in theory, does not require a third component to form the allylic or
homoallylic alcohol derivatives. However, both alkenes and aldehydes are generally unreactive
toward each other. Thus, activation of either or both components is necessary. The Lewis acid-
catalyzed carbonyl-ene reaction serves as a good example. Intermolecular carbonyl-ene reaction
between monosubstituted alkene and unactivated aldehydes such as acetaldehyde is not a
practical method under thermal conditions. The presence of a Lewis acid, however, allows the
coupling to proceed at room temperature. The Lewis acidic nature of silyl triflate in the nickel-
catalyzed alkene–aldehyde coupling reaction likely plays a similar role, providing sufficient activation of the electrophile for the nickel catalyst to promote the coupling reaction.

**Scheme 9**

Nickel-Catalyzed Alkyne–Aldehyde Coupling Reactions (Reductive):

![Chemical Structure](image1)

Nickel-Catalyzed Alkene–Aldehyde Coupling Reactions (Non-Reductive):

![Chemical Structure](image2)

The two classes of the nickel-catalyzed coupling reactions of alkene, aldehyde, and silyl triflate presented here represent unique, non-reductive coupling processes that allow the preparation of derivatives of allylic alcohols or homoallylic alcohols from readily available olefins. The selectivity for these two products is highly ligand dependent, and high selectivity in either direction is possible. These coupling reactions are mechanistically different from Lewis acid-catalyzed carbonyl-ene reactions, and conceptually, alkenes serve as substitutes for both allylmetal reagents and alkenylmetal reagents.

**References:**


20) (a) The stretching frequency (ν\textsubscript{CO}, cm\textsuperscript{-1}) of terminal CO of CpFe(CO)LCOMe (in cyclohexane at room temperature) is a measure of the σ-electron-donating ability to a metal center. A less electron-donating ligand usually has a higher frequency: Rahman, M.; Liu, H.-Y.; Eriks, K.; Prock, A.; Giering, W. P. *Organometallics* **1989,** 8, 1–7. (b) Tri-p-tolylphosphine (Table 3, entry 5), triphenylphosphine (entry 6), tris-(p-fluoro-phenyl)-phosphine (entry 7) and tris-(p-trifluoromethyl-phenyl)-phosphine (entry 9) have the same cone angle (145º) according to ref. 20a. (c) The frequency for (o-anisyl)\textsubscript{3}P was estimated from (p-anisyl)\textsubscript{3}P assuming they have similarly electron-donating property. Cone angle values and ν\textsubscript{CO} values were obtained from ref. 20a and the following: (d) Tolman, C. A. *Chem. Rev.* **1977,** 77, 313–348. (e) Otto, S. J. *Chem. Crystallo.ogr.* **2001,** 31, 185–190. (f) Rihimäki, H.; Kangas, T.; Suomalainen, P.; Reinius, H. K.; Jääskeläinen, S.; Haukka, M.; Krause, A. O. I.; Pakkanen, T. A.; Pursiainen, J. T. *J. Mol. Catal. A: Chem.* **2003,** 200, 81–94. (g) Steinmetz, W. E. *Quant. Struct.-Act. Relat.* **1996,** 15, 1–6.


22) A set of four control experiments in which Ni(cod)\textsubscript{2}, ligand, silyl triflate and the base was each removed from the ethylene–benzaldehyde coupling reaction. No coupling product was detected in any of the four experiments.

23) (a) Nickel:phosphine ratio is also important. A 1:2 Ni:phosphine ratio provides a higher yield than a 1:1 Ni:phosphine ratio in the coupling reaction. (b) No coupling was observed when Ni(cod)\textsubscript{2} / Ph\textsubscript{3}P was replaced with Pd(Ph\textsubscript{3}P)\textsubscript{4}.

24) Coupling of 3,3-dimethyl-1-butene and benzaldehyde under the standard coupling condition (EtOP\textsubscript{2}P, rt, 48h) affording an E-1,2-allylic alcohol product in 14% yield.

25) Procedure of the competition experiment: To a solution of Ni(cod)\textsubscript{2} (0.1 mmol) and the ligand (Ph\textsubscript{3}P or (EtO)\textsubscript{2}P, 0.2 mmol) in toluene (2.5 mL) at 23 °C under Ar were added a
monosubstituted alkene (2.5 mmol), methylenecyclohexane (2.5 mmol), triethylamine (3.0 mmol), \( p \)-anisaldehyde (0.5 mmol), and triethylsilyl triflate (0.875 mmol). The mixture was stirred 48 h at room temperature. The yields and ratios were determined by \( ^1H \) NMR of the crude reaction mixture. Ph$_3$P was the ligand in the reaction between allylbenzene and methylenecyclohexane. (EtO)$_2$P was the ligand in the reaction between 1-octene and methylenecyclohexane.

26) As a control experiment, methylenecyclohexane (300 mol\%) was coupled with \( p \)-anisaldehyde under standard condition (Ni(cod)$_2$, EtOPh$_2$P, Et$_3$SiOTf, Et$_3$N) to give 13% yield of the homoallylic alcohol product. To determine whether the formation of this coupling product requires Ni(cod)$_2$, another control experiment was carried out by stirring methylenecyclohexane, \( p \)-anisaldehyde and Et$_3$SiOTf at room temperature. No alkene–aldehyde coupling product was observed.


Experimental Section

General Information

Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of nitrogen or argon with rigid exclusion of moisture from reagents and glassware. Tetrahydrofuran and diethylether were distilled from a blue solution of sodium benzophenone ketyl. Dichloromethane and toluene were distilled from calcium hydride. Aromatic aldehydes were purchased from Aldrich Chemical Co. and used as received. Other aldehydes were distilled and saturated with nitrogen before use. Bis(cyclooctadienyl)nickel(0) (Ni(cod)₂) and tris-(o-methoxyphenyl)-phosphine and triphenylphosphine were purchased from Strem Chemicals, Inc., stored under nitrogen atmosphere and used without further purification. Ethylene was purchased from BOC Gases and used as received. 1-octene was purchased from Alfa Aesar and used as received. All other alkenes were purchased from Aldrich Chemical Co. and used as received. Dicyclohexylphenylphosphine and ethyldiphenylphosphinite were purchased from Aldrich Chemical Co., stored under nitrogen atmosphere and used without further purification. Triethylsilyl trifluoromethanesulfonate (TESOTf) and trimethylsilyl trifluoromethanesulfonate (TMSOTf) were purchased from Aldrich Chemical Co. and were distilled over calcium hydride before use. tert-Butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) was purchased from Alfa Aesar and was distilled over calcium hydride before use.

Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F₂₅₄ plates. The developed chromatogram was analyzed by UV lamp (254 nm), ethanolic phosphomolybdic acid (PMA) or potassium permanganate (KMnO₄). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230-400 mesh). ¹H and ¹³C NMR spectra were recorded on Varian 300 MHz, Varian 500 MHz or Bruker 400 MHz spectrometers in CDCl₃ or C₆D₆, unless otherwise noted. Chemical shifts in ¹H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm) or residual benzene (7.16 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constant in hertz (Hz), and integration. Chemical shifts of ¹³C NMR spectra are reported in ppm from the central peak of CDCl₃ (77.23 ppm) on the δ scale. Infrared (IR) spectra were recorded on a Perkin-Elmer 2000 FT-IR. High resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer by Dr. Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrument Facility. Chiral GC analysis was performed on a Varian CP-3800 gas chromatograph fitted with Chiralaldex B-PH, B-DA, and G-TA capillary columns. Chiral HPLC analysis was
performed on a Hewlett-Packard 1100 chromatograph equipped with a variable wavelength detector and Chiralcel OD or OD-H columns.

**Preparation of 2,2-dimethyl-3-oxo-propionic acid methyl ester**

3-Hydroxy-2,2-dimethyl-propionic acid methyl ester (15 g, 113 mmol) in 200 mL dichloromethane was cooled to 0 °C. Pyridinium chlorochromate (43 g, 200 mmol) was added. The mixture was slowly warmed to room temperature and stirred 24 h. The crude in dichloromethane was filtered through silica gel. Celite was added to the remaining black viscous oil from the reaction mixture until the viscous oil is all absorbed to the celite. Dichloromethane was added to this slurry and the dichloromethane solution was filtered through silica gel. Dichloromethane was removed at reduced pressure (80 Torr) to give a pale yellow crude oil. Fractional distillation removed residue dichloromethane and obtained 2,2-dimethyl-3-oxo-propionic acid methyl ester as a colorless oil (7 g, 48% yield).

$^1$H NMR (300 MHz, CDCl$_3$, δ): 9.60 (s, 1H); 3.70 (s, 3H); 1.29 (s, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$, δ): 199.1, 173.2, 53.9, 52.6, 19.7.

IR (NaCl, thin film): 2988, 2958, 1726, 1468, 1278, 1151, 866.

**Nickel-catalyzed couplings of ethylene and aldehydes (1a, 1b, 1c, 1d, 1i, 1j, 1l, 1m, 1n).**

**General procedure 1.** A 10 mL round bottom flask and a stir bar were oven-dried and brought into a glove box. Ni(cod)$_2$ (27.5 mg, 0.1 mmol, 20 mol%) and tris-o-methoxyphenylphosphine (70.5 mg, 0.2 mmol, 40 mol%) were added to the round bottom flask, the flask was sealed with a septum, and the sealed flask was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in toluene (2.5 mL) under argon and stirred 15 min at room temperature. The reaction mixture was purged with ethylene for 1 min to remove argon, taken care not to introduce oxygen. The ethylene atmosphere was maintained with an ethylene balloon. Triethylamine (418 µL, 3 mmol, 600 mol%) was added. Aldehyde (0.5 mmol, 100 mol%, as specified) was added. Silyl triflate (0.875 mmol, 175 mol%, as specified) was added. The mixture was stirred at room temperature for 3-18 h, as judged by the TLC of the reaction mixture. The mixture was filtered through a plug of silica gel. Solvent was removed under reduced pressure and the crude mixture was diluted in hexane. Purification
via flash chromatography on silica afforded the coupling product.

**Nickel-catalyzed couplings of ethylene and aldehydes (1e, 1f, 1g, 1h, 1k).**

**General procedure 2.** A 10 mL round bottom flask and a stir bar were oven-dried and brought into a glove box. Ni(cod)$_2$ (27.5 mg, 0.1 mmol, 20 mol%), tris-o-methoxyphenylphosphine (70.5 mg, 0.2 mmol, 40 mol%) and aldehyde (0.5 mmol, 100 mol%) were added to the round bottom flask, the flask was sealed with a septum, and the sealed flask was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in toluene (2.5 mL) under argon and stirred 15 min at room temperature. The reaction mixture was purged with ethylene for 1 min to remove argon, taken care not to introduce oxygen. The ethylene atmosphere was maintained with an ethylene balloon. Next triethylamine (418 µL, 3 mmol, 600 mol%) was added. Silyl triflate (0.875 mmol, 175 mol%, as specified) was added. The mixture was stirred at room temperature for 3-18 h, as judged by TLC of the reaction mixture. The mixture was filtered through a plug of silica gel. Solvent was removed under reduced pressure and the crude mixture was diluted in hexane. Purification via flash chromatography on silica afforded the coupling product.

![1a](image)

The reaction of ethylene and benzaldehyde (51 µL, 0.5 mmol) with Ni(cod)$_2$, tris-o-methoxy-phenylphosphine and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene following the general procedure 1 above, afforded 1a in 82% isolated yield as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$, δ): 7.32-7.45 (m, 4H); 7.29 (t, $J = 7.0$ Hz, 1H); 6.01 (ddd, $J = 6.0$, 10.2, 16.9 Hz, 1H); 5.34 (dt, $J = 1.5$, 16.9 Hz, 1H); 5.25 (d, $J = 5.9$ Hz, 1H); 5.13 (dt, $J = 1.5$, 10.2 Hz, 1H); 0.99 (t, $J = 8.0$ Hz, 9H); 0.66 (dq, $J = 1.8$, 7.8 Hz, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$, δ): 143.9, 141.8, 128.4, 127.3, 126.2, 113.7, 75.9, 7.0, 5.1.

IR (NaCl, thin film): 2956, 2877, 1640, 1454, 1240, 1065, 744, 699.

HRMS-ESI (m/z): [M + Na]$^+$ calcd for C$_{15}$H$_{24}$OSiNa, 271.1489; found, 271.1499.
The reaction of ethylene and \( p \)-tolualdehyde (59 \( \mu \text{L}, 0.5 \text{ mmol} \)) with \( \text{Ni(cod)}_2 \), tris-\( o \)-methoxy-phenylphosphine and TESOTf (197 \( \mu \text{L}, 0.875 \text{ mmol} \)), triethylamine in toluene following the general procedure 1 above, afforded 1b in 88\% isolated yield as a colorless oil.

\(^{1}\text{H NMR (400 MHz, CDCl}_{3}, \delta): 7.27 (d, J = 8.0, 2H); 7.16 (d, J = 8.0 \text{ Hz}, 2H); 5.97 (ddd, J = 5.9, 10.2, 16.9 \text{ Hz}, 1H); 5.30 (dt, J = 1.5, 17.0 \text{ Hz}, 1H); 5.17 (d, J = 5.9 \text{ Hz}, 1H); 5.09 (dt, J = 1.3, 10.2 \text{ Hz}, 1H); 2.37 (s, 3H); 0.97 (t, J = 7.9 \text{ Hz}, 9H); 0.65 (dq, J = 1.9, 7.5 \text{ Hz}, 6H).

\(^{13}\text{C NMR (100 MHz, CDCl}_{3}, \delta): 142.1, 141.1, 136.8, 129.1, 126.2, 113.4, 75.8, 21.3, 7.0, 5.2.

IR (NaCl, thin film): 2955, 2877, 1640, 1513, 1458, 1415, 1079, 1007, 844.

HRMS-ESI (m / z): [M + Na]\(^{+}\) calcd for \( C_{16}H_{26}OSiNa \), 285.1645; found, 285.1652.

The reaction of ethylene and \( o \)-tolualdehyde (58 \( \mu \text{L}, 0.5 \text{ mmol} \)) with \( \text{Ni(cod)}_2 \), tris-\( o \)-methoxy-phenylphosphine and TESOTf (197 \( \mu \text{L}, 0.875 \text{ mmol} \)), triethylamine in toluene following the general procedure 1 above, afforded 1c in 93\% isolated yield as a colorless oil.

\(^{1}\text{H NMR (400 MHz, CDCl}_{3}, \delta): 7.50 (d, J = 7.0, 1H); 7.11-7.24 (m, 3H); 5.93 (ddd, J = 5.7, 10.2, 17.0 \text{ Hz}, 1H); 5.36 (d, J = 5.6 \text{ Hz}, 1H); 5.22 (dt, J = 1.6, 17.1 \text{ Hz}, 1H); 5.08 (dt, J = 1.5, 10.2 \text{ Hz}, 1H); 2.34 (s, 3H); 0.95 (t, J = 8.0 \text{ Hz}, 9H); 0.61 (dq, J = 2.8, 7.5 \text{ Hz}, 6H).

\(^{13}\text{C NMR (100 MHz, CDCl}_{3}, \delta): 141.9, 140.7, 134.4, 130.3, 127.1, 126.5, 126.3, 113.7, 73.1, 19.4, 7.0, 5.1.

IR (NaCl, thin film): 2955, 2877, 1639, 1461, 1066, 1007, 744.

HRMS-ESI (m / z): [M + Na]\(^{+}\) calcd for \( C_{16}H_{26}OSiNa \), 285.1645; found, 285.1649.
The reaction of ethylene and \( p \)-anisaldehyde (61 \( \mu \)L, 0.5 mmol) with Ni\((\text{cod})_2\), tris-o-methoxy-phenylphosphine and TESOTf (197 \( \mu \)L, 0.875 mmol), triethylamine in toluene following the general procedure 1 above, afforded \( 1d \) in 95% isolated yield as a colorless oil.

\[ \begin{align*}
\text{OSiEt}_3 & \quad \textbf{1d} \\
\end{align*} \]

\( ^1\)H NMR (400 MHz, CDCl\(_3\), \( \delta \)): 7.30 (d, \( J = 8.7 \) Hz, 2H); 6.90 (d, \( J = 8.7 \) Hz, 2H); 5.97 (ddd, \( J = 5.9, 10.2, 16.9 \) Hz, 1H); 5.29 (dt, \( J = 1.4, 17.0 \) Hz, 1H); 5.16 (d, \( J = 5.9 \) Hz, 1H); 5.10 (dt, \( J = 1.4, 10.2 \) Hz, 1H); 3.83 (s, 3H); 0.96 (t, \( J = 7.9 \) Hz, 9H); 0.63 (dq, \( J = 1.8, 7.5 \) Hz, 6H).

\( ^{13}\)C NMR (100 MHz, CDCl\(_3\), \( \delta \)): 158.9, 142.0, 136.2, 127.4, 113.7, 113.4, 75.4, 55.4, 7.0, 5.1.

IR (NaCl, thin film): 2955, 2877, 1639, 1511, 1464, 1246, 1037, 744.

HRMS-ESI (m / z): [M + Na]\(^+\) calcd for C\(_{16}\)H\(_{26}\)O\(_2\)SiNa, 301.1600; found, 301.1586.

The reaction of ethylene and 2-naphthaldehyde (78.1 mg, 0.5 mmol) with Ni\((\text{cod})_2\), tris-o-methoxy-phenylphosphine and TESOTf (197 \( \mu \)L, 0.875 mmol), triethylamine in toluene following the general procedure 2 above, afforded \( 1e \) in 95% isolated yield as a colorless oil.

\[ \begin{align*}
\text{OSiEt}_3 & \quad \textbf{1e} \\
\end{align*} \]

\( ^1\)H NMR (400 MHz, CDCl\(_3\), \( \delta \)): 7.82-7.92 (m, 4H); 7.48-7.55 (m, 3H); 6.07 (ddd, \( J = 6.2, 10.2, 15.8 \) Hz, 1H); 5.35-5.45 (m, 2H); 5.17 (dt, \( J = 1.3, 10.1 \) Hz, 1H); 1.00 (t, \( J = 7.8 \) Hz, 9H); 0.68 (dq, \( J = 2.5, 7.5 \) Hz, 6H).

\( ^{13}\)C NMR (100 MHz, CDCl\(_3\), \( \delta \)): 141.7, 141.4, 133.5, 133.0, 128.2, 128.1, 127.7, 126.1, 125.8, 124.8, 124.6, 114.0, 76.0, 7.0, 5.1.

IR (NaCl, thin film): 2955, 2876, 1640, 1458, 1239, 1006, 743.

HRMS-ESI (m / z): [M + Na]\(^+\) calcd for C\(_{19}\)H\(_{26}\)OSiNa, 321.1651; found, 321.1642.
The reaction of ethylene and 2-naphthaldehyde (78.1 mg, 0.5 mmol) with Ni(cod)$_2$, tris- o-methoxy-phenylphosphine and TMSOTf (158 $\mu$L, 0.875 mmol), triethylamine in toluene following the general procedure 2 above, afforded 1f in 60% isolated yield as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$, $\delta$): 7.80-7.90 (m, 4H); 7.45-7.54 (m, 3H); 6.06 (ddd, $J = 5.6$, 10.2, 17.4 Hz, 1H); 5.30 (dt, $J = 1.5$, 17.3 Hz, 1H); 5.37 (bs, 1H); 5.17 (dt, $J = 1.4$, 10.2 Hz, 1H); 0.18 (s, 9H).

$^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$): 141.4, 141.0, 133.5, 133.0, 128.19, 128.18, 127.9, 126.2, 125.9, 124.9, 124.8, 114.4, 76.1, 0.4.

IR (NaCl, thin film): 2958, 1640, 1251, 1077, 841.

HRMS-ESI (m / z): [M + Na]$^+$ calcd for C$_{16}$H$_{20}$OSiNa, 279.1176; found, 279.1187.

---

The reaction of ethylene and 2-naphthaldehyde (78.1 mg, 0.5 mmol) with Ni(cod)$_2$, tris- o-methoxy-phenylphosphine and TBSOTf (201 $\mu$L, 0.875 mmol), triethylamine in toluene following the general procedure 2 above, afforded 1g in 67% isolated yield as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$, $\delta$): 7.80-7.92 (m, 4H); 7.45-7.55 (m, 3H); 6.04 (ddd, $J = 5.8$, 10.2, 16.8 Hz, 1H); 5.39 (dt, $J = 1.5$, 17.0 Hz, 1H); 5.38 (s, 1H); 5.14 (dt, $J = 1.5$, 10.2 Hz, 1H); 0.99 (s, 9H); 0.16 (s, 3H); 0.06 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$): 141.8, 141.4, 133.5, 133.0, 128.2, 128.1, 127.9, 126.1, 125.8, 124.8, 124.6, 113.8, 76.2, 26.1, 18.6, -4.4, -4.6.

IR (NaCl, thin film): 2956, 2857, 1636, 1472, 1252, 1081, 837.

HRMS-ESI (m / z): [M + Na]$^+$ calcd for C$_{19}$H$_{26}$OSiNa, 321.1651; found, 321.1643.
The reaction of ethylene and 1-methyl-2-indolecarboxaldehyde (79.6 mg, 0.5 mmol) with Ni(cod)$_2$, tris-$_o$-methoxy-phenylphosphine and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene following the general procedure 2 above, afforded **1h** in 67% isolated yield as a colorless oil.

$^{1}$H NMR (400 MHz, CDCl$_3$, δ): 7.63 (d, $J = 7.8$ Hz, 1H); 7.36 (d, $J = 8.2$ Hz, 1H); 7.26 (t, $J = 8.3$ Hz, 1H); 7.14 (t, $J = 7.9$ Hz, 1H); 6.43 (s, 1H); 6.13 (ddd, $J = 4.5$, 10.3, 17.1 Hz, 1H); 5.52 (ddd, $J = 1.7$, 1.7, 4.5 Hz , 1H); 5.39 (ddd, $J = 1.7$, 1.7, 17.1 Hz, 1H); 5.25 (ddd, $J = 1.7$, 1.7, 10.4, 1H); 3.82 (s, 3H); 0.98 (t, $J = 8.0$ Hz, 9H); 0.66 (dq, $J = 1.4$, 8.0 Hz, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$, δ): 140.6, 139.7, 138.5, 127.5, 121.5, 120.8, 119.4, 114.9, 109.1, 100.5, 70.4, 31.0, 7.0, 5.0.

IR (NaCl, thin film): 2955, 2911, 2876, 1911, 1758, 1641, 1469, 1238, 1009, 841, 731.

HRMS-ESI (m / z): [M + Na]$^+$ calcd for C$_{18}$H$_{28}$NOSiNa, 302.1935; found, 302.1944.

The reaction of ethylene and furan-2-carbaldehyde (41 µL, 0.5 mmol) with Ni(cod)$_2$, tris-$_o$-methoxy-phenylphosphine and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene following the general procedure 1 above, afforded **1i** in 38% isolated yield as a colorless oil.

$^{1}$H NMR (400 MHz, CDCl$_3$, δ): 7.37 (bs, 1H); 6.32 (dd, $J = 1.9$, 3.1 Hz, 1H); 6.22 (d, $J = 3.2$ Hz, 1H); 6.06 (m, 1H); 5.40 (d, $J = 17.1$ Hz, 1H); 5.21 (d, $J = 7.9$ Hz, 2H); 0.95 (t, $J = 7.9$ Hz, 9H); 0.63 (q, $J = 7.9$ Hz, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$, δ): 156.0, 142.1, 138.1, 115.3, 110.4, 106.4, 69.3, 6.9, 4.9.

IR (NaCl, thin film): 2956, 2878, 1646, 1459, 1237, 1010, 733.

HRMS-ESI (m / z): [M + Na]$^+$ calcd for C$_{13}$H$_{22}$O$_2$SiNa, 261.1287; found, 261.1285.
The reaction of ethylene and 4-(trifluoromethyl)-benzaldehyde (70 \( \mu \)L, 0.5 mmol) with Ni(cod)\(_2\), tris-\(\alpha\)-methoxy-phenylphosphine and TESOTf (197 \( \mu \)L, 0.875 mmol), triethylamine in toluene following the general procedure 1 above, afforded a mixture of 1j and triethylsilylethers of pinnacol coupling products. This mixture was subjected to TBAF to isolate 25% of the desilylated 1j as a colorless oil.

[1H NMR (400 MHz, CDCl\(_3\), \( \delta \)): 7.62 (d, \( J = 8.2 \) Hz, 2H); 7.50 (d, \( J = 8.4 \) Hz, 2H); 6.02 (ddd, \( J = 6.3, 10.3, 16.9 \) Hz, 1H); 5.38 (ddd, \( J = 1.2, 1.2, 17.0 \) Hz, 1H); 5.27 (bd, \( J = 7.0 \) Hz, 1H); 5.25 (ddd, \( J = 1.2, 1.2, 10.3 \) Hz, 1H); 2.10 (bs, 1H).

13C NMR (100 MHz, CDCl\(_3\), \( \delta \)): 146.5, 139.8, 130.0 (\( J = 32.3 \) Hz), 126.7, 125.7, 123.0, 116.4, 75.1.

19F NMR (376 MHz, CDCl\(_3\), \( \delta \)): -66.8 (s, 3F).

IR (NaCl, thin film): 3342, 1620, 1419, 1328, 1166, 1126, 1068, 931.

HRMS-ESI (m / z): [M + Na]\(^+\) calcd for C\(_{10}\)H\(_9\)OF\(_3\)SiNa, 202.0600; found, 202.0591.]

The reaction of ethylene and methyl-4-formyl-benzoate (88 mg, 0.536 mmol) with Ni(cod)\(_2\), tris-\(\alpha\)-methoxy-phenylphosphine and TESOTf (197 \( \mu \)L, 0.875 mmol), triethylamine in toluene following the general procedure 2 above, afforded 1k in 34% isolated yield as a colorless oil.

[1H NMR (400 MHz, CDCl\(_3\), \( \delta \)): 8.01 (d, \( J = 8.4 \) Hz, 2H); 7.43 (d, \( J = 8.1 \) Hz, 2H); 6.92 (ddd, \( J = 6.0, 10.2, 16.9 \) Hz, 1H); 5.31 (ddd, \( J = 1.5, 1.5, 17.0 \) Hz, 1H); 5.21 (bd, \( J = 6.0 \) Hz, 1H); 5.11 (ddd, \( J = 1.4, 1.4, 10.2 \) Hz, 1H); 3.91 (s, 3H); 0.93 (t, \( J = 7.8 \) Hz, 9H); 0.61 (dq, \( J = 1.7, 7.5 \) Hz, 6H).

13C NMR (100 MHz, CDCl\(_3\), \( \delta \)): 167.2, 149.1, 141.1, 129.8, 129.1, 126.1, 114.5, 75.6, 52.2, 6.9, 5.0.

IR (NaCl, thin film): 2954, 2912, 2877, 1727, 1610, 1436, 1278, 1113, 1019, 842, 745.

HRMS-ESI (m / z): [M + Na]\(^+\) calcd for C\(_{17}\)H\(_{26}\)O\(_3\)SiNa, 329.1543; found, 329.1548.]
The reaction of ethylene and pivaldehyde (55 \( \mu \)L, 0.5 mmol) with Ni(cod)\(_2\), tris-\( \sigma \)-methoxy-phenylphosphine and TESOTf (197 \( \mu \)L, 0.875 mmol), triethylamine in toluene following the general procedure 1 above, afforded 1l in 70% isolated yield as a colorless oil.

\(^1\)H NMR (400 MHz, CDCl\(_3\), \( \delta \)): 5.97 (ddd, \( J = 5.9, 10.2, 16.9 \) Hz, 1H); 5.11 (d, \( J = 8.5 \) Hz, 1H); 5.08 (bs, 1H); 3.67 (d, \( J = 7.5 \) Hz, 1H); 0.96 (t, \( J = 7.9 \) Hz, 9H); 0.86 (s, 9H); 0.63 (q, \( J = 7.7 \) Hz, 6H).

\(^1^3\)C NMR (100 MHz, CDCl\(_3\), \( \delta \)): 139.4, 115.8, 82.4, 35.5, 26.0, 7.2, 5.3.

IR (NaCl, thin film): 2955, 2877, 1641, 1462, 1239, 1082, 835.

The reaction of ethylene and 2,2-dimethyl-3-oxo-propionic acid methyl ester (70 mg, 0.54 mmol) with Ni(cod)\(_2\), tris-\( \sigma \)-methoxy-phenylphosphine and TESOTf (197 \( \mu \)L, 0.875 mmol), triethylamine in toluene following the general procedure 1 above, afforded 1m in 81% (0.28 mmol) isolated yield as a colorless oil.

\(^1\)H NMR (400 MHz, CDCl\(_3\), \( \delta \)): 5.75 (ddd, \( J = 7.6, 10.4, 17.5 \) Hz, 1H); 5.17 (bd, \( J = 17.3 \) Hz, 1H); 5.15 (bd, \( J = 10.3 \) Hz, 1H); 4.31 (d, \( J = 7.6 \) Hz, 1H); 3.66 (s, 3H); 1.15 (s, 3H); 1.05 (s, 3H); 0.92 (t, \( J = 7.9 \) Hz, 9H); 0.55 (dq, \( J = 1.5, 7.6 \) Hz, 6H).

\(^1^3\)C NMR (100 MHz, CDCl\(_3\), \( \delta \)): 177.4, 137.8, 117.3, 79.2, 51.8, 48.3, 21.4, 19.9, 7.0, 5.2.

IR (NaCl, thin film): 2954, 2878, 1745, 1732, 1642, 1468, 1261, 1087, 834.

HRMS-ESI (m / z): [M + Na]\(^+\) calcd for C\(_{14}\)H\(_{28}\)O\(_3\)SiNa, 295.1700; found, 295.1714.
The reaction of ethylene and cyclohexanecarboxaldehyde (60 µL, 0.5 mmol) with Ni(cod)$_2$, tris-o-methoxy-phenylphosphine and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene following the general procedure 1 above, afforded **1n** in 25% yield as determined by $^1$H NMR versus a standard. Another experiment was carried out under 2 atm of ethylene and yielded 34% **1n** and 66% silyl enol ether of cyclohexanecarboxaldehyde. Treatment of this mixture with a TBAF / THF / H$_2$O solution removed the silyl enol ether from the mixture and column chromatography isolated **1n** as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$, δ): 5.78 (ddd, $J = 7.0, 10.3, 17.3$ Hz, 1H); 5.07 (m, 2H); 3.78 (t, $J = 6.6$ Hz, 1H); 1.40-0.90 (m, 11H); 0.95 (t, $J = 8.0$ Hz, 9H); 0.59 (q, $J = 8.0$ Hz, 6H).

$^{13}$C NMR (125 MHz, CDCl$_3$, δ): 140.7, 114.8, 78.9, 44.5, 29.0, 29.0, 26.9, 26.5, 7.1, 5.2.

IR (NaCl, thin film): 2953, 2926, 2877, 1644, 1451, 1239, 1068, 743.

HRMS-ESI (m / z): [M + Na]$^+$ calcd for C$_{15}$H$_{30}$OSiNa, 277.1958; found, 277.1968.

**Nickel-catalyzed coupling of monosubstituted olefins and aldehydes (2a – 2p).**

**Nickel-catalyzed coupling of monosubstituted alkenes and aldehydes (homoallylic products)**

**General procedure 3.** A 10 mL test tube and a stir bar were oven-dried and brought into a glove box. Ni(cod)$_2$ (27.5 mg, 0.1 mmol, 20 mol%) and ligand (0.2 mmol, 40 mol% as specified) were added to the test tube, the test tube was sealed with a septum, and the sealed tube was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in toluene (2.5 mL) under argon and stirred 5 min at room temperature. Alkene (0.5 mL), triethylamine (418 µL, 3 mmol, 600 mol%) and then aldehyde (0.5 mmol, 100 mol%) were added. TESOTf (197 µL, 0.875 mmol, 175 mol%) was added. The mixture was stirred at room temperature for 48 h. The mixture was filtered through a plug of silica gel. Solvent was removed under reduced pressure and the crude mixture was diluted in hexane. Purification via flash chromatography on silica afforded the coupling product.
A 10 mL test tube and a stir bar were oven-dried and brought into a glove box. Ni(cod)$_2$ (27.5 mg, 0.1 mmol, 20 mol%) and EtOPh$_2$P (43 μl, 0.2 mmol, 40 mol%) were added to the round bottom flask, the flask was sealed with a septum, and the sealed flask was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in toluene (2.5 mL) under argon and stirred 5 min at room temperature. The reaction mixture was purged with propene for 1 min to remove argon, taken care not to introduce oxygen. The propene atmosphere was maintained with a propene balloon. Triethylamine (418 μL, 3 mmol, 600 mol%) was added. benzaldehyde (51 μL, 0.5 mmol, 100 mol%) was added. Silyl triflate (0.875 mmol, 175 mol%, as specified) was added. The mixture was stirred at room temperature for 48 h. The mixture was filtered through a plug of silica gel. Solvent was removed under reduced pressure and $^1$H NMR of the crude mixture indicated the total yield of 2a and 2a' was 73% and the ratio of 2a:2a' is 89:11. Purification via flash chromatography on silica afforded 2a and 2a' as colorless oils.

$^1$H NMR (400 MHz, CDCl$_3$, δ): 7.27-7.38 (m, 5H); 5.78-5.89 (m, 1H); 5.05-5.10 (m, 2H); 4.74 (dd, $J$ = 7.2, 5.5 Hz, 1H); 2.42-2.59 (m, 2H); 0.94 (t, $J$ = 7.9 Hz, 9H); 0.59 (dq, $J$ = 2.6, 7.9 Hz, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$, δ): 145.3, 135.4, 128.2, 127.2, 126.1, 117.0, 75.1, 45.6, 7.0, 5.0.

IR (NaCl, thin film): 2954, 2927, 2876, 1644, 1493, 1449, 1239, 1090, 858, 699.

HRMS-ESI (m / z): [M + Na]$^+$ calcd for C$_{16}$H$_{26}$OSiNa, 285.1645; found, 285.1633.

$^1$H NMR (400 MHz, CDCl$_3$, δ): 7.24-7.39 (m, 5H); 5.15 (m, 2H); 4.86 (s, 1H); 1.56 (s, 3H); 0.94 (t, $J$ = 7.8 Hz, 9H); 0.61 (q, $J$ = 7.8 Hz, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$, δ): 148.1, 143.5, 128.1, 127.0, 126.3, 111.0, 78.4, 17.4, 7.0, 5.0.

IR (NaCl, thin film): 2955, 2913, 2877, 1451, 1237, 1091, 1066, 1005, 899, 853, 740, 698.

HRMS-ESI (m / z): [M + Na]$^+$ calcd for C$_{16}$H$_{26}$OSiNa, 285.1645; found, 285.1651.
The reaction of 1-octene and benzaldehyde (51 µL, 0.5 mmol) with Ni(cod)2, EtOPh2P (43 µl, 0.2 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded 2b and 2b' in 85% total yield according to 1H NMR of the crude mixture and the ratio of 2b:2b' is 95:5. The E/Z ratio of 2b is 75:25. Purification via flash chromatography on silica afforded 2b and 2b' as colorless oils.

In another experiment, the reaction of 1-octene (1 mL) and benzaldehyde (51 µL, 0.5 mmol) with Ni(cod)2, Cy2PhP (56 mg, 0.2 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded 2b' and 2b in 73% total yield according to 1H NMR of the crude mixture and the ratio of 2b':2b is 71:29. Purification via flash chromatography on silica afforded 2b' and 2b in 70% isolated yield as a colorless oil.

1H NMR (400 MHz, CDCl3, δ): 7.20-7.40 (m, 5H); 5.30-5.50 (m, 2H); 4.63 (dd, J = 5.6, 7.2 Hz, 1H); 2.45 (quintet, J = 6.1 Hz, 1H); 2.35 (quintet, J = 5.9 Hz, 1H); 1.33 (m, 2H); 0.92 (t, J = 7.8 Hz, 12H); 0.56 (dq, J = 2.4, 7.6 Hz, 6H).
13C NMR (100 MHz, CDCl3, δ): 145.6, 133.3, 128.1, 127.1, 126.6, 126.2, 75.6, 44.5, 32.8, 31.6, 29.3, 22.8, 14.2, 7.0, 5.1.

1H NMR (400 MHz, CDCl3, δ): 7.36 (d, J = 7.0 Hz, 2H); 7.31 (t, J = 7.1 Hz, 2H); 7.24 (t, J = 7.2, 1H); 5.22 (bs, 1H); 5.15 (bs, 1H); 4.87 (s, 1H); 1.96 (pentet, J = 7.8 Hz, 1H); 1.76 (pentet, J = 8.0 Hz, 1H); 1.15-1.40 (m, 8H); 0.93 (t, J = 8.0 Hz, 9H); 0.87 (t, J = 6.8 Hz, 3H); 0.60 (dq, J = 1.6, 7.9 Hz, 6H).
13C NMR (100 MHz, CDCl3, δ): 152.3, 143.8, 128.1, 127.1, 126.6, 109.5, 78.3, 32.0, 30.8, 29.4,
The reaction of 1-octene and 4-anisaldehyde (61 µL, 0.5 mmol) with Ni(cod)2, EtOPh2P (43 µl, 0.2 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded 2c and 2c' in 85% total yield according to 1H NMR of the crude mixture and the ratio of 2c:2c' is > 95:5. The E / Z ratio of 2c is 75:25. Purification via flash chromatography on silica afforded 2c as a colorless oil. 2c' was not detected.

1H NMR (400 MHz, CDCl3, δ): 7.22 (d, J = 8.6 Hz, 2H); 6.84 (d, J = 8.6 Hz, 2H); 5.33-5.43 (m, 2H); 4.58 (dd, J = 6.1 Hz, 6.1 Hz, 1H); 3.81 (s, 3H); 2.27-2.42 (m, 2H); 1.93-1.98 (m, 2H); 1.22-1.60 (m, 6H); 0.95 (t, J = 8.0 Hz, 3H); 0.88 (t, J = 7.8 Hz, 9H); 0.53 (q, J = 7.8 Hz, 6H).

13C NMR (100 MHz, CDCl3, δ): 158.7, 137.9, 133.2, 127.3, 126.7, 113.4, 75.2, 55.4, 44.5, 32.8, 31.6, 29.3, 22.8, 14.3, 7.0, 5.0.

IR (NaCl, thin film): 2955, 2876, 1613, 1379, 1332, 1273, 1267, 1134, 752, 554, 445, 328, 316, 293, 228, 143, 70, 50.

The reaction of 1-octene and 4-chlorobenzaldehyde (70 mg, 0.5 mmol) with Ni(cod)$_2$, EtOPh$_2$P (43 µl, 0.2 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded 2d and 2d' in 37% total yield according to $^1$H NMR of the crude mixture and the ratio of 2d:2d' is > 95:5. The E / Z ratio of 2d is 74:26. Purification via flash chromatography on silica afforded 2d as a colorless oil. 2d' was not detected.

$^1$H NMR (400 MHz, CDCl$_3$, δ): 7.24 (m, 4H); 5.30-5.41 (m, 2H); 4.61 (dd, J = 6.1 Hz, 6.1 Hz, 1H); 2.26-2.40 (m, 2H); 1.89-1.97 (m, 2H); 1.21-1.59 (m, 6H); 0.94 (t, J = 8.0 Hz, 3H); 0.89 (t, J = 7.8 Hz, 9H); 0.54 (q, J = 7.8 Hz, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$, δ): 144.1, 133.7, 132.5, 128.2, 127.5, 126.0, 74.8, 44.4, 32.8, 31.5, 29.2, 22.7, 14.3, 7.0, 4.9.

IR (NaCl, thin film): 2956, 2876, 1647, 1456, 1089, 1066, 742.

HRMS-ESI (m / z): [M + Na]$^+$ calcd for C$_{15}$H$_{20}$Na, 223.1463; found, 223.1305.
The reaction of 1-octene and 2-naphthaldehyde (78 mg, 0.5 mmol) with Ni(cod)$_2$, EtOPh$_2$P (43 µl, 0.2 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded 2e and 2e' in 88% total yield according to $^1$H NMR of the crude mixture and the ratio of 2e:2e' is > 95:5. The $E$ / $Z$ ratio of 2e is 70:30. Purification via flash chromatography on silica afforded 2e as a colorless oil. 2e' was not detected.

$^1$H NMR (400 MHz, CDCl$_3$, δ): 7.83-7.92 (m, 3H); 7.80 (s, 1H); 7.48-7.59 (m, 3H); 5.43-5.53 (m, 2H); 4.89 (dd, $J = 6.9$, 13.2 Hz, 1H); 2.45-2.68 (m, 2H); 1.98-2.05 (m, 2H); 1.26-1.39 (m, 6H); 0.97 (t, $J = 8.0$ Hz, 9H); 0.94 (t, $J = 7.6$ Hz, 3H); 0.63 (q, $J = 4.1$, 8.0 Hz 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$, δ): 143.1, 133.4, 133.0, 132.3, 128.1, 127.9, 126.5, 126.0, 125.6, 125.6, 124.7, 124.7, 75.7, 44.4, 32.8, 31.7, 29.3, 22.8, 14.3, 7.0, 5.1.

IR (NaCl, thin film): 2956, 2929, 2875, 1458, 1414, 1377, 1239, 1086, 1005, 972, 744.

HRMS-ESI (m / z): [M + Na]$^+$ calcd for C$_{25}$H$_{38}$OSiNa, 405.2590; found, 405.2584.
The reaction of 1-octene and 1-methyl-2-indolecarboxaldehyde (79.6 mg, 0.5 mmol) with Ni(cod)$_2$, EtOPh$_2$P (43 µl, 0.2 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded 2f and 2f’ in 56% total yield according to $^1$H NMR of the crude mixture and the ratio of 2f:2f’ is > 95:5. The E/Z ratio of 2f is 83:17. Purification via flash chromatography on silica afforded 2f as a colorless oil. 2f’ was not detected.

$^1$H NMR (400 MHz, CDCl$_3$, $\delta$): 7.65 (d, $J$ = 7.8 Hz, 1H); 7.37 (d, $J$ = 8.2 Hz, 1H); 7.27 (t, $J$ = 7.1 Hz, 1H); 7.17 (t, $J$ = 7.1 Hz, 1H); 6.40 (s, 1H); 5.43-5.59 (m, 2H); 4.96 (dd, $J$ = 6.5, 7.4 Hz, 1H); 3.92 (s, 3H); 2.56-2.71 (m, 2H); 2.01-2.07 (m, 2H); 1.29-1.42 (m, 6H); 0.97 (t, $J$ = 8.0 Hz, 9H); 0.95 (t, $J$ = 4.0 Hz, 3H); 0.63 (dq, $J$ = 1.1, 8.0 Hz, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$): 142.3, 138.4, 133.7, 127.7, 126.2, 121.3, 120.7, 119.4, 109.1, 100.2, 70.6, 42.2, 32.8, 31.6, 31.0, 29.3, 22.8, 14.3, 7.0, 5.0.

IR (NaCl, thin film): 2954, 2927, 2874, 1466, 1339, 1236, 1072, 1010, 731.

HRMS-ESI (m / z): [M + Na]$^+$ calcd for C$_{24}$H$_{39}$ONSiNa, 408.2693; found, 408.2695.
The reaction of 1-octene and pivaldehyde (55 µL, 0.5 mmol) with Ni(cod)₂, EtOPh₂P (43 µl, 0.2 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded 2g and 2g' in 64% total yield according to ¹H NMR of the crude mixture and the ratio of 2g:2g' is > 95:5. The E/Z ratio of 2g is 78:22. Purification via flash chromatography on silica afforded 2g. 2g' was not detected.

¹H NMR (400 MHz, CDCl₃, δ): 5.37-5.53 (m, 2H); 3.37 (dd, J = 3.8, 7.4 Hz, 1H); 2.30-2.36 (m, 1H); 1.99-2.12 (m, 3H); 1.27-1.42 (m, 6H); 0.99 (t, J = 8.0 Hz, 9H); 0.92 (t, J = 6.8 Hz, 3H); 0.90 (s, 9H); 0.63 (q, J = 8.0 Hz, 6H).

¹³C NMR (100 MHz, CDCl₃, δ): 130.6, 128.5, 81.2, 36.2, 31.8, 31.4, 29.5, 27.6, 26.5, 22.8, 14.2, 7.3, 5.7.

IR (NaCl, thin film): 2956, 2876, 1466, 1238, 1096, 1009, 737.

HRMS-ESI (m / z): [M + Na]⁺ calcd for C₁₉H₄₀OSiNa, 335.2746; found, 335.2741.
The reaction of allylbenzene and benzaldehyde (51 µL, 0.5 mmol) with Ni(cod)₂, Ph₃P (52 mg, 0.2 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded 2h and 2h' in 86% total yield according to ¹H NMR of the crude mixture and the ratio of 2h:2h' is 92:8. The E / Z ratio of 2h is > 95:5. Purification via flash chromatography on silica afforded 2h as a colorless oil. 2h' was subjected to TBAF and the free alcohol was isolated by flash chromatography on silica as a colorless oil.

**2h**

¹H NMR (400 MHz, CDCl₃, δ): 7.30-7.50 (m, 10H); 6.51 (d, J = 15.9 Hz, 1H); 6.34 (dt, J = 7.2, 15.9 Hz, 1H); 4.89 (dd, J = 5.3, 7.2 Hz, 1H); 2.64-2.81 (m, 2H); 1.03 (t, J = 7.9 Hz, 9H); 0.68 (dq, J = 2.0, 7.9 Hz, 6H).

¹³C NMR (100 MHz, CDCl₃, δ): 145.5, 138.0, 132.4, 128.8, 128.4, 127.4, 127.2, 126.3, 126.2, 75.5, 45.0, 7.1, 5.2.

IR (NaCl, thin film): 3062, 3028, 2955, 2911, 2876, 1600, 1494, 1453, 1414, 1239, 1088, 1070, 1006, 965, 830, 742, 700.


**2h’**

¹H NMR (400 MHz, CDCl₃, δ): 7.39 (m, 4H), 7.29-7.35 (m, 3H), 7.22-7.24 (m, 1H), 7.13-7.15 (m, 2H), 5.37 (s, 1H); 5.15 (s, 1H); 4.93 (s, 1H); 3.38 (d, J = 15.5 Hz, 1H); 3.13 (d, J = 15.5 Hz, 1H); 1.24 (bs, 1H).

¹³C NMR (100 MHz, CDCl₃, δ): 150.6, 142.0, 139.3, 129.4, 128.7, 128.5, 128.1, 127.0, 126.4, 112.4, 76.7, 39.2.

IR (NaCl, thin film): 3377, 3061, 3028, 2919, 1494, 1453, 1025, 909, 750, 699.

HRMS-ESI (m / z): [M + Na]⁺ calcd for C₁₆H₁₆ONa, 247.1099; found, 247.1101.
The reaction of allylbenzene and o-anisaldehyde (60 µL, 0.5 mmol) with Ni(cod)₂, Ph₃P (52 mg, 0.2 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded 2i-ortho and 2i'-ortho in 78% total yield according to ¹H NMR of the crude mixture and the ratio of 2i-ortho:2i'-ortho is 92:8. The E/Z ratio of 2i-ortho is > 95:5. 2i-ortho was subjected to TBAF and the free alcohol was isolated as a colorless oil. Allylic alcohol 2i'-ortho was not isolated.

desilylated 2i-ortho

¹H NMR (400 MHz, CDCl₃, δ): 7.22-7.43 (m, 7H); 7.02 (t, J = 7.5 Hz, 1H); 6.93 (d, J = 8.1 Hz, 1H); 6.52 (d, J = 15.9 Hz, 1H); 6.31 (dt, J = 7.2, 15.9 Hz, 1H); 5.09 (dd, J = 5.1, 7.5 Hz, 1H); 3.89 (s, 3H); 2.69-2.81 (m, 3H).
¹³C NMR (100 MHz, CDCl₃, δ): 156.5, 137.6, 132.8, 131.9, 128.6, 128.5, 127.3, 127.0, 126.9, 126.3, 120.9, 110.6, 70.2, 55.5, 41.3.
IR (NaCl, thin film): 3399, 3026, 2935, 2836, 1601, 1491, 1464, 1438, 1287, 1240, 1181, 1049, 1029, 966, 753, 694.
HRMS-ESI (m/z): [M+Na]⁺ calcd for C₂₃H₃₂O₂SiNa, 391.2069; found, 391.2053.
The reaction of allylbenzene and \textit{m}-anisaldehyde (61 \textmu L, 0.5 mmol) with Ni(cod)\textsubscript{2}, Ph\textsubscript{3}P (52 mg, 0.2 mmol, 40 mol\%) and TESOTf (197 \textmu L, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded 2i-meta and 2i'-meta in 96\% total yield according to \textsuperscript{1}H NMR of the crude mixture and the ratio of 2i-meta:2i'-meta is 92:8. The \textit{E}/\textit{Z} ratio of 2i-meta is > 95:5. Purification via flash chromatography on silica afforded 2i-meta as a colorless oil. Allylic alcohol 2i'-meta was not isolated.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, \&): 7.25-7.41 (m, 6H), 7.03 (m, 1H), 7.0 (d, \textit{J} = 7.6 Hz, 1H); 6.87 (dd, \textit{J} = 0.8, 2.7 Hz, 1H); 6.48 (d, \textit{J} = 15.9 Hz, 1H); 6.30 (dt, \textit{J} = 7.2, 15.9 Hz, 1H); 3.87 (s, 3H); 2.61-2.75 (m, 2H), 0.99 (t, \textit{J} = 7.9 Hz, 9H); 0.64 (q, \textit{J} = 7.9 Hz, 6H).

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}, \&): 159.7, 147.1, 137.9, 134.0, 133.8, 132.3, 129.2, 128.9, 128.7, 128.6, 127.2, 127.1, 126.2, 118.4, 112.8, 111.3, 75.2, 55.3, 44.8, 7.0, 5.0.

IR (NaCl, thin film): 3027, 2954, 2910, 2876, 2835, 1601, 1587, 1488, 1456, 1435, 1359, 1320, 1284, 1263, 1153, 1083, 1050, 1006, 966, 943, 825, 779, 743, 699.

HRMS–ESI (m/z): [M+Na]\textsuperscript{+} calcd for C\textsubscript{23}H\textsubscript{32}O\textsubscript{2}SiNa, 391.2069; found, 391.1750.
The reaction of allylbenzene and o-anisaldehyde (61 \( \mu \text{L}, 0.5 \text{ mmol}) with Ni(cod)_2, \text{Ph}_3\text{P} (52 \text{ mg, 0.2 mmol, 40 mol\%}) and TESOTf (197 \( \mu \text{L}, 0.875 \text{ mmol}), triethylamine in toluene following the general procedure 3 above afforded 2i-para and 2i’-para in 99% total yield according to \(^1\text{H} \text{NMR} \) of the crude mixture and the ratio of 2i-para:2i’-para is 92:8. The \( E/Z \) ratio of 2i-para is > 95:5. Purification via flash chromatography on silica afforded 2i-para as a colorless oil. 2i’-para was not isolated.

In another experiment, general procedure 3 was followed, except that the reaction was carried out in five fold larger scale. The reaction was heated at 35 °C and 9 mL toluene was used as the solvent. This reaction afforded 2i-para and 2i’-para in 98% total yield according to \(^1\text{H} \text{NMR} \) of the crude mixture and the ratio of 2i-para:2i’-para is 92:8. The \( E/Z \) ratio of 2i-para is > 95:5. Purification via flash chromatography on silica afforded 2i-para as a colorless oil. 2i’-para was not isolated.

\[ \text{2i-para} \]

\[ \text{2i’-para} \]

\(^1\text{H} \text{NMR} \) (400 MHz, CDCl\(_3\), \( \delta \)): 7.49 (m, 7H); 7.00 (d, \( J = 8.6 \) Hz, 2H); 6.52 (d, \( J = 15.9 \) Hz, 1H); 6.35 (dt, \( J = 7.2, 15.9 \) Hz, 1H); 4.85 (dd, \( J = 6.4, 6.4 \) Hz, 1H); 3.89 (s, 3H); 2.63-2.81 (m, 2H); 1.04 (t, \( J = 7.8 \) Hz, 9H); 0.70 (q, \( J = 7.8 \) Hz, 6H).

\[^{13}\text{C} \text{NMR} \) (100 MHz, CDCl\(_3\), \( \delta \)): 159.0, 138.1, 137.7, 132.3, 128.7, 127.5, 127.3 127.2, 126.3, 113.7, 75.0, 55.4, 45.1, 7.1, 5.2.

IR (NaCl, thin film): 3027, 2954, 2910, 2875, 1612, 1511, 1414, 1302, 1248, 1171, 1081, 1005, 966, 836, 743, 693.

HRMS-ESI (m / z): [M + Na]\(^+\) calcd for C\(_2\text{3H}_{32}\text{O}_2\text{SiNa}, 391.2069\); found, 391.2057.
The reaction of allylbenzene and naphthaldehyde (78 mg, 0.5 mmol) with Ni(cod)$_2$, Ph$_3$P (52 mg, 0.2 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded 2j and 2j’ in 88% total yield according to $^1$H NMR of the crude mixture and the ratio of 2j:2j’ is 95:5. The $E$ / $Z$ ratio of 2j is > 95:5. Purification via flash chromatography on silica afforded 2j as a colorless oil. 2j’ was subjected to TBAF and the free alcohol was isolated by flash chromatography on silica as a colorless oil.

(2j)

$^1$H NMR (400 MHz, CDCl$_3$, δ): 7.90-7.96 (m, 4H); 7.67 (d, $J = 1.6$ Hz, 1H); 7.60-7.65 (m, 2H); 7.30-7.59 (m, 5H); 6.54 (d, $J = 15.9$ Hz, 1H); 6.36 (dt, $J = 7.2$, 15.9 Hz, 1H); 5.05 (dd, $J = 5.4$, 7.2 Hz, 1H); 2.74-2.89 (m, 2H); 1.03 (t, $J = 8.0$ Hz, 9H); 0.70 (dq, $J = 2.9$, 8.0 Hz, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$, δ): 142.9, 137.9, 133.4, 133.1, 132.4, 128.7, 128.1, 128.1, 127.9, 127.1, 126.2, 126.1, 125.7, 75.5, 44.9, 7.0, 5.1.

IR (NaCl, thin film): 3026, 2954, 2910, 2875, 1507, 1496, 1457, 1239, 1123, 1083, 1005, 965, 819, 744.

HRMS-ESI (m / z): [M + Na]$^+$ calcd for C$_{26}$H$_{32}$O$_x$SiNa, 411.2120; found, 411.2167.

desilylated 2j’

$^1$H NMR (400 MHz, CDCl$_3$, δ): 7.86-7.88 (m, 4H); 7.48-7.55 (m, 3H); 7.20-7.36 (m, 3H); 7.13-7.16 (m, 2H); 5.43 (s, 1H); 5.32 (s, 1H); 4.97 (s, 1H); 3.41 (d, $J = 15.6$ Hz, 1H); 3.16 (d, $J = 15.6$ Hz, 1H); 2.02 (bs, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$, δ): 150.5, 149.2, 139.4, 139.3, 133.4, 133.3, 129.4, 128.6, 128.2, 127.9, 126.4, 126.4, 126.2, 126.0, 124.9, 112.8, 77.4, 39.2.

IR (NaCl, thin film): 3365, 3058, 2923, 1495, 1453, 1031, 908, 819, 745, 700.

HRMS-ESI (m / z): [M + Na]$^+$ calcd for C$_{20}$H$_{18}$ONa, 297.1255; found, 297.1260.
The reaction of allylbenzene and 1-methyl-2-indolecarboxaldehyde (79.6 mg, 0.5 mmol) with Ni(cod)$_2$, Ph$_3$P (52 mg, 0.2 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded 2k in 57% total yield according to $^1$H NMR of the crude mixture and the ratio of 2k:2k' is > 95:5. The E / Z ratio of 2k is > 95:5. 2k' was not detected. 2k was subjected to TBAF and the free alcohols were isolated by flash chromatography on silica (buffered with Et$_3$N) as colorless oils.

In another experiment, the reaction of allylbenzene and 1-methyl-2-indolecarboxaldehyde (79.6 mg, 0.5 mmol) with Ni(cod)$_2$, Cy$_2$PhP (56 mg, 0.2 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded 2k' and 2k in 56% total yield according to $^1$H NMR of the crude mixture and the ratio of 2k':2k is 80:20. The E / Z ratio of 2k is > 95:5. Both 2k' and 2k were subjected to TBAF and the free alcohols were isolated by flash chromatography on silica (buffered with Et$_3$N) as colorless oils.

**desilylated 2k**

$^1$H NMR (400 MHz, CDCl$_3$, δ): 7.63 (d, $J = 7.8$ Hz, 1H); 7.20-7.41 (m, 7H); 7.14 (t, $J = 7.8$ Hz, 1H); 6.62 (d, $J = 15.8$ Hz, 1H); 6.55 (s, 1H); 6.34 (dt, $J = 7.3$, 15.8 Hz, 1H); 5.01 (m, 1H); 3.86 (s, 3H); 2.93-2.99 (m, 2H); 1.93 (bs, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$, δ): 149.2, 141.3, 138.1, 137.2, 133.8, 128.7, 127.6, 126.4, 125.7, 122.1, 121.0, 119.8, 109.3, 99.4, 66.9, 40.2, 30.4.

IR (NaCl, thin film): 3640, 3026, 2953, 2910, 2875, 1467, 1339, 1237, 1073, 1006, 966, 744.

HRMS-ESI (m / z): [M + Na]$^+$ calcd for C$_{19}$H$_{19}$ONa, 300.1364; found, 300.1365.
desilylated 2k'

$^1$H NMR (400 MHz, CDCl$_3$, $\delta$): 7.63 (d, 1H); 7.12-7.38 (m, 8H); 6.49 (s, 1H); 5.38 (s, 1H); 5.31 (s, 1H); 5.14 (s, 1H); 3.70 (s, 3H); 3.54 (d, $J = 15.3$ Hz, 1H); 3.33 (d, $J = 15.3$ Hz, 1H); 1.98 (d, $J = 5.1$Hz, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$): 148.7, 139.6, 139.1, 138.4, 129.3, 128.6, 127.3, 126.6, 122.0, 121.0, 119.7, 113.2, 109.3, 101.5, 69.6, 40.2, 30.3.

IR (NaCl, thin film): 3349, 3059, 3027, 2923, 1649, 1601, 1494, 1468, 1453, 1318, 1234, 1030, 968, 907, 751, 737, 700.

HRMS-ESI (m / z): [M + Na]$^+$ calcd for C$_{19}$H$_{19}$ONa, 300.1364; found, 300.1369.
The reaction of allylbenzene and pivaldehyde (55 μL, 0.5 mmol) with Ni(cod)$_2$, Ph$_3$P (52 mg, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded 21 in 65% total yield according to $^1$H NMR of the crude mixture and the ratio of 21:21' is > 95:5. The $E$ / $Z$ ratio of 21 is 78:22. 21' was not detected. Purification via flash chromatography on silica afforded 21 as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$, $\delta$): 7.22-7.40 (m, 5H); 6.43 (d, $J = 15.9$ Hz, 1H); 6.32 (dt, $J = 7.1$, 15.9 Hz, 1H); 3.50 (dd, $J = 3.4$, 7.7 Hz, 1H); 2.49-2.55 (m, 1H), 2.28-2.35 (m, 1H), 1.00 (t, $J = 8.0$ Hz, 9H); 0.96 (s, 9H); 0.64 (q, $J = 8.0$ Hz, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$): 138.1, 131.3, 129.7, 128.7, 127.0, 126.1, 81.0, 37.4, 36.2, 26.6, 7.3, 5.7.

HRMS–ESI (m/z): [M+Na]$^+$ calcd for C$_{20}$H$_{34}$OSiNa, 341.2277; found, 341.2263.
The reaction of 4-phenyl-1-butene and o-anisaldehyde (61 µL, 0.5 mmol) with Ni(cod)$_2$, Ph$_3$P (52 mg, 0.2 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded 2m and 2m' in 91% total yield according to $^1$H NMR of the crude mixture and the ratio of 2m:2m' is 92:8. The $E$ / $Z$ ratio of 2m is 68:32. Purification via flash chromatography on silica afforded 2m and 2m' as colorless oils.

$^1$H NMR (400 MHz, CDCl$_3$, $\delta$): 7.13-7.42 (m, 7H), 6.92 (d, $J = 8.7$ Hz, 2H), 5.49-5.69 (m, 2H), 4.76 (t, $J = 6.3$ Hz, 0.33 H), 4.70 (t, $J = 6.4$ Hz, 0.67 H), 3.87 (s, 3H), 3.37-3.39 (m, 2H), 2.35-2.81 (m, 2H), 0.96 (t, $J = 7.9$ Hz, 6H); 0.60 (q, $J = 7.9$ Hz, 9H).

$^1$H NMR (400 MHz, CDCl$_3$, $\delta$): 7.13-7.42 (m, 7H), 6.93 (d, $J = 8.7$ Hz, 2H), 5.34 (s, 1H), 5.19 (s, 1H), 5.00 (s, 1H), 3.86 (s, 3H), 2.61-2.79 (m, 2H), 2.26-2.42 (m, 1H), 2.16-2.22 (m, 1H), 1.07 (t, $J = 7.8$ Hz, 9H); 0.74 (q, $J = 7.9$ Hz, 6H).
The reaction of 4-methyl-1-pentene and o-anisaldehyde (61 µL, 0.5 mmol) with Ni(cod)$_2$, EtOPh$_2$P (43 µL, 0.2 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded 2n and 2n' in 82% total yield according to $^1$H NMR of the crude mixture and the ratio of 2n:2n' is > 95:5. The $E$/Z ratio of 2n is 81:19. 2n' was not detected. Purification via flash chromatography on silica afforded 2n as a colorless oil.

In another experiment, a 10 mL round bottom flask and a stir bar were oven-dried and brought into a glove box. Ni(cod)$_2$ (27.5 mg, 0.2 mmol, 20 mol%) and dicyclohexylphenylphosphine (55 mg, 0.4 mmol, 40 mol%) were added to the round bottom flask, the flask was sealed with a septum, and the sealed flask was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in toluene (2.5 mL) under argon and stirred 5 min at room temperature. 4-methyl-1-pentene (633 µL, 5 mmol, 1000 mol%) was added. Triethylamine (418 µL, 3 mmol, 600 mol%) was added. Benzaldehyde (51 µL, 0.5 mmol, 100 mol%) was added to the reaction mixture, followed by TESOTf (197 µL, 0.875 mmol, 175 mol%). The mixture was stirred at room temperature for 14 h. The mixture was filtered through a plug of silica gel. Solvent was removed under reduced pressure and NMR of the crude mixture indicated the ratio of 2n':2n is 75:25. Purification via flash chromatography on silica afforded 2n' in 44% isolated yield as a colorless oil and 2n in 10% isolated yield.

This reaction can be run according to general procedure 3, which also afforded 2n' and 2n in similar yield.
1H NMR (400 MHz, CDCl₃, δ): 7.30 (m, 5H); 5.40 (m, 2H); 4.63 (dd, J = 5.3, 7.3 Hz, 1H); 2.41 (quintet, J = 5.3 Hz, 1H); 2.30 (quintet, J = 5.5 Hz, 1H); 2.24 (septet, J = 6.7 Hz, 1H); 2.00 (m, 2H); 0.95 (dd, J = 6.7, 7.6 Hz, 6H); 0.89 (t, J = 7.9 Hz, 9H); 0.62 (q, J = 7.9 Hz, 6H).

13C NMR (100 MHz, CDCl₃, δ): 145.6, 140.2, 128.1, 127.0, 126.1, 123.7, 75.7, 44.5, 31.3, 22.6, 7.01, 5.0.

HRMS-ESI (m/z): [M + Na]⁺ calcd for C₁₉H₃₂OSiNa, 327.2115; found, 327.2121.

1H NMR (400 MHz, CDCl₃, δ): 7.36 (d, J = 7.8 Hz, 2H); 7.32 (t, J = 7.1 Hz, 2H); 7.25 (t, J = 7.1, 1H); 5.30 (bs, 1H); 5.12 (bs, 1H); 4.87 (bs, 1H); 1.65-1.85 (m, 3H); 0.93 (t, J = 8.0 Hz, 9H); 0.84 (d, J = 6.4 Hz, 3H); 0.82 (d, J = 6.2 Hz, 3H); 0.60 (dq, J = 1.3, 8.3 Hz, 6H).

13C NMR (100 MHz, CDCl₃, δ): 150.5, 143.7, 128.1, 127.1, 126.7, 110.7, 77.9, 41.1, 26.3, 23.0, 22.6, 7.0, 5.0.

IR (NaCl, thin film): 2955, 2877, 1646, 1454, 1088, 1067, 743.

HRMS-ESI (m/z): [M + Na]⁺ calcd for C₁₉H₃₂OSiNa, 327.2115; found, 327.2115.
The reaction of 3-methyl-1-butene and benzaldehyde (51 µL, 0.5 mmol) with Ni(cod)_2, EtOPh_2P (43 µL, 0.2 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded 2o and 2o' in 95% total yield according to ^1H NMR of the crude mixture and the ratio of 2o:2o' is 86:14. The E/Z ratio of 2o' is > 95:5. Purification via flash chromatography on silica afforded 2o. 2o' was not isolated.

^1H NMR (400 MHz, CDCl_3, δ): 7.27-7.43 (m, 5H); 5.19-5.24 (m, 1H); 4.68 (dd, J = 5.8, 7.2 Hz, 1H); 2.36-2.54 (m, 2H); 1.74 (d, J = 0.8 Hz, 3H); 1.58 (s, 3H); 0.95 (t, J = 7.8 Hz, 9H); 0.60 (dq, J = 3.4, 7.8 Hz, 6H).

^13C NMR (100 MHz, CDCl_3, δ): 145.8, 133.6, 128.1, 127.0, 126.1, 121.0, 75.4, 40.0, 26.0, 18.0, 7.0, 5.0.

IR (NaCl, thin film): 3028, 2956, 2877, 2912, 1454, 1414, 1377, 1239, 1089, 1069, 1005, 941, 744, 699.

HRMS-ESI (m/z): [M + Na]^+ calcd for C_{18}H_{30}OSiNa, 313.1964; found, 313.1966.
The reaction of vinylcyclohexane and benzaldehyde (51 µL, 0.5 mmol) with Ni(cod)$_2$, EtOPh$_2$P (43 µl, 0.2 mmol, 100 mol%) and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded 2p and 3p in 99% total yield according to $^1$H NMR of the crude mixture and the ratio of 2p:3p is 75:25. The $E/Z$ ratio of 3p is $> 95:5$. Purification via flash chromatography on silica afforded a mixture of 2p and 3p.

In another experiment, a 10 mL round bottom flask and a stir bar were oven-dried and brought into a glove box. Ni(cod)$_2$ (27.5 mg, 0.2 mmol, 20 mol%) and dicyclohexylphenylphosphine (55 mg, 0.4 mmol, 20 mol%) were added to the round bottom flask, the flask was sealed with a septum, and the sealed flask was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in toluene (2.5 mL) under argon and stirred 5 min at room temperature. Vinylcyclohexane (856 µL, 6.25 mmol, 1250 mol%) was added. Triethylamine (418 µL, 3 mmol, 600 mol%) was added. Benzaldehyde (51 µL, 0.5 mmol, 100 mol%) was added, followed by TESOTf (197 µL, 0.875 mmol, 175 mol%). The mixture was stirred at room temperature for 16 h. The mixture was filtered through a plug of silica gel. $^1$H NMR of the crude mixture indicated that 2p$'$ is the minor product, along with homoallylic product 2p and 1,3-disubstituted allicylic product 3p as major products. Purification via flash chromatography on silica afforded 2p$'$ in 5% isolated yield as a colorless oil.
\[ \text{OSiEt}_3 \]

**2p**

\[ ^1H \text{ NMR (}400 \text{ MHz, CDCl}_3, \delta): 7.24-7.42 (m, 5H); 5.14 (t, } J = 7.4 \text{ Hz, 1H); 4.66 (t, } J = 6.4 \text{ Hz, 1H); 2.37-2.52 (m, 2H); 2.00-2.11 (m, 3H); 1.50-1.78 (m, 3H); 1.03-1.48 (m, 4H); 0.94 (t, } J = 7.9 \text{ Hz, 9H); 0.59 (dq, } J = 2.8, 7.9 \text{ Hz, 6H).} \]

\[ ^13C \text{ NMR (}100 \text{ MHz, CDCl}_3, \delta): 145.7, 141.6, 128.0, 127.0, 126.2, 117.5, 75.6, 39.0, 37.5, 29.0, 28.7, 27.8, 27.1, 7.0, 5.0. \]

**2p’**

\[ ^1H \text{ NMR (}400 \text{ MHz, CDCl}_3, \delta): 7.33 (d, } J = 8.6 \text{ Hz, 2H); 7.29 (t, } J = 7.9 \text{, 2H); 7.22 (t, } J = 7.0 \text{ Hz, 1H); 5.23 (dd, } J = 1.3, 1.3 \text{ Hz, 1H); 5.14 (s, 1H); 4.90 (s, 1H); 1.2-2.0 (m, 11H); 0.91 (t, } J = 7.9 \text{ Hz, 9H); 0.58 (dq, } J = 0.5, 7.8 \text{ Hz, 6H).} \]

\[ ^13C \text{ NMR (}125 \text{ MHz, CDCl}_3, \delta): 157.7, 143.7, 128.0, 127.1, 126.9, 108.2, 77.6, 39.5, 34.5, 33.5, 27.1, 27.0, 26.5, 7.1, 5.0. \]

IR (NaCl, thin film): 2954, 2928, 2876, 2853, 1449, 1449, 1239, 1090, 858, 699.
HRMS-ESI (m / z): [M + Na]^+ calcd for C\(_{21}\)H\(_{34}\)OSiNa, 353.2271; found, 353.2269.

**3p**

\[ ^1H \text{ NMR (}400 \text{ MHz, CDCl}_3, \delta): 7.24-7.42 (m, 5H); 5.69 (dd, } J = 6.5, 15.4 \text{ Hz, 1H); 5.56 (dd, } J = 7.0, 15.4 \text{ Hz, 1H); 5.18 (d, } J = 7.0 \text{ Hz, 1H); 2.00-2.11 (m, 3H); 1.63-1.78 (m, 1H); 1.50-1.78 (m, 3H); 1.03-1.48 (m, 4H); 1.00 (t, } J = 8.0 \text{ Hz, 9H); 0.67 (dq, } J = 2.3, 8.0 \text{ Hz, 6H).} \]

\[ ^13C \text{ NMR (}100 \text{ MHz, CDCl}_3, \delta): 144.8, 136.9, 131.2, 128.2, 126.9, 126.1, 75.9, 40.4, 33.0, 32.9, 26.4, 26.2, 7.1, 5.2. \]

The following IR and HRMS data is from a mixture of 2p and 2p’.
IR (NaCl, thin film): 2954, 2928, 2876, 2853, 1449, 1414, 1238, 1086, 1067, 1007, 969, 829, 744, 699.
HRMS-ESI (m / z): [M + Na]^+ calcd for C\(_{21}\)H\(_{34}\)OSiNa, 353.2277; found, 353.2267.
The reaction of 3,3-dimethyl-1-butene and benzaldehyde (51 µL, 0.5 mmol) with Ni(cod)$_2$, EtOPh$_2$P (43 µL, 0.2 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded $3q$ only in 14% total yield according to $^1$H NMR of the crude mixture. Purification via flash chromatography on silica afforded $3q$ as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$, $\delta$): 7.30-7.41 (m, 5H), 5.82 (d, $J = 14.6$ Hz, 1H), 5.59 (dd, $J = 14.6$, 7.0 Hz, 1H), 5.18 (m, 1H), 1.88 (bs, 1H), 1.05 (s, 9H).

$^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$): 149.2, 143.8, 128.6, 127.6, 127.3, 126.4, 75.6, 33.1, 29.6.

IR (NaCl, thin film): 3657, 2954, 2876, 1457, 1238, 966, 737, 691.

HRMS–ESI (m/z): [M+Na]$^+$ calcd for C$_{19}$H$_{32}$OSiNa, 327.2115; found, 327.2105.
A 10 mL round bottom flask and a stir bar were oven-dried and brought into a glove box. Ni(cod)$_2$ (28 mg, 0.1 mmol, 20 mol%), dicyclohexylphenylphosphine (56 mg, 0.2 mmol, 40 mol%) and 2-naphthaldehyde (78 mg, 0.5 mmol, 100 mol%) were added to the round bottom flask, the flask was sealed with a septum, and the sealed flask was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in toluene (2.5 mL) under argon and stirred 5 min at room temperature. The system was purged with propene for 1 min. The propene atmosphere was maintained by a propene balloon. Triethylamine (418 µL, 3 mmol, 600 mol%) was added. TESOTf (197 µL, 0.875 mmol, 175 mol%) was added. The mixture was stirred at room temperature for 6 h. The mixture was diluted with hexane and filtered through a plug of silica gel. Solvent was removed under reduced pressure. Purification via flash chromatography on silica afforded 2r' in 73% isolated yield as a colorless oil and 2r in 14% isolated yield as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$, $\delta$): 7.86 (m, 4H); 7.50 (m, 3H); 5.33 (s, 1H); 5.26 (s, 1H); 4.94 (s, 1H); 1.62 (s, 3H); 1.00 (t, $J = 8.0$ Hz, 9H); 0.67 (dq, $J = 1.8$, 7.9 Hz, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$): 148.0, 141.0, 133.4, 133.0, 128.2, 127.8, 127.8, 126.0, 125.7, 124.9, 124.8, 78.6, 17.6, 7.1, 5.1.

IR (NaCl, thin film): 2955, 2912, 2876, 1652, 1508, 1457, 1238, 1084, 1005, 899, 742.

HRMS-ESI (m / z): [M + Na]$^+$ calcd for C$_{20}$H$_{28}$OSiNa, 335.1802; found, 335.1809.
$^1$H NMR (400 MHz, CDCl$_3$, δ): 7.83 (t, $J = 8.5$ Hz, 3H); 7.75 (s, 1H); 7.48 (m, 3H); 5.81 (m, 1H); 5.05 (m, 1H); 5.02 (m, 1H); 4.86 (t, $J = 5.9$ Hz); 2.55 (m, 2H); 0.91 (t, $J = 8.0$ Hz, 9H); 0.57 (dq, $J = 3.5$, 7.5 Hz, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$, δ): 142.8, 135.3, 133.4, 133.0, 128.1, 127.9, 127.9, 126.1, 125.7, 124.6, 75.2, 45.6, 7.0, 5.0.

IR (NaCl, thin film): 2955, 2876, 1458, 1239, 1084, 1005, 914, 817, 743.

HRMS-ESI (m / z): [M + Na]$^+$ calcd for C$_{20}$H$_{28}$OSiNa, 335.1802; found, 335.1808.
The reaction of propene (1 atm, balloon) and p-anisaldehyde (61 µL, 0.5 mmol) with Ni(cod)₂, Cy₂PhP (56 mg, 0.2 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene following the procedure for 2z' above afforded 2s' and 2s and the ratio of 2s':2s is 82:18. Purification via flash chromatography on silica afforded 2s' and 2s as a colorless mixture in 95% isolated yield.

1H NMR (400 MHz, CDCl₃, δ): 7.30 (d, J = 8.7 Hz, 2H); 6.90 (d, J = 8.7 Hz, 2H); 5.22 (s, 1H); 5.08 (s, 1H); 4.96 (s, 1H); 3.62 (s, 3H); 2.15 (s, 1H); 1.62 (s, 3H).

13C NMR (100 MHz, CDCl₃, δ): 159.3, 147.2, 134.3, 127.9, 113.9, 110.8, 77.5, 55.4, 18.7.

1H NMR (400 MHz, CDCl₃, δ): 7.30 (d, J = 8.7 Hz, 2H); 6.90 (d, J = 8.7 Hz, 2H); 5.82 (m, 1H); 5.08 (s, 1H); 4.96 (s, 1H); 3.62 (s, 3H); 2.15 (s, 1H); 1.62 (s, 3H).

13C NMR (100 MHz, CDCl₃, δ): 159.1, 136.2, 134.8, 127.3, 118.4, 113.9, 73.1, 55.4, 43.9.
A 10 mL round bottom flask and a stir bar were oven-dried and brought into a glove box. Ni(cod)$_2$ (27.5 mg, 0.2 mmol, 20 mol%) and dicyclohexylphenylphosphine (55 mg, 0.4 mmol, 40 mol%) were added to the round bottom flask, the flask was sealed with a septum, and the sealed flask was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in toluene (1.0 mL) under argon and stirred 5 min at room temperature. 7-methyl-1,7-octadiene (825 µL, 5 mmol, 1000 mol%) was added. Triethylamine (418 µL, 3 mmol, 600 mol%) was added. TESOTf (197 µL, 0.875 mmol, 175 mol%) was added. Benzaldehyde (51 µL, 0.5 mmol, 100 mol%) in 1.5 mL toluene was added to the reaction mixture over 6 min. The mixture was stirred at room temperature for 18 h. The mixture was filtered through a plug of silica gel. Solvent was removed under reduced pressure and $^1$H NMR of the crude mixture indicated the ratio of $2t'$:$2t$ is 71:29. Purification via flash chromatography on silica afforded $2t'$ in 50% isolated yield as a colorless oil and $2t$ in 22% isolated yield as a colorless oil.

This reaction can be run according to general procedure 3, which also afforded $2t'$ and $2t$ in similar yield.

$^1$H NMR (400 MHz, CDCl$_3$, δ): 7.40 (d, $J = 7.0$ Hz, 2H); 7.34 (t, $J = 7.8$ Hz, 2H); 7.27 (t, $J = 7.2$, 1H); 5.26 (bs, 1H); 5.18 (bs, 1H); 5.10 (t, $J = 7.2$ Hz, 1H); 4.81 (bs, 1H); 1.76-2.10 (m, 4H); 1.71 (s, 3H); 1.60 (s, 3H); 1.44 (quintet, $J = 7.7$ Hz, 2H); 0.97 (t, $J = 7.9$ Hz, 9H); 0.62 (dq, $J = 1.5$, 7.9 Hz, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$, δ): 152.1, 143.7, 131.6, 128.1, 127.1, 126.6, 124.8, 109.5, 78.2, 30.4, 28.2, 28.1, 25.9, 17.8, 7.0, 5.0.

IR (NaCl, thin film): 2955, 2877, 1647, 1456, 1091, 1067, 743.

HRMS-ESI (m / z): [M + Na]$^+$ calcd for C$_{22}$H$_{36}$OSiNa, 367.2427; found, 367.2431.
$^{1}$H NMR (400 MHz, CDCl$_3$, $\delta$): 7.30 (m, 5H); 5.45 (m, 2H); 5.15 (t, $J = 7.1$ Hz, 1H); 4.64 (dd, $J = 5.4$, 7.3 Hz, 1H); 2.45 (quintet, $J = 5.4$ Hz, 1H); 2.35 (quintet, $J = 5.9$ Hz, 1H); 2.05 (m, 4H); 1.62 (s, 3H); 1.72 (s, 3H); 0.92 (t, $J = 7.9$ Hz, 9H); 0.55 (dq, $J = 1.5$, 7.9 Hz, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$): 145.6, 132.8, 131.7, 128.1, 127.1, 126.9, 126.1, 124.4, 75.6, 44.5, 33.1, 28.2, 25.9, 17.9, 7.0, 5.0.

IR (NaCl, thin film): 2955, 2914, 2876, 1454, 1089, 1005, 969, 699.

HRMS-ESI (m / z): [M + Na]$^+$ calcd for C$_{22}$H$_{36}$OSiNa, 367.2427; found, 367.2430.
The reaction of allylphthalimide (281 mg, 1.5 mmol, 300 mol%) and benzaldehyde (51 µL, 0.5 mmol) with Ni(cod)\textsubscript{2}, dicyclohexylphenylphosphine (55 mg, 0.4 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene at 35 °C following the general procedure 3 above afforded 4a and 4a' in 67% total yield according to \textsuperscript{1}H NMR of the crude mixture and the ratio of 4a:4a' is 74:26. Purification via flash chromatography on silica afforded 4a as a mixture of 4a and the isomerized starting material.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, \(\delta\)): 7.77 (dd, \(J = 3.0, 5.4\) Hz, 2H); 7.73 (dd, \(J = 3.0, 5.4\) Hz, 2H); 7.13-7.41 (m, 5H); 5.36 (s, 1H), 5.30 (s, 1H), 4.99 (s, 1H), 4.26 (d, \(J = 16\) Hz, 1H), 4.08 (d, \(J = 16\) Hz, 1H), 0.91 (t, \(J = 7.9\) Hz, 9H); 0.59 (q, \(J = 7.9\) Hz, 6H).

The reaction of allylphthalimide (1.5 mmol, 300 mol%) and benzaldehyde (51 µL, 0.5 mmol) with Ni(cod)\textsubscript{2}, EtOPh\textsubscript{2}P (43 µL, 0.2 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene at 35 °C following the general procedure 3 above afforded 4a and 4a' in 43% total yield according to \textsuperscript{1}H NMR of the crude mixture and the ratio of 4a:4a' is 12:88. The E/Z ratio of 4a' is 60:40. Purification via flash chromatography on silica afforded 4a' as a mixture with the isomerized starting material.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, \(\delta\)): 7.86 (dd, \(J = 3.1, 5.4\) Hz, 2H); 7.73 (dd, \(J = 3.1, 5.4\) Hz, 2H); 7.25–7.37 (m, 5H); 6.62 (m, 2H); 4.76 (dd, \(J = 5.5, 6.9\) Hz, 1H); 2.47-2.60 (m, 2H); 0.89 (t, \(J = 8.0\) Hz, 9H); 0.56 (q, \(J = 2.8, 8.0\) Hz, 6H).

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}, \(\delta\)): 166.7, 149.2, 145.0, 134.5, 131.9, 128.2, 127.3, 126.1, 123.7, 119.5, 118.8, 75.0, 43.1, 7.0, 5.0.

IR (NaCl, thin film): 2954, 2876, 1781, 1721, 1384, 1088, 1069, 715, 701.

HRMS–ESI (m/z): [M+Na]\textsuperscript{+} calcd for C\textsubscript{18}H\textsubscript{14}NO\textsubscript{2}Na, 276.1025; found, 276.1022.
The reaction of homoallylphthalimide (1.5 mmol, 300 mol%) and o-anisaldehyde (61 µL, 0.5 mmol) with Ni(cod)$_2$, dicyclohexylphenylphosphine (55 mg, 0.4 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene at 35 °C following the general procedure 3 above afforded 4b and 4b' in 54% total yield according to $^1$H NMR of the crude mixture and the ratio of 4b:4b' is 71:29. Purification via flash chromatography on silica afforded 4b and 4b'.

$^1$H NMR (400 MHz, CDCl$_3$, δ): 7.81 (dd, $J$ = 3.0, 5.4, 2H); 7.70 (dd, $J$ = 3.0, 5.4, 2H); 7.26 (d, $J$ = 8.7 Hz, 2H); 6.79 (d, $J$ = 8.7 Hz, 2H); 5.27 (s, 1H); 5.15 (s, 1H); 4.99 (s, 1H); 3.66-3.86 (m, 2H); 3.78 (s, 3H); 2.32-2.40 (m, 1H); 2.16-2.23 (m, 1H); 0.90 (t, $J$ = 7.9 Hz, 9H); 0.57 (q, $J$ = 7.9 Hz, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$, δ): 168.4, 158.8, 148.6, 135.2, 134.0, 132.3, 127.7, 123.3, 113.5, 111.8, 77.6, 55.3, 37.2, 29.8, 7.0, 5.0.

IR (NaCl, thin film): 2954, 2876, 1773, 1715, 1511, 1467, 1431, 1395, 1354, 1247, 1078, 952, 719.

HRMS-ESI (m / z): [M + Na]$^+$ calcd for C$_{26}$H$_{33}$O$_4$SiNa, 474.2066; found, 474.2071.
The reaction of homoallylphthalimide (1.5 mmol, 300 mol%) and o-anisaldehyde (61 µL, 0.5 mmol) with Ni(cod)$_2$, Ph$_3$P (52 mg, 0.2 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene at 35 °C following the general procedure 3 above afforded 4b and 4b' in 76% total yield according to $^1$H NMR of the crude mixture and the ratio of 4b:4b' is <5:95. Treatment of 4b' with TBAF followed by flash chromatography on silica afforded desilylated 4b'.

$^1$H NMR (400 MHz, CDCl$_3$, δ): 7.86 (dd, $J = 3.1$, 5.4 Hz, 2H); 7.73 (dd, $J = 3.1$, 5.4 Hz, 2H); 7.25 (d, $J = 8.7$ Hz, 2H); 6.84 (d, $J = 8.7$ Hz, 2H); 5.73(dt, $J = 6.0$, 15.4 Hz, 1H); 5.62 (dt, $J = 6.0$, 15.4 Hz, 1H); 4.68 (dd, $J = 6.4$, 6.4 Hz, 1H); 4.25-4.33 (m, 2H); 3.78 (s, 3H); 2.46 (m, 2H), 2.09 (bs, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$, δ): 168.2, 159.1, 136.1, 134.1, 132.3, 130.8, 127.2, 127.1, 123.5, 113.9, 73.1, 55.4, 42.3, 39.7.

IR (NaCl, thin film): 3466, 2929, 1770, 1711, 1611, 1547, 1467, 1395, 1249, 1174, 1034, 833, 720.
The reaction of homoallyloxazolidinone (1.5 mmol, 300 mol%) and benzaldehyde (51 µL, 0.5 mmol) with Ni(cod)$_2$, dicyclohexylphenylphosphine (55 mg, 0.4 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene at room temperature following the general procedure 3 above afforded 4c and 4c' in 60% total yield according to $^1$H NMR of the crude mixture and the ratio of 4c:4c' is 83:17. Purification via flash chromatography on silica afforded 4c and 4c' as colorless oils.

$^1$H NMR (400 MHz, CDCl$_3$, δ): 7.23-7.38 (m, 5H); 5.31 (s, 1H); 5.20 (s, 1H); 5.00 (s, 1H); 4.16-4.21 (m, 2H); 3.19-3.36 (m, 4H); 2.02-2.26 (m, 2H); 0.93 (t, $J$ = 7.9 Hz, 9H); 0.60 (q, $J$ = 7.8 Hz, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$, δ): 158.4, 148.1, 143.1, 128.2, 127.4, 126.3, 112.0, 78.1, 61.8, 44.3, 42.8, 27.9, 7.0, 4.9.

IR (NaCl, thin film): 2955, 2912, 2876, 1753, 1484, 1426, 1265, 1089, 1067, 1044, 1007, 861, 744, 701.

HRMS-ESI (m/z): [M+Na]$^+$ calcd for C$_{20}$H$_{31}$NO$_3$Na, 384.1965; found, 384.1951.
The reaction of homoallylphthalimide (1.5 mmol, 300 mol%) and benzaldehyde (51 µL, 0.5 mmol) with Ni(cod)₂, EtOPh₂P (43 µL, 0.2 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene at room temperature following the general procedure 3 above afforded 4c and 4c' in 28% total yield according to ¹H NMR of the crude mixture and the ratio of 4c:4c' is 10:90. 4c' was subjected to TBAF and purification via flash chromatography on silica afforded a desilylated 4c'.

¹H NMR (400 MHz, CDCl₃, δ): 7.28-7.42 (m, 5H), 5.68 (dt, J = 5.7, 7.1 Hz, 1H), 5.49 (dt, J = 5.7, 7.1 Hz, 1H), 4.77 (dd, J = 6.7, 6.8 Hz, 1H), 4.28 (t, J = 8.0 Hz, 2H), 3.80-3.82 (m, 2H), 3.38 (dt, J = 2.5, 8.0 Hz, 2H), 2.53-2.59 (m, 2H), 2.11-2.17 (bs, 1H).

¹³C NMR (100 MHz, CDCl₃, δ): 158.4, 143.9, 131.2, 128.7, 127.8, 127.3, 126.0, 73.8, 61.9, 46.4, 44.2, 42.1.

IR (NaCl, thin film): 3421, 2919, 2361, 1734, 1653, 1490, 1437, 1259, 1038, 762, 702.

HRMS–ESI (m/z): [M+Na]⁺ calcd for C₁₄H₁₇NO₃Na, 270.1101; found, 270.1104.
The reaction of allylbenzoate (2.5 mmol, 500 mol%) and benzaldehyde (51 µL, 0.5 mmol) with Ni(cod)$_2$, dicyclohexylphenylphosphine (55 mg, 0.4 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded 4d and 4d' in <5% total yield according to $^1$H NMR of the crude mixture. 4d and 4d' were not isolated from the reaction mixture.

The reaction of allylbenzoate (2.5 mmol, 500 mol%) and benzaldehyde (51 µL, 0.5 mmol) with Ni(cod)$_2$, EtOPh$_2$P (43 µL, 0.2 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene at 35 °C following the general procedure 3 above afforded 4d and 4d' in <5% total yield according to $^1$H NMR of the crude mixture. 4d and 4d' were not isolated from the reaction mixture.
The reaction of homoallylbenzoate (1.5 mmol, 300 mol%) and benzaldehyde (51 µL, 0.5 mmol) with Ni(cod)₂, dicyclohexylphenylphosphine (55 mg, 0.4 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene at room temperature following the general procedure 3 above afforded 4e and 4e' in 21% total yield according to ¹H NMR of the crude mixture. 4e was subjected to TBAF and the free alcohol was isolated as a colorless oil.

[Desilylated 4e]

¹H NMR (400 MHz, CDCl₃, δ): 8.02 (d, J = 7.3 Hz, 2H); 7.58 (t, J = 7.3 Hz, 1H); 7.28 (m, 7H); 5.37 (s, 1H); 5.29 (s, 1H); 5.12 (s, 1H); 4.36-4.50 (m, 2H); 2.34-2.51 (m, 2H); 2.29 (bs, 1H).
¹³C NMR (100 MHz, CDCl₃, δ): 166.9, 147.0, 141.8, 133.1, 130.4, 129.7, 128.7, 128.5, 128.0, 126.7, 113.3, 77.6, 63.7, 31.3.
IR (NaCl, thin film): 3447, 3063, 3030, 2961, 1717, 1701, 1451, 1316, 1276, 1117, 1071, 1026, 912, 712, 701, 668.
HRMS – ESI (m/z): [M+Na]⁺ calcd for C₁₈H₁₈O₃Na, 305.1148; found, 305.1156.

[4e']

The reaction of homoallylbenzoate (1.5 mmol, 300 mol%) and benzaldehyde (51 µL, 0.5 mmol) with Ni(cod)₂, Ph₃P (52 mg, 0.2 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol), triethylamine in toluene at 35 °C following the general procedure 3 above afforded 4e and 4e' in <5% total yield according to ¹H NMR of the crude mixture and. 4e' was not isolated from the reaction mixture.
The reaction of 1-hexen-6-benzoate (510.3 mg, 2.5 mmol, 500 mol%) and o-anisaldehyde (61 µL, 0.5 mmol) with Ni(cod)$_2$, EtOPh$_2$P (43 µL, 0.2 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol, 175 mol%), triethylamine in toluene following the general procedure 3 above afforded 4f and 4f' in 44% total isolated yield after flash chromatography on silica and according to $^1$H NMR of the crude mixture the ratio of 4f:4f' is 73:27. 4f and 4f' were isolated together as a mixture.

The reaction of triethyl-hex-5-enyloxy-silane (1.5 mmol, 300 mol%) and o-anisaldehyde (61 µL, 0.5 mmol) with Ni(cod)$_2$, EtOPh$_2$P (43 µL, 0.2 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol, 175 mol%), triethylamine in toluene at 35 °C following the general procedure 3 above afforded 4g and 4g' in 66% total yield according to $^1$H NMR of the crude mixture and the ratio of 4g:4g' is 92:8. The $E$/Z ratio of 4g is 50:50. 4g' was not isolated from the mixture. 4g were subjected to TBAF and the free diols was isolated via flash chromatography on silica as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$, δ): 7.26-7.28 (m, 2H); 6.89 (d, $J = 8.6$ Hz, 2H); 5.41-5.63 (m, 2H), 4.70 (dd, $J = 4.8$, 8.0 Hz, 0.5 H), 4.64 (dd, $J = 7.2$, 7.2 Hz, 0.5 H), 3.81 (s, 3H), 3.60-3.65 (m, 2H), 2.39-2.62 (m, 2H), 2.10-2.27 (m, 2H), 1.89 (bs, 2H), 1.58-1.67 (m, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$, δ): 159.2, 159.2, 136.5, 136.4, 134.2, 132.5, 127.2, 127.2, 126.6, 126.1, 114.0, 113.9, 73.7, 73.4, 62.7, 62.0, 55.5, 42.8, 37.3, 32.3, 32.1, 29.5, 23.7.

IR (NaCl, thin film): 3354, 2933, 1612, 1513, 1442, 1303, 1247, 1175, 1035, 832.

HRMS–ESI (m/z): [M+Na]$^+$ calcd for C$_{26}$H$_{48}$O$_3$Si$_2$Na, 487.3040; found, 487.3017.
To β-Citronellene (0.5 mmol) in anhydrous CH₂Cl₂ (5 mL) was added Me₂AlCl (1.0 M in hexane, 1.1 mL) at 0 °C. The mixture was stirred at room temperature for 24 h. The reaction was quenched by diluting the reaction mixture with diethylether, followed by slow addition of water until gas evolution ceased. The organic layer was separated, and the aqueous layer was extracted with ether twice. The combined organic layers were washed with brine, dried and evaporated in vacuo. Purification via flash chromatography on silica gel afforded the coupling product 5a as a colorless oil. Homoallylic alcohol 5b was not detected.

\[
\text{HRMS }-\text{ESI (m/z): } [M+Na]^+ \text{ calcd for C}_{17}\text{H}_{24}\text{ONa}, 244.1822; \text{ found, 244.1817.}
\]

The reaction of β-Citronellene and benzaldehyde (51 µL, 0.5 mmol, 100 mol%) with Ni(cod)₂, EtOPh₂P (43 µl, 0.2 mmol, 40 mol%) and TESOTf (197 µL, 0.875 mmol, 175 mol%), triethylamine in toluene following the general procedure 3 above afforded 5b 75% total yield according to \(^1\)H NMR of the crude mixture and the E/Z ratio of 5b is 71:29. 5a was not detected. Purification via flash chromatography on silica afforded 5b as a colorless oil.

\[
\text{HRMS-ESI (m / z): } [M + Na]^+ \text{ calcd for C}_{23}\text{H}_{28}\text{OSiNa}, 381.2590; \text{ found, 381.2583.}
\]
2h (TES group deprotected)
Sb (TES deprotected)

TES deprotection, \( \text{mp: 62} \)}
Chapter 3

Synthetic Studies toward ent-Dioxepandehydrothrysiferol via an Epoxide-Opening Cascade
Introduction

Trans-Fused Polycyclic Ether Natural Products

Trans-fused polycyclic ethers constitute an important class of marine natural products that exhibit potent biological activities. Exemplified by the toxins brevetoxin-B and ciguatoxin, which are metabolites from dinoflagellates (Figure 1). Capable of binding to voltage-sensitive sodium channels in cell membranes and causing sodium ion influx into cells, these macromolecules are highly neurotoxic, causing massive fish kills and human poisoning. Some polyether natural products also display anticancer properties. Protoceratin II, a yessotoxin derivative with a sugar subunit, has an IC$_{50}$ value against human cancer cell lines of less than 0.5 nM.

These trans-fused polycyclic ether natural products feature a highly regular structural motif (Figure 1). Multiple five, six, seven, eight, and nine-membered cyclic ethers trans-fused together to create a ladder-like structure. Hence these trans-fused polycyclic ethers are collectively called ladder polyethers. The backbone of all ladder ethers is made up of repeating C–C–O subunits. The ring junctions throughout the macromolecular structure have a uniform trans-syn-trans pattern, i.e., trans stereochemistry across the C–C bond of each ring junction and a syn relationship of adjacent ring junctions. This dense but consistent array of stereocenters in ladder polyethers provides a formidable synthetic challenge.
Several total syntheses of trans-fused ladder ether natural products have been reported.\textsuperscript{1a,1b} The new methods invented for the synthesis of these natural products often represented the state of the art of organic chemistry at the time the total synthesis was reported. Some of the important strategies included alkenyl group-directed cyclization of hydroxy vinyl epoxide,\textsuperscript{1d,1e} Lewis acid-mediated allyl stannane addition to aldehydes,\textsuperscript{1f} ring expansion reactions,\textsuperscript{1g} selenium-induced epoxide-opening reactions,\textsuperscript{1h} hetero-Diels-Alder reactions,\textsuperscript{1i} samarium iodide-promoted cyclization,\textsuperscript{1j} and ring-closing metathesis.\textsuperscript{1i,1j}
In almost all syntheses of ladder ether natural products, one ether ring was formed at a time.\textsuperscript{1a,1b} The only case in which more than one ether ring was created in a single step in the context of ladder polyether synthesis was Holton’s synthesis of hemibrevetoxin B.\textsuperscript{1h} $N$-(phenylseleno)-phthalimide activation of an alkene triggered formation of the 6-7 fused ring system in hemibrevetoxin B. (Scheme 1)

**Scheme 1**

Holton:

```
\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) [circle,draw] {\text{\textit{N}}\text{SePh}};
\node (B) at (3,0) [circle,draw] {\text{\textit{OMOM}}};
\node (C) at (6,0) [circle,draw] {\text{\textit{Me}}};
\node (D) at (9,0) [circle,draw] {\text{\textit{OMOM}}};
\node (E) at (12,0) [circle,draw] {\text{\textit{Me}}};
\node (F) at (0,-3) [circle,draw] {\text{\textit{R = SiEt}_3}};
\node (G) at (3,-3) [circle,draw] {\text{\textit{OMOM}}};
\node (H) at (6,-3) [circle,draw] {\text{\textit{Me}}};
\node (I) at (9,-3) [circle,draw] {\text{\textit{OMOM}}};
\node (J) at (12,-3) [circle,draw] {\text{\textit{Me}}};
\node (K) at (0,-6) [circle,draw] {\text{\textit{Me}}};
\node (L) at (3,-6) [circle,draw] {\text{\textit{OMOM}}};
\node (M) at (6,-6) [circle,draw] {\text{\textit{Me}}};
\node (N) at (9,-6) [circle,draw] {\text{\textit{OMOM}}};
\node (O) at (12,-6) [circle,draw] {\text{\textit{Me}}};
\node (P) at (0,-9) [circle,draw] {\text{\textit{Me}}};
\node (Q) at (3,-9) [circle,draw] {\text{\textit{OMOM}}};
\node (R) at (6,-9) [circle,draw] {\text{\textit{Me}}};
\node (S) at (9,-9) [circle,draw] {\text{\textit{OMOM}}};
\node (T) at (12,-9) [circle,draw] {\text{\textit{Me}}};
\node (U) at (0,-12) [circle,draw] {\text{\textit{Me}}};
\node (V) at (3,-12) [circle,draw] {\text{\textit{OMOM}}};
\node (W) at (6,-12) [circle,draw] {\text{\textit{Me}}};
\node (X) at (9,-12) [circle,draw] {\text{\textit{OMOM}}};
\node (Y) at (12,-12) [circle,draw] {\text{\textit{Me}}};
\node (Z) at (0,-15) [circle,draw] {\text{\textit{Me}}};
\node (AA) at (3,-15) [circle,draw] {\text{\textit{OMOM}}};
\node (BB) at (6,-15) [circle,draw] {\text{\textit{Me}}};
\node (CC) at (9,-15) [circle,draw] {\text{\textit{OMOM}}};
\node (DD) at (12,-15) [circle,draw] {\text{\textit{Me}}};
\node (EE) at (0,-18) [circle,draw] {\text{\textit{Me}}};
\node (FF) at (3,-18) [circle,draw] {\text{\textit{OMOM}}};
\node (GG) at (6,-18) [circle,draw] {\text{\textit{Me}}};
\node (HH) at (9,-18) [circle,draw] {\text{\textit{OMOM}}};
\node (II) at (12,-18) [circle,draw] {\text{\textit{Me}}};
\node (JJ) at (0,-21) [circle,draw] {\text{\textit{Me}}};
\node (KK) at (3,-21) [circle,draw] {\text{\textit{OMOM}}};
\node (LL) at (6,-21) [circle,draw] {\text{\textit{Me}}};
\node (MM) at (9,-21) [circle,draw] {\text{\textit{OMOM}}};
\node (NN) at (12,-21) [circle,draw] {\text{\textit{Me}}};
\node (OO) at (0,-24) [circle,draw] {\text{\textit{Me}}};
\node (PP) at (3,-24) [circle,draw] {\text{\textit{OMOM}}};
\node (QQ) at (6,-24) [circle,draw] {\text{\textit{Me}}};
\node (QQQ) at (9,-24) [circle,draw] {\text{\textit{OMOM}}};
\node (QQQQ) at (12,-24) [circle,draw] {\text{\textit{Me}}};
\node (RR) at (0,-27) [circle,draw] {\text{\textit{Me}}};
\node (SS) at (3,-27) [circle,draw] {\text{\textit{OMOM}}};
\node (TT) at (6,-27) [circle,draw] {\text{\textit{Me}}};
\node (TTT) at (9,-27) [circle,draw] {\text{\textit{OMOM}}};
\node (TTTT) at (12,-27) [circle,draw] {\text{\textit{Me}}};
\node (UU) at (0,-30) [circle,draw] {\text{\textit{Me}}};
\node (VV) at (3,-30) [circle,draw] {\text{\textit{OMOM}}};
\node (WW) at (6,-30) [circle,draw] {\text{\textit{Me}}};
\node (WWW) at (9,-30) [circle,draw] {\text{\textit{OMOM}}};
\node (WWWV) at (12,-30) [circle,draw] {\text{\textit{Me}}};
\node (XX) at (0,-33) [circle,draw] {\text{\textit{Me}}};
\node (YY) at (3,-33) [circle,draw] {\text{\textit{OMOM}}};
\node (ZZ) at (6,-33) [circle,draw] {\text{\textit{Me}}};
\node (ZZZ) at (9,-33) [circle,draw] {\text{\textit{OMOM}}};
\node (ZZZZ) at (12,-33) [circle,draw] {\text{\textit{Me}}};
\end{tikzpicture}
\end{center}
```

**Synthesis of Fused Polycyclic Ether from Epoxide-Opening Cascades**

Nakanishi proposed that the biosynthesis of ladder polycyclic ether natural products proceeds via a cascade of epoxide-opening events.\textsuperscript{2} That is, a polyepoxide undergoes several consecutive and regioselective ring-opening events to yield trans-fused polycyclic ether natural product (Scheme 2). None of the total syntheses of marine fused polycyclic ethers reported to date has applied this strategy.
One major challenge of carrying out the Nakanishi proposal is the regioselective opening of every epoxide. Specifically, each epoxide needs to open the distal carbon of the next epoxide along the carbon backbone in order to create a fused cyclic ether system. (Scheme 3) This mode of cyclization is commonly termed *endo* cyclization. Very often, however, epoxide-opening at the proximal carbon of the next epoxide (*exo* cyclization) is a major competing reaction. The terms *exo* cyclization and *endo* cyclization, originated from the Baldwin’s rule,\(^{3a}\) were commonly used to describe the regioselectivity of epoxide-opening reactions. However, since both C–O bonds of the epoxide are outside the ring that will be formed after the cyclization, both modes of cyclization described in Scheme 3 can be defined as *exo* cyclization, according Baldwin’s interpretation.\(^{3a}\) To avoid confusion, the *exo / endo* terminology will not be used in the following text.
An early study of an intramolecular epoxide-opening reaction on a simple system by Coxon suggested that epoxide-opening at the proximal carbon predominated with disubstituted epoxides to yield a THF product over a THP product (Scheme 4). Ab-initio calculations at the MP2 level by Houk seemed to agree with this preference. The energy difference between THF formation and THP was calculated to be ~1.9 kcal/mol, corresponding to a 96:4 selectivity, favoring THF formation at room temperature (Scheme 4). In certain cases, this selectivity can be reversed with an appropriate external influence, such as antibodies or an appropriate Lewis acid catalyst. Alternatively, replacing the alkyl group on the distal carbon of a disubstituted epoxide with an alkenyl group can also lower the activation energy of a six-membered transition state.
Different functional groups have been installed on epoxides to bias regioselectivity in epoxide-opening cascades (Scheme 5). These functional groups are collectively called directing groups. Murai demonstrated such a cascade using epoxides with a methoxymethyl group as the directing group, to form the desired trans-fused polycyclic ether product.4 McDonald and Floreancig have used methyl-substituted epoxides in epoxide-opening cascade. 5,6 None of these directing groups are common in ladder ether natural products, hence limiting their utility in synthesis.

In a search for a removable directing group, Jamison has reported the use of a trimethylsilyl group as a directing group for epoxide-opening cascades (Scheme 6).7a Surprisingly, the fused cyclization product obtained at the end of the cascade had no trimethylsilyl group attached, and afforded fused-THP tetrad unit present in the majority of the ladder ether natural products. Thus, the trimethylsilyl group in effect acted as a “disappearing directing group”.

Furthermore, Jamison also reported that attaching a tetrahydropyran to a triepoxide unit allowed very selective epoxide-opening at the distal carbon of each epoxide without the use of
any directing group.\textsuperscript{7b} (Scheme 6) The use of a tetrahydropyran as a template to direct epoxide-opening cascades in water closely mimicked the biosynthesis of ladder ethers that Nakanishi proposed more than 20 years ago.

**Scheme 5**

Murai:

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

\[
\text{La}(\text{OTf})_3, \text{La}_2\text{O}_3, \text{H}_2\text{O}, \text{DCM}
\]

\[
9.3\%
\]

McDonald:

\[
\begin{align*}
\text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{1. BF}_3 \cdot \text{OEt}_2 & \quad \text{CH}_2\text{Cl}_2, -40 \degree \text{C}
\end{align*}
\]

\[
\begin{align*}
\text{2. p-Br-BzCl} & \quad \text{Et}_3\text{N}, \text{DCM}
\end{align*}
\]

\[
26\%
\]

R = p-Bromo-benzoyl

Floreancig and Houk:

\[
\begin{align*}
\text{Ph}_2\text{CH} & \quad \text{OMe} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me}
\end{align*}
\]

\[
\text{cat. NMe}_2\text{PF}_6
\]

\[
\begin{align*}
\text{O}_2, \text{hv} & \quad \text{toluene, rt}
\end{align*}
\]

\[
54\%
\]

\[
\begin{align*}
\text{Ph}_2\text{CH} & \quad \text{OMe} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me}
\end{align*}
\]

\[
\text{cat. NMe}_2\text{PF}_6
\]

\[
\begin{align*}
\text{O}_2, \text{hv} & \quad \text{toluene, rt}
\end{align*}
\]

\[
79\%
\]
Scheme 6

Dioxepandehydrothyrsiferol

To demonstrate the use of epoxide-opening cascades as an efficient strategy in the synthesis of fused-polycyclic ether natural products, we became interested in a fused polycyclic ether isolated from red algae *Laurencia viridis*. Dioxepandehydrothyrsiferol (1) is one of the many polycyclic ether secondary metabolites isolated from this red algae (Figure 2).\(^8a\) The repeating methyl groups suggested that 1 and other cyclic ethers isolated from *Laurencia viridis* are squalene-derived. Biological assays have shown that these polycyclic ethers are mild protein phosphatase inhibitors.\(^8b\) While *Laurencia viridis* is a prolific source of squalene-derived polyethers, other squalene-derived polyethers such as glabresol,\(^9a,9b\) armatol A,\(^10\) and many others have been isolated from other sources.\(^11\)

Similar to ladder polyethers such as brevetoxin B, 1 is characterized by an extensive fused ring system. An epoxide-opening cascade has been proposed for its biogenesis.\(^8a\) Whether or not 1 is prepared by Nature in this fashion, synthesis following this strategy would clearly offer a
significant simplification of the challenges it present. In this vein, glabresol was synthesized by
Corey using an epoxide-opening cascade.\textsuperscript{9a}

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

\textbf{Figure 2.} Dioxepanhydrothrysiferol (1) and other examples of polyether metabolites from \textit{Laurencia viridis}.

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

\textbf{Figure 3.} Examples of squalene polyethers isolated from other species.
Dioxepandehydrothyrsiferol (1) has structural feature different from most other fused polycyclic ether natural products. It has trans-anti-trans ring junctions throughout the fused ring system (Figure 2), rather than the trans-syn-trans junctions in all other known fused polycyclic ether natural products. Although a X-ray crystal structure was not available for dioxepandehydrothyrsiferol (1), NOSEY experiments\textsuperscript{8a} and comparison to venustatriol from Laurencia venusta\textsuperscript{8c} suggest that the trans-anti-trans-configuration would most likely cause the tetrahydropyran ring to adopt a boat structure.\textsuperscript{8d}

Most synthetic efforts toward fused polycyclic ethers have focused on developing strategies to create a trans-syn-trans ring systems. One of the goals toward the synthesis of dioxepandehydrothyrsiferol (1) therefore is to determine whether epoxide-opening cascade can produce fused polycyclic ether with trans-anti-trans junctions, and whether the cascade can accommodate formation of the strained tetrahydrofuran ring in this natural product.

*ent*-Dioxepandehydrothyrsiferol (*ent*-1) was targeted in this study rather than the natural configuration because the more readily available enantiomer of the Shi ketone for asymmetric epoxidation (derived from natural fructose) could be used. Therefore, the discussion below will be based on *ent*-1.
Synthesis of ent-Dioxepandehydrothyrsiferol via an Epoxide-Opening Cascade

The most direct cascade that addresses the above goal would be a bromonium-initiated cascade of a diepoxide allylic alcohol such as 2 (Scheme 7). However, due to the need to protect the terminal trisubstituted alkene during the installation of epoxides onto other alkenes, synthesis of this substrate would need as many steps as an iterative synthesis. This reduces the appeal of using an epoxide-opening cascade to synthesize ent-1.

Scheme 7

![Scheme 7](image)

An alternative cascade substrate that can be prepared in a shorter sequence would be triepoxide allylic alcohol 3 (Scheme 8). A Lewis acid-catalyzed epoxide-opening cascade should direct epoxide-opening at the more substituted carbon of each epoxide and provide the fused tricyclic ether system 4. Bromine displacement of a leaving group derived from the alcohol with inversion would install the bromine atom without a bromonium-initiated cascade.\textsuperscript{9c-9g} The triepoxide allylic alcohol substrate (3) also provides an opportunity to apply a nickel-catalyzed allene–aldehyde coupling as described in Chapter 1. The required aldehyde (5) and allene (6) could be prepared from farnesol and geraniol respectively.
Fused six-seven-seven ring structures similar to the one in \textit{ent-1} have been prepared by epoxide-opening cascades using two different initiation methods (Scheme 5). McDonald used Lewis acid to activate epoxides for cascade cyclization, while Floreancig initiated an epoxide-opening cascade with an oxocarbenium ion generated by the oxidative removal of a diphenylmethyl group. Floreancig’s examples also demonstrated that either \textit{syn} or \textit{anti} ring junctions can be formed through a cascade cyclization. Common to all known literature examples of successful epoxide-opening cascade with methyl substituted epoxides are the use of carbonate, carbamate, and ester as the terminating nucleophiles.\textsuperscript{12} Other terminating nucleophiles such as secondary alcohols have been used in other epoxide-opening cascades to prepare for example fused-THF tetrad with \textit{trans-syn-trans} junctions (Scheme 6). All of the pyran rings in the fused poly-THP adopt the chair conformation. There are, however, no known epoxide-opening cascade using a secondary alcohol as the terminating nucleophile to form a THP ring that has a boat conformation, as would be the case in \textit{ent-1}.
The THP ring in \textit{ent-1} is not in a chair conformation because the methyl group and the alkenyl group of the THP ring are \textit{syn} to each other. It was not clear from known examples of epoxide-opening cascades that the proposed cascade in Scheme 8 would proceed as desired due to the strained THP ring in \textit{ent-1}. Therefore the synthetic study of \textit{ent-1} began with an evaluation of reaction conditions to form the strained THP ring.

**Evaluation of Epoxide-Opening Substrates**

*Screening of Epoxide-Opening Reactions by 2º Allylic Alcohols*

Epoxy allylic alcohol 7 was prepared to investigate the formation of the THP ring in \textit{ent-1} (Scheme 9). To avoid premature epoxide-opening reaction during the synthesis of this substrate, a nickel-mediated coupling of allene 6 and aldehyde 8 was utilized.

**Scheme 9**

Allene 6 was prepared in six steps from geraniol (Scheme 10). Sharpless asymmetric epoxidation on geraniol,\textsuperscript{13} followed by a Shi asymmetric epoxidation furnished epoxy alcohol 10 with a diastereomeric ratio (dr) of 83:17.\textsuperscript{14} The dr and ee of 10 could be enhanced by recrystallization of the \textit{p}-nitrobenzoate derivative of alcohol 10. Alternatively, the mixture of diastereomers could be carried on and separated in subsequent steps. Payne rearrangement of alcohol 10 provided epoxide 11,\textsuperscript{15} which was opened with lithium acetylide to alkyne 12. The
alkyne was converted to allene 13 by a Crabbé homologation reaction.\textsuperscript{16} The two alcohols on allene 13 were protected as benzyl ethers to give allene 6.

Aldehyde 8 was prepared using a slightly modified method from Corey (Scheme 11).\textsuperscript{20f} Sharpless asymmetric epoxidation of farnesol followed by a Parikh-Doering oxidation provided epoxy aldehyde 16. Wittig olefination of aldehyde 16 furnished enoate 17 as a mixture of cis and trans isomers. Conjugate reduction of enoate 17 was best achieved with phenylsilane and a catalytic amount of Stryker reagent to prevent opening of the sensitive alkenyl-epoxide.\textsuperscript{17} The resulting ester 18 was reduced to aldehyde 8 by DIBAL.

Scheme 10

![Scheme 10 Diagram](image)
Allene 6 and aldehyde 8 was coupled in the presence of stoichiometric Ni(cod)$_2$ and tert-butyldimethylsilane to provide the desired allylic ether as a 50:50 mixture of diastereomers (Scheme 12). The silyl group was removed by TBAF to provide epoxy allylic alcohol 7 for cyclization studies.

The two diastereomers of epoxy alcohols (R)-7 and (S)-7 (as a 50:50 mixture, the only difference being the configuration of the allylic alcohol stereocenter) were subjected to a wide variety to Brønsted and Lewis acids to induce cyclization (Scheme 13). Four different cyclization products could be identified. Epoxide opening at the more substituted carbon (the distal carbon) of the epoxides yielded two THP rings (syn-THP (R)-20 and anti-THP (S)-20), one from each
diastereomer. Epoxide-opening at the less substituted carbon (the proximal carbon) of the epoxides yielded two THF rings (syn-THF (S)-20 and anti-THF (R)-20), also one from each diastereomer. The anti-THP product from the (S)-7 was the desired product for the synthesis of ent-1. The THP:THF ratio in the cyclization of epoxy alcohol 7 appeared to depend on the configuration of the allylic alcohol (Table 1).
Table 1. Cyclization Screen of Epoxy alcohol 7

<table>
<thead>
<tr>
<th>entry</th>
<th>activator</th>
<th>temperature (°C)</th>
<th>(S)-7 THP:THF</th>
<th>(R)-7 THP:THF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF₃OEt₂</td>
<td>-78/-40</td>
<td>45:55</td>
<td>95:5</td>
</tr>
<tr>
<td>2</td>
<td>Me₂AlCl</td>
<td>-78/-40</td>
<td>7:93</td>
<td>95:5</td>
</tr>
<tr>
<td>3</td>
<td>Et₂AlCl</td>
<td>-78/-40</td>
<td>8:92</td>
<td>95:5</td>
</tr>
<tr>
<td>4</td>
<td>Me₃Al</td>
<td>-45/rt</td>
<td>95:5</td>
<td>65:35</td>
</tr>
<tr>
<td>5</td>
<td>MgBr₂·Et₂</td>
<td>-45/rt</td>
<td>51:49</td>
<td>87:13</td>
</tr>
<tr>
<td>6</td>
<td>Yb(OTf)₃</td>
<td>-45/-30</td>
<td>11:89</td>
<td>90:10</td>
</tr>
<tr>
<td>7</td>
<td>Sc(OTf)₃</td>
<td>-45/-30</td>
<td>11:89</td>
<td>90:10</td>
</tr>
<tr>
<td>8</td>
<td>Zn(OTf)₂</td>
<td>-45/-30</td>
<td>9:91</td>
<td>90:10</td>
</tr>
<tr>
<td>9</td>
<td>Eu(OTf)₃</td>
<td>-78/rt</td>
<td>16:84</td>
<td>87:43</td>
</tr>
<tr>
<td>10</td>
<td>TiCl₄</td>
<td>-45/10</td>
<td>5:95</td>
<td>95:5</td>
</tr>
<tr>
<td>11</td>
<td>Ti(OiPr)₄/BINOL</td>
<td>-45/rt</td>
<td>34:66</td>
<td>95:5</td>
</tr>
<tr>
<td>12</td>
<td>none</td>
<td>rt/75</td>
<td>15:85</td>
<td>71:29</td>
</tr>
<tr>
<td>13</td>
<td>CSA</td>
<td>rt</td>
<td>30:70</td>
<td>50:50</td>
</tr>
<tr>
<td>14</td>
<td>N-boc-Arg-HCl</td>
<td>rt</td>
<td>13:87</td>
<td>50:50</td>
</tr>
</tbody>
</table>

Entries 1-11 were carried out in DCM. Entries 12-14 were carried out in CH₃CN. Reactions were quenched after starting material was consumed. Ratios were determined by NMR.

In almost all cases (R)-7 cyclized in the presence of a variety of Lewis acids to form syn-THP (R)-20 in high preference to anti-THF (R)-21 (Table 1, entries 1-11). Strong Lewis acid such as BF₃·OEt₂, Me₂AlCl, Et₂AlCl, MgBr₂·Et₂, TiCl₄, Ti(Oi-Pr)₄ / BINOL and various metal triflates provided greater than 85:15 THP:THF selectivity. Prootic acids such as CSA and N-boc-arginine-
HCl were not very selective and provided ~ 50:50 mixture of syn-THP and anti-THF (entries 13-14). Using other protic acids such as PPTS, tartaric acid, TsOH, and trifluoroacetic acid gave similar results as CSA. These results suggested that under Lewis acidic conditions epoxy allylic alcohol (R)-7 in general favored epoxide-opening at the more substituted carbon of the epoxide. Simple heating with no acid promoter was also more selective for THP over THF (entry 12).

The selectivity trend was very different with (S)-7. In the presence of either a Lewis acid or a protic acid the syn-THF (S)-21 product almost always predominated over anti-THP product (S)-20 (Table 1). The highest THP:THF selectivity was at ~50:50 using BF3•OEt2 (entry 1) and MgBr2•Et2O (entry 5). Simple heating with no acid promoter favored the THF product (entry 12).

The contrasting difference in THP/THF selectivity between (R)-7 and (S)-7 can be accounted for using a chair transition state model to form the THP product, which has also been suggested by Forsyth (Scheme 14).20g When (R)-7 was activated by Lewis or protic acids, partially positive charge was created at the more substituted carbon of the epoxide. The nucleophilic allylic alcohol approached the partially positive charge to form a six-membered transition state. The R diastereomer can accommodate both of the two larger substituents (alkenyl group of the allylic alcohol and alkyl group on the epoxide) at the equatorial positions of a chair transition state. This creates a 1,3-diaxial interaction only between a methyl group and a hydrogen atom, which is relatively tolerable. Therefore the THP is favored over the THF for (R)-7.

On the other hand, a similar chair transition state for the (S)-7 would produce a severe 1,3-diaxial interaction between the methyl group of the epoxide and the alkenyl group of the allylic alcohol (Scheme 14). Therefore it is not as favorable for the (S)-allylic alcohol to open the.
epoxide at the more substituted carbon to yield a THP ring. Opening the epoxide at the less substituted carbon becomes the lower energy pathway for the epoxide-opening reaction, yielding the THF product as the major product.

The same chair transition state model also predicts that if the 1,3-diaxial interaction between the nucleophile and the epoxide can be completely removed, a six-membered transition state should be favorable under acidic conditions and favor the formation of six-membered ring over five-membered ring product (Scheme 14). These conditions could be achieved using nucleophiles attached to sp$^2$-hybridized carbon atoms such as a ketone or a carboxylic acid ester.

**Scheme 14**

![Diagram showing (R)-diastereomer, (S)-diastereomer, and nucleophile with no stereocenter. Tolerable 1,3-diaxial interaction between alkenyl group and hydrogen. Unfavorable 1,3-diaxial interaction between methyl group and alkenyl group. No 1,3-diaxial interaction.]

**Screening of Epoxide-Opening Reactions by Nucleophiles with No Stereocenter**

Two trisubstituted epoxides with nucleophiles that have no stereocenter were prepared to evaluate the regioselectivity of intramolecular epoxide-opening under acid conditions (Scheme 15). A Pinnick oxidation of γ-epoxy aldehyde 8 provided γ-epoxy carboxylic acid 22 cleanly with no premature cyclization. Parikh-Doering oxidation of epoxy allylic alcohol (+/-)-7 afforded epoxy enone 23. Similar to the cyclization of epoxy allylic alcohol 7, epoxide-opening at the more substituted carbon (the distal carbon) would yield a six-membered ring whereas
epoxide-opening at the less substituted carbon (the proximal carbon) would yield a five-membered ring.

**Scheme 15**

Both epoxy carboxylic acid 22 and epoxy enone 23 favored the formation of six-membered rings under acidic conditions (Scheme 16). While (S)-7 exhibited poor selectivity for THP over THF (45:55) using BF$_3$•OEt$_2$ as the promoter, epoxy carboxylic acid 22 displayed superior selectivity for δ-lactone over γ-lactone under the same reaction conditions (95:5). Similarly, when epoxy enone 23 was treated with Amberlyst 15 at room temperature, dihydropyran was the major cyclization product (95:5). There are also isolated examples in the literature in which other nucleophiles such as ketone, enol, phenol, and cyanohydrin also favored 6-membered ring over 5-membered ring in intramolecular epoxide-opening reactions.

To conclude, unless there is strong destabilization for a six-membered transition state (such as a severe 1,3-diaxial interaction), epoxide-opening occurs at the more substituted carbon of the epoxide to yield a six-membered ring product.
Synthesis of the Tricyclic Ether Fragment via an Epoxide-Opening Cascade

The study of nucleophile-dependent regioselectivity in the epoxide-opening reactions was extended to triepoxide substrates (Scheme 17). Hence, besides the original proposal of using triepoxide allylic alcohol \( \text{3} \) to obtain the fused-cyclic ether system in \( \text{ent-1} \), a triepoxide substrate with a carboxylic acid nucleophile (26) was also evaluated. This second approach could be more advantageous in that the furan side chain of \( \text{ent-1} \) would be installed after the cascade cyclization. A stereoselective installation of the furan side chain might be possible by taking advantage of the conformation of the fused tricyclic ether system (24). On the other hand, the nickel-mediated reductive coupling approach to the triepoxide allylic alcohol substrate (3) was not enantioselective.
Treatment of triepoxide allylic alcohol 3 with BF₃•OEt₂ resulted in a complex mixture of products from both diastereomers. By comparing authentic samples of 4 and epi-4 prepared from an alternate route (vide infra), it can be concluded that a trace amount of the desired cyclization product (4) was formed (~ 5%), as well as its diastereomer epi-4 (<10%) (Scheme 18). The lower yield of alcohol 4, as compared to the yield of epi-4 seems to suggest that it is more difficult to form the THP ring in 4.

Scheme 18
Triepoxide carboxylic acid 28 would be too sensitive to be isolated from a Pinnick oxidation of the corresponding aldehyde 27 (Scheme 19).

Therefore triepoxide tert-butylester 29 was prepared instead. The tert-butyl group could be removed in situ with the Lewis used in the epoxide-opening cascade (Scheme 20).

**Scheme 19**

The triepoxide tert-butyl ester (29) was prepared in four steps from farnesol (Scheme 20). Sharpless asymmetric epoxidation followed by a Shi asymmetric epoxidation provide triepoxide allylic alcohol 30 as a mixture of diastereomers (dr ~ 83:17). Conversion of the alcohol to an iodide and displacement of the iodide with an enolate derived from tert-butyl acetate provided trioxide tert-butyl ester 29.

The triepoxide tert-butyl ester was treated with BF₃·OEt₂ to induce the epoxide-opening cascade (Scheme 20). A mixture of products was observed, but the major cyclization product was the desired fused tricyclic ether 31. Further purification with chlorotriethylsilane allowed isolation of 32 with dr > 95:5. The structure of 31 was confirmed by X-ray crystallography (Figure 4). Hence, using an epoxide-opening cascade the tricyclic ether system of ent-1 was obtained in six steps from farnesol.
Scheme 20

Figure 4. ORTEP drawing of 31. Ellipsoids are drawn at the 50% probability level. Hydrogen atoms are omitted (except O–H) for clarity.
Coupling of the Tricyclic Ether Fragment and the Tetrahydrofuran Fragment

Diastereoselective Formation of the Allylic Ether Stereocenter

With tricyclic ether fragment of ent-1 easily obtained in gram quantities, the nucleophilic addition of alkenyllithium 33 to lactone 32 was investigated (Scheme 21). The resulting lactol would then be reduced through an oxocarbenium intermediate.

Scheme 21

Alkenyl iodide 35 was prepared from epoxy furan 11 (Scheme 22). Addition of allenyl magnesium bromide to epoxy furan 11 followed by TIPS protection afforded alkyne 37 and the allenyl product, which were separated by column chromatography. Iodoboration of alkyne 37 with acetic acid workup isolated alkenyl iodide 35.

Scheme 22
Lithium halogen exchange of iodide 35 with tert-butyl lithium generated alkenyl lithium 33 in situ, which was able to add to n-butyraldehyde in the presence of CeCl₃ to give an allylic alcohol 38a (Table 2, entry 1). Quenching alkenyl lithium 33 with D₂O provided the deuterated alkene 38b (entry 2). The same alkenyl lithium (in the presence of CeCl₃) cannot add to any lactone, including valerolactone, lactone 39 and lactone 32. It appeared that the alkenyl cerium was not nucleophilic enough to add to any lactone. Only the protonated product 38c was observed after aqueous workup (entries 3-5).

**Table 2. Addition of Alkenyl Lithium 33 to Various Electrophiles**

<table>
<thead>
<tr>
<th>entry</th>
<th>electrophile (E⁺)</th>
<th>38</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me⁻CH₂CHO</td>
<td>38a</td>
</tr>
<tr>
<td>2ᵃ</td>
<td>D₂O</td>
<td>38b</td>
</tr>
<tr>
<td>3</td>
<td>i. CO₂</td>
<td>38c</td>
</tr>
<tr>
<td></td>
<td>ii. D₂O</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Me⁻CH₂CH₂CH₂CH₂CHO</td>
<td>38c</td>
</tr>
<tr>
<td>5</td>
<td>Me⁻CH₂CHO⁻</td>
<td>38c</td>
</tr>
</tbody>
</table>

ᵃ No CeCl₃ was added.
Inspecting the crystal structure of 32 revealed that the lactone was very hindered (Figure 4). One side of the lactone carbonyl was in the concave face of the tricyclic ether structure, while the other side of the lactone carbonyl was blocked by an axial methyl group. The presence of a triethyl silyl group on lactone 32 further increased the steric congestion of the concave face of the tricyclic ether.

To avoid the hindered cyclic ether system, lactone 32 was opened by LiAlH₄ reduction to a diol (Scheme 23). Protecting group manipulation followed by a Parikh-Doering oxidation of the primary alcohol provided aldehyde 40. Addition of alkenyl lithium 33 to the aldehyde provided an allylic alcohol. Oxidation of the allylic alcohol to an enone, and removal of trimethyl silyl group yielded alcohol 41. Treatment of this alcohol with mild acid provided enol ether 42, instead of the desired lactol (Scheme 24). Attempt to reduce the enol ether using sodium cyanoborohydride in the presence of acetic acid resulted in recovery of 42.
Nucleophilic addition reactions with lactone 32 were re-evaluated with a less basic and more nucleophilic species such as lithium TMS-acetylide (Scheme 25). In the presence of BF$_3$·OEt$_2$, lithium TMS-acetylide added to lactone 32 to form a lactol, which was prone to elimination. After an aqueous workup, the crude reaction mixture was immediately treated with triethylsilane and BF$_3$·OEt$_2$ to afford propargylic ether 43. A NOSEY experiment indicated that the propargylic proton was syn to the neighboring methyl group, corresponding to the undesired diastereomer. This result suggested that the concave face of the tricyclic ether ring exerted a stronger steric effect than the axial methyl group in the lactone.

To reverse the diastereoselectivity, lactone 32 was reduced by DIBAL to a hemiacetal (Scheme 25). Addition of TMSCN to the hemiacetal in the presence of BF$_3$·OEt$_2$ yielded the desired diastereomer as the major product$^{25}$ (44), along with the undesired diastereomer$^{25}$ (45). The selectivity may be due in part to an anomeric effect from the cyano group.$^{26a}$ Alternatively, the low diastereoselectivity of the cyanide addition reaction agreed with Woerpel’s observation that cyanide addition was less selective than addition of other nucleophiles such as allylsilane, possibly because cyanide addition is much faster.$^{26b}$

**Scheme 25**
Functionalization of Nitriles 44 and 45

Two classical transformations were envisioned for the installation of the furan side chain to nitrile 44 (Scheme 26). Alkyl metal 46 could either add directly to nitrile 44 to form a ketone, that could be converted to an exo-methylene group to give 4 after removal of the TES group. Alternatively, nitrile 44 could be reduced to aldehyde 47. Addition of alkyl metal 46 to this aldehyde, oxidation of the resulting alcohol, and methylenation of the ketone would also provide 4 after removal of the TES group.

Scheme 26

The nucleophilic addition of an alkyl metal to a nitrile was first studied on 48, which possesses a similar substitution pattern to nitrile 44 (Table 3). Methylmagnesium bromide added to nitrile 48 to provide methyl ketone 49a in good yield (entry 1). Addition of Ni(acac)₂ improved the yield of the methyl Grignard addition (entry 2). Dimethylzinc also added to nitrile 48 in the presence of Ni(acac)₂ in a similar yield as the addition of methyl Grignard alone (entry 3). Other alkyl nucleophiles such as pentylmagnesium bromide and even butyl lithium added to nitrile 48 to give ketone 49b and 49c respectively (entries 4-5).
Nitrile 44 (dr > 95:5) displayed very different reactivity (Table 4). No methyl ketone 50 was observed when methylmagnesium bromide was added alone (entry 1). A mixture of methylmagnesium bromide and Ni(acac)$_2$ allowed the addition to proceed and provided methyl ketone 50 in 50% yield with a slight erosion of diastereomeric ratio (93:7) after only 30 min (entry 2). Increasing the reaction time further eroded the diastereomeric ratio but increased the yield of methyl ketone (entries 3-4). Nitrile 44 was not very reactive to Me$_2$Zn / Ni(acac)$_2$, but no epimerization was observed after one hour (entry 5). Finally, slow addition of methylmagnesium bromide to a mixture of nitrile 44 and Ni(acac)$_2$ completely suppressed epimerization (entry 6).

On the other hand, addition of various methyl nucleophiles such as methylmagnesium bromide, trimethylaluminum, and dimethylzinc to nitrile 45 (dr > 95:5) in the presence of Ni(acac)$_2$ all provided methyl ketone 53 with only one diastereomer observed after 18 h at room temperature (Table 5).
**Table 4.** Methyl Nucleophile Addition Reactions to Nitrile 44

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>methyl nucleophile</th>
<th>temperature</th>
<th>time</th>
<th>yield (%)</th>
<th>dr&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeMgBr</td>
<td>-15 °C to -8 °C</td>
<td>30 min</td>
<td>&lt;1%</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>MeMgBr, Ni(acac)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-15 °C to -8 °C</td>
<td>30 min</td>
<td>50</td>
<td>93.7</td>
</tr>
<tr>
<td>3</td>
<td>MeMgBr, Ni(acac)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>4 °C</td>
<td>1 h</td>
<td>50</td>
<td>84:16</td>
</tr>
<tr>
<td>4</td>
<td>MeMgBr, Ni(acac)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>4 °C to rt</td>
<td>6 h</td>
<td>70</td>
<td>50:50</td>
</tr>
<tr>
<td>5</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;Zn, Ni(acac)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-15 °C</td>
<td>1 h</td>
<td>30&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>6&lt;sup&gt;d&lt;/sup&gt;</td>
<td>MeMgBr, Ni(acac)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-15 °C</td>
<td>1 h</td>
<td>50</td>
<td>&gt;95:5</td>
</tr>
</tbody>
</table>

<sup>a</sup> General procedure: Methyl nucleophile as described in the entry was dissolved in toluene. The reaction was cooled to the specified temperature. Nitrile 44 was added. The reaction was stirred for a specified time and warmed to the specified temperature. The reaction was quenched with 0.5M HCl.  
<sup>b</sup> Determined by <sup>1</sup>H NMR.  
<sup>c</sup> Yield was based on recovered nitrile.  
<sup>d</sup> MeMgBr was added to a mixture of nitrile and Ni(acac)<sub>2</sub> over 5 min.

**Table 5.** Methyl Nucleophile Addition Reactions to Nitrile 45

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>methyl nucleophile</th>
<th>temperature</th>
<th>time</th>
<th>yield (%)</th>
<th>dr&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeMgBr, Ni(acac)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>rt</td>
<td>18 h</td>
<td>58</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>2</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;Al, Ni(acac)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>rt</td>
<td>18 h</td>
<td>46</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>3</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;Zn, Ni(acac)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>rt</td>
<td>18 h</td>
<td>83</td>
<td>&gt;95:5</td>
</tr>
</tbody>
</table>

<sup>a</sup> General procedure: Methyl nucleophile as described in the entry was dissolved in toluene. The reaction was cooled to the specified temperature. Nitrile 45 was added. The reaction was stirred for a specified time and warmed to the specified temperature. The reaction was quenched with 0.5M HCl.  
<sup>b</sup> Determined by <sup>1</sup>H NMR.

Unfortunately, methyl-derived organometal reagents were the only alkyl nucleophiles that reacted with nitrile 44. Attempts to add <i>n</i>-pentylmagnesium bromide to a similar nitrile failed to provide the corresponding ketone.  

27
Converting nitrile 44 to aldehyde 47 should enhance its reactivity. Again, the reduction step was optimized first with simple nitrile 48. It was found that DIBAL was not a good reducing agent for this process (Table 6). Increasing the amount of DIBAL from 100 mol% to 200 mol% slightly increase the yield of aldehyde 55 but dramatically reduced the amount of recovered nitrile (entries 1-3). Further increase of the amount of DIBAL to 250 mol% and 300 mol% lowered the yield of aldehyde 55, and the recovery of the nitrile was less than 5% (entries 4-5). These observations seemed to be consistent with over-reduction of nitrile 48 by DIBAL. Use of bulkier reducing agents such as Schwartz’s reagent cleanly reduced nitrile 48 to aldehyde 55 with significantly improved yield (entry 6).

**Table 6. Nitrile Reduction to Aldehyde 55**

<table>
<thead>
<tr>
<th>entry</th>
<th>reducing agent</th>
<th>temperature</th>
<th>yield (%)</th>
<th>remaining 48 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DIBAL (100 mol%)</td>
<td>-15 °C</td>
<td>12</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>DIBAL (150 mol%)</td>
<td>-15 °C</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>DIBAL (200 mol%)</td>
<td>-15 °C</td>
<td>20</td>
<td>&lt;5</td>
</tr>
<tr>
<td>4</td>
<td>DIBAL (250 mol%)</td>
<td>-15 °C</td>
<td>2</td>
<td>&lt;5</td>
</tr>
<tr>
<td>5</td>
<td>DIBAL (300 mol%)</td>
<td>-15 °C</td>
<td>2</td>
<td>&lt;5</td>
</tr>
<tr>
<td>6</td>
<td>Cp₂ZrCl (100 mol%)</td>
<td>rt</td>
<td>80</td>
<td>0</td>
</tr>
</tbody>
</table>

However, reduction of nitrile 44 was not efficient even with Schwartz’s reagent (Scheme 27). Only 13% yield (BRSM) of aldehyde 47 could be obtained, as compared to 6% yield with DIBAL (no recovered starting material). Reduction of the diasteromeric nitrile 45 with Schwartz’s reagent provided better yield of aldehyde 56. Since aldehyde 47 was difficult to obtain in reasonable quantity, this route was not pursued further.
Taking advantage of the methyl ketone (50) that can be obtained from nitrile 44, conversion of methyl ketone 50 to an alkenyl triflate 57 would allow a Suzuki cross coupling with alkyl boron 58 (Scheme 28).28

When methyl ketone 50 was added to a mixture of LHMDS and Comins reagent at −78 °C, alkenyl triflate 57 was formed cleanly (Scheme 29). After an aqueous workup the crude could be used directly in the Suzuki coupling. If methyl ketone 50 was deprotonated with LHMDS before the addition the Comins reagent, a complex mixture of products was formed.
The boron alkyl reagent (58) was prepared from epoxy furan 11 (Scheme 30). Addition of trimethylsulfonium ylide to epoxy furan 11 followed by elimination provided allylic alcohol 59. After protection of both alcohols as TIPS ethers, hydroboration using 9-BBN dimer afforded boron alkyl reagent 58. Addition of aqueous Cs₂CO₃ destroyed excess 9-BBN and provided a base for the Suzuki coupling. Addition of the crude alkenyl triflate (57) and Pd(dppf)Cl₂ and heating for 18 h yielded the desired cross coupling product in approximately 50% yield. Treatment of the coupling product with TBAF removed the TES group to give alcohol 4 in 26% yield (from 50). Deprotection of the 2º TIPS group was also observed to give diol 60 in 20% yield (from 50).

Scheme 30

Installation of a Bromine Atom to the Terminal Oxepane

Alcohol 4 contains all the carbons and ether rings in ent-1. The last transformation required in order to obtain ent-1 is to convert alcohol 4 to a bromide. Alcohol 61 was used to investigate conditions for the preparation of bromide 62 (Scheme 31). Activation of the alcohol as a chloromesylate 63 followed by addition of LiBr resulted in elimination to alkene 64. The facile elimination can be explained by the β-hydrogen that is anti peri-planar to the chloromesylate,
based on the X-ray crystal structure of lactone 32 (Figure 4). Hydrobromination of alkene 64 with HBr led to decomposition of the cyclic ether.

Scheme 31

An alternative route to install the bromide at the terminal oxepane of ent-1 is being pursued. It is common to install a hindered bromide with substitution pattern similar to ent-1 through a bromonium cyclization reaction.\textsuperscript{30} Hence, a bromonium-initiated epoxide-opening cascade from diepoxide tert-butyl ester 65 might allow a one-step formation of the tricyclic ether system, with the bromide present in the cyclization product (66) (Scheme 32).

Scheme 32

Diepoxide 65 was prepared in a similar fashion as triepoxide 29. Alcohol 15 was protected as a TIPS ether. Allylic oxidation at the terminal alkene and subsequent conversion to allylic acetate 67 served to protect the terminal alkene from epoxidation in the next step.\textsuperscript{31} Shi epoxidation of 67 selectively epoxidized the internal alkene to diepoxide 68. Conversion of the acetate to a bromide, followed by a reduction by super hydride afforded diepoxide 69. Silyl group removal, conversion to an iodide, displacement of the iodide with lithium enolate from tert-butyl acetate
yielded diepoxide tert-butyl ester 65 for bromonium-initiated cascade (Scheme 34). Activation of 65 with Br(coll)₂ClO₄ resulted in a complex mixture of products that could not be separated cleanly. An authentic sample of the desired cyclization product is needed to conclude whether bromide 66 was formed during this cascade.

Scheme 33

Scheme 34

To prepare bromide 66 from a different route, diepoxide 65 was treated with BF₃·OEt₂ to induce an epoxide-opening cascade to afford two major cyclization products 71 and 72 (Scheme 35). These two products were separated by treatment with chlorotriphenylsilane, which selectively reacted with 71 to silyl ether 73. The configurations of 71 and 73 were confirmed by NOSEY experiments. Bromonium-initiated cyclization of 71 by NBS in 1,1,1,3,3,3-
hexafluoropropan-2-ol installed the bromine atom to the tricyclic ether (Scheme 36). The bromooxepane was obtained as a 63:37 mixture of diastereomers (66 and epi-66). A NOSEY experiment of this mixture confirmed that the major diastereomer was 66. Hence we now have a potential solution for the installation of the hindered bromide in ent-1.

**Scheme 35**

**Scheme 36**

**Conclusion**

Synthesis of the fused six-seven-seven cyclic ether in ent-1 through an epoxide-opening cascade strategy was explored. Formation of the strained tetrahydropyran ring in ent-1 directly from an epoxide-opening cascade of triepoxide allylic alcohol proved to be difficult. Alternatively, a δ-lactone was obtained using an epoxide-opening cascade of triepoxide tert-
butyl ester. The furan side chain was installed via a Suzuki coupling. Conversion of hindered alcohol to a bromide proved to be difficult. Alternatively, a bromonium cyclization allowed the formation of the desired bromo-oxepane.

References:


12) In the context of the synthesis of fused 6-7-7 ring systems. Polyepoxy alcohol has been used to synthesize poly-THFs using an epoxide-opening cascade, see reference 9a.


18) See chapter 1 of this thesis.


21) Triepoxide allylic alcohol was prepared from a nickel-catalyzed allene–aldehyde reductive coupling.

22) Pinnick oxidation of an epoxy aldehyde with one less epoxide unit resulted in premature cyclization. Therefore it was assumed that a Pinnick oxidation of triepoxide aldehyde 27 would cyclize even more readily.


25) To establish the stereochemistry of 44 and 45, a series of NOSEY experiments were carried out. NOSEY of 44 indicated no nOe interaction between the methyl hydrogens and the cyanohydrin hydrogen on the THP ring. Nitrile 44 was converted to 44-dibromoalkene. NOSEY of 44-dibromoalkene indicated nOe interaction between the methyl hydrogens on the THP and the alkenyl hydrogen, confirming that the methyl group and the cyanohydrin hydrogen on the THP of 44 were anti to each other. The methyl hydrogens and the cyanohydrin hydrogen on nitrile 45 overlapped in the 1H NMR spectrum. Conversion of 45 to 53 and a NOSEY experiment on 53 indicated nOe interaction between the methyl hydrogens on the THP and the α-hydroxy ketone hydrogen. This is consistent with the stereochemical assignment of 45.

26) (a) Booth, H.; Dixon, J. M.; Khedhair, K. A. Tetrahedron 1992, 48, 6161–6174. (b) Shenoy,
27) Addition nitrile 74 to a mixture of n-C₅H₁₁MgBr and Ni(acac)₂ yielded cyano-ketone 75.


32) The other two possible cyclization products were also observed in small quantity.

33) Alternatively, chlorotriethylsilane was also used (Et₃SiCl, imidazole, DMF / DCM, 45 °C), which provided better selectivity for 71.
Experimental Section

General Information

Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of nitrogen or argon with rigid exclusion of moisture from reagents and glassware. Tetrahydrofuran and diethylether were distilled from a blue solution of sodium benzophenone ketyl. Dichloromethane and toluene were distilled over calcium hydride. All other chemicals were used without purification, unless otherwise noted.

Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F$_{254}$ plates. The developed chromatogram was analyzed by UV lamp (254 nm), ethanolic phosphomolybdic acid (PMA) or potassium permanganate (KMnO$_4$). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230-400 mesh). $^1$H and $^{13}$C NMR spectra were recorded on Varian 300 MHz, Varian 500 MHz, Bruker 400 MHz, or Bruker 600 MHz spectrometer in CDCl$_3$ or C$_6$D$_6$, unless otherwise noted. Chemical shifts in $^1$H NMR spectra are reported in parts per million (ppm) on the $\delta$ scale from an internal standard of residual chloroform (7.27 ppm) or residual benzene (7.16 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constant in hertz (Hz), and integration. Chemical shifts of $^{13}$C NMR spectra are reported in ppm from the central peak of CDCl$_3$ (77.23 ppm) or C$_6$D$_6$ (128.39 ppm) on the $\delta$ scale. Infrared (IR) spectra were recorded on a Perkin-Elmer 2000 FT-IR. High resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer by Dr. Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrument Facility. Chiral GC analysis was performed on a Varian CP-3800 gas chromatograph fitted with Chiraldex B-PH, B-DA, and G-TA capillary columns. Chiral HPLC analysis was performed on a Hewlett-Packard 1100 chromatograph equipped with a variable wavelength detector and Chiralcel OD or OD-H, or AD-H columns. Specific Rotations ($[\alpha]^{20}_D$) were measured on a Perkin-Elmer 241 polarimeter at 589 nm.
L-(-)-Diethyltartrate (428 µL, 2.5 mmol, 12.5 mol%) and 4Å molecular sieves (2g, 0.1g / mmol) were placed in a 50 mL round bottom flask under a stream of argon. DCM (20 mL) was added at room temperature, followed by Ti(O-i-Pr)4 (600 µL, 2 mmol, 10 mol%). The mixture was stirred vigorously at room temperature for 20 min. tert-Butylhydroperoxide (4.54 mL, ~25 mmol, 125 mol%, 5-6 M in decane) was added and the mixture was stirred 5 min at room temperature. The mixture was cooled in a CH3CN / dry ice bath. The temperature was maintained below –40 °C. Farnesol (5.06 mL, 20 mmol, 100 mol%) was added and stirred in the CH3CN / dry ice bath for 10 h. The mixture was placed in the freezer overnight. The next day citric acid monohydrate (420.28 mg, 2 mmol, 10 mol%) was dissolved in 1:1 acetone / diethylether (~ 5 mL) and the solution was added to the reaction mixture. The mixture was stirred vigorously for 20 min at room temperature. Celite was added to the mixture and stirred vigorously for 1 min. The slurry was filtered through a thick pad of celite and the celite was washed with Et2O. The clear filtrate was washed with saturated Na2S2O3 and then dried with MgSO4. Column chromatography isolated 4.53 g of 15 (95% yield). The enantiomeric excess was determined by HPLC of the benzoate to be 87%.

1H NMR (400 MHz, CDCl3, δ): 5.10 (m, 2H); 3.84 (ddd, J = 4.3, 7.5, 12.0 Hz, 1H); 3.70 (ddd, J = 4.9, 6.7, 11.8 Hz, 1H); 2.99 (dd, J = 4.3, 6.7 Hz, 1H); 2.16-1.94 (m, 6H); 1.71 (m, 1H); 1.69 (s, 3H); 1.614 (s, 3H); 1.608 (s, 3H); 1.48 (m, 1H); 1.32 (s, 3H).

13C NMR (125 MHz, CDCl3, δ): 136.0, 131.6, 124.4, 123.3, 63.2, 61.6, 61.4, 39.8, 38.7, 26.8, 25.9, 23.8, 17.9, 17.0, 16.2.

IR (NaCl, thin film): 3422, 2919, 1456, 1384, 1033.


[α]20D –4.2 (c 1.93, CHCl3)

Chiral HPLC analysis: Analysis was performed on the corresponding benzoate (BzCl, Et3N, DMAP, DCM): (Chiralcel AD-H, hexanes:2-propanol, 99:1, 1.0 mL/min): tR(2S,3S) = 7.3 min; tR(2R, 3R) = 8.1 min. The enantiomeric excess was determined to be 87%.
Alcohol 15 (1.57g, 6.586 mmol, 100 mol%) was dissolved in dichloromethane (50 mL). Triethylamine (4.6 mL, 32.93 mmol, 500 mol%) was added at room temperature. Dimethylsulfoxide (12 mL) was added. The mixture was cooled in an ice/water bath. SO₃•pyridine complex (2.64 g, 16.47 mmol, 250 mol%) was added in one portion. Rinsed the wall of the flask with 5 mL dichloromethane. Stirred in the ice bath for 5 h. Temperature slowly rose to room temperature. The mixture was diluted with diethylether, washed with saturated NH₄Cl and dried with MgSO₄. Column chromatography isolated 1.38 g of 16 (88% yield).

1H NMR (400 MHz, CDCl₃, δ): 9.46 (d, J = 5.0 Hz, 1H); 5.08 (t, J = 7.0 Hz, 2H); 3.20 (d, J = 5.0Hz, 1H); 2.20-1.90 (m, 6H); 1.73 (m, 1H); 1.67 (s, 3H); 1.60 (s, 6H); 1.58 (m, 1H); 1.45 (s, 3H).

13C NMR (100 MHz, CDCl₃, δ): 199.8, 136.6, 131.7, 124.3, 122.6, 64.4, 63.7, 39.8, 38.5, 26.7, 25.9, 23.5, 17.9, 17.4, 16.2.

IR (NaCl, thin film): 2967, 2918, 1723, 1450, 1384.

HRMS-ESI (m / z): [M + Na]+ calcd for C₁₅H₂₄O₂Na, 259.1669; found, 259.1673. [α]₂₀°D +71.5 (c 2.0, CHCl₃)

Aldehyde 16 (1.38 g, 5.839 mmol, 100 mol%) was dissolved in dichloromethane (55 mL) at room temperature. (Methoxycarbonylmethylene)triphenylphosphorane (2.0 g, 11.68 mmol, 200 mol%) was added in one portion. The wall of the flask was rinsed with dichloromethane (5 mL). The mixture was stirred at room temperature overnight. The mixture was loaded directly to a silica column. Column chromatography isolated 1.57 g of 17 and its geometric isomer as a mixture (91% yield).

1H NMR (400 MHz, CDCl₃, δ): 6.84 (dd, J = 6.4, 15.7 Hz, 1H); 6.10 (dd, J = 1.0, 15.7 Hz, 1H); 5.08 (m, 2H); 3.75 (s, 3H); 3.33 (dd, J = 0.8, 6.4 Hz, 1H); 2.20-1.90 (m, 6H); 1.74 (m, 1H); 1.68 (s, 3H); 1.60 (s, 6H); 1.55 (s, 1H); 1.28 (s, 3H).

13C NMR (100 MHz, CDCl₃, δ): 166.3, 143.4, 136.2, 131.7, 124.5, 124.3, 123.2, 64.4, 61.6, 51.9, 39.8, 38.6, 26.8, 25.9, 23.5, 17.9, 16.1, 16.2.

IR (NaCl, thin film): 2946, 2919, 2857, 1726, 1437, 1263, 1171.


[α]₂₀°D +3.5 (c 1.7, CHCl₃)
Enoate 17 (1.210 g, 4.138 mmol, 100 mol%) was placed in a 100 mL round bottom flask. The flask was evacuated under vacuum and back-filled with argon. Tetrahydrofuran (30 mL) was added at room temperature, followed by phenylsilane (0.767 mL, 6.201 mmol, 150 mol%). The mixture was cooled in an ice/water bath. Triphenylphosphine-copper(I)-hydride-hexamer (161 mg, 0.08275 mmol, 2 mol%) was added in one portion. Rinse the wall of the flask with tetrahydrofuran (10 mL). Temperature gradually rose to room temperature. After a total of 2.5 h, TLC indicated that starting material was consumed. Still in the water bath, septum was removed and water (10 mL) was added. Bubbling occurred. The mixture was stirred in the water bath for 30 min. Celite was added while the mixture was vigorously stirring and the solid was filtered and rinsed with diethyl ether (200 mL). The filtrate was washed with saturated NH₄Cl. The organic fraction was dried with MgSO₄ and then filtered through a small plug of silica. Column chromatography isolated 1.2 g of ester 18 (98% yield).

$^1$H NMR (400 MHz, CDCl₃, δ): 5.08 (t, $J = 6.8$ Hz, 2H); 3.67 (s, 3H); 2.76 (dd, $J = 5.4$, 7.2 Hz, 1H); 2.47 (m, 2H); 2.20-1.60 (m, 9H); 1.67 (s, 3H); 1.59 (s, 6H); 1.42 (m, 1H); 1.27 (s, 3H).

$^1$H NMR (400 MHz, C₆D₆, δ): 5.23 (t, $J = 6.7$ Hz, 1H); 5.17 (t, $J = 7.1$ Hz, 1H); 3.31 (s, 3H); 2.62 (dd, $J = 5.6$, 7.1 Hz, 1H); 2.30-1.97 (m, 8H); 1.73 (m, 2H); 1.68 (s, 3H); 1.57 (s, 3H); 1.55 (s, 3H); 1.41 (m, 1H); 1.09 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl₃, δ): 173.5, 135.8, 131.6, 124.4, 123.6, 62.6, 61.3, 51.9, 39.8, 38.9, 31.1, 26.8, 35.9, 24.4, 23.9, 17.9, 16.7, 16.2.


IR (NaCl, thin film): 2925, 1741, 1437, 1384, 1170.

[α]$^2_{D}$ –9.05 (c 2.1, CHCl₃)
Ester 18 (966 mg, 3.281 mmol, 100 mol%) was dissolved in toluene (30 mL). The solution was cooled to –83 °C in a diethylether/dry ice bath. Stirred at –83 °C for 5 min. DIBAL solution (4.3 mL, 4.2652 mmol, 130 mol%, 1 M in toluene) was diluted with toluene (16 mL) and added to the reaction mixture over 45 min. The temperature was kept below –80 °C throughout the reaction. After the addition completed the mixture was stirred below –80 °C for 1 h. Methanol (4 mL) was added, followed by saturated Rochelle’s salt solution (30 mL). The cold bath was removed. The mixture was stirred for 1 h after the ice melted. The mixture was diluted with diethylether, washed with water and dried with MgSO₄. Column chromatography isolated 823 mg of 8 (94% yield).

¹H NMR (400 MHz, CDCl₃, δ): 9.82 (t, J = 1.2 Hz, 1H); 5.08 (t, J = 5.5 Hz, 2H); 2.74 (dd, J = 5.1, 7.6 Hz, 1H); 2.62 (m, 2H); 2.10-1.85 (m, 7H); 1.82-1.60 (m, 2H); 1.67 (s, 3H); 1.60 (s, 3H); 1.59 (s, 3H); 1.43 (m, 1H); 1.27 (s, 3H).

¹H NMR (400 MHz, C₆H₆, δ): 9.24 (s, 1H); 5.24 (t, J = 6.8 Hz, 1H); 5.17 (t, J = 6.1 Hz, 1H); 2.49 (dd, J = 5.2, 7.5 Hz, 1H); 2.51-2.48 (m, 8H); 1.68 (s, 3H); 1.64-1.34 (m, 4H); 1.57 (s, 3H); 1.56 (s, 3H); 1.05 (s, 3H).

¹³C NMR (100 MHz, CDCl₃, δ): 201.2, 135.8, 131.6, 124.4, 123.6, 62.5, 61.5, 41.0, 39.9, 38.8, 26.8, 25.6, 23.9, 21.6, 17.8, 16.8, 16.2.

¹³C NMR (100 MHz, C₆D₆, δ): 200.2, 135.8, 131.6, 125.2, 124.6, 62.3, 60.9, 41.2, 40.5, 39.3, 27.5, 26.2, 24.5, 22.1, 18.1, 17.0, 16.4.


IR (NaCl, thin film): 2966, 2924, 1726, 1451, 1385, 1108.

[α]ᵡ dioxide –10.4 (c 3.16, CH₂Cl₂)
[α]ᵡ dioxide –11.4 (c 4.23, CHCl₃)
L-(-)-Diethyltartrate (5.55 mL, 32.4 mmol, 12.5 mol%) and 4Å molecular sieves (26 g, 0.1 g / mmol alkene) were placed in a 500 mL Erlenmeyer flask under a stream of argon. Dichloromethane (260 mL) was added at room temperature, followed by Ti(Oi-Pr)₄ (7.7 mL, 25.9 mmol, 10 mol%). The mixture was stirred vigorously at room temperature for 20 min. tert-Butylhydroperoxide (59 mL, ~324 mmol, 125 mol%, 5-6 M in decane) was added and the mixture was stirred 10 min at room temperature. The mixture was cooled in a CH₃CN / dry ice bath. The temperature was maintained below –40 °C. Geraniol (45.5 mL, 259 mmol, 100 mol%) was added and stirred in the CH₃CN / dry ice bath for 10 h. The mixture was placed in the freezer overnight.

The next day citric acid monohydrate (5.44 g, 25.9 mmol, 10 mol%) was dissolved in 1:1 acetone / diethylether (just enough to dissolve all citric acid monohydrate) and the solution was added to the reaction mixture. The mixture was stirred vigorously for 1 h at room temperature. Celite was added to the mixture and stirred vigorously for 1 min. The slurry was filtered through a thick pad of celite and the celite was washed with Et₂O. The mixture was concentrated and saturated Na₂S₂O₃ (400 mL) was added to the ether solution. White solid precipitated, which was filtered with the aid of celite and silica gel to give a clear solution. Layers were separated.

Aqueous layer was extracted again with Et₂O. Combined organic solution was washed again with saturated Na₂S₂O₃ and then dried with MgSO₄. The organic solution was concentrated to ~400 mL. Sodium hydroxide solution in brine (32.4 mL, this solution was prepared from 30 g NaOH, 5 g NaCl and 90 mL H₂O) was added and the mixture was stirred vigorously in an ice / water bath for 45 min. The aqueous layer was separated and the organic layer was dried with MgSO₄. The organic solution was concentrated and vacuum distillation removed low boiling materials and isolated 42 g of epoxide 29 (95% yield). The crude was used directly.

The enantiomeric excess was determined by HPLC of the benzoate to be 84.5%.

1H NMR (500 MHz, CDCl₃, δ): 5.05 (t, J = 7.2 Hz, 1H); 3.79 (dd, J = 4.1, 12.2 Hz, 1H); 3.64 (dd, J = 6.9, 12.2 Hz, 1H); 2.96 (dd, J = 4.12, 6.9 Hz, 1H); 2.70 (bs, 1H); 2.06 (m, 2H); 1.66 (s, 3H); 1.58 (s, 3H); 1.44 (m, 1H); 1.27 (s, 3H).

13C NMR (125 MHz, CDCl₃, δ): 132.3, 123.4, 63.4, 61.5, 61.4, 38.6, 25.8, 23.8, 17.8, 16.9.

IR (NaCl, thin film): 3419, 2926, 1452, 1384, 1033.


[α]D²⁰ –4.7 (c 10.0, CHCl₃)

Chiral HPLC analysis: Analysis was performed on the corresponding benzoate of the epoxide alcohol (BzCl, Et₃N, DCM): Chiralcel AD-H, hexanes:2-propanol, 99:1, 1.0 mL/min. The retention times for the two enantiomers were 8.9 and 9.5 min.
Alcohol 9 (5.533 g, 32.5 mmol, 100 mol%), Bu₄NHSO₄ (441 mg, 1.3 mmol, 4 mol%), and (-)-Shi ketone (2.323 g, 9.75 mmol, 30 mol%) were placed in a 2 L bottle with a big stir bar. 0.05 M Na₂B₄O₇·10H₂O in 4×10⁻⁴ M EDTA (325 mL, 10 mL / mmol alkene) added, followed by a 1:2 mixture of CH₃CN / DMM (488 mL). This mixture was cooled in an ice / water bath and stirred vigorously. Oxone (27.57 g, 44.85 mmol, 138 mol%) in 4×10⁻⁴ M EDTA (214 mL, to make a 0.21 M oxone solution) and aqueous K₂CO₃ solution (0.89 M, same volume as the oxone solution) were added to the reaction mixture simultaneously over ~30 min. Once the addition completed the reaction mixture was stirred for another 15 min and quenched with water. The mixture was extracted with CH₂Cl₂ (1.5 L), dried with MgSO₄, and column chromatography isolated 5.024 g of epoxy-alcohol 10 (83% yield).

To upgrade the enantio- and diastereoratio of epoxy-alcohol 10, this epoxy-alcohol was converted to a p-nitrobenzoate (p-NO₂-BzCl, Et₃N, CH₂Cl₂, rt) and recrystallized to afford a pale yellow solid. Saponification of the resulting p-nitrobenzoate (1 M NaOH, 1:3 H₂O / THF, rt; Extraction with Et₂O) returned epoxy-alcohol 10 with 95% ee and 95:5 dr.

¹H NMR (400 MHz, CDCl₃, δ): 3.77 (dd, J = 5.4, 11.7 Hz, 1H); 3.67 (dd, J = 6.2, 11.8 Hz, 1H); 2.99 (t, J = 5.8 Hz, 1H); 2.74 (dd, J = 4.1, 8.1 Hz, 1H); 2.65 (bs, 1H); 1.91 (m, 1H); 1.81 (m, 1H); 1.56 (m, 2H); 1.310 (s, 3H); 1.306 (s, 3H); 1.28 (s, 3H).

¹³C NMR (100 MHz, CDCl₃, δ): 64.5, 63.0, 61.0, 60.9, 59.0, 36.3, 25.0, 24.9, 18.9, 16.6.

IR (NaCl, thin film): 3424, 2964, 1458, 1380, 1032.


[α]²⁰D +35.2 (c 1.1, CHCl₃) before recrystallization from benzoate.

[α]²⁰D +39.7 (c 3.2, CHCl₃) after recrystallization from benzoate.

Chiral HPLC analysis: Analysis was performed on the corresponding benzoate of the diepoxide alcohol (BzCl, Et₃N, DMAP, DCM): Chiralcel AD-H, hexanes:2-propanol, 99:1, 1.3 mL/min. The retention times for the four possible diastereomers were 28.6, 30.4, 32.6, and 49.3 min. The retention time of the desired diastereomer was 30.4 min.
Epoxyalcohol 10 (2.5132 g, 13.49 mmol, 100 mol%) was dissolved in THF (6 mL) in a 100 mL round bottom flask. The solution was stirred vigorously while NaOH solution (27 mL, 0.5 M, 100 mol%) was added at rt over 2 min. The mixture was stirred 16 h. It was diluted with Et₂O (350 mL) and the layers were separated. The aqueous layer was extracted again with 50 mL Et₂O. The combined organic solution was dried with MgSO₄. Column chromatography isolated 1.5 g of epoxide 11 (59% yield).

1H NMR (400 MHz, CDCl₃, δ): 3.76 (t, J = 7.4 Hz, 1H); 3.01 (dd, J = 2.8, 4.1 Hz, 1H); 2.72 (t, J = 4.8 Hz, 1H); 2.56 (dd, J = 2.8, 5.0 Hz, 1H); 2.16 (bs, 1H); 1.82 (m, 3H); 1.60 (m, 1H); 1.25 (s, 3H); 1.20 (s, 3H); 1.11 (s, 3H).

13C NMR (100 MHz, CDCl₃, δ): 86.9, 81.4, 70.8, 57.2, 44.0, 32.9, 27.6, 26.4, 24.4, 24.3.

IR (NaCl, thin film): 3474, 2976, 2874, 1465, 1373, 1055, 897.


[α]₂₀°D +2.08 (c 2.4, CHCl₃).

Epoxide 11 (1.220 g, 6.550 mmol, 100 mol%, dr 83:17) was placed in a round bottom flask and the flask purged with argon. Lithium acetylide ethylene diamine complex (2.128 g, 19.7 mmol, 300 mol%, previously stored in a glove box) was quickly added to the epoxide. DMSO (13 mL) was added to the mixture. The reaction was exothermic. The mixture was stirred at rt for 18 h. Epoxide 11 was all consumed as judged by GCMS. The reaction mixture was cooled in an ice / water bath and quenched with water. The mixture was acidified to pH ~3 by 1M HCl, extracted with Et₂O, and dried with MgSO₄. Column chromatography isolated 810 mg of 12 (58% yield).

IR (NaCl, thin film): 3420, 3310, 2975, 2120, 1457, 1377, 1075.
CuI (359 mg, 1.884 mmol, 50 mol%), (CH₂O)n (283 mg, 9.421 mmol, 250 mol%), and i-Pr₂NH (1.06 mL, 7.536 mmol, 200 mol%) were placed in a pressure vessel and connected to an Ar line. Alkyne 12 (800 mg, 3.768 mmol, 100 mol%) in minimal Et₂O was added, followed by dioxane (8 mL). Et₂O was removed by bubbling nitrogen through the solution. The pressure vessel was purged with argon, then quickly sealed with a screw cap. The mixture was heated to 100 °C for 14 h. The mixture was cooled to rt. Solid was removed by filtration over celite and washed with Et₂O. Solvent was removed and redissolved in Et₂O and water was added. The mixture was acidified with 1 M HCl. Layers were separated and the aqueous layer was extracted again with Et₂O. The organic solution was washed with saturated NaHCO₃ and dried with MgSO₄. Column chromatography allowed separation of any minor diastereomer (hexane/ethyl acetate) to yield 542 mg of allene 13 (63% yield).

¹H NMR (400 MHz, CDCl₃, δ): 5.23 (quintet, J = 6.9 Hz, 1H); 4.73 (m, 2H); 3.78 (dd, J = 6.0, 10.0 Hz, 1H); 3.63 (dt, J = 2.4, 4.8 Hz, 1H); 2.23 (s, 1H); 2.27 (m, 1H); 2.19-2.00 (m, 2H); 2.07 (s, 1H); 1.95-1.81 (m, 2H); 1.23 (s, 3H); 1.18 (s, 3H); 1.14 (s, 3H).


HRMS-ESI (m/z): [M + Na]⁺ calcd for C₁₃H₂₂O₃Na, 249.1461; found, 249.1459.

Allene 13 (390 mg, 1.723 mmol, 100 mol%) was dissolved in THF (6.4 mL). Sodium hydride (92 mg, 3.844 mmol, 223 mol%) was added and the reaction was stirred at rt for 2 min. Benzyl bromide (0.457 mL, 3.844 mmol, 223 mol%) and n-BuNI (473 mg, 1.281 mmol, 74 mol%) were added. The reaction was stirred at rt for 1 h and then 75 °C for 18 h. After the reaction mixture was cooled down to rt, it was poured into ice-cold water. This mixture was extracted with Et₂O and dried with MgSO₄. Column chromatography isolated 142 mg of monobenzylether (27% yield) and 446 mg of dibenzylether 6 (66% yield). (SN061379)

¹H NMR (400 MHz, CDCl₃, δ): 7.40-7.10 (m, 10H); 5.22 (quintet, J = 7.2 Hz, 1H); 4.73 (dd, J = 11.6, 37.2 Hz, 2H); 4.66 (dd, J = 2.8, 6.4 Hz, 2H); 4.56 (t, J = 2.4 Hz, 2H); 3.98 (dd, J = 6.0, 9.6 Hz, 1H); 3.48 (dd, J = 3.2, 8.8 Hz, 1H); 2.33 (m, 1H); 2.15 (m, 2H); 1.87 (m, 2H); 1.60 (m, 1H); 1.27 (s, 3H); 1.23 (s, 3H); 1.19 (s, 3H).

¹³C NMR (100 MHz, CDCl₃, δ): 209.3, 140.4, 139.5, 128.44, 128.35, 127.9, 127.5, 127.2, 127.1, 88.0, 86.23, 86.15, 85.0, 76.6, 74.8, 74.5, 64.5, 33.4, 31.4, 27.6, 24.3, 22.5, 22.0.
Ni(cod)$_2$ (309 mg, 1.1238 mmol, 100 mol%) and Cyp$_3$P (315 µL, 1.1238 mmol, 100 mol%) was placed into a flask in a glove box. The flask was sealed with a rubber septum and brought out of the glove box. Under argon, aldehyde 8 (594 mg, 2.2477 mmol, 200 mol%) in THF (31 mL) was added to the catalyst mixture at room temperature to yield an orange-yellow solution. TBSH (269 µL, 1.6857 mmol, 150 mol%) was added to the mixture. Allene 6 (440 mg, 1.1238 mmol, 100 mol%) in THF (20 mL) was added to the reaction mixture over 3 h. After addition completed, the reaction mixture was stirred for 15 min. Volatiles were removed by rotavap. The crude was dissolved in Et$_2$O, washed with sat. NH$_4$Cl, and dried with MgSO$_4$. Column chromatography isolated an allylic ether in 67% yield. The silyl group was removed by TBAF in THF to yield epoxy-alcohol 7.

$^1$H NMR (400 MHz, C$_6$D$_6$, δ): 7.42 (d, $J$ = 7.8 Hz, 2H); 7.39 (d, $J$ = 7.2 Hz, 2H); 7.23 (t, $J$ = 7.4 Hz, 4H); 7.12 (t, $J$ = 7.4 Hz, 2H); 5.21 (m, 2H); 5.14 (s, 0.5H); 5.10 (s, 0.5H); 4.88 (t, $J$ = 11.3 Hz, 2H); 4.64 (s, 0.5H); 4.61 (s, 0.5H); 4.50 (dd, $J$ = 11.9, 17.8 Hz, 2H); 4.08 (m, 0.5H); 4.00 (m, 0.5H); 3.96 (dd, $J$ = 5.6, 9.6 Hz, 1.5H); 3.41 (d, $J$ = 8.5 Hz, 1H); 2.67 (m, 1H); 2.35-1.38 (m, 20H); 1.68 (s, 3H); 1.57 (s, 6H); 1.25-1.12 (m, 12H).

$^{13}$C NMR (100 MHz, C$_6$D$_6$, δ): 152.8, 152.7, 141.2, 140.43, 140.41, 135.7, 131.6, 128.9, 128.8, 128.3, 128.2, 127.9, 127.6, 127.5, 125.2, 124.7, 109.9, 87.04, 87.00, 86.96, 85.5, 85.4, 76.6, 75.4, 75.2, 75.0, 74.8, 64.9, 63.7, 63.5, 61.1, 60.9, 40.5, 39.6, 39.5, 33.9, 33.7, 33.4, 33.3, 30.94, 30.90, 29.6, 29.4, 27.8, 27.5, 26.3, 25.9, 25.8, 24.8, 24.7, 24.55, 24.53, 23.0, 22.1, 22.0, 18.1, 17.19, 17.16, 16.4.
Screening of Epoxide-Opening Reactions by Epoxy-Alcohol 7

Epoxy-alcohol 7 (dr 50:50) was subjected to a variety of Lewis acids and protic acids. A mixture of THPs, (S)-20 and (R)-20, and THFs, (S)-21 and (R)-21 were observed. Both THPs (S)-20 and (R)-20 were separable by column chromatography (Et2O / C6H6). The two THFs, (S)-21 and (R)-21, were not separable by column chromatography. Also, Both THPs reacted with p-nitrobenzoyl chloride but not the two THFs.

\[ \text{(S)-20} \]

\[ \text{\H NMR (500 MHz, C}_6\text{D}_6, \delta): 7.46 (d, J = 7.0 Hz, 2H); 7.40 (d, J = 7.4 Hz, 2H); 7.23 (m, 4H); 7.12 (t, J = 7.0 Hz, 2H); 5.25 (m, 2H); 5.18 (s, 1H); 4.93 (s, 1H); 4.90 (d, J = 11.8 Hz, 1H); 4.67 (d, J = 11.6 Hz, 1H); 4.51 (q, J = 11.9 Hz, 1H); 3.98 (dd, J = 5.8, 9.9 Hz, 1H); 3.94 (d, J = 8.4 Hz, 1H); 3.43 (dd, J = 2.8, 9.2 Hz, 1H); 3.18 (s, 1H); 2.55 (m, 1H); 2.35-1.40 (m, 19H); 1.68 (s, 3H); 1.61 (s, 3H); 1.58 (s, 3H); 1.25 (s, 3H); 1.23 (s, 3H); 1.21 (s, 3H); 1.20 (s, 3H). \]

\[ \text{\textsuperscript{13}C NMR (125 MHz, C}_6\text{D}_6, \delta): 151.3, 141.3, 140.6, 135.5, 131.7, 128.9, 128.8, 127.8, 127.6, 127.5, 125.3, 125.5, 110.0, 87.1, 87.0, 85.5, 77.3, 76.5, 75.1, 73.1, 69.4, 64.9, 40.6, 34.4, 33.7, 31.2, 29.9, 27.8, 27.6, 27.5, 26.3, 24.9, 24.3, 23.3, 23.2, 22.4, 22.0, 18.1, 16.5.} \]

\[ \text{(R)-20} \]

\[ \text{\H NMR (500 MHz, C}_6\text{D}_6, \delta): 7.43 (d, J = 7.6 Hz, 2H); 7.39 (d, J = 7.0 Hz, 2H); 7.22 (m, 4H); 7.12 (m, 2H); 5.36 (t, J = 6.6 Hz, 1H); 5.25 (t, J = 6.4 Hz, 1H); 5.20 (s, 1H); 4.93 (s, 1H); 4.91 (d, J = 11.8 Hz, 1H); 4.66 (d, J = 11.8 Hz, 2H); 4.51 (q, J = 11.9 Hz, 2H); 3.99 (dd, J = 5.7, 9.8 Hz, 1H); 3.91 (d, J = 10.8 Hz, 1H); 3.43 (dd, J = 2.8, 9.5 Hz, 1H); 3.31 (s, 1H); 2.38 (m, 4H); 2.15 (m, 6H); 1.90-1.30 (m, 10H); 1.68 (s, 6H); 1.57 (s, 3H); 1.22 (s, 3H); 1.21 (s, 3H); 1.20 (s, 3H); 1.16 (s, 3H). \]

\[ \text{\textsuperscript{13}C NMR (125 MHz, C}_6\text{D}_6, \delta): 151.3, 141.3, 140.6, 135.2, 131.5, 128.9, 128.8, 128.1, 127.8, 127.6, 127.5, 126.0, 125.4, 109.7, 87.1, 87.0, 85.8, 77.2, 76.5, 75.3, 72.6, 72.3, 64.9, 41.7, 40.6, 33.6, 31.4, 31.3, 30.5, 29.3, 27.8, 27.6, 26.3, 24.9, 23.2, 22.2, 22.0, 18.1, 16.5, 15.5.} \]

1D nOe experiment suggested there was nOe interaction between the methyl group on the pyran and the allylic proton on the pyran (R)-20.
Aldehyde 8 (600 mg, 2.269 mmol, 100 mol%) was dissolved in 2-methyl-2-butene (60 mL, ~25 mL/mmol of aldehyde) at room temperature in a 250 mL Erlenmeyer flask. tert-butyl alcohol (60 mL) and water (30 mL) were added. NaH$_2$PO$_4$$\cdot$H$_2$O (1.252 g, 9.076 mmol, 400 mol%) was added and the mixture was stirred vigorously at rt for 5 min until the mixture became homogeneous. Sodium chlorite (1.231 g, 13.616 mmol, 600 mol%) was added in one portion. The mixture was stirred vigorously at rt for 1 h. The mixture was poured into 5% aqueous NaH$_2$PO$_4$ solution (200 mL) and extracted twice with diethylether (100 mL then 150 mL). The organic fraction was dried with MgSO$_4$. NMR of the crude reaction mixture showed the desired acid 22 and no cyclization product. The crude mixture was used directly in the next step.

$^1$H NMR (400 MHz, C$_6$D$_6$, $\delta$): 5.23 (t, $J = 6.7$ Hz, 1H); 5.16 (t, $J = 7.1$ Hz, 1H); 2.59 (t, $J = 6.7$ Hz, 1H); 2.4-2.0 (m, 9H); 1.69 (s, 3H); 1.60 (m, 1H); 1.58 (s, 3H); 1.56 (s, 3H); 1.40 (m, 1H); 1.08 (s, 3H).

$^{13}$C NMR (100 MHz, C$_6$D$_6$, $\delta$): 179.0, 135.8, 131.6, 125.2, 124.6, 62.2, 61.0, 40.5, 39.3, 31.5, 27.5, 26.2, 24.7, 24.5, 18.1, 17.0, 16.4.

HRMS-ESI (m / z): [M + Na]$^+$ calcd for C$_{17}$H$_{28}$O$_3$Na, 303.1931; found, 303.1929.

[$\alpha$]$^D_{20}$ = $-$8.4 (c 2.97, CH$_2$Cl$_2$)
Crude Acid 22 (~2.269 mmol, 100 mol%, used directly without purification) was dissolved in dichloromethane (45 mL). The solution was cooled to −78 °C. BF₃•OEt₂ was diluted in dichloromethane (5 mL) and added to the reaction mixture over 2 min. Temperature of the cold bath was maintained under −70 °C for 8 h. Acetone was added to the cold bath to warm the bath to −50 °C over 5 min. The reaction was quenched with saturated NaHCO₃ (20 mL). The flask was removed from the cold bath and warmed to room temperature. The mixture was extracted with dichloromethane. The organic layer was dried with MgSO₄. ¹H NMR of the crude mixture indicated δ-lactone 39:γ-lactone ratio of 95:5. Column chromatography separated the γ-lactone from δ-lactone 39 (OH). δ-lactone 39 (OH) and imidazole (232 mg, 3.404 mmol, ~150 mol%) were dissolved in N,N-dimethylformamide (12 mL). Under argon, chlorotriethylsilane (0.460 mL, 2.723 mmol, ~120 mol%) was added in one portion at room temperature. The solution was heated at 50°C-50°C for 4h. The reaction was removed from the oil bath and cooled to rt. The reaction was quenched with water (5 mL, exothermic). The mixture was diluted with diethylether (100 mL) and washed twice with saturated NH₄Cl. The organic fraction was dried with MgSO₄. Column chromatography isolated 658 mg of δ-lactone 39 (TES) (73% yield over three steps from aldehyde).

δ-lactone 39 (TES):
¹H NMR (400 MHz, C6D₆, δ): 5.23 (t, J = 6.8 Hz, 1H); 5.20 (t, J = 7.1 Hz, 1H); 3.51 (dd, J = 4.6, 7.2 Hz, 1H); 2.42 (dt, J = 7.3, 18 Hz, 1H); 2.30-2.00 (m, 7H); 1.68 (s, 3H); 1.60 (s, 3H); 1.57 (s, 3H); 1.60-1.40 (m, 4H); 1.21 (s, 3H); 0.89 (t, J = 8.0 Hz, 9H); 0.44 (q, J = 7.8 Hz, 6H).
¹³C NMR (100 MHz, C6D₆, δ): 168.8, 136.1, 131.6, 125.2, 124.5, 85.2, 69.6, 40.52, 40.49, 27.5, 21.3, 26.4, 16.4, 7.4, 5.6.
IR (NaCl, thin film): 2957, 2914, 2877, 1738, 1457, 1378, 1239, 1098, 1006, 745.
[α]²⁰D +18.0 (c 2.83, CH₂Cl₂)

γ-lactone 39b (OH):
¹H NMR (400 MHz, C6D₆, δ): 5.23 (t, J = 6.7 Hz, 1H); 5.17 (t, J = 7.0 Hz, 1H); 3.68 (s, 3H); 2.20-1.70 (m, 8H); 1.68 (s, 3H); 1.58 (s, 3H); 1.57 (s, 3H); 1.45-1.10 (m, 4H); 1.08 (s, 3H).
¹³C NMR (100 MHz, C6D₆, δ): 176.8, 135.8, 131.7, 125.1, 125.0, 85.5, 72.8, 40.5, 37.8, 29.1, 27.5, 26.2, 23.5, 23.5, 22.5, 22.1, 18.1, 16.4.
IR (NaCl, thin film): 3460, 2967, 2928, 1776, 1452, 1377, 1194, 992.
[α]²⁰D −2.7 (c 3.70, CH₂Cl₂)
Epoxy-alcohol 7 (20 mg, 0.02972 mmol, 100 mol%), triethylamine (17 µL, 400 mol%), DMSO (21 µL, 1000 mol%) were dissolved in DCM and cooled in an ice / water bath. SO$_3$pyr (9.5 mg, 200 mol%) was added in one portion. The cold bath was allowed to be warmed gradually to rt. The mixture was stirred for 3 d. The mixture was diluted in DCM, washed with water, and dried with MgSO$_4$. Column chromatography isolated 8 mg of 23 (40% yield).

$^1$H NMR (400 MHz, C$_6$D$_6$, $\delta$): 7.44 (d, $J = 7.0$ Hz, 2H); 7.40 (d, $J = 7.0$ Hz, 2H); 7.23 (q, $J = 7.3$ Hz, 4H); 7.12 (m, 2H); 5.55 (s, 1H); 5.33 (s, 1H); 5.22 (m, 2H); 4.88 (d, $J = 11.6$ Hz, 1H); 4.63 (d, $J = 11.7$ Hz, 1H); 4.50 (q, $J = 11.9$ Hz, 2H); 3.96 (dd, $J = 5.8, 9.8$ Hz, 1H); 3.37 (dd, $J = 2.9, 9.1$ Hz, 1H); 2.68 (dd, $J = 4.6, 7.9$ Hz, 1H); 2.57 (m, 3H); 2.12 (m, 7H); 1.96 (m, 1H); 1.86-1.52 (m, 7H); 1.67 (s, 3H); 1.57 (s, 6H); 1.45 (m, 2H); 1.21 (s, 3H); 1.19 (s, 3H); 1.17 (s, 3H); 1.14 (s, 3H).

$^{13}$C NMR (100 MHz, C$_6$D$_6$, $\delta$): 200.2, 149.5, 141.3, 140.5, 135.7, 131.6, 128.9, 127.9, 127.6, 127.5, 125.2, 124.7, 123.9, 86.9, 85.4, 76.5, 74.9, 64.9, 62.7, 61.0, 40.5, 39.5, 35.2, 33.7, 31.6, 29.2, 27.8, 27.5, 26.2, 24.7, 24.5, 24.3, 23.1, 22.1, 18.1, 17.2, 16.4.

Enone 23 (~5 mg) was dissolved in DCM (1.5 mL). Amberlyst 15 (2 mg) was added at rt. After stirring for 5 h, most enone 23 was consumed. Solid NaHCO$_3$ was added and the mixture was stirred 2h. The mixture was filtered through a cotton plug and concentrated. Column chromatography separated enone 23 from the cyclization product. The cyclization product was dissolved in DCM. Ac$_2$O, Et$_3$N and DMAP was added. The mixture was stirred 3 h at rt. After aqueous workup, column chromatography isolated the acetate. Comparison of NMR spectra of the acetate and the alcohol suggested that cyclization of enone 23 in Amberlyst 15 yielded a dihydropyran and not a dihydrofuran.

$^1$H NMR (500 MHz, C$_6$D$_6$, $\delta$): 7.43 (d, $J = 7.4$ Hz, 2H); 7.40 (d, $J = 7.7$ Hz, 2H); 7.22 (m, 4H); 7.11 (m, 2H); 5.79 (s, 1H); 5.23 (t, $J = 6.9$ Hz, 2H); 5.12 (t, $J = 5.9$ Hz, 1H); 5.02 (s, 1H); 4.90 (m, 2H); 4.63 (d, $J = 11.7$ Hz, 1H); 4.50 (q, $J = 11.7$ Hz, 2H); 3.98 (dd, $J = 5.7, 9.8$ Hz, 1H); 3.40 (m, 1H); 2.61 (m, 1H); 2.43 (m, 1H); 2.33 (m, 2H); 2.27-1.97 (m, 7H); 1.74 (m, 6H); 1.68 (s, 3H); 1.62 (s, 6H); 1.56 (s, 3H); 1.36 (m, 1H); 1.26 (s, 3H); 1.22 (s, 3H); 1.20 (s, 3H); 1.15 (s, 3H).
Synthesis of Triepoxide \textit{tert}-Butyl Ester 29 and Epoxide-Opening Cascade

Alcohol 15 (1.19 g, 5 mmol, 100 mol%), \( \text{Bu}_4\text{NHSO}_4 \) (0.679 g, 2 mmol, 40 mol%) and (--)-Shiketone (2.38 g, 10 mmol, 200 mol%) were placed into an 1L Erlenmeyer flask. 1:2 \( \text{CH}_3\text{CN} : \text{DMM} \) (200 mL) was added at room temperature. The mixture was cooled in an ice/water bath. Buffer solution (100 mL, 0.05 M \( \text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{H}_2\text{O} \), in 4x10^{-4} M \( \text{Na}_2\text{EDTA} \) solution) was added. \( \text{K}_2\text{CO}_3 \) solution (170 mL, 0.89 M in water) and oxone solution (24.9 g oxone dissolved in 4x10^{-4} M \( \text{Na}_2\text{EDTA} \) solution to 170 mL) were added simultaneously over 45 min. After the addition completed the mixture was stirred for 10 min. The mixture was diluted with water to dissolve all solid. The mixture was extracted twice with dichloromethane (500 mL then 300 mL). The dichloromethane extract was dried with \( \text{MgSO}_4 \).

The same procedure was performed three times. The combined crude was purified by column chromatography to yield 3.57 g of 30 (88% yield, average of three runs).

\( ^1\text{H NMR} \) (400 MHz, \( \text{CDCl}_3 \), \( \delta \)): 3.82-3.62 (m, 2H); 2.97 (t, \( J = 5.8 \) Hz, 1H); 2.75 (dd, \( J = 3.7, 7.7 \) Hz, 1H); 2.69 (t, \( J = 6.0 \) Hz, 1H); 2.62 (m, 1H); 1.96-1.48 (m, 8H); 1.30 (s, 3H); 1.291 (s, 3H); 1.289 (s, 3H); 1.25 (s, 3H).

\( ^{13}\text{C NMR} \) (100 MHz, \( \text{CDCl}_3 \), \( \delta \)): 64.0, 63.2, 63.0, 61.0, 60.9, 60.8, 58.7, 36.2, 35.2, 25.0, 24.7, 24.6, 18.8, 16.9, 16.5.

IR (NaCl, thin film): 3442, 2964, 1457, 1386, 1035.

HRMS-ESI (m/z): [M + Na]^+ calcd for \( \text{C}_{15}\text{H}_{26}\text{O}_4\text{Na} \), 293.172; found, 293.173.

\( [\alpha]^{20}_D +26.2 \) (c 2.10, \( \text{CHCl}_3 \))
Triphenylphosphine (5.83 g, 22.24 mmol, 120 mol%) and imidazole (3.03 g, 44.47 mmol, 240 mol%) were dissolved in 150 mL dichloromethane. The solution was stirred under argon and cooled in an ice/water bath. Iodine (5.64 g, 22.24 mmol, 120 mol%) was added in one portion. Once all iodine was dissolved, alcohol 30 (5.01 g, 18.53 mmol, 100 mol%) in 15 mL dichloromethane was added. The reaction mixture was stirred in the ice/water bath for 30 min. The ice/water bath was removed and the mixture was stirred at rt for 30 min. The mixture was diluted to 200 mL and washed with 2:1 saturated Na$_2$S$_2$O$_3$/brine (200 mL). The aqueous layer was extracted again with DCM (100 mL). The organic solution was dried with MgSO$_4$. The solution was concentrated to ~ 20 mL, diluted with 1:1 DCM/hexane, and loaded directly to a silica column that was packed with 1:1 DCM/hexane. Column chromatography isolated 6.1 g of iodide (87% yield).

$^1$H NMR (400 MHz, C$_6$D$_6$, $\delta$): 2.86 (dd, $J = 6.1$, 9.7 Hz, 1H); 2.77 (dd, $J = 6.2$, 7.9 Hz, 1H); 2.61 (dd, $J = 7.7$, 9.7 Hz, 1H); 2.51 (m, 2H); 1.75-1.33 (m, 8H); 1.13 (s, 3H); 1.08 (s, 3H); 1.06 (s, 3H); 0.93 (s, 3H).

$^{13}$C NMR (100 MHz, C$_6$D$_6$, $\delta$): 63.7, 63.6, 62.8, 62.5, 60.1, 58.0, 35.9, 35.7, 25.32, 25.30, 25.29, 19.2, 17.2, 16.0, 3.4.

IR (NaCl, thin film): 2963, 2927, 1460, 1385, 1250, 1176, 1121.

HRMS-ESI (m / z): [M + Na]$^+$ calcd for C$_{15}$H$_{23}$IO$_3$Na, 403.0741; found, 403.0732.

[$\alpha$]$^D_{20}$ +23.3 (c 3.5, CH$_2$Cl$_2$)
Diisopropylamine (7.53 mL, 53.74 mmol, 335 mmol%) was dissolved in 200 mL THF under argon. The solution was cooled to –78 °C and n-BuLi (19.9 mL, 49.72 mmol, 2.5M in hexane, 310 mol%) was added in one portion. The mixture was stirred at –78 °C for 1.5 h. tert-Butylacetate (6.92 mL, 51.33 mmol, 320 mol%) was added. The reaction mixture was stirred for another 1.5 h at –78 °C. Iodide from alcohol 30 (6.10 g, 16.04 mmol, 100 mol%) in THF (20 mL) was added to the reaction mixture. After 10 min at –78 °C HMPA (8.02 mL, 0.5 mL / mmol iodide) was added. The mixture was stirred for 35 min at –78 °C and quenched with saturated NH₄Cl. The reaction was removed from the cold bath and allowed to warm to rt. The mixture was diluted with Et₂O, washed with saturated NH₄Cl, and dried with MgSO₄. Column chromatography isolated 5.25 g of triepoxide tert-butylacetate 29 (88% yield).

$^1$H NMR (400 MHz, C₆D₆, δ): 2.64 (dd, $J = 5.5$, 7.1 Hz, 1H); 2.70- 2.45 (m, 2H); 2.35-2.20 (m, 2H); 1.85-1.62 (m, 3H); 1.58-1.42 (m, 7H); 1.37 (s, 9H); 1.14 (s, 3H); 1.09 (s, 3H); 1.08 (s, 3H); 1.06 (s, 3H).

$^{13}$C NMR (100 MHz, C₆D₆, δ): 172.3, 80.2, 63.7, 62.7, 62.6, 60.5, 60.0, 57.9, 36.3, 35.9, 32.9, 28.4, 25.4, 25.3, 25.1, 19.1, 17.2, 16.9.

IR (NaCl, thin film): 2965, 1728, 1462, 1367, 1153.

HRMS-ESI (m/z): [M + Na]$^+$ calcd for C$_{21}$H$_{36}$O$_5$Na, 391.2455; found, 391.2465.

[$\alpha$]$^0$$_{D} +4.3$ (c 5.6, CH$_2$Cl$_2$)
Ester 29 (5.15 g, 13.98 mmol, 100 mol%) and 1,2,3-trimethoxybenzene (4.7 mg, 26.95 mmol, 200 mol%) were dissolved in DCM (280 mL). The mixture was cooled under argon to –78 °C. BF$_3$•OEt$_2$ (1.77 mL, 13.98 mmol, 100 mol%) was added. The mixture was stirred at –78 °C for 1 h and quenched with saturated NaHCO$_3$ (50 mL) at –78 °C. The cold bath was removed and the mixture was warmed to rt. Layers were separated and the aqueous layer was extracted two times with DCM (2 x 100 mL). The extract was dried with MgSO$_4$. Column chromatography isolated cyclization product 31 in a concentrated DCM solution (~ 3-5 mL) and carried on directly to the next step.

$^1$H NMR (400 MHz, C$_6$D$_6$, δ): 4.14 (d, $J$ = 8.9 Hz, 1H); 3.64 (dd, $J$ = 5.1, 11.7 Hz, 1H); 3.40 (t, $J$ = 5.1 Hz, 1H); 2.27 (dt, $J$ = 3.5, 12.8 Hz, 1H); 2.16-2.00 (m, 2H); 1.90-1.45 (m, 10H); 1.26 (s, 3H); 1.20 (s, 3H); 1.13 (s, 3H); 0.97 (s, 3H).

$^{13}$C NMR (100 MHz, C$_6$D$_6$, δ): 169.3, 84.8, 80.5, 78.4, 76.7, 76.5, 68.7, 42.1, 31.9, 29.2, 29.1, 28.8, 26.1, 25.4, 22.9, 20.9, 20.7.

IR (NaCl, thin film): 3470, 2976, 2941, 1722, 1381, 1273, 1206, 1083.

HRMS-ESI (m/z): [M + Na]$^+$ calcd for C$_{17}$H$_{28}$O$_5$Na, 335.1829; found, 335.1833.

[$\alpha$]$^{20}_D$ –3.1 (c 1.3, CH$_2$Cl$_2$)

ORTEP diagrams of 31:
Alcohol 31 solution in DCM (~3-5 mL) from the previous step and imidazole (3 g, 44.07 mmol) were dissolved in DMF (20 mL) and fitted with a condenser. The reaction setup was purged with argon. Chlorotriethylsilane (3.0 mL, 17.87 mmol) was added to the reaction mixture at rt. The mixture was heated for 16 h at 45 °C and then quenched with MeOH (3 mL). The mixture was stirred for 45 min at 45 °C. The mixture was cooled to rt. The mixture was diluted with Et₂O, washed with saturated NH₄Cl and dried with MgSO₄. Column chromatography isolated 1.53 g of silyl ether 32 (25% from ester 29).

**1H NMR (400 MHz, C₆D₆, δ):** 4.18 (d, J = 9.1 Hz, 1H); 3.74 (dd, J = 5.0, 11.9 Hz, 1H); 3.55 (d, J = 6.7 Hz, 1H); 2.35-2.10 (m, 3H); 2.85-1.25 (m, 9H); 1.26 (s, 3H); 1.18 (s, 3H); 1.16 (s, 3H); 0.96 (s, 3H); 0.93 (t, J = 8.0 Hz, 9H); 0.47 (q, J = 7.9 Hz, 6H).

**13C NMR (100 MHz, C₆D₆, δ):** 168.0, 84.6, 80.3, 78.7, 78.0, 76.3, 69.3, 42.5, 32.0, 29.8, 28.9, 28.7, 26.6, 25.7, 23.6, 20.9, 20.7, 7.6, 5.5.

IR (NaCl, thin film): 2952, 1740, 1380, 1267, 1083, 738.

HRMS-ESI (m/z): [M + Na]⁺ calcd for C₂₃H₄₂O₅SiNa, 449.2694; found, 449.2698.

---

**Formation of Cyclic Enol Ether 42**

Ketone 41 was dissolved in DCM at room temperature. PPTS was added and the mixture was stirred until most of ketone 41 was consumed.

**1H NMR (400 MHz, C₆D₆, δ):** 5.78 (s, 1H); 5.13 (s, 1H); 5.11 (m, 1H); 4.32 (d, J = 9.2 Hz, 1H); 4.01 (dd, J = 6.8, 9.6 Hz, 1H); 3.92 (t, J = 5.0 Hz, 1H); 3.86 (dd, J = 6.3, 8.9 Hz, 1H); 3.61 (d, J = 6.7 Hz, 1H); 2.70 (m, 1H); 2.40 (m, 4H); 2.27-1.77 (m, 9H); 1.63 (m, 4H); 1.42 (s, 3H); 1.33 (s, 3H); 1.32 (s, 3H); 1.29 (s, 3H); 1.26 (s, 6H); 1.16 (m, 42 H); 1.02 (s, 3H); 0.98 (t, J = 7.9 Hz, 9H); 0.50 (q, J = 8.0 Hz, 6H).
Diastereoselective Reactions with Lactone 32

Trimethylsilylacetylene (31 µL, 0.2250 mmol, 400 mol%) was dissolved in THF (1 mL). The solution was cooled at −78 °C and n-BuLi (90 µL, 0.2250 mmol, 400 mol%) was added. The mixture was stirred at −78 °C for 5 min and then warmed in an ice/water bath for 15 min. The mixture was cooled to −78 °C again. BF₃·OEt₂ (29 µL, 0.2250 mmol, 400 mol%) was added. After 30 min at −78 °C lactone 32 in THF (1.5 mL) was added to the mixture over 1 min. The mixture was stirred 45 min at −78 °C and quenched with saturated NaHCO₃. The mixture was removed from the cold bath and quickly melted the solid. The mixture was diluted with Et₂O, washed with saturated NaHCO₃ twice, and dried with MgSO₄.

The mixture was concentrated and diluted in DCM (1 mL) and CH₃CN (0.2 mL). Triethylsilane (0.1 mL) and BF₃·OEt₂ (15 µL) were added to the crude at rt. The mixture was stirred 30 min and quenched with saturated NaHCO₃. The mixture was diluted with DCM, washed with NaHCO₃, and dried with MgSO₄. Column chromatography isolated 10 mg of propargyl ether 43 (45% from lactone 32). The stereochemistry of the propargyl ether was established by a NOSEY experiment.

¹H NMR (400 MHz, C₆D₆, δ): 4.21-4.15 (m, 2H); 3.56 (dd, J = 5.1, 11.3 Hz, 1H); 3.30 (t, J = 4.5 Hz, 1H); 2.30-1.39 (m, 12H); 1.30 (s, 3H); 1.27 (m, 1H); 1.11 (s, 3H); 0.94 (s, 3H); 0.16 (s, 9H).

¹³C NMR (100 MHz, C₆D₆, δ): 107.1, 88.0, 80.0, 78.7, 78.0, 77.0, 76.6, 70.8, 61.5, 42.5, 33.4, 29.5, 28.9, 28.6, 26.2, 22.7, 21.0, 16.2, 0.4.
Lactone 32 (1.50 g, 3.516 mmol, 100 mol%) was dissolved in toluene (50 mL) and cooled to –78 °C under argon. DIBAL (5.27 mL, 5.274 mmol, 1M in toluene) was diluted in toluene (15 mL) and the diluted DIBAL solution was added to the lactone solution over 40 min. After addition completed the reaction was stirred an extra 5 min. The reaction mixture was quenched with methanol (5.3 mL) and the mixture was stirred 10 min. The cold solution was poured into saturated Rochelle’s salt solution (200 mL), diluted with Et2O (100 mL), and stirred vigorously for 1 h. Layers were separated and the aqueous layer was extracted with diethylether. The organic mixture was dried with MgSO4 and concentrated. The crude hemiacetal was used directly.

The crude hemiacetal was dissolved in dichloromethane (35 mL) and cooled to –12 °C under argon. Trimethylsilylcyanide (2.2 mL, 17.58 mmol, 500 mol%) was added, followed by BF3·OEt2 (0.67 mL, 5.274 mmol, 150 mol%). The mixture was stirred 45 min and the temperature gradually rose to –5 °C. The reaction was quenched with 1:1:1 DCM/MeOH/Et3N (35 mL) and stirred 15 min at –5 °C. The mixture was diluted with Et2O, washed with saturated NaHCO3, and dried with MgSO4. Column chromatography isolated 600 mg of 44 (39%), 190 mg of 45 (12%), and 420 mg of cyclic enol ether (29%). NOSEY of 44 was consistent with its configuration. Configuration of 45 was confirmed from NOSEY of methyl ketone 53.

**44** (anti H / Me):

1H NMR (400 MHz, C6D6, δ): 4.18 (d, J = 10.2 Hz, 1H); 4.00 (d, J = 4.5 Hz, 1H); 3.56 (d, J = 6.8 Hz, 1H); 3.40 (dd, J = 4.5, 11.6 Hz, 1H); 2.16 (dt, J = 2.8, 13.2 Hz, 1H); 2.00-1.70 (m, 3H); 1.61 (s, 3H); 1.70-1.31 (m, 8H); 1.30 (s, 3H); 1.21 (s, 3H); 1.17 (m, 1H); 0.98 (s, 3H); 0.96 (t, J = 7.9 Hz, 9H); 0.50 (q, J = 7.8 Hz, 6H).

13C NMR (100 MHz, C6D6, δ): 120.7, 80.8, 80.2, 78.5, 78.1, 76.4, 71.2, 59.6, 42.8, 32.3, 29.8, 29.1, 28.8, 26.6, 25.1, 23.6, 21.0, 18.3, 7.6, 5.4.

IR (NaCl, thin film): 2950, 1458, 1379, 1233, 1100, 729.

HRMS-ESI (m/z): [M + Na]+ calcd for C24H43NO4SiNa, 460.2854; found, 460.2860. 

[α]20D +12.9 (c 3.1, CH2Cl2)

**45** (syn H / Me):

1H NMR (400 MHz, C6D6, δ): 4.21 (d, J = 10.0 Hz, 1H); 3.59 (dd, J = 2.4, 12.1 Hz, 1H); 3.56 (d, J = 6.8 Hz, 1H); 2.18 (dt, J = 2.7, 12.8 Hz, 1H); 1.84 (m, 1H); 1.72-1.38 (m, 8H); 1.32 (m, 1H); 1.30 (s, 3H); 1.21 (s, 3H); 1.17 (m, 1H); 0.98 (s, 3H); 0.96 (t, J = 7.9 Hz, 1H); 0.90 (s, 3H); 0.49 (q, J = 8.0 Hz, 6H).

13C NMR (100 MHz, C6D6, δ): 119.2, 80.1, 79.7, 78.6, 78.0, 76.3, 70.2, 59.6, 42.1, 32.2, 31.1, 29.2, 28.8, 27.6, 26.6, 23.6, 21.0, 15.7, 7.6, 5.5.

IR (NaCl, thin film): 2951, 2877, 1458, 1380, 1244, 1094, 738.

HRMS-ESI (m/z): [M + Na]+ calcd for C24H43NO4SiNa, 460.2854; found, 460.2867. 

[α]20D −7.0 (c 3.3, CH2Cl2)
32-cyclic enol

\[ ^1H\text{ NMR} \quad (400\text{ MHz, C}_6\text{D}_6, \delta): \]

- 6.23 (d, \( J = 6.1 \text{ Hz, 1H} \))
- 4.46 (dt, \( J = 2.4, 5.4 \text{ Hz, 1H} \))
- 4.30 (d, \( J = 9.9 \text{ Hz, 1H} \))
- 3.95 (dd, \( J = 6.7, 9.4 \text{ Hz, 1H} \))
- 3.60 (d, \( J = 6.9 \text{ Hz, 1H} \))
- 2.36 (dt, \( J = 3.0, 13.1 \text{ Hz, 1H} \))
- 2.30-1.80 (m, 5H)
- 1.68 (dt, \( J = 2.7, 14.4 \text{ Hz, 1H} \))
- 1.60 (m, 2H)
- 1.41 (m, 1H)
- 1.40 (s, 3H)
- 1.30 (s, 3H)
- 1.24 (s, 3H)
- 1.01 (s, 3H)
- 0.97 (t, \( J = 7.9 \text{ Hz, 9H} \))
- 0.50 (q, \( J = 7.9 \text{ Hz, 6H} \))

\[ ^13C\text{ NMR} \quad (100\text{ MHz, C}_6\text{D}_6, \delta): \]

- 141.7
- 97.5
- 79.8
- 78.7
- 78.6
- 78.2
- 77.2
- 68.6
- 42.5
- 31.9
- 29.2
- 28.8
- 27.8
- 26.7
- 23.8
- 21.2
- 17.8
- 7.6
- 5.5

IR (NaCl, thin film): 2952, 1656, 1445, 1380, 1248, 1081, 1045, 737.

HRMS-ESI (m/z): [M + Na]^+ calcd for C_{23}H_{42}O_4SiNa, 433.3745; found, 433.2755.

\([\alpha]^{20}_D +9.35\) (c 3.1, CH_2Cl_2)
Synthesis of Methyl ketones 50 and 53

Ni(acac)$_2$ (4 mg, 0.01578 mmol, 30 mol%) was dissolved in toluene (0.5 mL, saturated with N$_2$) and cooled in an ice/water bath. Dimethylzinc (80 µL, 0.16 mmol, 300 mol%, 2M in toluene) was added and stirred 15 min. The mixture turned from green to black. Nitrile 45 (23 mg, 0.0526 mmol, 100 mol%) was dissolved in toluene (0.5 mL) and added to the catalyst mixture. The mixture was stirred 18 h at rt. The mixture was cooled in an ice/water bath, poured into ice-cold HCl solution (2 mL, 0.5M), and rinsed with Et$_2$O. The mixture was stirred vigorously for 15 min. The mixture was diluted with Et$_2$O, washed with saturated NH$_4$Cl, and dried with MgSO$_4$. The crude was >90% pure by NMR (20 mg, 83% yield). NOSEY of 53 was consistent with the assigned configuration.

$^1$H NMR (400 MHz, C$_6$D$_6$, δ): 4.30 (d, $J = 10.3$ Hz, 1H); 3.68 (dd, $J = 2.7$, 11.8 Hz, 1H); 3.59 (d, $J = 6.8$ Hz, 1H); 3.51 (dd, $J = 5.0$, 11.3 Hz, 1H); 2.25 (dt, $J = 2.9$, 13.0 Hz, 1H); 1.35 (s, 3H); 2.00-1.42 (m, 10 H); 1.39 (m, 1H); 1.36 (s, 3H); 1.24 (s, 3H); 1.09 (s, 3H); 1.00 (s, 3H); 0.97 (t, $J = 7.9$ Hz, 9H); 0.50 (q, $J = 7.9$ Hz, 6H).

$^{13}$C NMR (100 MHz, C$_6$D$_6$, δ): 208.3, 79.9, 78.6, 78.2, 78.1, 76.6, 75.8, 71.2, 43.0, 32.2, 29.4, 28.8, 28.3, 26.7, 25.6, 23.6, 21.1, 16.2, 7.7, 5.5.
Ni(acac)₂ (9 mg, 0.03384 mmol, 37 mol%) was dissolved in toluene (0.9 mL, saturated with N₂) and cooled to –15 °C. Methylmagnesium bromide (200 µL, 0.2744 mmol, 300 mol%, 1.4M in 3:1 THF/toluene) was added and stirred 5 min. The mixture turned from green to black. Nitrile 44 (40 mg, 0.09147 mmol, 100 mol%, dr >95:5) was dissolved in toluene (1.3 mL) and added to the catalyst mixture. The mixture was stirred 30 min and temperature slowly warmed to –8 °C. The mixture was cooled in an ice/water bath, poured into ice-cold HCl solution (4 mL, 0.5M), and rinsed with Et₂O. The mixture was stirred vigorously for 15 min. The mixture was diluted with Et₂O, washed with saturated NH₄Cl, and dried with MgSO₄. Column chromatography isolated 21 mg of 50 (50% yield, dr 93:7)

1H NMR (400 MHz, C₆D₆, δ): 4.36 (d, J = 9.9 Hz, 1H); 3.71 (dd, J = 2.4, 6.3 Hz, 1H); 3.68 (m, 1H); 3.65 (d, J = 6.6 Hz, 1H); 2.45-2.25 (m, 2H); 2.06 (s, 3H); 2.12-1.82 (m, 4H); 1.75-1.55 (m, 5H); 1.45 (m, 1H); 1.41 (s, 3H); 1.29 (s, 3H); 1.20 (s, 3H); 1.06 (t, J = 8.1 Hz, 12H); 0.59 (q, J = 7.9 Hz, 6H).

13C NMR (100 MHz, C₆D₆, δ): 209.6, 79.9, 79.6, 78.5, 78.2, 76.7, 76.1, 71.8, 43.1, 32.2, 29.6, 28.8, 26.7, 26.4, 25.3, 24.5, 23.7, 21.1, 18.7, 7.7, 5.5.

IR (NaCl, thin film): 2952, 1719, 1457, 1379, 1243, 1101, 729.

HRMS-ESI (m/z): [M + Na]+ calcd for C₂₅H₄₆O₅SiNa, 477.3007; found, 477.3004.

[α]²⁰D −9.18 (c 4.7, CH₂Cl₂)
Comin’s reagent (40 mg, 0.1016 mmol, 115 mol%) was dissolved in THF (0.5 mL) and cooled to –78 °C. LHMDS (0.9 mL, 0.18 mmol, 200 mol%, 0.2M in THF, freshly prepared) was added to the Comin’s reagent solution. After stirring for 2 min at –78 °C, ketone 50 (40 mg, 0.8835 mmol, 100 mol%) in THF (1 mL) was added. More THF (0.5 mL) was used to rinse the wall of the flask. The mixture was stirred 2.5 h at –78 °C and then at 0°C for 30 min. The crude was diluted with Et₂O and washed with saturated NaHCO₃ and then twice with 1M NaOH. The crude was dried with MgSO₄ and concentrated. NMR of the crude indicated the presence of the alkenyl triflate 57 and HMDS. The crude was used directly in the next step. (SN081845)

1H NMR (400 MHz, C₆D₆, δ): 4.77 (dd, J = 1.1, 4.0 Hz, 1H); 4.54 (dd, J = 1.5, 3.9 Hz, 1H); 4.34 (m, 1H); 4.24 (d, J = 10.2 Hz, 1H); 3.66 (dd, J = 5.0, 11.2 Hz, 1H); 3.57 (m, 1H); 2.25 (t, J = 13.1 Hz, 1H); 1.99-1.15 (m, 11H); 1.41 (s, 3H); 1.33 (s, 3H); 1.30 (s, 3H); 1.20 (s, 3H); 1.00 (t, J = 8.0 Hz, 9H); 0.53 (q, J = 7.8 Hz, 6H).

13C NMR (100 MHz, C₆D₆, δ): 157.7, 104.9, 80.2, 79.6, 78.6, 78.1, 76.5, 71.2, 68.2, 67.8, 42.0, 32.5, 29.4, 28.8, 26.7, 26.1, 24.4, 23.6, 21.1, 19.3, 7.7, 5.5.

19F NMR (376 MHz, C₆D₆, δ): –76.32 (s, 3F). (Referenced with CF₃CH₂OH at –77.8 ppm)

HRMS-ESI (m/z): [M + Na]⁺ calcd for C₂₆H₄₅F₃O₇SSiNa, 609.2500; found, 609.2491.
Trimethylsulfonium iodide (102 mg, 0.5 mmol, 500 mol%) was mixed with THF (1 mL) and cooled in an ice / salt bath (–15 °C). n-Butyllithium (0.2 mL, 0.5 mmol, 500 mol%, 2.5M in hexane) was added. The reaction mixture was stirred 40 min and the temperature rose to –10 °C. Epoxide 11 (19 mg, 0.1 mmol, 100 mol%) in THF (1 mL) was added to the mixture. The mixture was stirred 3h and gradually warmed to rt. Triisopropylsilane (128 µL, 0.65 mmol, 650 mol%) was added and the mixture was stirred 4h at rt. The reaction was quenched with MeOH (0.2 mL) and stirred 5 min. The mixture was diluted with Et₂O, washed with saturated NH₄Cl, saturated NaHCO₃, and dried with MgSO₄. Column chromatography isolated mono-TIPS-ether. This intermediate was dissolved in DCM (2 mL). Triethylamine (100 µL) and TIPSOTf (100 µL) were added. The mixture was heated at 45 °C for 24 h. The mixture was quenched with MeOH (0.2 mL) and refluxed for 1h. The mixture was cooled to rt and diluted with Et₂O. The mixture was washed with water, saturated NaHCO₃, and dried with MgSO₄. Column chromatography isolated 33 mg of 59 (64% yield).

1H NMR (400 MHz, C₆D₆, δ): 5.82 (ddd, J = 7.5, 10.4, 17.6 Hz, 1H); 5.16 (d, J = 9.7 Hz, 1H); 5.02 (d, J = 10.4 Hz, 1H); 4.24 (d, J = 7.4 Hz, 1H); 3.98 (dd, J = 6.6, 8.8 Hz, 1H); 2.28 (m, 1H); 1.93 (m, 2H); 1.45 (m, 1H); 1.35 (s, 3H); 1.29 (s, 3H); 1.19 (s, 3H); 1.18-1.12 (m, 42H).

13C NMR (100 MHz, C₆D₆, δ): 140.0, 116.8, 88.5, 86.2, 81.1, 75.0, 33.2, 29.3, 27.6, 25.2, 24.8, 19.0, 18.9, 14.1, 13.6.


HRMS-ESI (m/z): [M + Na]+ calcd for C₂₉H₆₀O₃Si₂Na, 535.3973; found, 535.3983.

[α]²₀° D –2.7 (c = 4.5, CH₂Cl₂)
9-BBN dimer (24.4 mg, 0.1 mmol, 110 mol%) was placed in a Schlenk tube. Alkene 59 (51.3 mg, 0.1 mmol, 110 mol%) in THF (1 mL) was added under argon at rt. More THF (0.2 mL) was used for rinsing. The Schlenk tube was closed and the mixture was heated at 55 °C for 20 h. After the mixture was cooled to rt, Cesium carbonate solution (0.2 mL, 0.2 mmol, 220 mol%, 1M in H2O, saturated with nitrogen) was added under argon. Bubbling occurred immediately. The mixture was stirred at rt for 15 min. Crude alkenyl triflate 57 (~0.08835 mmol, 100 mol%) in THF (1 mL) was added. Pd(dppf)Cl₂ (8 mg, 0.01 mmol, 11 mol%) in DMF (1 mL) was added. The Schlenk tube was closed and the mixture was heated at 55 °C for 18 h. The reaction was cooled to room temperature. The crude was diluted with Et₂O, washed with 0.5M HCl and brine, and dried with MgSO₄. Column chromatography isolated cross coupling products. The mixture of products was dissolved in THF (5 mL) and TBAF (80 µL, 0.08 mmol, 1M THF) was added at rt. The reaction was stirred 1.25 h. The mixture was diluted with Et₂O and washed with H₂O. Column chromatography isolated TES deprotected cross coupling product 4 (19 mg, 26%) and also cross coupling product that has both TES and 2° TIPS group deprotected (60) (12 mg, 20%).

¹H NMR (600 MHz, C₆D₆, δ): 4.96 (s, 1H); 4.93 (s, 1H); 4.24 (m, 2H); 3.93 (t, J = 5.2 Hz, 1H); 3.89 (dd, J = 6.4, 9.0 Hz, 1H); 3.81 (dd, J = 4.3, 11.5 Hz, 1H); 3.20 (d, J = 6.3 Hz, 1H); 2.54 (m, 2H); 2.34 (t, J = 12.8 Hz, 1H); 2.24 (q, J = 10.4 Hz, 1H); 2.15-1.50 (m, 16H); 1.45 (s, 3H); 1.37 (s, 3H); 1.35 (s, 3H); 1.30 (s, 3H); 1.27 (s, 3H); 1.21 (m, 21H); 1.16 (m, 21H); 1.09 (s, 3H); 0.93 (s, 3H).

¹³C NMR (100 MHz, C₆D₆, δ): 152.9, 109.2, 87.8, 87.1, 80.1, 78.9, 78.7, 78.0, 77.2, 76.8, 74.9, 71.7, 70.8, 42.4, 36.0, 34.3, 32.4, 30.6, 29.9, 29.3, 29.0, 27.6, 27.5, 26.2, 25.42, 25.35, 23.1, 22.6, 21.1, 20.1, 19.11, 19.05, 14.12, 14.08.

IR (NaCl, thin film): 3451, 2943, 2866, 1463, 1380, 1082, 883.

HRMS-ESI (m/z): [M + Na]⁺ calcd for C₄₈H₉₂O₇Si₂Na, 859.6274; found, 859.6277.
Synthesis of Alkenyl Iodide 35

Magnesium turnings (245 mg, 10.07 mmol, 375 mol%), HgCl₂ (11 mg, 0.04028 mmol, 1.5 mol%) and I₂ (25 mg, 0.09850 mmol, 3.7 mol%) were purged under argon. Et₂O (8 mL) was added and the mixture was cooled in an ice / water bath. Propargyl bromide (1.2 g, 80% wt solution in toluene, 8.055 mmol, 300 mol%) was added slowly. The brown color disappeared and the addition continued with gentle bubbling. The mixture was stirred in the ice / water bath for 1 h.

In another flask epoxide 11 (500 mg, 2.685 mmol, 100 mol%) was dissolved in Et₂O (45 mL). This solution was cooled to –78 °C. Allenyl magnesium bromide as prepared above was transferred to the epoxide solution over 2 min. White precipitate appeared and stirred became difficult. Temperature was kept below –70 °C for 1 h and then allowed to warm to rt overnight. After a total of 18 h, starting material was all consumed as judged by GCMS. Reaction was cooled to –78 °C and quenched with saturated NH₄Cl. Once the solution was warmed to rt and all solid melted, the solution was diluted with Et₂O and layers were separated. The aqueous layer was extracted again with Et₂O. The organic solution was dried with MgSO₄. Column chromatography isolated 200 mg of alkyne 36, which was mixed with 10% allenyl product (~33% yield).

¹H NMR (400 MHz, CDCl₃, δ): 3.75 (t, J = 8.2 Hz, 1H); 3.62 (d, J = 10.7 Hz, 1H); 2.84 (s, 1H); 2.46-2.25 (m, 3H); 2.06 (m, 1H); 1.93 (t, J = 2.6 Hz, 1H); 1.80 (m, 2H); 1.60 (m, 1H); 1.50 (m, 1H); 1.16 (s, 3H); 1.11 (s, 3H); 1.09 (s, 3H).

¹³C NMR (100 MHz, CDCl₃, δ): 87.7, 85.9, 84.4, 75.2, 70.8, 68.6, 31.4, 30.7, 27.6, 26.8, 24.0, 23.8, 15.8.
Diol 36 (100 mg, 0.4419 mmol, 100 mol%) was dissolved in CH$_2$Cl$_2$ (5 mL) under argon, connected to a condenser. Triethylamine (0.3 mL, 2 mmol, 450 mol%) was added at rt, followed by TIPSOTf (0.29 mL, 1 mmol, 226 mol%). Rinsed the wall of condenser with CH$_2$Cl$_2$ (1 mL). The mixture was heated at 45 °C for 15 h. Once cooled to rt, the reaction was quenched with water. The mixture was diluted with Et$_2$O and the layers were separated. The ether layer was washed with saturated NaHCO$_3$ and dried with MgSO$_4$. Column chromatography separated the alkyne 37 (150 mg, 64%) from the allene isomer (84 mg, 36%) from the previous step.

$^1$H NMR (400 MHz, CDCl$_3$, $\delta$): 3.81 (dd, $J = 5.12$, 6.5 Hz, 1H); 3.72 (dd, $J = 6.5$, 8.6 Hz, 1H); 2.37 (dt, $J = 2.5$, 8.3 Hz, 2H); 2.10-1.80 (m, 4H); 1.92 (t, $J = 2.6$ Hz, 1H); 1.76-1.59 (m, 2H); 1.24 (s, 3H); 1.19 (s, 3H); 1.12 (s, 3H); 1.09 (s, 3H); 1.06 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$): 87.3, 86.2, 85.3, 76.3, 74.3, 68.2, 36.4, 33.5, 28.7, 26.6, 24.9, 21.7, 18.60, 18.58, 18.56, 15.8, 13.6, 13.4.

IR (NaCl, thin film): 3315, 2945, 2867, 2121, 1464, 1174, 883.

HRMS-ESI (m/z): [M + Na]$^+$ calcd for C$_{31}$H$_{62}$O$_3$Si$_2$Na, 561.4130; found, 561.4125.
Alkyne 37 (340 mg, 0.6308 mmol, 100 mol%) was dissolved in anhydrous pentane (6.3 mL) under argon. The solution was cooled in an ice / salt slush bath (–15 °C). B-I-9-BBN (660 µL, 0.6623 mmol, 1M in hexane, 105%) was added. The mixture was stirred in the cold bath for 2.5 h. Temperature slowly rose to 10 °C. AcOH (0.3 mL, ~ 0.5 mL / mmol alkyne) added and the mixture was stirred at ~5 °C for 2 h. The mixture was diluted with hexane (200 mL) and washed twice with a 1:1 mixture of sat. NaHCO₃ / sat. Na₂S₂O₃ solution. The organic fraction was dried with MgSO₄. Column chromatography isolated 362 mg of alkenyl iodide 35 and recovered 33 mg of alkyne 37 (86%, 95% yield BRSM).

^1^H NMR (400 MHz, C₆D₆, δ): 5.87 (s, 1H); 5.60 (s, 1H); 3.81 (t, J = 5.7 Hz, 1H); 3.78 (dd, J = 6.2, 9.2 Hz, 1H); 2.73 (m, 1H); 2.58 (m, 1H); 2.04 (m, 2H); 1.84 (m, 3H); 1.58 (m, 1H); 1.28 (s, 3H); 1.25 (s, 3H); 1.20-1.12 (m, 45H).

^1^3^C NMR (100 MHz, C₆D₆, δ): 125.5, 113.5, 88.0, 86.8, 77.7, 74.7, 43.3, 36.6, 35.5, 29.1, 27.3, 25.5, 22.6, 19.1, 19.03, 19.01, 14.1, 14.0.

IR (NaCl, thin film): 2944, 1617, 1464, 1382, 1172, 1098, 883.

[^2]D –10.0 (c = 3.0, CH₂Cl₂)

HRMS-ESI (m/z): [M + Na]+ calcd for C₃₁H₆₃O₃Si₂Na, 689.3252; found, 689.3274.
Alcohol 15 (11.95 g, 50.13 mmol, 100 mol%) and imidazole (7.5 g, 110 mmol, 220 mol%) were dissolved in DCM (150 mL). TIPSCI (11.8 mL, 55.15 mmol, 110 mol%) was added. The mixture was stirred at rt for 24 h. MeOH (7 mL) was added and the mixture was stirred 2 h at rt. The mixture was diluted with Et₂O, washed with water, and dried with MgSO₄. The crude TIPS ether was used directly.

The crude TIPS and salicylic acid (690 mg, 5 mmol, 10 mol%) were dissolved in DCM. t-BuOOH (13.6 mL, 75 mmol, ~5.5 M in decane) was added at rt, followed by SeO₂ (277 mg, 2.5 mmol, 5 mol%). The mixture was stirred at rt for 7.5 h. Crude was washed with 1:1 NaHCO₃/Na₂S₂O₃. The aqueous layer was extracted with DCM. The organic fraction was dried with MgSO₄. Column chromatography separated products from starting material. The recovered starting material (~10 g) was resubjected to the same reaction condition (350 mg salicylic acid, 6 mL t-BuOOH, 141 mg SeO₂). A total of ~9.3 g alcohols (a mixture regioisomers of allylic oxidation) were obtained.

The allylic alcohols were dissolved in DCM (120 mL). Triethylamine (7.58 mL) added, followed by Ac₂O (2.57 mL). The mixture was stirred 10 h at rt. More triethylamine (1 mL) and Ac₂O (1 mL) were added and the mixture was stirred for another 12 h. MeOH (5 mL) was added and the mixture was stirred 0.5 h. Volatiles were removed. Column chromatography isolated 7.265 g acetate 67 (32% yield from 15).

¹H NMR (500 MHz, C₆D₆, δ): 5.41 (t, J = 6.9 Hz, 1H); 5.14 (t, J = 7.1 Hz, 1H); 4.48 (s, 2H); 3.81 (ddd, J = 5.4, 11.2, 29.3 Hz, 2H); 3.01 (t, J = 5.3 Hz, 1H); 2.11 (m, 4H); 1.96 (m, 2H); 1.71 (s, 3H); 1.60 (m, 1H); 1.55 (s, 3H); 1.50 (s, 3H); 1.45 (m, 1H); 1.16 (s, 3H); 1.10 (m, 21H).

¹³C NMR (125 MHz, C₆D₆, δ): 170.3, 135.2, 131.0, 129.6, 124.8, 70.4, 63.5, 63.4, 60.1, 39.7, 39.2, 27.0, 24.4, 20.9, 18.7, 17.3, 16.3, 14.3, 12.6.
Acetate 67 (6.909 g, 14.74 mmol, 100 mol%) was dissolved in THF (150 mL) and MeOH (66 mL). Aqueous LiOH (44 mL, 22 mmol, 150 mol%, 0.5 M) was added at rt. Stirred 45 min at rt. Dilute with 100 mL 0.25M LiOH and brine. The mixture was extracted with DCM and dried with MgSO₄. Column chromatography isolated 4.9 g allylic alcohol.

Allylic alcohol (4.8 g, 11.249 mmol, 100 mol%) was dissolved in DCM (100 mL). Triethylamine (3.1 mL, 22.50 mmol, 200 mol%) was added. The mixture was cooled to −78 ºC. MsCl (1 mL, 12.94 mmol, 115 mol%) was added. The mixture was stirred 45 min at −78 ºC and −15 ºC to 0 ºC for another 45 min. LiBr (2.44 g, 28.13 mmol, 250 mol%) in THF (11 mL) was added. The mixture was stirred 45 min from 0 ºC to rt. The mixture was diluted with Et₂O and washed with brine. The aqueous layer was extracted with Et₂O. The ether solution was dried with MgSO₄. The crude mesylate was concentrated and used directly.

The crude mesylate was dissolved in THF (150 mL) and cooled to −78 ºC. LiBEt₃H (22.5 mL, 22.5 mmol, 200 mol%, 1M THF) was added. The mixture was stirred at −78 ºC for 1h. The reaction was vented with a needle. Water was added dropwise with mild bubbling observed. The mixture was removed from the cold bath. Once solid melted the mixture was diluted with Et₂O, washed with brine and dried with MgSO₄. Column chromatography isolated 2.9 g alkene 69 (49% yield from acetate 67).

¹H NMR (400 MHz, C₆D₆, δ): 5.12 (t, J = 7.2 Hz, 1H); 3.81 (d, J = 5.1 Hz, 2H); 2.97 (t, J = 5.2 Hz, 1H); 2.53 (m, 1H); 2.07 (m, 2H); 1.65 (s, 3H); 1.63-1.20 (m, 6H); 1.53 (s, 3H); 1.10 (m, 27H).

¹³C NMR (100 MHz, C₆D₆, δ): 131.8, 124.9, 63.7, 63.5, 63.0, 60.3, 59.8, 39.5, 36.2, 26.2, 25.4, 24.6, 18.6, 18.0, 17.2, 17.0, 12.6.
Alkene 69 (400 mg, 0.9739 mmol, 100 mol%) was dissolved in THF (3 mL). TBAF (2 mL, 2 mmol, 200 mol%) was added at rt. After 6 h at rt, the reaction was quenched with water. The mixture was diluted with Et₂O, washed with H₂O and dried with MgSO₄. After removal of solvents, the crude 70 was used directly.

Triphenylphosphine (307 mg, 1.169 mmol, 120 mol%) and imidazole (159 mg, 2.337 mmol, 240 mol%) were dissolved in DCM (5 mL) under argon. The mixture was cooled in an ice / water bath. Iodine (297 mg, 1.169 mmol, 120 mol%) was added in one portion. After most iodide dissolved, alcohol 70 (~0.9739 mmol, crude) in DCM (6 mL) was added. The mixture was stirred in an ice / water bath for 0.5 h and then room temperature for 0.5 h. Most DCM was removed by rotavap. The crude was loaded directly to a silica column (packed in 10% DCM / hexane). Column chromatography isolated the iodide in 86% yield from silyl ether 69.

Diisopropylamine (0.37 mL, 2.621 mmol, 310 mol%) was dissolved in THF (9 mL) and cooled at –78 ºC. n-BuLi (1 mL, 2.5 mmol, 300 mol%, 2.5 M in hexane) was added. The mixture was stirred 30 min at –78 ºC. tert-Butyl acetate (353 µL, 2.621 mmol, 310 mol%) was added. The mixture was stirred 45 min at –78 ºC. Iodide (308 mg, 0.8455 mmol, 100 mol%) in THF (6 mL) was added. After 5 min HMPA (423 µL, 0.5 mL / mmol iodide) was added. The mixture was stirred 40 min at –78 ºC. The mixture was quenched with sat. NH₄Cl. The mixture was removed from the cold bath. Once solid melted the mixture was diluted with Et₂O, washed with NH₄Cl, and dried with MgSO₄. Column chromatography isolated 65 in 82% yield.

¹H NMR (400 MHz, C₆D₆, δ): 5.12 (t, J = 7.1 Hz, 1H); 2.63 (t, J = 6.6 Hz, 1H); 2.53 (m, 1H); 2.26 (m, 2H); 2.39 (m, 2H); 1.90-1.20 (m, 8H); 1.64 (s, 3H); 1.53 (s, 3H); 1.36 (s, 9H); 1.11 (s, 3H); 1.06 (s, 3H).

¹³C NMR (100 MHz, C₆D₆, δ): 172.3, 131.8, 124.9, 80.2, 63.1, 62.6, 60.5, 60.3, 39.5, 36.4, 32.9, 28.4, 26.2, 25.5, 25.1, 24.6, 18.0, 17.0, 16.9.
Diepoxide 65 (40 mg, 0.1135 mmol, 100 mol%) and (1,2,3)-trimethoxybenzene (38 mg, 0.2269, 200 mol%) were dissolved in DCM (3 mL) and cooled to −78 ºC. BF₃·OEt₂ (14 µL, 0.1135 mmol, 100 mol%) was diluted in DCM (0.5 mL) and added to the mixture over 1 min. The mixture was stirred at −78 ºC for 1 h. The mixture was quenched with sat. NaHCO₃. The mixture was removed from the cold bath. Once solid melted the mixture was diluted with Et₂O, washed with NaHCO₃, and dried with MgSO₄. Column chromatography isolated 71 and 72 as inseparable mixture in 30% yield. NOSEY of 71 established its configuration as shown.

71:
¹H NMR (400 MHz, C₆D₆, δ): 5.24 (t, J = 5.9 Hz, 1H); 3.26 (d, J = 10.2 Hz, 1H); 3.12 (dd, J = 5.4, 11.6 Hz, 1H); 2.15 (m, 3H); 1.98 (m, 1H); 1.80-1.00 (m, 8H); 1.72 (s, 3H); 1.58 (s, 3H); 1.12 (s, 3H); 1.09 (s, 3H).
¹³C NMR (100 MHz, C₆D₆, δ): 168.8, 131.5, 125.7, 83.9, 80.3, 79.2, 69.0, 41.6, 37.8, 29.6, 29.0, 26.3, 25.0, 23.2, 20.4, 19.2, 18.1.

The mixture of 71 and 72 (12 mg, 0.04049 mmol, 100 mol%) and imidazole (11 mg, 0.1620 mmol, 400 mol%) were dissolved in DCM (3 mL). Ph₃SiCl (24 mg, 0.08097 mmol, 200 mol%) was added. The mixture was stirred at rt for 14 h. MeOH (0.25 mL) was added and stirred another 1 h. The mixture was diluted with Et₂O, washed with water, and dried with MgSO₄. Column chromatography (packed with toluene) in 2-5% Et₂O / toluene eluted 73 (16 mg) with a small amount of Ph₃Si protected 72. Flushing the column with 50% EtOAc / hexane eluted 72 (3 mg). The structure of 73 was confirmed with a NOSEY experiment.

73:
¹H NMR (600 MHz, C₆D₆, δ): 7.73 (m, 6H); 7.20 (m, 9H); 5.19 (t, J = 7.1 Hz, 1H); 3.75 (d, J = 10.3 Hz, 1H); 2.92 (dd, J = 5.4, 11.6 Hz, 1H); 2.18 (m, 2H); 2.04 (dd, J = 1.7, 7.7, 18.4 Hz, 1H); 1.90 (m, 1H); 1.81 (m, 1H); 1.71-1.10 (m, 7H); 1.70 (s, 3H); 1.57 (s, 3H); 1.37 (s, 3H); 1.06 (s, 3H).
¹³C NMR (100 MHz, C₆D₆, δ): 168.1, 136.2, 135.2, 130.9, 128.7, 125.5, 83.1, 82.2, 80.7, 69.0, 41.1, 37.4, 29.2, 28.7, 26.2, 24.9, 23.1, 20.4, 20.2, 18.1.
To alcohol 71 (9 mg, 0.03036 mmol, 100 mol%) and 4Å molecular sieves (50 mg) was added 1,1,1,3,3,3-hexafluoropropan-2-ol (1 mL) under argon. The slurry was cooled in an ice / water bath. NBS (6 mg, 0.03340 mmol, 110 mol%) was added and the mixture was stirred 10 min. More NBS (4 mg) added and stirred another 5 min. Solvent evaporated and the crude was loaded directly to a silica column (packed in 5% ethyl acetate / hexane). Column chromatography isolated ~ 5 mg (43%) bromides as a 63:37 mixture of diastereomers 66 and epi-66. A NOSEY experiment indicated that the major diastereomer was 66.

66:
\[^1\text{H NMR (400 MHz, C}_6\text{D}_6, \delta): 3.82 (m, 1H); 3.03 (dd, J = 5.4, 11.6 Hz, 1H); 2.96 (d, J = 10.2 Hz, 1H); 2.40-0.50 (m, 12H); 1.33 (s, 3H); 1.16 (s, 3H); 1.05 (s, 3H); 1.02 (s, 3H).\]
\[^{13}\text{C NMR (100 MHz, C}_6\text{D}_6, \delta): 168.1, 84.0, 79.5, 78.2, 76.2, 68.6, 59.7, 41.7, 39.7, 32.0, 29.2, 28.2, 25.8, 25.3, 25.0, 21.0, 20.5.\]

epi-66:
\[^1\text{H NMR (400 MHz, C}_6\text{D}_6, \delta): 4.09 (m, 1H); 4.01 (m, 1H); 3.60 (dd, J = 5.1, 11.7 Hz, 1H); 2.40-0.50 (m, 12H); 1.26 (s, 3H); 1.13 (s, 3H); 1.11 (s, 3H); 0.87 (s, 3H).\]
\[^{13}\text{C NMR (100 MHz, C}_6\text{D}_6, \delta): 168.1, 84.2, 80.1, 76.9, 76.1, 69.6, 66.6, 42.0, 35.2, 29.7, 29.4, 28.7, 28.6, 28.4, 25.6, 21.5, 20.6.\]
22

23
$\text{C}_6\text{D}_6$

30-iodide
32-enol ether
CDCl₃

37
$^{13}C_{6}D_{6}$ ep $^6$NOSEY

$^{13}C_{6}D_{6}$ epi $^{6}$NOSEY

$^{13}C_{6}D_{6}$ ep $^{6}$NOSEY
C_{6}D_{6} HMBC
C₆D₆ HSQC
CURRICULUM VITAE
Sze-Sze Ng

Education

2003–present  Massachusetts Institute of Technology

Pursuing Doctor of Philosophy in Chemistry

- Development of nickel-catalyzed carbon–carbon bond forming reactions under the supervision of Professor Timothy F. Jamison
- Synthetic studies toward ent-dioxepeandehydrothyrsiferol

1999–2003  University of Texas at Austin

Bachelor of Science in Chemistry

- Graduation with honors in May 2003

Professional Experience

2003–present  Massachusetts Institute of Technology

Research Assistant (Professor Timothy F. Jamison)

- Developed nickel-catalyzed, asymmetric reductive coupling of allenes and aldehydes via chirality transfer from chiral allenes
- Developed a new catalytic cycle for a nickel-catalyzed coupling of alkenes, aldehydes and silyl triflates
- Synthetic studies toward ent-dioxepeandehydrothyrsiferol via epoxide-opening cascade

2001–2003  University of Texas at Austin

Undergraduate Research Fellow (Professor Michael J. Krische)

- Developed organocatalytic reactions

Undergraduate Teaching Assistant

- Led recitations of introductory organic chemistry classes

2001   MD Anderson Cancer Center, Houston, TX

Summer  Undergraduate Research Intern (Professor Bimal K. Banik)

- Developed nitration of aromatic compounds on solid support

2000   MD Anderson Cancer Center, Houston, TX

Summer  Undergraduate Research Intern (Professor Bimal K. Banik)

- Synthesized a tricyclic β-lactam via a Heck reaction

Awards

2007–2008  Massachusetts Institute of Technology

- Eli Lilly Graduate Fellowship, 2007–2008

2006–2007  Massachusetts Institute of Technology

- Bristol-Myers Squibb Graduate Fellowship, 2006–2007
Awards (continued from last page)

2003–2004 Massachusetts Institute of Technology
- Dean of Science Teaching Fellow, Spring 2003
- Award for Outstanding Teaching from Chemistry Education Office, 2003–2004

1999–2003 University of Texas at Austin
- University Honors, Fall 1999–May 2003
- Unrestricted Endowed Presidential Scholarship, 2001–2002
- Dorothy B. Banks Scholarship, 2002–2003

Publications


**Presentations**

- **May 2007**  
  Bristol-Myers Squibb Chemistry Symposium, Lawrenceville, NJ

- **June 2007**  
  Roche Symposium – Excellence in Chemistry, Nutley, NJ

- **July 2007**  
  Organic Reactions and Processes Gordon Research Conference, Smithfield, RI (Poster)

- **Aug 2007**  
  ACS National Meeting, Boston, MA

- **Mar 2008**  
  Eli Lilly Grantee Symposium, Indianapolis, IN (Poster)