Progress in Nucleophilic Catalysis and Development of Nickel-Catalyzed Cross-Couplings of Propargylic Halides

by

Sean W. Smith

B.A., Chemistry and Biochemistry, 2004
University of Colorado, Boulder

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

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This doctoral thesis has been examined by a committee of the Department of Chemistry as follows:

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Professor Gregory C. Fu: ________________________________ Thesis Supervisor

Professor Timothy F. Jamison: ________________________________ Committee Member
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ABSTRACT

Chapter 1 describes the development of two organocatalytic processes. The first is a β-alkylation reaction of Michael acceptors, and represents a novel umpolung process catalyzed by N-heterocyclic carbenes. The second section discusses the first successful phosphine-catalyzed, γ-alkylation reaction of isomerizable allenoates. A highly enantioselective variant of this reaction is described.

Chapter 2 discusses nickel-catalyzed cross-coupling reactions of secondary propargylic halides with a variety of organozinc nucleophiles. Section 2.2 describes progress toward an asymmetric alkylation reaction. In Section 2.3, the development of the first alkyl-alkyl secondary-secondary cross-coupling is described; Section 2.4 describes the application of this coupling reaction to the formal synthesis of α-cembra-2,7,11-triene-4,6-diol. The last section of this thesis (Section 2.5) discusses the development of the first asymmetric Negishi reaction of arylzinc reagents with secondary electrophiles.

Thesis Supervisor: Gregory C. Fu
Title: Professor of Chemistry
Preface

Parts of this thesis have been adapted from the following articles written and co-written by the author. The following articles were reproduced in part with permission from the American Chemical Society and Wiley Interscience:

“Umpolung of Michael Acceptors Catalyzed by N-Heterocyclic Carbenes”

“Nickel-Catalyzed Asymmetric Cross-Couplings of Racemic Propargylic Halides with Arylzinc Reagents”

“Nickel-Catalyzed Negishi Cross-Couplings of Secondary Nucleophiles with Secondary Propargylic Electrophiles at Room Temperature”
Acknowledgements

I’ve been looking forward to writing the acknowledgements section of my thesis for some time now, but now that the time has come I’m finding it a bit more difficult than I had imagined. There are so many people over the years that have helped me scientifically or personally to get where I am today. I can only hope that in my actions I’ve already made it clear how much I have appreciated their support.

First of all I would like to thank my advisor, Greg. From the outset of my time in your lab I have had the opportunity to work on interesting projects. I think most importantly, I am appreciative of the level of freedom I’ve been given with respect to project selection and day to day progress. You set the bar high, but have let me figure out how to reach it. You have instilled the importance of independent learning and thoroughness. It’s been an interesting ride; I’ve certainly learned a great deal during my time in your lab and wish you and your future coworkers all the best.

I’d also like to thank my thesis committee chairman, Steve Buchwald; I appreciate your input during our various meetings.

There are many people who played a sizable role in my ending up at M.I.T. in the first place. My first “real” experience in the lab came during my internship at Array in 2001 and I was fortunate to be surrounded by wonderful people, Rob, Kyle and Kevin in particular in the analytical group. When I moved upstairs to try my hand at organic chemistry I couldn’t have found myself with a motlier crew; Todd, Tomas, Pu and Ben, you made for memorable summer of techno music and conversations not appropriate to be reproduced here.

I owe my undergraduate advisor Tarek a great deal of thanks. Not only did you accept me into your lab with minimal experience but you paired me up with an excellent mentor in Aaron Cullen. I learned a lot of things from you Aaron, though I never did develop a love for gambling or Hawaiian shirts. Tarek, I am very appreciative for the help you provided when I began applying to graduate schools and for the conversations we’ve had over the years when I happen to drop in unannounced. I’ve always valued your advice. I also want to thank the rest of the Sammakia lab: the two Marks, Diedre, Christian, Greg and Tim, who put up with my incessant playing of punk music and the Wedding Singer soundtrack.

A great group of people at Replidyne also should be mentioned, the two summers I spent working with Joe, Xicheng, Brian and Ted were a great deal of fun. Of course I want to thank Ming and Steve who I first met during that time. Whether for the days of climbing or the move out to Boston, you both have always been so willing to lend me a hand when I haven’t been in a position to do much for you in return.

During my first project in the group I was paired up with Christian Fischer; an outstanding chemist from whom I learned a great deal. In retrospect it was probably an ideal way to start in the group; a little competition never hurt anyone right? Fran, Steve, and Thomas - I’m glad I overlapped with you guys as well, I benefited greatly from some of your experience and insight. Ryan Wurz I want to thank you for your unwavering willingness to help and for the advice you gave me at about 11:45 one night as we were regenerating a glovebox.

When I first joined the lab Forrest and Luke were more than willing to initiate me, and although I never really did get into moonwalking, it certainly was a source of entertainment. I couldn’t have asked for a better neighbor than you, Luke, during the first couple of years. I don’t think there is a topic we haven’t discussed or debated. Forrest, we were on opposite ends of the lab but I knew I could always get a good chat out of you.
I wouldn’t necessarily have expected to make such good friends in the lab, but the times spent during the middle years with Jon, Mike and Jan are certainly unforgettable. Jon, from the time you let me crash at your place when my apartment flooded to now, you’ve been a great friend. You are one of the brightest people I know and I’m so happy for you, Kate and Nathan. Jan, I don’t imagine I’ll ever meet someone quite like you. Your willingness to try crazy ideas in and out of the lab always kept things interesting. Michael, you are one of the kindest people I know. I truly value the time you were here and I am glad we have stayed in touch.

The last couple of years have brought in a new batch of great people as well. Gerald, you are one of the most talkative and good natured people I think I’ve ever met; I have enjoyed the time we have spent as baymates. Nicolas, I think it is time to grab a coffee. I’ve enjoyed bouncing ideas off of you and all of our eclectic conversations; keep in touch. Max, Xing, Nathan and Sha I have learned from each of you. To the rest of the Fu lab, past and present, I wish you only the best.

I have had the pleasure of interacting quite a bit with our neighbors here on the third floor, the Buchwald lab. Alan, your encyclopedic knowledge puts me to shame, but I keep coming back for more. I may have been the only one from our year to join my lab, but having you right next door made it easier. Joe you are quite the character, it was great getting to know you better near the end of you time here and checking out movies no one else wanted to see. Tim, your sarcasm and irreverence, if not a source of motivation, were certainly entertaining. I’ve been fortunate to find other great people next door as well and I appreciate the conversations I’ve had with many of you. Mark, Pat, Jorge and Nan always had time to talk about whatever.

I want to thank the Muddy Wednesday crew as well: Leo, Xander, Becky, Marvin, Ziad and Galia, though due to our Wednesday group meetings I only showed up about 5% of the time it’s always been nice to know I can count on you guys and you’ve always welcomed me when I did turn up.

I think the biggest thanks of all must be reserved for my family. Grandma and Grandpa, your support has been unwavering and your confidence in me has been religious in fervor, it has meant so much. Elliot, I can’t express how happy I am that we’ve become such good friends, I wish you all of the best for the completion of your own graduate studies.

Mom and Dad there really isn’t anything I can say to you that would appropriately express how much your love and support has meant to me. From an early age you instilled the value of learning and the importance of critical thinking. You’ve always been there for me and listened when I needed to talk. You are my closest friends and this thesis is dedicated to you.
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<tr>
<td>Ac</td>
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<tr>
<td>Ad</td>
<td>adamantyl (tricyclo[3.3.1.1&lt;sup&gt;3&lt;/sup&gt;.7]decyl)</td>
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<tr>
<td>Ar</td>
<td>aryl</td>
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<td>BHT</td>
<td>2,6-di-&lt;i&gt;t&lt;/i&gt;-butyl-4-methylphenol</td>
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<td>BINAP</td>
<td>2,2'-bis(diphenylphosphino)-1,1'-binaphthalene</td>
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<td>Bn</td>
<td>benzyl</td>
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<td>Boc</td>
<td>tert-butoxycarbonyl</td>
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<td>Box</td>
<td>bisoxazoline</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
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<tr>
<td>c</td>
<td>optical rotation concentration (g/mL)</td>
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<tr>
<td>cod</td>
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<td>conv.</td>
<td>conversion</td>
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</tr>
<tr>
<td>d</td>
<td>doublet</td>
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<tr>
<td>DABCO</td>
<td>1,4-diazabicyclo[2.2.2]octane</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
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<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
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<td>DHFR</td>
<td>dihydrofolate reductase</td>
</tr>
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<td>DIBAL</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>diglyme</td>
<td>diethylene glycol dimethyl ether</td>
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<td>DMA</td>
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<td>4-dimethylaminopyridine</td>
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<td>dimethylformamide</td>
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<td>DMI</td>
<td>1,3-dimethyl-2-imidazolidinone</td>
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<td>dimethylsulfoxide</td>
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<tr>
<td>dppp</td>
<td>1,3-bis(diphenylphosphino)propane</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
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<td>Eq</td>
<td>equation</td>
</tr>
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<td>equiv</td>
<td>equivalent</td>
</tr>
<tr>
<td>Et</td>
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<td>Et-BPE</td>
<td>1,2-bis[2,5-diethylphospholano]ethane</td>
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<td>GC</td>
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<td>glyme</td>
<td>1,2-dimethoxyethane</td>
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<td>Hex</td>
<td>hexyl</td>
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<td>HMDS</td>
<td>hexamethyldisilazide</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
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<tr>
<td>HRMS</td>
<td>high-resolution mass spectrometry</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>i</td>
<td>iso</td>
</tr>
<tr>
<td>IC</td>
<td>half maximal inhibitory concentration</td>
</tr>
<tr>
<td>Im</td>
<td>imidazole</td>
</tr>
<tr>
<td>IMes</td>
<td>$N,N'$-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene</td>
</tr>
<tr>
<td>IPr</td>
<td>$N,N'$-bis(2,6-diisopropylphenyl)imidazol-2-ylidene</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LRMS</td>
<td>low-resolution mass spectrometry</td>
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<tr>
<td>m</td>
<td>multiplet</td>
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<tr>
<td>Me</td>
<td>methyl</td>
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<tr>
<td>Mes</td>
<td>mesityl [1,3,5-trimethylphenyl]</td>
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<tr>
<td>mol %</td>
<td>molar percentage</td>
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<tr>
<td>MONOPHOS</td>
<td>(3,5-dioxa-4-phosphacyclohepta[2,1-a;3,4-a']di-napthalen-4-yl)dimethylamine</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>Ms</td>
<td>methanesulfonyl</td>
</tr>
<tr>
<td>MTBE</td>
<td>tert-butylmethyl ether</td>
</tr>
<tr>
<td>MW</td>
<td>molecular weight</td>
</tr>
<tr>
<td>n</td>
<td>normal</td>
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<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
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<td>NHC</td>
<td>N-heterocyclic carbene</td>
</tr>
<tr>
<td>NMO</td>
<td>4-methylmorpholine N-oxide</td>
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<td>NMP</td>
<td>1-methyl-2-pyrrolidinone</td>
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<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
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<tr>
<td>NR</td>
<td>no reaction</td>
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<tr>
<td>o</td>
<td>ortho</td>
</tr>
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<td>para</td>
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<td>pyridinium chlorochromate</td>
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<td>phenyl</td>
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<td>Pr</td>
<td>propyl</td>
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<tr>
<td>q</td>
<td>quartet</td>
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<td>QUINAP</td>
<td>1-(2-diphenylphosphino-1-naphthyl)isoquinoline</td>
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rac racemic
r.t. room temperature
s singlet
s sec
SAR structure activity relationship
sept septet
SIMes $N,N'$-bis(2,4,6-trimethylphenyl)imidazolidin-2-ylidene
SIPr $N,N'$-bis(2,6-diisoproplyphenyl)imidazolidin-2-ylidene
t triplet
t tert
TBS tert-butyldimethylsilyl
TBAF tetrabutylammonium fluoride
TBAT tetrabutylammonium difluorotriphenylsilicate
Tf triflyl [trifluoromethylsulfonyl]
THF tetrahydrofuran
TLC thin layer chromatography
TPAP tetrabutylammonium perruthenate
TIPS triisopropylsilane
TMS trimethylsilane
Ts tosyl [(4-methylphenyl)sulfonyl]
CHAPTER 1

Progress in Nucleophilic Catalysis
Section 1.1

Umpolung of Michael Acceptors Catalyzed by N-Heterocyclic Carbenes
A. Introduction

Carbenes are amongst the most heavily investigated reactive species known to organic chemists.\(^1\) Carbenes are neutral compounds that possess a divalent carbon atom with an electron sextet.\(^2\) A unique subset of carbenes is known as N-heterocyclic carbenes, or NHCs. Scheme 1.1 illustrates the most common structural families of NHCs: thiazolylidene, imidazolylidene, imidazolinylidene and triazolylidene.

Scheme 1.1. Most Common Types of N-heterocyclic Carbenes.

One of the ever expanding applications of NHCs is their use as nucleophilic catalysts.\(^3\) The earliest report of an N-heterocyclic carbene acting as a nucleophilic catalyst was by Ugai in 1943. He showed that naturally occurring thiamin (\textit{NHC}1·HCl) catalyzes the self-condensation of benzaldehyde to generate benzoin.\(^4\) A mechanistic proposal from Breslow\(^5\) (Scheme 1.2) in 1958 suggested that the free base of thiamin adds in a 1,2-fashion to the aldehyde, generating tetrahedral intermediate I, which, following deprotonation, renders the nucleophilic intermediate II. Upon condensation and proton transfer, the adduct III releases the thiamin catalyst and the

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product, benzoin. Although there was some debate\(^6\) about this mechanism, it is now widely accepted.\(^7\)

**Scheme 1.2.** Breslow Mechanism for the Thiamin-Catalyzed Benzoin Condensation.

The study of NHCs as nucleophilic catalysts was a field that lay largely dormant for a considerable number of years. This is possibly a result of the difficulties associated with the synthesis and isolation of free carbenes. In the 1960’s Wanzlick studied the chemistry of NHCs, but never actually isolated them, often handling them in dimeric form.\(^8\) The first reports of

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stable, isolable carbenes by Bertrand\textsuperscript{9} and Arduengo\textsuperscript{2b} in the late 1980’s and early 1990’s sparked a reinvigoration of interest in these unique organocatalysts.

The most extensive applications of NHCs in organocatalysis have been to variants of the benzoin condensation (Scheme 1.3),\textsuperscript{10} the Stetter reaction (Scheme 1.4),\textsuperscript{11} and the umpolung of \(\alpha,\beta\)-unsaturated aldehydes to generate homoenolates (Schemes 1.5 and 1.6).\textsuperscript{12} In addition to inter- and intramolecular variants, the enantioselective benzoin reaction witnessed extraordinary developments as well.\textsuperscript{13,14} The Stetter reaction involves the same acyl anion intermediate (II) as in the benzoin condensation, but here the electrophilic partner is a Michael acceptor, rather than another aldehyde. The Stetter reaction has received at least as much attention\textsuperscript{15} as the benzoin condensation, and it too has seen a large number of enantioselective variants.

\textbf{Scheme 1.3. The Benzoin Condensation.}

\[ R^1\text{CHO} + R^2\text{CHO} \xrightarrow{\text{cat. NHC}} R^1\text{CH(OH)CH(OH)R}^2 \]

\textbf{Scheme 1.4. The Stetter Reaction.}

\[ R^1\text{CHO} + R^2\text{CH=CHR}^3\text{R}^4 \xrightarrow{\text{cat. NHC}} R^1\text{CH(OH)CH(OH)R}^2 \]


Scheme 1.5. NHC-Promoted Generation of a Homoenolate.

Perhaps the most diverse chemistry of NHC catalysis is the umpolung of α,β-unsaturated aldehydes to generate homoenolates (Scheme 1.6). An astounding number of reactions have been developed based on the addition of NHC-generated homoenolates to assorted electrophiles. These reactions include, though are by no means limited to, the addition to: aldehydes, imines, 1,2-cyclohexanedione, α,β-unsaturated aldehydes and α,β-unsaturated ketones. Also, homoenolate adducts have been shown to participate in Diels-Alder cycloaddition reactions with electron-deficient olefins.

Other processes have also been examined with NHCs as nucleophilic catalysts, including transesterification reactions, ring-opening reactions and polymerization reactions, among others.

Scheme 1.6. The Diverse Chemistry of NHC-generated Homoenolates.

In addition to being interesting nucleophilic catalysts, carbenes have also attracted a great deal of attention in the context of ligands for metals. In 2003, Dr. Matthias Eckhardt in the Fu group demonstrated, for the first time, that a carbene could serve as an excellent ligand in the palladium-catalyzed Sonogashira reaction between terminal alkynes and alkyl bromides and iodides (eq 1.1).

That carbenes could be used as ligands in coupling reactions of β-hydrogen containing electrophiles was surely in the mind of Dr. Dave Powell of the Fu group in 2004. During his studies toward the development of a Heck reaction\(^\text{27}\) between alkyl halides and electron-deficient olefins,\(^\text{28}\) he included them as ligands in his broad screen of reaction conditions. It was the incorporation of the NHC IMes as a ligand that led to the observation of product formation for the first time, in 1.2% yield by GC (eq 1.2). In short order, Dr. Powell conducted control experiments that revealed that product was generated more efficiently in the absence of palladium (24%, eq 1.2)!

The fact that this transformation was occurring in the absence of palladium was quite unexpected. It seemed necessary that the NHC itself was catalyzing this reaction. Our mechanistic hypothesis for this remarkable carbene-catalyzed cyclization is presented in Scheme 1.7. The catalyst (Nu:) adds to the electrophilic β carbon of the α,β-unsaturated ester, generating an enolate (A). Tautomerization then affords B, in which the β carbon is now nucleophilic. This represents an umpolung,\(^\text{29}\) as the β carbon of an α,β-unsaturated ester is generally electrophilic.\(^\text{30}\) Intramolecular displacement of the pendant leaving group results in ring formation (C); base mediated elimination releases the product and regenerates the active catalyst.

Dr. Powell moved quickly on this result and screened a variety of related, commercially available, NHC ligands (the free carbenes were generated in situ from the azolium salts via deprotonation with KOt-Bu). Table 1.1 illustrates the activity Dr. Powell observed for a selection of common NHCs in this transformation.


Scheme 1.7. Possible Mechanism for Carbene-catalyzed β-Alkylations of Michael Acceptors.

Table 1.1. Initial NHC·HX Examined in the Cyclization Reaction.
Dr. Powell continued to optimize this reaction, examining the impact of various reaction parameters on product formation. Inorganic bases such as $\text{K}_3\text{PO}_4$, $\text{Cs}_2\text{CO}_3$ and $\text{Rb}_2\text{CO}_3$ consistently outperformed amine and guanidine bases. Upon inspection of other potential NHC-HX precatalysts, both commercially available and easily synthesized ones, Ender’s triazolium carbene precursor$^{31}$ $\text{NHC7-HClO}_4$ proved to be best (Table 1.2, entry 6).

**Table 1.2.** Additional NHC-HX Examined in the Cyclization Reaction.

<table>
<thead>
<tr>
<th>entry</th>
<th>NHC-HX</th>
<th>GC yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NHC1-HCl</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>NHC3-HCl</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>3</td>
<td>NHC4-HCl</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>NHC5-HCl</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>NHC6-HCl</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>NHC7-HClO$_4$</td>
<td>34</td>
</tr>
</tbody>
</table>

Additional optimization of the reaction conditions with $\text{NHC7-HClO}_4$ proved fruitful. In fact, simply changing the reaction solvent from THF to dioxane, and increasing the reaction

---

temperature from 60 °C to 80 °C resulted in a dramatic improvement in yield. It was also observed that when using NHC7-HClO4, KOT-Bu was no longer necessary to generate the free carbene. Under these new conditions, the reaction then gave 82% of the desired product (eq 1.3).

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{OEt} & \quad \text{OEt} \\
\text{OTs} & \quad \text{OTs}
\end{align*}
\]

2.5 equiv K3PO4
dioxane, 80 °C

82% isolated yield

B. Results and Discussion

It was with this very promising starting point by Dr. Powell that I began my work in the Fu group in January of 2005. I was given the task of determining the scope of this reaction and finalizing the reaction conditions. Joining me in this endeavor was Dr. Christian Fischer, who had just recently completed the first catalytic, asymmetric cross-coupling reaction (see Chapter 2, introduction).

In his final report, Dr. Powell made reference to the sensitivity of this reaction, to both oxygen and water. For although NHC-HX, are stable to air, the free NHCs are not. Immediately after we began this project it was clear this was no case of understatement. The reproducibility observed during optimization of this reaction, as well as with our final conditions (vide infra), depended greatly on the quality of the anhydrous solvents used, and the expulsion of all moisture from the solid components. Upon depletion of the supply of K3PO4 used by Dr. Powell, we immediately encountered serious reproducibility problems. After extensive investigation of the proper preparation and quality of various reagents, we began productive study of the scope of this transformation. It should be noted that, for best results, the K3PO4 used in these transformations must be finely ground, dried in a vacuum oven at 150 °C for 24 hours and stored in a N2-filled glovebox.

Of immediate interest to us was the expansion of the scope of this reaction beyond α,β-unsaturated ethyl esters. We envisioned that a number of traditional Michael acceptors should participate in this intriguing cyclization reaction. Gratifyingly, an array of newly prepared Michael acceptors readily participated in the umpolung process. An exception to this general
observation was that under Dr. Powell’s reaction conditions, the cyclization to form a six-membered ring was not efficient (12% yield, eq 1.4).

Thus, in parallel to our preparation of an array of possible substrates, we also devoted time to surveying alternative reaction conditions to ensure we were working with ideal conditions. We hypothesized that perhaps a related NHC catalyst might be able to overcome the shortcomings of NHC7-HClO4. Effort was focused on the preparation of new NHC-HX compounds in the hope that we could find a catalyst capable of facilitating the six-membered ring closure. Early into these efforts we were rewarded with a promising catalyst, NHC8. The synthesis of NHC8-HClO4 is presented in Scheme 1.8. The addition of 4-methoxyaniline to benzoyl chloride cleanly generates N-(4-methoxyphenyl)benzamide, which can be converted into an imidoyl chloride through use of PCl5 at 80 °C. The crude imidoyl chloride is then condensed with the hydrochloride salt of (4-methoxyphenyl)hydrazine to access the immediate NHC8-HClO4 precursor. The triazolium synthesis is completed upon treatment of this material with acetic anhydride and formic acid; exchange of the counter-ion provides NHC8-HClO4 in analogous fashion to the method reported by Enders.
Scheme 1.8. Synthesis of NHC8·HClO4.

Preparation of trianisyl-substituted variant NHC9·HClO4 was carried out following this same route. Attempts to prepare the dimethylamino-variant (NHC10·HClO4) of this catalyst were unsuccessful, as the final triazolium-forming step failed. This failure was attributed to the basic dimethyl amines.

In any event, with NHC8·HClO4 in hand, we were able to finalize a single set of reaction conditions capable of facilitating the cyclization of an array of substrates. Table 1.3 illustrates our conditions, as well as the effect of various parameters on the efficiency of this transformation. Upon examination of Table 1.3, it is clear that the reactivity of the five- and six-membered ring substrates is markedly different. As previously discussed NHC7·HClO4 works quite well for the five-membered ring closure (91%), but not for the six-membered ring closure (37%). Other NHC catalysts are also ineffective at catalyzing this process (entries 4 and 5). A range of alternative classes of nucleophilic catalysts were also found incapable of promoting this
transformation (entries 6-10). Once we had sorted out our base preparation and drying procedure, we found that other inorganic bases could also be used under these reaction conditions (entry 11), but stronger bases such as KOt-Bu were completely ineffective. As held true for a wide range of reaction parameters, the dependence on solvent for the five-membered ring cyclization differed from that for the six-membered ring (entries 13 and 14). Neither ring closure was possible at room temperature, and control reactions showed no reaction in the absence of catalyst or base (entries 16-18).

Table 1.3. The Effect of Various Reaction Parameters on the NHC-Catalyzed β-Alkylation of a Michael Acceptor.

<table>
<thead>
<tr>
<th>entry</th>
<th>change from standard conditions</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n = 1</td>
</tr>
<tr>
<td>1</td>
<td>no change</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>10% NHC8-HClO₄ instead of 10% NHC8-HClO₄</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>10% NHC7-HClO₄ instead of 10% NHC8-HClO₄</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>10% IMes-HCl instead of 10% NHC8-HClO₄</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>10% NHC5-HCl instead of 10% NHC8-HClO₄</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>6</td>
<td>10% DABCO instead of 10% NHC8-HClO₄</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>7</td>
<td>10% DMAP instead of 10% NHC8-HClO₄</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>8</td>
<td>10% quinidinium instead of 10% NHC8-HClO₄</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>9</td>
<td>10% PPh₃ instead of 10% NHC8-HClO₄</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>10</td>
<td>10% PPh₂ instead of 10% NHC8-HClO₄</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>11</td>
<td>2.5 Cs₂CO₃ instead of 2.5 K₃PO₄</td>
<td>87</td>
</tr>
<tr>
<td>12</td>
<td>2.5 KOI-Bu instead of 2.5 K₃PO₄</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>13</td>
<td>dioxane instead of glyme</td>
<td>91</td>
</tr>
<tr>
<td>14</td>
<td>EtOAc instead of glyme</td>
<td>89</td>
</tr>
<tr>
<td>15</td>
<td>DMA instead of glyme</td>
<td>5</td>
</tr>
<tr>
<td>16</td>
<td>rt instead of 80 °C</td>
<td>16</td>
</tr>
<tr>
<td>17</td>
<td>no NHC8-HClO₄</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>18</td>
<td>no K₃PO₄</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by calibrated GC analysis, average of two experiments.

With our final conditions in hand we completed our determination of the scope of this reaction (Table 1.4). With respect to the leaving group, not only bromides (entry 1), but tosylates (entry 2) and even chlorides (entry 3) perform well. In addition to the α,β-unsaturated ethyl ester, α,β-unsaturated allyl esters (entry 4), Weinre amides (entry 5), and nitriles (entries 6 and 7) cyclize with good efficiency. We are also able to prepare an oxygen heterocycle via this
procedure (entry 8). As previously mentioned, six-membered rings are accessible (entry 9). Interestingly, even four-membered rings can be generated, although the yield is somewhat lower (entry 10).

Table 1.4. Scope of the NHC-Catalyzed β-Alkylation of Michael Acceptors.

<table>
<thead>
<tr>
<th>entry</th>
<th>starting material</th>
<th>reaction time (h)</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (X = Br)</td>
<td><img src="entry1.png" alt="Image" /></td>
<td>8</td>
<td>94</td>
</tr>
<tr>
<td>2 (X = OTs)</td>
<td><img src="entry2.png" alt="Image" /></td>
<td>16</td>
<td>94</td>
</tr>
<tr>
<td>3 (X = Cl)</td>
<td><img src="entry3.png" alt="Image" /></td>
<td>8</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td><img src="entry4.png" alt="Image" /></td>
<td>8</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td><img src="entry5.png" alt="Image" /></td>
<td>16</td>
<td>68</td>
</tr>
<tr>
<td>6 (X = Br)</td>
<td><img src="entry6.png" alt="Image" /></td>
<td>8</td>
<td>71</td>
</tr>
<tr>
<td>7 (X = OTs)</td>
<td><img src="entry7.png" alt="Image" /></td>
<td>8</td>
<td>84</td>
</tr>
<tr>
<td>8</td>
<td><img src="entry8.png" alt="Image" /></td>
<td>6</td>
<td>77</td>
</tr>
<tr>
<td>9</td>
<td><img src="entry9.png" alt="Image" /></td>
<td>16</td>
<td>81</td>
</tr>
<tr>
<td>10</td>
<td><img src="entry10.png" alt="Image" /></td>
<td>33</td>
<td>48&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield (average of two experiments). <sup>b</sup> 20% NHC8-HClO<sub>4</sub> was used, with dioxane as the solvent.
According to our proposed mechanism (Scheme 1.7), a tautomerization should take place between the initial addition adduct A and the β-nucleophilic intermediate B. To lend some support to this proposal, we examined the deuterium-exchange process illustrated in eq 1.5. Under our final reaction conditions, NHC8·HClO4 promotes a significant amount of scrambling between the α and β position. This is in sharp contrast to the result with a common nucleophilic catalyst, PBu3, in which essentially no exchange is observed.

As one might expect, there are a number of limitations to the cyclization reaction. Even with the more active NHC8·HClO4, and our best efforts, there were a variety of substrates which did not undergo cyclization. Some of these are illustrated in Scheme 1.9. Alkyl ketones not only did not cyclize, but under the final reaction conditions led to a number of unidentified decomposition products. Although we had success with formation of an oxygen heterocycle, nitrogen-containing substrates often decomposed under the reaction conditions. Attempts to perform a Claisen-type reaction were unsuccessful as well. Interestingly, the six-membered ring precursor bearing an alkyl chloride, rather than bromide, was completely unreactive. Seven- and eight-membered rings are not accessible via this route either. Extensive attempts were made to accomplish an intermolecular variant of this new reaction. In no instance was any desired product observed, no matter the type of alkyl halide used.
**Scheme 1.9.** Inefficient Substrates for the Umpolung Cyclization Reaction.

C. Conclusion

In conclusion, we have demonstrated that, for a range of Michael acceptors, a nucleophilic NHC is capable of catalyzing a unique intramolecular cyclization reaction which most likely proceeds via an umpolung process. Our proposed mechanism includes an unprecedented tautomerization which renders the normally electrophilic β-carbon of the α,β-unsaturated Michael acceptor nucleophilic and allows for an intramolecular β-alkylation to take place. This process was found to be amenable to α,β-unsaturated esters, amides, and nitriles; also a variety of ring sizes may be constructed this way.
D. Experimental

I. General

Unless otherwise noted, all reactions were carried out in oven-dried glassware under an atmosphere of argon. THF and CH₂Cl₂ were purified by passage through an alumina column as described by Grubbs. All chemicals were used without further purification, unless otherwise noted. Melting points were measured on a Hoover melting apparatus and are uncorrected.

The NHC-catalyzed β-alkylations are moisture sensitive. Therefore, before use, the K₃PO₄ must be dried in a vacuum oven at 150 °C for 24 hours (course K₃PO₄, e.g.; from Strem or Alfa-Aesar, must be ground into a fine powder prior to drying). The dry K₃PO₄ is stored in a glovebox.

II. Preparation of Substrates and Catalysts

These procedures have not been optimized.

Preparation of cyclization precursors (representative procedure): A 100-mL flask was charged with pyridinium chlorochromate (2.6 g, 12 mmol), evacuated, and back-filled with argon. To the orange solid were added CH₂Cl₂ (50 mL) and the bromoalcohol (10 mmol). The resultant dark-brown mixture was stirred for 3 hours at r.t., and then Et₂O (50 mL) was added, leading to the precipitation of a brown solid. After standing at r.t. for 2 h the crude aldehyde was filtered through a plug of silica gel under vacuum (washed with Et₂O). The green solution was concentrated and placed in a 100-mL flask under argon. After the addition of THF (50 mL) the Wittig reagent (14 mmol) was added in one portion at r.t. The reaction mixture was then adsorbed onto silica gel and purified by flash chromatography (hexanes/ethyl acetate or pentane/diethyl ether) to give the cyclization precursors as oils.

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33 Generally, the pre-formed phosphonium ylid was used. If the Wittig or Wittig-Horner reagent was generated in situ, the crude aldehyde was added to this mixture at -78 °C and then allowed to warm to r.t.
(E)-Ethyl-7-bromohept-2-enoate [CAS# 111710-77-1]. Prepared from 5-bromopentan-1-ol (TCI) and (carbethoxymethylene)triphenylphosphorane (Alfa-Aesar) by the representative procedure.

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 6.98-6.91 (m, 1H), 5.86-5.82 (m, 1H), 4.22-4.17 (m, 2H), 3.44-3.40 (m, 2H), 2.27-2.22 (m, 2H), 1.92-1.86 (m, 2H), 1.67-1.60 (m, 2H), 1.31-1.28 (m, 3H).

(E)-Ethyl-7-hydroxyhept-2-enoate [CAS# 96251-91-1]. Prepared from tetrahydropyran-2-ol according to a literature procedure.$^{34}$ Into a dried round bottom flask equipped with a magnetic stirbar and under an argon atmosphere was added tetrahydropyran-2-ol (2.40 g, 23.5 mmol), carboethoxymethylene triphenylphosphorane (11.2 g, 32.1 mmol; Alfa-Aesar) and CH$_2$Cl$_2$ (60 mL). The light yellow solution was stirred at room temperature for 48 hours and then concentrated. The resulting solid was taken up in 7:3 hexanes:Et$_2$O (60 mL), and the suspension was stirred at room temperature for 30 minutes, and then was filtered through filter paper on a Hirsch funnel, and was washed with hexanes. The clear filtrate was concentrated to an oil and purified by column chromatography through silica gel, eluting with 70:30 hexanes:EtOAc to give 3.33 g (82%) of the title compound as a light yellow oil. Analysis by $^1$H NMR revealed the product was obtained as an 8:1 mixture of E:Z stereoisomers.

$^1$H NMR (CDCl$_3$, 500 MHz, major isomer) $\delta$ 6.93 (dt, $J = 15.5$, 7.0 Hz, 1H), 5.80 (dt, $J = 15.5$, 1.5 Hz, 1H), 4.15 (q, $J = 7.0$ Hz, 2H), 3.62 (t, $J = 6.0$ Hz, 2H), 2.25-2.18 (m, 2H), 1.93 (br s, 1H), 1.60-1.50 (m, 4H), 1.26 (t, $J = 7.0$ Hz, 3H).

(E)-Ethyl-7-(tosyloxy)hept-2-enoate [CAS# 173043-75-9]. A solution of 7-hydroxyhept-2-enoic acid (3.00 g, 17.4 mmol) and pyridine (2.80 mL, 34.8 mmol) in CH₂Cl₂ (30 mL) was cooled to 0 °C in an ice bath, and tosyl chloride (5.0 g, 26 mmol) was added over a 10 minute period. The suspension was stirred at 0 °C for 1 hour, warmed to r.t., and stirred at this temperature for 16 hours. The reaction mixture was then poured into a 250-mL separatory funnel that contained aqueous HCl (1.0 M; 150 mL) and extracted with Et₂O (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO₄, filtered, and concentrated. Purification by column chromatography (90:10 hexanes:EtOAc) gave 3.58 g (63%) of the desired product as a colorless oil.

¹H NMR (CDCl₃, 500 MHz) δ 7.80 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 6.91-6.85 (m, 1H), 5.79-5.70 (m, 1H), 4.22-4.17 (m, 2H), 4.06-4.03 (m, 2H), 2.47 (s, 3H), 2.19-2.06 (m, 2H), 1.71-1.66 (m, 2H), 1.53-1.47 (m, 2H), 1.32-1.28 (m, 3H).

(E)-Ethyl-7-chlorohept-2-enoate [CAS# 107408-35-5]. Prepared from 5-chloropentan-1-ol (Lancaster) and (carbethoxymethylene)triphenylphosphorane (Alfa-Aesar) by the representative procedure.

¹H NMR (CDCl₃, 500 MHz) δ 6.96-6.90 (m, 1H), 5.85-5.81 (m, 1H), 4.20-4.16 (m, 2H), 3.55-3.52 (m, 2H), 2.23 (q, J = 7.3 Hz, 2H), 1.82-1.76 (m, 2H), 1.65-1.59 (m, 2H), 1.30-1.26 (m, 3H).
(E)-Allyl-7-bromohept-2-enoate. Prepared from 5-bromopentan-1-ol (TCI) and allyl P,P-diethylphosphonoacetate (Aldrich) by the representative procedure.

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.00-6.94 (m, 1H), 6.12-6.09 (m, 1H), 5.98-5.90 (m, 1H), 5.88-5.84 (m, 1H), 5.25-5.23 (m, 1H), 4.64-4.61 (m, 2H), 3.42-3.39 (m, 2H), 2.27-2.22 (m, 2H), 1.91-1.85 (m, 2H), 1.66-1.60 (m, 2H).

$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 166.1, 148.7, 132.2, 121.5, 118.1, 64.9, 33.2, 32.0, 31.2, 26.4.

IR (film) 2940, 2864, 1718, 1654, 1438, 1362, 1252, 1175, 1134, 1026, 988, 932 cm$^{-1}$.

HRMS (EI) calcd for C$_{10}$H$_{15}$BrO$_2$ (M$^+$) 246.0250, found 246.0230.

(E)-7-Bromo-N-methoxy-N-methylhept-2-enamide. Prepared from 5-bromopentan-1-ol (TCI) and N-methoxy-N-methyl-2-(triphenyl-phosphoranylidene)acetamide (Fluka) by the representative procedure.

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 6.98-6.94 (m, 1H), 6.43 (d, $J$ = 6.6 Hz, 1H), 3.71 (s, 3H), 3.44-3.41 (m, 2H), 3.25 (s, 3H), 2.29 (q, $J$ = 7.0 Hz, 2H), 1.93-1.88 (m, 2H), 1.66-1.63 (m, 2H);

$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 167.0, 146.9, 119.4, 61.9, 33.6, 32.5, 32.3, 31.7, 26.9.

IR (film) 3054, 2986, 2969, 2940, 2863, 2360, 2306, 1662, 1629, 1460, 1421, 1384, 1265, 1180, 996 cm$^{-1}$.

HRMS (EI) calcd for C$_9$H$_{16}$BrNO$_2$ (M$^+$) 249.0359, found 249.0491.
(E)-7-Bromohept-2-enenitrile [CAS# 99765-31-8]. Prepared from 5-bromopentan-1-ol (TCI) and (cyanomethyl)triphenylphosphonium chloride (Alfa-Aesar) by the representative procedure. \(^{35}\)

\(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 6.75-6.69 (m, 1H major), 6.53-6.44 (m, 1H minor), 5.36-5.30 (m, 1H major+minor), 3.42 (q, \(J = 6.3\) Hz, 2H major+minor), 2.47 (q, \(J = 6.3\) Hz, 2H minor), 2.26 (q, \(J = 7.2\) Hz, 2H major), 1.91-1.86 (m, 2H major+minor), 1.68-1.60 (m, 2H major+minor).

\(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 155.6, 154.8, 118.0, 101.0, 100.9, 33.8, 33.6, 33.0, 32.5, 32.5, 31.6, 27.3, 26.8.

(E)-6-Cyanohex-5-enyl 4-methylbenzenesulfonate. Prepared from the monotosylate of 1,5-dihydroxypentane\(^{36}\) and (cyanomethyl)triphenylphosphonium chloride (Alfa-Aesar) by the representative procedure. \(^{37}\)

\(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.79 (d, \(J = 8.2\) Hz, 2H major+minor), 7.37 (d, \(J = 8.2\) Hz, 2H major+minor), 6.67-6.61 (m, 1H major), 6.46-6.40 (m, 1H minor), 5.33-5.28 (m, 1H major+minor), 4.06-4.03 (m, 2H major+minor), 2.47 (s, 3H major+minor), 2.40 (q, \(J = 8.2\) Hz, 2H minor), 2.23-2.18 (m, 2H major), 1.71-1.65 (m, 2H major+minor), 1.56-1.49 (m, 2H major+minor).

\(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 155.4, 154.6, 145.6, 133.6, 130.6, 130.5, 128.6, 128.5, 117.9, 101.1, 101.0, 70.5, 70.4, 33.2, 33.1, 31.7, 28.8, 24.8, 24.2, 22.3.

IR (film) 3055, 2987, 2305, 1722, 1712, 1598, 1422, 1358, 1265, 1177 cm\(^{-1}\).

LRMS (ESI) calcd for C\(_{14}\)H\(_{17}\)NNaO\(_3\)S (M+Na\(^+\)) 302.1, found 302.1.

\(^{35}\) Compound was isolated and used in a 2:1, (E):(Z), isomeric mixture.


\(^{37}\) Compound was isolated and used in a 1.7:1, (E):(Z), isomeric mixture.
(E)-Ethyl 4-(2-bromoethoxy)but-2-enoate [CAS# 439665-65-3].

\[ \text{H NMR (CDCl}_3, 500 \text{ MHz}) \delta 6.96-6.92 \text{ (m, 1H), 6.12-6.09 (m, 1H), 4.23-4.19 (m, 4H), 3.80 (t, J = 6.1 Hz, 2H), 3.49 (t, J = 6.1 Hz, 2H), 1.31-1.27 (m, 3H).} \]

(E)-Ethyl-8-bromooct-2-enoate. Prepared from 6-bromohexan-1-ol (TCI) and (carbethoxymethylene)triphenyl-phosphorane (Alfa-Aesar) by the representative procedure.

\[ \text{H NMR (CDCl}_3, 500 \text{ MHz}) \delta 6.94 \text{ (dt, J = 15.6, 7.0 Hz, 1H), 5.82 (ddd, J = 15.6, 1.5, 0.9 Hz, 1H), 4.20-4.16 (m, 2H), 3.42-3.39 (m, 2H), 2.24-2.20 (m, 2H), 1.90-1.84 (m, 2H), 1.51-1.45 (m, 4H), 1.30-1.27 (m, 3H).} \]

\[ \text{C NMR (CDCl}_3, 125 \text{ MHz}) \delta 166.6, 148.7, 121.6, 60.2, 33.6, 32.5, 31.9, 27.6, 27.1, 14.2. \]

\[ \text{IR (film) 2981, 2936, 2860, 1717, 1655, 1463, 1445, 1367, 1308, 1268, 1241, 1221, 1187, 1134, 1096, 1043, 981 cm}^{-1}. \]

\[ \text{HRMS (EI) calcd for C}_{10}\text{H}_{17}\text{BrO}_2 (M^+) 248.0406, found 248.0411.} \]

(E)-Ethyl-6-bromohex-2-enoate [CAS# 71032-10-5]. Prepared from 4-bromobutan-1-ol (TCI) and (carbethoxymethyl-ene)triphenylphosphorane (Alfa-Aesar) by the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 6.98-6.91 (m, 1H), 5.91-5.85 (m, 1H), 4.20 (q, $J$ = 7.1 Hz, 2H), 3.42 (t, $J$ = 6.3 Hz, 2H), 2.40-2.36 (m, 2H), 2.06-2.00 (m, 2H), 1.29 (t, $J$ = 7.1 Hz, 3H).

NHC$_8$HClO$_4$. A 500-mL flask was charged with N-(4-methoxyphenyl)benzamide (24.9 g, 0.109 mol; TCI) and PCl$_5$ (22.9 g, 0.110 mol), evacuated, and back-filled with argon. The flask was fitted with a nitrogen-filled balloon and the mixture heated to 80 °C. Gas evolution was observed and the yellow-green solution was stirred for 90 minutes. The reaction mixture was cooled to r.t., and the volatiles were removed under reduced pressure. Solidification occurred and a green solid was obtained which was used directly in the next step without purification ($^1$H NMR analysis indicated complete conversion to the imidoyl chloride).

To the green solid was added THF (150 mL) and NEt$_3$ (42 mL, 0.30 mol) which led to discoloration. To the suspension was added 1-(4-methoxyphenyl)hydrazine hydrochloride (19.3 g, 0.110 mol; TCI) as a slurry in THF (100 mL) via a solid addition funnel slowly over the course of 30 minutes. The yellow suspension was stirred at r.t. for 18 h, then the volatiles were completely removed on a rotary evaporator. Acetic acid (2% aqueous solution, 200 mL) was added and the mixture stirred vigorously. The mixture was extracted with CH$_2$Cl$_2$ (5 x 100 mL), and the combined extracts washed with brine and dried over Na$_2$SO$_4$. Solvent evaporation gave a red oil/foam. The material (A) was used without purification in the subsequent step.

In a separate 500-mL 2-necked flask was mixed acetic anhydride (150 mL) and formic acid (75 mL) under argon. The mixture was heated to 60 °C for 20 minutes, then cooled to r.t. and transferred to A via cannula under argon. The red solution was stirred for 36 h at r.t. The volatiles were subsequently removed on a rotary evaporator and high vacuum. To the crude
Material was added perchloric acid (35% aqueous solution, 150 mL) and CH₂Cl₂ (150 mL). The mixture was stirred vigorously and after 30 minutes the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 100 mL) and the combined organic layers washed with brine, then dried over Na₂SO₄. Solvent evaporation gave a red oil which was dried on high vacuum for two days. Purification of the triazolium salt was achieved by repeated slow crystallization from acetone/diethyl ether at -20 °C. The obtained crude triazolium perchlorate was further purified by recrystallization from CH₂Cl₂ to give the title compound (4.81 g, 10% over all steps) as a colorless fluffy solid.

mp: 220 °C (methylene chloride);

¹H NMR (DMSO-d₆, 500 MHz) δ 11.16 (s, 1H), 8.00 (d, J = 8.8 Hz, 2H), 7.64-7.54 (m, 7H), 7.31 (d, J = 8.9 Hz, 2H), 7.20 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H), 3.84 (s, 3H).

¹³C NMR (DMSO-d₆, 125 MHz) δ 162.2, 161.9, 154.3, 133.4, 130.4, 130.4, 129.2, 129.1, 125.7, 123.7, 123.5, 116.5, 116.3, 57.0, 56.9.

IR (film) 3062, 2840, 1608, 1564, 1508, 1488, 1451, 1307, 1261, 1025, 834, 733, 694, 623 cm⁻¹.

HRMS (ESI) calcd for C₂₂H₂₀N₃O₂ (M⁺) 358.1550, found 358.1557; HRMS (ESI) calcd for ClO₄⁻ (M⁻) 98.9480, found 98.9483.

NHC9·HClO₄. A 500-mL, 2-necked, flask fitted with a reflux condenser was charged with p-methoxybenzoyl chloride (13.8 mL, 0.100 mol; TCI), evacuated, and back-filled with argon. Toluene (120 mL) was then added, followed by p-anisidine (12.3 g, 0.100 mol; Alfa-Aesar), while keeping the flask under a stream of argon. The amine slowly dissolved and precipitation occurred. The reaction mixture was heated to 120 °C overnight. The suspension was cooled to r.t. and filtered through a glass frit. The solid was washed with hexanes and dried

39 Initial crystallization can be difficult; it requires diluted conditions and may take up to 5 days.
40 CH₂Cl₂ was added at reflux until almost all solid had dissolved. After cooling to r.t. the mixture was cooled to -20 °C for 12 h and the crystallized solid collected with a filter frit. The solid was washed with a little cold CH₂Cl₂ and diethyl ether.
under high vacuum overnight. The amide (25.5 g) was obtained as a colorless, slightly violet solid which was used without further purification.

A 100-mL flask was charged with 4-methoxy-N-(4-methoxyphenyl)benzamide (5.15 g, 20.0 mmol) and PCl₅ (4.16 g, 20.0 mol), evacuated, and back-filled with argon. The flask was fitted with a nitrogen-filled balloon and the mixture was heated to 80 °C. Gas evolution was observed and the yellow-green solution was stirred for 2 h. The reaction mixture was cooled to r.t. and the volatiles removed at reduced pressure, leading to a green solid that was used in the next step without further purification (¹H NMR analysis indicated complete conversion to the imidoyl chloride).

To the green solid was added THF (60 mL), 1-(4-methoxyphenyl)hydrazine hydrochloride (3.50 g, 20.0 mmol; TCI), and NEt₃ (6.3 mL, 45 mmol). [CAUTION: While we have not observed an exotherm when conducting the reaction on this scale, the hydrazine addition on larger scale has led to significant warming of the reaction mixture. For large-scale reactions, we advise that the hydrazine be added as a slurry in THF (see preparation of 1).] The yellow suspension was stirred at r.t. for 20 h, and then the volatiles were removed on a rotary evaporator. Acetic acid (2% aqueous solution; 50 mL) was added and the mixture was stirred vigorously for 15 minutes. The mixture was extracted with CH₂Cl₂ (3 x 100 mL), and the combined extracts were washed with brine and dried over Na₂SO₄. Solvent evaporation gave a red oil/foam. The material was used without purification in the subsequent step.

In a separate 250-mL, 2-necked, flask was mixed acetic anhydride (50 mL) and formic acid (25 mL) under argon. The mixture was heated to 60 °C for 20 minutes, then cooled to r.t. and transferred to the amidine via cannula under argon. The red solution was stirred for 20 h at r.t. The volatiles were subsequently removed on a rotary evaporator and high vacuum. To the crude material was added perchloric acid (35% aqueous solution, 50 mL) and CH₂Cl₂ (50 mL). The mixture was stirred vigorously and after 30 minutes the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 50 mL) and the combined organic layers washed with brine and dried over Na₂SO₄. Solvent evaporation gave a red oil which was dried on high vacuum for two days. Crystallization of the triazolium salt was achieved using CH₂Cl₂/hexanes at -20 °C. The obtained crude triazolium perchlorate was purified by recrystallization from CH₂Cl₂ to give the title compound (1.07 g, 11% over all steps) as a beige fluffy solid.

mp: 112 °C
$^1$H NMR (DMSO-d$_6$, 500 MHz) $\delta$ 11.08 (s, 1H), 7.98 (d, $J$ = 9.2 Hz, 2H), 7.61 (d, $J$ = 8.9 Hz, 2H), 7.46 (d, $J$ = 8.8 Hz, 2H), 7.29 (d, $J$ = 9.2 Hz, 2H), 7.21 (d, $J$ = 8.9 Hz, 2H), 7.08 (d, $J$ = 8.8 Hz, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H).

$^{13}$C NMR (DMSO-d$_6$, 125 MHz) $\delta$ 162.0, 161.0, 160.7, 153.1, 130.8, 128.1, 128.0, 124.7, 122.3, 115.3, 115.2, 114.7, 114.4, 55.8, 55.8, 55.6.

IR (film) 3073, 2940, 2841, 1611, 1508, 1498, 1307, 1259, 1176, 1027, 835, 623 cm$^{-1}$.

HRMS (ESI) calcd for C$_{23}$H$_{22}$N$_3$O$_3$ (M$^+$) 388.1656, found 388.1653; HRMS (ESI) calcd for ClO$_4$ (M$^-$) 98.9480, found 98.9484.
Part III: NHC-Catalyzed β-Alkylations

Note: The NHC-catalyzed β-alkylations are moisture sensitive. Please see refer to the General section of this experimental for details.

General Procedure for Table 1.3. In a glove box, a 4-mL vial was charged with catalyst NHC8-HClO4 (4.6 mg, 0.010 mmol), K3PO4 (53 mg, 0.25 mmol), glyme (0.8 mL), and (E)-ethyl 8-bromooc-2-enoate (24.9 mg, 0.100 mmol). The vial was closed with a teflon cap, sealed with electrical tape, removed from the glove box, and immerged in a pre-heated oil bath at 80°C. After 16 h the vial was removed from the oil bath and 19 μl n-decane (0.10 mmol) was added. A couple of drops from the reaction mixture were passed through a plug of silica gel with diethyl ether. The filtrate was analyzed by GC to determine the conversion.

General Procedure for Table 1.4. In a glove box, a 20-mL vial was charged with catalyst NHC8-HClO4 (46 mg, 0.10 mmol), K3PO4 (0.53 g, 2.5 mmol; run 1: Strem; run 2: Lancaster), glyme (8 mL; Fluka, anhydrous), and the substrate (1.00 mmol). The vial was closed with a teflon cap, sealed with electrical tape, removed from the glove box, and immerged in a pre-heated oil bath at 80°C. After the indicated time, the vial was removed from the oil bath and the reaction mixture directly purified by flash chromatography (pentane/Et2O).

For entries 2, 6, 7, and 8 of Table 1.4, a small amount of isomerization to the β,γ-unsaturated product was observed if a long reaction time was employed.

Ethyl-2-cyclopentylideneacetate (Table 1.4, Entry 1) [CAS# 1903-22-6]. The compound was prepared according to the General Procedure. Reaction time: 8 hours. After chromatography on silica gel (pentane/Et2O 20:1), the desired compound was isolated as a colorless oil: run 1: 146 mg (95%); run 2: 143 mg (93%).

1H NMR (CDCl3, 500 MHz) δ 5.80-5.79 (m, 1H), 4.17-4.12 (m, 2H), 2.78-2.75 (m, 2H), 2.45-2.42 (m, 2H), 1.77-1.72 (m, 2H), 1.69-1.63 (m, 2H), 1.29-1.26 (m, 3H).
Ethyl-2-cyclopentylideneacetate (Table 1.4, Entry 2) [CAS# 1903-22-6]. The compound was prepared according to the General Procedure. Reaction time: 16 hours. After chromatography on silica gel (pentane/Et$_2$O 20:1), the desired compound was isolated as a colorless oil: run 1: 144 mg (94%); run 2: 143 mg (93%).

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 5.80-5.79 (m, 1H), 4.17-4.12 (m, 2H), 2.78-2.75 (m, 2H), 2.45-2.42 (m, 2H), 1.77-1.72 (m, 2H), 1.69-1.63 (m, 2H), 1.29-1.26 (m, 3H).

Ethyl-2-cyclopentylideneacetate (Table 1.4, Entry 3) [CAS# 1903-22-6]. The compound was prepared according to the General Procedure. Reaction time: 8 hours. After chromatography on silica gel (pentane/Et$_2$O 20:1), the desired compound was isolated as a colorless oil: run 1: 136 mg (88%); run 2: 139 mg (90%).

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 5.80-5.79 (m, 1H), 4.17-4.12 (m, 2H), 2.78-2.75 (m, 2H), 2.45-2.42 (m, 2H), 1.77-1.72 (m, 2H), 1.69-1.63 (m, 2H), 1.29-1.26 (m, 3H).

Allyl-2-cyclopentylideneacetate (Table 1.4, entry 4). The compound was prepared according to the General Procedure. Reaction time: 16 hours. After chromatography on silica gel (pentane/Et$_2$O 20:1), the desired compound was isolated as a colorless oil: run 1: 148 mg (89%); run 2: 144 mg (87%).
\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz) \(\delta\) 5.97-5.90 (m, 1H), 5.83 (d, \(J = 1.8\) Hz, 1H), 5.32 (dd, \(J = 18.6, 17.1\) Hz, 1H), 5.21 (d, \(J = 10.4\) Hz, 1H), 4.60-4.59 (m, 2H), 2.79-2.76 (m, 2H), 2.54-2.43 (m, 2H), 1.77-1.61 (m, 4H).

\textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75 MHz) \(\delta\) 169.9, 166.5, 132.7, 117.7, 111.3, 64.3, 36.0, 32.7, 26.4, 25.5.

IR (film) 2960, 1872, 1717, 1653, 1455, 1419, 1371, 1352, 1303, 1272, 1231, 1194, 1153, 1119, 1027, 993, 929, 857 cm\textsuperscript{-1}.

HRMS (EI) calcd for C\textsubscript{10}H\textsubscript{13}O\textsubscript{2} (M-H\textsuperscript{+}) 165.0916, found 165.0909.

![Structure 1](image1)

\textbf{2-Cyclopentylidene-\textit{N}-methoxy-\textit{N}-methylacetamide (Table 1.4, entry 5).} The compound was prepared according to the General Procedure. Reaction time: 8 hours. After chromatography on silica gel (pentane/Et\textsubscript{2}O 1:1), the desired compound was isolated as a colorless oil: run 1: 115 mg (68%); run 2: 114 mg (67%).

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz) \(\delta\) 6.33-6.31 (m, 1H), 3.70 (s, 3H), 3.20 (s, 3H), 2.84-2.81 (m, 2H), 2.49-2.46 (m, 2H), 1.76-1.73 (m, 2H), 1.67-1.64 (m, 2H).

\textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz) \(\delta\) 168.9, 167.9, 109.6, 62.1, 37.0, 33.1, 33.0, 27.3, 26.1.

IR (film) 3583, 3503, 3257, 3063, 2958, 2870, 2823, 1659, 1631, 1462, 1407, 1381, 1324, 1178, 1091 cm\textsuperscript{-1}.

HRMS (EI) calcd for C\textsubscript{9}H\textsubscript{15}NO\textsubscript{2} (M\textsuperscript{+}) 169.1097, found 169.1100.

![Structure 2](image2)

\textbf{2-Cyclopentylideneacetonitrile (Table 1.4, entry 6) [CAS# 5732-88-7].} The compound was prepared according to the General Procedure. Reaction time: 8 hours. Upon cooling, the reaction mixture was diluted with CH\textsubscript{2}Cl\textsubscript{2} (30 ml), transferred to a 150-mL separatory funnel and washed with distilled water (3 x 20 mL) and once with brine (50 mL). The organic layer was dried over Na\textsubscript{2}SO\textsubscript{4}. After filtration through a fritted funnel, the organic layer was concentrated.
The resultant dark-red oil was purified via kugelrohr distillation at 120 °C (10 torr; if the product was purified by flash chromatography, ~20% of the β,γ-unsaturated isomer was observed). The desired compound (20:1 mixture of the α,β: β,γ-unsaturated isomers) was isolated as a colorless oil: run 1: 78 mg (72%); run 2: 75 mg (70%).

1H NMR (CDCl₃, 300 MHz) δ 5.25-5.23 (m, 1H), 2.62-2.58 (m, 2H), 2.48-2.43 (m, 2H), 1.82-1.77 (m, 4H).

2-Cyclopentylideneacetonitrile (Table 1.4, entry 7) [CAS# 5732-88-7]. The compound was prepared according to the General Procedure. Reaction time: 8 hours. Upon cooling, the reaction mixture was diluted with CH₂Cl₂ (30 ml), transferred to a 150-mL separatory funnel and washed with distilled water (3 x 20 mL) and once with brine (50 mL). The organic layer was dried over Na₂SO₄. After filtration through a fritted funnel, the organic layer was concentrated via a rotary evaporator. The resultant dark-red oil was purified via kugelrohr distillation at 120 °C (10 torr; if the product was purified by flash chromatography, ~20% of the β,γ-unsaturated isomer was observed). The desired compound (20:1 mixture of the α,β: β,γ-unsaturated isomers) was isolated as a colorless oil: run 1: 92 mg (86%); run 2: 88 mg (82%).

1H NMR (CDCl₃, 300 MHz) δ 5.25-5.23 (m, 1H), 2.62-2.58 (m, 2H), 2.48-2.43 (m, 2H), 1.82-1.77 (m, 4H).

Ethyl-2-(dihydrofuran-3(2H)-ylidene)acetate (Table 1.4, entry 8). The compound was prepared according to the General Procedure. Reaction time: 6 hours. After chromatography on silica gel (pentane/Et₂O 6:1 → 3:1), the desired compound (2:1 mixture of the illustrated olefin isomers, along with ~5% of an unidentified isomer) was isolated as a colorless oil: run 1: 117 mg (75%); run 2: 124 mg (79%).
\(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 5.86-5.85 (m, 1H major), 5.80-5.79 (m, 1H minor), 4.72 (m, 2H major), 4.39 (m, 2H minor), 4.20-4.14 (m, 2H major+minor), 3.98 (d, \(J = 7.0\) Hz, 2H minor), 3.90-3.87 (m, 2H major), 3.05-3.02 (m, 2H minor), 2.74-2.71 (m, 2H major), 1.31-1.24 (m, 3H major+minor).

\(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 166.3, 166.1, 162.7, 161.7, 111.4, 110.2, 72.0, 71.5, 68.9, 67.0, 60.0, 59.9, 34.4, 32.6, 17.9, 14.3.

IR (film) 2981, 2860, 1710, 1667, 1373, 1351, 1215, 1124, 1076, 1035, 921, 851 cm\(^{-1}\).

HRMS (EI) calcd for C\(_8\)H\(_{12}\)O\(_3\) (M\(^+\)) 156.0781, found 156.0784.

**Ethyl-2-cyclohexylideneacetate (Table 1.4, entry 9) [CAS# 1552-92-7]**. The compound was prepared according to the General Procedure. Reaction time: 16 hours. After chromatography on silica gel (pentane/Et\(_2\)O 20:1), the desired compound was isolated as a colorless oil: run 1: 135 mg (80%); run 2: 136 mg (81%).

\(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 5.60 (s, 1H), 4.16-4.11 (m, 2H), 2.83-2.81 (m, 2H), 2.20-2.18 (m, 2H), 1.67-1.57 (m, 4H), 1.29-1.26 (m, 3H).

**Ethyl-2-cyclobutylideneacetate (Table 1.4, entry 10) [CAS# 27741-65-7]**. The compound was prepared according the other General Procedure, except that 20% of catalyst NHC\(_8\)HClO\(_4\) was used, and dioxane was employed as the solvent (a slightly lower yield was obtained when glyme was used). Reaction time: 33 hours. After chromatography on silica gel (pentane/Et\(_2\)O 20:1), the desired compound was isolated as a colorless oil: run 1: 66 mg (47%); run 2: 70 mg (49%).

\(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 5.59-5.57 (m, 1H), 4.14 (q, \(J = 7.2\) Hz, 2H), 3.15-3.12 (m, 2H), 2.85-2.83 (m, 2H), 2.09 (quintet, \(J = 7.9\) Hz, 2H), 1.27 (t, \(J = 7.2\) Hz, 3H).
E. $^1$H NMR Spectra of Selected Compounds
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expl szpul

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STANDARD PROTON PARAMETERS

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ACQUISITION

DEC. & VT

PROCESSING

DISPLAY
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### Chemical Shifts

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- **3.51**
- **4.00**
- **1.45**
- **4.70**
- **1.57**
- **6.45**
- **2.98**
- **4.58**
STANDARD PROTON PARAMETERS

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file  /data/export/-home/gfu/Tcf/bullwinkle/CF6-011fr37-50.fld
home/gfu/tcf/bullwinkle/dof 1498.1
link/CF6-011fr37--dm  nnn

ACQUISITION
def 16000
sfrq 499.749
fb  not used
sw 9988.0

PROCESSING

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rfp  0
th  7
ins  3.00
nn cdc ph
EXPL STDIH

SAMPLE
DATE Oct 19 2005
SOLVENT CDC13
FILE /data/export/~
HOME/GFU/TSM/MR Hat-
/TSM-02-086-pure.f-
ID
date Oct 19 2005
DEC. & VT

ACQUISITION

SFRQ 300.100
AT 1.895
NP 17984
SW 4598.5
FB not used
BS 16
TPWR 54
PW 7.0
D1 1.000
TOF 0
NT 16
CT 16
ALOCK n
GAIN not used

DISPLAY

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VS 152
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WC 250
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IS 303.43
RFL 2888.6
RFP 2181.7
TH 20
INS 1.000
NM CDC PH

DEC. & VT PROCESSING

W FILE

PPM

0.33 1.00
0.98
2.19 2.13
2.23 2.17
0.50 3.36

STANDARD IN OBSERVE

HBr

CH3CO

Et
STANDARD PROTON PARAMETERS

exp2 s2pul

Sample: date Jul 10 2005

Dec. & VT: dfrq 125.675

Solvent: DMSO dm 313

File: /data/export/ dpwr 34

Home: /home/gfu/tcf/bulw= dof 1498.1

Inkbe/PMPx2carbene= dm nnn

H.fld dmm w

ACQUISITION: dmf 10000

Sfrq 499.751 dsaq

Nh 11 dres 1.0

At. 3.277 Homo n

Sw 9988.8 wtfile

Nb not used proc ft

Bs 6 fn 65536 f

Tpwr 56 math f

Pw 8.2

Dl 3.000 werr

Tof 1498.1 wexp

Ct 16 wbs

Ct 16 wnt

Alock n

Gain not used

Flags: n

Display: n

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Sc 0

Wc 250

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Rfp 0

Th 7

Lin 4.000

Cdc

Ph C104

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ppm

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Table 1.4, entry 1
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Table 1.4, entry 2

![Carbon Dioxide Et diagram]
STANDARD PROTON PARAMETERS

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Solvent: CDC13
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ACQUISITION

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sw 9998.8
np 65536
fb not used
np 3.998
sw 14.883
nt 16
ct 8

DISPLAY

sp -11.8
wp 4001.6
sc 224
tc 0
wc 250
ht 16.01
is 1000.76
rf 4697.5
rf 3628.1

Table 1.4, entry 3
STANDARD PROTON PARAMETERS

Sample

Date: Aug 11 2005
Solvent: CDC13
File: /data/export/~gfu/Tcf/bullinkle/CF6-074fr16--32.fid

Acquisition

Sfrq: 499.749
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Fb: not used
Bs: 8
Tpwr: 56
Pw: 8.2
D1: 3.000
Tof: 1448.1
Nt: 16
Ct: 16
Allok: n
Gain: not used

Flags

Sp: 488.0
Wp: 3507.8
Vs: 69
Sc: 0
Wc: 250
Hzma: 14.03
Is: 718.64
Rfj: 4857.8
Rfp: 3628.1
Th: 7
Rms: 2.000

Display

Table 1.4, entry 4

- Table with entries and ppm values

- Graph with peaks and labels

- Chemical structure

- Notes and remarks
Table 1.4, entry 5
STANDARD IN OBSERVE

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| fb    | not used |
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| pw    | 7.0     |
| di    | 1.000   |
| tof   | 0       |
| nt    | 15      |
| ct    | 15      |
| alock | n       |
| gain  | not used |

FLAGS

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| in    | n       |
| dp    | y       |

DISPLAY

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| wp    | 2037.1  |
| vs    | 162     |
| sc    | 0       |
| wc    | 250     |
| hzmm  | 8.15    |
| is    | 138.93  |
| rfl   | 2898.6  |
| rfp   | 2181.7  |
| th    | 20      |
| ins   | 1.000   |
| nm    | cdc     |
| ph    | 0.32    |

Table 1.4, entry 6
Table 1.4, entry 7
STANDARD PROTON PARAMETERS

Sample: s2pul

Date: Oct 2 2005

Solvent: CDCl3

File: /data/export/dpwr

 Acquisition: 1H dseq 1.0

 Flags: n

Displacement: 4.1

Table 1.4, entry 8
Table 1.4, entry 9
Table 1.4, entry 10
Section 1.2

Asymmetric, Phosphine-Catalyzed $\gamma$-Alkylation of Allenoates with Nitromethane
A. Introduction

Similar to N-heterocyclic carbenes, it has only been relatively recent that the area of nucleophilic phosphine catalysis has seen a significant increase in development.\(^\text{41}\) Phosphines, long used as ligands for transition metal-catalyzed transformations,\(^\text{42}\) display a unique reactivity of their own in processes involving electron-deficient unsaturated carbon-carbon bonds,\(^\text{43,44}\) and as catalysts for the acylation of alcohols.\(^\text{45}\) Tricoordinate phosphorus compounds are fairly configurationally stable and bear a lone pair of electrons. This lone pair is responsible for much of the reactivity associated with phosphines, which tend to be less basic and more nucleophilic than amines. These properties taken together not only make phosphines interesting nucleophilic catalysts, but allow for the synthesis of \(P\)-chiral compounds for asymmetric catalysis.

The study of nucleophilic phosphine-catalyzed activation of alkynoates and allenoates found its roots in the discovery by Trost, in 1992, that phosphines were capable of catalyzing the isomerization of conjugated alkynoates and allenoates to dieneoates. This communication\(^\text{46}\) laid the groundwork for a wealth of new developments. The reaction displayed a broad scope: conjugated ketones, esters and amides participated in this process. It was also noted that unconjugated alkynes were unreactive and that ketones reacted much more rapidly than amides (Scheme 1.10).


Scheme 1.10. Phosphine-Catalyzed Isomerization Reaction Developed by Trost.

It was soon found that, through use of alkynoates incapable of isomerization to the diene, reaction intermediates could be intercepted by various strategies to carry out other transformations. In 1994, Trost published a PPh₃-catalyzed γ-addition of a wide variety of acidic carbon pronucleophiles (pKₐ < 16) to alkynoates incapable of isomerizing to the diene.⁴⁷ This method displayed a broad scope with respect to the incoming pronucleophile (Scheme 1.11). A buffer was required for high efficiency; it was believed this assisted proton transfers.

Scheme 1.11. Trost’s Umpolung γ-Alkylation of a Non-Isomerizable Alkynoates.

The work of Trost, and coworkers, set the groundwork for an asymmetric variant of this reaction developed by Zhang in 1998, in which the new chiral center is generated on the incoming pronucleophile (Scheme 1.12). Zhang made use of their newly developed phospa-bicyclo[2.2.1]heptane catalyst, and found that modest to good levels of enantioselectivity could be obtained with cyclic pronucleophiles. Under the buffered conditions, only substrates that would lead to the formation of quaternary stereocenters were presented. It is worth noting that, unlike the process described by Trost, this report made use of allenoates, and could be carried out at room temperature.

Scheme 1.12. Zhang’s Asymmetric γ-Alkylation of Non-Isomerizable Alkynoates.

Alvarez-Ibarra reported the addition of α-nitroesters to ethyl but-2-ynoate to generate γ,δ-didehydrohomoglutamates derivatives (Scheme 1.13). This racemic methodology is an extension of the alkylation work by Trost, with a pronucleophile not examined in the original report. For reasons that are unclear, this method makes use of an alkynoate again, and elevated temperatures. The scope presented in this report is general with respect to the α-nitroesters, but as before, the alkynoate is limited to one incapable of isomerization.

Despite these achievements, to the best of our knowledge, there have been no reports of successful γ-addition to isomerizable alkynoates or allenoates with carbon pronucleophiles. In fact the only two efficient γ-addition processes reported to date consist of intramolecular additions of oxygen pronucleophiles. The first of which was developed in racemic fashion by Trost in 1994. This methodology allows for the synthesis of an interesting selection of oxygen heterocycles (Scheme 1.14). During this study it was found that the use of a bidentate phosphine, an acetic acid additive and nonpolar solvents were crucial in favoring the addition product over isomerization. The second example of this transformation was completed by Dr. Ying Kit “Jack” Chung in the Fu lab this year (Scheme 1.15). Building off of the group’s previous success with monodentate phosphine catalysts, Dr. Chung developed an asymmetric variant of Trost’s heterocycle synthesis making use of the spirocyclic phosphine P3. This reaction displayed a broad scope and allowed access to the product in good to excellent levels of enantioselectivity. The methodology is capable of the construction of tetrahydrofurans, tetrahydropyrans and dihydrobenzopyrans.

50 The only examples of intermolecular γ-addition have been with nitrogen-based nucleophiles. For addition to ethyl pent-2-ynoate, see: Liu, B.; Davis, R.; Joshi, B.; Reynolds, D. W. J. Org. Chem. 2002, 67, 4595-4598 (17% yield for γ-addition of a thioamide); For addition to ethyl oct-2-ynoate, see: Trost, B. M.; Dake, G. R. J. Am. Chem. Soc. 1997, 119, 7595-7596 (8% yield for γ-addition of tetrahedrophthalimide).
**Scheme 1.14.** Trost’s Racemic Synthesis of Oxygen Heterocycles from Hydroxyl-2-alkynoates.

![Chemical structures and yields for Trost’s synthesis]

**Scheme 1.15.** Phosphine-Catalyzed Enantioselective Synthesis of Oxygen Heterocycles by Chung and Fu.

![Chemical structures and yields for Chung and Fu’s synthesis]
It was in this context that we began to think about developing an intermolecular \( \gamma \)-addition: the field was wide open. In the 17 years that has passed since the publication of Trost’s phosphine-catalyzed isomerization reaction, there have been no reports of a successful \( \gamma \)-alkylation reaction of isomerizable alkynoates or allenotes. We had great interest in attempting to realize this goal, thus we began to study the addition of carbon-based pronucleophiles to isomerizable alkynoates. We began this work with an open mind and with optimism that success in achieving the bond formation in an achiral fashion would smoothly translate to the development of an asymmetric variant of this new reaction.

**B. Results and Discussion**

The initial attempts to achieve \( \gamma \)-addition of an acidic carbon-based pronucleophile were carried out on the alkynoate illustrated in Scheme 1.16. A wide-range of potential pronucleophiles were examined with a selection of phosphines as catalysts; these reactions were run in a broad array of solvents, with and without additives and from room temperature to 100 °C. In no instance was any product formation observed. Our observations were that either the reaction conditions were too mild, and left us with remaining starting material, or when using elevated temperature, we saw complete conversion to the undesired isomerization product, the diene.

**Scheme 1.16. Preliminary Investigation Toward \( \gamma \)-Alkylations of Isomerizable Alkynoates.**
These results led us, of course, to think about means by which we could avoid diene and favor formation of the desired product. The currently accepted mechanism of alkynoate isomerization is illustrated in Scheme 1.17. Addition of the nucleophilic phosphine to the alkynoate generates an \( \alpha \)-vinyl enolate, \( \text{A} \), which through a series of proton transfer steps can lead to the resonance pair \( \text{B} \) (1 and 2). It is at \( \text{B} \) that Trost proposes that elimination of the phosphine can generate an allene. Although, spectroscopic detection of this intermediate has thus far been inconclusive, Trost and others have demonstrated that allenes are reactive under the isomerization conditions and do furnish dienoates, in similar fashion as alkynoates (see introduction). Subsequent proton-transfer events effect the walking of the anion down the alkyl side chain until it positioned appropriately, such that it may release the phosphine and generate the diene. Intermediate \( \text{B} \) along this pathway is also interesting because it is at this stage that we would like our pronucleophile to play the role of an acid, in order to generate an ion-pair between the phosphine-bound substrate, \( \text{C} \), and our newly-generated nucleophile. Formation of this ion-pair should enable the \( \gamma \)-addition to take place.

**Scheme 1.17.** Proposed Mechanism for both the Phosphine-catalyzed Isomerization and \( \gamma \)-Alkylation Reaction.
Why was it then that under no reaction conditions examined did we see any γ-addition product starting from the alkynoate? One hypothesis was that preference for one pathway over the other had to do with the entropy associated with bond formation versus another proton transfer. It was well understood that addition of most nucleophilic phosphines to alkynoates required elevated temperature, often between 60 °C and 100 °C. This is not typically the case for the addition of a phosphine to an allenoate. We postulated that perhaps by subjecting an allenoate to our reaction conditions we could run the reaction at room temperature, or lower, and favor the γ-addition over diene formation. Whether or not there is any validity to this line of thinking is still up for debate, as experiments to probe this idea were largely inconclusive. In any event, upon running the first reaction between an allenoate and an unhindered acidic carbon pronucleophile in the presence of PPh₃ provided the γ-addition product in excellent yield (eq 1.6).

```
O
O
Me
Me
EtO          MeO
O
O
Me
Me
EtO          MeO

10% PPh₃
toluene, r.t.  84% yield
```

This result was quite gratifying, but really was just a preview of things to come. It was of immense interest to investigate the ability of chiral phosphines to impart enantioselectivity in this new transformation. Of the phosphines examined for this transformation it became abundantly clear that the phosphine catalysts which had proved successful for Dr. Wurz’s and Dr. Wilson’s cycloaddition chemistry were once again going to be the frontrunners in this process. Application of the phenyl-substituted phosphine P₄ to this reactant pair led to the formation of product in 87% yield and 76% ee (eq 1.7).⁵²

---

⁵² The absolute stereochemistry of this product has not been determined.
Encouraged by this early result, we began looking at the scope of the reaction and were surprised to find that changing the alkyl chain on the allene from methyl to n-propyl resulted in the enantioselectivity of this transformation plummeting to 33%. Interestingly, we soon found that through the use of diisopropylmalonate in place of dimethylmalonate we could recover selectivities up to 78% ee in the addition to the n-propyl-substituted allene.

Concurrently with this work, we also found that nitromethane appeared to be a very suitable pronucleophile under similar reaction conditions. Table 1.5 illustrates the selectivity observed in the γ-alkylation of allenoates with nitromethane. Phosphepine P4 (entry 4) catalyzed the addition of nitromethane with a similar level of selectivity as it imparted for the malonate nucleophiles. It is notable that, use of phosphepines P2 or P3 (entries 1 and 2), both of which have been successful in other transformations, did not furnish an acceptable result. However, upon investigation of the related diethylamino-substituted phosphepine P1, we were pleased to achieve the desired γ-alkylation in both good yield and excellent ee (entry 1). Structurally similar phosphines P6 (entry 6) and MONOPHOS (entry 11) proved to be poor catalysts for this transformation, as are a variety of other commercially available chiral phosphines (entries 4, 5 and 7-10).

---

Table 1.5. Survey of Chiral Phosphine Catalysts for the γ-Alkylation of Allenoates with Nitromethane.\textsuperscript{a}

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\hline
entry & phosphine & yield (%)\textsuperscript{b} & ee (%)\textsuperscript{c} \\
\hline
1 & P1 & 83 & 93 \\
2 & P2 & 0 & - \\
3 & P3 & 47 & -83 \\
4 & P4 & 51 & 68 \\
5 & P5 & 64 & 63 \\
6 & P6 & 51 & 67 \\
7 & BINAP & 0 & - \\
8 & QUINAP & 0 & - \\
9 & Et-BPE & 36 & 22 \\
10 & Et-DUPHOS & 0 & - \\
11 & MONOPHOS & 0 & - \\
\hline
\end{tabular}
\end{table}

\textsuperscript{a} All data are the average of two experiments. \textsuperscript{b} The yield was determined by GC, calibrated using an internal standard. \textsuperscript{c} A negative value for the ee signifies that the illustrated enantiomer of the product is the minor product, rather than the major.

Due to their high synthetic versatility, we chose to examine the scope of this reaction using Weinreb amide-substituted allenes (Table 1.6).\textsuperscript{54} While the least hindered allenoate participates with the highest yield and enantioselectivity (entry 1), this phosphine-catalyzed γ-addition reaction is quite tolerant of branching adjacent to the allene (entries 3 and 4). This addition occurs smoothly in the presence of functional groups such as protected alcohols, esters and olefins (entries, 5-9).\textsuperscript{55,56,57}

\textsuperscript{54} For a review of the Weinreb amide, see: Balasubramaniam, S.; Aidhen, I. S. \textit{Synthesis} 2008, 3707-3738.

\textsuperscript{55} (a) Increasing the loading of phenol leads to formation of the undesired isomerization product. (b) The structure of the aryl alcohol does not have an impact on the selectivity observed. (c) Replacing phenol with benzoic acid leads
**Table 1.6.** Catalytic Asymmetric γ-Alkylation of Allenoates with Nitromethane.\textsuperscript{a}

\begin{figure}[h]
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\includegraphics[width=0.5\textwidth]{example}
\caption{Structure of the catalytic asymmetric γ-Alkylation reaction.}
\end{figure}

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<tr>
<td>8</td>
<td>(\text{Me-CO}_2\text{Me} )\textsuperscript{9}</td>
<td>83</td>
<td>92</td>
</tr>
<tr>
<td>9</td>
<td>(\text{Me-CO}_2\text{Me} )\textsuperscript{11}</td>
<td>84</td>
<td>93</td>
</tr>
</tbody>
</table>

\textsuperscript{a} All data are the average of two experiments. \textsuperscript{b} Yield of purified product. \textsuperscript{c} 15% (S)-P1 was used.

We were pleased to find that these reaction conditions, without modification, can be applied to other electron-deficient allenes. Thus, the allene can bear electron-withdrawing groups (EWG) other than the Weinreb amide (Table 1.7). A variety of esters give good yields and high levels of enantioselectivity (entries 1-3). Allenyl nitriles are reactive under these reaction conditions although, unlike for the other allenes, a mixture of olefins isomers is isolated (entry to inhibition of the γ-addition reaction. (d) Under these reaction conditions (with 15% P1) the tert-butyl substituted allene goes to 80% conversion by \textsuperscript{1}H NMR with 40% ee. (e) Dialkyl amides are not suitable substrates under these reaction conditions. (f) Nitrocyclohexane does not add under these reaction conditions. (g) These reaction conditions are not applicable to trisubstituted allenoates.

\textsuperscript{56} Phosphine P1 is reasonably stable. After exposure of the solid to air for 40 days at room temperature, no phosphine oxide was detected by \textsuperscript{31}P NMR.

\textsuperscript{57} According to \textsuperscript{31}P NMR spectroscopy, the resting state of P1 during the reaction is the free catalyst. Also, there is no observable interaction between P1 and phenol.
4). We also found that phosphonate esters perform well, particularly with respect to yield, though the level of enantioselectivity is somewhat lower (entry 5).\textsuperscript{58}

**Table 1.7.** Catalytic Asymmetric $\gamma$-Alkylation of Allenoates with Nitromethane.\textsuperscript{a}

![Scheme 1.18. Unsuccessful Allenes in the $\gamma$-Alkylation Reaction.](image)

In the course of developing this transformation, some limitations were revealed. Specifically, trisubstituted allenes and alkyl-substituted amides were not suitable substrates for this reaction (Scheme 1.18). Also, phenyl and alkyl ketones appear to be too reactive, as only diene was observed with these substrates.

**Scheme 1.18.** Unsuccessful Allenes in the $\gamma$-Alkylation Reaction.

\textsuperscript{58} Application of these reaction conditions to aryl or alkyl ketones results in the formation of diene.
Concurrent with the development of the nitromethane addition reaction, the reactivity of other acidic carbon pronucleophiles was examined. It appears that the efficiency of this reaction is not only highly dependent on the $pK_a$ of the pronucleophile, it is also very sensitive to steric hindrance about the nucleophilic carbon. Pronucleophiles that did not readily participate in a $\gamma$-addition process under the optimized nitromethane reaction conditions are illustrated in Scheme 1.19. Mention of these shortcomings is made in no way to discourage further work on this transformation, rather they are made to encourage the future investigation of this transformation. The ability to construct compounds via this strategy would be valuable, and perhaps future reaction conditions will display a broader scope with respect to the pronucleophile.

**Scheme 1.19. Ineffective Pronucleophiles Under the Finalized Allenoate Alkylation Conditions.**

![Scheme 1.19](image_url)

**C. Conclusion**

In conclusion, we have, for the first time, found reaction conditions that enable the $\gamma$-addition of an acidic pronucleophile to isomerizable allenoates. Success in this endeavor required utilizing allenoates in place of alkynoates as starting materials. Initially we found conditions that allowed for the racemic reaction to occur; we subsequently developed a highly enantioselective variant in which nitromethane served as the pronucleophile. This reaction takes place at room temperature, uses an easily prepared catalyst and has a broad scope with respect to the allenoate. Additional studies in this area are ongoing within the group, with Dr. Nicolas Marion and Dr. Jianwei Sun investigating the intermolecular $\gamma$-addition of other pronucleophiles.
D. Experimental

I. General

All reactions were carried out in oven-dried glassware under an atmosphere of argon. Et-BPE, Et-DUPHOS, MONOPHOS and QUINAP were purchased from Strem Chemicals. Phosphines P1, P2, P4, and P5 were provided by Evonik Industries (formerly Degussa) (we also prepared phosphines P1, P3, and P6 according to previously reported procedures\(^{59,60}\)). All other materials were purchased from commercial suppliers.

Low-resolution mass spectrometric measurements were performed on an Agilent LC/MSD-SL (ES+) LCMS system.

II. Preparation of Substrates

These procedures have not been optimized.

**Synthesis of Allenoates (representative procedure):** A 300 mL flask was charged with a phosphorane (14.5 g, 40.0 mmol), evacuated, and back-filled with argon. CH\(_2\)Cl\(_2\) (200 mL) and Et\(_3\)N (6.1 mL, 40.0 mmol) was added via syringe, and then the solution was cooled to -78 °C in a dry ice/acetone bath. The acyl chloride (40.0 mmol) was then added dropwise via syringe, over five min. The solution was allowed to warm to room temperature, and then the reaction was quenched by the addition of silica gel. Upon removal of the solvent with the aid of a rotary evaporator, this silica was loaded directly onto a pre-packed column and was purified via flash chromatography (hexanes/ethyl acetate), which furnished the alleneoate as an oil.


(±)-N-Methoxy-N-methylpenta-2,3-dienamide. Prepared from N-methoxy-N-methyl-2-(triphenylphosphoranylidene)acetamide and propionyl chloride via the representative procedure.

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 6.20-6.10 (m, 1H), 5.61 (quintet, $J = 7.3$ Hz, 1H), 3.71 (s, 3H), 3.23 (s, 3H), 1.80-1.76 (m, 3H).

$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 212.9, 166.1, 90.3, 85.9, 61.8, 32.7, 13.1.

IR (film) 3567, 2974, 2936, 2361, 2339, 1960, 1653, 1457, 1421, 1358 cm$^{-1}$.

LRMS (ES+) calcd for C$_7$H$_{12}$NO$_2$ (M+H$^+$) 142, found 142.

(±)-N-Methoxy-N-methylhepta-2,3-dienamide. Prepared from N-methoxy-N-methyl-2-(triphenylphosphoranylidene)acetamide and pentanoyl chloride via the representative procedure.

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 6.15 (quintet, $J = 2.9$ Hz, 1H), 5.64 (q, 6.8 Hz, 1H), 3.71 (s, 3H), 3.23 (s, 3H), 2.14-2.09 (m, 2H), 1.49 (sextet, $J = 7.4$ Hz, 2H), 0.95 (t, $J = 7.3$ Hz, 3H).

$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 212.2, 166.1, 95.2, 86.3, 61.5, 32.6, 29.7, 22.2, 13.6.

IR (film) 3567, 3291, 3042, 2961, 2935, 2873, 2361, 2339, 1958, 1653, 1463, 1424, 1364 cm$^{-1}$.

LRMS (ES+) calcd for C$_9$H$_{16}$NO$_2$ (M+H$^+$) 170, found 170.
(±)-N-Methoxy-N,5-dimethylhexa-2,3-dienamide. Prepared from N-methoxy-N-methyl-2-(triphenylphosphoranylidene)acetamide and isovaleroyl chloride via the representative procedure.

\[ \text{\^{1}H NMR (CDCl}_3, 500 MHz) \delta 6.20 (q, J = 3.1 Hz, 1H), 5.66 (t, J = 6.1 Hz, 1H), 3.71 (s, 3H), 3.23 (s, 3H), 2.52-2.42 (m, 1H), 1.08 (d, J = 6.7 Hz, 6H). \]

\[ \text{\^{13}C NMR (CDCl}_3, 125 MHz) \delta 211.1, 166.1, 102.6, 87.4, 61.8, 32.6, 27.7, 22.5, 22.3. \]

IR (film) 3291, 2963, 2937, 2871, 2361, 2339, 1957, 1653, 1465, 1384 cm\(^{-1}\).

LRMS (ES+) calcd for C\(_9\)H\(_{16}\)NO\(_2\) (M+H\(^+\)) 170, found 170.

(±)-5-Cyclopentyl-N-methoxy-N-methylpenta-2,3-dienamide. Prepared from N-methoxy-N-methyl-2-(triphenylphosphoranylidene)acetamide and 3-cyclopentyl-propanoyl chloride via the representative procedure.

\[ \text{\^{1}H NMR (CDCl}_3, 500 MHz) \delta 6.16-6.12 (m, 1H), 5.63 (q, J = 7.3 Hz, 1H), 3.71 (s, 3H), 3.26 (s, 3H), 2.14 (dt, J = 7.2, 2.8 Hz, 2H), 1.95 (septet, J = 7.6 Hz, 1H), 1.83-1.75 (m, 2H), 1.64-1.47 (m, 4H), 1.22-1.14 (2H). \]

\[ \text{\^{13}C NMR (CDCl}_3, 125 MHz) \delta 212.6, 166.2, 94.8, 85.9, 61.8, 39.7, 34.2, 32.7, 32.4, 25.4. \]

IR (film) 3290, 2948, 2867, 2361, 2339, 1654, 1424, 1363 cm\(^{-1}\).

LRMS (ES+) calcd for C\(_{12}\)H\(_{20}\)NO\(_2\) (M+H\(^+\)) 210, found 210.
(+)-8-(tert-Butyldimethylsilyloxy)-N-methoxy-N-methyl-2,3-dienamide. Prepared from N-methoxy-N-methyl-2-(triphenylphosphoranylidene)acetamide and 6-(tert-butylidimethylsilyloxy)hexanoyl chloride via the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 6.09-6.06 (m, 1H), 5.57 (t, $J = 6.7$ Hz, 1H), 3.63 (s, 3H), 3.56-3.52 (m, 2H), 3.16 (s, 3H), 2.15-2.05 (m, 2H), 1.60-1.38 (m, 4H), 0.81 (s, 9H), -0.04 (s, 6H).

$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 212.2, 166.1, 95.5, 86.5, 63.0, 61.8, 32.7, 32.3, 27.4, 26.1, 25.3, 18.5, -5.1.

IR (film) 3308, 2935, 2857, 2361, 1959, 1658, 1472 cm$^{-1}$.

LRMS (ES$^+$) calcd for C$_{16}$H$_{32}$NO$_3$Si (M+H$^+$) 314, found 314.

(+)-Methyl-8-(methoxy(methyl)amino)-8-oxoocta-5,6-dienoate. Prepared from N-methoxy-N-methyl-2-(triphenylphosphoranylidene)acetamide and methyl adipoyl chloride via the representative procedure.

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 6.18 (quintet, $J = 2.9$ Hz, 1H), 5.63 (q, $J = 6.7$ Hz, 1H), 3.71 (s, 3H), 3.66 (s, 3H), 3.23 (s, 3H), 2.39 (t, $J = 7.4$ Hz, 2H), 2.18 (qd, $J = 7.1$, 3.0 Hz, 2H), 1.80 (quintet, $J = 7.4$ Hz, 2H).

$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 212.3, 173.9, 165.9, 94.7, 86.9, 61.9, 51.7, 33.3, 32.8, 27.1, 24.1.

IR (film) 3282, 2951, 2361, 2339, 1959, 1734, 1653, 1639, 1457 cm$^{-1}$.

LRMS (ES$^+$) calcd for C$_{11}$H$_{18}$NO$_4$ (M+H$^+$) 228, found 228.
(+)-Methyl-10-(methoxy(methyl)amino)-10-oxodeca-7,8-dienoate. Prepared from N-methoxy-N-methyl-2-(triphenylphosphoranylidene)acetamide and methyl 8-chloro-8-oxooctanoate chloride\textsuperscript{61} via the representative procedure.

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz) \(\delta\) 6.06 (m, 1H), 5.52 (q, \(J = 2.3\) Hz, 1H), 3.61 (s, 3H), 3.55 (s, 3H), 3.13 (s, 3H), 2.20 (t, \(J = 7.4\) Hz, 2H), 2.06-2.01 (m, 2H), 1.56-1.49 (m, 2H), 1.42-1.35 (m, 2H), 1.31-1.24 (m, 2H).

\textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz) \(\delta\) 212.2, 174.2, 166.0, 95.3, 86.5, 61.8, 51.5, 34.0, 32.7, 28.6, 28.5, 27.4, 24.8.

IR (film) 3288, 2937, 2859, 2361, 2338, 1958, 1734, 1653 cm\textsuperscript{-1}.

LRMS (ES+) calcd for C\textsubscript{13}H\textsubscript{22}NO\textsubscript{4} (M+H\textsuperscript{+}) 256, found 256.


\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz) \(\delta\) 6.15 (quintet, \(J = 2.9\) Hz, 1H), 5.80 (qt, \(J = 10.3, 6.7\) Hz, 1H), 5.64 (q, \(J = 6.9\) Hz, 1H), 4.98 (dq, \(J = 17.1, 1.6\) Hz, 1H), 4.92 (dquintet, \(J = 10.2, 1.2\) Hz, 1H), 3.71 (s, 3H), 3.24 (s, 3H), 2.13 (qd, \(J = 7.0, 3.0\) Hz, 2H), 2.05-2.00 (m, 2H), 1.46 (quintet, \(J = 6.4\) Hz, 2H), 1.40-1.27 (m, 8H).

\textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz) \(\delta\) 212.3, 166.1, 139.4, 114.3, 95.7, 86.5, 61.9, 34.0, 29.4, 29.3, 29.23, 29.21, 29.12, 29.10, 27.8.

IR (film) 3075, 2927, 2855, 2361, 2338, 1959, 1653, 1464, 1423, 1362 cm\(^{-1}\).  
LRMS (ES+) calcd for C\(_{15}\)H\(_{26}\)NO\(_2\) (M+H\(^+\)) 252, found 252.

\[
\begin{align*}
\text{(±)-(Z)-N-Methoxy-N-methylnonadeca-2,3,10-trienamide}. \text{ Prepared from N-methoxy-N-methyl-2-(triphenylphosphoranylidene)acetamide and oleoyl chloride via the representative procedure.} \\
^1\text{H NMR (CDCl}_3, 500 \text{ MHz}) : \delta \text{ 6.15 (quintet, } J = 2.9 \text{ Hz, 1H), 5.64 (q, } J = 6.9 \text{ Hz, 1H),} \\
5.37-5.30 \text{ (m, 2H), 3.71 (s, 3H), 3.24 (s, 3H), 2.16-2.11 \text{ (m, 2H), 2.02-1.99 \text{ (m, 4H), 1.50 \text{ (m,} } \\
2\text{H), 1.37-1.22 \text{ (m, 18H), 0.88 \text{ (t, } J = 6.9 \text{ Hz, 3H).} }
\end{align*}
\]

\[
\begin{align*}
^13\text{C NMR (CDCl}_3, 125 \text{ MHz}) : \delta \text{ 212.3, 166.2, 130.1, 129.9, 95.6, 86.4, 61.8, 32.7, 32.1,} \\
29.9, 29.8, 29.7, 29.53, 29.52, 29.2, 29.1, 29.0, 27.8, 27.4, 27.3, 22.9, 14.3. \\
\text{IR (film) 3300, 3003, 2923, 2853, 2361, 2338, 1959, 1653, 1457, 1420, 1362 cm}^{-1}. \\
\text{LRMS (ES+) calcd for C}_{22}\text{H}_{40}\text{NO}_2 \text{ (M+H}^+) \text{ 350, found 350.}
\end{align*}
\]

\[
\begin{align*}
\text{(±)-Methyl-hepta-2,3-dienoate [111425-91-5]. \text{ Prepared from methyl (triphenylphosphoranylidene)acetate and pentanoyl chloride via the representative procedure.} } \\
^1\text{H NMR (CDCl}_3, 500 \text{ MHz}) : \delta \text{ 5.59 \text{ (m, 2H), 3.68 (s, 3H), 2.10-2.05 \text{ (m, 2H), 1.48-1.41} } \\
\text{(m, 2H), 0.91 (t, } J = 7.4 \text{ Hz, 3H).} \\
^13\text{C NMR (CDCl}_3, 125 \text{ MHz}) : \delta \text{ 212.6, 166.9, 95.4, 88.0, 52.1, 29.7, 22.1, 13.6.} \\
\text{IR (film) 2960, 2935, 2875, 2361, 2337, 1961, 1723, 1437, 1262 cm}^{-1}. \\
\text{LRMS (ES+) calcd for C}_{8}\text{H}_{13}\text{O}_2 \text{ (M+H}^+) \text{ 141, found 141.}
\end{align*}
\]

88
(±)-Ethyl-hepta-2,3-dienoate [861668-05-5]. Prepared from ethyl (triphenylphosphoranylidene)acetate and pentanoyl chloride via the representative procedure.

$^1$H NMR (CDCl₃, 500 MHz) δ 5.62-5.56 (m, 2H), 4.22-4.15 (m, 2H), 2.14-2.09 (m, 2H), 1.53-1.45 (m, 2H), 1.27 (t, $J = 5.7$ Hz, 3H), 0.95 (t, $J = 7.4$ Hz, 3H).

(±)-tert-Butyl-hepta-2,3-dienoate [151860-31-0]. Prepared from (tert-butoxycarbonylmethylene)triphenylphosphorane and pentanoyl chloride via the representative procedure.

$^1$H NMR (CDCl₃, 500 MHz) δ 5.55 (q, $J = 6.9$ Hz, 1H), 5.47 (q, $J = 2.6$ Hz, 1H), 2.09 (m, 2H), 1.52-1.42 (m, 11H), 0.95 (t, $J = 7.3$ Hz, 3H).

$^{13}$C NMR (CDCl₃, 125 MHz) δ 212.1, 165.8, 95.0, 89.9, 80.8, 29.8, 28.3, 22.2, 13.7.

IR (film) 3004, 2967, 2934, 2875, 2361, 2338, 1960, 1717, 1368, 1147 cm$^{-1}$.

LRMS (ES+) calcd for C₁₁H₁₉O₂ (M+H$^+$) 183, found 183.

(±)-Tetradeca-2,3-dienitrile. Prepared from (triphenylphosphoranylidene)-acetonitrile and dodecanoyl chloride via the representative procedure.

$^1$H NMR (CDCl₃, 500 MHz) δ 5.72 (q, $J = 7.1$ Hz, 1H), 5.20 (dt, $J = 6.5$, 3.1 Hz, 1H), 2.16-2.11 (m, 2H), 1.48-1.43 (m, 2H), 1.37-1.24 (m, 14H), 0.86 (t, $J = 6.9$ Hz, 3H).

$^{13}$C NMR (CDCl₃, 125 MHz) δ 215.4, 113.9, 97.1, 67.4, 32.1, 29.8, 29.7, 29.54, 29.51, 29.1, 28.6, 27.4, 22.9, 14.3.
IR (film) 3017, 2955, 2926, 2855, 2361, 2338, 2226, 1961, 1734, 1466 cm⁻¹.
LRMS (ES+) calcd for C₁₄H₂₄N (M⁺) 206, found 206.

(±)-Diethyl-octa-1,2-dienylphosphonate [344554-28-5]. Prepared according to a literature procedure.⁶²

¹H NMR (CDCl₃, 500 MHz)  δ 5.43 (sextet, J = 7.0 Hz, 1H), 5.29 (sextet, J = 3.4 Hz, 1H), 4.14-4.07 (m, 4H), 2.09 (quintet of doublets, J = 7.2, 3.4 Hz, 2H), 1.46-1.41 (m, 2H), 1.35-1.29 (m, 10H), 1.33 (t, J = 7.0 Hz, 3H).

¹³C NMR (CDCl₃, 125 MHz)  δ 211.9, 92.4, 80.8, 79.2, 62.2, 31.2, 28.67, 28.64, 27.4, 22.5, 16.4, 14.1.

IR (film) 3482, 2980, 2958, 2931, 2859, 2872, 2360, 2338, 1955, 1258 cm⁻¹.
LRMS (ES+) calcd for C₁₂H₂₄O₃P (M+H⁺) 247, found 247.

III. Asymmetric, Phosphine-Catalyzed γ-Alkylation

**General Procedure.** In a glove box, the catalyst (S)-P₁ (29 mg, 0.075 mmol, 10%) and phenol (7.0 mg, 0.075 mmol, 10%) were added to an oven-dried 20-mL vial. These solids were dissolved in anhydrous dioxane (15 mL), and then nitromethane (225 μL, 3.75 mmol, 5.5 equiv) and the allene (0.75 mmol) were added via syringe. The vial was capped and removed from the glove box, and the reaction mixture was stirred at room temperature for 15 h. It was then concentrated and purified by column chromatography (hexanes:ethyl acetate or hexanes: CH₂Cl₂). TLCs were visualized with KMnO₄ stain.

(E)-N-Methoxy-N-4-dimethyl-5-nitropent-2-enamide (Table 1.6, entry 1). The compound was prepared according to the general procedure with (±)-N-methoxy-N-methylpent-2,3-dienamide (106 mg, 0.75 mmol). After purification by flash chromatography (30% EtOAc in hexanes), the title compound was isolated as a colorless oil (144 mg, 95% yield) with 97% ee.

[α]D$^2$ = -45.4 (c = 1.0, CHCl₃). HPLC analysis of the product: Daicel CHIRALPAK OD-H column; 5.0% i-PrOH in hexanes; 1.0 mL/min; retention times: 38.7 min (minor), 44.5 min (major).

The second run was performed with (R)-P1. The product was isolated as a colorless oil (140 mg, 93% yield) with 97% ee.

$^1$H NMR (CDCl₃, 500 MHz) δ 6.73 (dd, J = 15.4, 7.8 Hz, 1H), 6.45 (d, J = 15.4 Hz, 1H), 4.37 (dd, J = 12.2, 7.7 Hz, 1H), 4.31 (dd, J = 12.2, 7.0 Hz, 1H), 3.63 (s, 3H), 3.18 (s, 1H), 3.24-3.15 (m, 1H), 1.15 (d, J = 6.8 Hz, 3H).

$^{13}$C NMR (CDCl₃, 125 MHz) δ 165.9, 145.2, 120.6, 79.9, 62.0, 35.8, 32.4, 17.0.

IR (film) 3287, 2972, 2361, 2339, 1669, 1558 cm$^{-1}$.

LRMS (ES+) calcd for C₈H₁₅N₂O₄ (M+H$^+$) 203, found 203.

(E)-N-Methoxy-N-methyl-4-(nitromethyl)hept-2-enamide (Table 1.6, entry 2). The compound was prepared according to the general procedure with (±)-N-methoxy-N-methylhepta-2,3-dienamide (127 mg, 0.75 mmol). After purification by flash chromatography (30% EtOAc in hexanes), the title compound was isolated as a colorless oil (137 mg, 80% yield) with 93% ee.
[α]D$^{22} = -29.7$ (c = 1.0, CHCl$_3$). HPLC analysis of the product: Daicel CHIRALPAK OD-H column; 5.0% i-PrOH in hexanes; 1.0 mL/min; retention times: 24.5 min (major), 28.7 min (minor).

The second run was performed with (R)-P1. The product was isolated as a colorless oil (141 mg, 82% yield) with 93% ee.

$^1$H NMR (CDCl$_3$, 500 MHz) δ 6.63 (dd, $J = 15.4$, 9.1 Hz, 1H), 6.44 (d, $J = 15.4$ Hz, 1H), 4.38 (dd, $J = 12.3$, 5.9 Hz, 1H), 4.30 (dd, $J = 12.2$, 8.9 Hz, 1H), 3.61 (s, 3H), 3.17 (s, 3H), 3.09-3.01 (m, 1H), 1.46-1.17 (m, 4H), 0.85 (t, $J = 7.2$ Hz, 3H).

$^{13}$C NMR (CDCl$_3$, 125 MHz) δ 165.7, 144.2, 122.0, 79.1, 62.0, 41.3, 33.6, 32.4, 20.0, 13.9.

IR (film) 2961, 2935, 2874, 2361, 2338, 1668, 1635, 1558, 1379 cm$^{-1}$.

LRMS (ES+) calcd for C$_{10}$H$_{19}$N$_2$O$_4$ (M+H$^+$) 231, found 231.

(E)-N-Methoxy-N,5-dimethyl-4-(nitromethyl)hex-2-enamide (Table 1.6, entry 3).

The compound was prepared according to the general procedure (except 15% catalyst was used) with (+)-N-methoxy-N,5-dimethylhexa-2,3-dienamide (127 mg, 0.75 mmol). After purification by flash chromatography (30% EtOAc in hexanes), the title compound was isolated as a colorless oil (102 mg, 60% yield) with 81% ee.

[α]D$^{22} = -29.9$ (c = 1.0, CHCl$_3$). HPLC analysis of the product: Daicel CHIRALPAK OD-H column; 5.0% i-PrOH in hexanes; 1.0 mL/min; retention times: 19.7 min (major), 24.0 min (minor).

The second run was performed with (R)-P1. The product was isolated as a colorless oil (108 mg, 63% yield) with 81% ee.

$^1$H NMR (CDCl$_3$, 500 MHz) δ 6.72 (dd, $J = 15.4$, 9.5 Hz, 1H), 6.44 (d, $J = 15.4$ Hz, 1H), 4.49 (dd, $J = 12.2$, 5.1 Hz, 1H), 4.35 (dd, $J = 12.1$, 9.8 Hz, 1H), 3.63 (s, 3H), 3.19 (s, 3H), 2.91 (septet, $J = 5.4$ Hz, 1H), 1.80 (sextet, $J = 6.7$ Hz, 1H), 0.92 (dd, $J = 13.0$, 6.7 Hz, 3H).

$^{13}$C NMR (CDCl$_3$, 125 MHz) δ 165.6, 142.5, 122.8, 77.9, 62.0, 47.6, 32.4, 30.0, 20.5, 19.2.
IR (film) 2965, 2876, 2361, 2338, 1668, 1653, 1635, 1558, 1472, 1457 cm\(^{-1}\).

LRMS (ES+) calcd for C\(_{10}\)H\(_{19}\)N\(_2\)O\(_4\) (M+H\(^+\)) 231, found 231.

\[ \text{LRMS (ES+)} \text{ calcd for C}_{10}\text{H}_{19}\text{N}_{2}\text{O}_{4} \text{ (M+H\(^+\)) 231, found 231.} \]

\[
\text{(E)-5-Cyclopentyl-N-methoxy-N-methyl-4-(nitromethyl)pent-2-enamide (Table 1.6, entry 4). The compound was prepared according to the general procedure with (±)-5-cyclopentyl-N-methoxy-N-methylpent-2,3-dienamide (157 mg, 0.75 mmol). After purification by flash chromatography (30% EtOAc in hexanes), the title compound was isolated as a colorless oil (146 mg, 72% yield) with 87% ee.} \\
\[
[\alpha]_{D}^{22} = -3.5 (c = 1.0, \text{CHCl}_3). \text{HPLC analysis of the product: Daicel CHIRALPAK OD-H column; 3.0% i-PrOH in hexanes; 1.0 mL/min; retention times: 33.7 min (major), 46.2 min (minor).} \\
\text{The second run was performed with (R)-P1. The product was isolated as a colorless oil (152 mg, 75% yield) with 86% ee.} \\
\]

\[
\begin{align*}
^1\text{H NMR (CDCl}_3, \text{500 MHz)} & \delta 6.65 (dd, J = 15.4, 9.4 \text{ Hz, 1H}), 6.47 (d, J = 15.4 \text{ Hz, 1H}), \\
 & 4.38 (dd, J = 12.3, 5.8 \text{ Hz, 1H}), 4.30 (dd, J = 12.2, 9.0 \text{ Hz, 1H}), 3.63 (s, 3H), 3.18 (s, 3H), 3.13-3.04 (m, 1H), 1.75-1.70 (m, 3H), 1.58-1.36 (m, 6H), 1.05-1.00 (m, 2H). \\
^13\text{C NMR (CDCl}_3, \text{125 MHz)} & \delta 165.7, 144.4, 122.0, 79.4, 62.0, 41.0, 38.0, 37.4, 33.3, 33.0, 32.4, 32.1, 25.23, 25.22. \\
\end{align*}
\]

IR (film) 2941, 2867, 2361, 2339, 1669, 1653, 1635, 1558 cm\(^{-1}\).

LRMS (ES+) calcd for C\(_{13}\)H\(_{22}\)N\(_2\)O\(_4\) (M+H\(^+\)) 271, found 271.
(E)-8-(tert-Butyldimethylsilyloxy)-N-methoxy-N-methyl-4-(nitromethyl)oct-2-enamide (Table 1.6, entry 5). The compound was prepared according to the general procedure with (±)-8-(tert-butyldimethylsilyloxy)-N-methoxy-N-methylocta-2,3-dienamide (235 mg, 0.75 mmol). After purification by flash chromatography (25% EtOAc in hexanes), the title compound was isolated as a colorless oil (156 mg, 56% yield) with 92% ee.

\[ [\alpha]_D^{22} = -19.2 \ (c = 1.0, \text{CHCl}_3) \]. HPLC analysis of the product: Daicel CHIRALPAK OD-H column; 5.0% i-PrOH in hexanes; 1.0 mL/min; retention times: 16.6 min (major), 18.4 min (minor).

The second run was performed with (R)-P1. The product was isolated as a colorless oil (163 mg, 58% yield) with 92% ee.

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 6.65 (dd, $J = 15.4, 9.1$ Hz, 1H), 6.5 (d, $J = 15.4$ Hz, 1H), 4.39 (dd, $J = 12.3, 6.0$ Hz, 1H), 4.32 (dd, $J = 12.3, 9.0$ Hz, 1H), 3.63 (s, 3H), 3.57-3.50 (m, 2H), 3.18 (s, 3H), 3.09-3.02 (m, 1H), 1.54-1.24 (m, 6H), 0.83 (s, 9H), -0.01 (s, 6H).

$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 165.6, 144.1, 122.1, 79.0, 62.9, 62.0, 41.6, 32.6, 31.4, 26.1, 23.3, 18.5, -5.1.

IR (film) 2933, 2858, 2361, 2339, 1668, 1653, 1635, 1557, 1380 cm$^{-1}$.

LRMS (ES+) calcd for C$_{17}$H$_{35}$N$_2$O$_5$Si (M+H$^+$) 375, found 375.

(E)-Methyl 8-(methoxy(methyl)amino)-5-(nitromethyl)-8-oxooct-6-enoate (Table 1.6, entry 6). The compound was prepared according to the general procedure with (±)-methyl 8-(methoxy(methyl)amino)-8-oxo-octa-5,6-dienoate (170 mg, 0.75 mmol). After purification by flash chromatography (15 $\rightarrow$ 50% EtOAc in hexanes), the title compound was isolated as a colorless oil (165 mg, 76% yield) with 94% ee.
[\alpha]_D^{22} = -29.7 (c = 1.0, CHCl_3). HPLC analysis of the product: Daicel CHIRALPAK AD-H column; 5.0% i-PrOH in hexanes; 1.0 mL/min; retention times: 59.9 min (major), 74.3 min (minor).

The second run was performed with (R)-P1. The product was isolated as a colorless oil (158 mg, 73% yield) with 92% ee.

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 6.61 (dd, $J = 15.4, 9.1$ Hz, 1H), 6.47 (d, $J = 15.5$ Hz, 1H), 4.39 (dd, $J = 12.4, 6.0$ Hz, 1H), 4.31 (dd, $J = 12.3, 8.8$ Hz, 1H), 3.61 (s, 3H), 3.58 (s, 3H), 3.16 (s, 3H), 3.08-3.00 (m, 1H), 2.25 (t, $J = 6.9$ Hz, 2H), 1.64-1.41 (m, 4H).

$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 173.5, 165.6, 143.5, 122.5, 78.8, 62.0, 51.8, 41.3, 33.6, 32.4, 30.8, 22.2.

IR (film) 2952, 2871, 2361, 2338, 1734, 1664, 1635, 1557 cm$^{-1}$.

LRMS (ES+) calcd for C$_{12}$H$_{21}$N$_2$O$_6$ (M+H$^+$) 289, found 289.

(E)-Methyl-10-(methoxy(methyl)amino)-7-(nitromethyl)-10-oxodec-8-enoate (Table 1.6, entry 7). The compound was prepared according to the general procedure with (±)-methyl 10-(methoxy(methyl)amino)-10-oxodeca-7,8-dienoate (191 mg, 0.75 mmol). After purification by flash chromatography (20 → 50% EtOAc in hexanes), the title compound was isolated as a colorless oil (195 mg, 82% yield) with 92% ee.

[\alpha]_D^{22} = -25.7 (c = 1.0, CHCl$_3$). HPLC analysis of the product: Daicel CHIRALPAK OD-H column; 5.0% i-PrOH in hexanes; 1.0 mL/min; retention times: 56.7 min (major), 63.5 min (minor).

The second run was performed with (R)-P1. The product was isolated as a colorless oil (193 mg, 82% yield) with 92% ee.

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 6.58 (dd, $J = 15.4, 9.1$ Hz, 1H), 6.40 (d, $J = 15.4$ Hz, 1H), 4.35 (dd, $J = 12.3, 5.9$ Hz, 1H), 4.28 (dd, $J = 12.3, 8.7$ Hz, 1H), 3.58 (s, 3H), 3.55 (s, 3H), 3.13 (s, 3H), 3.02-2.94 (m, 1H), 2.19 (t, $J = 7.4$ Hz, 3H), 1.52-1.16 (m, 7H).
$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 174.0, 165.7, 144.0, 122.1, 79.0, 61.9, 51.6, 41.4, 33.9, 32.3, 31.3, 28.9, 26.5, 24.7.

IR (film) 2938, 2861, 2361, 2339, 1734, 1558 cm$^{-1}$.

LRMS (ES$^+$) calcd for C$_{14}$H$_{25}$N$_2$O$_6$ (M$^+$) 317, found 317.

![Chemical structure of (E)-N-Methoxy-N-methyl-4-(nitromethyl)trideca-2,12-dienamide](image)

(E)-N-Methoxy-N-methyl-4-(nitromethyl)trideca-2,12-dienamide (Table 1.6, entry 8). The compound was prepared according to the general procedure with (±)-N-methoxy-N-methyltrideca-2,3,12-trienamide (189 mg, 0.75 mmol). After purification by flash chromatography (5 → 40% EtOAc in hexanes), the title compound was isolated as a colorless oil (199 mg, 85% yield) with 92% ee.

$[\alpha]_D^{22} = -26.0$ (c = 1.0, CHCl$_3$). HPLC analysis of the product: Daicel CHIRALPAK AD-H column; 5.0% i-PrOH in hexanes; 1.0 mL/min; retention times: 14.7 min (major), 18.0 min (minor).

The second run was performed with (R)-P1. The product was isolated as a colorless oil (190 mg, 81% yield) with 92% ee.

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 6.62 (dd, $J = 15.4$, 9.1 Hz, 1H), 6.43 (d, $J = 15.4$ Hz, 1H), 5.71 (ddt, $J = 17.0$, 10.2, 6.7 Hz, 1H), 4.93-4.83 (m, 2H), 4.37 (dd, $J = 12.3$, 6.0 Hz, 1H), 4.29 (dd, $J = 12.1$, 8.8 Hz, 1H), 3.60 (s, 3H), 3.16 (s, 3H), 3.06-2.98 (m, 1H), 1.97-1.93 (m, 2H), 1.48-1.14 (m, 12H).

$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 165.7, 144.3, 139.2, 122.0, 114.4, 79.1, 61.9, 60.5, 41.5, 33.9, 31.6, 29.4, 29.1, 29.0, 26.8, 14.3.

IR (film) 3289, 3075, 2925, 2855, 2361, 2339, 1653 cm$^{-1}$.

LRMS (ES$^+$) calcd for C$_{16}$H$_{29}$N$_2$O$_4$ (M$^+$) 313, found 313.
(2E,11Z)-N-Methoxy-N-methyl-4-(nitromethyl)icos-2,11-dienamide (Table 1.6, entry 9). The compound was prepared according to the general procedure with (+)-(Z)-N-methoxy-N-methylnonadeca-2,3,10-trienamide (262 mg, 0.75 mmol). After purification by flash chromatography (7 → 14% EtOAc in hexanes), the title compound was isolated as a colorless oil (257 mg, 83% yield) with 93% ee.

$\left[\alpha\right]_{D}^{22} = -24.0 \ (c = 1.0, \ \text{CHCl}_3)$. HPLC analysis of the product: Daicel CHIRALPAK OD-H column; 1.0% i-PrOH in hexanes; 1.0 mL/min; retention times: 57.4 min (major), 64.0 min (minor).

The second run was performed with (R)-P1. The product was isolated as a colorless oil (260 mg, 84% yield) with 93% ee.

$^1$H NMR (CDCl$_3$, 500 MHz) δ 6.64 (dd, $J = 15.4$, 9.4 Hz, 1H), 6.47 (dd, $J = 15.4$ Hz, 1H), 5.31-5.20 (m, 2H), 4.38 (dd, $J = 12.3$, 6.0 Hz, 1H), 4.30 (dd, $J = 12.1$, 8.9 Hz, 1H), 3.61 (s, 3H), 3.17 (s, 3H), 3.08-2.98 (m, 1H), 2.00-1.88 (m, 4H), 1.48-1.10 (m, 22H), 0.81 (t, $J = 6.5$ Hz, 3H).

$^{13}$C NMR (CDCl$_3$, 125 MHz) δ 165.8, 144.3, 130.2, 129.7, 122.0, 79.1, 61.9, 41.5, 36.8, 32.4, 32.0, 31.6, 29.9, 29.8, 29.7, 29.5, 29.4, 29.2, 27.4, 27.3, 26.9, 22.9, 14.3.

IR (film) 3003, 2926, 2855, 2361, 2339, 1667, 1635, 1557, 1464 cm$^{-1}$.

LRMS (ES+) calcd for C$_{23}$H$_{43}$N$_2$O$_4$ (M+H$^+$) 411, found 411.

(E)-Methyl-4-(nitromethyl)hept-2-enoate (Table 1.7, entry 1). The compound was prepared according to the general procedure with (+)-methyl hepta-2,3-dienoate (105 mg, 0.75
mmol). After purification by flash chromatography (30% hexanes in CH₂Cl₂), the title compound was isolated as a colorless oil (109 mg, 72% yield) with 92% ee.

\[ \alpha \]D²² = -31.8 (c = 1.0, CHCl₃). HPLC analysis of the product: Daicel CHIRALPAK OD-H column; 1.0% i-PrOH in hexanes; 1.0 mL/min; retention times: 24.8 min (minor), 32.7 min (major).

The second run was performed with (R)-P1. The product was isolated as a colorless oil (113 mg, 74% yield) with 93% ee.

\[^1^H\text{NMR (CDCl}_3, 500 MHz)\] \( \delta 6.72 (\text{dd, } J = 15.6, 9.1 \text{ Hz, 1H}), 5.90 (\text{d, } J = 15.7 \text{ Hz, 1H}), 4.42 (\text{dd, } J = 12.3, 5.9 \text{ Hz, 1H}), 3.85 (\text{dd, } J = 12.3, 8.7 \text{ Hz, 1H}), 3.73 (\text{s, 3H}), 3.10-3.03 (\text{m, 1H}), 1.50-1.25 (\text{m, 4H}), 0.91 (\text{t, } J = 7.3 \text{ Hz, 3H}). \)

\[^{13}C\text{NMR (CDCl}_3, 125 MHz)\] \( \delta 166.3, 146.1, 124.2, 78.9, 52.0, 41.0, 33.5, 20.0, 13.9. \)

IR (film) 2960, 2935, 2875, 2361, 2339, 1717, 1661, 1558, 1436 cm⁻¹.

LRMS (ES⁺) calcd for C₅H₁₆NO₄ (M+H⁺) 202, found 202.

(\(E\))-Ethyl-4-(nitromethyl)hept-2-enoate (Table 1.7, entry 2). The compound was prepared according to the general procedure with (+)-ethyl-hepta-2,3-dienoate (131 mg, 0.75 mmol). After purification by flash chromatography (30% hexanes in CH₂Cl₂), the title compound was isolated as a colorless oil (148 mg, 92% yield) with 91% ee.

\[ \alpha \]D²² = -29.5 (c = 1.0, CHCl₃). HPLC analysis of the product: Daicel CHIRALPAK OD-H column; 2.0% i-PrOH in hexanes; 1.0 mL/min; retention times: 15.2 min (minor), 18.1 min (major).

The second run was performed with (R)-P1. The product was isolated as a colorless oil (143 mg, 89% yield) with 92% ee.

\[^1^H\text{NMR (CDCl}_3, 500 MHz)\] \( \delta 6.66 (\text{dd, } J = 15.6, 9.0 \text{ Hz, 1H}), 5.85 (\text{d, } J = 15.6 \text{ Hz, 1H}), 4.39 (\text{dd, } J = 12.3, 5.9 \text{ Hz, 1H}), 4.32 (\text{dd, } J = 12.3, 8.6 \text{ Hz, 1H}), 4.14 (\text{q, } J = 7.1 \text{ Hz, 2H}), 3.06-2.98 (\text{m, 1H}), 1.44-1.22 (\text{m, 7H}), 0.87 (\text{t, } J = 7.2 \text{ Hz, 3H}). \)
\[ ^{13}\text{C NMR (CDCl}_3, 125 \text{ MHz)} \delta 165.9, 145.9, 124.4, 78.8, 60.8, 40.9, 33.5, 20.0, 14.3, 13.9. \]

IR (film) 2962, 2935, 2875, 2361, 2339, 1717, 1653, 1558 cm\(^{-1}\).
LRMS (ES+) calcd for C\(_{10}\)H\(_{18}\)NO\(_4\) (M\(^+\)) 216, found 216.

\[ \text{(E)-} \text{tert-Butyl-4-(nitromethyl)hept-2-enoate (Table 1.7, entry 3).} \] The compound was prepared according to the general procedure with (±)-tert-butyl-hepta-2,3-dienoate (137 mg, 0.75 mmol). After purification by flash chromatography (10% EtOAc in hexanes), the title compound was isolated as a colorless oil (173 mg, 95% yield) with 90% ee.

\[ [\alpha]_D^{22} = -29.4 \text{ (c = 1.0, CHCl}_3). \]
HPLC analysis of the product: Daicel CHIRALPAK OD-H column; 1.0% i-PrOH in hexanes; 1.0 mL/min; retention times: 13.6 min (minor), 17.4 min (major).

The second run was performed with (R)-P1. The product was isolated as a colorless oil (168 mg, 93% yield) with 90% ee.

\[ ^1\text{H NMR (CDCl}_3, 500 \text{ MHz)} \delta 6.56 (dd, J = 15.6, 9.0 \text{ Hz, 1H}), 5.77 (d, J = 15.6 \text{ Hz, 1H}), \\
4.37 (dd, J = 12.3, 6.1 \text{ Hz, 1H}), 4.31 (dd, J = 12.3, 8.5 \text{ Hz, 1H}), 3.04-2.96 (m, 1H), 1.42-1.20 (m, 13H), 0.86 (t, J = 6.6 \text{ Hz, 3H}). \]

\[ ^{13}\text{C NMR (CDCl}_3, 125 \text{ MHz)} \delta 165.1, 144.6, 126.1, 80.9, 78.9, 40.8, 33.5, 28.2, 20.0, 13.9. \]

IR (film) 2964, 2934, 2875, 2361, 2339, 1713, 1654, 1554, 1368, 1159 cm\(^{-1}\).
LRMS (ES+) calcd for C\(_8\)H\(_{12}\)NO\(_4\) (M-t-Bu\(^+\)) 186, found 186.

\[ \text{(E)-4-(Nitromethyl)tetradec-2-enenitrile (Table 1.7, entry 4).} \] The compound was prepared according to the general procedure (except 3.0 equiv of phenol was used) with (±)-
tetradeca-2,3-dienenitrile (154 mg, 0.75 mmol). After purification by flash chromatography (30% hexanes in CH₂Cl₂), the title compound was isolated as a colorless oil (96 mg, 48% yield (5:1 E:Z olefin isomers)) with 92% ee (E isomer) and 90% ee (Z isomer).

\[ \alpha_d^{22} = -26.1 \ (c = 1.0, \ CHCl_3). \] HPLC analysis of the product: Daicel CHIRALPAK OD-H column; 1.0% i-PrOH in hexanes; 1.0 mL/min; retention times: E isomer: 49.9 min (minor), 53.9 min (major); Z isomer: 24.2 min (minor), 32.7 min (major).

The second run was performed with (R)-P1. The product was isolated as a colorless oil (90 mg, 45% yield (5:1 E:Z olefin isomers)) with 92% ee (E isomer) and 91% ee (Z isomer).

\[ \alpha_d^{22} = -18.3 \ (c = 1.0, \ CHCl_3). \] HPLC analysis of the product: Daicel CHIRALPAK OD-H column; 2.0% i-PrOH in hexanes; 1.0 mL/min; retention times: 41.4 min (minor), 46.7 min (major).

(E)-Diethyl-3-(nitromethyl)oct-1-enylphosphonate (Table 1.7, entry 5). The compound was prepared according to the general procedure (except 3.0 equiv of phenol was used and the reaction mixture was heated at 60 °C) with (+)-diethyl octa-1,2-dienylphosphonate (185 mg, 0.75 mmol). After purification by flash chromatography (30% hexanes in EtOAc), the title compound was isolated as a colorless oil (203 mg, 89% yield) with 75% ee.

\[ \alpha_d^{22} = -18.3 \ (c = 1.0, \ CHCl_3). \] HPLC analysis of the product: Daicel CHIRALPAK OD-H column; 2.0% i-PrOH in hexanes; 1.0 mL/min; retention times: 41.4 min (minor), 46.7 min (major).
The second run was performed with (R)-P1. The product was isolated as a colorless oil (193 mg, 84% yield) with 72% ee.

¹H NMR (CDCl₃, 500 MHz) δ 6.45 (ddd, J = 21.6, 17.1, 8.7 Hz, 1H), 5.64 (dd, J = 18.9, 17.1 Hz, 1H), 4.35 (dd, J = 12.2, 5.6 Hz, 1H), 4.26 (dd, J = 12.2, 9.0 Hz, 1H), 4.01-3.87 (m, 4H), 2.96-2.89 (m, 1H), 1.42-1.30 (m, 2H), 1.28-1.11 (m, 12H), 0.77 (t, J = 6.6 Hz, 3H).

¹³C NMR (CDCl₃, 125 MHz) δ 150.6, 121.7, 78.8, 62.0, 43.2, 43.0, 31.5, 31.1, 26.4, 22.5, 16.5, 16.4, 14.0.

IR (film) 2958, 2932, 2860, 2361, 2339, 1639, 1553, 1380, 1246 cm⁻¹.

LRMS (ES+) calcd for C₁₃H₂₆NO₅P (M+H⁺) 308, found 308.

IV. Determination of Absolute Stereochemistry

The stereochemistry of the γ-alkylation products was assigned by correlation with known compounds.

1) (S)-3-methyl-2-(nitromethyl)butanal

![1) (S)-3-methyl-2-(nitromethyl)butanal](image)

2) (R)-tert-butyl 2-(hydroxymethyl)pentylcarbamate

![2) (R)-tert-butyl 2-(hydroxymethyl)pentylcarbamate](image)

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E. $^1$H NMR Spectra of Selected Compounds
STANDARD PROTON PARAMETERS

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date Feb 4 2009
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dn C13
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gain not used dres2 1.0

FLAGS

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ins 1.000 math
al 0.600 werr
wexp wbx
wnt wft
STANDARD PROTON PARAMETERS

expl  s2pul

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bs  63050  dfrq2  DEC2

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pw  8.6  dpwr2
q  2.000  dpwr1
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ct  16  dam2  200
alock  n  dseq1

FLAGS

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wc  250  dres3  1.0
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rs  33.57  wfile  PROCESSING
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ins  1.000  math  f
al  ph

werr  wexp
wes  wbt

DEC3

DEC2

MeO.  N
Me
Me

ppm
STANDARD PROTON PARAMETERS

exp1 s2pul

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np 63050 dres 1.0
sw 105942 homo n
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il n DEC3
in n dfrq3 0
dp y enz3
hs n dpwr3 1
sp 3.7 dmm3 c
wp 3990.6 dmm3 c
vs 26 dmm3 200
sc 6 dseq3 1.0
wc 250 dres3 1.0
hzmm 15.89 homo3 n
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rfl 9 proc ft
th 7 fn 262144
ins 1.000 math f
al cdc ph werr
wexp
wbs
wnt wft

ppm

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STANDARD 1H OBSERVE

expl stdih

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TPW: 54
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CT: 16
ALOCK: n
GAIN: n

DISPLAY
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Vs: 151
Sc: 0
WC: 250
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RFP: 0
TH: 20
INS: 1.000

FLAGS
II: n
IN: n
DP: y

PROCESSING
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PROC: 0
WERR: 0
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WN: 20.0

DEC. & VT
Dfrq: 300.107
DN: H1
DPWR: 30
DPO: 0
DM: 0
DMF: 0
TEMP: 20.0

MeO,N
Me
\[\text{MeO,N,Me} \quad \begin{array}{c}
\text{OTBS}
\end{array}\]

ppm
STANDARD PROTON PARAMETERS

SAMPLE

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solvent: CDCl3
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dtof: 1519.5
nt: 16
dtof2: 200

gain
flag
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wp: 3990.6
vs: 44
sc: 0
wc: 250
hzm: 15.86

PROCESSING
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rf2: 0
rfp: 0
th: 7
ins: 1.000
al: cdc

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des
wexp
wbs
wnt

prl

MeO

OMe

 samp

dec. & vt

1 ppm
STANDARD PROTON PARAMETERS

exp 52pul

SAMPLE DEC. & VT

date: Feb 4 2009
dfrq: 125.672

solvent: CDC13
dn: C13

dromm: /data/gfu/Tsm-12-130-2H.fld

dof: 0

ACQUISITION

dm: nnn

dfrq: 499.746
dmom: w

tn: H1
dmf: 10000

at: 3.001

dseq: 10000

np: 63050
dres: 1.0

sw: 10584.2

fb: not used

bs: dfrq2

dn: 0

dpwr: 56
dn2: 0

sw: 10.6

dpwr2: 1

tof: 1518.5

dm2: n

dseq: 63050

dres: 1.0

Dec 2

bs: dfrq2

dn: 0

dpwr: 56

dn2: 0

sw: 10.6

dpwr2: 1

tof: 1518.5

dm2: n

dseq: 63050

dres: 1.0

Dec 3

bs: dfrq3

dn: 0

dpwr: 56

dn2: 0

sw: 10.6

dpwr2: 1

tof: 1518.5

dm2: n

dseq: 63050

dres: 1.0

DISPLAY

sp: 3.7

wp: 3990.6
dm: 3

dseq: 63050

dres: 1.0

hzm: 15.86

flags: PROCESSING

rf: 1233.8

wfile: 0

proc: 7

ft: 262144

math: 1.000

plt: wc

ppm: 13.34

ppm: 2.75

ppm: 2.58

ppm: 3.70

ppm: 3.82

ppm: 2.24

ppm: 1.12

ppm: 1.00

MeO-N

Me
**STANDARD PROTON PARAMETERS**

**exp1 s2pul**

**SAMPLE**
- DEC & VT: 125.672
- dfq: 2009
- dfrq: 125.672

**solvent**
- CDC13
- dfrq: 30
- dfrq2: 3
- dfrq3: 3
- dfrq4: 3

**ACQUISITION**
- dm: 10000
- daf: 1
- daf2: 1
- daf3: 1
- daf4: 1

**flags**
- n: 1
- n: 1
- n: 1
- n: 1

**DISPLAY**
- sp: 3.7
- dp: 3.3
- hs: 2.2
- dp: 3.3
- hs: 2.2

**PROCESSING**
- wfr: 262144
- wfr: 262144

**Diagram**
- Chemical structure with peaks at various ppm values.
### STANDARD PROTON PARAMETERS

**Sample Date**: Feb 4 2009  
**Solvent**: CDC13  
**File**: /data/gfu/Tsm-12-053-H.fid  
**Acquisition**:  
- **sfrq**: 499.746  
- **tn**: H1, daf 10000  
- **at**: 3.001, dseq 1.0  
- **sw**: 1054.2, homo n  
- **fb**: not used  
- **bs**: 8, dfrq2  
- **tpwr**: 56, dn2  
- **pw**: 8.6, dpw2  
- **di**: 2.000, dof2  
- **tof**: 1519.5, dm2  
- **ct**: 8, daf2  
- **a lock**: not used  
- **FLAGS**:  
  - **tl**: n, DEC3  
  - **in**: dn3  
  - **hp**: dpr2  
  - **sp**: 3.7, dm3  
  - **wp**: 3995.6, ddmm  
  - **ve**: 37, dm2  
  - **sc**: 250, dres3  
  - **hc mm**: 15.59, hom2  
- **Processing**:  
  - **rf**: 1233.8, wtf  
  - **rfp**: proc  
  - **th**: 7, fn 262144  
  - **ins**: 2.000, math  
- **al**: cdc ph  
- **werr**: wexp  
- **wexp**: wbs  
- **wnt**: wft
STANDARD PROTON PARAMETERS

SAMPLE  DEC. & VT
date  Feb 28 2009  dfrq  125.672
solvent  CDCl3  dn  C13
home/gfu/Tsm/bullwinkle/Tsm-12-091-H
file/home/gfu/Tsm/bullwinkle/Tsm-12-091-H.fld

ACQUISITION
dfrq  499.746  dsq  125.672
tn  4.011  dres  1.0
at  3.001  homo  n
np  63050  temp  20.0
sw  10504.2
fb  not used
bs  8
tpwr  58 fn  262144
tp  8.6
wpp  2.000
tof  1519.5
nt  16
ct  8
wexp
wbs
wft

DISPLAY
sp  3.1
wp  3996.7
sc  8
ws  0
hzmm  15.99
ls  33.57
rf1  1233.8
wft

WFT

1-BuO

1.000
0.92
2.57
15.50
3.88
STANDARD PROTON PARAMETERS

exp1 s2pul

SAMPLE DEC. & VT
date Feb 4 2009 dfreq 125.672
solvent CDC13 dn C13
file /data/gfu/Tsm- dpwr 30
/Tsm-12-065-H.fid dof 0
ACQUISITION dm nnn
sfrq 498.746 dmm w
tn H1 dmf 10000
np 3.001 dseq 1.0
sw 10504.2 homo n
fb not used DEC2
bs 8 dfrq2
tpwr 58 dn2
pw 8.6 dpwr2
d1 2.000 dof2
tor 1518.5 dm2
nt 16 dmm2
c t 8 dmt2
alock n dseq2
gain not used dres2
FLAGS homo2 n
i l n dfrq3
in n dpwr3
dp y dn3
hs nn dpwr3
DISPLAY
sp 3.7 dm3
wp 3990.6 dmm3
vs 119 dmt3
sc 0 dseq3
wc 250 dres3
hzma 15.36 homo3
Is 33.57 PROCESSING
rfq 1233.8 wfile
rfp 0 proc
th 7 fn 262144
ins 1.000 math
ai ph s 1.000 math
werr
wexp
wbs
wnt

NC

ppm

1.17
1.00
0.31
3.45
3.90
6.68
1.21
35.72
STANDARD PROTON PARAMETERS

 SAMPLE DEC. & VT
date Feb 4 2009
dfqr 125.672
solvent CDC13
dm C13
file /data/gfu/Tsm-
dwpr 30
/Tsm-12-672-H.fid
dof 0
ACQUISITION
dm nnn
sfrq 499.746
tn H1
dof 10000
at 3.001
dseq 63050
np dres 1.0
sw 16506.2
fb not used
bs 0
tpwr 56
dn2
pw 8.6
dwpr2 1
dl 2.000
dof2 0
tof 1519.5
dm2 n
tc 16
ct 8
dm2 200
alock n
gain not used
fls Homo2
homo Homo2
DISPLAY Homo2
sp 3.7
dm3 n
wp 3990.6
dm3 c
vs 57
dm3 200
sc 0
dseq3 1.0
wc 250
dres3 n
hzm Homo3
ls 33.57
PROCCESSING
rf1 1233.8
rfp 0
proc ft
th 7
ins 1.000
at Cdc ph
werr
wekp
wbs
wnt

(CO)2N

Me

ppm

1.00 0.89 3.81 2.40 2.33 10.19 3.28
STANDARD PROTON PARAMETERS

SAMPLE

date Feb 15 2009
solvent CDCl3
file /data/export/home/gfu/Tsm/bulkwear/Tsm-13-007-H

ACQUISITION
sfrq 499.746
tn 3.601
np 63050
sw 10504.2
fb not used
bs 8
at 3.001
np 63050
sw 10504.2
fb not used
bs 8

Acquisition parameters:
sfrq 499.746
tn 3.601
np 63050
sw 10504.2
fb not used
bs 8

Table 1.6, entry 1

Table 1.6, entry 1

---

![NMR spectrum with chemical shifts and peaks marked](image)

Key peaks:
- 1.0 ppm (1H, MeO)
- 2.41 ppm (1H, v-CH)
- 3.55 ppm (2H, CH2)
- 4.56 ppm (1H, v-CH)
- 3.61 ppm (3H, Me)

---

**Chemical Structure**

![Chemical structure of compound](image)

MeO

---

**Diagram**

![NMR spectrum with peaks labeled](image)

---

**Table 1.6, entry 1**

<table>
<thead>
<tr>
<th>Peak (ppm)</th>
<th>Assignments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00</td>
<td>MeO</td>
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<tr>
<td>2.41</td>
<td>v-CH</td>
</tr>
<tr>
<td>3.55</td>
<td>CH2</td>
</tr>
<tr>
<td>4.56</td>
<td>v-CH</td>
</tr>
<tr>
<td>3.61</td>
<td>Me</td>
</tr>
</tbody>
</table>
STANDARD PROTON PARAMETERS

exp1 s2pul

SAMPLE

date Feb 15 2009
dfrr 125.672
dno C13
dfrq 499.746
dtres 1.0
dnp 63050
dsw 10504.2
fb not used
dpwr 8.6
dd 2.000
dtof 1511.5
nt 16
ct 8
alo not used
gain n
l flags n
in n
hI
h2
i3
i4
i5
i6
h6
h5
h4
h3
h2
h1
dsp n
vs 3994.4
sc 0
wc 250
h254 15.88
is 33.57
rf 1233.8
rfp 0
th 7
lins 1.000
al ph

Table 1.6, entry 2

MeO
N
\(\text{NO}_2\)

Me
\(\text{MeO.}~\text{NN NO}\)

2 Me

Table 1.6, entry 2

8.1 ppm
STANDARD PROTON PARAMETERS

SAMPLE

date Feb 15 2009
dfrq 125.672
det solvent CDCl3
file /data/export/
dpnr/home/gfu/Tsm/bullwinkle/Tsm-13-008-H
in1le/d
file /data/export/dpwr
home/gfu/Tsm/bullwinkle/Tsm-13-008-H

ACQUISITION

sfrq 499.746
tin 1.0
at 3.001
npn 60505
sw 10594.2
fb 2.000
bs 16
sw 10594.2

PROCESSING

bs 16
sw 1.0
werr 7

CAPTURE

to 1519.5
nc 8
ct 8

DISPLAY

sp 0.3
wp 5994.4
vs 68
sc 0
wc 250
hzm 15.98
is 33.57
rf1 1233.8
rhp 0
th 7
al 1.000

Table 1.6, entry 4
Table 1.6, entry 5
STANDARD PROTON PARAMETERS

`exp1 s2pul`

SAMPLE: DEC. & VT

date: Feb 15 2009
dfreq: 125.672
solvent: CDC13
dn: C13
file: /data/export/ dpwr 30
data: /home/gfu/Tsm/bullw-dof
inkey/Tsm-13-012-H- do file /data/export/- dpwr
acq/dam: w

ACQUISITION: def: 100000
sfreq: 499.746
dseq: 1.0
at: 3.001
np: 63050
sw: 105564.2
fb: not used
bc: 16
acq/proc: ft
bs: 8
math: 262144
ptwr: 56

acq/werr: 8.6
di: 2.000
acq/tof: 1518.5
acq/nt: 16
acq/wbs: 0
acq/wnt: wft
acq/wt: n
acq/flags: n
acq/dp: y
acq/hs: nn
acq/dsp: -0.8
acq/wp: 4000.2
acq/vs: 87
acq/sc: 0
acq/wc: 250
acq/hzmm: 16.00
acq/ls: 33.57
acq/rfl: 1233.8
acq/rfp: 0
acq/th: 7
acq/ins: 1.000
acq/ph: 1.000

Table 1.6, entry 6

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<th>0.98</th>
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</thead>
<tbody>
<tr>
<td>2.20</td>
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<td>1.10</td>
</tr>
<tr>
<td>2.27</td>
<td>4.74</td>
<td></td>
</tr>
</tbody>
</table>

Diagram of N=O-MeO'N=O2Me
Table 1.6, entry 7
STANDARD PROTON PARAMETERS

SAMPLE

date: Feb 15 2009
dfrq: 499.746
dn: 3.001

file: /data/export/-
home/gfu/Tsm/bullinkle/Tsm-13-010-H-
.fld

ACQUISITION

sfrq: 499.746
tn: 1.0
np: 63050
sw: 10504.2
fb: not used
bs: 8

pswr: 56
pw: 8.6
dl: 2.000
tof: 1513.5
nt: 16
ct: 0

alock: n
gain: not used

DISPLAY

sp: -0.8
wp: 4000.2
vs: 55
sc: 0
wc: 250
hzmm: 16.00
ls: 33.57
rf1: 1233.8
rfp: 0
th: 0
ins: 1.000
al: cdc
ph

Table 1.6, entry 8

<table>
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</thead>
<tbody>
<tr>
<td>7</td>
<td>1.00</td>
</tr>
<tr>
<td>6</td>
<td>0.99</td>
</tr>
<tr>
<td>5</td>
<td>0.86</td>
</tr>
<tr>
<td>4</td>
<td>1.76</td>
</tr>
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<td>3</td>
<td>2.10</td>
</tr>
<tr>
<td>2</td>
<td>2.35</td>
</tr>
<tr>
<td>1</td>
<td>2.30</td>
</tr>
</tbody>
</table>

123
STANDARD PROTON PARAMETERS

exp 1 s2p2

SAMPLE

Date Feb 15 2009
dfrq 499.746

Solvent CDCl3

File /data/export/~home/gfu/Tsm/bullinkle/Tsm-13-009-1

ACQUISITION
dacq 10000

Acq 499.746
dseq 1.0

At 3.001

NP 68050

SW 10504.2

fb not used

BS 8

tpwr 56

PW 8.6

di 2.000

tof 1519.5

nt 16

cf 0

alock n

Flags not used

flags

Display -0.8

WP 4000.2

VS 213

SC 0

WC 250

Hzmm 16.00

IS 33.57

RFL 1233.8

RFP 0

TH 7

INS 1.000

Al ph

Table 1.6, entry 9
Table 1.7, entry 1
STANDARD PROTON PARAMETERS

Sample 1 s2pul

Table 1.7, entry 2

![Chemical Structure](image)
STANDARD PROTON PARAMETERS

SAMPLE DEC. & VT
date Feb 29 2008 dfrq 125.672
solvent CDC13 dn C13
file /data/gfu/Tsm-
dof 0
_acq 3.001 dseq 1.0
sw 10548.2 dres n
fb not used temp 20.0
bs 8 DEC 1
pw 8.6 dn2
dl 2.000 dpwr2 1
tof 1519.5 dof2 0
ct 8 dam2 c
alock n daf2 200

gain not used dseq2
FLAGS dres2 1.0
l n homo2 n
in n
hs y dfrq3 0
DISPLAY dprw3 1
sp 4.4 dof3 0
wp 3993.2 dm3 n
vc 42 dam3 c
sc 0 dm3 200
wc 250 dseq3
hzm 15.7 dres3 1.0
is 33.57 homo3 n
rf1 1233.8 PROCESSING
rfp 0 wfile ft
th 7 proc fn 262144
ins 100.000 ph math f
werr wexp
wbs
wnt wft

Table 1.7, entry 3

[Chemical structure image]
STANDARD PROTON PARAMETERS

exp1 s2pu1

SAMPLE

date Feb 23 2009
dfreq 125.872
dofof.
solvent CDC13
dn C13
file /data/gfu/Tsm-13-036-H.fld
dpwr 30
dof 0

ACQUISITION

sfrq 499.746
dmm 10000
at 3.001
dseq 1.0
np 63050
dres 1.0
sw 1024.2
fb 20.0

tpwr 56
tof 1519.5
tn 18
ct 8

dseq 63050
dres 1.0

FLAGS

dseq 63050
dres 1.0

DISPLAY

sp 4.4
wp 3983.2
dm 69
dmm 0
df 250
hmm 15.87
is 33.57
rf 1233.6

PROCESSING

rfp 0
tn 7
ins 1.000
al 0.672

Table 1.7, entry 4

![N-alkenyl nitro compound](image)
STANDARD PROTON PARAMETERS

SAMPLE DATE DEC. & VT
date Feb 23 2009 dfreq 125.672
solvent CDCl3 dm 0
file /data/gfu/Tsm- dpwr 30
/Tsm-13-035-H.fid dof 0
ACQUISITION dm nn

sfrq 499.746 dm 0
ln H1 dmf 10000
at 3.001 dseq 1.0
hp 63050 dres n
sw 10504.2 homo n
fb not used temp 20.0
bs 8

tpwr 56 dfreq2 0
dw 8.6 dm2
id 2.000 dpwr2 1
tof 1515.5 dof2 0
t 16 dm2 n
c 8 dm3 c
alock n dm3 200

fls not used dseq2

FLAGS dres2 1.0

ll n homo2 n
ln n

DISPLAY dfreq3 0
dp y dm3

sp 4.4
wp 3993.2 dm3 n
vs 71 dm3 c
sc 0 dm3 200
wc 250 dseq3
zmm 15.87 dres3 1.0
is 33.57 homo3 n
rf 1233.8 PROCESSING

rt 0 wt file
th 7 proc
ins 100.000 ft
al ph 262144

werr
wexp
wbs
wnt wft

Table 1.7, entry 5

(EO)2P=(CH=CH-NO2)

Me
CHAPTER 2

Nickel-Catalyzed Negishi Cross-Couplings of Secondary Propargylic Electrophiles
Section 2.1

Introduction and Background
A. Introduction

In recent years, significant progress has been made in the area of transition metal-catalyzed cross-coupling. Cross-coupling reactions are generally defined as a set of reactions in which a new carbon-carbon bond ($R^1-R^2$) is formed through the union of an organometallic reagent ($R'^1-M^1$, where $R^1 = C, N, O, S, P, or B$) and a carbon electrophile ($R^2-X$, where $X = I, Br, Cl, OMs, OTf, or N_2; Ms = methanesulfonyl, Tf = trifluoromethanesulfonyl$) through the use of a transition metal catalyst. With respect to nomenclature, common names have been assigned to the various cross-coupling reactions based on the identity of $M^1$, often named after the individuals who contributed either to their discovery or subsequent development (Scheme 2.1).

A generalized mechanism is presented in Scheme 2.1. It has been traditionally held that inner-sphere cross-coupling reactions consist of three fundamental steps. There are instances in which the order of the first two steps may vary from that which is illustrated in Scheme 2.1. The process begins with the oxidative addition of a suitable catalyst ($LnM$) into the C–X bond of the organic electrophile. Transmetalation generates a diorganometallic intermediate ($LnMR^1R^2$), which then can reductively eliminate. This last step regenerates the transition metal catalyst ($LnM$) and releases the product ($R^1–R^2$). The overall efficiency of this three-step process is highly dependent on the nature of the metal and its associated ligands, which remain bound to the metal throughout this process.

---


67 The definition of “cross-coupling reaction” may be a subject of debate. We have chosen to define a cross-coupling reaction as a process in which both the nucleophilic atom of the organometallic reagent and the electrophilic carbon of the carbon electrophile are covalently bonded to a transition metal prior to reductive elimination. It should be noted that IUPAC has yet to put forth a definition of “cross-coupling reaction”.

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Scheme 2.1. Generalized Mechanism for Metal-Catalyzed Cross-Coupling Reactions.

![Diagram of the mechanism](image)

This mechanism, though simplified, is widely accepted, in particular for palladium catalysis, and is commonly referred to as a Pd$^{0}$/Pd$^{II}$ cycle, as these are the two oxidation states palladium holds during different stages of this process.

The mechanism shown in Scheme 2.1 is descriptive for cross-coupling reactions between organic partners not containing β-hydrogens, specifically sp- and sp$^2$-hybridized partners (such as aryl-, alkenyl- and alkynyl-electrophiles). The extension of cross-coupling reactions to β-hydrogen-containing alkyl electrophiles long remained elusive. This is, in part, due to the slower oxidative addition of LnM into more the electron-rich Ralkyl−X bonds and the commonly observed undesired reaction pathway known as β-hydride elimination. It is believed that agostic interactions between the transition metal and the β-hydrogens present on the alkyl electrophile trigger β-hydride elimination. Often β-hydride elimination outcompetes transmetallation and reductive elimination (see Scheme 2.2). Scheme 2.2 illustrates the commonly accepted

---


mechanism for a palladium-catalyzed cross-coupling of alkyl partners. For nickel-based cross-coupling reactions of alkyl fragments, the mechanism requires further study. 71,70a

Scheme 2.2. Generalized Mechanism for Metal-Catalyzed Cross-Coupling Reactions of β-Hydrogen Containing Alkyl Electrophiles.

Whereas the focus in cross-coupling chemistry traditionally has been on the formation of new sp²-sp² C–C bonds, 72 our group and others have been working to expand the scope of these processes to include new sp³-sp² and sp³-sp³ C–C bonds. 69,73


72 For work in this area from our group, see: Fu, G. C. Acc. Chem. Res. 2008, 41, 1555-1564, and references therein.

By the time I joined the Fu laboratory in 2004, substantial progress had been made on cross-coupling reactions of alkyl electrophiles; much of this work utilized palladium-based catalysts and bulky, electron-rich phosphines. The bulk of this work had been focused on the development of reaction conditions whereby primary nucleophiles could be coupled with primary electrophiles. The remainder of this section highlights some of the work performed in the Fu group prior to my joining. Developments which took place during my time in the group are discussed throughout Chapter 2.
B. Negishi Coupling Reaction

In 2003, Steve Zhou developed a catalyst that, for the first time, allowed for the cross-coupling of primary organozinc reagents with secondary electrophiles.\(^{74}\) This significant step forward required a shift from palladium to nickel. Nickel, which had been used by Kambe\(^{75}\) and Knochel\(^{76}\) to achieve primary-primary alkyl-alkyl cross-couplings, is believed to be a better catalyst for cross-coupling alkyl electrophiles because it is more reactive in the oxidative addition of alkyl electrophiles than palladium and it is less prone to undergo β-hydride elimination.\(^{77}\) Dr. Zhou’s Ni(cod)\(_2\)/(s-Bu)-Pybox catalyst displayed a broad scope (Scheme 2.3). With respect to the electrophile, both cyclic and acyclic secondary bromides and iodides coupled efficiently. An array of functional groups were compatible with the room-temperature reaction conditions, including ethers, acetics, esters, amides and protected amines.

Scheme 2.3. Nickel-Catalyzed Negishi Reactions of Alkyl Bromides and Iodides.

---

\(^{75}\) See ref 72g and 72h, and: (c) Terao, J.; Todo, H.; Ikumi, A.; Kambe, N. Angew. Chem. Int. Ed. 2004, 43, 6180-6182.
\(^{76}\) (a) Giovannini, R.; Stüdemann, T.; Dussin, G.; Knochel, P. Angew. Chem. Int. Ed. 1998, 37, 2387-2390. Also, see: ref. 72d.
Development of the first metal-catalyzed method for cross-coupling β-hydrogen containing secondary electrophiles, opened the door for asymmetric cross-coupling reactions, as a stereocenter may be produced at the carbon that bears the leaving group. The ability to control the configuration about this new stereocenter would clearly have a dramatic impact on the utility of this reaction. Dr. Zhou devoted considerable time towards the development of such a process. Among the many secondary electrophiles he studied in this context, benzylic bromides led to the most promising and exciting results. Dr. Zhou found that with (i-Pr)-Pybox he could obtain the product in up to 46% yield and 72% ee (eq 2.1).\(^7\)\(^8\) It is worth noting, that this remarkable process is stereoconvergent. The racemic starting material remains racemic throughout the reaction, and yet, one enantiomer of product is generated in preference over the other.

This preliminary work was further optimized by Forrest Arp; he found conditions for which a subclass of benzylic halides, α-bromoinanes, could participate in a stereoconvergent cross-coupling reaction with primary organozinc bromides, obtaining very high levels of enantioselectivity (Scheme 2.4).\(^7\)\(^9\) The nucleophilic coupling partner could possess a wide range of functionality: acetals, nitriles, primary alkyl chlorides, protected amines and ethers were well tolerated. Similar to the work by Dr. Zhou, a departure from the indane scaffold to an acylic benzylic bromide led to a dramatic loss of selectivity (95% → 75% ee).


Scheme 2.4. Catalytic Enantioselective Negishi Reactions of Racemic Secondary Benzylic Halides.

Concurrent to the work by Dr. Arp, Christian Fischer developed a similar set of reaction conditions which proved to be suitable for the cross-coupling of primary organozinc bromides with α-bromo amides in excellent enantioselectivities (Scheme 2.5). This method was the first reported example of an asymmetric cross-coupling of a secondary electrophile. Dr. Fischer was able to modulate both the reactivity and enantioselectivity of this transformation in part through variation of the amide nitrogen substituents; the N-phenyl, N-benzyl-amide proved to be the best combination. Importantly, an assortment of functionalized nucleophiles coupled well under these reaction conditions.

---

Scheme 2.5. Asymmetric Nickel-Catalyzed Cross-Couplings of Secondary α-Bromo Amides with Organozinc Reagents.

C. Suzuki Coupling Reaction

In 2003, during his next project, Dr. Zhou demonstrated that a nickel-based catalyst was not exclusively active for Negishi reactions, but also worked very well, once optimized, for Suzuki cross-coupling reactions between arylboronic acids and secondary electrophiles (Scheme 2.6). A Ni(cod)₂/bathophenanthroline-based catalyst system was capable of facilitating the coupling of an array of functionalized arylboronic acids; this included electron-rich and electron-poor nucleophiles (and even several heteroaromatic examples) with secondary bromides and iodides. There were some limitations with respect to the electrophilic partner; namely, cyclic and acyclic bromides more sterically demanding than cyclohexane or isopropyl bromide were not efficient. That being said, the development of this reaction set the groundwork for a great wealth of methodology which was developed over the next several years, particularly for Hiyama and Stille reactions (see the next two sections).

---


\[
\begin{align*}
R^1 R^2 X &\xrightarrow{4\% \text{ Ni(cod)}_2, 8\% \text{ bathophenanthroline}} (\text{HO})_2 B^- \text{Ar} \xrightarrow{\text{KOH-Bu}, s\text{-BuOH, } 60^\circ C} R^1 R^2 \text{Ar} \\
\text{11 examples; } &44-90\% \text{ yield}
\end{align*}
\]

D. Hiyama Coupling Reaction

Following Dr. Zhou’s initial success in his Suzuki cross-coupling reactions between arylboronic acids and secondary electrophiles, Dave Powell developed reaction conditions that allowed for the efficient coupling of secondary electrophiles with organosilicon reagents (Scheme 2.7).\textsuperscript{82} En route to accomplishing this goal, Dr. Powell found that air-stable nickel-glyme precatalysts were quite suitable to this new family of coupling reactions. It is worth noting that these nickel salts have now become a mainstay within the group, and have allowed for many of the new reactions to be carried out on the bench in the absence of a N\textsubscript{2}-filled glovebox. Dr. Powell’s reaction conditions made use of bathophenanthroline as the ligand, and cesium fluoride was used as an activator to generate intermediate silicates which undergo transmetalation more easily. This reaction displayed a broad scope with respect to the electrophile; several substrates which proved difficult for Dr. Zhou’s Suzuki reaction readily reacted under these conditions. Although even ortho-substituted nucleophiles performed well in this reaction, a drawback of using aryl trifluorosilanes is that often distillation is the only means by which these nucleophiles can be purified.


E. Stille Coupling Reaction

A nickel-based catalyst also proved to be effective for the Stille arylation of secondary electrophiles (Scheme 2.8).\textsuperscript{83} The NiCl\textsubscript{2}/bipyridine catalyzed reaction, developed by Dr. Powell and Dr. Toshihide Maki, displayed a scope similar to Dr. Powell’s Hiyama reaction (c.f. Scheme 2.7). This reaction had the distinct advantage that it was effective with trichloroaryl tin reagents, thus generating no triorganotin byproducts.\textsuperscript{84} Circumventing generation of triorganotin compounds not only simplifies purification of the resultant product, but also lowers the health risk associated with Stille reactions.


\textsuperscript{84} For the toxicity of triorganotins, see: Bulten, E. J.; Meinema, H. In \textit{Metals and Their Compounds in the Environment}; Merian, E., Ed.; VCH: New York, 1991; Chapter II.30, p. 1243.

F. Conclusion

Thus was the state of the art in 2005 regarding the coupling of secondary electrophiles; it has been exciting to participate and observe the developments which have taken place in the years since. When I began my study of nickel-catalyzed couplings of secondary propargylic halides, I had no way of predicting the path it would take. This chapter discusses work on the nickel-catalyzed couplings of secondary propargylic halides with a variety of organozinc nucleophiles. Section 2.2 describes progress toward an asymmetric alkylation reaction. In Section 2.3, the development of the first alkyl-alkyl secondary-secondary cross-coupling is described. Section 2.4 describes the application of this coupling reaction to the formal synthesis of α-cembra-2,7,11-triene-4,6-diol. The last section of this thesis (Section 2.5) discusses the development of the first asymmetric Negishi reaction of arylzinc reagents with secondary electrophiles.
Section 2.2

Nickel-Catalyzed Asymmetric Cross-Couplings of Racemic Propargylic Halides with Alkylzinc Reagents
A. Introduction

The first investigation of asymmetric transition metal-catalyzed cross-coupling reactions were carried out by Hayashi and Kumada in the mid-1970’s. In that work, the asymmetric, nickel-catalyzed cross-couplings with chiral bidentate phosphines allowed for the dynamic resolution of configurationally unstable benzylic magnesium reagents and the efficient coupling with sp²-hybridized electrophiles (in up to 17% ee). In short order, Hayashi and Kumada discovered that more efficient conditions could be developed through use of chiral, bidentate aminophosphine ligands. Thus, with the amino-alcohol derived ligand Valphos, enantioselectivities up to 83% could be obtained for the coupling of vinyl bromides with secondary benzylic magnesium reagents (eq 2.2).

\[
\text{racemic} \quad \text{MgCl} \quad \text{NiCl}_2 \quad \text{MeBr} \quad (S)\text{-Valphos} \quad \text{MeMe}_2 \text{N} \text{PPh}_2 \quad 83\% \text{ ee} \quad (S)\text{-Valphos}
\]

Additional study discovered that ferrocenyl-based aminophosphines of the type shown in equation 2.3 could provide even higher levels of enantioselectivity in the coupling of substituted vinyl bromides and α-(trimethylsilyl)benzylmagnesium bromide.

\[
\text{racemic} \quad \text{MgCl} \quad \text{SiMe}_3 \text{Br} \quad \text{Ph} \quad \text{PdCl}_2[(R)-(S)-\text{PPFA}] \quad 95\% \text{ ee} \quad \text{PdCl}_2[(R)-(S)-\text{PPFA}]
\]

When I joined the Fu group in 2004, Dr. Fischer and Dr. Arp had recently developed the first examples of asymmetric cross-coupling reactions of electrophiles bearing β-hydrogens (see...

---

introduction). As my umpolung project (Chapter 1, Section 1) was drawing to a close, I had a high level of interest in contributing to this exciting and new area of study. As success in these reactions had required the use of activated electrophiles, we chose to study the asymmetric alkylation of secondary propargylic halides. I felt that success in this study would allow for straightforward access to enantioenriched secondary propargylic compounds and would solve an unmet challenge.  

B. Results and Discussion

Naturally our first attempt of an asymmetric alkylation of secondary propargylic halides was simply to apply the final conditions which proved successful for Dr. Fischer and Dr. Arp. Thus, application of the NiCl2-glyme/(i-Pr)-Pybox reaction conditions to a trimethylsilyl-protected propargylic bromide was carried out. We were pleased to see that these reaction conditions furnished the desired product in good yield, albeit with modest selectivity (19% ee, eq 2.4).

![Chemical Reaction Diagram]

Examination of the group’s library of chiral Pybox ligands, a brief selection of which are illustrated in Table 2.1, presented a possible avenue for further optimization. The free-alcohol containing Pybox L5 revealed itself as the best of the group’s current library; although the yield was modest, the ee increased to 38%.

---


90 For a review on Pybox ligands, see: Desimoni, G.; Faita, G.; Quadrelli, P. Chem. Rev. 2003, 103, 3119-3154.
Table 2.1. Initial Foray into an Asymmetric Alkylation Reaction of Propargylic Halides.

<table>
<thead>
<tr>
<th>entry</th>
<th>Pybox ligand</th>
<th>GC yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L1</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>L2</td>
<td>90</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>L3</td>
<td>14</td>
<td>&lt;5</td>
</tr>
<tr>
<td>4</td>
<td>L4</td>
<td>92</td>
<td>23</td>
</tr>
<tr>
<td>5</td>
<td>L5</td>
<td>30</td>
<td>38</td>
</tr>
<tr>
<td>6</td>
<td>L6</td>
<td>21</td>
<td>21</td>
</tr>
</tbody>
</table>

Because of the noticeable difference in selectivity observed for L5 versus L4, it was hypothesized that the presence of a free alcohol, or even the deprotonated alcohol could have a positive impact on this coupling reaction. Pybox L5 requires a somewhat tedious multi-step synthesis\textsuperscript{91} and it was soon realized that ligand L7, which gave similar results under these reaction conditions, could be made on large scale in a single step.\textsuperscript{92} In fact, with Pybox L7,


reactions run at 0 °C, in which the electrophile was added last provided the desired product in 25% yield and 62% ee.

\[
\text{N} \text{N} \text{Ph,}\text{N} \text{u-Ph} \text{OH} \text{L7 HO}
\]

Over the next several months, a large variety of reaction conditions were surveyed. It was found that a THF:DMA solvent mixture was best; yields also increased upon addition of ZnBr\(_2\) as an additive (eq 2.5). All additional attempts to improve this reaction using L7 were unsuccessful.

Some time was devoted to improving the basic scaffold of L7. As it had been observed that the 5,5'-diphenyl substitution on the oxazolines was beneficial, a small set of Pybox ligands were synthesized in which the electronic character of these aryl groups was modified. Some time was also devoted to variation of the central pyridine ring (Scheme 2.9).

---

93 Other silyl- and acetone-based substituted propargylic halides did not offer any improvements with respect to enantioselectivity.
94 (a) L8 was prepared according to: Müller, P.; Boléa, C. *Helv. Chim. Acta.* **2001**, *84*, 1093-1111. (b) L9, L10 and L11 were prepared according to ref. 92.
Scheme 2.9. Analogues of Pybox L7.

Out of this work came only a marginal improvement to the selectivity; Pybox L9 was found capable of facilitating this coupling with 78% ee at low temperature. As is clear in equation 2.6, the efficiency of this reaction was quite poor, and in the end, this led us to consider other families of ligands.

In 2005, Beller and co-workers published a series of papers describing the synthesis of Pybim ligands, which performed reasonably in Ru-catalyzed asymmetric epoxidations. The similarity of these ligands to the Pybox family that we had been focusing on was clear, and the possible flexibility of their synthesis was considered attractive. A number of Pybim ligands (Scheme 2.10), reported by Beller, were prepared and applied to our asymmetric alkylation.

---

Scheme 2.10. Pybim Ligands.

The best results obtained, to date, with this family of ligands is shown in equation 2.7. It was found that the phenyl carbamate substituted Pybim ligand could impart the same level of enantioselectivity as L9. Once again, the low temperature necessary for this selectivity was detrimental to the overall reactivity of the system.

Allene formation

It is well established that palladium-catalyzed cross-coupling reactions of propargylic electrophiles with organometallic reagents typically provide the allene, rather than the alkyne, as the predominant product.96 We have observed that nickel-catalyzed alkylations of propargylic electrophiles with organometallic reagents can afford the allene, rather than the alkyne, as the predominant product.

---

halides always lead to formation of a propargylic product, when the ligand is tridentate. Interestingly, we have found that the regioselectivity of this reaction is dictated by choice of the ligand. Thus, nickel-catalyzed alkylation of propargylic halides lead to formation of allenes when a bidentate ligand is used (eq 2.8). Due in part to time constraints, a more thorough study of this reactivity was not pursued.

\[
\begin{align*}
\text{TMS} \equiv \equiv & \quad \text{Br} \quad \text{BrZn-}n\text{-Hex} \\
\text{racemic} & \quad \text{cat. Ni bidentate ligand} \\
\text{TMS} & \quad n\text{-Bu} \quad n\text{-Bu}
\end{align*}
\]

\text{(2.8)}

\text{yield and regioselectivity dependent on ligand}

C. Conclusion

It was at this stage of the project that we began to grow somewhat pessimistic about the success of this effort as a whole. Of the reaction conditions surveyed to date, we were capable of achieving the coupling in high yield, with low levels of selectivity, or in the instances where selectivity began to increase, the efficiency plummeted.

Our original reasons for studying this transformation were still of interest: there had been no reports of nickel-catalyzed cross-coupling reaction of secondary propargylic halides and we were observing high regioselectivity in these couplings. Thus nickel-based catalysis still seemed to be the ideal strategy for the synthesis of more complex propargylic compounds. We decided it would be interesting to investigate other families of organozinc reagents and their coupling reactions with propargylic halides. This decision proved to be an excellent one and the results of those efforts are described in the Sections 2.3-2.5.
D. Further Developments

Negishi Coupling Reaction

Coinciding with the initiation of the asymmetric alkylation of propargylic halides discussed in the previous section, Dr. Sunghee Son looked into the development of an asymmetric alkylation of allylic halides. Preliminary studies showed that the reaction could occur with high levels of enantioselectivity with styrenyl-type secondary bromides under the conditions Dr. Arp developed for his α-bromo indane coupling reaction. Unfortunately, low yields and decomposition of the starting material hampered progress on this coupling reaction. Dr. Son found that use of allylic chlorides was considerably more practical. After extensive studies, Dr. Son discovered that, moving away from (i-Pr)-Pybox to the unique homobenzylic substituted Pybox in addition to including 4.0 equivalents of anhydrous NaCl, she could accomplish the desired coupling not only in good yield, but with excellent levels of enantioselectivity (Scheme 2.11).\(^7\) The synthetic utility of this transformation was highlighted in Dr. Son’s concise formal synthesis of fluvirucinine A. Others have also seen the value of this reaction, as now the homobenzylic Pybox is commercially available.\(^8\)

Scheme 2.11. Nickel-Catalyzed Asymmetric Negishi Cross-Couplings of Secondary Allylic Chlorides with Alkylzincs.

\(^8\) Available from Aldrich, catalog number: 704059.
Suzuki Coupling Reaction

The first example of the coupling of an alkylboron reagent and a secondary alkyl electrophile was published in 2007. Dr. Bunnai Saito found that primary alkyl 9-BBN reagents could be coupled with a broad selection of secondary bromides using a NiCl₂·glyme/diamine-based catalyst (Scheme 2.12). ⁹⁹ Although some functionalized nucleophiles proved problematic under these reaction conditions (such as unhindered esters), the ease of nucleophile preparation certainly adds strength to this methodology.


It was of immediate interest to investigate an asymmetric variant of this new alkylation reaction. Upon examining the outcome of the reaction when (R,R)-N,N'-dimethyl-1,2-cyclohexanediamine was used in the coupling reaction described above, Dr. Saito was quite pleased to observe formation of the product in 58% ee. Following substantial optimization, an efficient, highly selective variant of this coupling was described in 2008 (Scheme 2.13). ¹⁰⁰ It was imperative that the electrophile be homobenzyllic in order to obtain high enantioselectivity.

---


**Scheme 2.13.** Enantioselective Alkyl-Alkyl Suzuki Cross-Couplings of Unactivated Homobenzylic Halides.

\[
\begin{align*}
\text{Ph} & \quad \text{R} \\
\text{Br} & \quad \text{9-BBN}-\text{R}_{\text{alkyl}} \\
\text{racemic} & \\
& \quad \text{Ni(cod)}_2 \quad \text{KOT-Bu} \\
& \quad \text{i-BuOH} \quad \text{i-Pr}_2\text{O}, 5^\circ \text{C} \\
& \quad \text{R}_{\text{alkyl}} \quad \text{MeHN} \quad \text{NHMe} \\
& \quad \text{Ph} \quad \text{Me} \\
\end{align*}
\]

10% Ni(cod)$_2$
12% (R,R)-N,N'-dimethyl-1,2-di-(m-C$_6$H$_4$CF$_3$)diamine

14 examples; 62-86% yield 40-94% ee

F$_3$C-\[\begin{array}{c}
\text{MeHN} \\
\text{NHMe}
\end{array}\]

84% yield 94% ee

68% yield 90% ee

68% yield 78% ee

74% yield 85% ee

\[
\begin{align*}
\text{Ph} & \quad \text{Me} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Me} \\
\text{OTBS} & \\
\text{O} & \quad \text{Me} \\
\text{O} & \quad \text{Me}
\end{align*}
\]
E. Experimental

I. General

All reactions were carried out in oven-dried glassware under an atmosphere of argon. N,N-Dimethylacetamide was purchased from Fluka (anhydrous). All other chemicals were purchased and used without further purification.

Low-resolution mass spectrometric measurements were performed on an Agilent (EI) GCMS system.

For preparation of starting materials, see Chapter 2, Section 3.

II. Starting Material

\[
\begin{align*}
\text{TMS} & \quad \text{n-Bu} \\
\text{Br} & \\
\end{align*}
\]

\(^1H\) NMR (CDCl\(_3\), 300 MHz) \(\delta\) 4.48 (t, \(J = 6.6\) Hz, 1H), 1.98 (q, 6.6 Hz, 2H), 1.54-1.44 (m, 2H), 1.33 (sextet, \(J = 7.2\) Hz, 2H), 0.92 (t, 7.2 Hz, 3H), 0.18-0.16 (m, 9H).

\(^13C\) NMR (CDCl\(_3\), 75 MHz) \(\delta\) 104.2, 92.0, 39.6, 37.6, 29.7, 22.1, 14.1, -0.02.

IR (film) 2959, 2863, 2361, 2338, 2174, 1457, 1250 cm\(^{-1}\).

HRMS (EI) calcd for C\(_9\)H\(_{16}\)BrSi (M-Me\(^+\)) 231, found 231.

III. Product Characterization

\[
\begin{align*}
\text{TMS} & \quad \text{n-Hex} \\
\text{n-Bu} & \\
\end{align*}
\]

\(^1H\) NMR (CDCl\(_3\), 300 MHz) \(\delta\) 2.38-2.24 (m, 1H), 1.45-1.20 (m, 16H), 0.94-0.82 (m, 6H), 0.12 (s, 9H).

LRMS (EI) calcd for C\(_{16}\)H\(_{32}\)Si (M\(^+\)) 252, found 252.
\(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 4.81-4.77 (m, 1H), 2.00-1.87 (m, 4H), 1.45-1.20 (m, 12H), 0.96-0.81 (m, 6H), 0.10 (s, 9H).

LRMS (El) calcd for C\(_{16}\)H\(_{32}\)Si (M\(^+\)) 252, found 252.

IV. Determination of Absolute Stereochemistry

For preparation of the chiral amide, see: Ref. 79
F. $^1$H NMR Spectra of Selected Compounds
exp2 std1h

SAMPLE

DATE Feb 4 2006

SOLVENT CDCl3

FILE /data/export/-
dpwr 30

HOME/gfu/Tsm/mrhat-
/Tsm-03-060.fid

ACQUISITION dme c

SFRQ 300.100

ACQ PROCESSING 200

TN 1.995

NP 17984

SW 4506.5

FB not used

BS 2

TPWR 54

PW 7.0

DI 1.000

tof 0

NT 32

cT 32

ALOCK n

GAIN not used

FLAGS n

DISPLAY

SP 2.2

WP 2398.2

VS 395

SC 8

WC 250

Hzmm 9.59

IS 139.74

Rf1 1179.1

RFP 0

TH 20

INS 1.000

nm cdc ph

TMS

n-Hex

n-Bu
STANDARD 1H OBSERVE

exp2 std1h

SAMPLE

date Feb 3 2006
dfrq 300.100

solvent CDC13
dn 30

tn 300.100 dmft

n-p 17984

sw 4506.5

tf w

tpwr 1.0
nd

dt 1.008

nt 16

ct 16

flags

DISPLAY

sp -302.3

wp 2700.2

vs 420

sc 0

wc 250

dm 10.80

dn 73.28

rf1 2808.6

rfp 2181.7

th 20

ins 1.088

nm cdc ph

---

7 6 5 4 3 2 1 -0

0.74 1.00 4.32 18.55 8.74 8.65
Section 2.3

Nickel-Catalyzed Negishi Cross-Couplings of Secondary Nucleophiles with Secondary Propargylic Electrophiles
A. Introduction

In previous sections we have described some recent progress toward extending the scope of transition metal-catalyzed cross-coupling reaction from the construction of sp\(^2\)-sp\(^2\) carbon-carbon bonds to that of sp\(^3\)-sp\(^3\) carbon-carbon bonds. Furthermore, a significant amount of work has been focused on the coupling of more sterically demanding coupling partners, including secondary alkyl electrophiles. We have seen that this area of progress was initiated in work by Zhou and Fu, in which it was reported that a Ni(cod)\(_2\)/s-Bu-Pybox system catalyzes Negishi reactions of secondary alkyl bromides and iodides with primary alkyl zinc reagents (eq 2.9).\(^{71,72d}\)

\[
\begin{align*}
R-X & \quad YZn-R_{alkyl} & \quad 4\% \text{Ni(cod)}_{2}\/or \quad 8\% \text{(s-Bu)-Pybox} & \quad R-R_{alkyl} \quad \text{DMA, r.t.} & \quad (s-Bu)-Pybox
\end{align*}
\]

In 2002, Knochel reported nickel-based reaction conditions for the cross-coupling of primary alkyl electrophiles with primary alkylzinc reagents. Additionally, it was reported that several cross-couplings of primary alkyl electrophiles and secondary organozinc reagents could be effected as well (Scheme 2.14).\(^{101}\)


In our continued study of alkyl cross-couplings it was of course of interest to study reactions of even more sterically demanding coupling partners; namely, the coupling of a secondary alkyl halide with a secondary organometallic reagent. Based on the ease of synthesis and high functional group compatibility of secondary organozinc halide reagents we chose to develop a Negishi cross-coupling reaction.\(^{102}\)

**B. Results and Discussion**

At the outset of this project, it was speculated that propargylic electrophiles might be an interesting entry into this new coupling reaction, as they can be thought of as one of the least sterically demanding secondary electrophiles one might imagine, and thus would be an ideal choice for an initial investigation. This hypothesis was quickly validated with an early hit. Thus, using 10% NiCl\(_2\)-glyme and 13% terpyridine in DMA led to formation of 28% of the desired coupling product (see eq 2.10).

---

\(^{102}\) For the preparation of organozinc halides, see the experimental section.
Upon further optimization, we soon found that we could further increase the yield to 44% simply by reducing the concentration of the reaction to 0.05 M. For some time, this proved to be the best result we could obtain, as we were unable to find reaction conditions which could evade the formation of a considerable amount of electrophile homocoupling. Our current theory to explain this homocoupling is as follows: we believe that transmetalation of the secondary organozinc halide reagent onto nickel is slow, allowing a [1,3]-isomerization to take place on the propargylic nickel species formed via oxidative addition (Scheme 2.15). In the cases where R is small, the equilibrium favors the allenynickel intermediate and it is this intermediate that proceeds to participate in undesired side reactions leading to the formation of the homocoupled products.

**Scheme 2.15.** Formation of Undesired Homocoupling Products.

Our thinking was that simply by increasing the steric demand of R we would be able to slow, or eliminate, this isomerization process and enable the initial oxidative addition adduct to undergo transmetallation and proceed to formation of the desired product (Scheme 2.16).
Table 2.2 summarizes the effect R has on the reaction efficiency. We see that, with a very small group such as methyl, we obtain only 15% of the desired product. As we increased the steric demand of the alkyne-capping group we see that conversion to desired product also increases. We were quite pleased to see that utilizing the sterically-demanding TIPS-protecting group allowed us to obtain 89% of the desired product.

Table 2.3 has been included to illustrate the impact of various other reaction parameters. In the absence of NiCl₂-glyme or terpyridine, essentially no carbon-carbon bond formation occurs (entries 2 and 3). Other ligands, both bidentate and tridentate, that have been examined are less useful than terpyridine (entries 4-6), as are solvents other than DMA (entries 7-9).

---

103 Terminal alkynes gave no detectable cross-coupling product.
Table 2.2. Effect of the Alkyne Substituent on the Efficiency of Negishi Reactions of Secondary Nucleophiles with Secondary Propargylic Electrophiles.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>R =</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I-Me</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>I-TMS</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>Si(Me)&lt;sub&gt;2&lt;/sub&gt;Ph</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>I-SiPh&lt;sub&gt;3&lt;/sub&gt;</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td>I-TIPS</td>
<td>89</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yield was determined by GC versus an internal standard.

Table 2.3. Negishi Reactions of Secondary Nucleophiles with Secondary Propargylic Electrophiles: Effect of Reaction Parameters.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>variation from &quot;standard&quot; conditions</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>no NiCl&lt;sub&gt;2&lt;/sub&gt;-glyme</td>
<td>&lt;5</td>
</tr>
<tr>
<td>3</td>
<td>no terpyridine</td>
<td>&lt;5</td>
</tr>
<tr>
<td>4</td>
<td>bipyridine, instead of terpyridine</td>
<td>&lt;5</td>
</tr>
<tr>
<td>5</td>
<td>isopropyl pybox, instead of terpyridine</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>2,6-bis(N-pyrazolyl)pyridine, instead of terpyridine</td>
<td>62</td>
</tr>
<tr>
<td>7</td>
<td>THF, instead of DMA</td>
<td>11</td>
</tr>
<tr>
<td>8</td>
<td>DMF, instead of DMA</td>
<td>9</td>
</tr>
<tr>
<td>9</td>
<td>DMI, instead of DMA</td>
<td>4</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yield was determined by GC versus an internal standard.
These optimized conditions (NiCl₂·glyme/terpyridine/DMA) can be applied to a broad range of Negishi cross-couplings of propargylic bromides (Table 2.4). Esters, olefins (no E/Z isomerization), ethers and carbamates are compatible with the reaction conditions.¹⁰⁴

Table 2.4. Room-Temperature Negishi Reactions of Secondary Nucleophiles with Secondary Propargylic Electrophiles.

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>alkyl</th>
<th>iZn-R¹</th>
<th>yield (%)ᵃ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TIPS</td>
<td>Me</td>
<td>iZn-Me</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>TIPS</td>
<td>CO₂Me</td>
<td>iZn-CO₂Me</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>TIPS</td>
<td>Et</td>
<td>iZn-Et</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>TIPS</td>
<td>Me</td>
<td>iZn-O</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>TIPS</td>
<td>Me</td>
<td>iZn-NCbz</td>
<td>74</td>
</tr>
<tr>
<td>6</td>
<td>TIPS</td>
<td>CO₂Me</td>
<td>iZn-Me-Me</td>
<td>63</td>
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<tr>
<td>7</td>
<td>'Bu</td>
<td>CO₂Me</td>
<td>iZn-Me</td>
<td>72</td>
</tr>
<tr>
<td>8</td>
<td>'Bu</td>
<td>Ph</td>
<td>iZn-Ph</td>
<td>73</td>
</tr>
</tbody>
</table>

ᵃ Isolated yield (average of two experiments).

In the interest of exploring the versatility of this catalyst, these reaction conditions can be applied without modification to Negishi reactions of less-hindered coupling partners. Thus,

¹⁰⁴ Notes: (a) In the absence of NiCl₂·glyme or terpyridine, essentially no cross-coupling occurs. (b) Organozinc iodides, rather than bromides, were employed owing to ease of synthesis. (c) Attempts to cross-couple an acetonitrile-protected or an aryl-substituted alkyne were not successful. (d) Under our standard conditions, Negishi reactions of hindered electrophiles (e.g., alkyl = iPr in Table 2.4) proceed in low yield, and unactivated alkyl chlorides are not suitable cross-coupling partners.
Primary organozinc bromides can be coupled in exceptional yield with secondary propargylic bromides. Also, the primary-primary coupling occurs without incident. It is worth noting that ethers, esters and unactivated alkyl chlorides are unaffected by these reaction conditions (see Table 2.5).\textsuperscript{105}

Table 2.5. Negishi Reactions of Primary Nucleophiles with Secondary and Primary Propargylic Electrophiles.

<table>
<thead>
<tr>
<th>entry</th>
<th>alkyl</th>
<th>BrZn-R\textsuperscript{1}</th>
<th>yield (%)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cl</td>
<td>BrZn-OBn</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>BrZn-OEt</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>BrZn-OEt</td>
<td>90</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Isolated yield (average of two experiments).

When we attempted to apply the NiCl\textsubscript{2}-glyme/terpyridine/DMA conditions to the coupling of more sterically demanding secondary organozinc reagents, we found that the efficiency of the reaction decreased dramatically (Equation 2.11). Accompanying the desired product, a substantial quantity of reduced electrophile was also observed (i.e. dehalogenation).

\textsuperscript{105} A Negishi cross-coupling of a primary propargylic bromide with a secondary alkylzinc reagent proceeded in low yield.
Fortunately, replacing terpyridine with the related tridentate ligand 2,6-bis(N-pyrazolyl)pyridine (L13) and using THF in place of DMA as the solvent solved this difficulty.\textsuperscript{106} We postulate that the slightly larger bite-angle of L13 is responsible for the recovery of reactivity. Once again, a very brief table describing the impact of various other reaction parameters has been included for illustrative purposes (Table 2.6). As before, in the absence of NiCl\textsubscript{2}-glyme or terpyridine, essentially no carbon-carbon bond formation occurs (entries 2 and 3). Other solvents, for example DMA, are inferior to THF but solvent mixtures can have a positive impact (entries 5 and 6).

**Table 2.6.** Negishi Reactions of Secondary Nucleophiles with Secondary Propargylic Electrophiles: Effect of Reaction Parameters.

<table>
<thead>
<tr>
<th>entry</th>
<th>variation from &quot;standard&quot; conditions</th>
<th>yield (%)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>no NiCl\textsubscript{2}-glyme</td>
<td>&lt;5</td>
</tr>
<tr>
<td>3</td>
<td>no 2,6-bis(N-pyrazolyl)pyridine</td>
<td>&lt;5</td>
</tr>
<tr>
<td>4</td>
<td>terpyridine, instead of 2,6-bis(N-pyrazolyl)pyridine</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>DMA, instead of THF</td>
<td>66</td>
</tr>
<tr>
<td>6</td>
<td>2:1 THF:DMA, instead of THF</td>
<td>72</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Yield was determined by GC versus an internal standard.

Thus, with a second set of reaction conditions (NiCl\textsubscript{2}-glyme/L13/THF) many additional coupling reactions between secondary propargylic electrophiles and more hindered secondary organozinc reagents may now be accomplished. As illustrated in Table 2.7, a variety of functional groups are tolerated, such as alkynes, unactivated chlorides and ethers.

\textsuperscript{106} Vicić et al., have reported that [Ni(cod)\textsubscript{2}]/2,6-bis(N-pyrazolyl)-pyridine in THF catalyzes the Negishi coupling of a primary alkylzinc reagent with a primary alkyl bromide (45\% yield) and with a primary alkyl iodide (67\% yield): Ref 68a.
Table 2.7. Room-Temperature Negishi Reactions of Secondary Nucleophiles with Secondary Propargylic Electrophiles.

We have determined that these reaction conditions do not work exclusively for propargylic bromides, but also for propargylic chlorides, still at room temperature (eqs. 2.12 and 2.13).
C. Conclusions

We have developed the first alkyl-alkyl secondary-secondary cross-coupling, specifically the nickel-catalyzed coupling of secondary propargylic bromides with secondary alkylzinc halide reagents. The catalyst systems presented are also capable of coupling primary alkylzinc bromides with primary and secondary propargylic bromides. This new methodology has also been shown to be capable of coupling propargylic chlorides. For a discussion of the application of this cross-coupling reaction to the formal synthesis of 2,7,11-cembratriene-4,6-diol, see Chapter 2, Section 3.
D. Experimental

I. General

All reactions were carried out in oven-dried glassware under an atmosphere of argon. \(N,N\)-Dimethylacetamide was purchased from Fluka (anhydrous), and THF was dried by passage over activated alumina. All other chemicals were purchased and used without further purification.

High-resolution mass spectrometric measurements were performed on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer system.

Low-resolution mass spectrometric measurements were performed on an Agilent GCMS system.

II. Preparation of Substrates

These procedures have not been optimized.

**Synthesis of Propargylic Alcohols (representative procedure):** A 100 mL flask was charged with (triisopropylsilyl)acetylene (2.2 mL, 10.0 mmol), evacuated, and back-filled with argon. THF (50 mL) was then added via syringe. The solution was then cooled to -78 °C in a dry ice/acetone bath. After 15 min of cooling, \(n\)-BuLi (6.6 mL of a 1.6 M solution in hexanes, 10.5 mmol) was added dropwise, via syringe. After an additional 20 min of stirring, the aldehyde (11.0 mmol) was added via syringe. The solution was allowed to warm to room temperature, at which point the reaction was quenched with an aqueous saturated ammonium chloride solution (25 mL). The layers were separated, and the aqueous layer was extracted twice with \(\text{CH}_2\text{Cl}_2\) (50 mL). The combined organic layers were washed with brine (50 mL) and dried over \(\text{MgSO}_4\), filtered and concentrated under reduced pressure. The resultant oil was purified via flash chromatography (hexanes/EtOAc or pentane/Et\(_2\)O) to give the propargylic alcohols as oils.
1-(Trimethylsilyl)hept-1-yn-3-ol [CAS # 75045-85-1]. Prepared from (trimethylsilyl)-acetylene and valeraldehyde by the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) δ 4.32 (t, $J = 6.6$ Hz, 1H), 2.20 (broad s, 1H), 1.71-1.62 (m, 2H), 1.46-1.23 (m, 4H), 0.89 (t, $J = 6.9$ Hz, 3H), 0.14 (s, 9H).

1-(Dimethyl(phenyl)silyl)hept-1-yn-3-ol. Prepared from (dimethyl(phenyl)silyl)acetylene and valeraldehyde by the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) δ 7.65-7.61 (m, 2H), 7.43-7.38 (m, 3H), 4.41 (t, $J = 6.9$ Hz, 1H), 1.78-1.64 (m, 2H), 1.49-1.32 (m, 4H), 0.93 (t, $J = 6.9$ Hz, 3H), 0.43 (s, 6H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) δ 133.9, 130.3, 129.7, 128.2, 108.9, 87.5, 63.1, 45.3, 37.6, 27.6, 26.2, 22.6, 22.3, 14.3, 14.1.

IR (film) 3384, 2959, 2872, 2361, 2171, 1675, 1428 cm$^{-1}$.

HRMS (ESI) calcd for C$_{15}$H$_{22}$OSi (M+Na$^+$) 269.1332, found 269.1332.

1-(Triphenylsilyl)hept-1-yn-3-ol. Prepared from (triphenylsilyl)acetylene and valeraldehyde by the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) δ 7.67-7.63 (m, 6H), 7.44-7.35 (m, 9H), 4.52 (t, $J = 6.3$ Hz, 1H), 1.86-1.78 (m, 2H), 1.55-1.32 (m, 4H), 0.92 (t, $J = 7.5$ Hz, 3H).
$^{13}$C NMR (CDCl$_3$, 75 MHz) δ 135.7, 133.5, 130.3, 128.2, 111.9, 84.7, 63.3, 37.6, 27.6, 22.6, 14.3.

IR (film) 3373, 3070, 2957, 2931, 2861, 1429, 1113 cm$^{-1}$.

HRMS (ESI) calcd for C$_{25}$H$_{26}$OSi (M+CH$_3$COO$^-$) 429.1880, found 429.1874.

\[
\text{TIPS} \quad \text{n-Bu} \quad \text{OH}
\]

1-(Triisopropylsilyl)hept-1-yn-3-ol. Prepared from (triisopropylsilyl)acetylene and valeraldehyde by the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) δ 4.38 (t, $J = 6.6$ Hz, 1H), 1.75-1.65 (m, 2H), 1.48-1.31 (m, 4H), 1.06-1.04 (m, 21H), 0.90 (t, $J = 7.4$ Hz, 3H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) δ 109.0, 85.6, 63.2, 45.6, 37.8, 27.5, 22.6, 18.7, 14.1.

IR (film) 3377, 2943, 2866, 2360, 1676, 1464, 1018 cm$^{-1}$.

HRMS (ESI) calcd for C$_{16}$H$_{31}$OSi (M-H$^+$) 267.2139, found 267.2142.

\[
\text{TIPS} \quad \text{MeO}_2\text{C} \quad \text{OH}
\]

Methyl-6-hydroxy-8-(triisopropylsilyloct-7-ynoate. Prepared from (triisopropylsilyl)acetylene and methyl-6-oxohexanoate by the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) δ 4.37 (dt, $J = 6.3, 4.8$ Hz, 1H), 3.64 (s, 3H), 2.30 (t, $J = 7.5, 4.8$ Hz, 1H), 1.75-1.61 (m, 4H), 1.54-1.46 (m, 2H), 1.05-1.04 (m, 21H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) δ 174.3, 108.8, 85.7, 62.8, 51.8, 37.7, 34.2, 24.9, 24.8, 18.8, 11.3.

IR (film) 3436, 2944, 2865, 2167, 1742, 1463, 1200, 1176, 1017 cm$^{-1}$.

HRMS (ESI) calcd for C$_{18}$H$_{37}$O$_3$Si (M+CH$_3$COO$^-$) 385.2405, found 385.2408.
**Methyl-6-hydroxy-9,9-dimethyldec-7-ynoate.** Prepared from 3,3-dimethylbut-1-yn and methyl-6-oxohexanoate by the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) δ 4.32 (t, $J = 6.3$ Hz, 1H), 3.64 (s, 3H), 2.30 (t, $J = 7.5$ Hz, 2H), 2.01 (bs, 1H), 1.68-1.59 (m, 4H), 1.49-1.41 (m, 2H), 1.18 (s, 9H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) δ 174.4, 94.0, 79.7, 62.5, 51.7, 37.9, 34.2, 31.2, 27.5, 25.0, 24.8.

IR (film) 3437, 2969, 2866, 1740, 1437, 1263, 1205, 1021 cm$^{-1}$.

HRMS (ESI) calcd for C$_{13}$H$_{22}$O$_3$ (M+Na$^+$) 249.1461, found 249.1465.

**6,6-Dimethyl-1-phenylhept-4-yn-3-ol.** Prepared from 3,3-dimethylbut-1-yn and 3-phenylpropanal by the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) δ 7.32-7.19 (m, 5H), 4.36 (t, $J = 6.6$ Hz, 1H), 2.78 (t, $J = 7.8$ Hz, 2H), 2.03-2.94 (m, 2H), 1.23 (s, 9H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) δ 141.8, 128.7, 128.6, 126.1, 94.5, 79.6, 62.2, 47.3, 39.9, 31.8, 31.2.

IR (film) 3430, 2971, 2252, 1665, 1454 cm$^{-1}$.

LRMS (El) calcd for C$_{15}$H$_{20}$O (M$^+$) 216, found 216.
(Z)-1-(triisopropylsilyl)dodec-9-yn-1-ol. Prepared from (triisopropylsilyl)-acetylene and (Z)-dec-7-enal by the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 5.40 (m, 2H), 4.38 (q, $J$ = 5.7, 1H), 2.07-1.98 (m, 4H), 1.83-1.81 (m, 1H), 1.75-1.64 (m, 2H), 1.50-1.45 (m, 2H), 1.37-1.32 (m, 4H), 1.06-1.04 (m, 21H), 0.94 (t, $J$ = 7.5 Hz, 3H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 131.9, 129.3, 109.0, 85.6, 63.2, 38.1, 29.9, 29.2, 27.2, 25.3, 20.7, 18.8, 14.6, 11.3.

IR (film) 3388, 2942, 2865, 1463, 1265, 1018, 883 cm$^{-1}$.

HRMS (EI) calcd for C$_{23}$H$_{43}$OSi (M+CH$_3$COO) 395.2976, found 395.2976.

Dodec-9-ynal [CAS # 131944-50-8]. A 300 mL flask was charged with pyridinium chlorochromate (5.2 g, 24.0 mmol), evacuated, and back-filled with argon. To the orange solid was added CH$_2$Cl$_2$ (100 mL) and dodec-9-yn-1-ol (3.6 g, 20 mmol). The resulting dark-brown reaction mixture was stirred for 3 h at r.t., and then Et$_2$O (100 mL) was added, leading to the precipitation of a brown solid. The mixture was allowed to stand at r.t. for 2 h, and then it was filtered through a plug of silica gel (washed with Et$_2$O). The solvent was removed, and the residue was purified by column chromatography (pentane:Et$_2$O 95:5) to give 2.3 g of the aldehyde as a clear colorless oil (63%).

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 9.76-9.75 (m, 1H), 2.42 (td, $J$ = 7.5, 1.8 Hz, 2H), 2.17-2.11 (m, 4H), 1.65-1.60 (m, 2H), 1.47-1.44 (m, 2H), 1.36-1.30 (m, 6H), 1.11 (t, $J$ = 6.6 Hz, 3H).
1-(Triisopropylsilyl)tetradeca-1,11-diyn-3-ol. Prepared from (triisopropylsilyl)-acetylene and dodec-9-ynal by the representative procedure.

\(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 4.37 (q, \(J = 12.0\) Hz, 1H), 2.18-2.08 (m, 4H), 1.86 (d, \(J = 5.4\) Hz), 1.71-1.64 (m, 2H), 1.49-1.43 (m, 4H), 1.38-1.30 (m, 6H), 1.10 (t, \(J = 7.2\) Hz, 3H), 1.06-1.04 (m, 21H).

\(^1^3\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 109.1, 85.6, 81.8, 79.7, 63.2, 38.1, 29.4, 29.34, 29.31, 29.0, 25.3, 18.9, 18.8, 14.6, 12.6, 11.3.

IR (film) 3330, 2939, 2864, 2168, 1463, 1320, 1017, 883 cm\(^{-1}\).

HRMS (EI) calcd for C\(_{25}\)H\(_{45}\)O\(_3\) (M+CH\(_3\)COO\(^-\)) 421.3132, found 421.3130.

4-(Triisopropylsilyl)but-3-yn-2-ol [CAS # 726202-65-9]. Prepared from (triisopropylsilyl)acetylene and acetaldehyde by the representative procedure.

\(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 4.53 (dq, \(J = 6.6, 1.2\) Hz, 1H), 1.75 (d, \(J = 5.1\) Hz, 1H), 1.47 (d, \(J = 6.6\) Hz, 3H), 1.06-1.04 (m, 21H).

6-Chloro-1-(triisopropylsilyl)hex-1-yn-3-ol. A 300 mL flask was charged with pyridinium chlorochromate (5.2 g, 24.0 mmol), evacuated, and back-filled with argon. To the orange solid was added CH\(_2\)Cl\(_2\) (100 mL) and 4-chlorobutanol (2.0 mL, 20 mmol). The resulting dark-brown reaction mixture was stirred for 3 h at r.t., and then Et\(_2\)O (100 mL) was added,
leading to the precipitation of a brown solid. The mixture was allowed to stand at r.t. for 2 h, and then it was filtered through a plug of silica gel (washed with Et₂O). The solvent was removed, and the residue was used as in the representative procedure.

\(^1\)H NMR (CDCl₃, 300 MHz) δ 4.44 (t, J = 6.3 Hz, 1H), 3.58 (t, J = 6.3 Hz, 2H), 2.17 (broad s, 1H), 2.00-1.92 (m, 2H), 1.88-1.80 (m, 2H), 1.05-1.04 (m, 21H).

\(^13\)C NMR (CDCl₃, 75 MHz) δ 108.3, 86.3, 62.4, 44.9, 35.2, 28.5, 18.8, 11.3.

IR (film) 3361, 2944, 2866, 2169, 1463, 1070 cm\(^{-1}\).

HRMS (ESI) calcd for C₁₇H₃₂ClOSi (M+CH₃COO⁻) 347.1804, found 347.1802.

7-(Benzyloxy)-1-(triisopropylsilyl)hept-1-yn-3-ol. A 300 mL flask was charged with pyridinium chlorochromate (6.6 g, 31.0 mmol), evacuated, and back-filled with argon. To the orange solid was added CH₂Cl₂ (125 mL) and 5-benzyloxy-1-pentanol (5.0 g, 25.7 mmol). The resulting dark-brown reaction mixture was stirred for 3 h at r.t., and then Et₂O (100 mL) was added, leading to the precipitation of a brown solid. The mixture was allowed to stand at r.t. for 2 h, and then it was filtered through a plug of silica gel (washed with Et₂O). The solvent was removed, and the residue was used as in the representative procedure.

\(^1\)H NMR (CDCl₃, 300 MHz) δ 7.38-7.26 (m, 5H), 4.50 (s, 2H), 4.39 (t, J = 6.3 Hz, 1H), 3.48 (t, J = 6.6 Hz, 2H), 1.84-1.53 (m, 7H), 1.06 (s, 21H).

\(^13\)C NMR (CDCl₃, 75 MHz) δ 138.7, 128.6, 127.9, 127.8, 108.9, 85.7, 73.1, 70.4, 63.1, 37.9, 29.5, 22.1, 18.8, 11.3.

IR (film) 3380, 2945, 2890, 2866, 2253, 1666, 1462 cm\(^{-1}\).

HRMS (ESI) calcd for C₂₅H₄₁O₄Si (M+CH₃COO⁻) 433.2769, found 433.2756.
5-Methyl-1-(triisopropylsilyl)hex-1-yn-3-ol [CAS # 913618-91-4]. Prepared from (triisopropylsilyl)acetylene and isobutyraldehyde by the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 4.44-4.37 (m, 1H), 1.99-1.96 (m, 1H), 1.86 (septet, $J = 6.6$ Hz, 1H), 1.68-1.50 (m, 2H), 1.07-1.05 (m, 21H), 0.93 (t, $J = 6.0$ Hz, 6H).

5-Phenyl-1-(triisopropylsilyl)pent-1-yn-3-ol. Prepared from (triisopropylsilyl)acetylene and 3-phenylpropanal by the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.32-7.18 (m, 5H), 4.40 (t, $J = 6.6$ Hz, 1H), 2.83 (t, $J = 8.1$ Hz, 2H), 2.08-1.96 (m, 2H), 1.09 (s, 21H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 141.6, 128.8, 128.7, 126.2, 108.6, 86.3, 62.6, 39.8, 31.7, 18.8, 11.3.

IR (film) 3428, 2945, 2866, 2253, 1727, 1462 cm$^{-1}$.

LRMS (EI) calcd for C$_{20}$H$_{32}$OSi (M$^+$) 316, found 316.

1-(Triisopropylsilyl)pent-1-yn-3-ol [CAS # 263720-71-4]. Prepared from (triisopropylsilyl)acetylene and propionaldehyde by the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 4.39-4.30 (m, 1H), 1.87-1.63 (m, 3H), 1.06-0.99 (m, 24H).
Synthesis of Propargylic Bromides (representative procedure). A 500 mL flask was charged with imidazole (1.3 g, 19.5 mmol), evacuated, and back-filled with argon. CH$_2$Cl$_2$ (100 mL) was added via syringe, followed by the addition of the propargylic alcohol (16.3 mmol). This solution was allowed to stir for 15 min. Next, dibromotriphenyl-phosphorane (8.24 g, 19.5 mmol) was added as a solid. The reaction was run under argon and monitored by TLC. Upon completion (usually 3-4 h), the reaction was quenched by the addition of silica gel, and was concentrated and dried under reduced pressure. Once dry, this plug of silica was subjected to flash chromatography (hexanes/ethyl acetate or pentane/diethyl ether) to give the propargylic bromides as oils.

(3-Bromohept-1-ynyl)trimethylsilane.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 4.48 (t, $J$ = 6.6 Hz, 1H), 1.98 (q, $J$ = 6.6 Hz, 2H), 1.54-1.44 (m, 2H), 1.33 (sextet, $J$ = 7.2 Hz, 2H), 0.92 (t, $J$ = 7.2 Hz, 3H), 0.18-0.16 (m, 9H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 104.2, 92.0, 39.6, 37.6, 29.7, 22.1, 14.1, 0.0.

IR (film) 2959, 2863, 2361, 2338, 2174, 1457, 1250 cm$^{-1}$.

HRMS (EI) calcd for C$_9$H$_{16}$BrSi (M-Me$^+$) 231, found 231.

(3-Bromohept-1-ynyl)dimethyl(phenyl)silane.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.70-7.60 (m, 2H), 7.45-7.38 (m, 3H), 4.57 (t, $J$ = 6.9 Hz, 1H), 2.10-2.02 (m, 2H), 1.65-1.50 (m, 2H), 1.39 (sextet, $J$ = 7.2 Hz, 2H), 0.96 (t, $J$ = 9.6 Hz, 3H), 0.47-0.44 (m, 6H).
\(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 136.8, 133.4, 129.8, 128.2, 105.9, 90.1, 39.5, 37.4, 29.8, 22.1, 14.2, -0.7.

IR (film) 2959, 2862, 2361, 2339, 1428, 1250, 1116 cm\(^{-1}\).

LRMS (EI) calcd for C\(_9\)H\(_{16}\)BrSi (M-C\(_6\)H\(_5^+\)) 231, found 231.

\[
\begin{array}{c}
\text{Ph}_3\text{Si} \\
\text{Br} \\
n-\text{Bu}
\end{array}
\]

(3-Bromohept-1-ynyl)triphenylsilane.

\(^{1}\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.67-7.63 (m, 6H), 7.47-7.36 (m, 9H), 4.64 (t, \(J = 6.6\) Hz, 1H), 2.13-2.06 (m, 2H), 1.64-1.53 (m, 2H), 1.38 (sextet, \(J = 7.5\) Hz, 2H), 0.94 (t, \(J = 9.6\) Hz, 3H).

\(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 135.7, 133.3, 130.3, 128.2, 108.0, 87.0, 39.4, 37.1, 29.8, 22.1, 14.2.

IR (film) 3069, 2957, 2930, 2361, 2339, 2174, 1429, 1114 cm\(^{-1}\).

LRMS (EI) calcd for C\(_{19}\)H\(_{20}\)BrSi (M-C\(_6\)H\(_5^+\)) 355, found 355.

\[
\begin{array}{c}
\text{TIPS} \\
\text{Br} \\
n-\text{Bu}
\end{array}
\]

(3-Bromohept-1-ynyl)triisopropylsilane.

\(^{1}\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 4.54 (t, \(J = 6.9\) Hz, 1H), 2.04-1.97 (m, 2H), 1.59-1.49 (m, 2H), 1.09-1.07 (m, 21H), 0.92 (t, \(J = 7.2\) Hz, 3H).

\(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 106.2, 88.8, 39.8, 37.8, 29.7, 22.1, 18.8, 14.2, 11.4.

IR (film) 3054, 2944, 2866, 2305, 1463, 1265 cm\(^{-1}\).

HRMS (EI) calcd for C\(_{16}\)H\(_{31}\)BrSi (M\(^+\)) 330.1373, found 330.1388.
Methyl-6-bromo-8-(triisopropylsilyl)oct-7-ynoate.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 4.54 (t, $J = 6.6$ Hz, 1H), 3.67 (s, 3H), 2.33 (t, $J = 7.5$ Hz, 2H), 2.02 (q, $J = 8.4$ Hz, 2H), 1.72-1.52 (m, 4H), 1.07 (s, 21H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 174.0, 105.8, 89.1, 51.8, 39.6, 37.2, 34.0, 27.0, 24.3, 18.7, 11.3.

IR (film) 2945, 2890, 2866, 2253, 1733, 1464 cm$^{-1}$.

HRMS (ESI) calcd for C$_{18}$H$_{33}$BrNaO$_2$Si (M+Na$^+$) 411.1325, found 411.0534.

Methyl-6-bromo-9,9-dimethyldec-7-ynoate.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 4.54 (t, $J = 6.6$ Hz, 1H), 2.34 (t, $J = 7.5$ Hz, 2H), 2.02-1.95 (m, 2H), 1.72-1.50 (m, 4H), 1.20 (s, 9H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 4.54 (t, $J = 6.3$ Hz, 1H), 3.64 (s, 3H), 2.33 (t, $J = 7.5$ Hz, 2H), 2.02-1.94 (m, 2H), 1.74-1.48 (m, 4H), 1.20 (s, 9H).

IR (film) 2969, 2867, 1740, 1436, 1363, 1265, 1203, 1170 cm$^{-1}$.

HRMS (ESI) calcd for C$_{13}$H$_{21}$BrNaO$_2$ (M+Na$^+$) 311.0617, found 311.0617.
(3-Bromo-6,6-dimethylhept-4-ynyl)benzene.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.33-7.17 (m, 5H), 4.49 (t, $J$ = 6.6 Hz, 1H), 2.84 (t, $J$ = 7.2 Hz, 2H), 2.32-2.24 (m, 2H), 1.23 (s, 9H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 140.6, 128.8, 128.7, 126.4, 96.9, 77.9, 42.0, 38.0, 33.8, 31.0, 27.9.

IR (film) 3028, 2970, 2929, 2865, 2245 cm$^{-1}$.

HRMS (EI) calcd for C$_{15}$H$_{19}$Br (M$^+$) 278.0665, found 278.0625.

(Z)-(3-Bromododec-9-en-1-ynyl)triisopropylsilane.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 5.49-5.28 (m, 2H), 4.53 (t, $J$ = 6.9 Hz, 1H), 2.06-1.94 (m, 6H), 1.62-1.49 (m, 2H), 1.42-1.30 (m, 4H), 1.06 (s, 21H), 0.98-0.92 (m, 3H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 132.0, 129.1, 106.1, 88.9, 40.0, 37.7, 29.7, 28.5, 27.4, 27.1, 20.7, 18.8, 14.6, 11.4.

IR (film) 3005, 2942, 2865, 2360, 2170, 1463 cm$^{-1}$.

LRMS (EI) calcd for C$_{18}$H$_{32}$BrSi (M-i-Pr$^+$) 355, found 355.
(3-Bromotetradeca-1,11-diynyl)triisopropylsilane.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 4.53 (t, $J = 6.6$ Hz, 1H), 2.19-2.09 (m, 4H), 2.03-1.95 (m, 2H), 1.60-1.26 (m, 10H), 1.13-1.04 (m, 24H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 106.1, 88.9, 81.8, 79.6, 40.0, 37.7, 29.3, 29.1, 28.9, 28.8, 27.5, 18.9, 18.8, 14.6, 12.6, 11.4.

IR (film) 2942, 2865, 2253, 1463 cm$^{-1}$.

HRMS (EI) calcd for C$_{20}$H$_{34}$BrSi (M$^+$) 381.1607, found 381.1113.

(3-Bromobut-1-ynyl)triisopropylsilane.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 4.63 (q, $J = 6.6$ Hz, 1H), 1.91 (d, $J = 6.9$ Hz, 3H), 1.07 (s, 21H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 107.3, 88.0, 31.8, 27.8, 18.8, 11.3.

IR (film) 2945, 2866, 2253, 1463, 1383 cm$^{-1}$.

HRMS (EI) calcd for C$_{13}$H$_{25}$BrSi (M$^+$) 288.0903, found 288.0900.

(3-Bromo-6-chlorohex-1-ynyl)triisopropylsilane.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 4.60 (t, $J = 6.5$ Hz, 1H), 3.64-3.56 (m, 2H), 2.21-2.15 (m, 2H), 2.09-2.03 (m, 2H), 1.07 (s, 21H).
$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 105.3, 89.7, 44.2, 37.0, 36.5, 30.3, 18.8, 11.3. 
IR (film) 2944, 2891, 2361, 2338, 1464 cm$^{-1}$.
HRMS (EI) calcd for C$_{12}$H$_{27}$BrClSi (M-i-Pr$^+$) 307.0281, found 307.0469.

![TIPS](image)

(7-(Benzyloxy)-3-bromohept-1-ynyl)triisopropylsilane.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.39-7.26 (m, 5H), 4.55 (t, $J = 6.6$ Hz, 1H), 4.50 (s, 2H), 3.50-3.46 (m, 2H), 2.18-1.99 (m, 2H), 1.68-1.63 (m, 2H), 1.07 (s, 21H).
$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 138.7, 128.6, 127.8, 127.7, 105.9, 89.1, 73.1, 70.2, 39.8, 37.6, 29.1, 24.4, 18.8, 11.4.
IR (film) 3030, 2942, 2865, 2170, 1462, 1363, 1104, 883 cm$^{-1}$.
HRMS (ESI) calcd for C$_{23}$H$_{37}$BrNaOSi (M+Na$^+$) 459.1689, found 459.1678

![TIPS](image)

(3-Bromo-5-methylhex-1-ynyl)triisopropylsilane.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 4.54 (t, $J = 7.5$ Hz, 1H), 1.95-1.86 (m, 3H), 1.06 (s, 21H), 0.94-0.92 (m, 6H).
$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 106.3, 88.7, 48.9, 36.3, 27.2, 22.2, 21.9, 18.7, 11.4.
IR (film) 2959, 2866, 2170, 1465 cm$^{-1}$.
HRMS (EI) calcd for C$_{16}$H$_{31}$BrSi (M$^+$) 330.1373, found 330.1379.
(3-Bromo-5-phenylpent-1-ynyl)triisopropylsilane.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.35-7.20 (m, 5H), 4.50 (t, $J = 6.6$ Hz, 1H), 2.90 (t, $J = 8.1$ Hz, 2H), 2.37-2.29 (m, 2H), 1.11 (s, 21H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 140.4, 130.3, 128.8, 126.5, 105.8, 89.4, 41.7, 36.8, 33.7, 18.8, 11.4.

IR (film) 3065, 3028, 2944, 2865, 2249, 2168, 1463 cm$^{-1}$.

LRMS (EI) calcd for C$_{20}$H$_{31}$BrSi (M$^+$) 378, found 378.

(3-Chloropent-1-ynyl)triisopropylsilane. Prepared by the representative procedure, substituting dichlorotriphenylphosphorane for dibromotriphenylphosphorane.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 4.53 (t, $J = 6.3$ Hz, 1H), 1.97 (dt, $J = 13.5$, 7.5 Hz, 2H), 1.10 (t, $J = 7.5$ Hz, 3H), 1.08-1.06 (m, 21H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 105.3, 87.9, 50.6, 32.8, 18.8, 11.3, 10.7.

IR (film) 2944, 2892, 2866, 2361, 2175, 1463 cm$^{-1}$.

LRMS (EI) calcd for C$_{14}$H$_{27}$ClSi (M$^+$) 258, found 258.
(3-Chloro-5-methylhex-1-ynyl)triisopropylsilane. Prepared by the representative procedure, substituting dichlorotriphenylphosphorane for dibromotriphenylphosphorane.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 4.58 (t, $J = 7.6$ Hz, 1H), 1.92 (sextet, $J = 7.3$ Hz, 1H), 1.86-1.81 (m, 2H), 1.08-1.07 (m, 21H), 0.94 (dd, $J = 6.5, 1.1$ Hz, 6H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 105.8, 87.6, 48.5, 47.7, 26.0, 22.2, 18.8, 11.3.

IR (film) 2959, 2944, 2893, 2867, 2361, 2339, 2173, 1464, 1386, 1368 cm$^{-1}$.

LRMS (EI) calcd for C$_{16}$H$_{31}$ClSi (M$^+$) 286, found 286.

(3-Bromoprop-1-ynyl)triisopropylsilane [CAS # 104465-98-7]. Prepared from 3-(triisopropylsilyl)-2-propyn-1-yl$^{107}$ by the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 3.94 (s, 2H), 1.06 (s, 21H).

Preparation of Alkyl Iodides (representative procedure): A 100 mL flask, wrapped in aluminium foil, was charged with imidazole (1.0 g, 14.7 mmol) and triphenylphosphine (3.9 g, 14.7 mmol), evacuated, and back-filled with argon. CH$_2$Cl$_2$ (40 mL) was added via syringe, followed by the addition of the alcohol (9.8 mmol). This solution was allowed to stir for 15 min. Next, iodine (3.75 g, 14.7 mmol) was added portionwise as a solid. The reaction was run under argon and monitored by TLC. Upon completion (usually 3-4 hours), the solvent was removed under reduced pressure and the resultant solid was triturated with 3:1 hexanes:Et$_2$O (60 mL) for 1 h, the solid was then removed via filtration and the solution was concentrated under reduced pressure to give the desired iodide as a crude oil. The iodide was then purified via distillation under reduced pressure.

4-Iodotetrahydro-2H-pyran [CAS # 25637-18-7]. Prepared from tetrahydro-pyran-4-ol by the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 4.45 (quintet, $J = 6.2$ Hz, 1H), 3.85-3.78 (m, 2H), 3.56-3.49 (m, 2H), 2.19-2.12 (m, 4H).

![Boc](image)

**tert-Butyl-4-iodopiperidine-1-carboxylate [CAS # 885275-003].** Prepared from benzyl 4-hydroxy-1-piperidinecarboxylate by the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.38-7.33 (m, 5H), 5.13 (s, 2H), 4.46 (quintet, $J = 6.0$ Hz, 1H), 3.69-3.61 (m, 2H), 3.44-3.36 (m, 2H), 2.90-2.60 (m, 4H).

![Me Me](image)

3-Iodopentane [CAS # 1809-05-8]. Prepared from 3-pentanol by the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 4.09-4.01 (m, 1H), 1.93-1.68 (m, 4H), 1.02 (t, $J = 6.9$ Hz, 6H).

![Iodocycloheptane](image)

**Iodocycloheptane [CAS # 2404-36-6].** Prepared from cycloheptanol by the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 4.48 (septet, $J = 4.5$ Hz, 1H), 2.33-2.11 (m, 4H), 1.60-1.55 (m, 6H), 1.48-1.39 (m, 2H).
**Iodocyclooctane [CAS # 1556-10-1].** Prepared from cyclooctanol by the representative procedure.

$^1\text{H NMR (CDCl}_3, 300 \text{ MHz)} \delta 4.60 \text{ (quintet, } J = 6.3 \text{ Hz, 1H), 2.27-2.20 \text{ (m, 4H), 1.70-1.42 \text{ (m, 10H).}}$

**Me$^3$C$^4$H$^2$I$^1$C$^6$H$^5$**

**Me$^3$C$^4$H$^2$I$^5$C$^6$H**

**Me$^3$C$^4$H$^2$I$^5$C$^6$H**

(3-Iodobutyl)benzene [CAS # 59456-20-1]. Prepared from 4-phenylbutan-2-ol by the representative procedure.

$^1\text{H NMR (CDCl}_3, 300 \text{ MHz)} \delta 7.32-7.19 \text{ (m, 5H), 4.17-4.05 \text{ (m, 1H), 2.90-2.80 \text{ (m, 1H), 2.75-2.64 \text{ (m, 1H), 2.22-2.09 \text{ (m, 1H), 1.95 \text{ (d, } J = 6.9 \text{ Hz, 3H), 1.95-1.82 \text{ (m, 1H).}}}$
Preparation of Organozinc Reagents: Conditions A (solvent: DMA). A 25 mL Schlenk flask was charged with zinc powder (0.98 g, 15 mmol) and heated to 80 °C under high vacuum for 30 min. After back-filling with argon, DMA (to give a total volume of 10 mL) and iodine (0.13 g, 0.50 mmol) were added. After the red color of iodine had faded, the alkyl halide (10 mmol) was added. The colorless reaction mixture was stirred for 6 h at 80 °C (the disappearance of the starting material and the formation of the organozinc reagent can readily be monitored by no-D NMR). The gray solution (~1.0 M) was transferred into a dry vessel via cannula. These organozinc solutions can be stored at room temperature for several weeks in a dry atmosphere without deterioration.

Preparation of Organozinc Reagents: Conditions B (solvent: THF). A 25 mL Schlenk flask was charged with zinc powder (0.98 g, 15 mmol) and heated to 80 °C under high vacuum for 30 min. After back-filling with argon, THF (to give a total volume of 10 mL) and iodine (0.13 g, 0.50 mmol) were added. After the red color of iodine had faded, the alkyl halide (10 mmol) was added. The colorless reaction mixture was stirred for 12 h at room temperature (the disappearance of the starting material and the formation of the organozinc reagent can readily be monitored by no-D NMR). The gray solution (~1.0 M) was transferred into a dry vessel via cannula. These organozinc solutions can be stored at room temperature for several weeks in a dry atmosphere without deterioration.

III. Preparation of Ligand

![L13, CAS # 123640-38-0] Prepared by a literature procedure.\textsuperscript{108}

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz) \(\delta\) 8.61 (dd, \(J = 2.9, 0.5\) Hz, 2H), 7.96 (dd, \(J = 8.5, 6.9\) Hz, 1H), 7.85 (d, \(J = 8.0\) Hz, 2H), 7.75 (d, \(J = 1\) Hz, 2H), 6.52 (dd, \(J = 2.5, 2.0\) Hz, 2H).

IV. Negishi Cross-Coupling Reactions

General Procedures

Negishi Cross-Coupling Reactions: General Procedure A (Table 2.3, 2.4 and eq 2.12). In the air (no special precautions are necessary), a 20 mL vial was charged with NiCl2·glyme (10.9 mg, 0.050 mmol) and terpyridine (11.6 mg, 0.050 mmol). The vial was purged with argon for 5 min, and then DMA (10.0 mL) was added via syringe. The resulting opaque, green solution was stirred at room temperature for 20 min, then the organozinc reagent (1.0 M in DMA; 0.80 mL, 0.80 mmol) was added. The resulting dark-brown reaction mixture was stirred for 10 min at room temperature. Next, the propargylic bromide (0.50 mmol) was added via syringe; the reaction mixture became light, but darkened over several hours. The reaction was allowed to run for 16 h at room temperature. Then, the excess organozinc reagent was quenched by the addition of EtOH (1.0 mL), and the brown mixture was diluted with 100 mL i-BuOMe, this solution was washed 3 times with 50 mL of water, once with brine, and then dried over MgSO4. After filtration, the solution was concentrated under reduced pressure and the resultant oil was purified by flash chromatography (hexanes/EtOAc or pentane/Et2O).

Negishi Cross-Coupling Reactions: General Procedure B (Table 2.6, 2.7 and eq 2.13). In the air (no special precautions are necessary), an oven-dried 4 mL vial, with teflon stirbar, was charged with NiCl2·glyme (5.5 mg, 0.025 mmol) and L13 (5.3 mg, 0.025 mmol). The vial was capped with a rubber septa and purged with argon for 5 min, and then THF (0.87 mL) was added via syringe. The resulting opaque, light green solution was stirred at room temperature for 20 min, then the organozinc reagent (~1.0 M in THF; 0.80 mL, 0.8 mmol) was added. The resulting dark-brown reaction mixture was stirred for 10 min at room temperature. Next, the propargylic bromide (0.50 mmol) was added via syringe. The reaction was allowed to run for 7 h at room temperature, under a positive atmosphere of argon. Then, the excess organozinc reagent was quenched by the addition of EtOH (0.5 mL), and the brown mixture was filtered through a short plug of silica gel, eluting with ~60 mL Et2O, which was subsequently concentrated. The resultant oil was purified by flash chromatography (hexanes/EtOAc or pentane/Et2O).
(3-Cyclohexylhept-1-ynyl)triisopropylsilane (Table 2.4, entry 1). The compound was prepared according to General Procedure A. After chromatography on silica gel (pentane), the desired compound was isolated as a colorless oil: run 1: 147 mg (88%); run 2: 149 mg (89%).

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 2.24 (quintet, $J = 4.7$ Hz, 1H), 1.82-1.63 (m, 5H), 1.53-1.19 (m, 12H), 1.08-1.05 (m, 21H), 0.90 (t, $J = 7.1$ Hz, 3H).

$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 111.8, 81.7, 81.6, 39.3, 32.4, 31.9, 30.2, 29.0, 26.9, 26.8, 26.6, 22.8, 18.9, 14.3, 11.6.

IR (film) 2928, 2864, 2723, 2361, 2338, 2163, 1463, 1381 cm$^{-1}$.

LRMS (EI) calcd for C$_{22}$H$_{42}$Si (M$^+$) 334, found 334.

Methyl-6-cyclohexyl-8-(triisopropylsilyl)oct-7-ynoate (Table 2.4, entry 2). The compound was prepared according to the General Procedure A. After chromatography on silica gel (pentane:Et$_2$O 100:1), the desired compound was isolated as a colorless oil: run 1: 140.5 mg (72%); run 2: 139.0 mg (71%).

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 3.66 (s, 3H), 2.31 (t, $J = 7.5$, 2H), 2.24 (quintet, $J = 4.5$ Hz, 1H), 1.79-1.17 (m, 17H), 1.07-1.05 (m, 21H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 174.4, 111.3, 82.0, 51.7, 41.6, 39.1, 34.3, 32.3, 31.8, 29.0, 27.6, 26.8, 26.7, 26.6, 25.0, 18.9, 11.5.

IR (film) 2928, 2864, 2255, 2163, 1736, 1462 cm$^{-1}$.

HRMS (EI) calcd for C$_{24}$H$_{44}$O$_2$NaSi (M+Na$^+$) 415.3003, found 415.2998.
**TIPS**

(Z)-(3-Cyclohexyldodec-9-en-1-ynyl)triisopropylsilane (Table 2.4, entry 3). The compound was prepared according to the General Procedure A. After chromatography on silica gel (pentane), the desired compound was isolated as a colorless oil: run 1: 143.3 mg (71%); run 2: 144.8 mg (72%).

\[\text{1H NMR (CDCl}_3, 300 MHz) \delta 5.36-5.31 (m, 2H), 2.25-2.21 (m, 1H), 2.05-1.97 (m, 4H), 1.80-1.07 (m, 19H), 1.07-1.05 (m, 21H), 0.97 (t, } J = 7.2 \text{ Hz, 3H).}\]

\[\text{13C NMR (CDCl}_3, 75 MHz) \delta 131.8, 129.6, 41.6, 39.4, 32.7, 31.9, 30.0, 29.3, 29.1, 27.9, 27.3, 26.9, 26.8, 26.6, 20.7, 18.9, 14.6, 11.6.}\]

IR (film) 2928, 2863, 2362, 2163, 1463, 995, 883 cm\(^{-1}\).

HRMS (EI) calcd for C\(_{24}\)H\(_{43}\)Si (M–i-Pr\(^+\)) 359.3128, found 359.3319.

**Triisopropyl(3-(tetrahydro-2H-pyran-4-yl)hept-1-ynyl)silane** (Table 2.4, entry 4). The compound was prepared according to the General Procedure A. After chromatography on silica gel (hexanes:Et\(_2\)O 10:1), the desired compound was isolated as a colorless oil: run 1: 113.9 mg (68%); run 2: 120.2 mg (72%).

\[\text{1H NMR (CDCl}_3, 300 MHz) \delta 4.01-3.94 (m, 2H), 3.39-3.34 (m, 2H), 2.27-2.25 (m, 1H), 1.72 (d, } J = 9 \text{ Hz, 1H), 1.57-1.51 (m, 5H), 1.46-1.29 (m, 5H), 1.07-1.04 (m, 21H), 0.89 (t, } J = 6.9 \text{ Hz, 3H).}\]

\[\text{13C NMR (CDCl}_3, 75 MHz) \delta 110.5, 82.6, 68.4, 68.3, 39.1, 38.8, 31.8, 31.5, 29.9, 29.8, 22.7, 18.9, 14.3, 11.5.}\]

IR (film) 2940, 2864, 2164, 1464, 1386, 1097, 883, 734 cm\(^{-1}\).

HRMS (ESI) calcd for C\(_{21}\)H\(_{40}\)NaOSi (M+Na\(^+\)) 359.2741, found 359.2727.
**TIPS**

**Me**

*tet-Butyl-4-(4-(triisopropylsilyl)but-3-yn-2-yl)piperidine-1-carboxylate** (Table 2.4, entry 5). The compound was prepared according to the General Procedure A. After chromatography on silica gel (hexanes:CH₂Cl₂:Et₂O 70:25:5), the desired compound was isolated as a colorless oil: run 1: 159.8 mg (75%); run 2: 162.5 mg (76%).

¹H NMR (CDCl₃, 300 MHz) δ 7.38-7.29 (m, 5H), 5.11 (d, J = 5.5 Hz, 2H), 4.23 (d, J = 30.4 Hz, 2H), 2.80-2.65 (m, 2H), 2.45-2.35 (m, 1H), 1.84 (d, J = 12.5 Hz, 1H), 1.68 (broad s, 1H), 1.46-1.30 (m, 3H), 1.17 (d, J = 7.0 Hz, 3H), 1.06-1.04 (m, 21H).

¹³C NMR (CDCl₃, 75 MHz) δ 155.4, 137.1, 128.7, 128.1, 11.6, 81.7, 67.1, 44.5, 44.4, 41.3, 32.4, 30.1, 18.8, 18.7, 11.4.

IR (film) 2944, 2865, 2253, 2163, 1688, 1449 cm⁻¹.

HRMS (ESI) calcd for C₂₆H₄₁NNaO₂Si (M+Na⁺) 450.2799, found 450.2797.

**TIPS**

**Me**

**Me0₂C**

*Methyl-6-isopropyl-8-(triisopropylsilyl)oct-7-ynoate** (Table 2.4, entry 6). The compound was prepared according to the General Procedure A. After chromatography on silica gel (pentane:Et₂O 100:1), the desired compound was isolated as a colorless oil: run 1: 114.0 mg (65%); run 2: 104.0 mg (60%).

¹H NMR (CDCl₃, 300 MHz) δ 3.66 (s, 3H), 2.21 (t, J = 7.5 Hz, 2H), 2.27-2.23 (m, 1H), 1.70-1.55 (m, 4H), 1.46-1.37 (m, 3H), 1.06-1.04 (m, 21H), 0.96 (dd, J = 15.7, 6.5 Hz, 6H).

¹³C NMR (CDCl₃, 75 MHz) δ 174.4, 110.8, 82.2, 51.7, 39.9, 34.2, 32.8, 31.8, 27.7, 25.0, 21.5, 18.9, 18.8, 11.5.

IR (film) 2942, 2865, 2164, 1744, 1463, 1173, 996, 883 cm⁻¹.

HRMS (ESI) calcd for C₂₁H₄₀O₂Si (M+Na⁺) 375.2690, found 375.2676.
Methyl-6-cyclohexyl-9,9-dimethyldec-7-ynoate (Table 2.4, entry 7). The compound was prepared according to the General Procedure A. After chromatography on silica gel (pentane:Et₂O 100:1), the desired compound was isolated as a colorless oil: run 1: 108.0 mg (74%); run 2: 102.0 mg (70%).

\[ \text{H NMR (CDCl}_3, 300 \text{ MHz) } \delta 3.65 \text{ (s, 3H), 2.30 (t, J = 7.5 Hz, 2H), 2.11-2.08 (m, 1H), 1.76-1.68 (m, 3H), 1.66-1.58 (m, 4H), 1.52-1.48 (m, 1H), 1.39-1.34 (m, 3H), 1.24-1.05 (m, 15H).} \]

\[ \text{C NMR (CDCl}_3, 75 \text{ MHz) } \delta 174.5, 91.2, 80.5, 51.7, 41.7, 37.8, 34.4, 32.4, 31.7, 29.2, 27.6, 27.5, 26.8, 26.7, 26.6, 25.1. \]

IR (film) 2968, 2928, 2855, 2254, 1731, 1450 cm⁻¹.

HRMS (ESI) calcd for C₁₉H₃₂NaO₂ (M+Na⁺) 315.2295, found 315.2287.

(3-Cyclopentyl-6,6-dimethylhept-4-ynyl)benzene (Table 2.4, entry 8). The compound was prepared according to the General Procedure A. After chromatography on silica gel (pentane), the desired compound was isolated as a colorless oil: run 1: 96.5 mg (72%); run 2: 98.5 mg (73%).

\[ \text{H NMR (CDCl}_3, 300 \text{ MHz) } \delta 7.34-7.20 (m, 5H), 2.93-2.87 (m, 1H), 2.74-2.68 (m, 1H), 2.32-2.27 (m, 1H), 1.89-1.85 (m, 1H), 1.79-1.29 (m, 10H), 1.28 (s, 9H). \]

\[ \text{C NMR (CDCl}_3, 75 \text{ MHz) } \delta 142.7, 128.5, 128.2, 125.6, 91.0, 80.3, 44.1, 36.6, 36.2, 33.9, 31.5, 30.9, 29.4, 27.4, 25.7, 25.6. \]

IR (film) 3063, 2963, 2868, 1704, 1453, 1264, 1202, 699 cm⁻¹.

HRMS (EI) calcd for C₂₀H₂₈ (M⁺) 268.2185, found 268.2185.
(6-(Benzyloxy)-3-(3-chloropropyl)hex-1-ynyl)triisopropylsilane (Table 2.5, entry 1). The compound was prepared according to the General Procedure A, the organozinc reagent was made from ((3-bromopropoxy)methyl)benzene via the General Procedure A. After chromatography on silica gel (hexanes:Et₂O 95:5), the desired compound was isolated as a colorless oil: run 1: 171.7 mg (97%); run 2: 175.1 mg (98%).

\(^1\)H NMR (CDCl₃, 300 MHz) δ 7.38-7.26 (m, 5H), 4.50 (s, 2H), 3.57 (t, \(J = 6.3\) Hz, 2H), 3.55 (dt, \(J = 6.0, 2.1\) Hz, 2H), 2.42 (septet, \(J = 4.8\) Hz, 1H), 2.10-1.42 (m, 10H), 1.07-1.02 (m, 21H).

\(^1\)C NMR (CDCl₃, 75 MHz) δ 138.8, 128.6, 127.8, 127.4, 111.5, 82.1, 72.9, 70.2, 45.2, 32.6, 32.2, 32.1, 30.6, 27.7, 18.9, 11.5.

IR (film) 2942, 2864, 2163, 1462, 1364, 1102, 883, 676 cm\(^{-1}\).

LRMS (El) calcd for C\(_{22}\)H\(_{34}\)ClOSi (M-i-Pr\(^+\)) 377, found 377.

Ethyl-7-phenethyl-9-(triisopropylsilyl)non-8-ynoate (Table 2.5, entry 2). The compound was prepared according to the General Procedure A, the organozinc reagent was made from ethyl 6-bromohexanoate via the General Procedure A. After chromatography on silica gel (hexanes:EtOAc 30:1), the desired compound was isolated as a colorless oil: run 1: 177.1 mg (95%); run 2: 180.6 mg (97%).

\(^1\)H NMR (CDCl₃, 300 MHz) δ 7.35-7.15 (m, 5H), 4.12 (q, \(J = 7.2\) Hz, 2H), 2.88 (quintet, \(J = 6.6\) Hz, 1H), 2.77-2.67 (m, 1H), 2.42-2.34 (m, 1H), 2.28 (t, \(J = 7.2\) Hz, 2H), 1.76-1.25 (m, 10H), 1.25 (t, \(J = 7.2\) Hz, 3H), 1.09-1.06 (m, 21H).

\(^1\)C NMR (CDCl₃, 75 MHz) δ 174.0, 142.5, 128.8, 128.6, 125.9, 112.3, 81.8, 60.4, 37.6, 35.3, 34.5, 33.9, 32.5, 29.2, 27.2, 25.1, 18.9, 14.5, 11.5.
IR (film) 2941, 2864, 2163, 1738, 1179, 883, 676 cm\(^{-1}\).
LRMS (El) calcd for C\(_{25}\)H\(_{39}\)O\(_2\)Si (M-i-Pr\(^+\)) 399, found 399.

Ethyl-9-(triisopropylsilyl)non-8-ynoate (Table 2.5, entry 3). The compound was prepared according to the General Procedure A. After chromatography on silica gel (hexanes:Et\(_2\)O 20:1), the desired compound was isolated as a colorless oil: run 1: 152.9 mg (89%); run 2: 150.5 mg (90%).

\(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 4.10 (q, \(J = 7.2\) Hz, 2H), 2.30-2.20 (m, 4H), 1.66-1.30 (m, 8H), 1.24 (t, \(J = 7.2\) Hz, 3H), 1.04-1.02 (m, 21H).

\(^13\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 174.0, 109.2, 80.3, 60.4, 34.5, 28.8, 28.7, 28.5, 25.0, 19.9, 18.8, 14.4, 11.5.

IR (film) 2942, 2865, 2361, 2338, 2254, 2169, 1727, 1464, 1194 cm\(^{-1}\).
LRMS (El) calcd for C\(_{20}\)H\(_{38}\)O\(_2\)Si (M\(^+\)) 338, found 338.

(3-Cycloheptylhept-1-ynyl)triisopropylsilane (Table 2.7, entry 1). The compound was prepared according to General Procedure B. After chromatography on silica gel (hexanes), the desired compound was isolated as a colorless oil: run 1: 146 mg (84%); run 2: 156 mg (89%).

\(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 2.30 (quintet, \(J = 4.5\) Hz, 1H), 1.76-1.65 (m, 5H), 1.59-1.24 (m, 14H), 1.08-1.04 (m, 21H), 0.90 (t, \(J = 7.1\) Hz, 3H).

\(^13\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 112.1, 81.2, 43.4, 40.3, 33.6, 32.6, 30.4, 30.3, 28.5, 28.4, 27.4, 27.1, 22.8, 18.9, 14.3, 11.5.

IR (film) 2929, 2863, 2723, 2361, 2338, 2163, 1463, 1380, 1365 cm\(^{-1}\).
LRMS (El) calcd for C\(_{23}\)H\(_{44}\)Si (M\(^+\)) 348, found 348.
(3-Cycloheptyltetradeca-1,11-diynyl)triisopropylsilane (Table 2.7, entry 2). The compound was prepared according to the General Procedure B. After chromatography on silica gel (hexanes), the desired compound was isolated as a colorless oil: run 1: 174.0 mg (79%); run 2: 170.8 mg (77%).

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 2.32-2.27 (m, 1H), 2.20-2.09 (m, 4H), 1.73-1.67 (m, 4H), 1.60-1.20 (m, 21H), 1.11 (t, $J = 7.2$ Hz, 3H), 1.08-1.04 (m, 21H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 112.2, 81.8, 81.3, 79.8, 43.4, 40.3, 33.6, 32.9, 30.4, 29.6, 29.4, 29.3, 29.1, 28.5, 28.4, 28.0, 27.4, 27.1, 19.0, 18.9, 14.6, 12.6, 11.6.

IR (film) 2928, 2862, 2163, 1462, 1320, 995 cm$^{-1}$.

HRMS (EI) calcd for $C_{27}H_{47}Si$ (M$^+$-i-Pr$^+$) 399.3441, found 399.3024.

(6-Chloro-3-cyclooctylhex-1-ynyl)triisopropylsilane (Table 2.7, entry 3). The compound was prepared according to the General Procedure B. After chromatography on silica gel (hexanes), the desired compound was isolated as a colorless oil: run 1: 156.0 mg (82%); run 2: 155.7 mg (82%).

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 3.59 (t, $J = 6.5$ Hz, 2H), 2.31 (dt, $J = 4.5, 6.0$ Hz, 1H), 2.18-2.00 (m, 1H), 1.92-1.82 (m, 1H), 1.78-1.40 (m, 17H), 1.07-1.04 (m, 21H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 111.1, 82.2, 45.3, 41.3, 40.1, 32.6, 31.1, 30.0, 29.6, 27.2, 26.8, 26.7, 25.9, 18.9, 11.5

IR (film) 2923, 2864, 2164, 1463, 995, 883, 676 cm$^{-1}$.

LRMS (EI) calcd for $C_{23}H_{43}ClSi$ (M$^+$) 382, found 382.
(3-Cyclooctyl-5-methylhex-1-ynyl)triisopropylsilane (Table 2.7, entry 4). The compound was prepared according to the General Procedure B. After chromatography on silica gel (hexanes), the desired compound was isolated as a colorless oil: run 1: 147.5 mg (81%); run 2: 147.2 mg (81%).

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 2.35 (dt, $J = 10.5, 4.5$ Hz, 1H), 1.90-1.83 (m, 1H), 1.76-1.38 (m, 16H), 1.16-1.08 (m, 1H), 1.06-1.03 (m, 21H), 0.93-0.87 (m, 6H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 112.0, 81.2, 42.0, 41.4, 38.8, 32.9, 29.5, 27.1, 26.9, 26.8, 26.7, 26.4, 26.0, 23.9, 21.8, 18.9, 11.6.

IR (film) 2924, 2865, 2164, 1465, 1383, 1071 cm$^{-1}$.

HRMS (EI) calcd for C$_{24}$H$_{46}$Si (M$^+$) 362.3363, found 362.3372.

Triisopropyl(3-(4-phenylbutan-2-yl)hept-1-ynyl)silane (Table 2.7, entry 5). The compound was prepared according to the General Procedure B (3.0 equiv RZnI was used). After chromatography on silica gel (hexanes), the desired compound was isolated as a colorless oil: run 1: 147.9 mg (77%); run 2: 141.7 mg (74%).

$^1$H NMR (CDCl$_3$, 300 MHz) 1:1 mixture of diastereomers, $\delta$ 7.31-7.18 (m, 10H), 2.81-2.71 (m, 1H), 2.67-2.60 (m, 2H), 2.57-2.44 (m, 2H), 2.37-2.30 (m, 1H), 1.90-1.83 (m, 2H), 1.66-1.24 (m, 14H), 1.09-0.99 (m, 50H), 0.95-0.87 (m, 6H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) 1:1 mixture of diastereomers, $\delta$ 143.1, 143.0, 128.62, 128.60, 128.5, 128.4, 125.8, 111.7, 110.6, 81.9, 81.8, 39.2, 37.8, 37.7, 36.4, 36.1, 35.1, 33.9, 33.8, 33.1, 31.9, 30.4, 30.2, 22.8, 18.9, 17.8, 15.7, 14.3, 11.6.

IR (film) 3027, 2941, 2864, 2164, 1496, 1462, 1380, 996, 908 cm$^{-1}$.

HRMS (EI) calcd for C$_{23}$H$_{37}$Si (M-i-Pr$^+$) 341.2659, found 341.2977.
(7-(Benzyloxy)-3-(pentan-3-yl)hept-1-ynyl)triisopropylsilane (Table 2.7, entry 6). The compound was prepared according to the General Procedure B (3.0 equiv RZnI was used). After chromatography on silica gel (preparative TLC; hexanes:Et₂O 100:1), the desired compound was isolated as a colorless oil: run 1: 109.0 mg (51%); run 2: 102.4 mg (48%).

¹H NMR (CDCl₃, 300 MHz) δ 7.35-7.27 (m, 5H), 4.50 (s, 2H), 3.47 (t, J = 6.6 Hz, 2H), 2.52-2.45 (m, 1H), 1.70-1.59 (m, 3H), 1.56-1.14 (m, 8H), 1.06-1.04 (m, 21H), 0.88 (t, J = 6.6 Hz, 6H).

¹³C NMR (CDCl₃, 75 MHz) δ 138.9, 128.6, 127.8, 127.7, 111.5, 81.6, 73.1, 70.7, 45.2, 35.5, 32.6, 29.9, 24.9, 24.2, 23.2, 18.9, 12.2, 11.9, 11.6.

IR (film) 2940, 2864, 2163, 1462, 1380, 1103, 883 cm⁻¹.

HRMS (ESI) calcd for C₂₈H₄₈NaOSi (M+Na⁺) 451.3367, found 451.3348.

Triisopropyl(5-methyl-3-(tetrahydro-2H-pyran-4-yl)hex-1-ynyl)silane (Eq 2.12). The compound was prepared according to General Procedure A. After chromatography on silica gel (0% → 8% Et₂O in hexanes), the desired compound was isolated as a colorless oil: run 1: 126 mg (75%); run 2: 128 mg (76%).

¹H NMR (CDCl₃, 300 MHz) δ 4.02-3.95 (m, 2H), 3.40-3.31 (m, 2H), 2.38-2.31 (m, 1H), 1.97-1.82 (m, 1H), 1.72-1.38 (m, 7H), 1.20-1.02 (m, 21H), 0.90 (dd, J = 13.2, 6.6 Hz, 6H).

¹³C NMR (CDCl₃, 75 MHz) δ 110.2, 82.7, 68.4, 68.3, 41.5, 39.5, 36.8, 31.6, 29.7, 26.3, 23.9, 21.6, 18.9, 11.5.

IR (film) 2956, 2941, 2865, 2361, 2339, 2163, 1465, 1385, 1368 cm⁻¹.

LRMS (EI) calcd for C₁₈H₃₃OSi (M-i-Pr⁺) 293, found 293.
(3-Cyclooctylpent-1-ynyl)triisopropylsilane (Eq 2.13). The compound was prepared according to the General Procedure B. After chromatography on silica gel (hexanes), the desired compound was isolated as a colorless oil: run 1: 123.8 mg (74%); run 2: 127.1 mg (76%).

$^1$H NMR (CDCl$_3$, 300 MHz) δ 2.22-2.16 (m, 1H), 1.75-1.40 (m, 17H), 1.10-0.98 (m, 24H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) δ 112.0, 81.3, 42.8, 40.9, 32.7, 29.4, 27.2, 26.9, 26.8, 26.8, 26.0, 18.9, 12.6, 11.5.

IR (film) 2924, 2864, 2722, 2163, 1463, 1381 cm$^{-1}$.

LRMS (El) calcd for C$_{22}$H$_{42}$Si (M$^+$) 334, found 334.
E. $^1$H NMR Spectra of Selected Compounds
STANDARD 1H OBSERVE

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na ph

TIPS
n-Bu

ppm

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STANDARD 1H OBSERVE

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ACQUISITION
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c1 16

FLAGS

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2.03

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TIPS
Et

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STANDARD 1H OBSERVE

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ACQUISITION

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DISPLAY

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STANDARD 1H OBSERVE

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STANDARD 1H OBSERVE

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flags

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DEC. & VT

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processing

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Table 2.4, entry 4

TIPS

n-Bu
Table 2.4, entry 5
Table 2.4, entry 6
**STANDARD PROTON PARAMETERS**

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- hs: nn

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- al cdc ph

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**Table 2.4, entry 7**

![NMR spectrum](image)

**Table 2.4, entry 7**

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TIPS

[Chemical structure image]

Table 2.7, entry 1
Table 2.7, entry 2
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Table 2.7, entry 3
Table 2.7, entry 4
Table 2.7, entry 5
STANDARD 1H OBSERVE

Eq 2.12
Section 2.4

Formal Synthesis of α-Cembra-2,7,11-triene-4,6-diol
A. Introduction

The cembranoids are a large family of diterpenes which have received a considerable amount of synthetic attention. In 1962, the α- and β-cembra-2,7,11-triene-4,6-diols (Scheme 2.17) were isolated by Roberts and Rowland from aged burley tobacco (*Nicotiana tabacum*). Not only have these cembranoids been found to act as growth regulators in the tobacco plant, when present in high concentrations they have been shown to increase the plant’s resistance to pests and fungal infections. Furthermore, these compounds have been shown to inhibit tumor promotion in mice.

Scheme 2.17. Structure of the α- and β-Cembra-2,7,11-triene-4,6-diols.

Despite the great attention devoted toward the synthesis of cembranoids, to date, only two groups have focused on the construction of the α- and β-cembra-2,7,11-triene-4,6-diols (see Scheme 2.18). A series of communications from Marshall described the application of their work on diastereoselective Wittig rearrangements to first the racemic and, later, the enantioselective syntheses of these diterpenes. Thomas et al. have also reported their efforts in the synthesis of

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these compounds.\textsuperscript{115} The synthesis performed by Thomas centers on the application of a macrocyclic olefination reaction to construct the medium-sized ring found in $\alpha$- and $\beta$-cembra-2,7,11-triene-4,6-diol.

\textbf{Scheme 2.18.} Previous Syntheses of $\alpha$-Cembra-2,7,11-triene-4,6-diol.

B. Results and Discussion

Following our development of the nickel-catalyzed Negishi cross-couplings of secondary nucleophiles with secondary propargylic electrophiles, described in the previous section, we were interested in utilizing this methodology in the synthesis of a natural product. We saw a racemic formal synthesis of $\alpha$-cembra-2,7,11-triene-4,6-diol (an intermediate in the Thomas

synthesis, 1, Scheme 2.18) as an excellent opportunity to highlight our new cross-coupling reaction.

With this objective in mind, we envisioned the 14-membered macrocycle could be constructed via an intramolecular aldol reaction (Scheme 2.19). The aldol precursor, 11, was to be accessed via elaboration of the terminal alkyne present in the deprotected product of our secondary-secondary Negishi cross-coupling, thus making use of the synthetic utility of alkynes as two carbon linkers. We envisioned that the isopropyl substituent could be installed by our Negishi reaction of a propargylic bromide, which we saw originating from farnesyl acetate. This strategy allowed us to purchase two of the tri-substituted olefins (in the desired configuration) which are present in the backbone of this diterpene.


![Scheme 2.19](image)

The Formal Synthesis of α-Cembra-2,7,11-triene-4,6-diol

As outlined in our retrosynthetic analysis, the formal synthesis of α-cembra-2,7,11-triene-4,6-diol commenced with farnesyl acetate. We utilized a modification of the three-step olefin cleavage protocol developed by Corey for his synthesis of Dolabellane,\(^\text{116}\) to access aldehyde 5 (Scheme 2.20). Treatment of farnesyl acetate with NBS in a mixture of THF/H\(_2\)O led to selective

formation of bromohydrin 2 (62%), which under mild basic conditions readily closed to give the trisubstituted epoxide 3 in nearly quantitative yield. These basic reaction conditions also led to the cleavage of the allylic acetate. This was not considered a problem, as it allowed us to install a somewhat more stable protecting group, a pivaloate (see 4), which could be easily removed in concert with another transformation later in the synthesis. Aqueous sodium periodate and periodic acid effected in situ epoxide opening and diol cleavage to produce aldehyde 5 in excellent yield (90%).

**Scheme 2.20. Synthesis of Aldehyde 5.**

Completion of our cross-coupling substrate, propargyl bromide 6, was accomplished via addition of lithiated TIPS-protected acetylene to aldehyde 5, and subsequent bromination using a phosphorus(V) brominating reagent, with imidazole as the base (Scheme 2.21, 86% over two steps).

**Scheme 2.21. Synthesis of Propargylic Bromide 6.**
With the cross-coupling precursor in hand, we were very interested in how well our newly developed coupling reaction would perform. We were pleased to see that 6 cross-coupled smoothly with isopropylzinc iodide under our standard conditions; due to the high value of the bromide we opted to use 3.0 equivalents of the nucleophilic partner for a slight improvement in yield. Although the reaction proceeded without incident on 1.6 gram scale (7, 61%), somewhat lower yields were obtained when the scale was increased to 5.0 grams (52%). Deprotection of the alkynyl silyl-protecting group proceeded in nearly quantitative yields with 1.0 equivalent of TBAF in refluxing THF to give the terminal alkyne 8.

**Scheme 2.22.** Large-Scale Negishi Reaction of Propargylic Bromide 6.

Construction of diol 10 commenced with a simple alkynylation of acetaldehyde with 8, which proceeded in acceptable yield (61%) to give propargylic alcohol 9. At this stage we were set to generate the third E-olefin present in the macrocycle and remove the pivaloate protecting group. This reduction was accomplished through the use of LiAlH₄, in refluxing THF, to provide diol 10 in excellent yield (95%, ~1:1 dr).

**Scheme 2.23.** Synthesis of Diol 10.

The mixture of diastereoisomers at this stage was of no concern, as we next needed to oxidize both the primary and secondary allylic alcohols in order to access our desired aldol.
reaction precursor 11. We felt it would be ideal to accomplish both oxidation reactions in a single experimental step. We initially attempted a PCC oxidation and were pleased to obtain the desired dicarbonyl in 57% yield. Unfortunately, even after column chromatography, precursor 11 obtained via this oxidation had a tendency to decompose upon sitting, even under inert gas and at low temperature. At the time, the presence of trace chromium was deemed the culprit for this instability. Thus, another oxidation method was required. The mild oxidation reagent MnO₂ was tested next, as it is known to be very effective for allylic alcohol oxidations. It was soon determined that the MnO₂ required activation by heat for any reactivity to be observed. Disappointingly, the activated MnO₂ rapidly oxidized the primary alcohol, but yielded only trace amounts of the bis-oxidation product, even under high reagent loading or extended reaction times. Exceptional reactivity was observed once we applied Ley’s TPAP oxidation conditions to this substrate. To our delight 10% TPAP, with 3.0 equivalents NMO as the reoxidant, generated 11 within 30 minutes in 97% yield (Table 2.8).

Table 2.8. Oxidation of Diol 10.

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<td>2</td>
<td>MnO₂ (20.0 equiv), CH₂Cl₂, 24 h</td>
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<tr>
<td>3</td>
<td>activated MnO₂ (20.0 equiv), CH₂Cl₂, 24 h</td>
<td>15% 10 recovered 60% mono-oxidation trace 11</td>
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<tr>
<td>4</td>
<td>10% TPAP, NMO (3.0 equiv), 4Å MS, MeCN/CH₂Cl₂, 12 h</td>
<td>96% 11</td>
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<tr>
<td>5</td>
<td>10% TPAP, NMO (3.0 equiv), 4Å MS, MeCN/CH₂Cl₂, 30 min</td>
<td>97% 11</td>
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We were now poised to evaluate the second key step in our formal synthesis, the macrocyclic, intramolecular aldol reaction of 11 to produce aldol 12. It was understood that this reaction was going to be difficult for a number of reasons; not only are macrocyclic, intramolecular aldol reactions relatively uncommon, our starting material contains an enolizable vinylogous aldehyde and a vinylogous methyl ketone, a combination likely to participate in a variety of undesirable reactions. Also, it was our goal to isolate the desired diastereoisomer, and we had no concrete reasons to believe this isomer would be generated, much less favored. With these potential difficulties in the back of our mind, we proceeded to investigate this interesting transformation.

![Diagram of structure 12]

We initiated our study with conditions originally reported by Evans (TiCl₄, Et₃N, CH₂Cl₂, -78 °C), and for which a modification had been reported by Danishefsky in his synthesis of the macrocycle rapamycin. The rapamycin synthesis relies on closure of a 31-membered ring via an aldol reaction of an α-methoxy ketone with a vinylogous aldehyde (11% yield; with TiCl₃Oi-Pr, Et₃N, CH₂Cl₂, -78 °C). Application of these reaction conditions to our system only resulted in the formation of presumed polymerization products. After attempting to generate the desired ketone enolate with a variety of bases including n-BuLi and LDA, we began to see promising reactivity with HMDS bases such as KHMDS. Ultimately we found that through

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120 For a similar approach, see Danishefsky's synthesis of the Epothilones A and B; ref. 118e.
the use of low temperature (-78 °C) and KHMDS, we were able to achieve this difficult bond formation. The best results were obtained when we carried out the alcohol-protection on the crude material from this aldol reaction; this strategy greatly eased the purification and we isolated the desired product, I, as a single diastereoisomer, in 19% yield over two steps (Scheme 2.24). To date, we have not found a satisfactory rationale to explain the apparent high stereoselectivity of this reaction. Nevertheless, this unique intramolecular, macrocyclic aldol reaction served as an ideal solution for the completion of our formal synthesis of α-cembra-2,7,11-triene-4,6-diol.

**Scheme 2.24.** Intramolecular, Macrocyclic Aldol Reaction: Completion of the Formal Synthesis.

![Scheme 2.24](image)

C. Conclusion

In conclusion we completed a formal synthesis of α-cembra-2,7,11-triene-4,6-diol, compound I; the antepenultimate intermediate in Thomas’ synthesis was constructed in 12 steps. The construction of this diterpene in 14 steps is a significant improvement over the 21-step process developed by Marshall and the 23 steps required by Thomas. This synthesis, starting with farnesyl acetate, made use of our nickel-catalyzed secondary-secondary cross-coupling reaction, the powerful linking ability of alkynes, and an intramolecular macrocyclic aldol reaction to construct the final 14-membered ring.
D. Experimental

I. General

All reactions were carried out in oven-dried glassware under an atmosphere of argon. $N,N$-Dimethylacetamide was purchased from Fluka (anhydrous), and THF, $Et_2O$, toluene and CH$_2$Cl$_2$ were dried by passage over activated alumina. All other chemicals were purchased and used without further purification.

High-resolution mass spectrometric measurements were performed on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer system.

Low-resolution mass spectrometric measurements were performed on an Agilent LC/MSD-SL (ES+) LCMS system.

II. Formal Synthesis of 2,7,11-Cembratriene-4,6-diol

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

[CAS # 54795-59-4]. Prepared by a literature procedure.$^{116}$ Farnesyl acetate (20.0 g, 75.6 mmol) was taken up in THF (1700 mL) and cooled to 0 °C. To this solution was added water (1500 mL) until the solution became cloudy. $N$-bromosuccinimide (14.8 g, 83.2 mmol) was added portionwise over 1 h. The reaction was allowed to stir an additional hour at 0 °C, the THF was then removed \textit{in vacuo} at 5 °C and the resultant suspension was extracted with 20% Et$_2$O in hexanes (4 x 350 mL). The combined organic layers were washed with brine, dried over MgSO$_4$, filtered and concentrated \textit{in vacuo} to give a yellow oil. Purification via chromatography (10% → 20% Et$_2$O in hexanes) gave 16.9 g (62%) of the desired bromohyrin 2 as a colorless oil.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 5.33 (tq, $J$ = 6.9, 1.2 Hz, 1H), 5.17 (tq, $J$ = 7.0, 1.1 Hz, 1H), 4.58 (d, $J$ = 6.9 Hz, 2H), 3.95 (dd, $J$ = 11.4, 1.8 Hz, 1H), 2.38-2.20 (m, 2H), 2.18-1.90 (m, 9H), 1.83-1.65 (m, 1H), 1.69 (s, 3H), 1.58 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H).
Bromohydrin 2 (16.9 g, 46.7 mmol) was taken up in anhydrous MeOH (360 mL) and was treated with K₂CO₃ (16.1 g, 116.7 mmol). The suspension was stirred at room temperature for 2 h. The solvent was removed in vacuo and the residue was taken up in Et₂O (200 mL) and filtered through a plug of celite which was washed with Et₂O (500 mL). The combined Et₂O fractions were then washed with brine, dried over Na₂SO₄, filtered and dried in vacuo to give 10.8 g (97%) of the desired epoxide 3 as a colorless oil.

¹H NMR (CDCl₃, 300 MHz) δ 5.39 (tq, J = 5.7, 1.2 Hz, 1H), 5.14 (tq, J = 6.3, 1.2 Hz, 1H), 4.12 (d, J = 6.3 Hz, 2H), 2.69 (t, J = 6.0 Hz, 1H), 2.16-1.98 (m, 6H), 1.66-1.54 (m, 9H), 1.28 (s, 3H), 1.24 (s, 3H).

Epoxide 3 (10.8 g, 45.3 mmol) and dry CH₂Cl₂ (113 mL) were added to an oven-dried round-bottomed flask under argon. After addition of NEt₃ (25.3 mL, 181.2 mmol), the stirred solution was cooled to 0 °C. Once chilled, pivaloyl chloride (11.2 mL, 90.6 mmol) was added dropwise over 10 min via syringe. The ice bath was then removed and the reaction was allowed to stir at room temperature for 3 h. The reaction was quenched by the addition of saturated aqueous NH₄Cl (120 mL), this solution was allowed to stir for 1 h. The layers were then separated and the aqueous layer was washed with CH₂Cl₂ (3 x 75 mL). The combined organic fractions were dried over Na₂SO₄, filtered, and concentrated. Column chromatography (11% Et₂O in hexanes) gave 13.9 g (95%) of the desired pivaloate ester 4 as a colorless oil.
$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 5.31 (tq, $J$ = 6.0, 1.0 Hz, 1H), 5.14 (tq, $J$ = 7.0, 1.0 Hz, 1H), 4.56 (d, $J$ = 7.0 Hz, 2H), 2.70, (t, $J$ = 6.0 Hz, 1H), 2.19-2.03 (m, 6H), 1.69-1.58 (m, 2H), 1.61 (s, 3H), 1.30 (s, 3H), 1.26 (s, 3H), 1.19 (s, 9H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 178.8, 141.7, 134.7, 124.5, 118.9, 64.4, 61.5, 58.5, 39.6, 38.9, 36.5, 27.6, 27.5, 26.4, 25.1, 18.9, 16.7, 16.2.

IR (film) 2963, 2931, 2361, 2339, 2251, 1726, 1283, 1155, 916 cm$^{-1}$.

LRMS (EI) calcd for C$_{20}$H$_{34}$O$_3$ (M$^+$) 322, found 322.

Pivaloate ester 4 (6.48 g, 20.0 mmol) was taken up in THF (120 mL) and H$_2$O (25 mL), and cooled to 0 °C. NaIO$_4$ (2.5 g, 11.5 mmol) and HIO$_4 \cdot$2H$_2$O (5.0 g, 22.1 mmol) were then added in one portion. The reaction was allowed to warm to room temperature and was stirred another 30 min. The reaction was then quenched with 60 mL saturated aqueous NaHCO$_3$. The solution was extracted with 1:1 EtOAc:hexanes (2 x 200 mL), washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated. Column chromatography (9% Et$_2$O in hexanes) gave 5.06 g (90%) of the desired aldehyde 5 as a colorless oil.

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 9.72 (t, $J$ = 2.0 Hz, 1H), 5.28 (tq, $J$ = 7.0, 1.0 Hz, 1H), 5.10 (tq, $J$ = 5.5, 1.0 Hz, 1H), 4.54 (dd, $J$ = 7.0, 0.5 Hz, 2H), 2.51-2.47 (m, 2H), 2.29 (t, $J$ = 7.5 Hz, 2H), 2.17-2.00 (m, 4H), 1.67 (s, 3H), 1.59 (s, 3H), 1.17 (s, 9H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 202.8, 178.8, 141.5, 134.6, 124.9, 119.1, 61.5, 42.5, 39.4, 38.9, 32.0, 27.4, 26.3, 16.7, 16.3.

IR (film) 2973, 2934, 2718, 2361, 2339, 1726, 1480, 1282, 1154 cm$^{-1}$.

LRMS (EI) calcd for C$_{17}$H$_{28}$O$_3$ (M$^+$) 280, found 280.
Triisopropylacetylene (3.25 g, 17.8 mmol) was added to an oven-dried round-bottomed flask under argon. To the flask was added 75 mL of dry THF via syringe. The solution was cooled to -78 °C, with a dry ice/acetone bath, and treated with n-BuLi (11.1 mL, 17.8 mmol, 1.6 M in hexanes), and allowed to stir for 30 min. At this point aldehyde 5 (5.0 g, 17.8 mmol) in 25 mL THF at -78 °C was added via cannula. The reaction was allowed to stir at -78 °C for an additional 30 min, at which point the dry ice/acetone bath was removed and the reaction was left to warm to 0 °C and quenched with saturated aqueous NH₄Cl (50 mL). The suspension was extracted with EtOAc (3 x 75 mL). The combined organic fractions were washed with brine, dried over MgSO₄, filtered, and concentrated. Column chromatography (9% Et₂O in hexanes) gave 7.88 g (95%) of the desired propargylic alcohol 12 as a colorless oil.

¹H NMR (CDCl₃, 300 MHz) δ 5.30 (tq, J = 6.6, 1.2 Hz, 1H), 5.16 (tq, J = 6.9, 1.2 Hz, 1H), 4.56 (d, J = 6.9 Hz, 2H), 4.36 (q, J = 6.0 Hz, 1H), 2.20-2.00 (m, 6H), 1.96 (d, J = 5.7 Hz, 1H), 1.86-1.74 (m, 2H), 1.68 (s, 3H), 1.61 (s, 3H), 1.18 (s, 9H), 1.07 (s, 21H).

¹³C NMR (CDCl₃, 75 MHz) δ 178.9, 141.6, 134.9, 124.9, 119.1, 108.9, 85.8, 62.9, 61.6, 39.6, 38.9, 36.3, 35.4, 27.4, 26.4, 18.8, 16.7, 16.1, 11.3.

IR (film) 3447, 2943, 2865, 2361, 2339, 2168, 1729, 1458, 1283, 1154 cm⁻¹.

LRMS (ESI) calcd for C₂₈H₅₀NaO₃Si (M+Na⁺) 485, found 485
Prepared from propargylic alcohol 12 (7.7 g, 16.6 mmol) and the representative bromination procedure from Chapter 2, section 2. Column chromatography (3% Et₂O in hexanes) gave 7.85 g (9%) of the desired propargylic bromide 6 as a colorless oil.

\(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 5.32 (tq, \(J = 6.9, 1.2\) Hz, 1H), 5.16 (tq, \(J = 6.9, 1.2\) Hz, 1H), 4.56 (d, \(J = 6.9\) Hz, 2H), 4.55 (t, \(J = 6.6\) Hz, 1H), 2.25-2.17 (m, 2H), 2.16-2.00 (m 6H), 1.70 (s, 3H), 1.60 (s, 3H), 1.19 (s, 9H), 1.07 (s, 21H).

\(^1\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 178.8, 141.7, 133.4, 125.7, 119.0, 106.0, 89.0, 61.5, 39.6, 38.9, 38.5, 37.4, 37.2, 27.4, 26.4, 18.8, 16.7, 16.2, 11.4.

IR (film) 3054, 2944, 2866, 2361, 2339, 1771, 1265, 1158, 740 cm\(^{-1}\).

LRMS (EI) calcd for C\(_{28}\)H\(_{49}\)BrO\(_2\)Si (M\(^+\)) 524, found 524.

In the air, a 100 mL round-bottomed flask was charged with NiCl\(_2\)-glyme (65.7 mg, 0.30 mmol) and terpyridine (69.9 mg, 0.30 mmol). The vial was purged with argon for 5 min, and then DMA (60.0 mL) was added via syringe. The resulting opaque, green solution was stirred at room temperature for 20 min, then isopropylzinc iodide (1.0 M in DMA; 9.0 mL, 9.0 mmol) was added. The resulting dark-brown reaction mixture was stirred for 10 min at room temperature. Next, the propargylic bromide 6 (1.57 g, 3.0 mmol) was added via syringe; the reaction mixture became light, but darkened over several hours. The reaction was allowed to run for 16 h at room temperature. Then, the excess organozinc reagent was quenched by the addition of EtOH (2.0
mL), and the brown mixture was diluted with 100 mL t-BuOMe, this solution was washed 3 times with 50 mL of H₂O, once with brine, and then dried over MgSO₄. After filtration, the solution was concentrated under reduced pressure and the resultant oil was purified by flash chromatography (3% Et₂O in hexanes) to provide 900 mg (61%) of the desired ester 7 as a colorless oil.

\(^{1}\)H NMR (CDCl₃, 500 MHz) \(\delta\) 5.32 (tq, \(J = 6.9, 1.2\) Hz, 1H), 5.13 (tq, \(J = 6.9, 1.2\) Hz, 1H), 4.56 (d, \(J = 7.0\) Hz, 2H), 2.27-2.17 (m, 2H), 2.14-2.03 (m, 5H), 1.69 (s, 3H), 1.69-1.62 (m, 1H), 1.59 (s, 3H), 1.51-1.47 (m, 2H), 1.19 (s, 9H), 1.04 (s, 21H), 0.98 (d, \(J = 6.5\) Hz, 3H), 0.96 (d, \(J = 7.0\) Hz, 3H).

\(^{13}\)C NMR (CDCl₃, 75 MHz) \(\delta\) 178.8, 141.9, 135.4, 124.3, 118.8, 110.9, 82.2, 61.6, 39.7, 39.6, 38.9, 38.7, 38.0, 31.8, 27.4, 26.5, 21.5, 18.9, 16.7, 16.7, 16.1, 11.6.

IR (film) 2942, 2865, 2361, 2339, 2168, 1732, 1463, 1283, 1153 cm⁻¹.

LRMS (ESI) calcd for C₃₁H₅₆NaO₂Si (M+Na\(^{+}\)) 511, found 511.

![Ester 7](image_url)

Ester 7 (44.8 mg, 0.092 mmol) was added to an oven-dried round-bottomed flask under argon. To the flask was added THF (1.5 mL) via syringe, followed by the addition of tetrabutyl ammonium fluoride (92 µL, 0.092 mmol, 1.0 M solution in THF). The solution was heated at reflux for 15 min, once cooled to room temperature, the reaction was quenched with saturated aqueous NH₄Cl (1.0 mL). The suspension was extracted with Et₂O (3 x 5 mL). The combined organic fractions were washed with brine, dried over MgSO₄, filtered, and concentrated. Column chromatography (2% Et₂O in hexanes) gave 30.0 mg (99%) of the desired alkyne 8 as a colorless oil.

\(^{1}\)H NMR (CDCl₃, 500 MHz) \(\delta\) 5.32 (tq, \(J = 6.9, 1.2\) Hz, 1H), 5.14 (tq, \(J = 6.9, 1.2\) Hz, 1H), 4.56 (d, \(J = 7.0\) Hz, 2H), 2.29-2.16 (m, 2H), 2.15-2.00 (m, 6H), 1.74-1.64 (m, 4H), 1.60 (s, 3H), 1.55-1.50 (m, 2H), 1.20 (s, 9H), 0.98 (d, \(J = 7.0\) Hz, 3H), 0.96 (d, \(J = 6.5\) Hz, 3H).
$^{13}$C NMR (CDCl$_3$, 75 MHz) δ 178.9, 141.8, 135.1, 124.3, 118.9, 86.4, 70.4, 61.6, 39.7, 38.9, 38.2, 37.7, 31.4, 31.1, 27.4, 26.4, 21.2, 18.5, 16.7, 16.2.

IR (film) 3309, 2961, 2928, 2872, 2361, 2339, 1723, 1457, 1282, 1152 cm$^{-1}$.

LRMS (EI) calcd for C$_{22}$H$_{36}$O$_2$ (M$^+$) 332, found 332.

Alkyne 8 (1.35 g, 4.07 mmol) was added to an oven-dried round-bottomed flask under argon. To the flask was added THF (30 mL) via syringe. The solution was cooled to -78 °C, with a dry ice/acetone bath, and treated with n-BuLi (2.54 mL, 4.07 mmol, 1.6 M in hexanes), and allowed to stir for 30 min. At this point, acetaldehyde (1.2 mL, 20.3 mmol) was added via syringe. The reaction was allowed to stir at -78 °C for an additional 30 min, at which point the dry ice/acetone bath was removed and the reaction was left to warm to 0 °C and quenched with saturated aqueous NH$_4$Cl (30 mL). The suspension was extracted with EtOAc (3 x 75 mL). The combined organic fractions were washed with brine, dried over MgSO$_4$, filtered, and concentrated. Column chromatography (12% Et$_2$O in hexanes) gave 930 mg (61%) of the desired propargylic alcohol 9 as a clear colorless oil.

$^1$H NMR (CDCl$_3$, 300 MHz) 1:1 mixture of diastereomers, δ 5.32 (tq, J = 6.9, 1.2 Hz, 2H), 5.14 (tq, J = 6.9, 1.2 Hz, 2H), 4.56 (d, J = 7.0 Hz, 4H), 4.57-4.49 (m, 2H), 2.12-1.95 (m, 14H), 1.78 (dd, J = 5.1, 2.1 Hz, 2H), 1.69 (s, 6H), 1.70-1.65 (m, 2H), 1.59 (s, 6H), 1.48 (q, J = 7.5 Hz, 4H), 1.44 (d, J = 6.6 Hz, 6H), 1.19 (s, 18H), 0.95 (d, J = 6.9 Hz, 6H), 0.92 (d, J = 6.6 Hz, 6H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) 1:1 mixture of diastereomers, δ 179.0, 178.9, 141.8, 141.8, 135.2, 134.6, 124.9, 124.3, 119.5, 119.0, 118.9, 96.6, 86.3, 84.8, 83.8, 83.8, 61.6, 61.5, 58.8, 39.7, 39.6, 38.9, 38.8, 38.7, 38.3, 37.9, 37.7, 37.2, 36.8, 36.3, 33.3, 31.7, 31.5, 31.4, 31.1, 30.3, 27.4, 27.3, 26.5, 26.4, 25.2, 21.4, 21.3, 18.8, 18.6, 16.7, 16.7, 16.2, 16.1.

IR (film) 3429, 2963, 2928, 2873, 2361, 2339, 2206, 1727, 1675, 1427, 1284, 1157 cm$^{-1}$. 

256
THF (1 mL) was added to an oven-dried round-bottomed flask under argon. To the flask was added LiAlH\(_4\) (800 \(\mu\)L, 1.59 mmol, 2.0 M solution in THF). To this stirring solution was added a solution of propargylic alcohol 9 (200 mg, 0.53 mmol) in THF (5.0 mL) dropwise via syringe. This mixture was heated at reflux for 3 h. After cooling to room temperature the reaction was further cooled to 0 °C, and quenched by dropwise addition of saturated aqueous Rochell’s salt (1.5 mL). The resultant mixture was filtered and the precipitate was washed with Et\(_2\)O (15 mL), the filtrate was concentrated. Column chromatography (50% EtOAc in hexanes) gave 148.0 mg (95%) of the desired allylic alcohol 10 as a clear colorless oil.

\(^1\)H NMR (CDCl\(_3\), 500 MHz) \textbf{1:1 mixture of diastereomers} \(\delta\) 5.45-5.29 (m, 6H), 5.08-5.03 (m, 2H), 4.25 (quintet, \(J = 6.5\) Hz, 2H), 4.12 (d, \(J = 7.0\) Hz, 4H), 2.13-2.05 (m, 4H), 2.04-1.99 (m, 4H), 1.98-1.77 (m, 8H), 1.73-1.66 (m, 2H), 1.64 (s, 6H), 1.58-1.45 (m, 4H), 1.55 (s, 6H), 1.24 (dd, \(J = 6.5, 2.5\) Hz, 6H), 0.85-0.77 (m, 12H).

\(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \textbf{1:1 mixture of diastereomers} \(\delta\) 139.6, 135.9, 135.8, 135.6, 132.7, 132.7, 132.7, 124.0, 123.9, 123.8, 69.3, 59.6, 59.5, 48.3, 48.2, 39.7, 39.7, 37.7, 37.6, 31.9, 31.8, 30.5, 30.3, 26.3, 26.2, 23.9, 23.8, 20.9, 20.8, 19.2, 19.1, 16.4, 16.2, 16.1.

IR (film) 3333, 2960, 2928, 2871, 2240, 1742, 1667, 1450, 1384, 1367, 974 cm\(^{-1}\).

LRMS (EI) calcd for C\(_{19}\)H\(_{34}\)O\(_2\) (M\(^+\)) 294, found 294.
Allylic alcohol 10 (260 mg, 0.89 mmol) was added to an oven-dried round-bottomed flask under argon. To the flask was added \( \text{CH}_2\text{Cl}_2 \) (6 mL) and MeCN (600 μL) via syringe, followed by \( N \)-methyl morpholine oxide (310 mg, 2.64 mmol) and oven-dried 4 Å molecular sieves (430 mg). To this stirring solution was next added tetrapropylammonium perruthenate (31.0 mg, 0.088 mmol). After 30 min the reaction was diluted with \( \text{CH}_2\text{Cl}_2 \) (25 mL) and filtered through a plug of silica gel, eluting with EtOAc (200 mL). Upon concentration, the resultant oil was purified via column chromatography (20% EtOAc in hexanes) to give 250.7 mg (97%) of the desired aldehyde 11 as a clear colorless oil.

\(^1\text{H} \text{NMR (CDCl}_3 \text{, 300 MHz)} \delta 9.99 \text{ (d, } J = 8.1 \text{ Hz, 1H), 6.58 \text{ (dd, } J = 15.9, 9.6 \text{ Hz, 1H), 6.01 \text{ (dd, } J = 15.9, 0.6 \text{ Hz, 1H), 5.87 \text{ (dq, } J = 7.8, 1.2 \text{ Hz, 1H), 5.08-5.05 \text{ (m, 1H), 2.26 \text{ (s, 3H), 2.25-2.19 \text{ (m, 4H), 2.17 \text{ (d, } J =1.5 \text{ Hz, 3H), 1.99-1.60 \text{ (m, 10H), 1.58 \text{ (s, 3H), 1.44-1.32 \text{ (m, 1H), 0.89 \text{ (d, } J = 6.6 \text{ Hz, 3H), 0.85 \text{ (d, } J = 6.9 \text{ Hz, 3H).}} \)

\(^{13}\text{C} \text{ NMR (CDCl}_3 \text{, 75 MHz)} \delta 198.7, 191.5, 163.9, 150.9, 136.4, 132.6, 127.6, 123.1, 49.1, 40.7, 37.7, 31.9, 29.9, 27.3, 25.8, 20.9, 19.4, 17.4, 16.3.

IR (film) 3055, 2862, 2360, 2336, 1697, 1671, 1422, 1368, 1265, 738 cm\(^{-1}\).

LRMS (EI) calcd for C\(_{19}\)H\(_{30}\)O\(_2\) (M\(^+\)) 290, found 290.
Aldehyde 11 (40.0 mg, 0.137 mmol) was added to an oven-dried round-bottomed flask and placed under argon. To the flask was added anhydrous THF (137 mL), this solution was cooled to -78 °C and treated with KHMDS (1.65 mL of 0.5 M solution in toluene, 0.413 mmol). The reaction was allowed to stir for 6 h at -78 °C. The reaction was then quenched via filtration though a short plug of silica gel, which was washed with Et₂O (500 mL). The filtrate was concentrated and filtered through another short plug of silica, eluting with 2:1 hexanes:EtOAc (200 mL), this solution was then concentrated. The crude aldol (11.2 mg) was then taken up in dry CH₂Cl₂ (1.5 mL), under argon. To this solution was added imidazole (7.9 mg, 0.116 mmol) and t-BuPh₂SiCl (31.8 mg, 0.116 mmol) at room temperature. The reaction was allowed to stir for 12 h at which point it was quenched with saturated aqueous NH₄Cl solution and extracted with CH₂Cl₂ (3 x 5 mL), the combined organic layers were dried over dried over MgSO₄, filtered, and concentrated. Column chromatography (3% EtOAc in hexanes) gave 14.8 mg (19% over two steps) of racemic 7,11-Dimethyl-4-isopropyl-13-(tert-butyl-diphenylsilyloxy)cyclotetradeca-2,7,11-triene-1-one 1 as a clear oil.

**Synthetic:**

**¹H NMR (CDCl₃, 500 MHz) δ 7.69-7.64 (m, 4H), 7.42-7.32 (m, 6H), 6.47 (dd, J = 15.5, 10.0 Hz, 1H), 5.74 (d, J = 15.9 Hz, 1H), 5.06 (d, J = 9.5 Hz, 1H), 4.82 (dt, J = 8.5, 4.5 Hz, 1H), 4.67 (m, 1H), 3.00 (dd, J = 15.5, 10.5 Hz, 1H), 2.60 (dd, J = 15.5, 4.5 Hz, 1H), 2.02-1.84 (m, 4H), 1.74-1.66 (m, 2H), 1.59-1.52 (m, 4H), 1.50 (s, 3H), 1.45-1.33 (m, 2H), 1.03-1.02 (m, 10H), 0.85 (d, J = 6.5 Hz, 3H), 0.81 (d, J = 6.5 Hz, 3H).

**¹³C NMR (CDCl₃, 75 MHz) δ 198.4, 151.1, 137.5, 136.1, 136.0, 134.5, 134.3, 133.7, 131.9, 129.8, 129.7, 127.8, 127.5, 127.3, 125.7, 67.6, 50.3, 48.2, 38.6, 37.6, 33.1, 27.7, 27.1, 24.0, 20.6, 19.9, 19.4, 16.3, 15.6.

**IR (film) 3054, 2960, 2929, 2857, 2360, 2306, 1680, 1658, 1620, 1428, 1265, 1111, 1058, 823, 740, 705 cm⁻¹.**
MS (El) calcd for C_{35}H_{48}O_{2}Si (M+Na\textsuperscript{+}) 551.3, found 551.3.

**Literature:**\textsuperscript{115a}

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz) \(\delta\) 7.70 (m, 4H), 7.38 (m, 6H), 6.50 (dd, \(J = 15, 9\) Hz, 1H), 5.75 (d, \(J = 15, 1\)H), 5.08 (d, \(J = 8, 1\)H), 4.80 (m, 1H), 4.68 (m, 1H), 3.12 (dd, \(J = 15, 10\) Hz, 1H), 2.60 (dd, \(J = 15, 4\) Hz, 1H), 2.1-1.4 (m, 10H), 1.6 (s, 3H), 1.5 (s, 3H), 1.00 (s, 9H), 0.86 (d, \(J = 6\) Hz, 3H), 0.82 (d, \(J = 6\) Hz, 3H).

\textsuperscript{13}C NMR Not Reported.

IR (film) 1687, 1662, 1621, 1428, 1111, 1057, 823, 740, 703 cm\textsuperscript{-1}.

HRMS (El) calcd for C_{35}H_{48}O_{2}Si (M\textsuperscript{+}) 528.3423, found 528.3414.
E. $^1$H NMR Spectra of Selected Compounds
STANDARD 1H OBSERVE

expl stdih

date Apr 11 2007
dfrq 300.101

solvent CDC13
dn H1

file /data/export/
dpwr 30
home/gfu/Tsm/Tsm/Tsm-07-112H.fid
dof 0

ACQUISITION

dmm c

dfreq 300.101
dmf 200

acq H1

flag

ACQ Flags

flags

DISPLAY

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wp 2485.9

vs 151

sc 0

wc 250

hzmm 9.62

is 500.00

rf1 800.4

rfp 0

th 0

ins 2.000

nm ph

ppm

Jf! 0.96

Lj 0.96

Lj 0.96

21 ppm

0.96

0.86

2.00

1.00

5.95

1.93

1.04

3.01

8.11

1.182.89
STANDARD 1H OBSERVE

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/Tem-07-113H.fld dm     nnn
ACQUISITION  dam   c
sfrq   300.181   damf   200
tn       H1   PROCESSING
at       4.003   wfile
np       48052   proc
sw       6000.4   ft
fb       not used
bs       6   werr
tpwr      54   wexp
dp       8.0   wbs
di      0.050   wnt
tol       867.7
nt       16
tc       16
tlock     n
gain     not used
1)       n
ln       n
dp       y
DISPLAY  -2.1
sp       2405.9
wp       151
vs       250
fsc       0
wc
hzam      5.62
is  500.00
rtl       600.4
rpf       8
th       20
ins     2.080
mm

2.06
0.95  0.96
STANDARD PROTON PARAMETERS

exp3  s2pul

SAMPLE

date May 21 2007
dfrq 125.672
dtof 1519.5
dseq 63050
dres 105542.2
d RES

dn

dfrq 498.746

dt

df

acq

ACQUISITION

dfrq 125.672

dfrq2

ACQUISITION

dfrq 125.672

dfrq3

ACQUISITION

flags

PROCESSING
STANDARD 1H OBSERVE

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expl std1h

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date Apr 12 2007 dfreq 300.100
solvent CDC13 dn H1
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dr file/home/gfu/Tsm/hrat-
/Tsm-07-118H.fid dm nnn
ACQUISITION dmw c
sfrq 300.101 dm f 200
at H1 PROCESSING
np 48052 proc ft
sw 6002.0 fn 131072
fb not used
bs 6 werr
wimp 54 wexp
lp 8.0 wbs
d1 6.050 wnt
tof 867.7
nt 16
t 16
ALLOC n
gain not used
FLAGS
i1 n
i2 n
dp y
DISPLAY
sp -5.3
wp 2406.0
vs 151
sc 0
wc 250
hzm 9.62
hs 580.00
rfv 600.4
rfp 0
th 20
ins 2.000
nm ph 2.000
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![NMR Spectrum Image]

---

ppm 19.25 9.56 5.00 6.02 2.15 3.14 9.56 2.00 0.98 0.96 1.03 2.96
STANDARD PROTON PARAMETERS

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dof 0
inkle/Tsm-07-127-c dm nnn
rosscoupling.fld dmm w
ACQUISITION daf 10000
sfrq 498.746 dsrq 1.0
at 3.001 homo n
np 63658 PROCESSING
sw 10594.2 wtfile
fb not used proc ft
bs 8 tn 262144
wp 8.6
pw 2.00 werr
tof 1515.5 wexp
nt 16 wbs
cf 16 wnt wft
lock n
FLAGS
fl n
in n
dp y
hs nn
DISPLAY
sp 3.5
wp 3986.9
vs 31
sc 0
wc 250
hzm 15.98
ls 33.57
rt 4585.6
rtp 3628.1
th 7
ins 2.000
al cdc ph

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![Chemical Structure Diagram](attachment:image.png)
STANDARD PROTON PARAMETERS

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ACQUISITION  daf  10000
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at  3.001  homo  n
np  63059
sw  12594.2  wtfile
fb  not used  proc  ft
bs  8  Fm  262144
wpr  56  math
rpr  8.6
sw  2.000  werr
nt  16  wbs
ct  16  wnt
alock  not used
flag  n
display  n
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wp  4000.0
vs  92
sc  0
wc  250
hzmm  16.50
is  2.19
rf1  4865.7
rfp  3626.1
th  7
ins  2.000
ai  cdc  ph

1  2  3  4  5  6  7  ppm

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1.99  2.87  3.70  8.18  5.77

269
STANDARD PROTON PARAMETERS

SAMPLE: Ms

DATE: Jun 4 2007

SOLVENT: CDCl3

HOME/GPU/TSM/BUW-

INKLE/TSM-08-043H-

FID: DATASET

ACQUISITION: dat

SFRQ: 499.746

T0: 11.3

NP: 83658

DI: 2.800

TOF: 1513.5

NT: 256

CI: 194

NLOCK: n

GAIN: not used

FLAGS: n

DISPLAY: -14.5

WP: 4913.3

SC: 56

WC: 256

HZAM: 16.05

IS: 33.57

RFI: 4864.6

RFP: 3626.1

TH: 4

INS: cdc ph

AL: cdc

[Chemical structure diagram]

[Graph with peaks at ppm values]
Section 2.5

Nickel-Catalyzed Asymmetric Cross-Couplings of Racemic Propargylic Halides with Arylzinc Reagents
A. Introduction

In Chapter 2, Section 2.2 we discussed the development of the first secondary-secondary cross-coupling reaction, namely, the nickel-catalyzed cross-coupling of secondary propargylic halides with secondary alkylzinc iodide reagents. Despite achieving only modest success in our attempts to develop an asymmetric alkylation of propargylic halides (Chapter 2, Section 2.1), we were still interested in exploring the possibilities of this class of electrophiles. Furthermore, as we had now seen that the apparent rate of transmetalation was dependent on the nature of the organometallic reagent, we were quite curious about not only the transmetalation rate with aryl nucleophiles, but also whether this would have an exploitable impact on the possibility to develop an asymmetric arylation. At the outset of this work there had been no reports of asymmetric Negishi arylation reactions of alkyl electrophiles.

B. Results and Discussion

Encouraged by the modest levels of success obtained in the alkylation chemistry and by the work of others in the group with Pybox ligands, we undertook an exploration of reaction conditions towards the development of the arylation reaction illustrated in eq 2.14, where the electrophile was a TMS-protected secondary propargylic bromide and the initial nucleophile was ZnPh₂.

\[
\text{racemic} \quad \text{TMS-CH₃C≡CHBr} \quad \text{ZnPh₂} \quad \text{nickel pybox} \quad \text{TMS-CH₃C≡CHPh} \quad \text{goal: high yield, high ee}
\]

(2.14)

The first attempt at this cross-coupling was performed on a propargylic bromide with diphenylzinc (1.5 equiv) using 10% NiCl₂·glyme and 13% (i-Pr)-Pybox in DMA at room temperature, as illustrated in eq 2.15. We were quite pleased to obtain 31% of the desired product, in a quite promising level of enantioselectivity (60% ee).
In our initial studies we found that a solvent mixture (3:1 toluene:THF) appeared to give the best results; the THF was thought to be required, in part, to solublize the ZnPh₂, which at this stage of the project was purchased from Aldrich (92% purity). A broad ligand survey revealed that a number of Pybox ligands imparted a good level of enantioselectivity to this transformation.

**Table 2.9.** Initial Pybox Screening for the Asymmetric Negishi Arylation of Propargylic Bromides.

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<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<th>Pybox, oxazoline =</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>16</td>
<td>56</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Yield was determined by GC versus an internal standard. <sup>b</sup> Determined by Chiral GC.
Due in part to its commercial availability, a considerable amount of effort was devoted towards further optimization of this reaction with (i-Pr)-Pybox as the ligand. We observed that the efficiency of this reaction was highly dependent on the quality of the Ph₂Zn, and that different batches of material from Aldrich had dramatically different reactivity. At times, the material from Aldrich failed to produce any cross-coupling product. This problem was rectified by changing the source of the Ph₂Zn to Strem (99% purity).

Despite finding a solution to our reproducibility problems, the project was still plagued by low yields and ee's in the 70's. We thought, due to the positive effect which was observed in our earlier alkylation work, that a survey of additives may be worth examining. To our delight a number of additives did have a positive impact on this coupling reaction. The addition of 1.0 equiv of InBr₃ or La(OTf)₃ reduced the quantity of nucleophile homocoupling and appeared to have a positive impact on the enantioselectivity (Table 2.10). In further studies we found that by using only 50% La(OTf)₃ we could not only see improved selectivity (74% → 83% ee), but that the efficiency of the reaction improved dramatically (34% → 94% ee). Extensive screening of other lanthanide-based additives furnished no improvement over this result.

Table 2.10. Effect of Additives on the Asymmetric Negishi Arylation of Propargylic Bromides.

<table>
<thead>
<tr>
<th>entry</th>
<th>additive</th>
<th>X equiv</th>
<th>yield (%)ᵃ</th>
<th>ee (%)ᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>N/A</td>
<td>27</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>La(OTf)₃</td>
<td>0.2</td>
<td>86</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>La(OTf)₃</td>
<td>0.5</td>
<td>94</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>La(OTf)₃</td>
<td>0.7</td>
<td>88</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>La(OTf)₃</td>
<td>1.0</td>
<td>45</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>InBr₃</td>
<td>0.5</td>
<td>71</td>
<td>76</td>
</tr>
<tr>
<td>7</td>
<td>InBr₃</td>
<td>1.0</td>
<td>56</td>
<td>81</td>
</tr>
<tr>
<td>8</td>
<td>InBr₃</td>
<td>1.5</td>
<td>1</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

ᵃ Yield was determined by GC versus an internal standard.
b Determined by chiral GC.

¹²¹ It is worth noting that independent synthesis of InPh₃ showed that this reagent does not cross-couple efficiently under these reaction conditions.
After thorough screening of lanthanide additives, the best result obtained while using (s-Bu)-Pybox was at -20 °C in glyme; we could obtain 90% ee with 14% yield. At this stage, we thought that our reaction conditions may have changed enough that it would make sense to reexamine the ligands from Table 2.9, as we may have unwisely been optimizing a local maximum and our new reaction conditions may work better with an alternative ligand. To our delight, this turned out to be true, and we soon found that the use of indanyl pybox, L6, at 0 °C gave the desired product in 71% yield and 90% ee (eq 2.16). Furthermore, it soon became apparent that the La(OTf)₃ additive was no longer required.

Shortly after making this discovery, the reaction conditions were further optimized, leading to an improvement in the chemical yield and selectivity (eq 2.17).

Unfortunately, diarylzinc reagents are not widely available and as we were interested in the development of a reaction with a broad scope, we realized we needed reliable access to functionalized diarylzinc reagents. Control experiments suggested our reaction was not tolerant of stoichiometric magnesium or lithium halide salts. Indeed, attempts to generate diarylzinc reagents via transmetallation of aryl-Grignard or aryllithium reagents failed to produce desirable results in the coupling reaction. Careful trituration and removal of magnesium halide salts after transmetallation did produce reactive diarylzinc reagents (see Scheme 2.25). However, this

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process was not attractive experimentally and we desired a more straightforward and operationally simple route to our arylzinc reagents.

Scheme 2.25. Transmetalation Reactions to Synthesize ZnAr₂.

In 2002, Bolm and coworkers reported a transmetallation from boron to zinc, generating arylzinc reagents from boronic acids and diethylzinc; our initial attempts with this protocol were ineffective in our coupling (eq 2.18). The major product under these reaction conditions was that derived from ethyl-transfer from the excess ZnEt₂. Gratifyingly, modification of this procedure (eq 2.19) allowed us to successfully generate arylzinc reagents in situ that performed quite well in this cross-coupling reaction.

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With optimized conditions (eq 2.19) in hand, we set out to establish the scope of this cross-coupling reaction. Beginning with trimethylsilyl-protected propargylic bromides, with which the optimization had been carried out, we were pleased to discover that these propargylic bromides undergo couplings with a range of arylzinc reagents in high ee (Table 2.11). Unfunctionalized arylzinc reagents couple efficiently (entries 1 and 2). A protected aryl diol couples in good yield, regardless of the size of the alkyl group on the electrophile (entries 3 and 4). Coupling of ortho-substituted nucleophiles is possible in very good ee, but with only modest efficiency (entry 5). Functionalization of the electrophile is also well tolerated, as are alkyl ethers and meta-substitution on the nucleophile (entries 6 and 7).

---

125 We were unsuccessful in our attempts to transmetalate o-tolylboronic acid.
Table 2.11. Asymmetric Cross-Couplings of TMS-Protected Propargylic Bromides with Arylzinc Reagents.

<table>
<thead>
<tr>
<th>entry</th>
<th>alkyl</th>
<th>arylzinc reagent</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-Bu</td>
<td><img src="image" alt="Structure" /></td>
<td>92</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>n-Bu</td>
<td><img src="image" alt="Structure" /></td>
<td>70&lt;sup&gt;c&lt;/sup&gt;</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td><img src="image" alt="Structure" /></td>
<td>75</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>i-Bu</td>
<td><img src="image" alt="Structure" /></td>
<td>71</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>n-Bu</td>
<td><img src="image" alt="Structure" /></td>
<td>39</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td>76</td>
<td>94</td>
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<tr>
<td>7</td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td>79</td>
<td>94</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield, average of two reactions. <sup>b</sup> Determined by HPLC or GC. <sup>c</sup> 3.0 equiv ArZnEt used.

Trimethylsilyl-protected alkynes are not unique in their ability to participate in this coupling reaction. Other common silyl-based protecting group may also be used; for example, (dimethyl)phenylsilyl- and TIPS-protected propargylic bromides react quite effectively in this coupling under the standard conditions (eqs 2.20 and 2.21).
Not only propargylic bromides, but also chlorides, undergo cross-coupling under our standard conditions (eq 2.22). Although the yield is somewhat lower, the ee, not surprisingly, is essentially identical to that observed for the reaction of the corresponding bromide.

Gratifyingly, these reaction conditions can also be applied to a broad spectrum of differentially alkyl substituted propargylic bromides, still resulting in exclusive formation of enantioenriched alkynes (Table 2.12). A full range of alkyl substituted propargylic bromides readily participate in this asymmetric coupling reaction; the alkyl substituent can range in size from methyl to tert-butyl (entries 1-5). Phenyl-substituted propargylic bromides also couple in high yield and ee (entry 6).

\[ \text{Ph(}Me)_2\text{Si} \text{EtZn} \xrightarrow{3.0\% \text{NiCl}_2 \text{-glyme}} \text{Ph(}Me)_2\text{Si} \text{F} \]

\[ \text{racemic} \quad \text{88% yield} \quad 88\% \text{ ee} \]

\[ \text{TIPS} \text{Bracem} \text{EtZn}t-\text{Bu} \xrightarrow{3.0\% \text{NiCl}_2 \text{-glyme}} \text{TIPS} \text{Bracem} \text{Ph-ZnEt} \]

\[ \text{racemic} \quad \text{81% yield} \quad 93\% \text{ ee} \]

\[ \text{TMS} \text{Cln-Bu} \xrightarrow{3.0\% \text{NiCl}_2 \text{-glyme}} \text{TMS} \text{Phn-Bu} \]

\[ \text{racemic} \quad \text{61% yield} \quad 91\% \text{ ee} \]

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126 Note: Under our standard conditions, (a) a cross-coupling between the propargylic bromide in Entry 3, Table 2.11 and the zinc reagent derived from p-trifluoromethylphenyl boronic proceeded in 31% isolated yield and 86% ee. Personal correspondence with Prof. C. Bolm and Dr. J. Rudolph leads us to believe that the transmetalation is the problematic step. (b) All attempts at vinylations have been unsuccessful thus far.
Table 2.12. Asymmetric Cross-Couplings of Propargylic Bromides with Arylzinc Reagents.

<table>
<thead>
<tr>
<th>entry</th>
<th>propargylic bromide</th>
<th>arylzinc reagent</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;Br</td>
<td><img src="image" alt="Racemic ArZnEt" /></td>
<td>81</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;Br</td>
<td><img src="image" alt="3.0 equiv ArZnEt" /></td>
<td>78&lt;sup&gt;c&lt;/sup&gt;</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;Br</td>
<td><img src="image" alt="OMe" /></td>
<td>76</td>
<td>91</td>
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<td>4</td>
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<td><img src="image" alt="OMe" /></td>
<td>63</td>
<td>89</td>
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<tr>
<td>5</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;Br</td>
<td><img src="image" alt="OMe" /></td>
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<td>6</td>
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<td><img src="image" alt="OMe" /></td>
<td>88</td>
<td>89</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield, average of two reactions. <sup>b</sup> Determined by HPLC or GC. <sup>c</sup> 3.0 equiv ArZnEt used.

In 2007, Wright and Anderson reported a number of new, highly efficient ligands for dihydrofolate reductase (DHFR) from *Cryptosporidium hominis* and *Toxoplasma gondii*, two apicomplexan parasitic protozoa responsible for wasting disease, neonatal death and cerebral inflammation.<sup>127</sup> The most biologically active of these new compounds was 13 (Scheme 2.26).

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Compound 14 was an intermediate en route to 13 and is clearly accessible in short order via the method just described. Originally, 14 was prepared in 5 steps (22% yield), in which the stereochemistry was installed through use of Evans stoichiometric chiral-auxiliary chemistry. It is now possible to generate 14 in two steps\(^{128}\) (63% yield) in a catalytic, enantioselective fashion (Scheme 2.27). It is also worth noting that this cross-coupling scales up well and can be easily run on a gram scale.

\(^{128}\) This synthesis begins with commercially available 4-(trimethylsilyl)but-3-yn-2-ol.
Scheme 2.27. Improved Synthesis of a Dihydrofolate Reductase Inhibition Ligand.

Allene formation

As was discussed in Chapter 2, Section 2, transition metal-catalyzed cross-coupling reactions of propargylic electrophiles with organometallic reagents typically provide the allene, rather than the alkyne, as the predominant product.\textsuperscript{94} In our studies of this asymmetric arylation, we once again found conditions that favor formation of allenic products over propargylic ones. When applying our standard conditions to propargylic halides, in which the alkyne is substituted with an electron-withdrawing substituent, such as an ester, we isolated only an allene (eq 2.23). Interestingly, this allene was formed in 47\% ee.\textsuperscript{129} To date, attempts to improve the observed selectivity have not been fruitful.\textsuperscript{130} Also, the arylation regioselectivity has the same ligand dependence as was observed for our asymmetric alkylation: nickel-catalyzed arylations of propargylic halides lead to formation of allenes when a bidentate ligand is used. Due in part to time constraints, a more thorough study of this reactivity was not performed.

\textsuperscript{129} Absolute configuration of the product has not been determined.
\textsuperscript{130} Koyel Bhattacharyya, an undergraduate researcher in our lab, carried out the studies based on this initial result. Improving the enantioselectivity of this transformation has proven difficult.
C. Conclusion

In this section, we have described the development of the first catalytic asymmetric cross-couplings of secondary propargylic bromides. Furthermore this method represents the first example of an asymmetric Negishi-type arylation of an alkyl electrophile. Importantly, transmetalation from readily available, and stable, arylboronic acids allows easy and straightforward preparation of the mixed arylzinc reagents used in this coupling. This method, allows access to a wide range of differently substituted, enantioenriched alkynes from easily prepared racemic propargylic halides.
D. Further Developments

This section highlights some of the recent progress made within the Fu group on a variety of arylation reactions. Specifically it includes a description of nickel-catalyzed Negishi, Suzuki, Hiyama and Kumada arylation reactions.

Negishi Coupling Reaction

In 2009, Pam Lundin and Jorge Esquivias published the first catalytic, asymmetric method for the cross-coupling of arylzinc reagents with α-bromoketones (Scheme 2.28). They found that through use of the Pybox ligand L14, high yields and enantioselectivities could be obtained in the coupling of arylzinc iodides and α-bromoaryl ketones. Across the spectrum, the level of enantioselectivity observed for this process was exceptionally high and only ortho-substitution on the electrophile caused a slight decrease.

Scheme 2.28. The First Catalytic Asymmetric Cross-Coupling of Arylzinc Reagents with α-Bromoketones.

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Suzuki Coupling Reaction

An important development in the cross-coupling of secondary alkyl electrophiles came in 2006, when Dr. Francisco González-Bobes developed a set of reaction conditions which overcame some of the limitations of Dr. Zhou’s initial report. In a move away from more traditional sp²-hybridized nitrogen-based ligands, Dr. González-Bobes found that amino alcohols could serve as excellent ligands in a nickel-catalyzed Suzuki reaction of unactivated alkyl halides and boronic acids. Orthogonal sets of reaction conditions were developed for the coupling of bromide and iodides (Scheme 2.29) and that of chlorides (Scheme 2.30). These reaction conditions were much more tolerant with respect to the steric hindrance about the alkyl halide and thus were able to not only efficiently couple larger cyclic electrophiles, but also a variety of acyclic electrophiles.


**Scheme 2.30.** NiCl$_2$-glyme/Prolinol-Catalyzed Suzuki Cross-Couplings of Secondary Alkyl Chlorides.

$$\text{R}_{\text{alkyl}} - X \xrightarrow{\text{6\% NiCl$_2$-glyme}} (\text{HO})_2\text{B} - \text{Ar} \xrightarrow{\text{12\% prolinol, KHMDS, i-ProH, 60 °C}} \text{R}_{\text{alkyl}} - \text{Ar}$$

5 examples; 46-84% yield

![Chemical structures](image)

### Hiyama Coupling Reaction

Just as Dr. Powell’s Hiyama$^{81}$ and Stille$^{82}$ cross-coupling reactions built off the success of Dr. Zhou’s Suzuki reaction, the development of second generation arylation reactions had their roots in Dr. González-Bobes’ Ni/amino alcohol Suzuki arylation reaction. The discovery that amino alcohols could serve as ligands in cross-coupling reactions was exciting for two main reasons. The first was that a large number of these compounds are commercially available and/or easily prepared. The second, and more important reason, is that although sp$^2$-hybridized nitrogen-based ligands had proved their utility in a number of coupling reactions, these same reactions were inefficient when the steric demand immediately adjacent to the nitrogen was increased. This clearly posed a significant impediment to the development of asymmetric arylation reactions.

As the group’s primary successes in developing asymmetric cross-coupling reactions had required the use of activated electrophiles; en route to developing an asymmetric Hiyama arylation reaction, Neil Strotman and Stefan Sommer developed conditions under which activated electrophiles coupled efficiently with trifluorosilicon reagents mediated by an amino alcohol, norephedrine (Scheme 2.31).$^{133}$ This arylation reaction displayed an impressively broad electrophile scope, allowing for the coupling of not only unactivated, cyclic and acyclic electrophiles, but also for an array of activated ones. α-Bromoketones, esters, amides,

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phosphonates, nitriles and allylic chlorides all furnished good yields of the desired arylated products.

**Scheme 2.31.** Hiyama Reactions of Activated and Unactivated Secondary Halides Catalyzed by a Nickel/Norephedrine Complex.

Dr. Strotman continued his work in the area of Hiyama chemistry with the development of an asymmetric arylation of \( \alpha \)-bromoesters (Scheme 2.32). Low levels of enantioselectivity were observed in coupling reactions using trifluorosilanes and amino alcohol ligands, but this was resolved by moving to trimethoxysilanes and diamine ligands. Early into this work it became clear that there was a requirement of a very sterically demanding ester in order to obtain good levels of enantioselectivity. After exploration of various bulky esters, it was found that a BHT-ester proved best. Upon Dr. Stroman’s departure, Xing Dai worked to finalize the reaction conditions and explored the scope of this transformation.\(^{134}\) For a series of \( \alpha \)-bromo BHT-esters, the yield and selectivity for phenylation was good to excellent. Unfortunately, a large number of functionalized trimethoxyaryl silanes either did not couple efficiently, or the newly generated chiral center was racemized under the basic reaction conditions. Dr. Dai did accomplish asymmetric vinylations under these reaction conditions, representing another first for the group.

Scheme 2.32. Catalytic Asymmetric Hiyama Cross-Couplings of Racemic α-Bromoesters.

\[ \text{BHTO} \text{O} \text{R} \]
\[ \text{Br} \]
\[ \text{BHTO} \text{O} \text{R} \] \[ \text{Br} \]
\[ \text{BHTO} \text{O} \text{R} \]

\[ \text{racemic} \]

BHT = 2,6-di-t-butyl-4-methylphenol
TBAT = \( [\text{F}_2\text{SiPh}_3]^+\text{[NBu}_4^-\]

17 examples; 64-84% yield
75-99% ee

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
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<td>80%</td>
<td>99%</td>
</tr>
<tr>
<td>2</td>
<td>78%</td>
<td>89%</td>
</tr>
<tr>
<td>3</td>
<td>74%</td>
<td>93%</td>
</tr>
<tr>
<td>4</td>
<td>66%</td>
<td>89%</td>
</tr>
<tr>
<td>5</td>
<td>72%</td>
<td>92%</td>
</tr>
</tbody>
</table>
E. Experimental

I. General

All reactions were carried out in oven-dried glassware under an atmosphere of argon. All chemicals, including NiCl$_2$·glyme (Strem), ligand L6 (Aldrich; Strem), ZnEt$_2$ (Strem), and glyme (Fluka), were purchased and used without further purification.

II. Preparation of Substrates

These procedures have not been optimized.

**Synthesis of Propargylic Alcohols (representative procedure):** A 100 mL flask was charged with a terminal alkyne (10.0 mmol), evacuated, and back-filled with argon. THF (50 mL) was then added via syringe. The solution was then cooled to -78 °C in a dry ice/acetone bath. After 15 min of cooling, n-BuLi (6.6 mL of a 1.6 M solution in hexanes, 10.5 mmol) was added dropwise, via syringe. After an additional 20 min of stirring, the aldehyde (11.0 mmol) was added via syringe. The solution was allowed to warm to room temperature, at which point the reaction was quenched with an aqueous saturated ammonium chloride solution (25 mL). The layers were separated, and the aqueous layer was extracted twice with CH$_2$Cl$_2$ (50 mL). The combined organic layers were washed with brine (50 mL) and dried over MgSO$_4$, filtered and concentrated under reduced pressure. The resultant oil was purified via flash chromatography (hexanes/EtOAc or pentane/Et$_2$O) to give the propargylic alcohols as oils.

(±)-1-(Trimethylsilyl)hept-1-yn-3-ol [CAS # 75045-85-1]. Prepared from (trimethylsilyl)acetylene and valeraldehyde by the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) δ 4.32 (t, $J$ = 6.6 Hz, 1H), 2.20 (broad s, 1H), 1.71-1.62 (m, 2H), 1.46-1.23 (m, 4H), 0.89 (t, $J$ = 6.9 Hz, 3H), 0.14 (s, 9H).
(±)-5-Methyl-1-(trimethylsilyl)hex-1-yn-3-ol [CAS # 80352-60-9] Prepared from (trimethylsilyl)acetylene and isobutyraldehyde by the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 4.38 (t, $J = 6.8$ Hz, 1H), 1.82 (septet, $J = 6.7$ Hz, 1H), 1.67-1.47 (m, 2H), 0.92 (dd, $J = 6.0$, $J = 3.0$ Hz, 6H), 0.16-0.15 (m, 9H).

(±)-1-(Triisopropylsilyl)pent-1-yn-3-ol [CAS # 263720-71-4] Prepared from (triisopropylsilyl)acetylene and propionaldehyde by the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 4.39-4.30 (m, 1H), 1.87-1.63 (m, 3H), 1.06-0.99 (m, 24H).

1-(Dimethyl(phenyl)silyl)hept-1-yn-3-ol. Prepared from (dimethylphenylsilyl)-acetylene and valeraldehyde by the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.65-7.61 (m, 2H), 7.43-7.38 (m, 3H), 4.41 (t, $J = 6.9$ Hz, 1H), 1.78-1.64 (m, 2H), 1.49-1.32 (m, 4H), 0.93 (t, $J = 6.9$ Hz, 3H), 0.43 (s, 6H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 133.9, 130.3, 129.7, 128.2, 108.9, 87.5, 63.1, 45.3, 37.6, 27.6, 26.2, 22.6, 22.3, 14.3, 14.1.

IR (film) 3384, 2959, 2872, 2361, 2171, 1675, 1428 cm$^{-1}$.

HRMS (ESI) calcd for C$_{15}$H$_{22}$OSi (M+Na$^+$) 269.1332, found 269.1332.
(±)-5-Methyl-1-(triisopropylsilyl)hex-1-yn-3-ol [CAS # 913618-91-4] Prepared from isobutyraldehyde by the representative procedure.

\[^1\text{H} \text{ NMR (CDCl}_3, 300 \text{ MHz)} \delta 4.44-4.37 (m, 1H), 1.99-1.96 (m, 1H), 1.86 (septet, J = 6.6 Hz, 1H), 1.68-1.50 (m, 2H), 1.07-1.05 (m, 21H), 0.93 (t, J = 6.0 Hz, 6H).\]

Synthesis of Propargylic Bromides (representative procedure). A 500 mL flask was charged with imidazole (1.3 g, 19.5 mmol), evacuated, and back-filled with argon. CH\(_2\)Cl\(_2\) (100 mL) was added via syringe, followed by the addition of the propargylic alcohol (16.3 mmol). This solution was allowed to stir for 15 min. Next, dibromotriphenylphosphorane (8.24 g, 19.5 mmol) was added as a solid. The reaction was run under argon and monitored by TLC. Upon completion (usually 3-4 h), the reaction was quenched by the addition of silica gel, and was concentrated and dried under reduced pressure. Once dry, this plug of silica was subjected to flash chromatography (hexanes/EtOAc or pentane/Et\(_2\)O) to give the propargylic bromides as oils.

(±)-2-Bromohex-3-yne [CAS # 109-48-8]. Prepared from (±)-hex-3-yn-2-ol by the representative procedure.

\[^1\text{H} \text{ NMR (CDCl}_3, 300 \text{ MHz)} \delta 4.62 (qt, J = 6.8, 2.1 \text{ Hz, 1H}), 2.22 (qd, J = 7.5, 2.1 \text{ Hz, 2H}), 2.79 (d, J = 6.8 \text{ Hz, 3H}), 1.11 (t, J = 7.5 \text{ Hz, 3H}).\]
(±)-(3-Bromopent-1-ynyl)cyclohexane. Prepared from (±)-1-cyclohexylpent-1-yn-3-ol by the representative procedure. (±)-1-Cyclohexylpent-1-yn-3-ol [CAS # 185322-10-5] was prepared from ethynylcyclohexane and propionaldehyde by the representative propargylic alcohol procedure and used without intermediate purification.

$^1$H NMR (CDCl$_3$, 300 MHz) δ 4.58-4.51 (m, 1H), 2.49-2.38 (m, 1H), 1.98 (quintet, $J = 6.1$ Hz, 2H), 1.82-1.62 (m, 4H), 1.50-1.24 (m, 6H), 1.06 (t, $J = 7.2$ Hz, 3H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) δ 92.6, 79.4, 40.6, 33.8, 32.6, 29.3, 26.1, 24.9, 12.0.

IR (film) 2972, 2932, 2854, 2360, 2340, 2234, 1448, 1173 cm$^{-1}$.

LRMS (EI) calcd for C$_{11}$H$_{17}$ (M-Br$^+$) 149, found 149.

(±)-5-Bromo-8-chloro-2,2-dimethyloct-3-yne. A 300 mL flask was charged with pyridinium chlorochromate (5.2 g, 24.0 mmol), evacuated, and back-filled with argon. To the orange solid was added CH$_2$Cl$_2$ (100 mL) and 4-chlorobutanol (2.0 mL, 20 mmol). The resulting dark-brown reaction mixture was stirred for 3 h at r.t., and then Et$_2$O (100 mL) was added, leading to the precipitation of a brown solid. The mixture was allowed to stand at r.t. for 2 h, and then it was filtered through a plug of silica gel (washed with Et$_2$O). The solvent was removed, and the residue was used as in the representative propargylic alcohol procedure. The crude (±)-1-chloro-7,7-dimethyloct-5-yn-4-ol was then brominated via the representative procedure

$^1$H NMR (CDCl$_3$, 300 MHz) δ 4.59 (t, $J = 6.0$ Hz, 1H), 3.58 (t, $J = 6.7$ Hz, 2H), 2.17-2.08 (m, 2H), 2.05-1.96 (m, 2H), 1.20 (s, 9H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) δ 97.0, 77.6, 44.2, 37.6, 37.4, 30.9, 30.4, 27.8.

IR (film) 2969, 2867, 2360, 2340, 2236, 1475, 1456, 1363, 1264 cm$^{-1}$.

LRMS (EI) calcd for C$_{10}$H$_{16}$BrCl (M-Br$^+$) 171, found 171.
(-)-(3-Bromohept-1-ynyl)trimethylsilane. Prepared from (+)-1-(trimethylsilyl)hept-1-yn-3-ol by the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 4.48 (t, $J = 6.6$ Hz, 1H), 1.98 (q, $J = 6.6$ Hz, 2H), 1.54-1.44 (m, 2H), 1.33 (sextet, $J = 7.2$ Hz, 2H), 0.92 (t, 7.2 Hz, 3H), 0.18-0.16 (m, 9H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 104.2, 92.0, 39.6, 37.6, 29.7, 22.1, 14.1, 0.0.

IR (film) 2959, 2863, 2361, 2338, 2174, 1457, 1250 cm$^{-1}$.

LRMS (EI) calcd for C$_9$H$_{16}$BrSi (M-i-Pr)$^+$ 231, found 231.

(±)-(3-Bromo-5-methylhex-1-ynyl)trimethylsilane. Prepared from (±)-5-methyl-1-(trimethylsilyl)hex-1-yn-3-ol by the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 4.50 (t, $J = 7.3$ Hz, 1H), 1.94-1.86 (m, 3H), 0.92 (dd, $J = 6.5$, 2.6 Hz, 6H), 0.16 (s, 9H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 104.3, 91.9, 48.7, 36.1, 27.0, 22.1, 22.0, 0.0.

IR (film) 2960, 2871, 2360, 2340, 2173, 1469, 1250, 1170 cm$^{-1}$.

LRMS (EI) calcd for C$_{10}$H$_{19}$Si (M-Br)$^+$ 167, found 167.

(±)-(3-Bromobut-1-ynyl)trimethylsilane [CAS # 2004440-80-8] Prepared from (±)-4-(trimethylsilyl)but-3-yn-2-ol by the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 4.59 (q, $J = 7.0$ Hz, 1H), 1.88 (d, $J = 6.1$ Hz, 3H), 0.16 (s, 9H).
(±)-4-Bromohex-2-yne [CAS # 99979-72-3] Prepared from (±)-hex-4-yn-3-ol by the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 4.51-4.45 (m, 1H), 1.97 (quintet, $J = 7.4$ Hz, 2H), 1.87-1.86 (m, 3H), 1.05 (t, $J = 7.2$ Hz, 3H).

(±)-(3-Bromopent-1-ynyl)triisopropylsilane [CAS # 234110-29-3] Prepared from (±)-1-(Triisopropylsilyl)pent-1-yn-3-ol by the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 4.53 (t, $J = 6.2$ Hz, 1H), 2.02 (quintet, $J = 7.2$ Hz, 2H), 1.11 (t, $J = 7.2$ Hz, 3H), 1.07 (s, 21H).

(±)-3-Bromopent-1-ynyl)benzene [CAS # 27975-78-6] Prepared from (±)-1-phenyl-1-phenyn-3-ol by the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.47-7.43 (m, 2H), 7.34-7.31 (m, 3H), 4.77 (t, $J = 6.3$ Hz, 1H), 2.13 (quintet, $J = 7.2$ Hz, 2H), 1.17 (t, $J = 7.2$ Hz, 3H).
(±)-(3-Bromohept-1-ynyl)dimethyl(phenyl)silane. Prepared from (±)-1-(dimethyl(phenyl)silyl)hept-1-yn-3-ol by the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.70-7.60 (m, 2H), 7.45-7.38 (m, 3H), 4.57 (t, $J = 6.9$ Hz, 1H), 2.10-2.02 (m, 2H), 1.65-1.50 (m, 2H), 1.39 (sextet, $J = 7.2$ Hz, 2H), 0.96 (t, $J = 9.6$ Hz, 3H), 0.47-0.44 (m, 6H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 136.8, 133.4, 129.8, 128.2, 105.9, 90.1, 39.5, 37.4, 29.8, 22.1, 14.2, -0.7.

IR (film) 2959, 2862, 2361, 2339, 1428, 1250, 1116 cm$^{-1}$.

LRMS (EI) calcd for C$_9$H$_{16}$BrSi (M-C$_6$H$_5^+$) 231, found 231.

(±)-(3-Bromo-5-methylhex-1-ynyl)triisopropylsilane. Prepared from (±)-5-methyl-1-(triisopropylsilyl)hex-1-yn-3-ol by the representative procedure.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 4.54 (t, $J = 7.5$ Hz, 1H), 1.95-1.86 (m, 3H), 1.06 (s, 21H), 0.94-0.92 (m, 6H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 106.3, 88.7, 48.9, 36.3, 27.2, 22.2, 21.9, 18.7, 11.4.

IR (film) 2959, 2866, 2170, 1465 cm$^{-1}$.

HRMS (EI) calcd for C$_{16}$H$_{31}$BrSi (M$^+$) 330.1373, found 330.1379.

(±)-Ethyl 6-bromo-8-(trimethylsilyl)oct-7-ynoate. Prepared from (±)-ethyl 6-hydroxy-8-(trimethylsilyl)oct-7-ynoate by the representative procedure. (±)-Ethyl 6-hydroxy-8-
(trimethylsilyl)oct-7-ynoate was prepared from (trimethylsilyl)acetylene and ethyl 6-oxohexanoate\textsuperscript{135} by the representative propargylic alcohol procedure, and used without intermediate purification.

$^1$H NMR (CDCl\textsubscript{3}, 300 MHz) $\delta$ 4.47 (t, $J = 6.7$ Hz, 1H), 4.09 (q, $J = 7.1$ Hz, 2H), 2.29 (t, $J = 7.1$ Hz, 2H), 1.97 (q, $J = 6.8$ Hz, 2H), 1.63 (sextet, $J = 7.1$ Hz, 2H), 1.57-1.48 (m, 2H), 1.22 (t, $J = 7.1$ Hz, 3H), 0.14 (s, 9H).

$^{13}$C NMR (CDCl\textsubscript{3}, 75 MHz) $\delta$ 173.5, 103.8, 92.2, 60.5, 39.4, 37.1, 34.3, 27.0, 24.2, 14.5, -0.1.

IR (film) 2958, 2867, 2360, 2340, 2170, 1735, 1457, 1373, 1250, 1181 cm\textsuperscript{-1}.

LRMS (EI) calcd for C\textsubscript{12}H\textsubscript{20}BrO\textsubscript{2}Si (M-CH\textsubscript{3})\textsuperscript{+} 303, found 303.

\begin{center}
\includegraphics[width=0.2\textwidth]{image}
\end{center}

(\pm)-(Z)-(3-Bromododec-9-en-1-ynyl)trimethylsilane. Prepared from (\pm)-(Z)-1-(trimethylsilyl)dodec-9-en-1-yn-3-ol by the representative procedure. (\pm)-(Z)-1-(Trimethylsilyl)dodec-9-en-1-yn-3-ol was prepared from (trimethylsilyl)acetylene and (Z)-dec-7-enal by the representative propargylic alcohol procedure and used without intermediate purification.

$^1$H NMR (CDCl\textsubscript{3}, 300 MHz) $\delta$ 5.41-5.26 (m, 2H), 4.49 (t, $J = 6.8$ Hz, 1H), 2.08-1.94 (m, 6H), 1.57-1.47 (m, 2H), 1.40-1.30 (m, 4H), 0.95 (t, $J = 7.5$ Hz, 3H), 0.17 (s, 9H).

$^{13}$C NMR (CDCl\textsubscript{3}, 75 MHz) $\delta$ 132.0, 129.1, 104.2, 92.0, 39.8, 37.6, 29.7, 28.4, 27.4, 27.1, 20.8, 14.6, -0.2.

IR (film) 3005, 2961, 2932, 2857, 2360, 2340, 2172, 1457, 1250 cm\textsuperscript{-1}.

LRMS (EI) calcd for C\textsubscript{15}H\textsubscript{27}Si (M-Br\textsuperscript{+}) 235, found 235.

III. Cross-Coupling Reactions

Standard Conditions:

**Preparation of the arylzinc reagents**: Set up in a nitrogen glovebox. In 20 mL vial, Et₂Zn (neat, 366 µL, 3.5 mmol) was added dropwise to a solution of boronic acid (2.5 mmol) in glyme (5.0 mL). The vial capped and heated at 60 °C for 12 h.

**General Procedure.** In a N₂-filled glovebox, a 4 mL vial was charged with NiCl₂-glyme (3.3 mg, 0.0150 mmol), (-)-L₆ (7.7 mg, 0.0195 mmol), then glyme (1.3 mL). This solution was stirred for 10 min. Then the arylzinc reagent was added (0.5 M in glyme, 2.0 mL, 1.0 mmol) and the vial was capped with a septum. This solution was stirred for 10 min at room temperature and then the vial was placed into a -20 °C bath. The reaction mixture was stirred for 10 min, and then the propargylic bromide was added via syringe (0.5 mmol). The reaction was stirred for 14 h at -20 °C. Then, the excess arylzinc reagent was quenched with EtOH (0.3 mL). The mixture was passed through a short plug of silica (eluting with 1:1 Hexanes: Et₂O) to remove inorganic salts and most of the glyme. The filtrate was concentrated, and the resultant oil was purified by flash chromatography.
Conditions under which Ph$_2$Zn may be coupled efficiently.

In a N$_2$-filled glovebox, a 4 mL vial was charged with NiCl$_2$-glyme (8.2 mg, 0.0150 mmol), (-)-L6 (19.1 mg, 0.0195 mmol), then glyme (1.25 mL). This solution was stirred for 10 min. Then a solution of Ph$_2$Zn (Strem, 99%) was added (153 mg in 1.25 mL glyme, 1.4 equiv, 0.7 mmol) and the vial was capped with a septum. This solution was stirred for 10 min at room temperature and then the vial was placed into a -20 °C bath. The reaction mixture was stirred for 10 min, and then (±)-(3-bromohept-1-ynyl)trimethylsilane (124 mg, 0.5 mmol) was added via syringe. The reaction was stirred for 1 h at -20 °C. Then, the excess arylzinc reagent was quenched with EtOH (0.3 mL). The mixture was passed through a short plug of silica (eluting with 1:1 Hexanes: Et$_2$O) to remove inorganic salts and most of the glyme. The filtrate was concentrated, and the resultant oil was purified by flash chromatography (0 → 5% Et$_2$O in hexanes), (S)-trimethyl(3-phenylhept-1-ynyl)silane was isolated as a colorless oil (98.0 mg, 80% yield) with 91% ee (see eq 2.19 for assay information).
IV. Eqs 2.18 and 2.19, Conditions/Products

Eq 2.18:

Preparation of the arylzinc reagent (Eq 2.18): Set up in a nitrogen glovebox. In 20 mL vial, Et₂Zn (neat, 628 μL, 6.0 mmol) was added dropwise to a solution of phenylboronic acid (243 mg, 2.0 mmol) in toluene (13.3 mL). The vial capped and heated at 60 °C for 12 h.

Trimethyl(3-phenylhept-1-ynyl)silane (Eq 2.18). In a nitrogen glovebox, a 20 mL vial was charged with NiCl₂·glyme (3.3 mg, 0.0150 mmol), (-)-L₆ (7.7 mg, 0.0195 mmol), then glyme (1.3 mL). This solution was stirred for 10 min. Then the arylzinc reagent (from above) was added (0.15 M in toluene, 6.7 mL, 1.0 mmol) and the vial was capped with a septum. This solution was stirred for 10 min at room temperature and then the vial was placed into a -20 °C bath. The reaction mixture was stirred for 10 min, and then the (+)-(3-bromohept-1-ynyl)trimethylsilane (124 mg, 0.5 mmol) was added via syringe. The reaction was stirred for 14 h at -20 °C. Then, the excess arylzinc reagent was quenched with EtOH (0.3 mL). The mixture was passed through a short plug of silica (eluting with 1:1 Hexanes: Et₂O) to remove inorganic salts and most of the glyme. The filtrate was concentrated, and analyzed by GC. The product was not isolated, as it was clear that the reaction had given <5% yield (73% ee, see eq 2.19 for assay information).
Eq 2.19:

(R)-Trimethyl(3-phenylhept-1-ynyl)silane (Eq 2.19). The compound was prepared according to the General Procedure with (±)-(3-bromohept-1-ynyl)trimethylsilane (124 mg, 0.5 mmol) and the arylzinc reagent (~0.5 M in glyme; 2.0 mL, 1.0 mmol). After purification by column chromatography (0 → 5% Et₂O in hexanes), the title compound was isolated as a colorless oil (110.0 mg, 90% yield) with 92% ee.

\([\alpha]_D^{22} = +11.6 \ (c = 1.0, \text{CHCl}_3)\). Chiral GC analysis of the product: Chirasil Dex CB column; method: 100 °C → 130 °C @ 10 °C/min, hold 10 min, then → 170 °C @ 9 °C/min, hold 5 min, flow rate 1.0 mL/min; retention times: 15.5 min (major), 15.3 min (minor).

\(^1\text{H} \text{NMR (CDCl}_3, 500 \text{MHz)} \ \delta \ 7.37-7.23 \ (m, 5H), 3.65 \ (t, J = 7.2 \text{ Hz}, 1H), 1.77-1.72 \ (m, 2H), 1.48-1.29 \ (m, 4H), 0.91 \ (t, J = 7.1 \text{ Hz}), 0.26 \ (s, 9H).

\(^{13}\text{C} \text{NMR (CDCl}_3, 125 \text{ MHz)} \ \delta \ 142.3, 128.6, 127.7, 126.8, 108.8, 87.2, 39.0, 38.7, 29.7, 22.6, 14.2, 0.4.

IR (film) 3086, 3063, 3029, 2958, 2934, 2873, 2860, 2361, 2339, 2172, 1494, 1453, 1249 cm\(^{-1}\).

LRMS (EI) calcd for C\(_{16}\)H\(_{24}\)Si (M\(^+\)) 244, found 244.
V. Asymmetric Negishi Cross-Coupling Reactions

![Chemical structure](image)

**Trimethyl(3-p-tolyhept-1-ynyl)Silane (Table 2.11, entry 1).** The compound was prepared according to the General Procedure with (±)-(3-bromohept-1-ynyl)trimethylsilane (124 mg, 0.5 mmol) and the arylzinc reagent (~0.5 M in glyme; 2.0 mL, 1.0 mmol). After purification by column chromatography (0 → 5% Et₂O in hexanes), the title compound was isolated as a colorless oil (121.0 mg, 94% yield) with 94% ee.

\[ \alpha \] \text{D}^2 = +7.7 (c = 1.0, CHCl₃). Chiral GC analysis of the product: Chirasil Dex CB column; method: 100 °C → 130 °C @ 10 °C/min, hold 10 min, then → 170 °C @ 9 °C/min, hold 5 min, flow rate 1.0 mL/min; retention times: 18.0 min (major), 17.9 min (minor).

The second run was performed with (+)-L6. The product was isolated as a colorless oil (116.2 mg, 90% yield) with 92% ee.

\[ \alpha \] \text{D}^2 = +7.7 (c = 1.0, CHCl₃). Chiral GC analysis of the product: Chirasil Dex CB column; method: 100 °C → 130 °C @ 10 °C/min, hold 10 min, then → 170 °C @ 9 °C/min, hold 5 min, flow rate 1.0 mL/min; retention times: 18.0 min (major), 17.9 min (minor).

The second run was performed with (+)-L6. The product was isolated as a colorless oil (116.2 mg, 90% yield) with 92% ee.

\[ \alpha \] \text{D}^2 = +7.7 (c = 1.0, CHCl₃). Chiral GC analysis of the product: Chirasil Dex CB column; method: 100 °C → 130 °C @ 10 °C/min, hold 10 min, then → 170 °C @ 9 °C/min, hold 5 min, flow rate 1.0 mL/min; retention times: 18.0 min (major), 17.9 min (minor).

- **H NMR (CDCl₃, 300 MHz)** \( \delta 7.23 \text{ (d, } J = 8.1 \text{ Hz, 2H), 7.12 \text{ (d, } J = 8.2 \text{ Hz, 2H), 3.59 \text{ (t, } J = 7.2 \text{ Hz, 1H), 2.33 \text{ (s, 3H), 1.74-1.66 \text{ (m, 2H), 1.44-1.25 \text{ (m, 4H), 0.88 \text{ (t, } J = 7.0 \text{ Hz, 3H), 0.17 \text{ (s, 9H)).}}}

- **C NMR (CDCl₃, 75 MHz)** \( \delta 139.3, 136.3, 129.3, 127.6, 109.1, 86.9, 38.7, 38.6, 29.7, 22.6, 21.3, 14.2, 0.5.

IR (film) 2958, 2933, 2860, 2360, 2340, 1271, 1513, 1457, 1249 cm⁻¹.

LRMS (EI) calcd for C₁₇H₂₆Si (M⁺) 258, found 258.
Trimethyl(3-(naphthalen-2-yl)hept-1-ynyl)silane (Table 2.11, entry 2). The compound was prepared according to the General Procedure, except that 6% catalyst and 3.0 equivalents of arylzinc reagent were used, with (±)-(3-bromohept-1-ynyl)trimethylsilane (124 mg, 0.5 mmol) and the arylzinc reagent (~0.5 M in glyme; 3.0 mL, 1.5 mmol). After purification by column chromatography (0 → 4% Et₂O in hexanes), the title compound was isolated as a colorless oil (106.7 mg, 72% yield) with 93% ee.

\[ \alpha \] D \text{22} = +2.6 (c = 1.0, CHCl₃). HPLC analysis of the product: Daicel CHIRALPAK OD-H column; solvent system: 100% hexanes; 1.0 mL/min; retention times: 8.3 min (major), 11.2 min (minor).

The second run was performed with (+)-L6. The product was isolated as a colorless oil (100.4 mg, 68% yield) with 92% ee.

\(^1^H\) NMR (CDCl₃, 300 MHz) \( \delta \) 7.83-7.78 (m, 4H), 7.50-7.43 (m, 3H), 3.79 (t, \( J = 7.1 \) Hz, 1H), 1.85-1.77 (m, 2H), 1.46-1.29 (m, 4H), 0.88 (t, \( J = 7.0 \) Hz, 3H), 0.21-0.20 (m, 9H)

\(^1^3^C\) NMR (CDCl₃, 75 MHz) \( \delta \) 139.7, 133.7, 132.6, 128.3, 128.0, 127.9, 126.2, 126.1, 125.7, 108.8, 87.5, 39.1, 34.4, 29.7, 22.7, 14.3, 0.5.

IR (film) 3055, 2958, 2859, 2361, 2340, 2169, 1943, 1507, 1457, 1249 cm\(^{-1}\).

LRMS (EI) calcd for C\textsubscript{20}H\textsubscript{26}Si (M\(^+\)) 294, found 294.

(3-(Benzo[d][1,3]dioxol-5-yl)but-1-ynyl)trimethylsilane (Table 2.11, entry 3). The compound was prepared according to the General Procedure with (±)-(3-bromobut-1-ynyl)trimethylsilane (103 mg, 0.5 mmol) and the arylzinc reagent (~0.5 M in glyme; 2.0 mL, 1.0 mmol). After purification by column chromatography (0 → 5% Et₂O in hexanes), the title compound was isolated as a colorless oil (100.0 mg, 69% yield) with 95% ee.
[\alpha]_D^{22} = +9.5 \text{ (c = 1.0, CHCl}_3)$. HPLC analysis of the product: Daicel CHIRALPAK OJ-H column; solvent system: 100% hexanes; 1.0 mL/min; retention times: 6.5 min (major), 6.9 min (minor).

The second run was performed with (+)-L6. The product was isolated as a colorless oil (103.4 mg, 72% yield) with 91% ee.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 6.89 (d, $J = 1.7$ Hz, 1H), 6.81 (dd, $J = 8.0, 1.7$ Hz, 1H), 6.75 (d, $J = 8.0$ Hz, 1H), 5.94 (s, 2H), 3.70 (q, $J = 14.3$ Hz, 1H), 1.43 (d, $J = 7.1$ Hz, 3H), 0.17 (s, 9H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 147.9, 146.4, 137.3, 120.1, 109.7, 108.4, 107.7, 101.1, 86.4, 32.8, 25.1, 0.4.

IR (film) 2961, 2930, 2897, 2777, 2361, 2339, 2169, 1505, 1487, 1438, 1297, 1249 cm$^{-}$

LRMS (EI) calcd for C$_{14}$H$_{18}$O$_2$Si (M$^+$) 246, found 246.

(3-(Benzo[d][1,3]dioxol-5-yl)-5-methylhex-1-ynyl)trimethylsilane (Table 2.11, entry 4). The compound was prepared according to the General Procedure with (±)-(3-bromo-5-methylhex-1-ynyl)trimethylsilane (124 mg, 0.5 mmol) and the arylzinc reagent (~0.5 M in glyme; 2.0 mL, 1.0 mmol). After purification by column chromatography (0 → 5% Et$_2$O in hexanes), the title compound was isolated as a colorless oil (100.0 mg, 69% yield) with 95% ee.

$[\alpha]_D^{22} = +10.5 \text{ (c = 1.0, CHCl}_3)$. HPLC analysis of the product: Daicel CHIRALPAK OJ-H column; solvent system: 100% hexanes; 1.0 mL/min; retention times: 5.0 min (major), 5.5 min (minor).

The second run was performed with (+)-L6. The product was isolated as a colorless oil (103.4 mg, 72% yield) with 91% ee.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 6.86 (d, $J = 1.6$ Hz, 1H), 6.75 (d, $J = 1.5$ Hz, 1H), 6.74 (d, $J = 0.6$ Hz, 1H), 5.94 (s, 2H), 3.59 (dd, $J = 9.2, 6.6$ Hz, 1H), 1.82-1.59 (m, 2H), 1.49-1.39 (m, 1H), 0.92 (d, $J = 6.5$ Hz, 6H), 0.16 (s, 9H).
13C NMR (CDCl₃, 75 MHz) δ 147.9, 146.4, 136.5, 120.6, 108.9, 108.3, 108.1, 101.1, 87.0, 48.4, 36.8, 26.1, 23.1, 22.2, 0.4.
IR (film) 2957, 2870, 2776, 2361, 2339, 2168, 1504, 1487, 1249 cm⁻¹.
LRMS (EI) calcd for C₁₇H₂₄O₂Si (M⁺) 288, found 288.

(3-(2-Methoxyphenyl)hept-1-ynyl)trimethylsilane (Table 2.11, entry 5). The compound was prepared according to the General Procedure (except the reaction was run at room temperature for 6 h, and the arylzinc reagent was prepared in toluene), with (+)-(3-bromohept-1-ynyl)trimethylsilane (124 mg, 0.5 mmol) and the arylzinc reagent (~0.3 M in toluene; 3.3 mL, 2.0 mmol). After purification by column chromatography (0 → 5% Et₂O in hexanes), the title compound was isolated as a colorless oil (51.0 mg, 37% yield) with 91% ee.

[α]D²² = +15.8 (c = 1.0, CHCl₃). HPLC analysis of the product: Daicel CHIRALPAK OD column; solvent system: 100% hexanes; 0.2 mL/min; retention times: 23.7 min (major), 24.8 min (minor).

The second run was performed with (+)-L6. The product was isolated as a colorless oil (56.0 mg, 41% yield, 92% ee)

1H NMR (CDCl₃, 300 MHz) δ 7.53 (dd, J = 7.5, 1.7 Hz, 1H), 7.21 (td, J = 8.1, 5.7 Hz, 1H), 6.98-6.95 (m, 1H), 6.85-6.83 (m, 1H), 4.12 (dd, J = 8.6, 5.2 Hz, 1H), 3.82 (s, 3H), 1.74-1.67 (m, 1H), 1.63-1.55 (m, 1H), 1.47-1.26 (m, 4H), 0.89 (t, J = 7.2 Hz, 3H), 0.18 (s, 9H).

13C NMR (CDCl₃, 75 MHz) δ 156.3, 130.7, 128.7, 127.8, 120.8, 110.5, 109.5, 86.3, 55.6, 36.7, 32.0, 29.7, 22.5, 14.2, 0.5.
IR (film) 2958, 2860, 2836, 2360, 2340, 2169, 1600, 1588, 1492, 1464, 1438, 1246 cm⁻¹.
LRMS (EI) calcd for C₁₇H₂₆OSi (M⁺) 274, found 274.


**Ethyl 6-(4-(**tert**-butoxymethyl)phenyl)-8-(trimethylsilyl)oct-7-ynoate (Table 2.11, entry 6).** The compound was prepared according to the General Procedure with (±)-ethyl 6-bromo-8-(trimethylsilyl)oct-7-ynoate (153 mg, 0.5 mmol) and the arylzinc reagent (~0.5 M in glyme; 2.0 mL, 1.0 mmol). After purification by column chromatography (0 → 12% Et₂O in hexanes), the title compound was isolated as a colorless oil (152.6 mg, 76% yield) with 94% ee. 

\[ \alpha \]D 22 = +7.0 (c = 1.0, CHCl₃). HPLC analysis of the product: Daicel CHIRALPAK OD column; solvent system: 0.2% IPA in hexanes; 0.1 mL/min; retention times: 57.5 min (major), 62.9 min (minor).

The second run was performed with (+)-L6. The product was isolated as a colorless oil (151.4 mg, 75% yield) with 94% ee.

\(^1\)H NMR (CDCl₃, 300 MHz) δ 7.28 (broad s, 4H), 4.42 (s, 2H), 4.10 (q, \(J = 7.1\) Hz, 2H), 3.61 (t, \(J = 7.3\) Hz, 1H),

\(^13\)C NMR (CDCl₃, 75 MHz) δ 173.9, 140.8, 138.4, 127.9, 127.6, 108.6, 87.3, 73.6, 64.1, 60.4, 38.5, 38.3, 34.5, 27.9, 27.0, 24.9, 14.5, 0.4.

IR (film) 2973, 2864, 2360, 2340, 2171, 1734, 1388, 1363 cm⁻¹.

LRMS (EI) calcd for C_{23}H_{35}O_3Si (M-Me⁺) 387, found 387.

\(\frac{Z}{Z}\)-(3-(3-Methoxyphenyl)dodec-9-en-1-ynyl)trimethylsilane (Table 2.11, entry 7). The compound was prepared according to the General Procedure with (±)-(\(Z\)-(3-bromododec-9-en-1-ynyl)trimethylsilane (158 mg, 0.5 mmol) and the arylzinc reagent (~0.5 M in glyme; 2.0 mL, 1.0 mmol). After purification by column chromatography (0 → 4% Et₂O in hexanes), the title compound was isolated as a colorless oil (135.4 mg, 79% yield) with 94% ee.
[α]D^22 = +15.9 (c = 1.0, CHCl₃). HPLC analysis of the product: Daicel CHIRALPAK OD-H column; solvent system: 100% hexanes; 1.0 mL/min; retention times: 11.4 min (major), 8.7 min (minor).

The second run was performed with (+)-L6. The product was isolated as a colorless oil (133.0 mg, 78% yield) with 94% ee.

1H NMR (CDCl₃, 300 MHz) δ 7.26-7.21 (m, 1H), 6.95-6.90 (m, 2H), 6.80-6.76 (m, 1H), 5.43-5.27 (m, 2H), 3.82 (s, 3H), 3.62 (t, J = 7.2 Hz, 1H), 2.08-1.96 (m, 4H), 1.78-1.68 (m, 2H), 1.48-1.25 (m, 6H), 0.96 (t, J = 7.4 Hz, 3H), 0.19 (s, 9H).

13C NMR (CDCl₃, 75 MHz) δ 159.9, 143.9, 131.9, 129.6, 129.4, 120.1, 113.3, 112.2, 108.7, 87.4, 55.4, 39.0, 38.7, 29.8, 29.0, 27.3, 27.2, 20.7, 16.6, 0.4.

IR (film) 3003, 2933, 2856, 2360, 2340, 2171, 1601, 1586, 1488, 1456, 1436 cm⁻¹.

LRMS (EI) calcd for C₂₂H₃₄OSi (M⁺) 342, found 342.

Eq 2.20:

(3-(4-Fluorophenyl)hept-1-ynyl)dimethyl(phenyl)silane (eq 2.20). The compound was prepared according to the General Procedure with (±)-(3-bromohept-1-ynyl)dimethyl(phenyl)silane (155 mg, 0.5 mmol) and the arylzinc reagent (~0.5 M in glyme; 2.0 mL, 1.0 mmol). After purification by column chromatography (0 → 5% Et₂O in hexanes), the title compound was isolated as a colorless oil (139.7 mg, 86% yield) with 90% ee.

[α]D^22 = -7.3 (c = 1.0, CHCl₃). Chiral GC analysis of the desilylated product: Chirasil Dex CB column; method: 100 °C → 130 °C @ 10 °C/min, hold 10 min, then → 170 °C @ 9 °C/min, hold 5 min, flow rate 1.0 mL/min; retention times: 8.2 min (major), 8.4 min (minor).

The second run was performed with (+)-L6. The product was isolated as a colorless oil (144.6 mg, 89% yield) with 85% ee.

1H NMR (CDCl₃, 300 MHz) δ 7.67-7.63 (m, 2H), 7.40-7.29 (m, 5H), 7.00 (t, J = 8.8 Hz, 2H), 3.67 (t, J = 7.2 Hz, 1H), 1.78-1.68 (m, 2H), 1.45-1.26 (m, 4H), 0.89 (t, J = 7.1 Hz, 3H), 0.43-0.41 (m, 6H).
\[^{13}\text{C} \text{ NMR (CDCl}_3, 75 \text{ MHz)} \delta 137.8, 133.9, 129.6, 129.2, 129.1, 128.1, 115.6, 115.3, 110.5, 85.5, 38.7, 38.4, 29.7, 22.6, 14.3, -0.3.\]

\[^{19}\text{F} \text{ NMR (CDCl}_3, 282 \text{ MHz)} \delta -117.0.\]

IR (film) 3069, 2958, 2932, 2860, 2360, 2340, 2172, 1604, 1508, 1428, 1249 cm\(^{-1}\).

LRMS (EI) calcd for C\(_{21}\)H\(_{25}\)FSi (M\(^+\)) 324, found 324.

Eq 2.21:

\((3-(4-\text{tert-Butylphenyl})\text{pent-1-ynyl})\text{triisopropylsilane (eq 2.21).}\) The compound was prepared according to the General Procedure with (±)-(3-Bromopent-1-ynyl)triisopropylsilane (152 mg, 0.5 mmol) and the arylzinc reagent (−0.5 M in glyme; 2.0 mL, 1.0 mmol). After purification by column chromatography (0 → 4% Et\(_2\)O in hexanes), the title compound was isolated as a colorless oil (136.5 mg, 77% yield) with 92% ee.

\([\alpha]_D^{22} = +14.4 \ (c = 1.0, \ \text{CHCl}_3).\) Chiral GC analysis of the desilylated product: Chirasil Dex CB column; method: 100 °C → 130 °C @ 10 °C/min, hold 10 min, then → 170 °C @ 9 °C/min, hold 5 min, flow rate 1.0 mL/min; retention times: 15.2 min (major), 15.8 min (minor).

The second run was performed with (+)-L6. The product was isolated as a colorless oil (150.3 mg, 84% yield) with 93% ee.

\(^1\text{H} \text{ NMR (CDCl}_3, 300 \text{ MHz)} \delta 7.35-7.28 \ (m, 4\text{H}), 3.63 \ (dd, J = 8.4, 5.3 \text{ Hz}, 1\text{H}), 1.88-1.62 \ (m, 2\text{H}), 1.32 \ (s, 9\text{H}), 1.10-1.08 \ (m, 21\text{H}), 1.02 \ (t, J = 7.3 \text{ Hz}, 3\text{H}).\]

\(^{13}\text{C} \text{ NMR (CDCl}_3, 75 \text{ MHz)} \delta 149.4, 139.0, 127.4, 125.4, 110.2, 83.4, 40.1, 34.7, 32.4, 31.7, 19.0, 12.0, 11.6.\)

IR (film) 2961, 2865, 2361, 2340, 2169, 1507, 1463 cm\(^{-1}\).

LRMS (EI) calcd for C\(_{24}\)H\(_{40}\)Si (M\(^+\)) 356, found 356.
Trimethyl(3-phenylhept-1-ynyl)silane (eq 2.22). The compound was prepared according to the General Procedure with (+)-(3-chlorohept-1-ynyl)trimethylsilane (101 mg, 0.50 mmol) (Note: the reaction was run for 48 h). After purification by flash chromatography (0 → 5% Et₂O in hexanes), the title compound was isolated as a colorless oil (76 mg, 62% yield) with 91% ee.

The second run was performed with (+)-L6. The product was isolated as a colorless oil (73 mg, 60% yield) with 91% ee. For characterization data, see the description of eq 2.19.

6-(Hex-4-yn-3-yl)-2,3-dihydrobenzo[b][1,4]dioxine (Table 2.12, entry 1). The compound was prepared according to the General Procedure with (±)-(4-bromohex-2-yne (80.5 mg, 0.5 mmol) and the arylzinc reagent (–0.5 M in glyme; 2.0 mL, 1.0 mmol). After purification by column chromatography (0 → 4% Et₂O in hexanes), the title compound was isolated as a colorless oil (87.0 mg, 81% yield) with 90% ee.

\[ \alpha \] d{\text{22}} = +4.8 (c = 1.0, CHCl₃). Chiral GC analysis of the product: Chirasil Dex CB column; method: 100 °C → 190 °C @ 5 °C/min, hold 30 min, flow rate 1.0 mL/min; retention times: 12.0 min (major), 11.9 min (minor).

The second run was performed with (+)-L6. The product was isolated as a colorless oil (87.6 mg, 81% yield) with 86% ee.

1H NMR (CDCl₃, 300 MHz) δ 6.90-6.86 (m, 1H), 6.97 (d, \( J = 1.2 \) Hz, 2H), 4.24 (s, 4H), 3.43-3.35 (m, 1H), 1.85 (d, \( J = 2.5 \) Hz, 3H), 1.73-1.63 (m, 2H), 0.95 (t, \( J = 7.3 \) Hz, 3H).

13C NMR (CDCl₃, 75 MHz) δ 143.4, 142.3, 136.4, 120.6, 117.2, 116.4, 81.1, 78.5, 64.6, 64.5, 38.9, 31.9, 12.0, 3.9.

IR (film) 2967, 2931, 2874, 2361, 2339, 1952, 1734, 1683, 1590, 1506 cm⁻¹.

LRMS (EI) calcd for C₁₄H₁₆O₂ (M⁺) 216, found 216.
5-(Hex-4-yn-3-yl)-1-methyl-1H-indole (Table 2.12, entry 2). The compound was prepared according to the General Procedure, except that 6% catalyst and 3.0 equivalents of arylzinc reagent were used, with (±)-(4-bromohex-2-ynyl) (80.5 mg, 0.5 mmol) and the arylzinc reagent (~0.5 M in glyme; 3.0 mL, 1.5 mmol). After purification by column chromatography (0 → 25% CH₂Cl₂ in hexanes), the title compound was isolated as a colorless oil (84.0 mg, 80% yield) with 86% ee.

[α]_D^{22} = +3.6 (c = 0.5, CHCl₃). HPLC analysis of the product: Daicel CHIRALPAK OD-H column; solvent system: 2.0% IPA in hexanes; 1.0 mL/min; retention times: 7.9 min (major), 8.5 min (minor).

The second run was performed with (+)-L6. The product was isolated as a colorless oil (80.5 mg, 76% yield) with 82% ee.

^1H NMR (CDCl₃, 300 MHz) δ 7.66-7.65 (m, 1H), 7.33-7.25 (m, 2H), 7.07 (d, J = 3.0 Hz, 1H), 6.50 (dd, J = 3.1, 0.7 Hz, 1H), 3.79 (s, 3H), 3.70-3.63 (m, 1H), 1.94 (d, J = 2.4 Hz, 3H), 1.86 (quintet, J = 7.2 Hz, 2H), 1.05 (t, J = 7.3 Hz, 3H).

^13C NMR (CDCl₃, 75 MHz) δ 135.9, 133.9, 129.3, 128.7, 121.6, 119.6, 109.3, 101.0, 82.2, 78.1, 33.1, 32.4, 12.3, 4.0.

IR (film) 2962, 2927, 2871, 2819, 2360, 2340, 1513, 1490 cm⁻¹.

LRMS (EI) calcd for C₁₅H₁₇N (M⁺) 211, found 211.

1-(Hex-3-yn-2-yl)-4-methoxybenzene (Table 2.12, entry 3). The compound was prepared according to the General Procedure with (±)-2-bromohex-3-ynyl (80.5 mg, 0.5 mmol) and the arylzinc reagent (~0.5 M in glyme; 2.0 mL, 1.0 mmol). After purification by column
chromatography (0 → 4% Et₂O in hexanes), the title compound was isolated as a colorless oil (70.5 mg, 75% yield) with 93% ee.

\[ \alpha_d^{22} = -2.7 \] (c = 0.5, CHCl₃). Chiral GC analysis of the product: Chirasil Dex CB column; method: 100 °C → 130 °C @ 10 °C/min, hold 10 min, then → 170 °C @ 9 °C/min, hold 5 min, flow rate 1.0 mL/min; retention times: 15.8 min (major), 15.6 min (minor).

The second run was performed with (+)-L6. The product was isolated as a colorless oil (72.6 mg, 77% yield) with 89% ee.

\[ \alpha_d^{22} = +6.3 \] (c = 1.0, CHCl₃). HPLC analysis of the product: Daicel CHIRALPAK OJ-H column; solvent system: 100% hexanes; 1.0 mL/min; retention times: 8.8 min (major), 12.8 min (minor).

The second run was performed with (+)-L6. The product was isolated as a colorless oil (77.6 mg, 61% yield) with 89% ee.

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1-(1-Cyclohexylpent-1-yn-3-yl)-4-methoxybenzene (Table 2.12, entry 4). The compound was prepared according to the General Procedure with (±)-(3-Bromopent-1-ynyl)cyclohexane (115 mg, 0.5 mmol) and the arylzinc reagent (~0.5 M in glyme; 2.0 mL, 1.0 mmol). After purification by column chromatography (0 → 5% Et₂O in hexanes), the title compound was isolated as a colorless oil (81.9 mg, 64% yield) with 89% ee.

\[ \alpha_d^{22} = +6.3 \] (c = 1.0, CHCl₃). HPLC analysis of the product: Daicel CHIRALPAK OJ-H column; solvent system: 100% hexanes; 1.0 mL/min; retention times: 8.8 min (major), 12.8 min (minor).

The second run was performed with (+)-L6. The product was isolated as a colorless oil (77.6 mg, 61% yield) with 89% ee.
\(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 2.27 (d, \(J = 8.8\) Hz, 2H), 6.84 (d, \(J = 8.8\) Hz, 2H), 3.79 (s, 3H), 3.51 (ddd, \(J = 13.8, 5.9, 2.0\) Hz, 1H), 2.47-2.37 (m, 1H), 1.86-1.62 (m, 6H), 1.52-1.38 (m, 3H), 1.38-1.24 (m, 3H), 0.96 (t, \(J = 7.2\) Hz, 3H).

\(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 158.3, 135.3, 128.6, 113.8, 87.7, 81.9, 55.4, 38.7, 33.3, 32.4, 29.4, 26.2, 25.1, 11.9.

IR (film) 2927, 2853, 2361, 2339, 1884, 1611, 1508, 1448 cm\(^{-1}\).

LRMS (EI) calcd for C\(_{18}\)H\(_{24}\)O (M\(^+\)) 256, found 256.

![Structure Image]

1-(1-Chloro-7,7-dimethyloct-5-yn-4-yl)-4-methylbenzene (Table 2.12, entry 5). The compound was prepared according to the General Procedure with (+)-5-bromo-8-chloro-2,2-dimethyloct-3-yne (126 mg, 0.5 mmol) and the arylzinc reagent (~0.5 M in glyme; 2.0 mL, 1.0 mmol). After purification by column chromatography (0 → 5% Et\(_2\)O in hexanes), the title compound was isolated as a colorless oil (109.0 mg, 83% yield) with 92% ee.

\([\alpha]_D^{22} = -2.6\) (c = 1.0, CHCl\(_3\)). Chiral GC analysis of the product: Chirasil Dex CB column; method: 100 °C → 170 °C @ 10 °C/min, hold 20 min, then → 190 °C @ 10 °C/min, hold 5 min, flow rate 1.0 mL/min; retention times: 14.0 min (major), 13.8 min (minor).

The second run was performed with (+)-L6. The product was isolated as a colorless oil (103.8 mg, 79% yield) with 91% ee.

\(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.25 (d, \(J = 8.1\) Hz, 2H), 7.12 (d, \(J = 7.8\) Hz, 2H), 3.63-3.55 (m, 2H), 3.54 (t, \(J = 6.3\) Hz, 1H), 2.33 (s, 3H), 1.95-1.67 (m, 4H), 1.24 (s, 9H).

\(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 139.7, 136.3, 129.3, 127.4, 92.7, 79.6, 45.2, 36.8, 36.4, 31.6, 30.5, 27.7, 21.3.

IR (film) 2967, 2361, 2340, 1684, 1607, 1456 cm\(^{-1}\).

LRMS (EI) calcd for C\(_{17}\)H\(_{23}\)Cl (M\(^+\)) 262, found 262.
Pent-1-yne-1,3-diyl dibenzene (Table 2.12, entry 6). The compound was prepared according to the General Procedure with (±)-(3-bromopent-1-ynyl)benzene (112 mg, 0.5 mmol) and the arylzinc reagent (~0.5 M in glyme; 2.0 mL, 1.0 mmol). After purification by column chromatography (0 → 4% Et₂O in hexanes), the title compound was isolated as a colorless oil (92.1 mg, 84% yield) with 89% ee.

\[ \alpha \]D

= -4.5 (c = 1.65, CHCl₃). HPLC analysis of the product: Daicel CHIRALPAK OJ-H column; solvent system: 100% hexanes; 1.0 mL/min; retention times: 21.7 min (major), 20.2 min (minor).

The second run was performed with (+)-L6. The product was isolated as a colorless oil (89.0 mg, 81% yield) with 88% ee.

\( ^1 \)H NMR (CDCl₃, 300 MHz) \( \delta \) 7.47-7.25 (m, 10H), 3.79 (t, \( J = 7.5 \) Hz, 1H), 1.92-1.81 (m, 2H), 1.01 (t, \( J = 7.3 \) Hz, 3H).

\( ^{13} \)C NMR (CDCl₃, 75 MHz) \( \delta \) 142.2, 131.9, 128.7, 128.0, 127.8, 126.9, 124.1, 91.7, 83.6, 40.2, 32.0, 12.2.

IR (film) 2968, 2361, 2339, 2200, 1684, 1598, 1559, 1490 cm\(^{-1}\).

LRMS (EI) calcd for C\(_{17}\)H\(_{16}\) (M\(^+\)) 220, found 220.

VI. Application: Formal synthesis of a dihydrofolate reductase inhibition ligand

\(+\)-3-Bromobut-1-ynyl)trimethylsilane [CAS # 2004440-80-8] A 500 mL flask was charged with imidazole (5.8 g, 85.0 mmol), evacuated, and back-filled with argon. CH\(_2\)Cl\(_2\) (350 mL) was added via syringe, followed by the addition of (±)-4-(trimethylsilyl)but-3-yn-2-ol (11.8
ml, 70.4 mmol). This solution was allowed to stir for 15 minutes, then cooled to 0 °C (due to scale). Next, dibromotriphenylphosphorane (36.0 g, 85.0 mmol) was added as a solid, the reaction was then removed from the ice bath and allowed to stir at room temperature. The reaction was run under argon and monitored by TLC. Upon completion (4 hours), the solvent was removed under reduced pressure, and to the resultant solid was added 300 mL 1:1 Et₂O:hexanes. This was allowed to stir for 30 minutes, then the solid was filtered off and the solution was concentrated to an oil. The product was then distilled at 40 °C (3.5 torr), 13.1 g (92%) was collected as a colorless oil.

\[^1\text{H NMR (CDCl}_3, 300 \text{ MHz)} \delta 4.59 (q, J = 7.0 \text{ Hz}, 1\text{H}), 1.88 (d, J = 6.1 \text{ Hz}, 3\text{H}), 0.16 (s, 9\text{H})\].

5-(But-3-yn-2-yl)-1,2,3-trimethoxybenzene [CAS # 931103-15-0] (Scheme 2.27). In a nitrogen glovebox, a 100 mL flask, equipped with a stirbar, was charged with NiCl₂·glyme (33 mg, 0.150 mmol), (-)-L6 (77 mg, 0.195 mmol), then glyme (8.3 mL). This solution was stirred for 10 minutes. Then the arylzinc reagent was added (0.5 M in glyme, 20.0 mL, 10.0 mmol) and the flask was capped with a septum, and removed from the glovebox. This solution was stirred for 10 minutes at room temperature then (±)-(3-bromobut-1-ynyl)trimethylsilane (1.03 g, 5.0 mmol) was added via syringe. The reaction was stirred for 6 h at room temperature. Then, the excess arylzinc reagent was quenched with ethanol (2.0 mL). The mixture was passed through a short plug of silica (eluting with 1:1 hexanes: Et₂O) to remove inorganic salts and most of the glyme. The filtrate was concentrated, and to the resultant oil was added methanol (25.0 mL) and K₂CO₃ (2.0 g, 15.0 mmol), this heterogenous mixture was stirred at room temperature for one hour. The solution was then diluted with EtOAc (~25 mL) and was washed with 1M HCl. The aqueous layer was then extracted twice more with EtOAc and the combined organic fractions were washed with brine and dried over MgSO₄. The solid was filtered off and the solution was concentrated to an oil, this oil was purified via column chromatography (20% Et₂O in Hexanes). Residual 1,2,3-trimethoxybenzene (protonated arylzinc reagent) was then removed under
reduced pressure and gentle heating (200 mtorr, 50 °C). The product was obtained as a light yellow oil: 0.725 g (66%, 92% ee).

\[ \alpha_d^{22} = +12.6 \ (c = 1.0, CHCl_3) \]. HPLC analysis of the product: Daicel CHIRALPAK OJ-H column; solvent system: 1.0% IPA in hexanes; 1.0 mL/min; retention times: 25.0 min (major), 21.2 min (minor).

\(^1H\) NMR (CDCl\(_3\), 300 MHz) \( \delta \) 6.61 (s, 2H), 3.87 (s, 6H), 3.83 (s, 3H), 3.71 (qd, \( J = 7.1, 2.5 \) Hz, 1H), 2.29 (d, \( J = 2.6 \) Hz, 1H), 1.51 (d, \( J = 7.2 \) Hz, 3H).

The second run was performed with (+)-L6. The product was isolated as a colorless oil: 0.757 mg (69% yield, 93% ee).

\[ \alpha_d^{22} = -10.6 \ (c = 1.0, CHCl_3) \].

VII. Determination of Absolute Stereochemistry

\( (S) \)-Hexan-2-ylbenzene [CAS # 99439-78-8].

\(^1H\) NMR (CDCl\(_3\), 500 MHz) \( \delta \) 7.31-7.17 (m, 5H), 2.68 (sextet, \( J = 6.9 \) Hz, 1H), 1.64-1.50 (m, 2H), 1.33-1.11 (m, 7H), 0.86 (t, \( J = 7.0 \) Hz, 3H).


\( (S) \)-Trimethyl(3-phenylhept-1-ynyl)silane.

See Section IV (eq 2.19) for characterization.
For the synthesis of the starting material, refer to entry 3, table 2 in Dai, X; Strotman, N.A.; Fu, G.C. J. Am. Chem. Soc. 2008, 130, 3302-3303.

Stereochemistry was assigned by comparison of the chiral GC elusion order of (S)-trimethyl(3-phenylhept-1-ynyl)silane with that observed in eq 2.19.
F. \(^1\)H NMR Spectra for Selected Compounds
STANDARD 1H OBSERVE

expl stdih

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ACQUISITION  dmcr  200
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np  48552
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Br
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Gain not used

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ppm

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ACQUISITION

sfrq 300.108
tn H1

ACQUISITION

at 4.003

ACQUISITION

np 40052

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sw 6002.4

ACQUISITION

fb not used

ACQUISITION

bs 16

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tpwr 54

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pw 8.0

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d solvent CDC13
d ACQUISITION
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dfrq 300.108
temp 20.0
tn H1
at 4.003
np 48092
nt 16
sw 6002.4
fb not used
bs 16
wp 2399.7
wexp
pw 8.0
wht
d 0.050
wnt
tof 867.7
tf 16
tc 16
tlock n
gain not used

FLAGS

sp 1.2
wp 2399.7
vs 292
sc 0
wc 250
hzmm 9.69
ls 596.80
rf1 861.9
rfp 0
th 20
ins 1.000

DISPLAY

TMS

ppm

7 6 5 4 3 2 1

1.00 3.20 6.65 9.25

nm ph
STANDARD 1H OBSERVE

expl std1h

SAMPLE

date Feb 17 2008
dfrq 300.107
solvent CDCl3
dn H1
file/data/export/
dpwr 30
home/gfu/Tsm/mrhat/
dof 0
/Tsm-10-042-5-H.1-
dm nnn
dm H1
def 200

ACQUISITION

sfrq 300.108
tn H1
temp 20.0
at 4.003
np 48852
sw 6002.4
fb not used
bs 16
pw 8.0
di 0.059
sw 6002.4
ct 16
tof 867.7
ct 16
alock n

FLAGS

ii n
in n
sc
whm
rf 1
rfp
th
ins
nm

DISPLAY

sp 1.2
wp 2399.7
vs 151
sc 0
wc 250
hzm 9.60
fs 560.00
rt 661.0

Me-Br

TMS

ppm

7 6 5 4 3 2 1

1.00 3.35 9.20

1.000
STANDARD 1H OBSERVE

**SAMPLE**
- Date: Feb 17 2008
- Solvent: CDC13
- File: /data/export/-home/gfu/Tsm/arhat-/Tsm-10-042-a-H.fl-

**ACQUISITION**
- Sfreq: 300.108
- Tn: 4.003
- Np: 48052
- Sw: 6002.4
- Tb: not used
- Bs: 16
- Tpwr: 54
- Gv: 8.0
- Dl: 0.050
- Tof: 867.7
- Nt: 16
- Ct: 16
- Alock: not used
- Flags: n

**DISPLAY**
- Sp: 1.2
- Wp: 2393.7
- Vs: 151
- Sc: 0
- Wc: 250
- Hzm: 9.60
- Is: 560.00
- RfI: 661.0
- Rfp: 0
- Th: 20
- Ins: 1.000

**PROCESSED DATA**
- Dfrq: 300.107
- Dn: M1
- DoF: 0
- Dm: c
- Dm: nnn
- DaF: 200
- Temp: 20.0

**GRAPHICAL DATA**
- ppm Scale: 2.50 - 3.38
- Integration: 1.00
- Integration: 2.32
- Integration: 3.66
TIPS

Eq 2.17
TIPS

Eq 2.18
Table 2.11, entry 1
Table 2.11, entry 2
Table 2.11, entry 3
Table 2.11, entry 4
STANDARD PROTON PARAMETERS

exp3 s2pul

SAMPLE DEC. & VT
date Mar 20 2008 dfrq 125.672
solvent CDC13 dn 013
dfrq /data/gfu/Tsm-
dpwr 30
/Tsm-10-066-2H.fid dof 0
ACQUISITION dm mnn
df 499.746 dmm w
at 3.001 dseq
np 63950 dres 1.0
sw 18584.2 homon n
fb not used DEC2
bs 0 dfrq2 0
tpwr 59 dm2
pw 8.6 dpwr2 1
dl 2.000 dof2 0
tof 1519.5 dm2 n
t 16 dmm2 c
dt 16 dfr2 290
dlock n dseq2
gain not used dres2 1.0
FLAGS homo2 n
ll n DEC3
dp y dm3 n
dh y 0
DISPLAY
sp 0.0 dm3 n
wp 4801.5 dmm3 c
vs 42 dfr3 200
sc 0 dseq3
wc 250 dres3 1.0
hzmm 16.01 homom3 n
ls 33.57 PROCESSING
rf1 1233.8 wfile
rfp 0 proc ft
th 7 fn 262144
ins 1.000 math f
ai cdc ph werr
wexp
wbs
wnt
wft

Table 2.11, entry 5

TIPS
n-Bu
MeO

MeO

ppm
STANDARD 1H OBSERVE

expl std1h

SAMPLE

date Feb 19 2008
dfrq 300.107
solvent CDC13
dm
file/home/gfu/Tsm/mrhat-Tsm-10-046-2-H.f1
at

ACQUISITION

dfrq 300.108
tn H1
acq
nt

PROCESING

wtfile proc ft

FLAGS

DISPLAY

TMS

Table 2.11, entry 6
Table 2.11, entry 7
STANDARD 1H OBSERVE

expl std1h

SAMPLE date Feb 3 2008 dfreq 300.107
solvent CDC3 solvent 30
file /data/export/ dprw 30
home/gfu/Tsm/erbat- dof 0
/Tsm-10-015-H.fid dm nnn
ACQUISITION dmm c
sfrq 300.108 dam 200
H1 temp 20.0
at 4.003 PROCESSING
np 48052 wfile ft
sw 6002.4 proc ft
fb not used fn 131072
bs 8
wexp 8.0
sw 6002.4
wbs tof 867.7
wnt
ct 16
ct 16
alock n
flag not used
fl
dp n
dp y
DISPLAY sp -2.1
wp 2400.1
vs 151
sc 0
wc 250
hrem 9.01
ls 580.00
rf1 661.0
rfp
th 20
th
nm ph 1.999

Ph(Me)2Si

n-Bu

Eq 2.20

3.10 1.93

2.39 2.41

1.00

2.36 5.48 3.86

7.50
STANDARD 1H OBSERVE

SAMPLE

date Feb 3 2008
solvent CDC13
file /data/export/-
/home/gfu/Tsm/chem-
/Tsm-10-012-M.fid
ACQUISITION
dam c
sfrq 300.108
tn H1 temp 20.0
at 4.003
np 49052
sw 6002.4
fb not used
bs a
tpw 54
pw 8.0
sw 8.550
tof 867.7
ct 16
nt 16
flags

DISPLAY

sp 2.1
wp 2402.1
vs 151
sc 0
wc 250
hmm 9.61
is 580.00
rfl 661.0
rtf 0
th 23
ins ph 1.000

ACQUISITION

dam c
sfrq 300.108
tn H1 temp 20.0
at 4.003
np 49052
sw 6002.4
fb not used
bs a
tpw 54
pw 8.0
sw 8.550
tof 867.7
ct 16
nt 16
flags

DISPLAY

sp 2.1
wp 2402.1
vs 151
sc 0
wc 250
hmm 9.61
is 580.00
rfl 661.0
rtf 0
th 23
ins ph 1.000

Eq 2.21

TIPS

\[
\text{Eq 2.21}
\]

n-Bu

1.00

1.97

8.96

4.49

3.77
STANDARD 1H OBSERVE

Eq 2.22

n-Bu

TIPS

Eq 2.22
Table 2.12, entry 1
Table 2.12, entry 2
STANDARD 1H OBSERVE

SAMPLE DEC. & VT

- expl stdlh
- date Feb 3 2008 dfrq 300.107
dsolvent CDCl3
dfile /data/export/- dpwr 30
dhome/gfu/Tsm/mrhat- dof 0
d/home/gfu/Tsm/Mrhat- dof
dm nnn
-dm nnn
dfrq 300.107
def 200
dir
H1 temp 20.0
at 4.0082 PROCESSING
np 48052 wfile
sw 6002.4 proc ft
dm not used
bs 0

twr 54 werr
pw 6.0 wesp
dl 0.050 wbs
dl 607.7 wnt
t 0
ct 16
alock not used

- FLAGS
- sp -2.1
- wp 2402.1
- vs 151
- sc 0
- wc 250
- hzmm 9.61
- is 580.00
- rfl 661.0
- rfp 0
- th 20
- ins 1.000

- Table 2.12, entry 3

Table 2.12, entry 3
Table 2.12, entry 4
Table 2.12, entry 5
Table 2.12, entry 6
CONCLUSION
Conclusion

The primary objective of the work presented in this thesis was to discover and develop new processes for the construction of carbon-carbon bonds. Specifically, we were most interested in catalytic methods. The ability to construct a bond between two molecules, which in the absence of a catalyst, would be unreactive toward one another is truly a powerful means by which to generate, and control, the complexity of many organic compounds. This work centered on the application of two families of catalysts: organocatalysts and transition metal catalysts. The first family used, organocatalysts, falls into a smaller classification which is nucleophilic catalysts; meaning, the reactivity that these catalysts enable is accessed through the facility of a nucleophile to generate reactive intermediates. The second type of catalysis developed was transition metal catalysis; specifically, we made use of nickel-based catalysts to generate bonds between organic electrophiles and organometallic nucleophiles.

Nucleophilic Catalysis

This thesis described the development of two organocatalytic processes. The first methodology presented was a β-alkylation reaction of Michael acceptors, catalyzed by a nucleophilic N-heterocyclic carbene (NHC). The role of the NHC was to facilitate an umpolung process in which the normally electrophilic β position of a Michael acceptor becomes nucleophilic and can displace an alkyl electrophile to generate a carbon-carbon bond. This methodology, in a similar vein to the groundbreaking work on homoenolates by Bode and Glorius, opens the door for continued exploration of the reactivity this β-nucleophilic intermediate possesses.

The second organocatalytic process described also represents an umpolung process, although in this case the catalyst was a nucleophilic phosphine. This method for the intermolecular γ-alkylation of isomerizable allenoates represents a solution to a challenge presented over 17 years ago when Trost first reported a phosphine-catalyzed isomerization of alkynoates to dienoates. Not only have a set of reaction conditions been developed for the construction of carbon-carbon bonds in this fashion, it has been done in a highly asymmetric
fashion. Thus, a variety of racemic allenoates may be alkylated with nitromethane in enantiomeric excesses greater than 90%, in good to excellent yields.

**Transition Metal Catalysis**

In the sections on nickel-catalyzed cross-coupling reactions we described a number of “firsts” in the field. We began with the development of an asymmetric alkylation of secondary propargylic halides, and although the results never matched our expectations a number of highly interesting observations were made regarding the regioselectivity of these nickel-catalyzed processes. We have described the ability to control the production of proparglic or allenic products through selection of the appropriate ligand, an option not amenable to palladium catalysis for this family of electrophiles.

As can be seen, our building frustration during the development of the asymmetric alkylation reaction encouraged us to explore a greater diversity of cross-coupling reactions of propargylic halides and resulted in a number of satisfying discoveries. The first of these resulted in the description of the first alkyl-alkyl secondary-secondary cross-coupling reaction. Specifically, secondary propargylic electrophiles were coupled with secondary organozinc reagents, through the application of a nickel-based catalyst system, allowing for the construction of two contiguous tertiary carbon centers. Furthermore, this new reaction allowed us to complete a concise synthesis of a biologically active diterpene in significantly fewer steps than were required in previous studies.

The synthetic value of alkyl-alkyl cross-coupling reactions will undoubtedly grow as two things happen; the first is the ability to couple evermore sterically demanding reaction partners. Secondly, once more sterically demanding reaction partners can be coupled, the ability to control the absolute stereochemistry of the newly formed stereogenic centers is of immense importance. The final section of this thesis describes our development of the first asymmetric Negishi arylation of a secondary alkyl electrophile. It was found that a nickel-Pybox complex was capable of coupling secondary propargylic halides with mixed zinc reagents, generated through the transmetalation of arylboronic acids, with excellent levels of enantioselectivity. Of further interest was that this process was amenable to a wide range of differentially substituted propargylic halides, including: silyl-, alkyl- and aryl-substituted propargylic halides. This
arylation reaction allows facile access to a new family of antibiotics developed by Wright and Anderson, and has found applications in their ongoing studies.

**Final Comment**

The purpose of developing new reaction methodology is not only to gain understanding of, and control over, the reactivity of the elements, but also to decrease the difficulty of constructing compounds of human interest. It is our sincere hope that the work contained in this thesis has met this ideal.
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Experience
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Medicinal Chemistry, Director: Dr. Joseph Guiles  
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University of Colorado  
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Array BioPharma (summer)  
Lead Generation, Group Leader: Dr. Todd Romoff  
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Publications

* Editor's choice: "Hot Paper"