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UMI
SELECTIVE PALLADIUM- AND RHODIUM-CATALYZED PROCESSES:
I. ENANTIOSELECTIVE SYNTHESIS OF TETRAHYDROQUINOLINES,
II. THE ASYMMETRIC HYDROFORMYLATION REACTION,
III. S ILYLSTANNYLIATION-CYCLIZATION OF DIynes AND ALLENEYNES.

D ISSERTATION

Presented in Partial Fulfillment of the Requirements for the Degree Doctor of
Philosophy in the Graduate School of The Ohio State University

By
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* * * * *

The Ohio State University
2002

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ABSTRACT

Chapter 1. Sharpless asymmetric epoxidation (>90% e.e.) of a o-nitrocinamyl alcohol led to an intermediate that was transformed into a 3-hydroxy-substituted tetrahydroquinoline. High-yielding Heck coupling of an o-nitroaryl iodide and α-acetamidoacrylate followed by a highly enantioselective rhodium-catalyzed asymmetric hydrogenation (>98% e.e.) gave a rapid and general entry into both R and S amino acids, which were further reacted to produce a 3-amino-substituted tetrahydroquinolines. Both the 3-hydroxy and 3-amino tetrahydroquinolines could serve as intermediates for the synthesis of biologically relevant cyclopropapyrroloindoles.

Chapter 2. The ability of DIOP derivatives to function as ligands in the rhodium-catalyzed asymmetric hydroformylation reaction was investigated. Under mild reaction conditions (3-10 bars of H$_2$/CO gas pressure, 30-60°C), the hydroformylation of styrene, 2-vinylnaphthalene, vinyl acetate and N-vinylphthalimide using [1,4-disubstituted DIOP] ligands derived from D-mannitol led to improved regioselectivities (e.g. linear to branched aldehyde ratio of 15 : 85 for the hydroformylation of styrene
using (RSSR)-1,4-dimethyl-DIOP), compared to DIOP (e.g. linear to branched aldehyde ratio of 38 : 62 for the hydroformylation of styrene under the same reaction conditions). Steric (varying substituents at C1 and C4) or electronic (electron-withdrawing or donating groups on the phosphorous aryl rings) tuning of the modified DIOP ligands had little influence on the regioselection, possibly due to the lack of flexibility imposed by the isopropylidene ring which contains the C2-C3 bond.

Chapter 3. The first example of a (Z,Z)-bis-alkyldienecyclohexane was synthesized by palladium-catalyzed silylstannylation-cyclization of a cis-4,5-O-isopropylidene-1,7-octadiyne-4,5-diol. The steric bulk of the silyl and stannyl substituents created an axial chirality in the structure, and the molecule exists as two diastereoisomers that do not display any fluxional behavior at temperatures below 60°C. This provided the first definitive example of a (Z,Z)-1,4-silylstannyldiene in which the atropisomerism has been frozen at or above room temperature. Silylstannylation of allenynes derived from succinimide gave a rapid entry into highly functionalized indolizidines. While attempts synthesize bicyclic β-lactams by this route have not yet succeeded, preparation of several potentially useful allylstannane intermediates from β-lactam substrates highlighted the remarkable functional group compatibility of the silylstannylation reaction.
To my parents,

To my husband.

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ACKNOWLEDGMENTS

I would like to express my gratitude to Professor RajanBabu for his guidance during the course of my doctoral studies. His dedication, enthusiasm and work ethic have contributed to my development both as a chemist and a professional. I am deeply thankful to my adviser for the opportunity he gave me to be part of his research group of talented chemists.

Special thanks go to Philippe Gastaud, Dr. Yuan-Yong Yan, Dr. Sandra Warren and Dr. Seughoon Shin for their expertise and cooperation through some of my research projects.

Finally, I would like to acknowledge my parents Guy and Jacqueline Dagommer and my husband Dr. Fabrice Gallou for their love, unfailing understanding and continuous support.
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LIST OF ABBREVIATIONS

Å                  Angström
Ac                 acetyl
acac               acetylacetonate
AD                 asymmetric dihydroxylation
ADDP               1,1’-(azodicarbonyl)dipiperidine
AIBN               2,2’-azoisobutyronitrile
[α]                specific rotation
Ar                 aryl
atm                atmosphere
ax                 axial
b                  branched; broad (NMR)
BINAP              2,2’-bis-(diphenylphosphino)-1,1’-binaphthyl
BINAPHOS           2-(diphenylphosphino)-2’-[2,2’-bis-phosphito]-1,1’-binaphthyl]-1,1’-binaphthyl
BISBI              2,2’-bis-(diphenylphosphinomethyl)-1,1’-biphenyl
Bn                 benzyl
Boc                t-butoxycarbonyl
b.p.               boiling point
Bu                 butyl
Bz                 benzoyl
°C                 degree Celsius
calcd              calculated (MS)
Cl                 spirocyclopropylcyclohexadienone
1,la,2,3-tetrahydro-5-H-cycloprop[c]indol-5-one
15 cm              1 / centimeter (IR)
COD                1,5-cyclooctadiene
COSY               correlated spectroscopy (NMR)
CPI                cyclopropapyrrol[indole]
Cy                 cyclohexyl
δ                  chemical shift in ppm, downfield from TMS (NMR)
d                 doublet (NMR)
dba                dibenzylideneacetone

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<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DEAD</td>
<td>diethyl azodicarboxylate</td>
</tr>
<tr>
<td>DET</td>
<td>diethyl tetratate</td>
</tr>
<tr>
<td>Dibal-H</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DIOP</td>
<td>2,3-O-isopropyldiene-2,3-dihydroxy-1,4-bis-(diphenylphosphino)-butane</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMP</td>
<td>dimethoxypropane</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleoside</td>
</tr>
<tr>
<td>dppb</td>
<td>1,2-bis-(diphenylphosphino)butane</td>
</tr>
<tr>
<td>dppe</td>
<td>1,2-bis-(diphenylphosphino)ethane</td>
</tr>
<tr>
<td>dppm</td>
<td>1,2-bis-(diphenylphosphino)methane</td>
</tr>
<tr>
<td>dppm-cyh</td>
<td>1,2-bis-(diphenylphosphinomethyl)cyclohexane</td>
</tr>
<tr>
<td>dppm-nor</td>
<td>2,3-bis-(diphenylphosphinomethyl)nordihydrane</td>
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<tr>
<td>1,2-dpp-benzene</td>
<td>1,2-bis-(diphenylphosphino)benzene</td>
</tr>
<tr>
<td>dppp</td>
<td>1,2-bis-(diphenylphosphino)propane</td>
</tr>
<tr>
<td>DuPhos</td>
<td>substituted 1,2-bis-(diphenylphosphino)benzene</td>
</tr>
<tr>
<td>ea, ee</td>
<td>equatorial-axial, equatorial-equatorial</td>
</tr>
<tr>
<td>e.e.</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>El</td>
<td>electronic ionization (MS)</td>
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<tr>
<td>eq</td>
<td>equatorial</td>
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<tr>
<td>equiv.</td>
<td>equivalent</td>
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<td>ES</td>
<td>electron spray (MS)</td>
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<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>eV</td>
<td>(MS)</td>
</tr>
<tr>
<td>g, mg, μg</td>
<td>gram, milligram, microgram</td>
</tr>
<tr>
<td>GABA</td>
<td>γ-aminobutyric acid</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
</tr>
<tr>
<td>HPLC</td>
<td>high pressure liquid chromatography</td>
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<tr>
<td>HR</td>
<td>high resolution (MS)</td>
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<tr>
<td>Hz, MHz</td>
<td>hertz, megahertz (NMR)</td>
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<tr>
<td>i</td>
<td>iso</td>
</tr>
<tr>
<td>IR</td>
<td>Infra Red</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant (NMR)</td>
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<tr>
<td>I</td>
<td>linear</td>
</tr>
<tr>
<td>L, L*</td>
<td>ligand, chiral ligand</td>
</tr>
<tr>
<td>m</td>
<td>multiplet (NMR)</td>
</tr>
<tr>
<td>M</td>
<td>molarity; metal</td>
</tr>
<tr>
<td>M*</td>
<td>molecular ion (MS)</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-chloroperbenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
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<tr>
<td>min</td>
<td>minute</td>
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CHAPTER 1

ASYMMETRIC SYNTHESIS OF FUNCTIONALIZED
1,2,3,4-TETRAHYDROQUINOLINES

1.1 Background.

Naturally occurring tetrahydroquinolines have recently attracted considerable attention due to the wide range of biological activities exhibited by such compounds. Among them, 2-methyl-1,2,3,4-tetrahydroquinoline, present in human brain, is believed to hold a key role in the induction of Parkinson’s disease. A variety of structurally simple tetrahydroquinolines have been synthesized and tested. Several have been used as active pharmaceutical ingredients, such as virantmycin, a potent antibiotic against various RNA and DNA viruses. A wide scope of biological activities is commonly observed with tetrahydroquinolines, bearing simple to complex substituents, such as
antidepressants, antiulcer, cardiovascular, antiarrythmic, antitumor, antirheumatic activities. For example, 2-methyl-5-hydroxy-1,2,3,4-tetrahydroquinoline displays an analgesic activity one eighth as potent as morphine; 1,2,3,4-tetrahydroquinoline-4-carboxylic acid, having a γ-aminobutyric acid (GABA) like activity, was prepared for use in tissue irrigating solutions to promote corneal deswelling during otic surgery; 1,2,3,4-tetrahydro-8-quinolinol derivatives and pharmaceutically acceptable salts thereof were found useful as leukotriene-inhibiting antiallergenic agents. From an industrial chemistry perspective, tetrahydroquinoline derivatives have also proved to be useful pesticides, antioxidant corrosion inhibitors and various types of dyes, from hair dyes to more technical dyes, such as high sensitivity photosensetizers in photography.

![2-Methyl-1,2,3,4-tetrahydroquinoline and Virantmycin](image)

**Figure 1.1 : Structures of Selected Tetrahydroquinolines.**

In addition, tetrahydroquinolines can be considered as precursors for the duocarmycins and related natural products. The antitumor antibiotic (+)-CC 1065, first isolated in 1978 from *Streptomyces zelensis* at Upjohn, is one of the most active cytotoxic compounds *in vitro* and *in vivo*. Its structure consists of three substituted...
pyrrolo[3,2c]indole moieties, two of which are identical. The third, the A unit also called cyclopropa-pyrrolo-indole unit (abbreviated as CPI), contains the unusual spirocyclopropylcyclohexadienone moiety (CI unit). CC-1065 is an alkylating agent which shows its highest activity against cancer cells during mitosis. However it cannot be used as a drug because of a delayed liver toxicity. Biological studies have shown that the A unit alkylates DNA reversibly and sequence-selectively at AT-rich minor groove sites whereas the B/C units are responsible for the high binding specificity to the DNA.

Isolated in Japan from Streptomyces DO, the duocarmycins show the same antitumor antibiotic activity as CC 1065, but excitingly, lack the delayed fatal toxicity.7

Figure 1.2: Structure of (+)-CC 1065.
Since the disclosure of CC 1065 and the duocarmycins, extensive work has been devoted to defining, understanding and exploiting their properties.\textsuperscript{7} In this effort, many analogs have been synthesized in attempts to avoid the undesirable side effects of CC 1065 and to maintain the cytotoxic potency against tumor cells at the same time. As these agents have been shown to alkylate DNA on the least substituted carbon of the cyclopropane of unit A, the Cl moiety (1,1a,2,3-tetrahydro-5\textit{H}-cycloprop[e]indol-5-one) has been defined as the common pharmacophore.

\begin{center}
\begin{tikzpicture}
\draw[thick] (0,0) circle (1cm);
\draw[thick] (0,0) -- (1,0);
\draw[thick] (0,0) -- (0,1);
\draw[thick] (0,0) -- (-1,0);
\node at (0,0) {R};
\node at (0,1) {N} ;
\node at (0,-1) {1} ;
\end{tikzpicture}
\end{center}

**Figure 1.3 : Cl Moiety.**

Despite the numerous reported approaches to the Cl unit, the only synthesis of an optically pure compound was reported by Boger, via chemical resolution. Boger's synthesis\textsuperscript{8} starts first with an aryl radical-alkene cyclization to install the indole and then a Weinstein Ar-3’ alkylation\textsuperscript{9} to introduce the cyclopropane. Low temperature, acid-catalyzed bromination of the commercially available 3-benzyloxyaniline followed by N-Boc protection and N-alkylation gave compound 3. The self-terminating 5-\textit{exo-trig} aryl radical-alkene cyclization provided the 3-vinyl indole 4 in excellent yield. An
ozonolysis-reduction sequence led to alcohol 5a which was resolved to provide the enantiomerically pure alcohol. Mesylation of 5a and deprotection of the phenol led to the cyclization precursor. Finally, the spirocyclization was achieved by reaction of sodium hydride to give 1 in ten steps and 4% overall yield.

Scheme 1.1: Boger's Enantioselective Synthesis of CI Moiety.
With the same approach, Boger and co-workers also reported the synthesis of N-phenylsulfonyl-CI.\textsuperscript{8} However, their first attempt at spirocyclization by Mitsunobu reaction on N-SO\textsubscript{2}Ph-5a resulted in an inseparable mixture of Mitsunobu by-products. The novel reagent system 1,1’-(azodicarbonyl)dipiperidine (ADDP)-tributylphosphine (TBP)\textsuperscript{10} was the chosen alternative to perform a clean and quantitative spirocyclization.\textsuperscript{11,12,13} This new system was shown to activate nitrogen or carbon nucleophiles, otherwise inert or poorly reactive with typical Mitsunobu reagents (DEAD-PPh\textsubscript{3} system), to react with secondary alcohols satisfactorily forming C-N or C-C bonds.
Scheme 1.2: Spirocyclization in Natsume’s Total Synthesis of (+)-Duocarmycin SA.

Natsume\textsuperscript{11} and Boger\textsuperscript{12} both successfully used highly substituted pyrrolothetrahydroquinoline intermediates such as 6 for the construction of the spirocyclic moiety in their total syntheses of the Duocarmycins.
Pioneering work by Boger\textsuperscript{13} reports a moderately successful catalytic \textit{cis}-dihydroxylation in 78\% e.e., reaction which necessitated preparative HPLC purification of the intermediate before further steps in the synthesis of Duocarmycin A.

![Scheme 1.3: cis-Dihydroxylation in Boger's Synthesis of (+)-Duocarmycin A](image)

Scheme 1.3: \textit{cis}-Dihydroxylation in Boger's Synthesis of (+)-Duocarmycin A.

The importance of substituted tetrahydroquinolines and the lack of efficient method to generate such systems prompted us to investigate a broadly applicable, highly enantioselective synthesis of tetrahydroquinolines. For this purpose, we

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explored a Sharpless asymmetric epoxidation route and the utility of ligands previously designed in our group for a Rh-catalyzed asymmetric hydrogenation route.

![Scheme 1.4: Retrosynthetic Scheme.](image)

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1.2 Sharpless Epoxidation Route.

A general method to obtain a tetrahydroquinoline involves an intramolecular cyclization and we envisioned to form the $\text{N}_1-\text{C}_2$ bond by nucleophilic displacement of a leaving group at $\text{C}_2$. The chirality at $\text{C}_3$ would be installed by Sharpless epoxidation on a cinnamyl alcohol, itself obtained by Heck reaction of an aryl halide and methyl acrylate.

Previous work by Philippe Gastaud in our group has shown that tetrafluoroborate diazonium salt 11, formed from the commercially available 4-methoxy-2-nitroaniline 10, submitted to modified Heck reaction conditions (copper chloride, Li$_2$PdCl$_4$ in methanol) led to the expected $E$-cinnamic acid methyl ester 12 in a moderate 31% yield. A more efficient method was therefore investigated. Aniline 10 could be modified to the aryl iodide 13 by Sandmeyer reaction. Heck’s original procedure (Et$_3$N, Pd(OAc)$_2$, acetonitrile) on 13 afforded the $E$-cinnamate as a single isomer in 94% yield and subsequent reduction with Dibal-H gave the alcohol 14 in 84% yield.
With the allylic alcohol 14 in hand, the Sharpless epoxidation\textsuperscript{20} was performed. Optimal results were obtained with 10 mol\% Ti\((i\text{-OPr})_4\), 14 mol\% of \((+)-\text{DET}\) at -30°C for 6 days to give the epoxy alcohol 15 in 60% yield and over 90\% e.e.. (The enantiomeric excess was determined by \textsuperscript{19}F NMR of the corresponding Mosher ester.)\textsuperscript{21} To confirm the structure of the chiral epoxide and validate the analysis, the racemic epoxide was synthesized with \textit{m}-CPBA in 80\% yield.\textsuperscript{22} The unusual reaction conditions are due to several factors. First, cinnamyl alcohols have reportedly been

\begin{scheme}
\textbf{Scheme 1.5: Synthesis of the Epoxidation Precursor.}
\end{scheme}
described as poor substrates for the Sharpless epoxidation as the aryl group decreases the electron density of the olefin.\textsuperscript{19} Furthermore, 3-aryl-2,3-epoxypropanols are prone to facile ring opening mediated by Ti(IV).\textsuperscript{23} Finally, the presence of a nitro group in the ortho position on the aryl group retards the epoxide formation.\textsuperscript{24} Careful aging of the catalytic system and the low reaction temperature are therefore critical. Thus, this result represents one of the rare examples of a Sharpless epoxidation of an \(\alpha\)-cinnamyl derivative.

Scheme 1.6: Sharpless Epoxidation of an \(\alpha\)-Nitrocinnamyl Derivative.

Formation of the heterocycle from the epoxy alcohol requires three extra steps: regioselective opening of the epoxide, reduction of the nitro group and final intramolecular nucleophilic substitution. We hoped to take advantage of the reports of the utility of PtO\(_2\) catalyst for the regioselective opening of 1-phenyl-1,2-epoxy-3-tosyl propane at C\(_2\) \textsuperscript{25} and for the reductive cyclization of 2-(2-nitro)phenylpropan-1-yl methanesulfonate in presence of Et\(_3\)N\textsuperscript{26} to obtain the tetrahydroquinoline in a one-pot
fashion. Unfortunately, all our attempts, using a variety of platinum and palladium catalysts (Pd/C, Pd/BaSO₄, PtO₂) in varying amounts (1 to 20 mol%) and in both protic and aprotic solvents failed.¹⁵

A stepwise approach was more successful. Regioselective opening of the epoxide with various hydrides (LiBH₄, Dibal-H) gave the desired product in low yields at best.²⁷ The presence of the nitro group in ortho on the aryl ring explains the low yields as it would rather favor the regioselective opening of the epoxide at C₃. However, treatment of the epoxy tosylate 16 with MgI₂ at -55°C afforded an iodo hydroxy tosylate that was hydrogenated quickly without purification using PtO₂ (6 psi H₂ gas for 10 minutes).²⁸ The nitro group was then reduced using iron in the presence of dilute HCl.²⁹ Neutralization by addition of ammonia allowed for the cyclization to occur, thus affording the expected tetrahydroquinoline. The resulting secondary amine was extremely labile and regioselective tosylamide protection was required to isolate a stable derivative.³⁰
Boron tribromide has been reported as the reagent of choice for the cleavage of methyl phenyl ethers in the numerous syntheses of the Duocarmycins and related structures. After 1 h at -78°C followed by 1 h at -20°C, no reaction could be observed by TLC. The deprotection reaction started after 3 h when the temperature reached 20°C and the product was isolated in very low yield. We also tried to use BBr₃·SMe₂, a more stable and milder reagent which usually requires higher reaction temperatures than BBr₃ to cleave the carbon-oxygen bond. However, in our case, the reaction mixture decomposed rapidly at temperature below -20°C. We finally obtained the deprotected...
product cleanly using a solution of BBr₃ 1 M in dichloromethane. We were unfortunately unable to repeat the reaction on a larger scale.

![Diagram of chemical reaction]

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Reaction Conditions</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>BBr₃ 1 M in hexane</td>
<td>-78°C, 1h then -20°C, 1h</td>
<td>no reaction</td>
</tr>
<tr>
<td>BBr₃ 1 M in hexane</td>
<td>-78°C, 1h, -20°C, 1h then</td>
<td>low yield</td>
</tr>
<tr>
<td></td>
<td>0°C to 20°C, 2h</td>
<td></td>
</tr>
<tr>
<td>BBr₃,SMe₂ 1 M in CH₂Cl₂</td>
<td>-78°C, 1h to -20°C over 1h</td>
<td>decomposition observed by TLC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BBr₃ 1 M in CH₂Cl₂</td>
<td>-78°C, 1h, -20°C, 2h then</td>
<td>quantitative</td>
</tr>
<tr>
<td></td>
<td>0°C, 30 min.</td>
<td></td>
</tr>
</tbody>
</table>

Table 1.1: Attempted Phenol Deprotection.

In summary, this route afforded 7-methoxy-1-(4-toluenesulfonyl)-1,2,3,4-tetrahydroquinolin-3-ol 18 in a 9-step linear sequence and 19% overall yield.

Although this route was synthetically successful, the modest 60% yield and 90% e.e. of the key step combined with its long reaction time (6 days) were considered major drawbacks as they did not meet our expectations and requirements of practicality.
1.3 Asymmetric Hydrogenation Route.

An alternative approach was designed which kept the general strategy for the elaboration of the cycle but the asymmetry would be introduced this time by enantioselective hydrogenation.

The cinnamate may be obtained by three pathways. In the first route, the cinnamate 20 was prepared via Heck reaction in a sealed tube at 80°C for 24 h in 84% yield and 84/16 Z/E ratio. The second pathway involves the synthesis of an aryl nitrile 21 by Sandmeyer reaction, followed by reduction to the corresponding benzaldehyde 22. The Wadsworth-Emmons coupling on 22 proceeded efficiently yielding the cinnamate 20 in 90% yield and 90/10 Z/E ratio (Scheme 1.8). Despite comparable results, the Heck route was preferred for several reasons.
a. HCl then NaNO₂, H₂O, -5°C. b. KI, H₂O, 88% (2 steps). c. Methyl-2-acetamidoacrylate (19), Pd(OAc)₂, Bu₄NCl, NaHCO₃, sealed tube, 80°C, 24 h, 84%, 84/16 Z/E. d. HCl then NaNO₂, H₂O, -5°C. e. KCN, H₂O, 78% (2 steps). f. Dibal-H, toluene, Et₂O, -78°C to 0°C, 99%. g. Methyl-2-acetamido-2-(dimethoxyphosphinyl)-acetate (23), DBU, CH₂Cl₂, rt, 2 h, 90/10 Z/E.

Scheme 1.8: Cinnamate Formation by Heck or Wadsworth-Emmons Coupling.

First, while the synthesis of phosphonate 23 is well described in the literature, it involves a long 4-step sequence starting from benzyl carbamate and glyoxylic acid (Scheme 1.9). Each step also required column chromatographic purification. By comparison, the acetamido acrylate 19 was synthesized in 2 steps from DL-serine methyl ester. The procedure described in a patent separated the two acetylated products by careful spinning-band distillation (difference in boiling points of 2°C).
Instead, we optimized the synthesis by distillation of the mixture of mono- and diacetylated compounds followed by basic treatment with potassium bicarbonate in methanol at room temperature overnight. This gave the pure monoacetate 19 in an overall 38% yield (Scheme 1.10).

\[
\begin{align*}
\text{24} + \text{25} & \xrightarrow{a,b} \text{26} \xrightarrow{c,d} \text{23} \\
& \text{a. Et}_2O, \text{rt}, 24 \text{ h, 76%}. \quad \text{b. H}_2\text{SO}_4, \text{MeOH, rt, 48 \text{ h, 93%}}. \quad \text{c. PCl}_3, \text{P(OMe)}_3, \text{toluene, 70}^\circ\text{C, 45%}. \quad \text{d. H}_2, \text{Pd/C (10%), Ac}_2\text{O, MeOH, rt, 3 \text{ h, 92%}}.
\end{align*}
\]

Scheme 1.9: Synthesis of the Phosphonate for the Wadsworth-Emmons Reaction.

\[
\begin{align*}
\text{27} & \xrightarrow{a,b} \text{28, 29, 19} \\
& \text{a. Ac}_2\text{O, pyridine, 2 h.} \quad \text{b. K}_2\text{CO}_3, \text{MeOH, 16 h, 38% (2 steps)}. \quad \text{c. H}_2, \text{Pd/C (10%), Ac}_2\text{O, MeOH, rt, 3 h, 92%}}.
\end{align*}
\]

Scheme 1.10: An Improved Synthesis of 2-Acetamidoacrylate.

The third pathway to the dehydroaminoacid 20 uses the most common route for the synthesis of dehydroaminoacids. This involves the formation of an azalactone. This route led to the cinnamate in a 94/6 Z/E ratio (Scheme 1.11).
a. N-Acetylglycine, Ac₂O, NaOAc, 100°C, 2 h.  b. NaOMe, MeOH, rt, 16 h, 55% (2 steps), 94/6 Z/E.

Scheme 1.11: Azalactone Pathway.

However, the biggest disadvantage to Wadsworth-Emmons and azalactone routes resides in the difficult synthesis of 4-methoxy-2-nitrobenzaldehyde. Several syntheses of 22 are reported in the literature, most of which use 4-methoxy-2-nitrotoluene as starting material. Monobromination of 30 followed by oxidation or via an enamine were reliable routes.³⁸ Unfortunatly, the cost of the starting material was a severe limitation in our case.³⁹
Scheme 1.12: Synthesis of 4-Methoxy-2-nitrobenzaldehyde from the Corresponding Toluene.

Carbonylative Pd-catalyzed reaction of arenediazonium tetrafluoroborates with polymethylhydrosiloxane (PMHS) has been reported to allow the formation of aromatic aldehydes in good yields. The presence of a nitro group in the ortho position in our molecule enhanced the formation of the reduced product. Thus the Stille coupling gave an inseparable mixture of aldehyde and reduced arene, consistently in large favor of the arene. Variations of reaction time, catalyst loading or silane did not improve either the yield or the ratio of the two products.
Scheme 1.13: Stille Carbonylation of an Arene Diazonium Salt using PMHS and CO.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Silane</th>
<th>Catalyst Amount</th>
<th>Reaction Time</th>
<th>Isolated Yield (%)</th>
<th>22 : 33 Ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PMHSb</td>
<td>2 mol%</td>
<td>21 h</td>
<td>-</td>
<td>1 : 3</td>
</tr>
<tr>
<td>2</td>
<td>PMHS</td>
<td>5 mol%</td>
<td>16 h</td>
<td>16</td>
<td>1 : 15</td>
</tr>
<tr>
<td>3</td>
<td>PMHS</td>
<td>4 mol%</td>
<td>3 h</td>
<td>60</td>
<td>1 : 9</td>
</tr>
<tr>
<td>4</td>
<td>PMHS</td>
<td>4 mol%</td>
<td>5 h</td>
<td>73</td>
<td>1 : 8</td>
</tr>
<tr>
<td>5</td>
<td>TIPSHc</td>
<td>4 mol%</td>
<td>30 min</td>
<td>21</td>
<td>1 : 6</td>
</tr>
</tbody>
</table>


Table 1.1: Stille Carbonylation of an Arene Diazonium Salt using PMHS and CO.

Another attempt at Stille carbonylation using aryl iodide, tributyltin hydride and tetrakis-triphenylphosphine palladium was also unsuccessful.41

Scheme 1.14: Stille Carbonylation of an Aryl Iodide using Bu$_3$SnH and CO.

a. Bu$_3$SnH, Pd(PPh$_3$)$_4$, CO, toluene, 50°C, 2.5 h.
Attempts at obtaining the benzaldehyde 22 by direct Sandmeyer reaction on the arene diazonium chloride 34, formed \textit{in situ}, using a solution of formaldoxime gave an unstable product in low yields and poor quality.\textsuperscript{16}

\begin{center}
\includegraphics[width=\textwidth]{scheme115.png}
\end{center}

\textbf{Scheme 1.15 : Sandmeyer Reaction using Formaldoxime.}

Finally, the only useful synthesis of benzaldehyde 22, as shown in Scheme 1.8, by formation of an aryl nitrile was extremely efficient on small scale (77\% yield, 2 steps). However, the yield of the sequence dropped considerably upon scale-up. As a consequence, the Heck reaction route was chosen as the most practical way to the dehydroaminoacids. A number of dehydroaminoacids bearing a variety of substituents on the aryl group could be prepared by this route.
Figure 1.5: (Z)-2-N-Acetyl-3-(4-methoxy-2-nitrophenyl)acrylic acid methyl ester 20.

With the cinnamate 20 in hand, the key asymmetric hydrogenation could be attempted. Ligands $L_1^*$ and $L_2^*$ were synthesized on the basic assumption that the enantioselectivity of the reaction depends on the local chirality, i.e. the chirality of the two vicinal carbons to which the chelating phosphorous atoms are attached (and also that there is no large disruption of the equatorial arrangement of the rest of the sugar backbone). Thus, it should be possible to make both enantiomers of a product using the most commonly available D sugar backbone. Indeed this highly tunable series of ligands, derived from D-glucose, has been reported to provide a general access to optically pure amino acids.\textsuperscript{42}
The rhodium-catalyzed asymmetric hydrogenation was carried out in THF using 0.2 mol% of catalyst 36 for 15 minutes at room temperature. The (S)-amino acid 35 was obtained in 98% yield and over 99% e.e. We also had access to the opposite enantiomer of the amino acid with catalyst 37 under the same reaction conditions. The $R$ enantiomer was thus obtained in 99% yield and 96% e.e.
Scheme 1.16 : Rh-Catalyzed Asymmetric Hydrogenation of Dehydroaminoacids.

Figure 1.7 : Hydrogenation Catalysts.

Reduction of the ester with Super Hydride to the corresponding alcohol followed by tosylation resulted in the formation of an oxazoline with only traces of
the expected product. We assumed that the tosylation was slower than the oxazoline formation (prompted by the presence of Et$_3$N in the medium). The faster mesylation was therefore attempted and the crude NMR showed a clean product 40 which was used without further purification. Reductive cyclization,\textsuperscript{45} usually conducted in ethanol to give a secondary amine cleanly, in our case yielded a white crystalline ethoxyamine 41. Deprotection of the ethoxyamine using Zn dust in AcOH led to the expected unprotected tetrahydroquinoline 42 which could not be isolated cleanly.

\begin{center}
\begin{tikzpicture}
\node (35) at (0,0) {\includegraphics[width=0.8\textwidth]{image}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 1.17: Ethoxyamine Formation in the Catalytic Reduction.}

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Use of THF as a solvent finally afforded the unprotected tetrahydroquinoline, but compound 42 did not survive purification over silica gel as the secondary amine proton was particularly labile. Tosylation of the crude tetrahydroquinoline 42 led to the stable 43 in 46% for the 3-step sequence.

The overall sequence for the synthesis of 3-acetamido-7-methoxy-1-(4-toluenesulfonyl)-1,2,3,4-tetrahydroquinoline 43 proceeded 7 steps and in 24% overall yield.

![Chemical structure](image)

a. MsCl, Et₃N, CH₂Cl₂, 0°C, 30 min. b. H₂, Pd / C (10%), Et₃N, rt, 20 min. c. TsCl, Et₃N, CH₂Cl₂, 0°C, 15 min. then rt, 16 h, 46% (3 steps).

Scheme 1.18: Tetrahydroquinoline Formation by Reductive Cyclization.

To facilitate further transformations, the N-acetyl group could be exchanged for an N-Boc group by the method published by Burk without epimerization of the chiral center.
Tetrahydroquinoline 44 is an excellent candidate for further elaboration. Indeed, were a reliable procedure for the deprotection of the phenol to be established, one could easily envision to synthesize the Cl moiety 1 by Winstein spirocyclization of 3-amino-7-hydroxy-1-(4-toluenesulfonyl)-1,2,3,4-tetrahydroquinoline diazonium salt 45 derived from 44.

Scheme 1.19: N-Ac / N-Boc Exchange.

Scheme 1.20: Winstein Spirocyclization.
1.4 Conclusion.

In summary, two independent and reliable routes to enantiomerically enriched 3-substituted tetrahydroquinolines based on highly selective catalytic reactions have been demonstrated. The Sharpless epoxidation proceeded to give an epoxy alcohol in > 90% e.e.. The asymmetric hydrogenation route proved to be a rapid and general pathway for the synthesis of amino acids and gave access to both R and S enantiomers in > 98% e.e.. Both the hydroxy and the amino moieties are excellent handles for further elaboration of the tetrahydroquinolines into pharmacologically active compounds.
1.5 Experimental Section.

**General Methods.** Reactions were carried out in oven- or flame-dried glassware under a nitrogen atmosphere, unless otherwise noted. All solvents used were reagent grade. Diethyl ether, hexanes and tetrahydofuran (THF) were freshly distilled from sodium/benzophenone. Dichloromethane and toluene were freshly distilled from calcium hydride. Triethylamine was distilled from calcium hydride and stored over potassium hydroxide. Acetonitrile was dried over silica, distilled from calcium hydride and stored over 4 Å molecular sieves. Pyridine was distilled and stored over potassium hydroxide. Acetic anhydride was azeotroped with toluene, distilled and stored over 4 Å molecular sieves. Anhydrous N,N-dimethylformamide was purchased from Fischer and used without purification. Acetone was dried over 4 Å molecular sieves for 2 hours prior to use. Except as otherwise indicated, all reactions were magnetically stirred and monitored by thin layer chromatography on E. Merck precoated (0.25 mm) silica gel 60 F<sub>254</sub> plates. Flash chromatography was conducted by using silica gel 40 (Scientific Adsorbents Incorporated, Microns Flash). Chiral gas chromatographic separations were accomplished using Chirasil L-Val on WCOT fused silica (25 m x 0.25 mm, 0.12 µm film thickness) capillary GC column purchased from Chromapack (column A). The settings were as follow: temperature 190°C; time 30 min. Other gas chromatographic (GC) analyses were performed on a HP-ultra-1 crosslinked methyl silicone capillary column (25 m length x 0.2 mm i.d) (column B). The settings were as follow: initial temperature, 200°C; initial time, 5 min; rate, 5°C/min; final temperature,
250°C; final time, 30 min. Yields, unless otherwise stated, refer to chromatographically and spectroscopically pure compounds. Melting points were determined on a Thomas Hoover uni-melt apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 series FTIR. $^1$H, $^19$F and $^{13}$C NMR spectra were recorded on a Bruker Aspect 200, 250, 400 or 500 MHz spectrometer. Chemical shift are reported relative to chloroform as standard at $\delta = 7.26$ for $^1$H and $\delta = 77.0$ for $^{13}$C. Coupling constants are reported in Hertz (Hz). Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. High-resolution mass spectra for 16, 17, 18, 20 and 41 were recorded on a Kratos VG 70-250s at a ionization energy of 70 eV and for 43 on the Micromas QTOF Electrospray mass spectrometer. Compounds for which exact mass is reported exhibited no significant $m/z$ greater than the one of the parent peak. Microanalyses were performed by Atlantic Microlab, Inc.

4-Methoxy-2-nitrophenyl nitrile (21). A mixture of 4-methoxy-2-nitroaniline (166 µL, 200 mg, 1.19 mmol) and concentrated hydrochloric acid (0.30 mL, 3.6 mmol, 3 equiv.) in water (0.30 mL) was heated to reflux for 20 minutes, then cooled to 0°C in an ice-salt bath. A cold solution of sodium nitrite (255 mg, 3.7 mmol, 3.1 equiv.) in water (1 mL) was added dropwise over 15 minutes while stirring. The solution was stirred for 15 minutes and was then added dropwise below the surface of a
mechanically stirred cold solution of potassium cyanide (444 mg, 6.8 mmol, 5.7 equiv.) and copper cyanide (306 mg, 3.4 mmol, 2.8 equiv.) in water (2.5 mL). The mixture was heated to reflux for 2 hours, then taken in diethyl ether, washed with a saturated solution of sodium bicarbonate and hydrochloric acid 10%, dried (magnesium sulfate) and concentrated to form dark red crystals in 78% yield; m.p. 129-131°C; $^1$H NMR (CDCl$_3$, 200 MHz): $\delta$ 7.80 (d, J = 8.5, 1 H), 7.78 (d, J = 3.1, 1 H), 7.27 (dd, J = 8.7, 2.5, 1 H), 4.00 (s, 3 H); $^{13}$C NMR (CDCl$_3$, 63 MHz): $\delta$ 163.3, 136.7, 136.5, 119.7, 115.2, 111.4, 111.1, 56.6; IR: 2231, 1621, 1546, 1503, 1351, 1320, 1286 cm$^{-1}$; GC (column B): $t_R$ 14.3 min. [ID-I-144]

4-Methoxy-2-nitrobenzaldehyde (22). A cold (-78°C), magnetically stirred solution of 4-methoxy-2-nitrophenyl nitrile (360 mg, 2 mmol) in toluene (10 ml) and ether (10 ml) was treated with DIBAL (2.7 ml of 1.5 M in toluene, 4 mmol, 2 equiv.) and allowed to warm to 0°C after 30 min. After 20 min at 0°C, the reaction mixture was quenched with methanol (10mL) and triethylamine (14 mL). The intermediate imine was hydrolyzed with silica gel. The mixture was filtered through a short column of silica gel (elution with 5% ethyl acetate in petroleum ether), and the eluate was concentrated in vacuo to provide 365 mg (99%) of the aldehyde as a yellow solid.
Another procedure was to add DIBAL (400 µL of a 1.5 M solution in toluene, 0.59 mmol, 1.05 equiv.) to a cold (0°C) solution of 4-methoxy-2-nitrophenyl nitrile (100 mg, 0.56 mmol) in toluene (2 mL) and ether (1 mL). The reaction mixture was stirred at 0°C for 1 hour then quenched with methanol (1 mL) and HCl 1 M (1 mL). The reaction mixture was let to warm to room temperature and more HCl 1 M (10 mL) is added. The mixture was extracted with diethyl ether (4 x 10 mL) and washed with water (10 mL), dried (magnesium sulfate) and concentrated. The crude compound was purified by flash chromatography (SiO2, hexane / ethyl acetate, 1/1) and gave 86 mg (85%) of yellow crystals. m.p. 84-86°C; 1H NMR (CDCl3, 200 MHz): δ 10.2 (s, 1 H), 7.90 (d, J = 8.7, 1 H), 7.45 (d, J = 2.5, 1H), 7.15 (dd, J = 9.7, 1.9, 1 H), 3.90 (s, 3 H); 13C NMR (CDCl3, 50 MHz): δ 187.0, 163.7, 151.4, 131.5, 123.2, 118.9, 109.7, 56.5; IR: 1692, 1615, 1537, 1499, 1352, 1244 cm⁻¹; GC (column B): tR 11.2 min.

(Z)-2-N-Acetyl-3-(4-methoxy-2-nitrophenyl)acrylic acid methyl ester (20).

*Via Wadsworth-Emmons reaction.* To a solution of methyl-2-acetylamino-2-(dimethoxyphosphinyl)-acetate (220 mg, 0.91 mmol) in dichloromethane (1.7 mL) was added DBU (0.13 mL, 132 mg, 0.97 mmol, 1.05 equiv). After 10 minutes, 4-methoxy-2-nitrobenzaldehyde was added. The mixture was stirred at room
temperature for 2 h. The solution was then diluted in ethyl acetate (20 mL) and washed with 1 M sulfuric acid (5 mL), dried (magnesium sulfate) and concentrated under vacuum. The residue was filtered through silica gel (hexane / ethyl acetate, 1/1) to remove excess phosphorylglycine ester. The ratio $E/Z$ of the product (yield 90\%) was determined by $^1$H NMR to be 10/90. An attempt was made to isomerize the product in benzene containing thiophenol and AIBN at 80 °C for 4 hours. The resulting product unfortunately showed a $E/Z$ ratio 18/81. **Z isomer:** m.p. 134-136°C; $^1$H NMR (CDCl$_3$, 250 MHz): δ 7.65 (s, 1 H), 7.60 (d, J = 2.6, 1 H), 7.45 (s, 1 H), 7.35 (d, J = 8.6, 1 H), 7.10 (dd, J = 8.7, 2.6, 1 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 1.97 (s, 3 H); $^{13}$C NMR (CDCl$_3$, 63 MHz): δ 167.8, 165.1, 159.8, 148.1, 130.7, 125.0, 119.9, 109.2, 55.8, 52.9, 23.3; IR: 1698, 1531, 1348 cm$^{-1}$; Anal. found (calcd): C 52.96, (53.06); H 4.76, (4.80); N 9.50, (9.52); GC (column B): $t_R$ 16.8 min. **E isomer:** m.p. 113-115°C; $^1$H NMR (CDCl$_3$, 250 MHz): δ 8.33 (s, 1 H), 7.70 (s, 1 H), 7.60 (d, J = 2.6, 1 H), 7.21 (d, J = 8.6, 1 H), 7.11 (dd, J = 8.6, 2.6, 1 H), 3.90 (s, 3 H), 3.55 (s, 3 H), 2.18 (s, 3 H); $^{13}$C NMR (CDCl$_3$, 63 MHz): δ 168.7, 164.1, 159.0, 147.5, 132.1, 125.5, 124.1, 123.1, 119.3, 108.5, 55.7, 52.3, 26.4; IR: 1686, 1527, 1349 cm$^{-1}$; HRMS calcd for C$_{13}$H$_{14}$N$_2$O$_6$: $M^+$ = 294.0852, found 294.0866; GC (column B): $t_R$ 17.0 min. [ID-I-149]
Methyl 2-acetamido acrylate (19). A mixture of DL-serine methyl ester hydrochloride (13.52 g, 86.9 mmol), diisopropylethylamine (44.2 mL) and acetic anhydride (88.4 mL) was heated to reflux for 2 hours. The volatiles were distilled off under high vacuum and the residue was taken up in ether (500 mL) and washed with 1 N HCl (100 mL). Saturated aqueous sodium bicarbonate was added and the mixture was stirred for 1 h. The ether layer was washed with water (50 mL) and was dried over magnesium sulfate. The solvent was removed at reduced pressure and the red residue was distilled at 90°C under 0.4 torr to afford 5 g of a mixture methyl-2-N-acetylamino acrylate and methyl-2-N,N'-diacetylamino acrylate. This mixture was taken in 25 mL of absolute methanol and was stirred with 1 equiv. of solid sodium bicarbonate overnight. Filtration and evaporation of the solvent afforded 5.1 g of the monoacetylated compound (38% yield). $^1$H NMR (CDCl$_3$, 250 MHz): $\delta$ 7.85 (s, 1 H), 6.65 (s, 1 H), 5.90 (s, 1 H), 3.85 (s, 3 H), 2.15 (s, 3 H); $^{13}$C NMR (CDCl$_3$, 63 MHz): $\delta$ 168.9, 130.9, 108.7, 52.9, 24.5; IR: 3406, 1721, 1692 cm$^{-1}$. [ID-II-40]
2-N-Acetyl-2-amino-3-(4-methoxy-2-nitrophenyl)acrylic acid methyl ester (20). Via Heck reaction. A mixture of 4-iodo-3-nitroanisole (500 mg, 1.79 mmol), methyl 2-acetamido acrylate (305 mg, 2.13 mmol, 1.2 equiv.), palladium acetate (46 mg, 0.20 mmol, 11.5 mol%), tetrabutyl ammonium chloride hydrate (587 mg, 2.15 mmol, 1.2 equiv.) and sodium bicarbonate (407 mg, 4.84 mmol, 2.7 equiv.) was flushed with nitrogen and heated in a sealed tube at 80°C. After 24 h of reaction, the tube was cooled to room temperature and the reaction mixture taken in 50 mL of dichloromethane and washed three times with 10 mL of water. The combined organic layers were dried on magnesium sulfate and the solvent was removed by concentration under vacuum (no heat). The oily residue was purified by flash chromatography (SiO₂, hexane / ethyl acetate, 2/1). The yellow product was a mixture of the Z and E isomers (84% yield, 86% Z and 14% E). The isomers were separated by flash chromatography (SiO₂, hexane / ethyl acetate, 3/1). Identified as described earlier. [ID-I-36]
(Z)-2-(4-methoxy-2-nitrophenyl)-4-(thienylenylene)-5-oxazolactone (29).

A mixture of 4-methoxy-2-nitrobenzaldehyde (30 mg, 0.17 mmol), N-acetylglycine (19.4 mg, 0.17 mmol, 1 equiv.), acetic anhydride (95 µl) and anhydrous sodium acetate (13.6 mg, 0.17 mmol, 1 equiv.) was heated at 100°C for 2 hours. The mixture was allowed to cool to room temperature and poured into ethanol / water (2/3, 20 ml). The solid azolactone was isolated by filtration, washed with ethanol, dried (magnesium sulfate) and recrystallized from acetonitrile to give whitish crystals in 57% yield. m.p. 130-132°C; $^1$H NMR (CDCl$_3$, 200 MHz): $\delta$ 7.60 (s, 1 H), 7.55 (d, $J = 2.6$, 1 H), 7.35 (d, $J = 8.2$, 1 H), 7.07 (dd, $J = 8.7$, 2.6, 1 H), 3.85 (s, 3 H), 3.82 (s, 3 H); $^{13}$C NMR (CDCl$_3$, 63 MHz): $\delta$ 168.3, 165.1, 159.8, 130.8, 127.9, 125.2, 122.7, 119.9, 109.3, 55.8, 52.9, 23.2; IR: 1722, 1698, 1620, 1565, 1531, 1494, 1439, 1348 cm$^{-1}$. [ID-I-102]

Via oxazolactone opening. A suspension of the unsaturated (Z)-2-(4-methoxy-2-
nitrophenyl)-4-(thienylmethylene)-5-oxazolactone (84 mg, 0.3 mmol) in a solution of sodium methoxide (0.81 mg, 0.015 mmol, 4.7 mol%) in absolute methanol (1.2 ml) was stirred at room temperature until the starting material was completely dissolved. The solution was filtered and evaporated *in vacuo*. The resultant solid was purified by chromatography (SiO₂, hexane / ethyl acetate, 1/1) to give the ester in 96% yield and in an *E* / *Z* ratio of 6/94. Identified as described earlier. [ID-I-96]

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\text{(S)-35}
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*(S)-2-N-acetyl-2-amino-3-(4-methoxy-2-nitrophenyl) propionic acid methyl ester (35).* In an inert atmosphere drybox, a Fisher-Porter apparatus was charged with (Z)-2-N-acetyl-2-amino-3-(4-methoxy-2-nitrophenyl) acrylic acid methyl ester (530 mg, 1.8 mmol), phenyl-[(4,6-O-benzylidene-2,3-bis-O-[(3,5-dimethylphenyl)phosphinol]-β-D-glucopyranoside)Rh(COD)]'SbF₆⁻ (5 mg, 0.004 mmol, 0.2 mol%) and THF (8 mL). After sealing, the tube was removed from the drybox and placed behind proper shielding. With adequate stirring of the solution at room temperature, the tube was charged with 45 psi of H₂ gas and subsequently evacuated. This procedure was repeated twice. The tube was charged with 45 psi of H₂ and recharged as necessary to maintain 45 psi. After 15 minutes, the tube was vented and the solution concentrated to give an orange oil that was purified by chromatography (SiO₂, hexane / ethyl acetate
1/2) to give a yellow solid 35 in 98% yield and 2% yield of the (E)-cinnamate 20. m.p. 109-111°C; \(^1\)H NMR (CDCl\(_3\), 250 MHz): \(\delta\) 7.40 (d, \(J = 2.6, 1\) H), 7.25 (d, \(J = 8.7, 1\) H), 7.05 (dd, \(J = 8.6, 2.6, 1\) H), 6.50 (d, \(J = 7.9, 1\) H), 4.85 (dd, \(J = 13.8, 8.0, 1\) H), 3.82 (s, 3 H), 3.65 (s, 3 H), 3.30 (ddd, \(J = 55.5, 13.9, 5.9, 2\) H), 1.90 (s, 3 H); \(^{13}\)C NMR (CDCl\(_3\), 63 MHz): \(\delta\) 171.9, 169.9, 158.8, 150.0, 133.5, 123.2, 119.6, 109.5, 55.7, 52.8, 52.4, 34.1, 22.8; IR: 1740, 1676, 1532 cm\(^{-1}\); \([\alpha]_D^{21}\) +47° (c 2, CHCl\(_3\)); Anal. found (calcd): C 52.61, (52.70); H 5.44, (5.44); N 9.46, (9.76); GC (column B: 200/5/5/220/25): \(t_R\) 15.0 min; GC (column A: 190/30): \(t_R\) 22.9 min (0.3% R), \(t_R\) 25.2 min (99.6% S), 99.2% ee. The product was recrystallized from ethyl acetate / petroleum ether 95/5; GC (column A): \(t_R\) 22.9 min (0.2% R), \(t_R\) 25.2 min (99.8% S), 99.6% ee. [ID-I-112]

(R)-2-N-acetyl-2-amino-3-(4-methoxy-2-nitrophenyl) propionic acid methyl ester. In an inert atmosphere drybox, a Fisher-Porter apparatus was charged with (Z)-2-N-acetyl-2-amino-3-(4-methoxy-2-nitrophenyl) acrylic acid methyl ester (46 mg, 0.15 mmol), \([(\text{methyl-2,6-di-O-benzoyl-3,4-bis-O-[bis93,5-dimethylphenyl]phosphino}-\alpha-D-glucopyranoside)\text{Rh(COD)}])^+\text{SbF}_6^-\) (0.5 mg, 0.003 mmol, 0.24 mol%)\(^{10}\) and THF (1 mL). After sealing, the tube is removed from the
drybox and placed behind proper shielding. With adequate stirring of the solution at room temperature, the tube was charged with 45 psi of H\(_2\) gas and was subsequently evacuated. This procedure was repeated twice. The tube was charged with 45 psi of H\(_2\) and recharged as necessary to maintain 45 psi. After 15 minutes, the tube was vented and the solution concentrated to give an orange oil that was purified by chromatography (SiO\(_2\), hexane / ethyl acetate 1/2) to give 46 mg of a yellow solid (99% yield). m.p. 109-111°C; \(^1\)H NMR (CDCl\(_3\), 250 MHz): \(\delta\) 7.40 (d, \(J = 2.6, 1\) H), 7.25 (d, \(J = 8.7, 1\) H), 7.05 (dd, \(J = 8.6, 2.6, 1\) H), 6.50 (d, \(J = 7.9, 1\) H), 4.85 (dd, \(J = 13.8, 8.0, 1\) H), 3.82 (s, 3 H), 3.65 (s, 3 H), 3.30 (ddd, \(J = 55.5, 13.9, 5.9, 2\) H), 1.90 (s, 3 H); \(^{13}\)C NMR (CDCl\(_3\), 63 MHz): \(\delta\) 171.9, 169.9, 158.8, 150.0, 133.5, 123.2, 119.6, 109.5, 55.7, 52.8, 52.4, 34.1, 22.8; IR: 1740, 1676, 1532 cm\(^{-1}\); GC (column B): t\(_R\) 15.0 min. The enantioselectivity as determined by GC analysis (column A) was 96.6%ee. [ID-I-110]

\[(S)-N-(1-hydroxymethyl-2-(4-methoxy-2-nitrophenyl)-ethyl)-acetamide\] (38). Super Hydride\(^8\) (1.5 M in THF, 1.85 mL, 1.85 mmol, 2.2 equiv.), was added to a stirred solution of (S)-2-N-acetyl-2-amino-3-(4-methoxy-2-nitrophenyl) propionic acid methyl ester (250 mg, 0.84 mmol) in THF (10 mL) at 0°C. The reaction mixture was
stirred at 0°C for 1 hour. The reaction was quenched with water (3 mL) and the aqueous layer was extracted with CH$_2$Cl$_2$ (5 x 20 mL). The organic extracts were combined, washed with water, dried (magnesium sulfate) and concentrated to give an pink oil that was purified by chromatography (SiO$_2$, ethyl acetate / methanol, 20/1) to give 190 mg (87%) of a pale yellow oil that solidified under vacuum. m.p. 105-108°C; $^1$H NMR (CDCl$_3$, 200 MHz): $\delta$ 7.38 (d, $J = 2.7$, 1 H), 7.32 (d, $J = 8.9$, 1 H), 7.08 (dd, $J = 8.6$, 2.7, 1 H), 6.50 (d, $J = 8.1$, 1 H), 4.20 (m, 1 H), 3.82 (s, 3 H), 3.62 (m, 2 H), 3.05 (ddd, $J = 23.0$, 13.9, 6.0, 3 H), 1.88 (s, 3 H); $^{13}$C NMR (CDCl$_3$, 50 MHz): $\delta$ 171.0, 158.6, 150.2, 133.5, 125.0, 119.9, 109.3, 64.3, 55.8, 53.0, 32.9, 23.2; IR: 3430, 1660, 1531, 1442, 1352, 1252 cm$^{-1}$; $[\alpha]_D^{21}$ $-42.5^\circ$ (c 0.8, CHCl$_3$); Anal. found (calcd): C 53.73, (53.64); H 6.01, (6.06); N 10.44, (10.30); GC (column B): $t_R$ 9.5 min; GC (column A: initial temperature, 160°C; initial time, 10 min; rate, 5 °C/min; final temperature, 190°C; final time, 20 min): $t_R$ 11.2 min. [ID-I-117]

(N)-2-Methyl-4-(4-methoxy-2-nitrophenyl) oxazoline (39). Via tosylate. To a mixture of N-(1-hydroxymethyl-2-(4-methoxy-2-nitrophenyl)-ethyl)-acetamide (54 mg, 0.20 mmol), and triethylamine (34 µL, 0.24 mmol, 1.2 equiv.) in dichloromethane (1 mL) cooled to 0°C was added dropwise toluenesulfonyl chloride (42 mg, 0.22 mmol,
1.1 equiv) in dichloromethane (1 mL). The mixture was left to warm to room temperature overnight. As the reaction did not seem to progress, 4-dimethylamino pyridine (2 mg, 0.02 mmol, 10 mol%) was added and the reaction mixture was left stirring for one more hour. The reaction mixture was then quenched with saturated solution of ammonium chloride (20 mL), the aqueous layer was washed with diethyl ether (4 x 20 mL), the combined organic layers were washed with brine (10 mL) and water (10 mL), dried (MgSO₄) and concentrated. The crude compound was purified by flash chromatography (silica gel, ethyl acetate) to give 30 mg (60% yield) of a yellowish oil. ¹H NMR (CDCl₃, 500 MHz): δ 7.45 (d, J = 2.7, 1 H), 7.30 (d, J = 8.5, 1 H), 7.10 (dd, J = 8.6, 2.6, 1 H), 4.37 (m, 1 H), 4.30 (t, J = 8.3-9.3, 1 H), 3.90 (t, J = 7.6-7.9, 1 H), 3.82 (s, 3 H), 3.08 (dd, J = 13.8, 5.1, 1 H), 3.01 (dd, J = 13.8, 7.9, 1 H), 1.90 (s, 3 H); ¹³C NMR (CDCl₃, 125 MHz): δ 165.2, 158.6, 150.0, 133.8, 125.2, 119.7, 109.4, 72.1, 66.7, 56.0, 38.2, 13.9; IR: 2970, 1671, 1530, 1350 cm⁻¹. [ID-II-73]

![39](image)

(S)-2-Methyl-4-(4-methoxy-2-nitrophenyl) oxazoline (39). *Via mesylate.*

To a mixture of N-(1-hydroxymethyl-2-(4-methoxy-2-nitrophenyl)-ethyl)-acetamide (15 mg, 0.056 mmol), and triethylamine (10 μL, 0.067 mmol, 1.2 equiv) in dichloromethane (1 mL) cooled to 0°C was added dropwise methanesulfonyl chloride.
(5 \mu L, 0.061 mmol, 1.1 equiv) and the mixture was stirred for 30 minutes at 0°C. The reaction mixture was then quenched with saturated solution of ammonium chloride (20 mL), the aqueous layer was washed with diethyl ether (4 x 20 mL), the combined organic layers were washed with brine (10 mL) and water (10 mL), dried (MgSO₄) and concentrated. The crude compound was diluted in THF (1mL) and the solution was cooled to 0°C. A solution of potassium tert-butoxide 1M in tert-butanol (56 \mu L, 0.056 mmol, 1.0 equiv) was then added and the reaction mixture was allowed to slowly warm to room temperature overnight. The mixture was then poured into ethyl acetate (20 mL) and washed twice with saturated solution of sodium bicarbonate (20 mL). The organic layer was dried (magnesium sulfate) and gave 10 mg (71% yield) of a yellowish oil. Identified as described earlier. [ID-II-79]

![Structural formula](image)

\((S)-N-(1\text{-methanesulfonyloxymethyl-2-(4\text{-methoxy-2-nitrophenyl)-ethyl)-acetamide (40)}}\). To a mixture of \((S)-N-(1\text{-hydroxymethyl-2-(4\text{-methoxy-2-nitrophenyl)-ethyl)-acetamide (5 mg, 0.019 mmol), and triethylamine (2.9 } \mu L, 0.020 mmol, 1.1 \text{ equiv.) in dichloromethane (1 mL) cooled to 0°C was added dropwise methylenesulfonyl chloride (1.7 } \mu L, 0.022 mmol, 1.2 \text{ equiv.). The mixture was stirred at 0°C for 30 minutes. The reaction was quenched with saturated solution of ammonium
chloride (10 mL), the aqueous layer was washed with diethyl ether (4 x 10 mL), the combined organic layers were washed with brine (5 mL) and water (5 mL), dried (magnesium sulfate) and concentrated. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.98 (bs, 1 H), 7.47 (d, $J = 2.7$, 1 H), 7.42 (d, $J = 8.6$, 1 H), 7.11 (dd, $J = 8.6, 2.7$, 1 H), 4.30 (dd, $J = 12.1, 3.5$, 1 H), 4.12 (dd, $J = 12.2, 5.8$, 1 H), 3.83 (m, 1 H), 3.82 (s, 3 H), 3.38 (dd, $J = 8.7, 5.9$, 1 H), 3.28 (dd, $J = 14.0, 8.8$, 1H), 2.71 (s, 3 H), 2.09 (s, 3 H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 171.0, 159.5, 149.8, 134.5, 122.5, 120.4, 110.3, 62.7, 56.0, 51.3, 39.5, 32.6, 20.8. [ID-I-248]

(S)-3-Acetamido-7-methoxy-1-ethoxy-1,2,3,4-tetrahydroquinoline (41). To a mixture of (S)-N-(1-hydroxymethyl-2-(4-methoxy-2-nitrophenyl)-ethyl)-acetamide (10 mg, 0.038 mmol), and triethylamine (5.8 $\mu$L, 0.040 mmol, 1.1 equiv.) in dichloromethane (1 mL) cooled to 0°C was added dropwise methylenesulfonyl chloride (3.4$\mu$L, 0.044 mmol, 1.2 equiv.). The mixture was stirred at 0°C for 30 minutes. The reaction was quenched with saturated solution of ammonium chloride (10 mL), the aqueous layer was washed with diethyl ether (4 x 10 mL), the combined organic layers were washed with brine (5 mL) and water (5 mL), dried (magnesium sulfate) and concentrated. The crude yellow oil was diluted in absolute ethanol (1 mL) and transferred to a Fisher-Porter tube containing Pd/C (10%, about 10 mol%) in absolute...
ethanol (1 mL). After sealing, the tube was placed behind proper shielding. With
adequate stirring of the solution at room temperature, the tube was charged with 45 psi
of H₂ gas and vented. This procedure was repeated twice. The tube was charged with
45 psi of H₂ and recharged as necessary to maintain 45 psi. After 2 hours, the tube was
vented and the solution filtrated on silica gel and concentrated to give a colorless oil
that purified by preparative column chromatography (ethyl acetate) to give 9 mg (90%
yield) of a white solid. ¹H NMR (CDCl₃, 400 MHz): δ 6.85 (d, J = 8.1, 1 H), 6.20 (d,
J = 2.1, 1 H), 6.19 (dd, J = 8.1, 2.1, 1 H), 5.75 (bd, J = 5.4, 1 H), 4.44 (m, 1 H), 3.76
(s, 3 H), 3.40 (m, 1 H) overlapping 3.39 (dd, J = 10.0, 1.6, 1 H), 3.20 (hex, J = 7.2, 1
H), 3.09 (dt, J = 11.5, 2.6, 1 H), 2.95 (dd, J = 17.4, 4.5, 1 H), 2.62 (m, 1 H), 1.90 (s, 3
H), 1.11 (t, J = 7.0, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 168.6, 158.6, 144.0, 129.9,
110.5, 99.9, 96.7, 54.2, 50.7, 44.3, 41.0, 31.7, 22.5, 9.6; HRMS calcd for C₁₄H₂₆N₂O₃:
M⁺⁺ = 264.1474, found 264.1438. [ID-I-224]

(S)-3-Acetamido-7-methoxy-1-(4-toluenesulfonyl)-1,2,3,4-
tetrahydroquinoline (43). Synthesis of the intermediate: (S)-3-Acetamido-7-
methoxy-1,2,3,4-tetrahydro-quinoline. To a mixture of (S)-N-(1-hydroxymethyl-2-(4-
methoxy-2-nitrophenyl)-ethyl)-acetamide (100 mg, 0.37 mmol), and triethylamine (57
µL, 0.41 mmol, 1.1 equiv.) in dichloromethane (1 mL) cooled to 0°C was added
dropwise methanesulfonyl chloride (35μL, 0.4S mmol, 1.2 equiv.). The mixture was stirred at 0°C for 30 minutes. The reaction was quenched with saturated solution of ammonium chloride (10 mL), the aqueous layer was washed with diethyl ether (4 x 10 mL), the combined organic layers were washed with brine (5 mL) and water (5 mL), dried (magnesium sulfate) and concentrated. The crude yellow oil was diluted in THF (2 mL) and transferred to a Fisher-Porter tube containing Pd/C (10%, 40 mg, 10 mol%) in THF (1 mL). After sealing, the tube was placed behind proper shielding. With adequate stirring of the solution at room temperature, the tube was charged with 45 psi of H₂ gas and vented. This procedure was repeated twice. The tube was charged with 45 psi of H₂ and recharged as necessary to maintain 45 psi. After 1 hour, the tube was vented and the solution filtrated on silica gel and concentrated to give a colorless oil that would not even permit purification by preparative column chromatography (ethyl acetate). The following data has been deciphered from the crude compound obtained.

^1H NMR (CDCl₃, 400 MHz): δ 6.86 (d, J = 5.1, 1 H), 6.35 (d, J = 6.8, 1 H), 6.24 (dd, J = 10.6, 2.5, 1 H), 6.22 (bd, J = 2.3, 1 H), 4.01 (m, 1 H), 3.73 (s, 3+1 H), 3.56 (m, 1 H), 2.72 (m, 1 H), 2.59 (m, 1 H), 1.98 (s, 3 H), 1.83 (m, 1H); ^13C NMR (CDCl₃, 100 MHz): δ 170.9, 159.5, 146.2, 131.7, 115.1, 104.0, 101.8, 62.3, 55.1, 51.8, 32.1, 23.3.

The crude (S)-3-acetamido-7-methoxy-1,2,3,4-tetrahydroquinoline was diluted in CH₂Cl₂ (2 mL), Et₃N (57 μL, 0.41 mmol, 1.1 equiv.) and TsCl (71 mg, 0.37 mmol, 1.0 equiv.) were added at 0°C. The mixture was stirred at that temperature for 15 minutes, let to warm up at room temperature and stirred overnight. The reaction mixture was taken in 10 mL of water, the organic layer was extracted 5 times with 20
mL of ether, dried over magnesium sulfate and concentrated. The crude compound was purified by column chromatography (SiO2, hexane / ethyl acetate, 3/1) to give the expected product in 46% yield (3 steps). 1H NMR (CDCl3, 400 MHz): δ 10.38 (bs, 1H), 7.64 (d, J = 8.3, 2 H), 7.18 (d, J = 7.9, 2 H), 7.00 (d, J = 2.6, 1 H), 6.86 (d, J = 8.4, 1H), 6.56 (dd, J = 8.4, 2.6, 1H), 4.33 (dd, J = 9.6, 8.6, 1 H), 4.08 (qm, J = 8.7, 1 H), 3.78 (dd seen as t, J = 8.6, 1 H), 3.72 (s, 3 H), 2.44 (dd, J = 14.4, 2.6, 1 H), 2.35 (s, 3H), 2.23 (dd, J = 14.3, 8.9, 1 H), 2.02 (s, 3 H); 13C NMR (CDCl3, 100 MHz): δ 166.9, 159.2, 143.1, 138.3, 137.5, 131.9, 129.5, 129.2, 126.9, 123.4, 111.2, 109.5, 72.0, 67.6, 55.3, 50.8, 37.2, 21.5, 13.9; IR: 2924, 1734, 1508, 1157 cm⁻¹; [α]D21 -10° (c 1.5, CHCl3); HRMS calcd for C19H22N2O4SNa: M⁺ = 397.1198, found 397.1183.

(ID-II-15)

(S)-3-tert-Butoxycarbonyl-7-methoxy-1-(4-toluenesulfonyl)-1,2,3,4-tetrahydroquinoline (44). (S)-3-Acetamido-7-methoxy-1-(4-toluenesulfonyl)-1,2,3,4-tetrahydroquinoline (30 mg, 0.080 mmol) and DMAP (2 mg, 0.016mmol, 0.2 equiv.) were dissolved in THF (1 mL). Di-tert-butoxy dicarbonate (35 mg, 0.160 mmol, 2 equiv.) was added and the mixture was heated to reflux for 4 hours. After cooling to room temperature, methanol (1mL) and hydrazine (10 μL, 0.320 mmol, 4 equiv.) were added and the mixture was stirred at room temperature for 4 hours. The reaction was

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poured into dichloromethane and washed with 1 N HCl, CuSO₄, and NaHCO₃ saturated, dried (magnesium sulfate) and evaporated. The crude product was purified by column chromatography (SiO₂, hexane / ethyl acetate, 3/1) to give 9 mg of the pure expected compound (26% yield in 2 steps). ¹H NMR (CDCl₃, 500 MHz): δ 7.68 (d, J = 8.3, 2 H), 7.23 (d, J = 8.1, 2 H), 7.17 (d, J = 2.5, 1 H), 6.97 (d, J = 8.4, 1 H), 6.67 (dd, J = 8.4, 2.5, 1 H), 5.04 (bs, 1 H), 3.82 (s, 3 H), 3.62 (dd, J = 10.8, 3.3, 1 H), 3.47 (dd overlapping a m, 1 H + 1 H), 2.45 (m, 2 H), 2.42 (s, 3 H), 1.53 (s, 9 H); ¹³C NMR (CDCl₃, 75 MHz): δ 193.1, 160.5, 159.0, 143.3, 136.9, 131.5, 129.4, 127.1, 122.2, 111.9, 109.5, 80.3, 61.8, 55.4, 53.3, 31.6, 28.4, 21.5; IR: 3434, 1731, 1509, 1374 cm⁻¹; [α]D₂¹ -2° (c 5, CHCl₃). [ID-II-19]
CHAPTER 2

STUDIES ON THE ASYMMETRIC HYDROFORMYLATION REACTION
USING CARBOHYDRATE-DERIVED PHOSPHOLANES

2.1 Background.

2.1.1 The Asymmetric Hydroformylation Reaction.

As one of the oldest industrial processes,\textsuperscript{46,47} hydroformylation is one of the most extensively studied reactions in organic chemistry. In a single step, three readily available components are combined cleanly into aldehydes to make this transformation a highly efficient and atom-economic C-C bond formation reaction. The development of better asymmetric hydroformylation catalysts continue to be a challenging issue, as the chemoselectivity (\textit{i.e.} hydroformylation vs hydrogenation), regioselectivity (\textit{i.e.}
branched vs linear aldehyde formation) and enantioselectivity must all be excellent in order to have a viable commercial process.

\[
\begin{align*}
R & \quad + \text{CO} + \text{H}_2 \quad \xrightarrow{\text{cat.} / \text{L}^*} \quad R' \quad \text{CHO} \\
R' & = \text{alkyl, aryl, acetoxy} \quad \text{linear (l)} \\
R'' & = \text{branch (b)}
\end{align*}
\]

Scheme 2.1: Asymmetric Hydroformylation Reaction.

The original catalyst \([\text{Co}_2\text{(CO)}_8]\) typically required 200-300 bar of gas pressure and temperatures over 160°C. A real breakthrough was later achieved with the introduction of rhodium catalysts such as \([\text{HRh(CO)(PPh}_3\text{)}_3]\) which enabled the process to operate at 10-25 bar and 100°C. The presence of PPh\(_3\) increased the stability of the rhodium catalysts, inhibited the hydrogenation reaction and enhanced the regioselectivities. A variety of enantiopure diphosphines, diphosphinites, phosphine-phosphites, dithiols, P,N-ligands and P,S-ligands have been developed as chiral ligands for rhodium catalysts. Representative chiral ligands discussed in this chapter are shown in Figure 2.1. Particularly, BINAPHOS ligand, a bidentate phosphine-phosphinite, proved to give high enantioselectivities in the asymmetric hydroformylation of styrene and vinyl acetate.
Scheme 2.2 : Hydroformylation with BINAPHOS as Ligand.

The reaction is most commonly run using a neutral catalyst such as [Rh(CO)\(_2\)(acac)] at high gas pressure (10 to 100 bar) and temperature (60 to 100°C).\(^{49}\)

In comparison, the cationic rhodium catalysts almost passed unnoticed in the literature in spite of the very mild reaction conditions (1 bar, 22°C) and their efficient chemo- and regioselectivities.\(^{50}\)

Scheme 2.3 : Hydroformylation with Cationic Catalyst.

Despite the development of a wide variety of phosphine ligands, no detailed understanding has yet emerged to explain how those ligands control the selectivity in the asymmetric hydroformylation reaction.

51
Figure 2.1: Bidentate Ligands.
The dissociation mechanism proposed by Wilkinson is the most generally accepted. In this mechanism, (i) dissociation of CO from the HRh(CO)\(_2\)L\(_2\) 18-electron complex A generates a coordinatively unsaturated 16-electron species HRh(CO)L\(_2\) B, (ii) coordination of the olefin followed by olefin insertion in the Rh-H bond forms the alkyl-Rh(CO)L\(_2\) complex D, (iii) coordination of CO is followed by migratory insertion of alkyl group to one of the coordinated carbon monoxides and (iv) oxidative addition of molecular hydrogen, followed by reductive elimination produces the aldehydes and regenerates the active catalyst B, which completes the catalytic cycle. According to this mechanism (for the hydroformylation of 1-hexene), the selectivity is determined in the step that converts a five coordinate L\(_2\)Rh(CO)H(alkene) (C) into either a linear or a branched four-coordinate L\(_2\)Rh(CO)(alkyl) (D). Therefore, the regioselective outcome is determined by the approach of the alkene to the HRh(CO)L\(_2\) complex B. The enantioselectivity is also determined at this stage and depends on which of the Re or Si face of the olefin coordinates to the central metal.
Scheme 2.4: Wilkinson's Dissociative Mechanism for Hydroformylation.\textsuperscript{51}

To achieve excellent selectivity, it is essential to generate the most catalytically active species exclusively so that the reaction can be carried out at the lowest possible temperature. Brown and Kent\textsuperscript{32} have shown that the PPh\textsubscript{3}-modified complex \((\text{PPh}_3)_2\text{Rh(CO)}_2\text{H}\) exists as a 85 : 15 mixture of two trigonal bipyramidal isomers in diequatorial (ee) to equatorial-apical (ea) at -55°C. These two isomers are rapidly equilibrating at higher temperatures. Thus, it seemed highly desirable to control this
type of equilibrium to generate the best catalyst structure for the regio- and enantioselective asymmetric hydroformylation using chelating bidentate ligands.

\[ \text{ee} \xrightarrow{\text{L}''\text{Rh-CO} \leftrightarrow \text{OC}''\text{Rh-CO}} \text{ea} \]

Scheme 2.5 : Trigonal Bipyramidal Isomers of (PPh₃)₂Rh(CO)₂H.

Assuming that this equilibrium had a direct influence on the regioselectivity outcome, both Casey\textsuperscript{53} and van Leeuven\textsuperscript{54} studied the effect of steric and stereoelectronic tuning in bidentate phosphines on the ee : ea ratio and l : b ratio in the aldehyde product.

\[ \text{Bu}^- + \text{CO} + \text{H}_2 \xrightarrow{0.2 \text{ mol}\% \ [\text{Rh(acac})(\text{CO})_2]} 0.2 \text{ mol}\% \text{diphosphine} \xrightarrow{5 \text{ bar, } 34^\circ\text{C, } 1 \text{ h}} \text{Bu}^\cdot \text{CHO} + \text{Bu}^- \]

Scheme 2.6 : Casey and van Leeuven’s Studies on 1-Hexene.

A strong relationship was shown between the regioselectivity and the natural bite angle\textsuperscript{55} of the diphosphine as, in studies on 1-hexene, dppe (narrow bite angle of
85°; see p. 52 for structure) gave a 28 : 72 branched to linear ratio whereas BISBI (wide bite angle of 120°; see p. 52 for structure) gave a higher percentage (98.5%) of the linear aldehyde. Furthermore, dppe coordinated preferably in an equatorial-apical fashion whereas BISBI preferred a diequatorial coordination.\textsuperscript{53a}

![Figure 2.2: Natural Bite Angle.](image)

<table>
<thead>
<tr>
<th>Bidentate Ligand</th>
<th>Natural Bite Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>dppe</td>
<td>85°</td>
</tr>
<tr>
<td>dppp</td>
<td>91°</td>
</tr>
<tr>
<td>dppb</td>
<td>99°</td>
</tr>
<tr>
<td>dppm-cyh</td>
<td>90°</td>
</tr>
<tr>
<td>dppm-nor</td>
<td>97°</td>
</tr>
<tr>
<td>norphos</td>
<td>123°</td>
</tr>
<tr>
<td>1,2-dpp-benzene</td>
<td>83°</td>
</tr>
<tr>
<td>trixanphos</td>
<td>110°</td>
</tr>
<tr>
<td>BISBI</td>
<td>120°</td>
</tr>
<tr>
<td>BINAP</td>
<td>92°</td>
</tr>
<tr>
<td>Me-DuPhos</td>
<td>83°</td>
</tr>
<tr>
<td>DIOP</td>
<td>98°</td>
</tr>
</tbody>
</table>

Table 2.1: Natural Bite Angle of Selected Bidentate Ligands.
Substitution of the phenyl groups on the phosphorous atoms with electron-withdrawing 3,5-trifluoromethylphenyl groups resulted in a decrease of the linear ratio in the case of dppe while it increased the proportion of the linear aldehyde for BISBI.\textsuperscript{53b} Therefore, Casey and co-workers concluded that electron-withdrawing substituents on phosphines in the equatorial position gave high $l:b$ ratios, while electron-withdrawing substituents on phosphines in the apical position gave low $l:b$.

On the other hand, van Leeuwen insisted that the results of Casey’s study could not be described in terms of electronic effects only, since there were major steric differences between the ee and ea coordinating diphosphines. In an attempt to study the exact nature of the electronic effect in the hydroformylation reaction, van Leeuwen’s group synthesized a series of trixanphos ligands with varying basicities (see p. 52 for structure). In this series of ligands, steric differences were minimal so that purely electronic effects would be investigated.\textsuperscript{54}

van Leeuwen and co-workers reached the conclusion that the equilibrium between ee and ea in the (diphosphine)Rh(CO)$_2$H complex was indeed dependent on the phosphine basicity, as decreasing the phosphine basicity ($R = \text{CF}_3$) shifted the equilibrium to ee coordination. However and most remarkably, the $l:b$ ratio remained unchanged thus demonstrating that the electronic properties of the diphosphine ligand and their coordination mode did not influence the regioselectivity. In other words, in Casey’s research, the electronic groups had an effect on the bite angle of the phosphine which in turn had an effect on the regioselectivity.
In their discussion, van Leeuwen and co-workers suggested that a CO dissociation from both isomeric ee and ea five-coordinate (diphosphine)Rh(CO)$_2$H A complexes occurred to give the same four-coordinate (diphosphine)Rh(CO)H B in the hydroformylation cycle. The existence of such a coordinate had already been postulated by Wilkinson and co-workers.$^{52,55}$

The regioselectivity would then be controlled by the alkene attack on the four-coordinate complex via a square-pyramidal transition state H. Increasing the bite angle of the diphosphine in the four-coordinate intermediate would result in increased coordination volume around the rhodium center by the ligand, consequently creating more steric hindrance for the alkene entering the coordination sphere.

In spite of many detailed investigations, at this point it is not clear which factors are responsible for the differing selectivities with various ligands. Casey succinctly summarized the status of the current debate in a recent paper. He states$^{53b}$: "The regioselectivity of hydroformylation is governed by a complex web of electronic and steric effects that have so far defied unraveling."
Scheme 2.7: van Leeuven's Revised Mechanism.\textsuperscript{54a}

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2.1.2 D-Mannitol-Derived Phospholanes.

The carbohydrate chiral pool with its wide array of stereochemical and functional group diversity is a popular source of starting materials in organic synthesis and has recently attracted broad attention as ligand precursors for asymmetric catalysis. In previous work in Dr. RajanBabu’s group, carbohydrate-derived diarylphosphinite complexes of transition metals have been shown to catalyze a variety of carbon-carbon and carbon-hydrogen bond formation reactions such as hydrogenation, hydrovinylation or hydrocyanation.57-61

Dr. Yan in our group evaluated the ability of DIOP to function as a ligand in the Rh-catalyzed asymmetric hydrogenation of enamides.57c Under the reaction conditions, (RR)-DIOP gave 53.2%e.e. (S) of the hydrogenated product N-acetyl-1-phenylethylamine. The (SSSS)-dimethyl analog 71 (Table 2.2) was a poorer ligand giving only 20%e.e.. Removal of the two oxygen atoms from DIOP restored some of the selectivity as indicated by the 91%e.e. observed with 81. The (RSSR)-dimethyl analog 69 was one of the best ligands for the asymmetric reduction of an enamide, giving up to 98.4%e.e. Thus the chirality of the α-substituent was shown to be the control element in the reaction. Since 81 is a better ligand than 71, it is reasonable to assume that the cis-relationship of the dioxolane oxygens and the methyl groups in 71 contribute to unfavorable interactions in the diastereomeric complexes leading to the (S) product. No such interactions are present in the relevant intermediate leading to
the \((R)\) product from 69 (the dioxolane oxygens and the methyl groups are \textit{trans} to each other). Thus \((RR)-81\) and \((RSSR)-69\) give high selectivities for the \((R)\) product.

![Chemical structure](image)

\textbf{Scheme 2.8: Asymmetric Hydrogenation of Enamides using Modified DIOP Ligands.}

\begin{center}
\begin{tabular}{lc}
\hline
\textbf{Ligand L*} & \textbf{e.e.\% (config)} \\
\hline
(RR)-DIOP & 53.2 (S) \\
(SSSS)-71 & 20.4 (S) \\
(RR)-81 & 91.1 (R) \\
(RSSR)-69 & 98.4 (R) \\
\hline
\end{tabular}
\end{center}

\textit{a.} Determined by GC.

\textbf{Table 2.2: Asymmetric Hydrogenation of Enamides using Modified DIOP Ligands.}

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As the same remarkable results were observed in the Pd-catalyzed allylation reaction,\textsuperscript{60c} we had high hopes that our modified DIOP ligands would lead to improved enantioselectivities in the hydroformylation reaction.

Furthermore, the modular construction of these ligands renders them especially amenable to electronic and steric tuning. The polyhydroxylic nature of their deprotected derivatives makes them water-soluble. This provides an entry to biphasic chemistry, where starting material and product are contained in the organic phase while the catalyst is immobilized in the aqueous phase and available for reuse in subsequent cycles.
2.2 Preliminary Studies on the Asymmetric Hydroformylation Reaction.

2.2.1 Cationic Rhodium Catalyst.

Our preliminary studies on the hydroformylation of styrene were carried out using \((R,R)\)-DIOP as a chiral ligand in order to determine the optimum reaction conditions and the feasibility of using a cationic catalyst to run the reaction at mild gas pressure and temperature.
4 mol% Cat. / \text{L} \\
8 mol% \text{Et}_3\text{N} \\
\text{p}, \text{T}, \text{t} \\
\text{Ph} + \text{CO} + \text{H}_2 \\
\rightarrow \text{Ph} \text{CHO} \\
0.6 \text{ mmol} \\

Table 2.3 : Studies on Cationic Catalyst, Solvent and Molarity for Hydroformylation of Styrene using DIOP as Ligand.

A few trends were observed from this initial screening. Reactions ran at room temperature using preformed (entries 9 through 12) or \textit{in situ}-generated catalyst-ligand system (entries 1 to 3) were slow but showed high selectivity for the branched aldehyde. Increase of molarity and temperature (entries 4, 7 and 8) helped the reaction to go to completion although the regioselectivity dropped slightly. Increase of gas
pressure (entries 4 compared to 5, 9 to 10 and 11 to 12) did not reduce the reaction time and did not seem to have any real effect on the l : b ratio.

Therefore, our choice of reaction conditions were as follows: 3 bar, 40°C, 20 h in a Fisher-Porter tube. Those were the mildest conditions that would allow for completion of the reaction with good regioselectivity.

\[
\begin{align*}
\text{Ph} + \text{CO} + \text{H}_2 & \rightarrow \text{Ph} = \text{CHO} + \text{Ph} \text{CHO} \\
49 & \quad \text{0.6 mmol}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat. Loading</th>
<th>Conversion*</th>
<th>l : b$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>0.4 mol%</td>
<td>49%</td>
<td>34 : 66</td>
</tr>
<tr>
<td>14</td>
<td>1.0 mol%</td>
<td>50%</td>
<td>25 : 75</td>
</tr>
<tr>
<td>15</td>
<td>2.0 mol%</td>
<td>95%</td>
<td>37 : 63</td>
</tr>
<tr>
<td>7</td>
<td>4.0 mol%</td>
<td>99%</td>
<td>25 : 75</td>
</tr>
</tbody>
</table>

a. Conversion was determined by regular GC (see experimentals). b. linear : branched ratio was determined by GC and verified by $^1$H NMR (see experimentals).

Table 2.4 : Studies on the Catalyst Loading for Hydroformylation of Styrene using Cationic Catalyst.

As shown in Table 2.4, the catalyst loading could not be reduced in order to enable the reaction to go to completion. It was however noteworthy that the regioselectivity was not significantly influenced.
4 mol% [Rh\(^{\text{III}}\)(NBD)\(_2\)X]
4 mol% L / 8 mol% Et\(_3\)N
CH\(_2\)Cl\(_2\) (0.5 M)

\[
\text{Ph} + \text{CO} + \text{H}_2 \stackrel{p, T, t}{\longrightarrow} \text{PhCHO} + \text{Ph}
\]

0.6 mmol

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>L(^a)</th>
<th>p(^b)</th>
<th>T(^c)</th>
<th>t(^d)</th>
<th>Conv.(^e)</th>
<th>1 : b(^f)</th>
<th>%e.e.(^g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>BF(_4)^(-)</td>
<td>PPh(_3)</td>
<td>3 bar</td>
<td>40°C</td>
<td>20 h</td>
<td>100%</td>
<td>22 : 78</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>BF(_4)^(-)</td>
<td>(RR)-DIOP</td>
<td>3 bar</td>
<td>40°C</td>
<td>20 h</td>
<td>99%</td>
<td>25 : 75</td>
<td>0</td>
</tr>
<tr>
<td>17(^h)</td>
<td>BF(_4)^(-)</td>
<td>(RR)-DIOP</td>
<td>3 bar</td>
<td>40°C</td>
<td>20 h</td>
<td>100%</td>
<td>37 : 63</td>
<td>3 (R)</td>
</tr>
<tr>
<td>18</td>
<td>SbF(_6)^(-)</td>
<td>(RR)-DIOP</td>
<td>3 bar</td>
<td>30°C</td>
<td>20 h</td>
<td>73%</td>
<td>33 : 67</td>
<td>0</td>
</tr>
<tr>
<td>19</td>
<td>SbF(_6)^(-)</td>
<td>(RR)-DIOP</td>
<td>10 bar</td>
<td>22°C</td>
<td>2 h</td>
<td>3%</td>
<td>29 : 71</td>
<td>-</td>
</tr>
<tr>
<td>20</td>
<td>SbF(_6)^(-)</td>
<td>(RR)-DIOP</td>
<td>10 bar</td>
<td>50°C</td>
<td>2 h</td>
<td>99%</td>
<td>59 : 41</td>
<td>-</td>
</tr>
<tr>
<td>21</td>
<td>OT(_{\text{F}})^(-)</td>
<td>(RR)-DIOP</td>
<td>3 bar</td>
<td>40°C</td>
<td>20 h</td>
<td>100%</td>
<td>28 : 72</td>
<td>6 (S)</td>
</tr>
<tr>
<td>22(^h)</td>
<td>OT(_{\text{F}})^(-)</td>
<td>(RR)-DIOP</td>
<td>3 bar</td>
<td>40°C</td>
<td>20 h</td>
<td>100%</td>
<td>36 : 64</td>
<td>4 (R)</td>
</tr>
</tbody>
</table>

\(^a\) 4 mol% of diphosphines and 8 mol% of monophosphines. \(^b\) p = gas pressure (bar). For reactions at p ≤ 4 bar, hydroformylation were run in a Fisher-Porter tube; for reactions at p ≥ 10 bar, hydroformylations were run in a PARR reactor. \(^c\) T = temperature (°C). \(^d\) t = reaction time (h). \(^e\) Conversion was determined by regular GC (see experimentals). \(^f\) linear : branched ratio was determined by GC and verified by \(^1\)H NMR (see experimentals). \(^g\) The enantiomeric excess was determined by GC (Chirasil-L-Val) of the (-) menthyl ester of the corresponding acids. \(^h\) Reaction ran on a 2 mmol scale.

**Table 2.5**: Influence of the Counterion on the Hydroformylation of Styrene using Cationic Catalyst.

Finally, the influence of the counterion of the cationic catalyst was studied. As shown by entries 7, 18 and 21, it had little or no effect on the regioselectivity. Larger scale reactions afforded the same and therefore reliable results (entries 7 compared to 17 and 21 to 22). To reduce the reaction time, the pressure and the temperature were increased (entries 19 and 20) but resulted in reverse regioselectivity, where the linear aldehyde was then the major product. Finally, the enantiomeric excesses obtained from this last set of experiments were very low and the configurations obtained using (RR)-
DIOP were contradictory (entries 21 and 22 show opposite configurations and about 5% e.e.). We believe that the triethylamine, needed to activate the catalyst, racemized the branched aldehyde formed.

Therefore, despite the attractive mild reactions conditions used here (3 bar, 40°C, 20 h, Fisher-Porter tube), this route was not investigated any further.

2.2.2 Neutral Catalyst.

We then turned our efforts to neutral reaction conditions to avoid possible racemization of the chiral product. The [Rh(CO)₂(acac)] and [Rh(CO)₂Cl₂] catalysts are commonly used in conjunction with chelating phosphines at high pressure (above 10 bar) and temperature (>100°C) for the hydroformylation.⁶² Complete conversion of styrene using these harsh reaction conditions give the branched aldehyde as the major product in high yields.⁶²⁻⁶⁴ Enantioselectivity up to 94% e.e. were reported.⁶²⁶ However, Buchwald and co-workers ⁶²⁵ reported the hydroformylation of monosubstituted alkenes at 1 bar and a room temperature.

Our studies started with the hydroformylation of styrene with 0.5 mmol of [Rh(i-Bu-acac)(CO)₂] as the catalyst and (RR)-DIOP as the ligand.
0.5 mol% \([\text{Rh}(\text{r-Bu-acac})(\text{CO})_2]q \]

\[
\text{Ph} + \text{CO} + \text{H}_2 \xrightarrow{\text{p, } T, \text{t}} \text{PhCHO} + \text{Ph}
\]

0.6 mmol

<table>
<thead>
<tr>
<th>Entry</th>
<th>(L^a)</th>
<th>(p^b)</th>
<th>(T^c)</th>
<th>(t^d)</th>
<th>Conv.(^e)</th>
<th>(l: b^f)</th>
<th>%e.e.(^g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23(^h)</td>
<td>(RR)-DIOP</td>
<td>10 bar</td>
<td>80°C</td>
<td>1.5 h</td>
<td>100%</td>
<td>53 : 47</td>
<td>15 (R)</td>
</tr>
<tr>
<td>24(^i)</td>
<td>(RR)-DIOP</td>
<td>10 bar</td>
<td>80°C</td>
<td>1.5 h</td>
<td>100%</td>
<td>48 : 52</td>
<td>15 (R)</td>
</tr>
<tr>
<td>25</td>
<td>PPh(_3)</td>
<td>10 bar</td>
<td>80°C</td>
<td>1 h</td>
<td>100%</td>
<td>53 : 47</td>
<td>0</td>
</tr>
<tr>
<td>26</td>
<td>(RR)-DIOP</td>
<td>10 bar</td>
<td>80°C</td>
<td>1.5 h</td>
<td>100%</td>
<td>60 : 40</td>
<td>-</td>
</tr>
<tr>
<td>27</td>
<td>(RR)-DIOP</td>
<td>5 bar</td>
<td>80°C</td>
<td>1.5 h</td>
<td>100%</td>
<td>67 : 33</td>
<td>-</td>
</tr>
<tr>
<td>28</td>
<td>(RR)-DIOP</td>
<td>5 bar</td>
<td>60°C</td>
<td>1.5 h</td>
<td>99%</td>
<td>57 : 43</td>
<td>-</td>
</tr>
<tr>
<td>29</td>
<td>(RR)-DIOP</td>
<td>5 bar</td>
<td>30°C</td>
<td>1.5 h</td>
<td>95%</td>
<td>48 : 52</td>
<td>-</td>
</tr>
<tr>
<td>30</td>
<td>(RR)-DIOP</td>
<td>3 bar</td>
<td>22°C</td>
<td>3 h</td>
<td>1%</td>
<td>56 : 44</td>
<td>-</td>
</tr>
<tr>
<td>31</td>
<td>(RR)-DIOP</td>
<td>3 bar</td>
<td>30°C</td>
<td>1.5 h</td>
<td>99%</td>
<td>38 : 62</td>
<td>12 (R)</td>
</tr>
<tr>
<td>32(^i)</td>
<td>(RR)-DIOP</td>
<td>3 bar</td>
<td>40°C</td>
<td>2 h</td>
<td>10%</td>
<td>37 : 63</td>
<td>4 (R)</td>
</tr>
<tr>
<td>33(^i)</td>
<td>(RR)-DIOP</td>
<td>3 bar</td>
<td>40°C</td>
<td>20 h</td>
<td>35%</td>
<td>37 : 63</td>
<td>4 (R)</td>
</tr>
<tr>
<td>34(^k)</td>
<td>(RR)-DIOP</td>
<td>3 bar</td>
<td>40°C</td>
<td>20 h</td>
<td>99%</td>
<td>19 : 81</td>
<td>10 (R)</td>
</tr>
</tbody>
</table>

\(^a\) 0.75 mol% of diphosphines and 1.5 mol% of monophosphines. \(^b\) \(p = \) gas pressure (bar). For reactions at \(p \leq 4\) bar, hydroformylation were run in a Fisher-Porter tube; for reactions at \(p \geq 10\) bar, hydroformylations were run in a PARR reactor. \(^c\) \(T = \) temperature (°C). \(^d\) \(t = \) reaction time (h). \(^e\) Conversion was determined by regular GC (see experimentals). \(^f\) linear : branched ratio was determined by GC and verified by \(^1^\text{H} \) NMR (see experimentals). \(^g\) The enantiomeric excess was determined by GC (Chirasil-L-Val) of the (-) menthyl ester of the corresponding acids. \(^h\) Reaction ran using 5 mol% of catalyst and 7.5 mol% of phosphine. \(^i\) Reaction ran on a 12 mmol scale. \(^j\) Reaction ran on a 6 mmol scale. \(^k\) Reaction ran on a 2 mmol scale.

Table 2.6: Determination of Reaction Conditions for the Hydroformylation of Styrene using Neutral Catalyst.

Overall, mediocre regioselectivities were observed under harsh reaction conditions (10 bar, 80°C). Decrease of pressure and temperature (entries 26 to 31), seemed to favor the formation of the branched aldehyde. Both regio- and enantioselectivities obtained in entry 31 were comparable to those in the literature.\(^{53}\)
Indeed, Hayashi and coworkers reported the hydroformylation of styrene using (RR)-
DIOP (65 bar, 80°C) to give a 32 / 68 l : b ratio and 12% e.e. (R).

On a larger scale, under those mild conditions the reaction was observed
(entries 32 to 34) to slow down. Results of incomplete reactions were inconsistent
which seemed to indicate that the hydroformylation evolved in a non-linear fashion (i.e.
the branched to linear ratio and the enantioselectivity varied with the progress of the
reaction). The reactions therefore had to be pushed to completion for the consistency
of the discussion.

We also scanned the possible utility of DuPhos ligands for the hydroformylation
of styrene. Indeed, DuPhos ligands have a smaller bite angle than DIOP ligands
(DuPhos : 83°; DIOP : 98°) and are more basic. According to Casey and van
Leeuven's research, that should lead respectively to a better regioselectivity and
enantioselectivity.
0.5 mol% [Rh(\(\tau\)-Bu-acac)(CO)\(_2\)]

0.75 mol% Me-DuPhos

toluene (0.5 M) \(\rightarrow\) PhCHO

\[
\begin{align*}
0.6 \text{ mmol} \\
\text{Entry} & \quad p^a & T^b & t^c & \text{Conv.}^d & \text{l : b}^e & \%\text{e.e.}^f \\
35 & 3 \text{ bar} & 40^\circ \text{C} & 1.5 \text{ h} & 2\% & 24 : 76 & - \\
36 & 10 \text{ bar} & 60^\circ \text{C} & 1.5 \text{ h} & 50\% & 2 : 98 & 20 (R) \\
37 & 3 \text{ bar} & 60^\circ \text{C} & 20 \text{ h} & 99\% & 17 : 83 & 8 (S) \\
38 & 10 \text{ bar} & 60^\circ \text{C} & 20 \text{ h} & 97\% & 0.5 : 99.5 & - \\
39 & 10 \text{ bar} & 60^\circ \text{C} & 20 \text{ h} & 100\% & 8 : 92 & - \\
40 & 10 \text{ bar} & 60^\circ \text{C} & 3 \text{ h} & 99\% & 0.5 : 99.5 & - \\
41 & 40 \text{ bar} & 80^\circ \text{C} & 6 \text{ h} & 94\% & 15 : 85 & - \\
\end{align*}
\]

a. \(p = \) gas pressure (bar). For reactions at \(p \leq 4 \text{ bar}\), hydroformylation were run in a Fisher-Porter tube; for reactions at \(p \geq 10 \text{ bar}\), hydroformylations were run in a PARR reactor. b. \(T = \) temperature (\(^\circ\)C). c. \(t = \) reaction time (h). d. Conversion was determined by regular GC (see experimentals). e. linear : branched ratio was determined by GC and verified by \(^1\text{H} \) NMR (see experimentals). f. The enantiomeric excess was determined by GC (Chirasil-L-Val) of the (-) menthyl ester of the corresponding acids.

Table 2.7: Hydroformylation of Styrene with DuPhos Ligand.

Improved regioselectivities were observed (entries 38 and 40). We were however startled by the variations in regioselectivities and the even more by the opposite absolute configurations of the enantiomeric excesses observed in entries 36 and 37. Indeed, the \(^1\text{H} \) NMR clearly showed the presence of an unexpected compound as the major product, possibly obtained by reaction of the aldehydes 50 and 51, since the aldehydes were isolated in less than 10\% yield. After careful chromatography, the aldolisation product 52 was isolated and characterized.
Figure 2.3 : Aldolization Product in Hydroformylation of Styrene using DuPhos as Ligand.

The high basicity of the DuPhos ligand most probably caused this aldol reaction (no aldolisation was noted using DIOP as a ligand). Our preliminary studies therefore prompted us to restrict our research to DIOP-like ligands in our library.
2.3 Phospholanes Synthesis.

Initial investigations by Dr. Yan in our group showed that the monoprotected tetraol 53 could be a key intermediate in the synthetic plans. Depending on the specific sequence of reactions that followed, two diastereomeric bis-epoxide 54 and 59 could be prepared. These epoxides were further elaborated into diols 55-58 and 60-63 by hydride- or copper-mediated ring-opening. A variety of 1,4-diols could thus easily be synthesized. bis-Epoxide 54 led to (RRRR)-diols while 59 afforded (SRRS)-diols.
Each diol was transformed separately into a number of DIOP-like ligands via the intermediate dimesylates. Dr. Yan reacted those versatile dimesylates with various phosphide reagents to give phospholanes which were purified by column chromatography in an inert atmosphere. We were unfortunately unable to isolate the phospholanes bearing long-chain substituents at C₁ and C₄ cleanly with the same
technique. For example, diphosphine 65 was too apolar (Rf > 0.9 in hexane) to separate from remaining unreacted HPPh₂ (Scheme 2.10).

\[
\begin{align*}
\text{57} & \xrightarrow{a} \text{64} & \text{b} \xrightarrow{} \text{65} \\
\text{a. MsCl, pyr., 0°C, 66%} & \text{ b. LiPPh₂, rt.}
\end{align*}
\]

Scheme 2.10 : Phospholanes Synthesis.

In the case of dibenzyl-substituted dimesylate 66, attempt to synthesize the corresponding phospholane, by displacement of the leaving groups using LiPPh₂ prepared \textit{in-situ}, led to an inseparable mixture of products, tentatively identified as mono- and dielimination products 67 and 68 (Scheme 2.11).

\[
\begin{align*}
\text{66} & \xrightarrow{a} \text{67} + \text{68} \\
\text{a. LiPPh₂, rt.}
\end{align*}
\]

Scheme 2.11 : Elimination Products from 66.
In summary, I had in hand the following library of functionalized bis-phospholanes for the study of the asymmetric hydroformylation reaction.

![Figure 2.4: Ligand Library for the Asymmetric Hydroformylation Studies.](image-url)
2.4 Studies on the Asymmetric Hydroformylation Reaction.

2.4.1 Studies on Styrene.

Styrene and its derivatives have been most intensively studied as substrates for the asymmetric hydroformylation because of their high reactivity and high selectivity for yielding branched aldehydes. Furthermore, aldehydes derived from these olefins can be converted to various pharmaceuticals such as non-steroidal antiinflammatory agents. For example, the well-known drug (S)-Ibuprofen can synthesized from the branched aldehyde 51. A successful regio- and enantioselective hydroformylation on 4-isobutylstyrene would make the synthesis of ibuprofen an expedient and environment-friendly process. Our ligand library was tested for the hydroformylation of styrene first using the reaction conditions determined earlier (3 bar pressure of H$_2$ / CO gas, 40°C and 20 h).

![Figure 2.5: (S)-Ibuprofen.](image-url)

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0.5 mol% [Rh(t-Bu-acac)(CO)₂]

0.75 mol% L

toluene (0.5 M)

\[
\begin{array}{c}
\text{Ph} + \text{CO} + \text{H}_2 \xrightarrow{\text{p, T, t}} \text{PhCHO} + \text{Ph} \\
\text{49} \\
\text{50 (l)} \\
\text{51 (b)}
\end{array}
\]

0.6 mmol

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<thead>
<tr>
<th>Entry</th>
<th>L</th>
<th>p(^a)</th>
<th>T(^b)</th>
<th>t(^c)</th>
<th>Conv.(^d)</th>
<th>Yield</th>
<th>l : b(^e)</th>
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<td>69</td>
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<td>40°C</td>
<td>20 h</td>
<td>100%</td>
<td>100%</td>
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</tr>
<tr>
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<td>3 h</td>
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<td>100%</td>
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</tr>
<tr>
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<td>1%</td>
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<td>-</td>
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<td>7 : 93</td>
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<td>40%</td>
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<td>36 : 64</td>
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<td>20 h</td>
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<td>8 : 92</td>
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<td>3 h</td>
<td>100%</td>
<td>100%</td>
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<td>100%</td>
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<td>57(^f)</td>
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<td>3 bar</td>
<td>40°C</td>
<td>3 h</td>
<td>100%</td>
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<td>10 bar</td>
<td>60°C</td>
<td>3 h</td>
<td>60%</td>
<td>-</td>
<td>45 : 55</td>
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\(^{a}\) p = gas pressure (bar). For reactions at p ≤ 4 bar, hydroformylation were run in a Fisher-Porter tube; for reactions at p > 10 bar, hydroformylations were run in a PARR reactor. \(^{b}\) T = temperature (°C). \(^{c}\) t = reaction time (h). \(^{d}\) Conversion was determined by regular GC (see experimentals). \(^{e}\) Linear : branched ratio was determined by GC and verified by \(^1\)H NMR (see experimentals). \(^{f}\) Reaction ran using 2 mol% of diphosphine so that ligand / catalyst = 4.

Table 2.8: Determination of Optimal Reaction Conditions for Hydroformylation of Styrene using DIOP-Derived Ligands.

In all cases except for 69, our ligands required slightly higher pressure and temperature than DIOP in order for the reaction to go to completion. This was probably due to steric effects created by the presence of substituents at C₁ and C₄.
Furthermore, 69 seemed to form a more active complex with the rhodium catalyst compared to its diastereoisomer 71 (see entries 42 compared to 51 and 48 to 51) as the reaction was much faster using 69. A simple explanation would start with a possible ground state conformation of the HRh(CO)(L*) complex.57c The methyl groups in (RSSR)-69 are in quasi-equatorial orientation and reinforce one stable ground state conformation of the corresponding precatalyst. In (SSSS)-71, the quasi-axial orientation of the two methyl groups destabilize this conformation, apparently requiring a distortion of the ligand to minimize the steric interaction as 71 coordinates to the rhodium metal (Figure 2.6). This distortion would understandably be energy-demanding and harsher pressure and temperature conditions are needed for the reaction to proceed to completion.

Substitution at C₁ and C₄ improved the selectivity of the process (entries 31 to 42). This substitution most probably forced the phenyl groups into a conformation that would favor the approach of the alkene to the rhodium complex to produce mainly the branched aldehyde.
Finally, harsher reaction conditions had a dramatic effect on the regioselectivity. As for DIOP, higher pressure and temperature disfavored the formation of the branched aldehyde. However, as mentionned before results obtained for reaction that did not go to completion were unreliable. As a consequence of this non-linear effect, the full study of the hydroformylation reaction on styrene using our DIOP derivatives was conducted under 10 bar of gas pressure at 60°C for 3 hours.
0.5 mol% [Rh(t-Bu-acac)(CO)$_2$] + CO + H$_2$ → 0.75 mol% L toluene (0.5 M) 10 bar, 60°C, 3 h

0.6 mmol

<table>
<thead>
<tr>
<th>Entry</th>
<th>L</th>
<th>Yield</th>
<th>l : b</th>
<th>%e.e.</th>
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</thead>
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<td>60 : 40</td>
<td>15 (R)</td>
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<td>27 : 73</td>
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</tr>
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<td>45</td>
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<td>60</td>
<td>78</td>
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<td>50 : 50</td>
<td>6 (R)</td>
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<td>48 : 52</td>
<td>0</td>
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<td>61</td>
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<td>79</td>
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<td>6 (R)</td>
</tr>
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<td>66</td>
<td>80</td>
<td>100%</td>
<td>38 : 62</td>
<td>5 (R)</td>
</tr>
<tr>
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<td>83</td>
<td>100%</td>
<td>45 : 55</td>
<td>10 (R)</td>
</tr>
<tr>
<td>68</td>
<td>84</td>
<td>100%</td>
<td>42 : 58</td>
<td>9 (R)</td>
</tr>
<tr>
<td>69</td>
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<td>100%</td>
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<td>70</td>
<td>86</td>
<td>100%</td>
<td>52 : 48</td>
<td>0</td>
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a. Except for entry 57, all reactions went to completion. b. linear : branched ratio was determined by GC and verified by $^1$H NMR (see experimentals). c. The enantiomeric excess was determined by GC (Chirasil-L-Val) of the (+) menthyl ester of the corresponding acids.

Table 2.9 : Hydroformylation of Styrene using DIOP-Derived Ligands.

At higher gas pressure and temperature, the type of substitution at C$_1$ and C$_4$ (entries 45, 59, 44, 61) seemed of little importance to the regioselectivity as the l : b

80

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ratio remained relatively constant (about 60% of the branched aldehyde). There was a complete loss of selectivity using those harsh reaction conditions.

Removal of the isopropylidene group using ligand 84 resulted in a clear improvement on the regioselectivity (entry 54 showed a 27 : 73 linear to branched ratio). Apparently, the methyl groups at C\textsubscript{1} and C\textsubscript{4}, relieved of the hindrance and lock of the C\textsubscript{2}-C\textsubscript{3} bond, positionned the phenyl groups of dppb in a conformation for maximum selectivity.

Electronic tuning of the phosphorous phenyl groups led to remarkable observations. Introduction of electron-withdrawing trifluoromethyl groups or inductive electron-donating methyl groups in \textit{meta} had no effect on the regioselectivity as the l : b ratios remained around 40 : 60 (entries 63 and 64). However, when a methoxy group (strongly electron-donating by resonance) was placed in \textit{para}, it resulted in a dramatic reversal of regioselectivity as the linear aldehyde was produced in a 71% proportion (entry 62).

The mixture of aldehydes was oxidized with potassium permanganate and combined with (-)-menthol. The menthyl esters were analyzed by chiral GC to determine the enantiomeric excesses. Unfortunately, none of our DIOP-derivatives gave any noticable enantioselectivity.
2.4.2 Studies on Vinyl Naphthalene.

Naproxen is another valuable non-steroidal antiinflammatory agent that one could envision to synthesize by hydroformylation of 6-methoxy-2-vinylnaphthalene followed by oxidation. A viable process has however not yet emerged and industrial production of the drug involving a classical resolution of a mixture of the acids is still largely preferred. Here again we tested our ligands for the hydroformylation of unsubstituted vinyl naphthalene, as a model for the requisite aldehyde precursor.

Figure 2.7: (S)-Naproxen.

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0.5 mol% $[\text{Rh}(\text{-Bu-acac})(\text{CO})_2]$ L / toluene p, T, t

\[
\begin{align*}
\text{Naphth} & \quad + \text{CO} + \text{H}_2 \quad \text{Naphth} \quad + \text{CHO} \\
\text{p, T, t} & \quad \text{p, T, t} \\
87 & \quad 88 \ (\text{l}) \quad 89 \ (\text{b})
\end{align*}
\]

0.6 mmol

<table>
<thead>
<tr>
<th>Entry</th>
<th>$L^a$</th>
<th>$M$</th>
<th>$p^b$</th>
<th>$T^c$</th>
<th>$t^d$</th>
<th>Conv.$^e$</th>
<th>Yield</th>
<th>l : b$^f$</th>
<th>%e.e.$^g$</th>
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<td>60%</td>
<td>-</td>
<td>42 : 58</td>
<td>-</td>
</tr>
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<td>72</td>
<td>(RR)-DIOP</td>
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<td>3 bar</td>
<td>40°C</td>
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<td>91%</td>
<td>45%</td>
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<td>89 (S)</td>
</tr>
<tr>
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<td>(RR)-DIOP</td>
<td>0.5</td>
<td>3 bar</td>
<td>60°C</td>
<td>20 h</td>
<td>94%</td>
<td>54%</td>
<td>55 : 45</td>
<td>91 (S)</td>
</tr>
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<td>3 bar</td>
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<td>20 h</td>
<td>100%</td>
<td>100%</td>
<td>36 : 64</td>
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<tr>
<td>75$^h$</td>
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<td>100%</td>
<td>17 : 83</td>
<td>5 (S)</td>
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<td>60°C</td>
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<td>20 h</td>
<td>100%</td>
<td>100%</td>
<td>15 : 85</td>
<td>13 (S)</td>
</tr>
</tbody>
</table>

a. 0.75 mol% diphosphine or 1.5 mol% monophosphine. b. $p =$ gas pressure (bar). For reactions at $p \leq 4$ bar, hydroformylation were run in a Fisher-Porter tube; for reactions at $p \geq 10$ bar, hydroformylations were run in a PARR reactor. c. $T =$ temperature (°C). d. $t =$ reaction time (h). e. Conversion was determined by regular GC (see experimentals). f. linear : branched ratio was determined by GC and verified by $^1H$ NMR (see experimentals). g. The enantiomeric excess was determined by GC (Chirasil-L-Val) of the (-) menthyl ester of the corresponding acids. h. Reaction ran on 1.5 mmol scale.

Table 2.10 : Hydroformylation of Vinyl Naphthalene.

Increase of the bulk and electron density of the aromatic ring caused by the naphthalene ring instead of a benzene ring had apparently little consequence on the regioselectivity. Overall, the trends were similar to those described for the hydroformylation of styrene. Increasing the concentration of the reaction mixture to
2 M in toluene enabled the hydroformylation to be run at 3 bar and 40°C (entries 71 to 74). Indeed, milder reaction conditions were preferable as they gave better regioselectivities (entry 77 vs. 78 and 80 vs. 82). Only regio-and enantioselectivities of completed reactions were reliable and reproducible (entries 74, 80 and 84).

The enantioselectivity obtained using DIOP was remarkable. Indeed, the hydroformylation of vinyl naphthalene was completed using 3 bar of gas pressure, at 40°C for 20 h and gave 64% of the branched aldehyde in 77%e.e. (entry 74). To the best of our knowledge, the hydroformylation of vinyl naphthalene using DIOP has never been published. The figures given here are nevertheless real and reliable as completed reactions were repeated with the same success.

![Figure 2.8: GC Trace of the Diastereomeric Mixture of the (-)-Menthyl Esters Derived from the Branched Aldehyde 89 (entry 83).](image)

Figure 2.8: GC Trace of the Diastereomeric Mixture of the (-)-Menthyl Esters Derived from the Branched Aldehyde 89 (entry 83).

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2.4.3 Studies on Vinyl Acetate.

Asymmetric hydroformylation of functionalized alkenes can serve as useful method for the syntheses of polyfunctionalized intermediates to biologically active compounds. In particular, reaction of vinyl acetate gives 2-acetoxypropanal accompanied by small amounts of 3-acetoxypropanal. 2-Acetoxypropanal can be readily converted to lactic acid derivatives\textsuperscript{65a} that have been attracting interest as a monomer of biodegradable or bioabsorbable polymers.\textsuperscript{65b} 2-Acetoxypropanal can also be regarded as a precursor of optically active synthetic building blocks such as 1,2-propanediol.
0.3 mol% [Rh(t-Bu-acac)(CO)₂]

\[
\text{AcO}^\rightarrow + \text{CO} + \text{H}_2 \xrightarrow{\text{L} / \text{toluene}} \xrightarrow{3 \text{ bar}, 40^\circ\text{C}, 20 \text{ h}} \text{AcO}^\rightarrow \xrightarrow{\text{CHO}} \xrightarrow{\text{CHO}}
\]

0.6 mmol

<table>
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<tr>
<th>Entry</th>
<th>L (^a)</th>
<th>M</th>
<th>Conv. (^b)</th>
<th>l : b (^c)</th>
<th>%e.e. (^d)</th>
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<tr>
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<td>PPh₃</td>
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<tr>
<td>89</td>
<td>(RR)-DIOP</td>
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<td>3%</td>
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<tr>
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<td>17 : 83</td>
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<tr>
<td>91</td>
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<td>94</td>
<td>71</td>
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<td>100%</td>
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<td>4 : 96</td>
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<td>3 : 97</td>
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<td>102</td>
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<td>5 : 95</td>
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<tr>
<td>103</td>
<td>76</td>
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<td>100%</td>
<td>3 : 97</td>
<td>14 (S)</td>
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<td>104</td>
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<td>14 (S)</td>
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<td>105</td>
<td>78</td>
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<td>100%</td>
<td>9 : 91</td>
<td>24 (S)</td>
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<tr>
<td>106</td>
<td>83</td>
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<td>107</td>
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<td>4 : 96</td>
<td>14 (S)</td>
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<tr>
<td>108</td>
<td>85</td>
<td>2</td>
<td>100%</td>
<td>11 : 89</td>
<td>42 (S)</td>
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</tbody>
</table>

\(a\) 0.75 mol% diphosphine or 1.5 mol% monophosphine  
\(b\) Conversion was determined by regular GC (see experimentals).  
\(c\) linear : branched ratio was determined by GC and verified by \(^1\)H NMR (see experimentals).  
\(d\) The enantiomeric excess was determined by GC (Cyclodex-B) and the absolute configuration was assigned by comparison of the sample's optical purity to that of the literature.\(^4\)

Table 2.11: Hydroformylation of Vinyl Acetate.
Our preliminary studies with PPh₃ and DIOP showed that the hydroformylation of vinyl acetate could be conducted under 3 bar of gas pressure and at 40°C for 20 h at a 2 M concentration in toluene. Entry 92 (Table 2.11, p. 86 was repeated several times and ensures the reliability of this study as the regio- and stereoselectivities are the same than those found in the literature.⁶⁴

All our DIOP-derived ligands led to enhanced regioselectivity compared to DIOP itself. Indeed, where (RR)-DIOP gave a 14 : 86 linear to branched ratio, our ligands resulted in 1 : b ratios of 4 : 96 (entry 92 vs entries 93, 94 and 97 to 104). Surprisingly, ligand 75, bearing electron-donating groups on the aryl rings attached to the phosphorous atoms, did not reverse the regioselectivity as it had in the case of styrene (entry 102). As a comparison, Nozaki’s hydroformylation of vinyl acetate with BINAPHOS gave the branched aldehyde in 86% ratio and 92% e.e. (see Scheme 2.2, p.65).⁴⁸

From a stereochemical point of view, the absolute configuration at C₁ and C₄ seemed critical as (1R,4R)-diphosphines almost all led to racemized 92 (entries 93, 95, 97 and 102). On the other hand, diphosphinites with the (1R,4R) absolute stereochemistry led to better and opposite enantioselectivities, 30% e.e. (S), than the 15% e.e. (R) of their (1S,4S) diastereoisomers (entry 98 vs. 99 and 100 vs. 101). However, except for ligand 85 (entry 108), the enantiomeric excesses obtained were consistently lower than the 40% e.e. using DIOP.
2.4.4 Early Studies on Vinyl Phthalimide.

Vinyl phthalimide was another substrate of interest as the branched aldehyde 95 is considered a valuable entry into optically active amino acids. Oxidation of the branched aldehyde and deprotection of the amino group leads to alanine.

![Chemical reaction diagram]

0.5 mol% \([\text{Rh}(t-\text{Bu-acac})(\text{CO})_2] \]

\[ \text{Phth} + \text{CO} + \text{H}_2 \xrightarrow{\text{p, T, t}} \text{Phth} + \text{Phth} \]

<table>
<thead>
<tr>
<th>Entry</th>
<th>(L^a)</th>
<th>(M)</th>
<th>(p^b) (bar)</th>
<th>(T^c) (°C)</th>
<th>(t^d) (h)</th>
<th>(\text{Conv.}^e)</th>
<th>Yield</th>
<th>(l : b^f)</th>
<th>%e.e.(^g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>109</td>
<td>(\text{PPh}_3)</td>
<td>0.5</td>
<td>3</td>
<td>40</td>
<td>20</td>
<td>98%</td>
<td>93%</td>
<td>6 : 94</td>
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<tr>
<td>110</td>
<td>(\text{PPh}_3)</td>
<td>0.5</td>
<td>3</td>
<td>40</td>
<td>2</td>
<td>23%</td>
<td>-</td>
<td>6 : 94</td>
<td>-</td>
</tr>
<tr>
<td>111</td>
<td>((RR))-DIOP</td>
<td>0.5</td>
<td>3</td>
<td>40</td>
<td>20</td>
<td>20%</td>
<td>-</td>
<td>10 : 90</td>
<td>-</td>
</tr>
<tr>
<td>112</td>
<td>((RR))-DIOP</td>
<td>0.5</td>
<td>3</td>
<td>40</td>
<td>20</td>
<td>26%</td>
<td>-</td>
<td>8 : 92</td>
<td>-</td>
</tr>
<tr>
<td>113</td>
<td>((RR))-DIOP</td>
<td>0.5</td>
<td>3</td>
<td>60</td>
<td>20</td>
<td>63%</td>
<td>-</td>
<td>12 : 88</td>
<td>-</td>
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<tr>
<td>114</td>
<td>((RR))-DIOP</td>
<td>0.5</td>
<td>3</td>
<td>60</td>
<td>2</td>
<td>40%</td>
<td>-</td>
<td>14 : 86</td>
<td>-</td>
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<tr>
<td>115</td>
<td>((RR))-DIOP</td>
<td>2</td>
<td>3</td>
<td>40</td>
<td>20</td>
<td>56%</td>
<td>-</td>
<td>12 : 88</td>
<td>2</td>
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<tr>
<td>116</td>
<td>((RR))-DIOP</td>
<td>2</td>
<td>3</td>
<td>60</td>
<td>20</td>
<td>99%</td>
<td>99%</td>
<td>14 : 86</td>
<td>2</td>
</tr>
</tbody>
</table>

\(a\) 0.75 mol% diphosphine or 1.5 mol% monophosphine. \(b\) \(p\) = gas pressure (bar). For reactions at \(p \leq 4\) bar, hydroformylation were run in a Fisher-Porter tube; for reactions at \(p \geq 10\) bar, hydroformylations were run in a PARR reactor. \(c\) \(T\) = temperature (°C). \(d\) \(t\) = reaction time (h). \(e\) Conversion was determined by regular GC (see experimentals). \(f\) linear : branched ratio was determined by GC and verified by \(^1\text{H} NMR\) (see experimentals). \(g\) The enantiomeric excess was determined by GC (Chirasil-L-Val) of the (-) menthyl ester of the corresponding acids.

Table 2.12: Hydroformylation of Vinyl Phthalimide.

Our preliminary studies on vinyl phthalimide have shown a remarkable regioselectivity in favor of the desired branched aldehyde 95. Using \((R,R)\)-DIOP, the
hydroformylation proceeded to completion at a 2 M concentration in toluene under 3 bar of gas pressure at 60°C and led to a 14 : 86 linear to branched ratio (entry 116). However, the enantioselectivities obtained were practically zero. As a comparison, Nozaki’s hydroformylation of vinyl phthalimide using BINAPHOS at 100 bar, 60°C for 40 h gave the branched aldehyde 95 in 89% ratio and 85% e.e. (Scheme 2.2, p. 65).

Considering the trends observed for styrene, vinyl naphthalene and vinyl acetate, our studies on the hydroformylation of vinyl phthalimide were not carried further.
2.5 Conclusion.

In summary, we have shown, as others before us, that lower pressure and temperature are not only sufficient for the hydroformylation to go to completion but also ensure a better regioselectivity.

Testing our ligands, we discovered that substitution on DIOP ligand at C₁ and C₄ led to an enhanced regioselectivity. However, the type of steric substitution or introduction of electron-withdrawing groups on the aryl rings on the phosphorus atoms had little or no influence on the regioselectivity. Only in the case of styrene, electron-donating groups had a drastic effect as it completely reversed the regioselectivity in favor of the linear aldehyde.

The fact that the (SSSS)-modified-DIOP ligands required harsher pressure and temperature than the corresponding (RSSR) diastereoisomers clearly indicated that a distortion was needed for ligands with the (SSSS) configuration to coordinate to the rhodium center, or such substitution entailed more energetic reorganizations of the ligands in the catalytic cycle.

As removal of the isopropylidene ring on our ligands led to increased regioselectivity, we believe that the lack of flexibility at the C₂-C₃ bond to be responsible for the absence of real breakthrough in our studies.
2.6 Experimental Section.

**General Methods.** Reactions were carried out in oven- or flame-dried glassware under a nitrogen atmosphere, unless otherwise noted. All solvents used were reagent grade. Diethyl ether, hexanes and tetrahydrofuran (THF) were freshly distilled from sodium/benzophenone. Dichloromethane and toluene were freshly distilled from calcium hydride. Triethylamine was distilled from calcium hydride and stored over potassium hydroxide. Pyridine was distilled and stored over potassium hydroxide. Acetone was dried over 4 Å molecular sieves for 2 hours prior to use. Except as otherwise indicated, all reactions were magnetically stirred and monitored by thin layer chromatography on E. Merck precoated (0.25 mm) silica gel 60 F$_{254}$ plates. Flash chromatography was conducted by using silica gel 40 (Scientific Adsorbents Incorporated, Microns Flash). Chiral gas chromatographic separations were accomplished using Chirasil L-Val on WCOT fused silica (25 m x 0.25 mm, 0.12 μm film thickness) capillary GC column purchased from Chromapack (column A). Other gas chromatographic (GC) analyses were performed on a HP-ultra-1 crosslinked methyl silicone capillary column (25 m length x 0.2 mm i.d) (column B) or on Cyclodex B (column C). Yields, unless otherwise stated, refer to chromatographically and spectroscopically pure compounds. Melting points were determined on a Thomas Hoover uni-melt apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 series FTIR. $^1$H, $^{19}$F and $^{13}$C NMR spectra were recorded on a Bruker Aspect 200, 250, 400 or 500 MHz spectrometer. Chemical shift are reported
relative to chloroform as standard at δ = 7.26 for 1H and δ = 77.0 for 13C. Coupling constants are reported in Hertz (Hz). Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. High-resolution mass spectra for 57, 67 and 68 were recorded on the Micromas QTOF Electrospray mass spectrometer. Compounds for which exact mass is reported exhibited no significant m/z greater than the one of the parent peak.

![Chemical Structure](image)

**General procedure for the copper-mediated epoxide ring opening.**

To magnesium turnings (235 mg, 9.67 mmol, 3 equiv.) in 5 mL of THF was added aryl bromide (9.98 mmol, 3.1 equiv.) in 5 mL of THF. The resulting mixture was stirred for 30 minutes and then cuprous iodide (190 mg, 0.99 mmol, 0.3 equiv) was added and the mixture cooled to -30°C. A solution of the bis-epoxide (600 mg, 3.22 mmol) in 2 mL of THF was then added dropwise. After the addition was complete, the mixture was stirred for 3h and then quenched by being poured into 10 mL of cold saturated aqueous ammonium chloride solution. The solution was extracted with ether and the organic layers were combined, dried, and concentrated to afford a compound that was purified by column chromatography (hexane / EtOAc 5/1).
1,6-Dideoxy-1,6-diphenyl-3,4-\(\beta\)-isopropylidene-D-mannitol (56). 90% yield. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.22 (m, 10 H), 3.78 (m, 2 H), 3.65 (m, 4 H), 3.07 (d, \(J = 13.5\), 2 H), 2.64 (dd, \(J = 13.9\), 7.1, 2 H), 1.44 (s, 6 H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 137.8, 129.6, 128.2, 126.1, 108.8, 82.2, 73.3, 40.1, 26.8; IR (neat): 1496, 1454, 1380 cm\(^{-1}\). [ID-III-10]

1,6-Dideoxy-1,6-diphenyl-3,4-\(\beta\)-isopropylidene-D-iditol (61). 89% yield. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.26 (m, 10 H), 4.04 (m, 2 H), 3.74 (m, 2 H), 2.86 (dd, \(J = 13.7\), 8.4, 2 H), 2.78 (dd, \(J = 13.8\), 5.5, 2 H), 2.11 (d, \(J = 8.1\), 2 H), 1.49 (s, 6 H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 137.9, 129.2, 128.5, 126.5, 109.4, 78.7, 71.0, 41.2, 27.2; IR (neat): 1371 cm\(^{-1}\); [\(\alpha\)]\(_D\)\(^{23}\) +23\(^\circ\) (c 3.3, CHCl\(_3\)). [ID-III-10]
1,6-Dideoxy-1,6-diheptyl-3,4-O-isopropylidene-D-mannitol (57). 90% yield. m. p. 48-50°C; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 3.74 (s, 2 H), 3.62 (m, 2 H), 3.54 (m, 2 H), 1.72 (m, 2 H), 1.49 (m, 2 H), 1.36 (s, 6 H), 1.27 (m, 20 H), 0.85 (t, $J$ = 6.4, 6 H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 108.7, 83.2, 73.2, 34.2, 31.9, 29.6, 29.3, 26.9, 25.2, 22.6, 14.1; IR (CHCl$_3$): 1521, 1466, 1381, 1372 cm$^{-1}$; $\lbrack \alpha \rbrack_D^{23} +21^{\circ}$ (c 3.2, CHCl$_3$); Anal. found (calcd): C 70.34, (69.91); H 11.81, (11.78); HRMS calcd for C$_{19}$H$_{22}$N$_2$O$_4$Na: M$^{+}$ = 397.1198, found 397.1183. [ID-III-11]

1,6-Dideoxy-1,6-diheptyl-3,4-O-isopropylidene-D-iditol (62). 65% yield of an oil. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 3.81 (m, 2 H), 3.40 (m, 2 H), 2.36 (bs, 2 H), 1.42 (m, 4 H), 1.33 (s, 6 H), 1.19 (m, 20 H), 0.79 (t, $J$ = 6.6, 6 H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 108.9, 79.8, 70.0, 34.6, 31.7, 29.4, 29.1, 27.1, 25.7, 22.5, 13.9; IR (neat): 1462, 1379, 1217 cm$^{-1}$; $\lbrack \alpha \rbrack_D^{23} -1.3^{\circ}$ (c 9.2, CHCl$_3$). [ID-III-23]
1,6-Dideoxy-1,6-diundecyl-3,4-O-isopropylidene-D-mannitol (58). 91% yield. m.p. 67-70°C; \(^{1}\text{H} \text{NMR (CDCl}_3, 400 \text{ MHz):} \delta 4.10 \text{(bs, 2 H), 3.61 (m, 2 H), 3.51 (m, 2 H), 1.72 (m, 2 H), 1.33 (s, 6 H), 1.23 (m, 36 H), 0.85 (t, J = 6.6, 6 H);}^{13}\text{C NMR (CDCl}_3, 100 \text{ MHz):} \delta 108.7, 83.2, 73.2, 34.3, 31.9, 29.7, 29.6, 29.4, 26.9, 25.2, 22.7, 14.1; \text{IR (CHCl}_3): 1466, 1372 \text{ cm}^{-1}; [\alpha]_D^{23} +11^\circ (c 1.7, \text{CHCl}_3). [\text{ID-III-12]}

1,6-Dideoxy-1,6-diundecyl-3,4-O-isopropylidene-D-iditol (63). 54% yield. \(^{1}\text{H} \text{NMR (CDCl}_3, 400 \text{ MHz):} \delta 3.81 \text{(sm, 2 H), 3.40 (d, J = 7.6, 2 H), 2.36 (sm, 2 H), 1.38 (m, 8 H), 1.32 (s, 6 H), 1.17 (m, 32 H), 0.79 (t, J = 6.6, 6 H);}^{13}\text{C NMR (CDCl}_3, 100 \text{ MHz):} \delta 108.9, 79.8, 69.9, 34.6, 31.8, 29.5, 29.4, 29.2, 27.1, 25.7, 22.5, 13.9; \text{IR (neat):} 1466, 1379, 1216 \text{ cm}^{-1}; [\alpha]_D^{23} +1^\circ (c 7.2, \text{CHCl}_3); \text{Anal. found (calcd):} \text{C 73.87, (73.99); H 12.11, (12.42). [ID-III-12]}

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General procedure for the mesylation of diols.

To a solution of the diol (0.53 mmol) in 3 mL pyridine was added methanesulfonyl chloride (228 μL, 2.94 mmol, 5.5 equiv.). The mixture was stirred at 0°C for 2 hours and kept in the refrigerator overnight. The mixture was poured into 10 mL of ice-cold water and extracted with CH₂Cl₂ (3 x 10 mL). The combined extracts were successively washed with 10 mL each of 3 N HCl and saturated NaCl solution and dried with anhydrous magnesium sulfate. Removal of the solvent on the rotatory evaporator gave the crude product which was purified by chromatography (eluant: hexane / ethyl acetate 3/1).

1,6-Dideoxy-1,6-diphenyl-3,4-O-isopropylidene-D-mannitol

Dimethylsulfonate (66). 78% yield. ¹H NMR (CDCl₃, 400 MHz): δ 7.27 (m, 10 H), 4.88 (m, 2 H), 4.26 (m, 2 H), 3.14 (dd, J = 14.7, 3.4, 2 H), 3.03 (dd, J = 14.8, 8.6, 2
H), 2.33 (s, 6 H), 1.50 (s, 6 H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 135.9, 129.9, 128.5, 127.1, 111.4, 82.7, 78.7, 37.5, 36.2, 27.1. [ID-III-16]

\[
\begin{align*}
\text{1,6-Dideoxy-1,6-diphenyl-3,4-O-isopropylidene-D-iditol} \\
\text{Dimethylsulfonate. 58% yield.} \\
\text{$^1$H NMR (CDCl}_3, 400 MHz): \delta 7.28 (m, 10 H), 4.99 (dd, J = 10.2, 3.9, 2 H), 4.17 (s, 2 H), 3.17 (dd, J = 14.3, 10.2, 2 H), 3.07 (dd, J = 14.2, 3.9, 2 H), 2.16 (s, 6 H), 1.49 (s, 6 H); \text{ $^{13}$C NMR (CDCl}_3, 100 MHz): \delta 136.9, 129.7, 128.7, 127.2, 109.3, 81.0, 38.4, 37.4, 26.6. [ID-III-17]
\end{align*}
\]

\[
\begin{align*}
\text{1,6-Dideoxy-1,6-diheptyl-3,4-O-isopropylidene-D-mannitol} \\
\text{Dimethylsulfonate (64). 66% yield.} \\
\text{$^1$H NMR (CDCl}_3, 400 MHz): \delta 4.66 (m, 2 H), 4.09 (m, 2 H), 3.02 (s, 6 H), 1.72 (m, 4 H), 1.35 (s, 6 H) overlapping 1.36 (m, 4 H), 1.27 (m, 16 H), 0.81 (t, J = 6.5, 6 H); \text{ $^{13}$C NMR (CDCl}_3, 100 MHz): \delta 110.7, 81.5,
\end{align*}
\]

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78.7, 38.6, 31.5, 30.4, 29.1, 28.8, 26.9, 24.3, 22.4, 13.8; IR (neat): 1343, 1175 cm\(^{-1}\);
\([\alpha]_D^18\) +18° (c 18.2, CDCl\(_3\)). [ID-III-24]

![](image)

1,6-Dideoxy-1,6-diheptyl-3,4-\(\O\)-isopropylidene-D-iditol Dimethylsulfonate.

64% yield. \(^1\)H NMR (CDCl\(_3\), 250 MHz): \(\delta\) 4.73 (t, J = 6.6, 2 H), 4.11 (t, J = 1.3, 2 H), 3.06 (s, 6 H), 1.77 (m, 4 H), 1.40 (m overlapping s, 4 + 6 H), 1.26 (m, 16 H), 0.86 (t, J = 6.9, 6 H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 109.5, 79.8, 76.9, 38.6, 31.6, 31.5, 29.0, 28.8, 26.7, 25.1, 22.4, 13.8; IR (neat): 1460, 1352 cm\(^{-1}\); \([\alpha]_D^18\) -7° (c 24.7, CDCl\(_3\)). [ID-III-25]

![](image)

1,6-Dideoxy-1,6-diundecyl-3,4-\(\O\)-isopropylidene-D-mannitol Dimethylsulfonate. 77% yield. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 4.69 (m, 2 H), 4.13 (m, 2 H), 3.04 (s, 6 H), 1.74 (m, 4 H), 1.42 (m, 4 H) overlapping 1.37 (s, 6 H), 1.21 (m, 32 H), 0.82 (t, J = 6.6, 6 H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 110.9, 81.6, 78.8,
38.7, 31.8, 30.5, 29.5, 29.5, 29.4, 29.3, 29.2, 27.0, 24.4, 22.5, 14.0; IR (neat): 1467, 1344 cm\(^{-1}\); \([\alpha]_D^{23} +17^\circ (c 6.3, \text{CHCl}_3)\). [ID-III-32]

![](image)

1,6-Dideoxy-1,6-diundecyl-3,4-O-isopropylidene-D-iditol

Dimethylsulfonate. 69% yield. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta 4.68 (m, 2 \text{H}), 4.07 (m, 2 \text{H}), 3.02 (s, 6 \text{H}), 1.72 (m, 4 \text{H}), 1.36 (m \text{ overlapping s, } 4 + 6 \text{H}), 1.20 (m, 32 \text{H}), 0.82 (t, J = 6.3, 6 \text{H}); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta 109.6, 79.8, 77.0, 38.7, 31.8, 31.6, 29.5, 29.4, 29.2, 29.2, 29.1, 26.7, 25.2, 22.5, 13.9; \) IR (neat): 1467, 1355 cm\(^{-1}\); \([\alpha]_D^{20} -7^\circ (c 3.6, \text{CHCl}_3)\). [ID-III-33]

![](image)

**General procedure for synthesis of phospholanes.**

To a solution of diphenylphosphine (329 mg, 1.76 mmol, 2.2 equiv.) in 5 mL of THF at -78°C, \(n\)-BuLi (3.5 mL, 2.4 mmol, 3 equiv., 0.7 M in hexane) was added dropwise and the mixture was stirred for 1 h at room temperature. To the resulting
deep red solution cooled back to -78°C was added a solution of the dimesylate 5 (0.80 mmol) in 3 mL of THF. The mixture was stirred 6 h at room temperature. A few drops of methanol were added to quench any excess of n-BuLi. The solvent was pumped off, collecting the volatile materials at liquid nitrogen temperature. The crude product was purified by flash chromatography (eluant: hexane) in the dry box to obtain the diphosphine.

Mesylates of 57, 62, 58 and 63 were reacted following the above procedure. In all cases, no diphosphine could be isolated cleanly. At best, the expected products could be separated from the elimination products (Rf of 0.3-0.5 in hexane) but they were too apolar (Rf > 0.9 in hexane) to be cleaned of remaining HPPh₂.

When dimesylate 66 was reacted, no diphosphine could be isolated. Instead, an inseparable mixture of products was obtained, that was tentatively identified as a 1 : 2 mixture of elimination products 67 and 68.

![1:2 Mixture of compounds](image)

1:2 Mixture of (1E, 3R, 4R, 5S)-1,6-diphenyl-5-diphenylphosphino-3,4-O-isopropylidenehex-1-ene-3,4-diol (67) and (1E, 3R, 4R, 5E)-1,6-diphenyl-3,4-O-isopropylidenehex-1,5-diene-3,4-diol (68). ¹H NMR (CDCl₃, 500 MHz): δ 7.65 (m,
4 H), 7.46-7.25 (m, 24 H), 7.13 (d, J = 7.1, 6 H), 6.78 (d, J = 15.9, 2 H), 6.51 (d, J = 15.8, 1 H), 6.29 (m, 2 H), 5.88 (dd, J = 15.8, 7.6, 1 H), 4.80 (m, 1 H), 4.45 (m, 2 H), 3.98 (m, 1 H), 2.93 (m, 1 H), 2.82 (m, 2 H), 1.62 (s, 3H), 1.61 (s, 3H), 1.49 (s, 6 H);

$^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 140.5, 137.3, 134.7, 134.5, 134.5, 133.3, 133.2, 129.0, 128.8, 128.7, 128.6, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 126.7, 126.6, 125.0, 109.3, 108.7, 82.3, 80.0, 79.9, 79.8, 38.2, 38.0, 35.8, 35.7, 31.6, 27.2, 27.1, 26.9, 22.6, 14.1; $^{31}$P NMR (CDCl$_3$, 202 MHz): $\delta$ -10.3. [ID-III-85]

\[
\text{R} \quad + \text{CO} + \text{H}_2 \xrightarrow{\text{cat. / L}^*} \text{R} \quad \text{CHO} + \quad \text{CHO}
\]

**General procedure for the hydroformylation reaction.**

Inside the dry box, in a Fisher-Porter tube or a PARR glass vessel were introduced the rhodium catalyst and the phophine. Solvent was added and the mixture was stirred for 1 minute before adding the substituted olefin (and triethylamine in the case of the cationic catalyst; and 1 equiv. of triphenylmethane as internal standard in the case of vinyl acetate). The vessel was sealed and taken outside the drybox, flushed with the 1 : 1 mixture of CO / H$_2$ gases three times before leaving it to stir for 2 to 96 h. The tube was then vented and the reaction mixture passed through a pad of celite.

For styrene (49), vinyl naphthalene (87) and vinyl phthalimide (93), the GC of the crude was recorded on column B, the solvent was then evaporated and the $^1$H NMR of the crude was taken. The weigh of the crude determined the yield. To the crude aldehydes was added a 1 M solution of potassium permanganate in acetone (1.2

101

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equiv.) and magnesium sulfate. The resulting mixture was stirred for 2 h at room temperature and the solvent was removed under reduced pressure. The residue was extracted with hot water (3 x 1 mL) and filtered. The filtrate was washed with chloroform (1 mL) and acidified with 1 N HCl to pH 2, and then extracted with chloroform (3 x 5 mL). The combined organic extracts were dried over magnesium sulfate and concentrated to dryness in vacuo to afford the corresponding acids. To determine the enantiomeric excess, the crude acids were converted to the corresponding (-) menthyl esters by mixing with of the esterification solution (1.5 equiv., 1 M in DCC) and then stirring the resulting mixture for 30 minutes; the esterification solution was prepared dissolving (-) menthol (5g), dicyclohexylcarbodiimide (1.32 g), 4-dimethylaminopyridine (156 mg), p-toluenesulfonic acid (122 mg) in dichloromethane (6.4 mL). The mixture of diastereomeric ester was analysed by GC (column A or B).

For vinyl acetate (90), the $^1$H NMR of the crude mixture was taken. The conversion is determined by comparison to the peak of triphenylmethane $\delta$ 5.48. The enantiomeric excess is determined by GC (column C).

![Ph$_2$CHO](image)

3-Phenylpropanal (50). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 9.81 (t, $J = 1.4$, 1 H), 7.31 (m, 3 H), 7.22 (m, 2 H), 2.97 (t, $J = 7.6$, 1 H), 2.78 (d, $J = 7.6$, 2 H); GC (column B: initial temperature 50°C, initial time 10 min., rate 5°C/min., final temperature 102°C, retention time 2.78 min.)
250°C, final time 30 min.): $t_R$ 23.7 min; GC of the (-) menthyl ester of the corresponding acid (column A: temperature 140°C, time 30 min.): $t_R$ 23.6 min. [ID-III-50]

\[
\begin{align*}
\text{CHO} \\
\text{Ph} \\
51
\end{align*}
\]

2-Phenylpropanal (51). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 9.69 (d, $J = 1.4$, 1 H), 7.21 (m, 5 H), 3.64 (q, $J = 11.2$, 1 H), 1.46 (d, $J = 11.3$, 3 H); GC (column B: initial temperature 50°C, initial time 10 min., rate 5°C/min., final temperature 250°C, final time 30 min.): $t_R$ 21.8 min; GC of the (-) menthyl ester of the corresponding acid (column A: temperature 140°C, time 30 min.): R isomer $t_R$ 23.3 min, S isomer $t_R$ 24.4 min. [ID-III-50]

\[
\begin{align*}
\text{CHO} \\
\text{88}
\end{align*}
\]

3-Naphthylpropanal (88). partial $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 9.90 (t, 1 H), 3.18 (d, $J = 7.2$, 2 H), 2.90 (d, $J = 7.2$, 2 H); GC (column B: initial temperature 130°C, initial time 5 min., rate 5°C/min., final temperature 250°C, final time 30 min.): $t_R$ 18.1 min.; GC of (-) methyl ester of the corresponding acid (column B: initial
temperature 130°C, initial time 5 min., rate 5°C/min., final temperature 250°C, final time 30 min.): $t_R$ 25.5 min. [ID-III-80]

![Chemical structure of 2-Naphthylpropanal](image)

**2-Naphthylpropanal.** partial $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 9.84 (d, 1 H), 3.85 (q, $J = 6.6$, 1 H), 1.62 (d, $J = 7.0$, 3 H); GC (column B: initial temperature 130°C, initial time 5 min., rate 5°C/min., final temperature 250°C, final time 30 min.): $t_R$ 16.8 min. [ID-III-80]

![Chemical structure of (-)-Menthyl-2-naphthylpropanoate](image)

**(-)-Menthyl-2-naphthylpropanoate.** $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.83 (m, 3 H), 7.77 (s, 1 H), 7.48 (m, 2 H), 4.78-4.62 (m, 1 H), 3.95-3.85 (m, 1 H), 2.04 (dm, $J = 18.9$, 1 H), 1.86 (m, 1 H), 1.80-0.80 (series of m, 13H), 0.77 (d, $J = 11.1$, 2 H), 0.62 (d, $J = 11.2$, 2 H), 0.52 (d, $J = 11.1$); IR (CHCl$_3$): 1719, 1458, 1376, 1320, 1190; GC (column B: initial temperature 130°C, initial time 5 min., rate 5°C/min., final temperature 250°C, final time 30 min.): $R$ isomer $t_R$ 34.0 min., $S$ isomer $t_R$ 34.3 min;
GC (column A: temperature 190°C, time 30 min.): $R$ isomer $t_R$ 19.4 min., $S$ isomer $t_R$ 20.8 min. [ID-III-80]

3-Acetoxypropanal (91). Under the reaction conditions, 3-acetoxypropanal rapidly decomposed in acetic acid and propenal. The latter can further be transformed in propanal. In any case, peaks appear on the $^1$H NMR at $\delta$ 9.99 and $\delta$ 9.93, which integration are added together to calculate the ratio of 3-acetoxypropanal in the mixture. [ID-III-83]

2-Acetoxypropanal (92). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 9.74 (s, 1 H), 5.36 (q, $J$ = 7.2, 1 H), 2.43 (s, 3 H), 1.67 (d, $J$ = 7.2, 3 H); GC (column C: temperature 60°C, time 30 min.): $t_R$ 12.2 min. and 12.6 min. [ID-III-83]
3-Phthalimidylpropanal. partial $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 9.97 (t, 1 H), 4.09 (d, J = 7.0, 2 H), 2.92 (d, J = 7.0, 2 H); GC (column B: initial temperature 130°C, initial time 5 min., rate 5°C/min., final temperature 250°C, final time 30 min.): $t_R$ 19.0 min. [ID-III-87]

![Chemical Structure](image)

2-Phthalimidylpropanal (95). partial $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 9.87 (d, 1 H), 4.81 (q, J = 7.3, 1 H), 1.68 (d, J = 7.3, 3 H); GC (column B: initial temperature 130°C, initial time 5 min., rate 5°C/min., final temperature 250°C, final time 30 min.): $t_R$ 17.4 min. [ID-III-87]

![Chemical Structure](image)

(-)-Menthyl-2-phthalimidylpropanoate. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.84 (m, 2 H), 7.72 (m, 2 H), 4.93 (q, J = 7.3, 1 H), 4.73-4.63 (m, 1 H), 2.06 (m, 1 H), 1.69-0.68 (series of m, 21H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 169.2, 167.5, 134.0, 132.1, 123.4, 123.4, 47.9, 47.8, 47.0, 46.9, 40.6, 40.5, 34.2, 31.4, 26.4, 26.0, 23.6,
23.3, 21.9, 20.7, 16.4, 16.1, 15.2, 15.2; GC (column B: initial temperature 130°C, initial time 5 min., rate 5°C/min., final temperature 250°C, final time 30 min.): \( t_R \) 34.8 min., \( t_R \) 35.3 min; GC (column A: temperature 130°C, time 30 min.): \( t_R \) 26.5 min., \( t_R \) 27.9 min; HRMS calcd for \( C_{21}H_{27}NO_4Na \): \( M^+ = 380.18322 \), found 380.182002. [ID-III-87]
CHAPTER 3

SILYLSTANNYLATION-CYCLIZATION
OF 1,7-DIYNES AND 1,7-ALLENEYNES

3.1 Background.

Five- and six-membered carbocyclic and heterocyclic compounds constitute a large proportion of biologically relevant natural and non-natural products. Investigations toward the development of new catalytic processes for the synthesis of such molecules were initiated in our group. Unactivated olefins and acetylenes are particularly attractive precursors as they are potent latent functional groups, compatible with many classical synthetic transformations that rely on nucleophilic and electrophilic reagents. Since activation of these functionalities is best carried out with transition metals, it would allow for the catalytic tandem formation of several bonds. With the
notable exceptions of Heck and metathesis reactions, very few carbocyclic ring formation reactions are known to proceed with high degree of enantioselectivity and there is considerable room for further developments in this area.\textsuperscript{66} In 1985, two independent studies\textsuperscript{67} showed that trialkyltintrialkysilanes underwent Pd(0)-catalyzed addition to acetylenes with high regio- and stereoselectivity.

More recently, our group has demonstrated that $\text{R}_3\text{Sn-SiR}_3^-$ reagents added to 1,6-diynes, could cyclize and form (Z,Z)-1,3-dienes, an example of which is shown in Scheme 3.1.\textsuperscript{68} This palladium-catalyzed bis-functionalization/cyclization proceeded in good yields and with excellent stereochemical control. The reaction proved to be air and moisture-tolerant and was compatible with common functional groups such as ethers, esters, amides, carbonyl groups and even tertiary amines. Furthermore, the tin and silane moieties obtained by silylstannylation of acetylenes and olefins provide excellent handles for further synthetic elaborations.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=\textwidth]{Scheme3.1.png}};
\end{tikzpicture}
\end{center}

Scheme 3.1 : Silylstannylation-Cyclization of Symmetrical 1,6-Diynes.
From a structural point of view, irradiation of the olefinic signal caused enhancement of the peaks for the ring CH₂, which supported the (ZZ)-assignment for the 1,3-diene. In addition, sterically demanding silicon and tin substituents impose a non-polar, therefore helically chiral, conformation to the diene. Dynamic NMR studies have shown that those (Z,Z)-1,2-bis-alkylidene cyclopentanes are highly fluctuional molecules, showing fast equilibration between the two atropisomers. For example, the ring methylene of 97-98 appeared as two broad doublets (¹H NMR, CDCl₃) at 27°C and resolved into four sets of ABX patterns in the spectra taken at temperatures below -40°C. All the changes observed in the ¹H NMR and ¹³C NMR are in complete agreement with the suggested slow-equilibrating presence of two sets of diastereoisomers at low temperature. Indeed, most signals doubled in going down in temperature from 27°C to -40°C, including the tin signal in the ¹¹⁹Sn NMR spectrum.

The postulated mechanism for this reaction possibly involves a typical Pd(0)-Pd(II) catalytic cycle. The reaction is initiated by the oxidative addition of the tinsilane reagent to Pd(0). Coordination to the diyne 99 is followed by cis-silapalladation. The next steps are a cis-carbopalladation and a reductive elimination to afford the silylstannyl carbocycle 103 and the regenerated Pd(0). Direct reductive elimination from 101 gives the non-cyclized product, silylstanny lacetylene 104 as a side-product.
Scheme 3.2: Postulated Mechanism for the Silylstannylation-Cyclization of α,ω-Diynes.

This and all other related X-Y mediated cyclizations (R$_3$Si-SiR$_3$, R$_3$Si-BR$_2$, R$_3$Sn-BR$_2$, R$_3$Si-H, R$_3$Sn-H) on unsymmetrical substrates have raised the issue of regioselectivity. For example, the silylstannylation of proline-derived diyne 105 gave essentially a 1:1 mixture of regioisomers.
To circumvent this problem, Dr. Shin in our group has demonstrated that the different reactivities of allenes and acetylenes in palladium-catalyzed X-Y addition cyclization could be exploited. Indeed, the cyclization of a 1,6-alleneyenes gave highly substituted alkylidene cyclopentanes. The higher reactivity of the allene moiety led to the key intermediate 109. The regioselectivity was determined by nOe, where the silane was in vinylic position and the tin, allylic. Further reaction on 109 gave the cyclized product 110, in which the identity of the SnCH and the geometry of the double bond were clear respectively from the coupling pattern (δ 6.40 (s, J_{Sn-H} = 74 Hz)) and nOe difference spectrum.
A mechanism that would account for the observed results was proposed, which relied on a typical Pd(0)-Pd(II) catalytic cycle. Bidentate coordination of the Pd(II) on the allene and acetylene would lead to the more stable anti \( \pi \)-allyl Pd-complex 112, which upon reductive elimination with formation of the less congested allylstannane and regeneration of Pd(0) would give the uncyclized product 109. A more energetically demanding insertion of the acetylene into this \( \pi \)-allyl Pd-complex takes place at a higher temperature, leading to the cyclic product 110.

Scheme 3.5: Postulated Mechanism for the Silylstannylation-Cyclization of \( \alpha, \omega \)-Alleneynes.

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At this early stage of our efforts to demonstrate the versatility of the silylstannylation-cyclization of diynes, a number of issues need to be addressed.

Preliminary studies on six-membered ring formations using the silylstannylation of linear 1,7-diynes have shown that addition of the silylstannane to only one acetylene occurred with no cyclization. Apparently, the two alkynes are too far apart to allow for cyclization. If this is indeed the case, will removing one degree of the freedom enable the cyclization (i.e. locking the free rotation of one of the bonds along the chain to bring the two terminal acetylenes closer together)?

Secondly, despite extensive research on symmetrical, unsymmetrical and bicyclic substituted 1,2-(Z,Z)-bis-alkylidenecyclopentanes not one structure could be isolated that would show a frozen (non-fluxional) equilibrium of two isomers at temperatures above 20°C, even with very bulky stannyl and silyl substituents. We are therefore to study the possibility of 1,2-(Z,Z)-bis-alkylidenecyclohexanes that will have a sufficiently large activation barrier for the epimerization to permit the isolation of the atropisomers.

We are also raising the question whether 1,7-allenynes would be more or less reactive substrates compared to the corresponding diynes toward the silylstannylation-cyclization reaction for the formation of six-membered rings. And if so, what would the stereochemical outcome be?

Finally, we are interested in exploring the functional group compatibility of the reaction conditions with sensitive functional groups. For this, several substrates with a β-lactam scaffolding were prepared, and their cyclization studied.
3.2 Silylstannylation of Symmetrical 1,7-Diynes.

We started our investigations on a compound we had already synthesized (see section 2.3), namely the symmetrical 1,6-dideoxy-3,4-O-isopropylidene-D-mannitol-2,5-dimethanesulfonate 114. However, displacement of the mesylates by lithium trimethylsilylacetylene or by Finkelstein exchange was ineffective. As primary mesylates are preferred substrates for S_N2 displacements, we decided to synthesize 2,3-O-isopropylidene-D-threitol-1,4-dimethanesulfonate 116.

![Scheme 3.6: Attempted Nucleophilic Displacement using Lithium Trimethylsilylacetylene.](image)

Diol protection on (-)-diethyl tartrate, followed by reduction and mesylation led to the expected compound 116 in three steps and 65% overall yield. Unfortunately, the expected displacement of the mesylates by Lewid acid-mediated reaction of lithium trimethylsilylacetylene did not proceed. Indeed, Takano and coworkers have also...
observed that all attempts to displace mesylates, tosylates or halides on this particular sugar derivative with lithium acetylenes were unsuccessful.\textsuperscript{72}

\[\text{(-)-DET} \xrightarrow{a,b,c} \text{116} \xrightarrow{d} \text{117}\]

a. \((\text{MeO})_2\text{CMe}_2, \text{TsOH, DMF.} \)  
 b. \(\text{LiAlH}_4, \text{THF.} \)  
 c. \(\text{MsCl, pyr.} \)  
 d. trimethylsilyl acetylene, \(n-\text{BuLi, then 116, BF}_3\cdot\text{OEt}_2\).

Scheme 3.7: Attempted Preparation of Symmetrical 1,7-Diyne from (-)-DET.

An alternative synthesis of 117 involved the silylethynylation of the commercially available DL-butadienediepoxide followed by acetonization of diol \textsuperscript{120}.\textsuperscript{72,73} The desilylated product proved to be quite unstable to air, moisture and light. Storage was avoided and it was therefore synthesized from the \textit{bis}-trimethylsilyl derivative as needed.
Scheme 3.8: Preparation of trans-Locked Symmetrical 1,7-Diyne.

Under the usual reaction conditions (1 equiv. Bu₃SnSiMe₃, 2 mol% Pd₂(dba)₃, 10 mol% P(C₆F₅)₃, 0.6 M in benzene at rt for 24h), the reaction surprisingly led to the formation of dimer 122. Interestingly, Ph₃SnSiMe₂-t-Bu was shown in previous studies to afford results similar to Bu₃SnSiMe₃, but with increased reactivity. However, reaction of 121 with Ph₃SnSiMe₂-t-Bu was very slow and decomposition occurred before any noticeable desired reaction took place.
Scheme 3.9: Silylstannylation of Symmetrical trans-Locked 1,7-Diyne.

Careful chromatography enabled us to isolate one of the dimerization products 122. Spectroscopy spectra (\(^1\)H NMR, COSY, \(^{13}\)C NMR) and molecular weight (determined by MS) confirmed the presence of a dimer with 50 protons, with only one SnCH and one SiCH olefinic proton. The diene should be s-trans as a consequence of the bulk of the silyl and stannyl substituents. Irradiation of SiCH led to enhancement of a CH\(_2\) signal (no enhancement of the SnCH was observed) and in turn irradiation of this CH\(_2\) gave enhanced SnBu\(_3\) peaks. Also, irradiation of SnCH led to enhancement of another CH\(_2\) signal (no enhancement of the SiCH was observed) and in turn irradiation of that CH\(_2\) gave enhanced SiMe\(_3\) peaks. This information meant the stereochemistry was either (Z,s-trans,Z) or (E,s-trans,E). As no long-range coupling was observed by \(^1\)H NMR or COSY between SiCH and CH\(_2\)\(^9\) or SnCH and CH\(_2\)\(^6\), we tended toward the (Z,s-trans,Z) arrangement (although this may not be a very reliable criterion in the absence of appropriate models). The E geometry was of the double bonds was also

---

117 121 122

\(\text{a. } \text{K}_2\text{CO}_3, \text{MeOH, rt, 73\%. b. } \text{Bu}_3\text{SnSiMe}_3, \text{Pd}_2(\text{dba})_3, \text{P(C}_6\text{F}_5)_3, \text{C}_6\text{D}_6, \text{rt, 60\%}.)\)
procluded by the syn-carbametallation, and the reductive elimination of Pd(0) with retention of stereochemistry in the last step of the reaction mechanism.

\[
\begin{align*}
(Z,s\text{-}trans,Z) & \quad (E,s\text{-}trans,E) \\
\begin{array}{c}
\text{Me}_3\text{Si} \\
\text{Me}_3\text{Si}
\end{array} & \begin{array}{c}
\text{Me}_3\text{Si} \\
\text{Me}_3\text{Si}
\end{array}
\end{align*}
\]

Figure 3.1: Tentative Stereochemical Assignment of 122.

Previous work by Dr. Warren in our group had shown that silylstannylation of linear 1,7-diynes only led to the formation of C-Sn and C-Si bonds without cyclization. In certain cases, we observed an additional intermolecular C-C bond formation resulting in the dimerization of the substrate (Scheme 3.9). To enhance the intramolecular C-C bond formation, several options are at hand. Dilution of the reaction has in many cases been shown to be a simple solution to the dimerization issue. We have to note however that Tamao and Ito have performed their nickel-catalyzed hydrosilation-cyclization of 121 at the same 0.6 M concentration. Dilution of the reaction mixture to 0.06 M led in our case to decomposition before any
silylstannylation of the diyne could be observed. Another idea would be to bring the
two acetylenic ends even closer together by having a cis ring junction instead of the
\textit{trans} as in 121.

The \textit{meso}-1,3-butadiene diepoxide 123 was synthesized in two steps from the
commercially available erythritol. Careful tosylation led to the regioselective reaction
of the primary alcohols and displacement of the tosylates in basic medium gave 123.
The \textit{cis}-locked symmetrical 1,7-diyne was obtained as described earlier for 121 by
epoxide opening, \textit{cis}-dil protection and terminal acetylene deprotection. As with 121,
124 was not very stable upon storage in the fridge and was synthesized from the TMS-
protected diacetylene as needed for the silylstannylation reaction.

\begin{center}
\begin{tikzpicture}
\node at (0,0) [below] {\textbf{Scheme 3.10 : Preparation of \textit{cis}-Locked Symmetrical 1,7-Diyne.}};
\end{tikzpicture}
\end{center}

The silylstannylation-cyclization proceeded to completion by NMR and the
product 125 was isolated in 56\% yield. The stereochemistry was determined by nOe.
Each olefinic proton was shown to be close in space to one ring methylene (each SiCH and SnCH interacting with a different ring CH₂). Furthermore, the olefinic proton did not show any interaction with each other by nOe, which demonstrated the the (ZZ)-configuration in 125. This is the first example of the formation of (Z,Z)-bis-alkylidene cyclohexane by silylstannylation-cyclization.

![Chemical structures](image)

a. Bu₃SnSiMe₃, Pd3(dba)3, P(C₆F₅)₃, C₆D₆, rt, 56%.

Scheme 3.11: First Example of the Formation of a (Z,Z)-bis-alkylidene cyclohexane.

The (Z,Z)-arrangement of diene 125 is puckered as a consequence of the bulk of the silyl and stannyl groups. This creates a helical chirality. The reaction should lead to a 1:1 mixture of two diastereomeric 125, A and B. If the molecule is fluxional, isomers A and B should be in equilibrium respectively with A' and B'. B and A' as well as A and B' are mirror images. Therefore, if A and B are rapidly equilibrating, only one structure should be observed by NMR.
Scheme 3.12: Helical Isomers of (Z,Z)-Diene 125.

At room temperature, all the $^1$H NMR, $^{13}$C NMR and $^{119}$Sn spectra showed double the number of peaks expected. The $^1$H NMR of 125 showed two peaks with the typical Sn-H coupling ($J_{\text{Sn-H}} = 31$ Hz), each integrating for 1 H. In the same region, two other peaks (each integrating for 1 H) are observed, which correspond to the olefinic proton in $\alpha$ of the TMS group. Furthermore, two distinct sharp peaks appeared in the TMS region, each integrating for 9 H per olefinic proton. The $^{13}$C NMR spectrum showed two peaks in the TMS region and four C-H in the olefinic region and the $^{119}$Sn NMR clearly showed two peaks at room temperature. The molecular weight determined by MS confirmed the presence of a monomer consistent with 125. In other words, unlike (Z,Z)-bis-alkylidenebicyclo[2.2.1]heptanes for which the two
isomers were frozen only at lower temperatures,\textsuperscript{48a,68c} \textit{the two diastereoisomers A and B of 125 are not fluxional at room temperature.}

Finally, dynamic NMR studies showed that the diastereoisomers are not exchanging at temperatures between -60°C and +60°C, as the $^1$H NMR spectrum of 125 remained unchanged (as shown by the olefinic region in Figure 3.1). This is the first example of a structure with a helical chirality, for which the energy barrier between the atropisomers is so large that they are not interconverting at temperatures lower than at least +60°C.

Preliminary studies have shown that the two sets of diastereoisomers of two enantiomers could be separated by chiral HPLC (OD-H column in hexanes at 0.4 mL/min.). Unfortunately, the 4 peaks overlap and therefore cannot be considered as conclusive evidence of a 1 : 1 : 1 : 1 mixture of isomers of 125. As the diastereoisomers are not separable by chromatography, continuing work in our group has been initiated to study the asymmetric version of this reaction \textit{i.e.} the possible utility of a chiral ligand to favor the formation of one of the helical isomers.
Figure 3.2: Olefinic Region of Dynamic $^1\text{H}$ NMR of (Z,Z)-Diene 125.
One of the striking features of the silylstannylation-cyclization is its remarkable functional group compatibility, including the tolerance of basic amino groups. We decided to explore this aspect in the context of pyrrolizidine and indolizidine skeletal frames. Several important biologically relevant compounds are represented by these N-heterocyclic ring systems. For example, Indolizidine 223A is a prototypical member of highly substituted (5,6,8-trialkyl)-indolizidines, the most recently disclosed class among these important natural products from South American frogs. Our methodology would install latent functionalities in an advanced indolizidine intermediate, which would be exploited for further regioselective elaboration of the molecule.
3.3.1 Attempted Cyclization of Unsymmetrical Diynes.

We started our investigations on structures derived from the commercially available succinimide 126 and 4-benzoyloxyazetidinone 133.

Carbinol amide 129 was obtained by Mitsunobu coupling of propargyl alcohol with succinimide\(^\text{76}\) followed by treatment of the imide 128 with sodium borohydride in acidic ethanol.\(^\text{77}\) Rapid Lewis acid-mediated reaction of 129 with tributylstannylallene 130 led to the unsymmetrical diyne 131.\(^\text{78,79}\) Under the usual reaction conditions (2 mol\% Pd\(_2\)(dba)\(_3\), 10 mol\% P(C\(_6\)F\(_5\))\(_3\) in C\(_6\)D\(_6\)), the silylstannylation reaction of 131 using Bu\(_3\)SnSiMe\(_3\) slowly decomposed without formation of any detectable cyclized or non-cyclized product (as judged by the absence of peaks in the olefinic region). Using Ph\(_3\)SnSiMe\(_2\)-\(t\)-Bu, the reaction proved to be slow at room temperature; but after 15 days, the only product isolated was the dimer 132 in 42\% yield. We performed the same reaction at 60°C overnight and it yielded the same dimer 132 (12\% yield).
a. PPh₃, DEAD, THF, 68%. b. NaBH₄, HCl, EtOH, 0°C, 43%. c. tributylstannyllallene (130), TMSOTf, CH₂Cl₂, rt, 61%. d. Ph₃SnSiMe₂-t-Bu, Pd₂(dbk)₃, P(C₂F₅)₃, C₆D₆, rt, 15 d, 42%; 60°C, 16 h, 12%.

Scheme 3.13: Silylstannylation of Unsymmetrical 1,7-Diyne Derived from Succinimide.

Similarly, silylstannylation of 134, prepared in two steps from 4-benzoylazetidinone by successive reaction with tri-n-butylstannyllallene 130 followed by propargyl bromide,⁸⁰ led to dimerization products 135 and 136 (as proven by NMR and MS) regardless of the nature of the tin silane used. As before, attempts at diluting the reaction mixture made the reaction slower and favored the formation of decomposition products. As diyne 134 was racemic, each dimer was produced as a 1:1 mixture of (R*,R*) and (R*,S*) diastereoisomers. The stereochemistry was tentatively determined to be (Z,s-trans,Z). As in 122, irradiation of SiCH enhanced a CH₂ signal, which
irradiated in turn enhanced the SnBu$_3$ peaks. And, no long-range correlation was observed between these olefinic protons and the corresponding CH$_2$.

![Scheme 3.14: Silylstannylation of Azetidinone-Containing 1,7-Diyne.](image)

<table>
<thead>
<tr>
<th>Step</th>
<th>Reaction</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>tri-n-butylstannyllallene (130), TMSOTf, CH$_2$Cl$_2$, rt, 84%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b.</td>
<td>propargyl bromide, KOH, dicyclohexano-18-crown-6, C$_6$H$_6$, rt, 57%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.</td>
<td>Bu$_3$SnSiMe$_3$, Pd$_2$(dba)$_3$, P(C$_6$F$_3$)$_3$, C$_6$D$_6$, rt to 40°C, 66%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d.</td>
<td>Ph$_3$SnSiMe$_2$-t-Bu, Pd$_2$(dba)$_3$, P(C$_6$F$_3$)$_3$, C$_6$D$_6$, rt to 40°C, 38%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In summary, silylstannylation of non-symmetrical 1,7-diynes consistently led to dimeric products instead of the desired bicyclic compounds. Apparently, the two acetylenic moieties in 131 and 134 are too far apart to allow for cyclization, or the strain in a bicyclic [4.2.0] system prevents the annulation reaction. Pyramidalization of...
the nitrogen could keep the two acetylenic moieties far apart. It appears that a strictly cis-locked conformation is necessary to achieve the silylstannylation-cyclization successfully.

3.3.2 Silylstannylation-Cyclization as a Route to Functionalized Indolizidines.

A facile entry into indolizidines using our methodology would involve the silylstannylation-cyclization of 1,7-alleneynes derived from succinimides.

Alleneyne 140 was synthesized by a rapid sequence of Mitsunobu coupling of succinimide 126 and 3-butyn-1-ol 137, partial reduction to carbinol derivative 138 and Lewis acid-mediated reaction of the carbinol with propargyltrimethylsilane.

![Scheme 3.15: Preparation of a 1,7-Alleneyne Derived from Succinimide.](image)

a. PPh₃, DEAD, THF, rt, 68%. b. NaBH₄, HCl, EtOH, 0°C, 50%. c. propargyltrimethylsilane (139), BF₃·OEt₂, CH₂Cl₂, rt, 88%.

Under the usual reaction conditions (2 mol% Pd₂(dba)₃, 10 mol% P(C₆F₅)₃ in C₆D₆), the silylstannane Bu₃SnSiMe₃ added rapidly to alleneyne 140 to give the
addition product 141 (rt, 15 min.). More energy (60°C, 18 h) was required to perform the cyclization. The bicyclic system 142 could thus be obtained in sequential steps through 141 or directly from 140.

Scheme 3.16: Silylstannylation-Cyclization of 5-Allenyl-1-(3-butynyl)-2-pyrrolidinone 140.

The expected $E$ configuration of the olefin in 141 was confirmed by nOe, as irradiation of the olefinic proton enhanced the TMS signal. For the geometry of the trisubstituted olefin in 142, irradiation of the olefinic SnCH enhanced the $\text{CH}_2$ signal (but not $H^6$) and proved the arrangement to be $Z$. In addition, molecular orbital calculations (MM2 level, Spartan and Chem 3D) had predicted that the trans ($H^3,H^6$) configuration would be favored as it is less energetically demanding (by 2 kcal/mol) than the corresponding cis arrangement. Indeed, the stereochemistry in 142 at C5-C6.
has been determined to be *trans* by \(^1\)H NMR (large coupling constant of 8.6 Hz) and by nOe experiments (irradiation of \(H^6\) did not enhance the \(H^5\) signal, and *vice-versa*).

The regioisomeric alleneyne 144 was prepared by Mitsunobu coupling to allenyl alcohol 143 with succinimide, partial reduction and final reaction with tributylstannylallene 130. The presence of both the acetylenic and allenic moieties in 144 was ascertained by IR, in which both the stretches at 3300 cm\(^{-1}\) and 1950 cm\(^{-1}\) unmistakably appeared.

\[
\begin{align*}
\text{O} & \quad \text{NH} + \quad \text{HO} \\
\text{126} & \quad \text{143} & \quad \text{144} \\
\end{align*}
\]

a. PPh\(_3\), DEAD, THF, rt, 99%. b. NaBH\(_4\), HCl, EtOH, 0°C, 55%. c. tri-\(n\)-butylstannylallene (130), TMSOTf, CH\(_2\)Cl\(_2\), rt, 88%. d. Bu\(_3\)SnSiMe\(_3\), Pd\(_2\)(dba)\(_3\), P(C\(_6\)F\(_3\))\(_2\), C\(_6\)D\(_6\), rt, 88%. e. Ph\(_3\)SnSiMe\(_2\)-\(t\)-Bu, Pd\(_2\)(dba)\(_3\), P(C\(_6\)F\(_3\))\(_2\), C\(_6\)D\(_6\), 40°C, 41%.

**Scheme 3.17**: Silylstannylation of 1-(2,3-Butadienyl)-5-(2-propynyl)-2-pyrrolidinone 144.
Silylstannylation of 144 using Bu$_3$SnSiMe$_3$ rapidly yielded 145 but would not react any further under a number of reaction conditions like varying temperature, time and type of phosphine ligands used including a recently reported procedure which shows the use of divalent Pd and Pt (Table 3.1)\textsuperscript{81}. On the other hand silylstannylation of 144 using Ph$_3$SnSiMe$_2$-t-Bu led to 146 cleanly. As before, the (E) geometry of the olefin in 145, the (Z) geometry of the trisubstituted alkene and the trans arrangement of (H$^3$,H$^6$) in 146 were determined by nOe. Indeed, irradiation of the olefinic proton in

![](image1)

<table>
<thead>
<tr>
<th>Catalytic System*</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd$_2$(dba)$_3$ / P(C$_6$F$_5$)$_3$</td>
<td>C$_6$D$_6$</td>
<td>80°C</td>
<td>24 h</td>
</tr>
<tr>
<td>Pd$_2$(dba)$_3$ / P(o-tolyl)$_3$</td>
<td>C$_6$D$_6$</td>
<td>80°C</td>
<td>24 h</td>
</tr>
<tr>
<td>Pd$_2$(dba)$_3$ / (t-Bu)$_2$P(O)H</td>
<td>C$_6$D$_6$</td>
<td>80°C</td>
<td>3 h</td>
</tr>
<tr>
<td>(EtS)$_2$PtCl$_2$</td>
<td>MeOD</td>
<td>60°C</td>
<td>24 h</td>
</tr>
<tr>
<td>(EtS)$_2$PtCl$_2$</td>
<td>acetone-d$_6$</td>
<td>25°C</td>
<td>7 d</td>
</tr>
<tr>
<td>(EtS)$_2$PtCl$_2$</td>
<td>acetone-d$_6$</td>
<td>40°C</td>
<td>24 h</td>
</tr>
<tr>
<td>(PhCN)$_2$PtCl$_2$</td>
<td>MeOD</td>
<td>60°C</td>
<td>14 h</td>
</tr>
<tr>
<td>(PhCN)$_2$PtCl$_2$</td>
<td>MeOD</td>
<td>40°C</td>
<td>20 h</td>
</tr>
<tr>
<td>(PhCN)$_2$PtCl$_2$</td>
<td>acetone-d$_6$</td>
<td>25°C</td>
<td>7 d</td>
</tr>
<tr>
<td>(PhCN)$_2$PtCl$_2$</td>
<td>acetone-d$_6$</td>
<td>40°C</td>
<td>24 h</td>
</tr>
<tr>
<td>PdCl$_2$</td>
<td>MeOD</td>
<td>60°C</td>
<td>14 h</td>
</tr>
<tr>
<td>PdCl$_2$</td>
<td>MeOD</td>
<td>40°C</td>
<td>24 h</td>
</tr>
<tr>
<td>Pd(OAc)$_2$</td>
<td>MeOD</td>
<td>60°C</td>
<td>14 h</td>
</tr>
</tbody>
</table>

\textsuperscript{a} For M(0) catalyst: 2 mol% of catalyst + 10 mol% of phosphine. For M(II) catalysts: 5 mol% of catalyst.

Table 3.1: Attempted Cyclizations on 145.

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145 gave an enhanced TMS signal but no Bu$_2$SnCH$_2$ signals. In 146, irradiation of $H^6$ did not enhance either the olefinic SnCH or $H^5$ but clearly, irradiation of the olefinic SnCH led to an enhanced signal for $H^6$ and irradiation of $H^5$ gave enhanced Si(CH$_3$)$_2$ peaks.

3.3.3 Attempted Entry into Bicyclic $\beta$-lactams.

Bicyclic $\beta$-lactams, best exemplified by thienamycin (Figure 3.4), belong to an important class of antibacterial compounds$^{82}$ that could be approached through the silylstannylation-cyclization route. The commercially available [3R(1'R,4R)-4-acetoxy-3-[1-((tert-butyldimethylsilyloxy)ethyl]-azetidinone 147 is an ideal starting material for the preparation of several precursor alleneynes and diynes needed for the cyclization studies.

![Figure 3.4: Thienamycin](image)

Figure 3.4: Thienamycin

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As summarized in Table 3.2, our attempts to synthesize 1,7-alleneynes by Mitsunobu reaction on 4-allenyl or 4-propargyl azetidinones were unsuccessful. To our surprise, coupling of 4-benzoyloxy azetidionone with 4-butyn-1-ol by Mitsunobu reaction gave 4-benzoyloxy-1-butyne in 76% yield.

<table>
<thead>
<tr>
<th>β-lactam</th>
<th>Alcohol</th>
<th>Reaction Outcomea</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Diagram" /></td>
<td><img src="image2" alt="Diagram" /></td>
<td>no reaction observed on TLC</td>
</tr>
<tr>
<td><img src="image3" alt="Diagram" /></td>
<td><img src="image4" alt="Diagram" /></td>
<td>no identifiable product isolated</td>
</tr>
<tr>
<td><img src="image5" alt="Diagram" /></td>
<td><img src="image6" alt="Diagram" /></td>
<td>decomposition observed on TLC</td>
</tr>
<tr>
<td><img src="image7" alt="Diagram" /></td>
<td><img src="image8" alt="Diagram" /></td>
<td>76% yield</td>
</tr>
</tbody>
</table>

a. Reaction conditions: 1 equiv. alcohol + 1 equiv. PPh₃ then 1 equiv. DEAD, rt, 3h.

Table 3.2: Attempted Mitsunobu Reactions on β-lactams.

The allene 148 was synthesized following Liebeskind’s procedure using Lewis acid-mediated reaction of azetidinone 147 with propargyltrimethylsilane.⁷９ As shown in Scheme 3.19, the trans stereochemistry was retained in 148. Nucleophilic attack of
sodium salt of 148 on propargyl bromide or allyl bromide led to 1,6-alleneyne 149 or 1,6-alleneene 151 respectively.

\[ \text{Scheme 3.18 : Synthesis of Azetidinone-Derived 1,6-Alleneyne and 1,6-Alleneene.} \]

Under the usual reaction conditions (2 mol% Pd$_2$(dba)$_3$, 10 mol% P(C$_6$F$_5$)$_3$ in C$_6$D$_6$), silylstannylation of 149 using Bu$_3$SnSiMe$_3$ led to the addition product 150 (rt, 15 min.). However, the reaction mixture decomposed rapidly. Apparently, alleneynes derived from azetidinone are less stable to the reaction conditions than the corresponding alleneynes derived from succinimide. Any attempts to force the cyclization of 150 by raising the temperature (to 80°C, 60°C or 40°C) invariably led to decomposition products. Use of alternative phosphine ligands (P(o-tolyl)$_3$ instead of P(C$_6$F$_5$)$_3$) led to lower yield of 150 and faster decomposition (by NMR). Finally, use of
Ph3SnSiMe2-t-Bu made the reaction slower and did not yield the expected bicyclic system. Similarly, silylstannylation of 151 rapidly produced the addition product 152 (rt, 15 min.). Unlike acetylene 151, however, olefin 152 was extremely stable under the reaction conditions, as the reaction mixture did not decompose even after 7 days at 80°C.

\[ \text{TBDM SO} \]

\[ \begin{array}{c}
\text{R=propargyl} \\
\text{R=allyl}
\end{array} \]

Scheme 3.19: Silylstannylation of Azetidinone-Derived 1,6-Alleneyne 149 and 1,6-Allenene 151.

In both cases, irradiation of the olefinic proton of the trisubstituted olefin, gave enhanced signals for the TMS methyl protons, thus confirming the \( E \) stereochemistry of the olefin.

The increased distance between the acetylenic or olefinic groups brought by the pyramidalization of nitrogen and the inherent strain in the bicyclo[3.2.0]heterocyclic system maybe responsible for the resistance to cyclization in these substrates. However, the products 150 and 152 are potentially useful precursors for the synthesis.

\[ \text{a. Bu3SnSiMe3, Pd2(dba)3, P(C6F5)3, C6D6, rt, R = propargyl : 23%, R = allyl : 82%.} \]
of the bicyclic β-lactams by alternate methods. Lewis acid as well as metal mediated\textsuperscript{81} reactions of allylstannanes and free radical methodology could be employed for the eventual cyclization of these substrates. Such studies will be initiated in our group in due course.
3.4 Conclusion.

We have demonstrated, for the first time, that silylstannylation-cyclization can be employed for the synthesis of 6-membered compounds. The feasibility of cyclization of 1,7-diynes appears to depend on the relative distance between the two acetylenes. Compounds where the dipropargyl substituents were *cis* to one another, as appendages in a 5-membered ring, underwent the reaction with remarkable ease, where as when these substituents were *trans*, a high-yielding dimerization ensued. Likewise, when one of the propargyl groups was linked to the nitrogen of a β-lactam and the other attached to the 2-position, no cyclization was observed. Instead, dimerization was the major pathway.

The product obtained from a *cis*-locked dipropargyl compound was the first confirmed example of a *(Z,Z)-bis*-alkyldienecyclohexane that existed as two atropisomeric diastereoisomers at room temperature. Dynamic NMR studies show that these diastereoisomers did not interconvert at temperatures as high as 60°C.

We have confirmed that, in several instances, the allene moiety in an alleneyne was more reactive towards silylstannanes, but the subsequent cyclization was more energy demanding. Higher temperatures were needed for the cyclization of the initially formed allylstannanes. In the case of 1,7-alleneynes derived from succinimide, the bicyclic structures consistently gave a *cis* configuration of the vinylsilane with respect to the proton at the ring junction. The resulting compounds provide a potentially useful entry into highly functionalized indolizidines. A related approach to bicyclic...
\(\beta\)-lactams starting from \(N\)-propargyl-2-(allenyl)azetidinone has not yet succeeded. However, several of the intermediates obtained are potentially useful for the synthesis of the target structures via other cyclization methods.

Ongoing research in our group examines the asymmetric version of the silylstannylation-cyclization of 1,6- or 1,7-allenynes and diynes. Such studies on the silylstannylation of \(cis\)-locked 1,7-diynes might reveal the generation of enantioselective atropisomerism in diyne cyclizations.
3.5 Experimental Section.

General Methods. Reactions were carried out in oven- or flame-dried glassware under a nitrogen atmosphere, unless otherwise noted. All solvents used were reagent grade. Diethyl ether, hexanes and tetrahydofuran (THF) were freshly distilled from sodium/benzophenone. Dichloromethane and toluene were freshly distilled from calcium hydride. Triethylamine was distilled from calcium hydride and stored over potassium hydroxide. Acetonitrile was dried over silica, distilled from calcium hydride and stored over 4 Å molecular sieves. Pyridine was distilled and stored over potassium hydroxide. Acetic anhydride was azeotroped with toluene, distilled and stored over 4 Å molecular sieves. Anhydrous N,N-dimethylformamide was purchased from Fischer and used without purification. Acetone was dried over 4 Å molecular sieves for 2 hours prior to use. Except as otherwise indicated, all reactions were magnetically stirred and monitored by thin layer chromatography on E. Merck precoated (0.25 mm) silica gel 60 F254 plates. Flash chromatography was conducted by using silica gel 40 (Scientific Adsorbents Incorporated, Microns Flash). Yields, unless otherwise stated, refer to chromatographically and spectroscopically pure compounds. Melting points were determined on a Thomas Hoover uni-melt apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 series FTIR. $^1$H, $^{19}$F and $^{13}$C NMR spectra were recorded on a Bruker Aspect 200, 250, 400 or 500 MHz spectrometer. Chemical shift are reported relative to chloroform as standard at $\delta = 7.26$ for $^1$H and $\delta = 77.0$ for $^{13}$C. Coupling constants are reported in Hertz (Hz).
High-resolution mass spectra were recorded on the Micromas QTOF Electrospray mass spectrometer. Compounds for which exact mass is reported exhibited no significant m/z greater than the one of the parent peak. Compounds 130 and 139 were either obtained from a commercial source or prepared according to the literature.78

(R',R')-1,8-dimethylsilylethane-4,5-diol-1,7-diyne (120). To a solution of trimethylsilylacetylene (3.6 mL, 25.5 mmol, 2.2 equiv.) in 50 mL of THF cooled at -20°C, n-butyllithium (20.0 mL, 1.3 M in hexanes, 25.5 mmol, 2.2 equiv.) was added dropwise. The mixture was stirred at room temperature for 30 minutes and cooled again to -20°C. Commercially available DL-1,3-butadiene diepoxide (0.9 mL, 11.6 mmol) in 20 mL of THF and boron trifluoride etherate (3.3 mL, 25.5 mmol, 2.2 equiv.) were added dropwise. The reaction was then stirred at that temperature for 2 h. The mixture was poured on a cold solution of ammonium chloride. The aqueous layer was extracted three times with 10 mL of diethyl ether. The organic layers were combined and washed with 10 mL of water, dried over MgSO4 and concentrated. The crude compound was chromatographed (SiO2, hexanes / ethyl acetate 6/1) to give 2.1 g (65% yield) of a white solid. 1H NMR (250 MHz, CDCl3): δ 3.80 (bs, 2 H, OH), 2.70 (m, 2
(R',R')-1,8-ditrimethylsilyl-4,5-O-isopropylideneoctane-4,5-diol-1,7-diyn (117). To a solution of (R',R')-1,8-ditrimethylsilyloctane-4,5-diol-1,7-diyn (350 mg, 1.24 mmol) in 10 mL of DMF, 2,2-dimethoxypropane (305 µL, 2.48 mmol, 2 equiv.) and p-toluenesulfonic acid (47 mg, 0.25 mmol, 0.2 equiv.) were added. The mixture was stirred at room temperature overnight and then poured on a cold solution of ammonium chloride. The aqueous layer was extracted three times with 5 mL of diethyl ether. The organic layers were combined and washed with 5 mL of water, dried over MgSO₄ and concentrated. The crude compound was chromatographed (SiO₂, hexanes / ethyl acetate 9/1) to give 360 mg (90% yield) of a light yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 3.94 (t, J = 3.0, 2 H, CH), 2.62 (m, 4 H, CH₂), 1.39 (s, 6 H, C(CH₃)₃), 0.11 (s, 18 H, SiCH₃); ¹³C NMR (100 MHz, CDCl₃): δ 108.7, 101.8, 87.4, 77.3, 27.1, 23.8, -0.1. [ID-III-170]
(R',R')-4,5-O-Isopropylideneoctane-4,5-diol-1,7-diyne (121). A solution of
(R',R')-1,8-ditrimethylsilyl-4,5-O-isopropylideneoctane-4,5-diol-1,7-diyne (290 mg,
0.90 mmol) in 5 mL of dry methanol was treated by potassium carbonate (720 mg,
5.21, 5.5 equiv.) for 30 minutes at room temperature. Filtration and concentration
afforded 120 mg (73%) of a light yellow oil. \(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)): \(\delta\) 3.77 (m, 2
H, OH), 2.30 (m, 4 H, CH\(_2\)), 1.68 (t, \(J = 2.6\), 2 H, \(H^1\)), 1.33 (s, 6 H, CH\(_3\)); \(^13\)C NMR
(125 MHz, C\(_6\)D\(_6\)): \(\delta\) 108.9, 79.9, 78.0, 71.0, 27.3, 22.9. Due to its relative instability,
compound 121 was fully characterized as reaction product 122. [ID-III-171]

(7Z,8Z)-4,5,10,11-Di-O-isopropylidene-7-[(tri-n-butylstannyl)methylene]-
8-[(trimethylsilyl)methylene]-1,13-tetradecyne-7,8-diene-4,5,10,11-tetraol (122).
To a solution of (R',R')-4,5-O-isopropylideneoctane-4,5-diol-1,7-diyne (120 mg, 0.66
mmol) in 1 mL C\(_6\)D\(_6\) were added Bu\(_3\)SnSiMe\(_3\) (232 \(\mu\)L, 0.66 mmol, 1 equiv.),
Pd₂(dba)₃ (12 mg, 0.013 mmol, 2 mol%) and P(C₆F₅)₃ (40 mg, 0.07 mmol, 10 mol%).

The reaction was monitored by ¹H NMR. After 24 h at room temperature, the reaction was complete (100% yield by NMR). The solvent was evaporated and the crude mixture purified by column chromatography (SiO₂: hexanes) to give 294 mg (60% isolated yield) of a colorless oil. ¹H NMR (500 MHz, C₆D₆): δ 6.20 (t, J = 30.1, 1 H, SnCH), 5.73 (s, 1 H, SiCH), 4.25 (m, 1 H, H⁹), 4.23 (m, 1 H, H⁶), 3.75 (m, 1 H, H₁⁰), 3.70 (m, 1 H, H⁵), 2.69 (m, 2 H, H⁷ + H¹¹), 2.60 (m, 2 H, H⁸ + H⁴), 2.43 (m, 2 H, H¹²), 2.38 (m, 2 H, H³), 1.82 (m, 1 H, H¹⁴), 1.80 (m, 1 H, H¹), 1.68 (m, 6 H, SnCH₂), 1.40 (m, 24 H, SnCH₂(C₂F₅)₂ + C(CH₃)₃), 0.97 (t, J = 7.3, 9 H, Sn(CH₂)₃CH₃), 0.27 (s, 9 H, SiCH₃); nOe: SnCH → H⁶: 3%, SiCH → H³: 3%, H⁹ → SnBu₃: 2%, H⁶ → SiMe₃: 1%, SnCH → SiCH: 0%, SnBu₃ → SiMe₃: 0%; ¹³C NMR (100 MHz, C₆D₆): δ 158.2, 158.0, 157.7, 157.4, 126.3, 125.9, 125.6, 109.0, 108.9, 108.8, 108.7, 80.3, 80.2, 80.1, 79.1, 79.0, 78.9, 78.8, 71.2, 71.1, 45.0, 44.9, 30.2, 29.8, 27.8, 27.7, 27.6, 27.4, 27.4, 22.8, 22.7, 22.7, 14.0, 10.8, 10.7, 0.6, 0.5; ¹¹⁹Sn (186 MHz, C₆D₆) δ - 63.8; IR (film): 1530, 1423 cm⁻¹; HRMS calcd for C₃₇H₆₄O₄SiSnNa: M⁺⁺ = 743.34882, found 743.35140. [ID-III-192]
**meso-1,3-Butadiene diepoxide (123).** *Synthesis of the intermediate: 1,4-Ditosyl Erythritol.* Erythritol (4 g, 33 mmol) was dissolved in pyridine (80 mL) and cooled to -20°C. A solution of tosyl chloride (12.5 g, 66 mmol, 2 equiv.) in dichloromethane (40 mL) was added dropwise over a period of 8 hours. The reaction mixture was stirred for another 16 h while warming to room temperature. After concentration *in vacuo*, dichloromethane was added to the mixture, and the organic layer was washed with aqueous 1 M sulfuric acid, water, and brine. After drying of MgSO₄ and evaporation of the solvent, 22 g of the product was obtained (64%). As the compound would largely decompose on silica, it was decided to use it as a crude in the next step. [ID-III-218]

To a suspension of crude *meso*-1,4-ditoluenesulfonyl-erythritol (25 g, 89.8 mmol) in diethyl ether (180 mL) was added KOH (11.6 g, 207 mmol, 2.3 equiv.) in water (35 mL) over 15 minutes. The mixture was stirred at room temperature for 45 minutes then decanted. The aqueous layer was extracted with dichloromethane. The combined organic layer was dried (MgSO₄) and concentrated. The residue was distilled at atmospheric pressure to give 3.5 g (45% yield) of a colorless oil. b. p. 138°C (lit. 136-138°C); ¹H NMR (500 MHz, CDCl₃): δ 2.88 (m, 2 H), 2.75 (m, 2 H), 2.62 (m, 2 H); ¹³C NMR (125 MHz, CDCl₃): δ 50.7, 44.9. [ID-III 220]
meso-1,8-ditrimethylsilyloctane-4,5-diol-1,7-diyne. To a solution of trimethylsilylacetylene (3.6 mL, 25.5 mmol, 2.2 equiv.) in 50 mL of THF cooled at -20°C, n-butyllithium (20.0 mL, 1.3 M in hexanes, 25.5 mmol, 2.2 equiv.) was added dropwise. The mixture was stirred at room temperature for 30 minutes and cooled again to -20°C. meso-1,3-Butadiene diepoxide (0.9 mL, 11.6 mmol) in 20 mL of THF and boron trifluoride etherate (3.3 mL, 25.5 mmol, 2.2 equiv.) were added dropwise. The reaction was then stirred at that temperature for 2 h. The mixture was poured on a cold solution of ammonium chloride. The aqueous layer was extracted three times with 10 mL of diethyl ether. The organic layers were combined and washed with 10 mL of water, dried over MgSO₄ and concentrated. The crude compound was chromatographed (SiO₂, hexanes / ethyl acetate 6/1) to give 2.3 g (71% yield) of a white solid. $^1$H NMR (500 MHz, CDCl₃): δ 3.74 (bs, 2 H, OH), 2.56 (m, 4 H, CH₂), 2.34 (m, 2 H, CH), 0.18 (s, 18 H, SiCH₃); $^{13}$C NMR (125 MHz, CDCl₃): δ 102.5, 88.5, 71.2, 24.3, 0.0. The compound was fully characterized as the acetonide. [ID-III-221]
To a solution of meso-1,8-ditrimethylsilyl-4,5-O-isopropylideneoctane-4,5-diol-1,7-diyne (1 g, 3.54 mmol) in 20 mL of DME, 2-methoxypropene (0.51 mL, 5.33 mmol, 1.5 equiv.) and SnCl₂ (330 mg, 1.71 mmol, 0.5 equiv.) were added. The mixture was refluxed for 2 h and then poured on a cold solution of ammonium chloride. The aqueous layer was extracted three times with 10 mL of diethyl ether. The organic layers were combined and washed with 10 mL of water, dried over MgSO₄ and concentrated. The crude compound was chromatographed (SiO₂, hexanes / ethyl acetate 9/1) to give 70 mg (6% yield) of a light yellow oil. ¹H NMR (400 MHz, C₆D₆): δ 4.16 (m, 2 H, CH), 2.51 (m, 4 H, CH₂), 1.41 (s, 3 H, CH₃), 1.14 (s, 3 H, CH₃), 0.15 (s, 18 H, SiCH₃); ¹³C NMR (100 MHz, C₆D₆): δ 108.6, 103.7, 86.6, 76.0, 27.9, 25.4, 21.9, 0.0; IR (neat): 2179, 1380 cm⁻¹; HRMS calcd for C₁₇H₃₀O₂Si₂Na: M⁺⁺ = 345.167652, found 345.166647. [ID-III-222]
**meso-4,5-O-Isopropylideneoctane-4,5-diol-1,7-diyne (124).** A solution of
*meso*-1,8-ditrimethylsilyl-4,5-*O*-isopropylideneoctane-4,5-diol-1,7-diyne (40 mg, 0.12
mmol) in 5 mL of dry methanol was treated by potassium carbonate (94 mg, 0.68, 5.5
equiv.) for 30 minutes at room temperature. Filtration and concentration afforded 18
mg (80%) of a light yellow oil. $^1$H NMR (500 MHz, C$_6$D$_6$): $\delta$ 4.06 (m, 2 H, $H^4$), 2.27
(m, 4 H, $H^3$), 1.69 (t, $J = 2.6$, 2 H, $H^1$), 1.39 (s, 3 H, $CH_3$), 1.15 (s, 3 H, $CH_3$); $^{13}$C
NMR (125 MHz, C$_6$D$_6$): $\delta$ 108.6, 80.5, 75.3, 70.5, 28.0, 25.5, 20.4. [ID-III-224]

![Diagram of meso-4,5-O-Isopropylideneoctane-4,5-diol-1,7-diyne (124)]

**$(1Z,2Z)$-4,5-Di-*O*-isopropylidene-1-[(tri-*n*-butylstannyl)methylene]-2-
[(trimethylsilyl)methylene]-cyclohexane-1,2-diene-4,5-diol (125).** To a solution of
*meso*-4,5-*O*-isopropylideneoctane-4,5-diol-1,7-diyne (18 mg, 0.10 mmol) in 1 mL C$_6$D$_6$
were added Bu$_3$SnSiMe$_3$ (35 $\mu$L, 0.10 mmol, 1 equiv.), Pd$_2$(dba)$_3$ (1.8 mg, 0.002, 2
mol%) and P(C₆F₃)₃ (5.3 mg, 0.01 mmol, 10 mol%). The reaction was monitored by ¹H NMR. After 24 h at room temperature, the reaction was complete (100% yield by NMR). The solvent was evaporated and the crude mixture purified by column chromatography (SiO₂: hexanes) to give 30 mg (56% isolated yield) of a colorless oil.

¹H NMR (500 MHz, C₆D₆): δ 5.79 (d, J = 1.5, J_Sn-H = 30.8, 1 H, SnCH⁸), 5.63 (s, J_Sn-H = 31.5, 1 H, SnCH⁸), 5.40 (d, J = 1.5, 1 H, SiCH⁸), 5.18 (s, 1 H, SiCH⁸), 4.16-4.07 (m, 2 H, H⁴ + H⁷), 4.04-3.95 (m, 2 H, H⁵ + H⁶), 2.80 (m, 2 H, H⁸), 2.73 (m, 2 H, H⁹), 2.64 (m, 2 H, H¹⁰), 2.54 (m, 2 H, H¹¹), 1.66 (m, 12 H, SnCH₂), 1.55 (s, 3 H, C(CH₃)), 1.50 (s, 3 H, C(CH₃)), 1.41 (m, 12 H, SnCH₂CH₂), 1.30 (s, 3 H, C(CH₃)), 1.29 (s, 3 H, C(CH₃)), 1.03 (m, 12 H, Sn(CH₂)₂CH₂), 0.95 (td, J = 7.3, 1.7, 18 H, Sn(CH₂)₂CH₂), 0.19 (s, 9 H, SiCH₃), 0.18 (s, 9 H, SiCH₃); nOe: SnCH⁸ → H⁸: 4%, SiCH⁸ → H⁸: 3%, SnCH⁸ → SnBu₃: 3%, SiCH⁸ → H⁸: 3%, SnCH⁸ → SnBu₃: 20%, SiCH⁸ → SiMe₃: 2%; ¹³C NMR (125 MHz, C₆D₆): δ 157.2, 156.6, 156.5, 155.9, 126.1, 125.1, 124.9, 124.1, 108.7, 77.6, 77.5, 76.0, 75.8, 48.3, 47.9, 43.9, 43.4, 30.2, 29.7, 29.6, 29.5, 29.0, 28.9, 28.0, 27.8, 27.7, 26.6, 13.9, 10.9, 10.8, 0.7, 0.6; ¹¹⁹Sn (186 MHz, C₆D₆) δ - 61.4, -61.6; IR (film): 1460, 1377 cm⁻¹; HRMS calcd for C₃₀H₃₈O₃SiSnNa (123 + THF): M⁺ = 637.3772, found 637.3727. [ID-III-224]
1-(2-Propynyl)-2,5-pyrrolidinedione (128). To a solution of mixture of 2-propyn-1-ol (590 µL, 10.1 mmol, 1 equiv.), succinimide (1 g, 10.1 mmol) and triphenylphosphine (2.65, 10.1 mmol, 1 equiv.) in 20 mL THF was added a solution of diethyl diazodicarboxylate (1.59 mL, 10.1 mmol, 1 equiv.) in 10 mL of THF over a period of 30 minutes. The resulting solutions was stirred at room temperature for 3 h, and the solvent was removed in vacuo. The resulting crude mixture was column chromatographed (SiO₂: dichloromethane) to give 968 mg (68% yield) of a colorless oil. \(^{1}\)H NMR (400 MHz, CDCl₃): \(\delta 4.19 \text{ (d, } J = 2.5, 2 \text{ H, NCH}_2\text{)}, 2.69 \text{ (s, } 4 \text{ H, COCH}_2\text{), } 2.13 \text{ (t, } J = 2.4, 1 \text{ H, CCH)}; \) \(^{13}\)C NMR (100 MHz, CDCl₃): \(\delta 175.7, 76.5, 71.2, 28.0, 27.5. \) [ID-III-174]

5-Ethoxy-1-(2-propynyl)-2-pyrrolidinone (129). To a solution of 1-(2-propynyl)-2,5-pyrrolidinedione (1.13 g, 8.0 mmol) in 20 mL of absolute ethanol cooled in an ice-water bath was added sodium borohydride (1.82 g, 48.0 mmol, 6 equiv.). A
2.0 M solution of hydrogen chloride in absolute ethanol was added at a rate of 2 drops every 5 minutes over a period 2 h and 30 minutes. The reaction was then acidified with 2 M hydrogen chloride in absolute ethanol to approximately pH 3. The resulting mixture was stirred at 0°C for an additional hour and basicified by a saturated solution of sodium bicarbonate. The mixture was extracted 3 times by 20 mL of chloroform. The organic layers were combined and washed with 10 mL of brine, dried (MgSO₄) and concentrated. The material was column chromatographed (SiO₂: hexanes / ethyl acetate 1/1) to give 586 mg (43% yield) of a colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 5.03 (dd, J = 6.4, 1.6, 1 H, H₅), 4.38 (dd, J = 17.5, 2.6, 1 H, NCH₂), 3.62 (ddd, J = 17.4, 2.4, 0.9, 1 H, NCH₂), 3.45 (qd, J = 7.0, 2.7, 2 H, OCH₂CH₃), 2.40 (quintuplet, J = 8.6, 1 H, H₆), 2.22 (ddd, J = 27.2, 10.0, 3.3, 1 H, H₇), 2.15 (t, J = 2.6, 1 H, CCH), 2.10 (m, 1 H, H₈), 1.86 (m, 1 H, H₉), 1.12 (t, J = 7.0, 3 H, OCH₂CH₃);
¹³C NMR (125 MHz, CDCl₃): δ 173.7, 87.8, 77.7, 71.8, 62.3, 29.4, 28.6, 24.8, 15.1.

1-(2-Propynyl)-5-(2-propynyl)-2-pyrrolidinone (131). A solution of 5-ethoxy-1-(2-propynyl)-2-pyrrolidinone (200 mg, 0.58 mmol) in 5 mL of dichloromethane was treated with allenyl tributylstannane (750 µL, 2.44 mmol, 2.1
equiv.) and trimethylsilyltriflate (404 μL, 1.10 mmol, 1.9 equiv.) at room temperature and stirred for 30 minutes. The reaction mixture was then poured onto 10 mL of brine. The aqueous layer was extracted three times by 10 mL of chloroform. The combined organic layers were washed with 5 mL of water, dried (MgSO₄) and concentrated. The material was column chromatographed (SiO₂: hexanes / ethyl acetate 1/1) to give 240 mg (61% yield) of a colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 4.52 (dm, J = 17.8, 1 H, NCH₂), 3.88 (m, 1 H, H₂), 3.63 (dm, J = 17.7, 1 H, NCH₂), 2.45 (m, 2 + 1 H, CH₂CH₂ + H₂), 2.29 (m, 1 H, H₂), 2.18 (m overlapping t, J = 2.6, 1 + 1 H, CCH₂ + H₂), 1.95 (t, J = 2.6, 1 H, CCH₂), 1.91 (m, 1 H, H₂); ¹³C NMR (100 MHz, CDCl₃): δ 174.4, 78.8, 77.3, 72.2, 71.2, 55.2, 29.9, 29.8, 23.2, 23.0; IR (film): 3291, 2928, 1681, 1417, 1305 cm⁻¹; HRMS calcd for C₁₈H₁₁NO: M⁺ = 161.083515, found 161.0841. [ID-III-191]

(2Z,3Z)-1,4-Di-[5-(2-propynyl)]-pyrrolidinone-2-[(tri-n-butylstannyl)methylene]-3-[(trimethylsilyl)methylene]-butane (132). To a solution of 1-(2-Propynyl)-5-(2-propynyl)-2-pyrrolidinone (20 mg, 0.11 mmol) in 1 mL C₆D₆ were added Ph₃SnSiMe₂-t-Bu (56 mg, 0.11 mmol, 1 equiv.), Pd₂(dba)₃ (2.5 mg, 0.04
mmol, 2 mol%) and P(C₆F₅)₃ (6.3 mg, 0.01 mmol, 10 mol%). The reaction was monitored by ¹H NMR. After 15 days at room temperature, the reaction was complete (100% yield by NMR). The solvent was evaporated and the crude mixture purified by column chromatography (SiO₂: hexanes) to give 40 mg (42% isolated yield) of a colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 7.71 (dd, J = 7.8, 1.3, JSn-H = 23.6, 6 H, SnPh(o)), 7.22 (m, 6 H, SnPh(m)), 7.16 (m, 3 H, SnPh(p)), 6.27 (s, JSn-H = 35.4, 1 H, SnCH), 5.40 (s, 1 H, SiCH₂), 4.80 (d, J = 16.6, 1 H, H'), 4.35 (d, J = 16.0, 1 H, H'), 3.88 (d, J = 17.7, 1 H, H'), 3.64 (m, 1 H, H'), 3.27 (m, 1 H, H'), 3.05 (m, 1 H, H'), 2.25 (m, 2 H, CH₂CH₂), 2.05 (m, 2 H, CH₂CH₂), 1.78 (m, 1 H, H') overlapping 1.70 (m, 2 H, H'), 1.61 (t, J = 2.6, 1 H, CCH), 1.56 (t, J = 2.6, 1 H, CCH), 1.52 (m, 1 H, H'), 1.22 (m, 4 H, H₃), 0.91 (s, 9 H, SiBu₃), 0.27 (bs, 3 H, SiCH₃), -0.01 (bs, 3 H, SiCH₃); ¹³C NMR (125 MHz, CDCl₃): δ 204.0, 174.7, 174.0, 157.0, 153.4, 139.1, 137.7, 129.4, 128.8, 104.3, 103.3, 80.1, 79.9, 71.3, 71.1, 63.6, 56.3, 49.5, 30.0, 29.6, 29.5, 26.9, 24.1, 23.9, 23.2, 23.0, 18.2, 17.1, 15.5, -4.5, -4.6; IR (film): 1681, 1429 cm⁻¹. [ID-III-204]

4-(2-Propynyl)-azetidinone. A solution of 4-benzoyloxy azetidinone (1 g, 5.23 mmol) in 15 mL of dichloromethane was treated with allenyl tributylstannane (3.56 mL, 10.98 mmol, 2.1 equiv.) and trimethylsilyl triflate (1.80 mL, 3.94 mmol, 1.9
equiv.) at room temperature and stirred for 30 minutes. The reaction mixture was the poured onto 10 mL of brine. The aqueous layer was extracted three times by 10 mL of chloroform. The combined organic layers were washed with 5 mL of water, dried (MgSO₄) and concentrated. The material was column chromatographed (SiO₂: hexanes / ethyl acetate 1/1) to give 480 mg (84% yield) of a yellow solid. m.p. 95-97°C; ¹H NMR (500 MHz, CDCl₃): δ 6.50 (bs, 1 H, NH), 3.76 (qd, J = 5.9, 2.3, 1 H, H¹), 3.05 (ddd, J = 14.9, 4.9, 2.0, 1 H, H²), 2.70 (ddd, J = 14.5, 2.2, 1.4, 1 H, H³), 2.48 (m, 2 H, CH₂CH₂), 2.02 (t, J = 2.6, 1 H, CCH); ¹³C NMR (100 MHz, CDCl₃): δ 167.5, 79.0, 70.9, 46.0, 42.9, 24.8; IR (film): 3307, 1762, 1363 cm⁻¹. [ID-III-200]

1-(2-Propynyl)-4-(2-propynyl)-azetidinone (134). A solution of 4-(2-propynyl)-azetidinone (55 mg, 0.5 mmol) and dicyclohexyl-18-crown-6 (18.6 mg, 0.05 mmol, 0.1 equiv.) in 5 mL of benzene at room temperature was added sequentially powdered, fused KOH (45.2 mg, 0.8 mmol, 1.6 equiv.) and propargyl bromide (112.5 mg, 80% weight in toluene, 0.76 mmol, 1.5 equiv.). The resulting mixture was stirred at room temperature for 5 h. The mixture was then partitioned between ethyl acetate (10 mL) and ice-water (10 mL). The organic layers was washed with 5 mL of brine, dried (MgSO₄) and concentrated. The material was column chromatographed (SiO₂: hexanes / ethyl acetate 1/1) to give 42 mg (57% yield) of a yellow oil. ¹H NMR (500
MHz, C<sub>d6</sub>): δ 3.86 (dd, J = 17.9, 2.6, 1 H, <sup>1</sup>H), 3.46 (dd, J = 17.9, 2.1, 1 H, <sup>2</sup>H), 3.19 (m, 1 H, <sup>2</sup>H), 2.44 (dd, J = 14.4, 5.1, 1 H, NCH<sub>2</sub>), 2.31 (dd, J = 14.1, 2.1, 1 H, NCH<sub>2</sub>), 1.96 (dd, J = 5.3, 2.7, 2 H, CH<sub>2</sub>CH<sub>2</sub>), 1.89 (t, J = 2.5, 1 H, CCH<sup>3</sup>), 1.74 (t, J = 2.6, 1 H, CCH<sup>3</sup>); <sup>13</sup>C NMR (100 MHz, C<sub>d6</sub>): δ 164.9, 78.9, 77.6, 72.4, 71.5, 49.1, 42.4, 29.9, 22.3; IR (film): 2252, 1754 cm<sup>-1</sup>; HRMS calcd for C<sub>9</sub>H<sub>9</sub>NO: M<sup>+</sup> = 147.0678, found 147.0683. [ID-III-201]

(2Z,3Z)-1,4-Di-[4-(2-propynyl)]-azetidinone-2-[(tri-n-butylstannyl)methylene]-3-[(trimethylsilyl)methylene]-butane (135). To a solution of 1-(2-propynyl)-4-(2-propynyl)-azetidinone (20 mg, 0.13 mmol) in 1 mL C<sub>d6</sub> were added Bu<sub>3</sub>SnSiMe<sub>3</sub> (45 µL, 0.13 mmol, 1 equiv.), Pd<sub>2</sub>(dba)<sub>3</sub> (2.5 mg, 0.003 mmol, 2 mol%) and P(C<sub>6</sub>F<sub>3</sub>)<sub>3</sub> (7.3 mg, 0.013 mmol, 10 mol%). The reaction was monitored by <sup>1</sup>H NMR. After 4 h at room temperature and 4 h at 40°C, the reaction was complete (100% yield by NMR). The solvent was evaporated and the crude mixture purified by column chromatography (SiO<sub>2</sub>: hexanes) to give two diastereoisomeric dimers in 12 mg (36% isolated yield) and 10 mg (30% yield) of colorless oils. First diastereoisomer: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 5.20 (s, J<sub>Sn-H</sub> = 25.5, 1 H, SnCH), 5.47 (s, 1 H, SiCH),
4.14 (dd, J = 17.1, 1.3, 1 H, H¹), 4.02 (dd, J = 17.4, 1.4, 1 H, H³), 3.78 (m, 2 H, H⁴),
3.56 (d, J = 17.1, 1 H, H²), 3.46 (d, J = 17.5, 1 H, H⁴), 3.13 (m, 2 H, CH²CH₂), 2.84
(m, 2 H, CH³CH₂), 2.55 (m, 4 H, H⁵), 2.05 (m, 2 H, CCH), 1.44 (m, 6 H, SnCH₂),
1.28 (m, 6 H, SnCH₂CH₂), 0.88 (t, 15 H, Sn(CH₂)₂CH₂CH₂), 0.10 (s, 9 H, SiCH₃);
nOe : SnCH → H¹ : 3%, SnCH → CH⁴CH₂ : 6%, SiCH → H² : 2%; ¹³C NMR
(125 MHz, C₆D₆): δ 166.1, 165.9, 153.2, 152.7, 79.0, 78.9, 71.8, 71.7, 49.8, 49.5,
49.5, 49.3, 42.2, 31.9, 30.2, 30.1, 29.8, 29.7, 29.6, 28.0, 27.8, 27.5, 23.1, 23.0, 22.0,
21.8, 18.2, 15.5, 14.3, 14.3, 13.9, 10.7, 0.3; ¹¹⁹Sn (186 MHz, CDCl₃) δ -59.2; IR
(film): 3307, 1745, 1520, 1422, 1398 cm⁻¹; HRMS calcd for C₃₃H₆₄N₂O₂SiSnNa: M⁺ =
743.348825, found 743.35140. Second diastereoisomer: ¹H NMR (500 MHz,
CDCl₃): δ 5.92 (s, JSn-H = 25.3, 1 H, SnCH), 5.50 (s, 1 H, SiCH), 4.06 (dd, J = 17.1,
1.3, 1 H, H¹), 3.94 (dd, J = 17.3, 1.3, 1 H, H³), 3.77 (m, 2 H, H⁴), 3.66 (d, J = 17.2, 1
H, H²), 3.59 (d, J = 17.3, 1 H, H⁴), 3.11 (dt, J = 14.9, 5.8, 2 H, CH⁴CH₂), 2.84 (ddd, J
= 14.7, 8.3, 2.1, 2 H, CH⁵CH₂), 2.55 (m, 4 H, H⁵), 2.05 (m, 2 H, CCH), 1.45 (m, 6 H,
SnCH₂), 1.27 (m, 6 H, SnCH₂CH₂), 0.86 (t, 15 H, Sn(CH₂)₂CH₂CH₂), 0.08 (s, 9 H,
SiCH₃); ¹³C NMR (125 MHz, C₆D₆): δ 166.1, 165.9, 153.2, 152.7, 79.0, 79.0, 71.8,
71.7, 49.8, 49.5, 49.3, 42.2, 31.9, 30.2, 30.1, 29.8, 29.7, 29.6, 28.0, 27.8, 27.5,
23.1, 23.0, 22.0, 21.8, 18.2, 15.5, 14.3, 14.3, 13.9, 10.7, 0.3; ¹¹⁹Sn (186 MHz, CDCl₃)
δ -59.2; IR (film): 3308, 1747, 1524, 1423 cm⁻¹. [ID-III-206]
(2Z,3Z)-1,4-Di-[4-(2-propynyl)]-azetidinone-2-[(dimethyl-t-butylsilyl)methylene]-3-[(triphenylstannyl)methylene]-butane (136). To a solution of 1-(2-propynyl)-4-(2-propynyl)-azetidinone (20 mg, 0.13 mmol) in 1 mL C₆D₆ were added Ph₃SnSiMe₂-t-Bu (64 mg, 0.13 mmol, 1 equiv.), Pd₂(dba)₃ (2.5 mg, 0.003 mmol, 2 mol%) and P(C₆F₅)₃ (7.3 mg, 0.013 mmol, 10 mol%). The reaction was monitored by ¹H NMR. After 4 h at room temperature and 4 h at 40°C, the reaction was complete (100% yield by NMR). The solvent was evaporated and the crude mixture purified by column chromatography (SiO₂: hexanes) to give 13 mg (38% isolated yield) of a colorless oil. ¹H NMR (500 MHz, C₆D₆): δ 7.70 (dd, J = 5.8, 1.3, 6 H, SnPh(o)), 7.22 (m, 6 H, SnPh(m)), 7.15 (m, 3 H, SnPh(p)), 6.52 (s, JₚH = 32.4, 1 H, SnCH), 5.49 (s, 1 H, SiCH), 4.36 (d, J = 17.6, 1 H, H₁), 4.01 (d, J = 16.2, 1 H, H₄), 3.84 (d, J = 17.9, 1 H, H₄), 3.41 (bs, 1 H, H₄), 3.26 (m, 1 H, H₄), 3.18 (m, 1 H, H₄), 2.59 (m, 2 H, CH₂CH₂), 2.48 (dd, J = 14.5, 2.3, 1 H, CH₃CH₂), 2.34 (dd, J = 16.6, 2.1, 1 H, CH₃CH₂) overlapping 2.32 (m 1 H, H₃), 2.07 (m, 1 H, H₃), 1.77 (m, 2 H, H₃), 1.70 (t, J = 2.6, 1 H, CCH), 1.62 (t, J = 2.6, 1 H, CCH), 0.87 (s, 9 H, SiBu), 0.08 (bs, 3 H, SiCH₃), -0.02 (bs, 3 H, SiCH₃); nOe : SnCH → H₁ : 2%, SiCH → H₄ : 2%; ¹³C NMR (125 MHz, C₆D₆): δ 166.5, 165.8, 156.9, 152.9, 138.9, 137.7, 136.5, 129.5,
1-(3-Butynyl)-2,5-pyrrolidinedione. To a solution of mixture of 3-butyn-1-ol (764 µL, 10.1 mmol, 1 equiv.), succinimide (1 g, 10.1 mmol) and triphenylphosphine (2.65, 10.1 mmol, 1 equiv.) in 20 mL THF was added a solution of diethyl diazodicarboxylate (1.59 mL, 10.1 mmol, 1 equiv.) in 10 mL of THF over a period of 30 minutes. The resulting solutions was stirred at room temperature for 3 h, and the solvent was removed in vacuo. The resulting crude mixture was column chromatographed (SiO2: dichloromethane) to give 1.05 g (68% yield) of a colorless oil. 

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.56 (d, $J = 9.5$, 2 H, NCH$_2$), 2.62 (s, 4 H, CCH$_2$), 2.39 (m, 2 H, NCH$_2$CH$_2$), 1.88 (t, $J = 2.6$, 1 H, CCH); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 176.7, 79.9, 70.0, 36.8, 27.9, 17.0. [ID-III-175]
5-Ethoxy-1-(3-butynyl)-2-pyrrolidinone (138). To a solution of 1-(3-butynyl)-2,5-pyrrolidinedione (400 mg, 2.57 mmol) in 10 mL of absolute ethanol cooled in an ice-water bath was added sodium borohydride (600 mg, 15.42 mmol, 6 equiv.). A 2.0 M solution of hydrogen chloride in absolute ethanol was added at a rate of 2 drops every 5 minutes over a period 2 h and 30 minutes. The reaction was then acidified with 2 M hydrogen chloride in absolute ethanol to approximately pH 3. The resulting mixture was stirred at 0°C for an additional hour and basicified by a saturated solution of sodium bicarbonate. The mixture was extracted 3 times by 20 mL of chloroform. The organic layers were combined and washed with 10 mL of brine, dried (MgSO₄) and concentrated. The material was column chromatographed (SiO₂: hexanes / ethyl acetate 1/1) to give 240 mg (50% yield) of a colorless oil. ^1H NMR (250 MHz, CDCl₃): δ 5.01 (d, J = 4.8, 1 H, H*), 3.52 (m, 1 H, NCH₂), 3.39 (m, 2 H, OCH₂), 3.24 (m, 1 H, NCH₂), 2.38 (m, 2 + 1 H, NCH₂CH₂ + H*), 2.21 (m, 2 H, H* + H*), 1.90 (t, J = 2.6, 1 H, CCH overlapping m, 1 H, H*), 1.12 (t, J = 7.0, 3 H, OCH₂CH₂); ^13C NMR (63 MHz, CDCl₃): δ 17487, 89.5, 81.4, 69.5, 61.5, 39.2, 28.6, 24.6, 17.7, 15.1. [ID-III-173]
5-Allenyl-1-(3-butynyl)-2-pyrrolidinone (140). A solution of 5-ethoxy-1-(3-butynyl)-2-pyrrolidinone (100 mg, 0.54 mmol) in 5 mL of dichloromethane was treated with propargyltrimethylsilane (242 µL, 1.62 mmol, 3 equiv.) and borontrifluoride etherate (205 µL, 1.62 mmol, 3 equiv.) at 0°C. The reaction was allowed to warm to room temperature over 30 minutes. The mixture was then poured onto 10 mL of brine. The aqueous layer was extracted three times by 10 mL of chloroform. The combined organic layers were washed with 5 mL of water, dried (MgSO₄) and concentrated. The material was column chromatographed (SiO₂: hexanes / ethyl acetate 1/1) to give 85 mg (88% yield) of a colorless oil. \(^1\)H NMR (500 MHz, C₆D₆): δ 4.57 (m, 1 H, CH₂CH), 4.46 (m, 2 H, CHCCCH₂), 3.70 (m overlapping quintuplet, J = 7.7, 1 + 1 H, H^δ + NCH₂), 2.97 (quintuplet, J = 7.1, 1 H, NCH₂), 2.30 (m, 1 H, H^δ), 2.18 (m, 1 H, H^δ), 2.00 (m, 1 H, NCH₂CH₂), 1.89 (m, 1 H, NCH₂CH₂), 1.72 (t, J = 2.6, 1 H, CCH), 1.60 (m, 1 H, H^δ), 1.18 (m, 1 H, H^δ); \(^1^3\)C NMR (125 MHz, C₆D₆): δ 208.6, 173.4, 91.6, 81.9, 76.7, 70.1, 57.8, 39.8, 29.6, 26.1, 17.7; IR (film): 3308, 1682 cm\(^{-1}\); HRMS calcd for C₁₁H₁₃NO: M⁺ = 175.0991, found 175.0974. [ID-III-179]
5-(1-E-3-Tri-n-butylstannyl-2-trimethylsilylpropenyl)-1-(3-butynyl)-2-pyrrolidinone (141). To a solution of 5-allenyl-1-(3-butynyl)-2-pyrrolidinone (15 mg, 0.08 mmol) in 1 mL C₆D₆ were added Bu₃SnSiMe₃ (29 µL, 0.08 mmol, 1 equiv.), Pd₂(dba)₃ (1.5 mg, 0.002 mmol, 2 mol%) and P(C₆F₅)₃ (5.0 mg, 0.008 mmol, 10 mol%). The reaction was monitored by ¹H NMR. After 15 minutes at room temperature, the reaction was complete (100% yield by NMR). The solvent was evaporated and the crude mixture purified by column chromatography (SiO₂: hexanes / diethyl ether 1/1) to give 20 mg (44% isolated yield) of a colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 5.20 (q, J = 9.1, 1 H, CH₂C), 4.43 (m, 1 H, H'), 3.52 (quintuplet, J = 6.9, 1 H, NCH₂), 3.05 (quintuplet, J = 7.2, 1 H, NCH₂), 2.46 (m, 1 H, H'), 2.35 (m, 3 H, H' + NCH₂CH₂), 2.18 (m, 1 H, H'), 2.11 (dd, J = 7.9, 2.1, 1 H, H'), 1.91 (t, J = 2.7, 1 H, CCH), 1.74 (d, J = 11.3, 1 H, SnCH₂CSi), 1.63 (m, 1 H, SnCH₂CSi), 1.45 (m, 6 H, SnCH₂), 1.28 (m, 6 H, SnCH₂CH₂), 0.88 (m, 15 H, Sn(CH₂)₂CH₂CH₃), 0.05 (s, 9 H, SiCH₃); nOe : CH₂CH → SiMe₃ : 2%; ¹³C NMR (125 MHz, CDCl₃): δ 175.0, 146.6, 131.8, 81.6, 69.6, 56.2, 39.8, 30.3, 29.1, 27.4, 25.7, 17.9, 13.6, 12.9, 10.1, -1.6; ¹¹⁹Sn (186 MHz, CDCl₃) δ -18.6; IR (film): 3312, 1681, 1455, 1417 cm⁻¹.

This compound was fully characterized as the bicyclic 142. [ID-III-193]
trans-Z-[3,4]-Bicyclo-1-N-2-oxo-7-[(tri-n-butylstannyl)methylene]-6-[(1-trimethylsilyl)ethene]-octane (142). To a solution of 5-allenyl-1-(3-butynyl)-2-pyrrolidinone (15 mg, 0.08 mmol) in 1 mL C₆D₆ were added Bu₃SnSiMe₃ (29 μL, 0.08 mmol, 1 equiv.), Pd₂dba₃ (1.5 mg, 0.002 mmol, 2 mol%) and P(C₆F₅)₃ (5.0 mg, 0.008 mmol, 10 mol%). The reaction was monitored by ¹H NMR. After 18 h at 60°C, the reaction was complete (100% yield by NMR). The solvent was evaporated and the crude mixture purified by column chromatography (SiO₂: hexanes / diethyl ether 1/1) to give 5 mg (11% isolated yield) of a colorless oil. The same product could be obtained in 41% yield by reaction of 5-(1-E-3-tri-n-butylstannyl-2-trimethylsilylpropenyl)-1-(3-butynyl)-2-pyrrolidinone with 2 mol% of Pd₂dba₃ and 10 mol% of P(C₆F₅)₃ in 1 mL of C₆D₆. ¹H NMR (500 MHz, CDCl₃): δ 5.81 (s, JSn-H = 28.0, 1 H, SnCH), 5.67 (dm, J = 2.5, 1 H, C=CH₂), 5.50 (d, J = 2.6, 1 H, C=CH₂), 3.82 (ddd, J = 8.6, 6.7, 1.3, 1 H, H₅), 3.64 (m, 1 H, H₇), 3.23 (m, 1 H, H₆), 2.98 (d, J = 8.6, 1 H, H₈), 2.71 (m, 1 H, H₉), 2.41 (m, 1 H, H₆), 2.34 (t, J = 7.5, 2 H, H₇), 2.14 (m, 1 H, H₈), 1.62 (m, 1 H, H₉), 1.42 (m, 6 H, SnCH₂), 1.27 (m, 6 H, SnCH₂CH₂), 0.85 (m, 15 H, Sn(CH₂)₂CH₂), 0.13 (s, 9 H, SiCH₃); nOe: SnCH → H₇: 3%, SnCH → H₈: 0%, H₇ → H₈: 0%; ¹³C NMR (125 MHz, CDCl₃): δ 174.2, 153.9, 150.5, 129.1, 128.9, 60.3, 58.6, 41.0, 36.1, 162
l-(2,3-Butadienyl)-2,5-pyrrolidinedione. To a solution of mixture of 2,3-butadien-1-ol (1.10 g, 19.6 mmol, 1 equiv.), succinimide (1.94 g, 19.6 mmol) and triphenylphosphine (5.15, 19.6 mmol, 1 equiv.) in 20 mL THF was added a solution of diethyl diazodicarbonate (3.1 mL, 19.6 mmol, 1 equiv.) in 10 mL of THF over a period of 30 minutes. The resulting solutions was stirred at room temperature for 3 h, and the solvent was removed in vacuo. The resulting crude mixture was column chromatographed (SiO₂: dichloromethane) to give 2.70 g (99% yield) of a colorless oil. 

$^{1}H$ NMR (250 MHz, CDCl₃): $\delta$ 4.97 (m, 1 H, CCH), 4.63 (m, 2 H, CCH₂), 3.89 (m, 2 H, NCH₂), 2.54 (s, 4 H, H₃); $^{13}C$ NMR (63 MHz, CDCl₃): $\delta$ 207.8, 176.5, 85.1, 77.3, 36.2, 27.7. [ID-III-180]
5-Ethoxy-1-(2,3-butadienyl)-2-pyrrolidinone. To a solution of 1-(2,3-butadienyl)-2,5-pyrrolidinedione (450 mg, 2.9 mmol) in 20 mL of absolute ethanol cooled in an ice-water bath was added sodium borohydride (660 mg, 17.4 mmol, 6 equiv.). A 2.0 M solution of hydrogen chloride in absolute ethanol was added at a rate of 2 drops every 5 minutes over a period 2 h and 30 minutes. The reaction was then acidified with 2 M hydrogen chloride in absolute ethanol to approximately pH 3. The resulting mixture was stirred at 0°C for an additional 30 minutes and basicified by a saturated solution of sodium bicarbonate. The mixture was extracted 3 times by 20 mL of chloroform. The organic layers were combined and washed with 10 mL of brine, dried (MgSO₄) and concentrated. The material was column chromatographed (SiO₂: hexanes / ethyl acetate 1/1) to give 280 mg (55% yield) of a colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 5.08 (m, 1 H, H₂), 4.97 (m, 1 H, CH), 4.76 (m, 2 H, CH₂), 4.22 (dm, J = 14.0, 1 H, NCH₂), 3.57 (m, 1 H, NCH₂), 3.46 (q, J = 7.0, 2 H, OCH₂), 2.50 (m, 1 H, H'), 2.30 (m, 1 H, H'), 2.03 (m, 1 H, H'), 1.94 (m, 1 H, H'), 1.19 (t, J = 7.0, 3 H, OCH₂H₂); ¹³C NMR (125 MHz, CDCl₃): δ 209.1, 174.5, 88.5, 86.2, 76.6, 62.0, 38.7, 29.0, 25.0, 15.3. [ID-III-188]
1-(2,3-Butadienyl)-5-(2-propynyl)-2-pyrrolidinone (144). A solution of 5-ethoxy-1-(2,3-butadienyl)-2-pyrrolidinone (180 mg, 0.97 mmol) in 5 mL of dichloromethane was treated with allenyl tributylstannane (606 μL, 2.04 mmol, 2.1 equiv.) and trimethylsilyltriflate (335 μL, 1.84 mmol, 1.9 equiv.) at room temperature and stirred for 30 minutes. The reaction mixture was then poured onto 10 mL of brine. The aqueous layer was extracted three times by 10 mL of chloroform. The combined organic layers were washed with 5 mL of water, dried (MgSO₄) and concentrated. The material was column chromatographed (SiO₂: hexanes / ethyl acetate 1/1) to give 156 mg (88% yield) of a colorless oil. \(^1\)H NMR (500 MHz, CDCl₃): δ 5.03 (quintuplet, J = 6.6, 1 H, CCH), 4.76 (m, 2 H, CCH₂), 4.27 (dm, J = 15.1, 1 H, NCH₂), 3.78 (m, 1 H, \(H^5\)), 3.51 (ddd, J = 15.2, 7.5, 0.6, 1 H, NCH₂), 2.44 (m, 2 + 1 H, CH\(^3\)CH₂ + \(H^4\)), 2.30 (m, 1 H, \(H^4\)), 2.16 (m, 1 H, \(H^5\)), 1.95 (t, J = 2.6, 1 H, CH\(^2\)CH₂CCH), 1.90 (m, 1 H, \(H^3\)); \(^13\)C NMR (125 MHz, CDCl₃): δ 209.0, 174.8, 85.9, 79.2, 76.7, 71.0, 55.7, 39.0, 30.0, 23.4, 23.1; IR (film): 3296, 1955, 1682 cm\(^{-1}\); HRMS calcd for C\(_{11}\)H\(_{13}\)NO: M\(^+\) = 175.0991, found 175.1004. [ID-III-190]
5-(2-Propynyl)-1-(2-E-4-tri-n-butylstannyl-3-triaethylsilylbutenyl)-2-pyrrolidinone (145). To a solution of 1-(2,3-butadienyl)-5-(2-propynyl)-2-pyrrolidinone (20 mg, 0.11 mmol) in 1 mL C₆D₆ were added Bu₃SnSiMe₃ (36 µL, 0.11 mmol, 1 equiv.), Pd₂(dba)₃ (2 mg, 0.002 mmol, 2 mol%) and P(C₆F₅)₃ (6 mg, 0.011 mmol, 10 mol%). The reaction was monitored by ¹H NMR. After 4 h at room temperature, the reaction was complete (100% yield by NMR). The solvent was evaporated and the crude mixture purified by column chromatography (SiO₂: hexanes / diethyl ether 2/1) to give 46 mg (80% isolated yield) of a colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 5.27 (dd, J = 6.5, 5.5, 1 H, NCH₂CH), 4.08 (dd, J = 15.9, 5.3, 1 H, NCH₂), 3.71-3.64 (m overlapping dd, J = 16.2, 6.1, 1 + 1 H, NCH₂ + H*), 2.52 (m, 1 H, H*), 2.40 (m, 2 H, CH*CH₂), 2.35 (m, 1 H, H*), 2.15 (m, 1 H, H*), 1.95 (m, 2 H, H* + CCH), 1.86 (d, J = 11.4, JSn-H = 32.9, 2 H, SnCH₂CSi), 1.63 (m, 6 H, SnCH₂), 1.40 (m, 6 H, SnCH₂CH₂), 1.00 (m, 15 H, Sn(CH₂)₂CH₂CH₃), 0.16 (s, 9 H, SiCH₃); nOe : NCH₂CH → SiMe₃ : 2%, NCH₂CH → SnCH₂CSi : 0%; ¹³C NMR (125 MHz, C₆D₆): δ 173.5, 144.8, 128.6, 79.8, 71.2, 56.2, 39.5, 29.9, 29.7, 29.6, 27.8, 23.7, 13.9, 13.6, 10.6, -1.4; ¹⁹Sn (186 MHz, CDCl₃) δ -17.8; IR (film): 3312, 1695 cm⁻¹; HRMS calcd for C₂₆H₄₉NOSiSnNa: M⁺⁺ = 562.24977, found 562.24654. [ID-III-196]
Attempted cyclizations of 145 are described in Table 3.1. [ID-III-202] and [ID-III-234]

trans-\(Z\)-[3,4]-Bicyclo-1-N-2-oxo-8-[(1-dimethyl-t-silyl)ethene]-7-

\((\text{triphenylstannyl})\text{methylen}-\text{octane}\) (146). To a solution of 1-(2,3-butadienyl)-5-(2-propynyl)-2-pyrrolidinone (20 mg, 0.11 mmol) in 1 mL \(\text{C}_6\text{D}_6\) were added \(\text{Ph}_3\text{SnSiMe}_2\text{-t-Bu}\) (52 mg, 0.11 mmol, 1 equiv.), \(\text{Pd}_2(\text{dba})_3\) (2 mg, 0.002 mmol, 2 mol%) and \(\text{P}(\text{C}_6\text{F}_5)_3\) (6 mg, 0.011 mmol, 10 mol%). The reaction was monitored by \(^1\text{H}\) NMR. After 18 h at 40°C, the reaction was complete (100% yield by NMR). The solvent was evaporated and the crude mixture purified by column chromatography (\(\text{SiO}_2\): hexanes / diethyl ether 2/1) to give 29 mg (41% isolated yield) of a colorless oil. The same product could be obtained by reaction of 5-(2-propynyl)-1-(2-E-4-tri-n-butylstannyl-3-trimethylsilylbutenyl)-2-pyrrolidinone with 2 mol% of \(\text{Pd}_2(\text{dba})_3\) and 10 mol% of \(\text{P}(\text{C}_6\text{F}_5)_3\) in 1 mL of \(\text{C}_6\text{D}_6\). \(^1\text{H}\) NMR (500 MHz, \(\text{C}_6\text{D}_6\)): \(\delta\) 7.60 (dd, \(J = 7.8, 1.4, 6\) H, \(\text{SnPh}(\phi)\)), 7.20 (m, 9 H, \(\text{SnPh}(m + p)\)), 6.04 (s, \(J_{\text{Sn-H}} = 28.0, 1\) H, \(\text{SnCH}_2\)), 5.84 (t, \(J = 2.1, 1\) H, \(\text{SiCCH}_2\)), 5.45 (t, \(J = 2.1, 1\) H, \(\text{SiCCH}_2\)), 3.92 (dd, \(J = 13.2, 6.7, 1\) H, \(H^p\)), 3.57 (m, 1 H, \(H^p\)), 3.50 (m, 1 H, \(H^p\)), 3.23 (dd, \(J = 13.2, 5.2, 1\) H, \(H^p\)), 2.52

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(dd, J = 6.0, 1.6, 1 H, H\textsuperscript{a}), 2.06-1.96 (m, 2 H, H\textsuperscript{b} overlapping m, 1 H, H\textsuperscript{c}), 1.34 (m, 1 H, H\textsuperscript{d}), 1.09 (m, 1 H, H\textsuperscript{e}), 0.75 (s, 9 H, SiBu), -0.17 (s, 3 H, SiCH\textsubscript{3}), -0.24 (s, 3 H, SiCH\textsubscript{3}); nOe : SnCH \rightarrow H\textsuperscript{f} : 3\%, SnCH \rightarrow H\textsuperscript{g} : 0\%, H\textsuperscript{b} \rightarrow SiBu : 1\%, H\textsuperscript{d} \rightarrow H\textsuperscript{e} : 0\%; \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) : δ 173.4, 156.8, 151.9, 139.1, 137.4, 129.3, 129.0, 125.5, 53.6, 50.7, 44.0, 42.0, 31.1, 27.3, 26.8, 17.3, -3.4, -5.5; \textsuperscript{119}Sn (186 MHz, C\textsubscript{6}D\textsubscript{6}) δ -152.0; IR (film) : 1682, 1428 cm\textsuperscript{-1}; HRMS calcd for C\textsubscript{35}H\textsubscript{33}NOSiSnNa: M\textsuperscript{+} = 664.202829, found 664.207532. [ID-III-203]
OTBDMS

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\begin{align*}
\text{O} & \quad \text{N} \\
\text{H} & \\
\text{O} & \\
\end{align*}
\]
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[3\([R(1'R,4'R)-3-[1-(\text{tert-Butyldimethylsilyloxy})\text{ethyl}]-4-(1,2-\text{propadienyl})-\text{azetidinone (148).}]

A solution of [3\([R(1'R,4'R)-4-\text{acetoxy}-3-[1-(\text{tert-Butyldimethylsilyloxy})\text{ethyl}]-\text{azetidinone (100 mg, 0.35 mmol) in 5 mL of hexane was treated with propargyltrimethylsilane (234 \mu L, 1.56 mmol, 4.5 equiv.) and borontrifluoride etherate (198 \mu L, 1.56 mmol, 4.5 equiv.) at 0 °C. The reaction was allowed to warm to room temperature over 30 minutes and stirred at room temperature for 16 h. The mixture was then poured onto 10 mL of brine. The aqueous layer was extracted three times by 10 mL of chloroform. The combined organic layers were washed with 5 mL of water, dried (MgSO₄) and concentrated. The material was column chromatographed (SiO₂: hexanes / ethyl acetate 1/1) to give 80 mg (85% yield) of a white crystalline compound. m.p. 72-74°C; \(^1\)H NMR (500 MHz, CDCl₃): \(\delta 6.18 \text{ (bs, 1 H, NH)}\), 5.24 (q, \(J = 6.7\), 1 H, CH\(^3\)CH), 4.84 (m, 2 H, CCH₂), 4.17 (2 overlapping m, 1 + 1 H, \(H^3 + H^4\)), 2.93 (m, 1 H, CHOSi), 1.16 (d, \(J = 6.2\), 3 H, CH₃), 0.85 (s, 9 H, SiBu), 0.06 (s, 6 H, SiCH₃); \(^1\)C NMR (125 MHz, CDCl₃): \(\delta 208.1\),...
168.2, 91.5, 77.6, 66.0, 65.2, 48.7, 25.7, 22.3, -5.1; IR (film): 1756 cm⁻¹. The material was fully characterized in the next step as alleneyne 149. [ID-III-238]

![Diagram of molecule 149]

[3R(1'R,4R)-3-[1-(tert-Butyldimethylsilyloxy)ethyl]-4-(1,2-propadienyl)-1-N-(2-propynyl)-azetidinone (149).] To a suspension of NaH (80% in mineral oil, 12.3 mg, 0.41 mmol, 1.1 equiv.) in 5 mL of THF at 0°C was added [3R(1'R,4R)-3-[1-(tert-butyldimethylsilyloxy)ethyl]-4-(1,2-propadienyl)-azetidinone (100 mg, 0.37 mmol) in 2 mL THF over 15 minutes. The mixture was stirred at 0°C for an additional 15 minutes and was let to warm at room temperature. After 30 minutes, propargyl bromide (80% solution in toluene, 61 mg, 0.41 mmol, 1.1 equiv.) was added dropwise. The reaction mixture was stirred at room temperature for 2 hours and then taken in 10 mL of ammonium chloride. The organic layer was washed with 10 mL of a saturated solution of sodium bicarbonate. The aqueous layer was extracted 3 times with 10 mL of diethyl ether. The combined organic layers were dried (MgSO₄) and concentrated. The residue was purified by column chromatography (SiO₂: hexanes / ethyl acetate 5/1) to give 111 mg (94% yield) of a clear oil. ¹H NMR (500 MHz, CDCl₃): δ 5.21 (q, J = 6.7, 1 H, CH₃CH), 4.86 (m, 2 H, CCH₂), 4.25 (dd, J = 7.5, 1.6, 1 H, H¹), 4.18 (m, 1 H, H²) overlapping 4.16 (dd, J = 17.8, 2.5, 1 H, NCH₂), 3.75 (dd, J = 17.8, 2.5, 1 H,
NCH₂), 2.93 (m, 1 H, CHOSi), 2.18 (t, J = 2.5, 1 H, NCH₂CCH), 1.17 (d, J = 6.2, 3 H, CH₃), 0.84 (s, 9 H, SiBu), 0.04 (s, 6 H, SiCH₃); \(^{13}\)C NMR (125 MHz, CDCl₃): δ 209.1, 166.9, 89.5, 77.3, 76.9, 72.2, 65.0, 64.9, 52.2, 29.6, 25.7, 22.4, 17.9, -4.4, -5.0; IR (film): 3311, 1955, 1761 cm⁻¹; HRMS calcd for C₁₇H₂₇NO₂SiNa: M⁺ = 328.17032, found 328.16976. [ID-in-244]

\[ 3R(1'R,4R)-3-[1-(\text{tert-Butyldimethylsilyloxy})ethyl]-1-N-(2-propynyl)-4-(3-tri-n-butylstannyl-2-trimethylsilyl-1-propenyl)-azetidinone \ (150) \]

To a solution of [3R(1'R,4R)-3-[1-(\text{tert-Butyldimethylsilyloxy})ethyl]-4-(1,2-propadienyl)-1-N-(2-propynyl)-azetidinone (16 mg, 0.05 mmol) in 1 mL C₆D₆ were added Bu₃SnSiMe₃ (18 µL, 0.05 mmol, 1 equiv.), Pd₂(dba)₃ (1 mg, 0.001 mmol, 2 mol%) and P(C₆F₅)₃ (3 mg, 0.005 mmol, 10 mol%). The reaction was monitored by \(^1\)H NMR. After 15 minutes at room temperature, the reaction was complete (100% yield by NMR). The solvent was evaporated and the crude mixture purified by column chromatography (SiO₂: hexanes / diethyl ether 5/1) to give 8 mg (23% isolated yield) of a colorless oil. \(^1\)H NMR (500 MHz, C₆D₆): δ 5.47 (d, J = 9.4, 1 H, CH₄CH), 4.62 (dd, J = 9.4, 2.1, 1 H, H⁺), 4.20 (m, 1 H, H⁻), 4.00 (dd, J = 17.9, 2.5, 1 H, NCH₂), 3.56 (dd, J = 17.9, 2.5, 1 H, NCH₂), 2.70 (t, J = 2.4, 1 H, CHOSi), 2.17 (dd, J₈H = 38.3, J = 11.7, 2 H, SnCH₂CSi), 1.84 (t,
J = 2.5, 1 H, NCH₂CCH), 1.63 (m, 6 H, SnCH₂), 1.40 (m, 6 H, SnCH₂CH₂), 1.08 (m, 6 + 3 H, Sn(CH₂)₂CH₂ + CH₃), 1.03 (s, 9 H, OSiBu), 0.96 (t, J = 7.3, 9 H, Sn(CH₂)₃CH₃), 0.26 (s, 3 H, OSiCH₃), 0.15 (s, 9 H, CSiCH₃), 0.14 (s, 3 H, OSiCH₃); nOe: CHCH → CHOSi: 2%, CH₄CH → CSiCH₃: 1%; ¹³C NMR (125 MHz, C₆D₆): δ 205.5, 166.5, 147.5, 131.0, 79.8, 71.6, 66.6, 64.8, 50.4, 29.7, 29.2, 27.9, 26.3, 22.8, 18.4, 14.0, 13.9, 10.7, -1.3, -4.2, -4.5; ¹¹⁹Sn (186 MHz, C₆D₆) δ -20.6; IR (film): 1743 cm⁻¹; HRMS calcd for C₃₂H₆₉NO₂Si₂SnNa: M⁺ = 693.33117, found 693.33396. [ID-in-245]

The same reaction mixture left for longer reaction time (1 h) at room temperature or left at higher temperatures (30 to 60°C) for short periods of time (10-20 minutes) decomposed rapidly (NMR).

[3R(1',4R)-3-[1-(tert-Butyldimethylsilyloxy)ethyl]-4-(1,2-propadienyl)-N-(2-propenyl)-azetidinone (151). To a suspension of NaH (80% in mineral oil, 30 mg, 1.03 mmol, 1.1 equiv.) in 5 mL of THF at 0°C was added [3R(1',4R)-3-[1-(tert-butyldimethylsilyloxy)ethyl]-4-(1,2-propadienyl)-azetidinone (250 mg, 0.93 mmol) in 2 mL THF over 15 minutes. The mixture was stirred at 0°C for an additionnal 15 minutes and was let to warm at room temperature. After 30 minutes, allyl bromide (89
µL, 1.03 mmol, 1.1 equiv.) was added dropwise. The reaction mixture was stirred at room temperature for 2 hours and then taken in 10 mL of ammonium chloride. The organic layer was washed with 10 mL of a saturated solution of sodium bicarbonate. The aqueous layer was extracted 3 times with 10 mL of diethyl ether. The combined organic layers were dried (MgSO$_4$) and concentrated. The residue was purified by column chromatography (SiO$_2$: hexanes / ethyl acetate 5/1) to give 120 mg (42% yield) of a clear oil. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.70 (q, $J = 6.7$, 1 H, NCH$_2$CH), 5.18 (dd, $J = 17.1$, 1.5, 1 H, NCH$_2$CH$_2$), 5.12 (2 overlapping m, 1 + 1 H, NCH$_2$CHCH$_2$ + CH$^t$CH), 4.80 (dd, $J = 7.0$, 0.8, 2 H, CH$^t$CHCH$_2$), 4.17 (m, 1 H, $H^3$), 4.09 (dd, $J = 7.8$, 1.6, 1 H, $H^4$), 3.95 (ddt, $J = 15.5$, 5.5, 1.4, 1 H, NCH$_2$), 3.55 (ddd, $J = 15.6$, 7.0, 0.9, 1 H, NCH$_2$) 2.89 (m, 1 H, CHOSi), 1.15 (d, $J = 6.3$, 3 H, CH$_3$), 0.83 (s, 9 H, SiBu), 0.04 (s, 3 H, SiCH$_3$), 0.02 (s, 3 H, SiCH$_3$); $^{13}$C NMR (63 MHz, CDCl$_3$): $\delta$ 209.0, 167.2, 131.8, 118.3, 89.6, 77.0, 65.0, 64.6, 52.1, 43.1, 25.7, 22.4, 17.8, -4.5, -4.9; IR (film): 2930, 1955, 1758 cm$^{-1}$; HRMS calcd for C$_{17}$H$_{39}$NO$_2$SiNa: $M^{+}$ = 330.18597, found 330.18495. [ID-III-248]

![Structure](image)

$[3(R',R,4R)-3-[1-(tert-Butyldimethylsilyloxy)ethyl]-1-N-(2-propynyl)-4-(3-tri-n-butylstannyl-2-trimethylsilyl-1-propenyl)-azetidinone (152).]$ To a solution of

173

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[3R(1'R,4'R)-3-[1-((tert-Butyldimethylsilyloxy)ethyl)-4-(1,2-propadienyl)-1-N-(2-propynyl)-azetidinone (25 mg, 0.08 mmol) in 1 mL C₆D₆ were added Bu₃SnSiMe₃ (29 µL, 0.08 mmol, 1 equiv.), Pd₂(dba)₃ (2 mg, 0.001 mmol, 2 mol%) and P(C₆F₅)₃ (5 mg, 0.008 mmol, 10 mol%). The reaction was monitored by $^1$H NMR. After 15 minutes at room temperature, the reaction was complete (100% yield by NMR). The solvent was evaporated and the crude mixture purified by column chromatography (SiO₂: hexanes / diethyl ether 5/1) to give 45 mg (82% isolated yield) of a colorless oil. $^1$H NMR (500 MHz, C₆D₆): δ 5.76 (m, 1 H, NCH₂CH), 5.44 (d, J = 9.4, 1 H, CH₄CH), 5.20 (ddd, J = 15.8, 2.9, 1.4, 1 H, NCH₂CHCH₂), 5.03 (dd, J = 10.2, 1.4, 1 H, NCH₂CHCH₂), 4.52 (dd, J = 9.4, 2.1, 1 H, H₃), 4.25 (dq, J = 6.2, 2.4, CHO₃Si), 3.92 (ddt, J = 16.1, 5.1, 1.5, 1 H, NCH₃), 3.53 (dd, J = 16.1, 6.0, 1 H, NCH₂), 2.74 (t, J = 2.3, 1 H, H₃), 2.07 (dd, J₉ₛ+H₃ = 38.3, J = 11.7, 2 H, SnCH₂CSi), 1.59 (m, 6 H, SnCH₂), 1.38 (m, 6 H, SnCH₂CH₂), 1.08 (d, J = 6.3, 3 H, CH₃), 1.02 (s, 9 H, OSiBu overlapping m, 6 H, Sn(CH₂)₂CH₂), 0.94 (t, J = 7.4, 9 H, Sn(CH₂)₃CH₃), 0.24 (s, 3 H, OSiCH₃), 0.14 (s, 3 H, OSiCH₃), 0.12 (s, 9 H, CSiCH₃); nOe: CH₄CH → CHO₃Si: 3%, CH₄CH → CSiCH₃: 2%; $^{13}$C NMR (125 MHz, C₆D₆): δ 206.0, 167.1, 147.2, 134.0, 131.6, 116.9, 66.2, 64.8, 50.2, 43.1, 29.7, 29.6, 29.5, 27.8, 26.2, 22.9, 18.4, 13.9, 13.8, 10.7, -1.4, -4.4, -4.4; $^{119}$Sn (186 MHz, C₆D₆) δ -20.3; IR (film): 1759 cm⁻¹; HRMS calcd for C₃₂H₆₅NO₂Si₂SnNa: M⁺⁺ = 694.34682, found 694.34175. [ID-III-249]
REFERENCES


175


(24) Examples of Sharpless epoxidation of ortho-substituted cinnamyl alcohol derivatives are rare; no examples of the especially valuable 2-nitrocinnamyl alcohols have been reported previously. Yields and selectivities for these reactions are generally low. See for example: (a) Medina, E.; Vidal-Ferran, A.; Moyano, A.; Pericás, M. A.; Riera, A. Tetrahedron: Asymmetry 1997, 8, 1581. (b) Takahashi, K.; Ogata, M. J. Org. Chem. 1987, 52, 1877.


(32) Sandmeyer, T. Ber. 1884, 17, 2650.


(39) Aldrich: 4-methyl-3-nitroanisole 5 g for about $120.


(46) The process was discovered in 1938 by Otto Roelen at Ruhrchemie, when it was first commercialized.


178


(64) Hobbs, C. F.; Knowles, W. S. J. Org. Chem. 1981, 46, 4422. The optical rotation for the pure (S)-2-acetoxypropanal was determined to be [α]D = -34.9° (c 5.0, toluene).


(74) Muller, J. M.; Schlitter, E.; Bein, H. J. Experientia 1952, 8, 338.


Selected $^1\!H$ NMR, $^{13}\!C$ NMR, $^{119}\!Sn$ NMR Spectra and GC Traces.
$^1$H NMR: (CDCl$_3$, 250 MHz)
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25.233

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NUL FACTOR-1.0000E+00

184
GC Trace (Chirasil-L-Val: 190°C, 30 min.)

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185
$^1$H NMR (CDCl$_3$, 400 MHz)
$^1$H NMR (CDCl$_3$, 400 MHz)
\[ ^{13}C \text{NMR (CDCl}_3, 100 \text{ MHz)} \]
$^1$H NMR (CDCl$_3$, 500 MHz)
$^1$H NMR (CDCl$_3$, 400 MHz)
$^1$H NMR (CDCl$_3$, 400 MHz)

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1H NMR (CDCl₃, 400 MHz)
$^1$H NMR (CDCl$_3$, 400 MHz)
Ligand: (RR)-DIOP (entry 42)

GC Trace (silicon: 50°C, 10 min., 5°C/min., 250°C, 30 min.)

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ATTEMPT WRITE PAST END OF FILE

RUN# 2548 JUN 9, 1982 13:51:53

IDENTIFIER: OCMET 2DAYS

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23.546 455608 PB .057 14.67502

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$^1$H NMR (CDCl$_3$, 400 MHz)

$\text{Ph}_2\text{C} = \text{CHO} + \text{Ph}_2\text{C} = \text{CHO}$

$\text{PS} (b = 15:85)$

50

51

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Ligand: PPh₃ (entry 25)

GC Trace (Chirasil-L-Val: 140°C, 30 min.)

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KUNA 623 SEP 9, 1981 18:31:22

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208
Ligand: (RR)-DIOP (entry 71)

$^1$H NMR (CDCl$_3$, 400 MHz)
GC Trace (silicon: 130°C, 5 min., 5°C/min., 250°C, 30 min.)

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212
Ligand: PPh₃ (entry 76)

GC Trace (silicon: 130°C, 5 min., 5°C/min., 250°C, 30 min.)

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VINYL NAPHTALENE 87

STOP

TOTAL AREA = 4807338
NUL FACTOR = 1.0000E+00
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Ligand: PPh₃ (entry 76)

GC Trace (silicon: 130°C, 5 min., 5°C/min., 250°C, 30 min.)

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RUN# 2522    JUN 7, 1992 19:03:35

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214
Ligand: (RR)-DIOP (entry 72)

GC Trace (silicon: 130°C, 5 min., 5°C/min., 250°C, 30 min.)

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ATTEMPTED WRITE PAST END OF FILE

RUN# 2507 JUN 6, 1902 19:40:43

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89% e.e. (S)

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NUL FACTOR = 1.0000E+00

215
Ligand: 71 (entry 79)

GC Trace (silicon: 130°C, 5 min., 5°C/min., 250°C, 30 min.)

START
IF

(R)

IF

STOP

Error storing signal to M: SIGNAL .5MA
ATTEMPTED WRITE PAST END OF FILE

RUN: 2760  JUL 5, 1902  00:22:47

IDENTIFIER: OCLET 2DAYS

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35.022  13367  VP  .002  1.02003

TOTAL AREA=1310448
MUL FACTOR=1.0000E+09

216

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Ligand: (RR)-DIOP (entry 92)

$^{1}H$ NMR (CDCl$_3$, 400 MHz)
Ligand: PPh₃ (entry 88)

GC Trace (Cyclodex B: 60°C, 30 min.)

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RUNN 599 SEP 1, 1981 01:38:28

SIGNAL FILE: M: SIGNAL.BNA

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Ligand: PPh\textsubscript{3} (entry 109)

GC Trace (silicon: 130°C, 5 min., 5°C/min., 250°C, 30 min.)

Vinyl Phthalimide 93

Closing signal file: SIGNAL.BNC

RUN: 2463 JUN 1, 1992 22:44:47

IDENTIFIER: DCNET 2DAYS
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1 : b = 6 : 94

(b) 95

188x699
Phth\[\text{CHO}\]

\[94\text{ (l)}\]

Phth\[\text{CHO}\]

\[95\text{ (b)}\]

Ligand: PPh\textsubscript{3} (entry 109)

\[^1\text{H NMR (CDCl}_3, 400 \text{ MHz)}\]
Ligand: PPh$_3$ (entry 109)

GC Trace (Chirasil-L-Val: 130°C, 30 min.)

START: not ready

(R)

(S)

Closing signal file M:SIGNAL.BNC

RUN# 676 SEP 16, 1981 08:08:10

SIGNAL FILE: M:SIGNAL.BNC

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| 25.668 | 59785| VP   | .296   | 53.65494|      |

TOTAL AREA- 111425
MUL FACTOR-1.0000E+00

222
Ligand: PPh₃ (entry 109)

GC Trace (silicon: 130°C, 5 min., 5°C/min., 250°C, 30 min.)

Closing signal file H:SIGNAL.BNC

RUN# 2523 JUN 7. 1992 19:43:56
IDENTIFIER: OCHEM 2DAYS
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$^1$H NMR (C$_6$D$_6$, 500 MHz)
nOe difference (CDCl₃, 500 MHz)
$^{119}\text{Sn NMR (CD}_2\text{Cl}_2, 186 MHz)$

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1H NMR (CDCl₃, 500 MHz)
$^{1}H$ NMR (C$_6$D$_6$, 500 MHz)
$^1\text{H NMR (CDCl}_3, 500 \text{ MHz)}$
$^1$H NMR (CD$_3$OD, 500 MHz)
\[^1\text{H} \text{NMR (CDCl}_3, 500 \text{ MHz)}\]
$^{13}$C NMR (CDCl$_3$, 125 MHz)
$^1$H NMR (CDCl$_3$, 500 MHz)
nOe difference (CDCl₃, 500 MHz)
$^1$H NMR (CDCl$_3$, 500 MHz)
$^{1}H$ NMR (CDCl$_3$, 500 MHz)
$^1$H NMR (CDCl$_3$, 500 MHz)
$\text{OTBDMS}$

$\text{SiMe}_3$

$\text{SnBu}_3$

$152$

$^1H$ NMR ($C_6D_6$, 500 MHz)